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EMERGING TRENDS IN PHARMA AND BIOMEDICAL SCIENCE VOLUME III

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Mr. C. P. Bhagat
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PREFACE

The fields of pharmaceutical and biomedical sciences are witnessing unprecedented growth and transformation in the 21st century. With the advent of cutting-edge technologies, personalized medicine, advanced drug delivery systems, biotechnological innovations, and a deeper understanding of disease mechanisms, researchers and practitioners are redefining healthcare every day.

This book, Emerging Trends in Pharma and Biomedical Science, is a humble yet focused attempt to compile recent developments, novel methodologies, and evolving perspectives that are shaping these dynamic disciplines. The chapters included herein cover diverse topics ranging from innovative drug discovery approaches and nanotechnology-based therapeutics to breakthroughs in diagnostics, regenerative medicine, and translational research. Each contribution has been thoughtfully curated to provide readers with both foundational insights and glimpses of the future directions these fields are poised to take.

This compilation aims to serve as a valuable resource for students, educators, researchers, and industry professionals alike, inspiring them to explore new ideas, foster interdisciplinary collaborations, and contribute to the advancement of science and healthcare. We sincerely hope that the collective efforts of the contributing authors and editors will ignite curiosity and encourage further research and innovation.

We express our heartfelt gratitude to all the authors, reviewers, and supporters whose dedication and expertise have made this book possible. It is our aspiration that this work will spark meaningful dialogue and provide guidance to those striving to address the ever-evolving challenges in pharma and biomedical science for the betterment of society.

- Editors

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UNMASKING MOEBIUS SYNDROME: ETIOPATHOGENESIS, CLINICAL FEATURES, AND EVOLVING THERAPEUTIC STRATEGIES

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Abstract:
Moebius syndrome is a rare, congenital, non-progressive neurological disorder predominantly affecting the sixth (abducens) and seventh (facial) cranial nerves. It presents clinically with bilateral facial paralysis and impaired ocular abduction, leading to significant challenges in facial expression, eye movement, speech, and feeding. The disorder frequently coexists with limb abnormalities, musculoskeletal malformations such as Poland sequence, and orofacial defects. Although the precise etiology remains unclear, a multifactorial origin involving genetic mutations (e.g., PLXND1, REV3L), intrauterine ischemic events, and teratogenic exposure is widely accepted. Diagnosis relies on clinical features, neuroimaging, and exclusion of other conditions. Management is multidisciplinary, encompassing surgical, rehabilitative, and supportive interventions to enhance facial function, motor abilities, speech, and psychosocial adaptation. Despite significant challenges, affected individuals often demonstrate adaptive strategies to communicate and integrate socially. Increasing awareness, advocacy, and early interventions are key to improving quality of life and long-term outcomes.

Keywords: Moebius Syndrome, Cranial Nerve Palsy, Facial Paralysis, Congenital Limb Abnomalities, Neurodevelopmental Disorder

Introduction:

Moebius syndrome is a rare, non-progressive, congenital neurological disorder primarily characterized by facial paralysis and impaired ocular abduction due to involvement of the sixth (abducens) and seventh (facial) cranial nerves. These nerves are crucial for lateral eye movement and facial expressions, respectively. Bilateral facial diplegia is often present, leading to a distinct facial appearance with a mask-like expression, absence of blinking, and an inability to smile, frown, pucker lips, or raise eyebrows. When the sixth cranial nerve is affected, patients cannot abduct their eyes past the midline, resulting in strabismus and difficulty in lateral gaze [1,2].In addition to cranial nerve deficits, approximately 15–20% of individuals with Moebius syndrome exhibit musculoskeletal abnormalities, including hypoplasia or aplasia of the pectoral muscles (particularly Poland anomaly), limb defects such as clubfoot, syndactyly, or brachydactyly, and orofacial malformations like micrognathia and high-arched palate [3,4]. The etiology of Moebius syndrome remains unclear, although several hypotheses have been proposed. These include vascular disruption during embryogenesis, teratogenic exposure to agents such as misoprostol or cocaine, and potential genetic contributions. Mutations in genes such as *PLXND1* and *REV3L* have been implicated in familial or syndromic forms of the disorder [5,6]. Although Moebius syndrome is present at birth, it is non-degenerative, and many affected individuals demonstrate normal cognitive development. Nevertheless, the inability to display facial expressions can lead to profound social and emotional challenges. Misinterpretation of emotional cues due to the absence of facial movement may result in social difficulties, stigmatization, and psychological distress. If adequate support is not provided, these challenges can significantly impact the individual's quality of life [7]. Despite these difficulties, individuals with Moebius syndrome often show notable adaptability. They employ compensatory communication methods, including enhanced vocal intonation, hand gestures, and body language, to effectively convey emotions and intentions. Interventions such as psychological counseling, speech therapy, and occupational therapy play a crucial role in improving functional outcomes and emotional well-being. Occupational therapy contributes to the development of fine motor skills, daily living abilities, and adaptive strategies that promote greater independence and quality of life, particularly in children with associated limb anomalies or motor delays. Speech therapy is essential for improving articulation, oral-motor coordination, and swallowing functions, thereby facilitating clearer communication and safer feeding practices [8]. Public awareness of Moebius syndrome remains limited, leading to frequent misunderstandings and the burden of constant explanation by affected individuals. Promoting advocacy, inclusive education, and community-based awareness initiatives is essential to reduce stigma and foster a more understanding and inclusive environment for those living with this complex condition [9].

History

The clinical understanding and characterization of Moebius syndrome have evolved significantly over more than a century, shaped by progressive insights from case reports and medical reviews. The earliest known documentation dates back to 1880, when Albrecht von Graefe described a case involving congenital bilateral paralysis of the sixth (abducens) and seventh (facial) cranial nerves in a single patient, establishing a foundational observation of the disorder [10].Subsequently, in 1888, the German neurologist Paul Julius Möbius expanded on this observation by reviewing a small series of patients presenting with congenital, non-progressive, bilateral facial and abducens nerve palsy, one of whom he personally examined and illustrated. It is from Möbius's description that the condition acquired its eponym, "Moebius syndrome." In 1939, Henderson conducted a comprehensive literature review and identified approximately sixty cases of congenital facial diplegia reported up to that point. He emphasized that facial diplegia, frequently accompanied by other cranial nerve palsies—most commonly involving the sixth nerve—and limb malformations, should form the clinical basis for diagnosing Moebius syndrome [11]. This expanded the understanding of the syndrome beyond isolated cranial nerve dysfunction to include systemic developmental anomalies. Further refinement occurred in 1953, when Richards synthesized existing literature and proposed a broader clinical definition. He identified the core features of Moebius syndrome as partial or complete facial paralysis, unilateral or bilateral impairment in ocular abduction, and the presence of congenital limb anomalies. Richards also noted possible involvement of the branchial musculature, including pectoralis muscle hypoplasia and bulbar dysfunction, thereby acknowledging the multi-system nature of the disorder [12–15].

Clinical Features

Moebius syndrome is a congenital, non-progressive neurological disorder that presents with a spectrum of cranial nerve deficits, musculoskeletal anomalies, and occasionally neurodevelopmental or behavioral issues. The syndrome most commonly involves dysfunction of the sixth (abducens) and seventh (facial) cranial nerves but may extend to other cranial nerves and systems, resulting in a broad clinical phenotype [16–18]. Bilateral facial paralysis is the cardinal feature of Moebius syndrome. It is typically recognized at birth by a lack of facial expression, absence of a smile or frown, and incomplete eyelid closure during sleep. Infants often demonstrate poor sucking and difficulty breastfeeding due to impaired lip seal and weak orobuccal musculature. As speech develops, articulation difficulties arise, particularly with labial consonants (e.g., /p/, /b/, /m/), due to reduced lip movement and tone [16]. Ocular abduction deficit is present in approximately 75% of patients due to sixth nerve palsy, resulting in impaired lateral eye movement. This limitation often leads to strabismus and compensatory head turning to fixate objects. Conjugate horizontal gaze palsy may also be observed in severe cases [16,17]. In about 25% of cases, the twelfth cranial nerve (hypoglossal) is affected, leading to tongue atrophy, limited tongue protrusion, and poor oral-motor coordination. These impairments may contribute to difficulties with swallowing (dysphagia) and speech articulation [17]. Limb and skeletal malformations are frequently associated with Moebius syndrome. These may include clubfoot (Talipes Equinovarus), congenital limb reduction defects such as amelia, ectrodactyly, or congenital amputation, syndactyly (webbed fingers), brachydactyly (short fingers), and hypoplasia or absence of digits or limb bones [16,18]. Some children exhibit developmental motor delays, particularly in gross motor milestones during infancy. Although most achieve age-appropriate motor skills with time, subtle deficits in hand-eye coordination, fine motor tasks, and balance may persist into school age, necessitating occupational and physical therapy. Approximately 15% of Moebius syndrome patients have features of Poland sequence, characterized by unilateral hypoplasia or aplasia of the pectoralis major muscle and ipsilateral upper limb anomalies, including shortened or malformed digits. This combination suggests a possible shared embryologic vascular disruption mechanism [17]. Other musculoskeletal findings may include hypoplasia or absence of trunk muscles, such as the pectoralis minor, trapezius, and latissimus dorsi. Some individuals display autism spectrum-like behaviors, including impaired social interaction, communication deficits, and repetitive behaviors, reported in approximately 30–40% of patients. Importantly, cognitive development is generally within the normal range, although mild intellectual disability has been reported in a minority of cases [17,18].

Causes

Moebius syndrome is a congenital neurodevelopmental disorder with a multifactorial etiology, involving both genetic and environmental components. Although the exact pathogenesis remains incompletely understood, research indicates a spectrum of contributing factors that may vary across individuals, highlighting the etiological heterogeneity of the syndrome [19,20]. Genetic factors are implicated in a subset of Moebius syndrome cases. Although most cases appear sporadically without a family history, some demonstrate familial inheritance. Sporadic mutations have been identified in genes such as PLXND1 (plexin D1) and REV3L (REV3-like DNA-directed polymerase ζ catalytic subunit) located on chromosome 13q12.2–q13. These genes are involved in axonal guidance and DNA replication/repair, and mutations have been confirmed in animal models to cause phenotypes resembling Moebius syndrome, suggesting their critical role in hindbrain development [21,22]. Rare familial cases of Moebius syndrome have been reported with autosomal dominant transmission patterns. These suggest that in some instances, a single copy of a mutated gene may be sufficient to produce the phenotype, though penetrance and expressivity may vary [23]. Environmental and developmental factors are also significant contributors to Moebius syndrome. One widely accepted hypothesis is intrauterine ischemia of the developing brainstem during early gestation. This ischemic event likely affects the rhombencephalon, particularly the regions housing the sixth and seventh cranial nerve nuclei. Potential causes of ischemia include uteroplacental insufficiency, vascular malformations, or mechanical compression. These disturbances during critical windows of embryogenesis can lead to localized hypoxia, impairing neurogenesis and neuronal migration, and thereby contributing to the characteristic cranial nerve deficits and associated anomalies observed in Moebius syndrome [24,25].

Teratogenic exposure has also been linked to Moebius syndrome. Maternal use of misoprostol, cocaine, or other vasoactive substances during the first trimester may disrupt embryonic vasculature or neural migration, increasing the risk for developmental anomalies [26,27]. The constellation of symptoms observed in Moebius syndrome suggests a developmental defect of the hindbrain and adjacent mesodermal tissues. These defects may arise from genetic mutations affecting neurogenesis, angiogenesis, or tissue morphogenesis, or from environmental insults during critical periods of embryonic development [25,27]. The clinical and genetic heterogeneity of Moebius syndrome implies that multiple distinct pathogenic mechanisms may underlie its development. In some individuals, the syndrome may be primarily genetic, while in others it may result from intrauterine disruption or teratogen exposure. This underscores the need for personalized diagnostic and therapeutic strategies, as well as continued research to elucidate the specific mechanisms in individual cases [19,28,29].

Pathophysiology

The pathophysiology of Moebius syndrome is complex and multifactorial, involving disturbances in the development of the brainstem, particularly the rhombencephalon, during early embryogenesis. The syndrome is primarily characterized by congenital, non-progressive palsies of cranial nerves—most consistently the sixth (abducens) and seventh (facial)—resulting in impaired facial expression and ocular abduction. However, additional cranial nerves (III, V, IX, X, and XII) and other systems may also be affected, contributing to the diverse clinical spectrum. Disruption of Cranial Nerve Nuclei Development The hallmark of Moebius syndrome lies in the hypoplasia or agenesis of cranial nerve nuclei, particularly those located in the caudal pons and medulla. Autopsy studies and imaging findings have shown absence, underdevelopment, or atrophy of the abducens and facial nerve nuclei in the brainstem. These abnormalities result in the paralysis of extraocular and facial muscles, manifesting as strabismus and facial diplegia [30,31]. Vascular Disruption Theory One widely supported theory suggests that Moebius syndrome results from interrupted vascular supply—specifically subclavian artery supply disruption—to the developing brainstem during the fourth to sixth weeks of gestation. This ischemic event is hypothesized to selectively damage the developing cranial nerve nuclei and adjacent mesodermal tissues. It may also explain the frequent co-occurrence of limb anomalies, such as Poland sequence or limb reduction defects, which are believed to stem from disruption in the embryonic subclavian or vertebral arteries [30,32]. Genetic and Molecular Contributions Although most cases are sporadic, several genetic mutations have been implicated in Moebius syndrome, offering insight into molecular mechanisms. PLXND1 (plexin-D1) is involved in axonal guidance and vascular development. Mutations in this gene may impair the navigation of motor neuron projections in the brainstem. REV3L (REV3-like DNA polymerase zeta catalytic subunit) is associated with DNA repair during development. Loss-of-function mutations can result in disrupted cranial nerve development [33]. These mutations have been shown to cause similar cranial nerve phenotypes in animal models, reinforcing the idea that gene-environment interactions are critical to pathogenesis. Hindbrain Maldevelopment Neuroimaging studies using MRI and diffusion tensor imaging (DTI) have confirmed structural anomalies of the hindbrain, including flattening of the fourth ventricle floor, hypoplasia of the pons, and absent facial colliculi. These features are consistent with developmental anomalies of rhombencephalic structures, affecting the trajectory and integrity of motor and sensory cranial nerves [31,34]. Neuromuscular and Myopathic Findings In addition to central nervous system abnormalities, some studies have documented myopathic or neurogenic changes in the muscles innervated by affected cranial nerves, such as facial and extraocular muscles. Electromyographic studies (EMG) in Moebius patients have demonstrated reduced or absent motor unit potentials, further supporting a peripheral neuromuscular component in select cases.

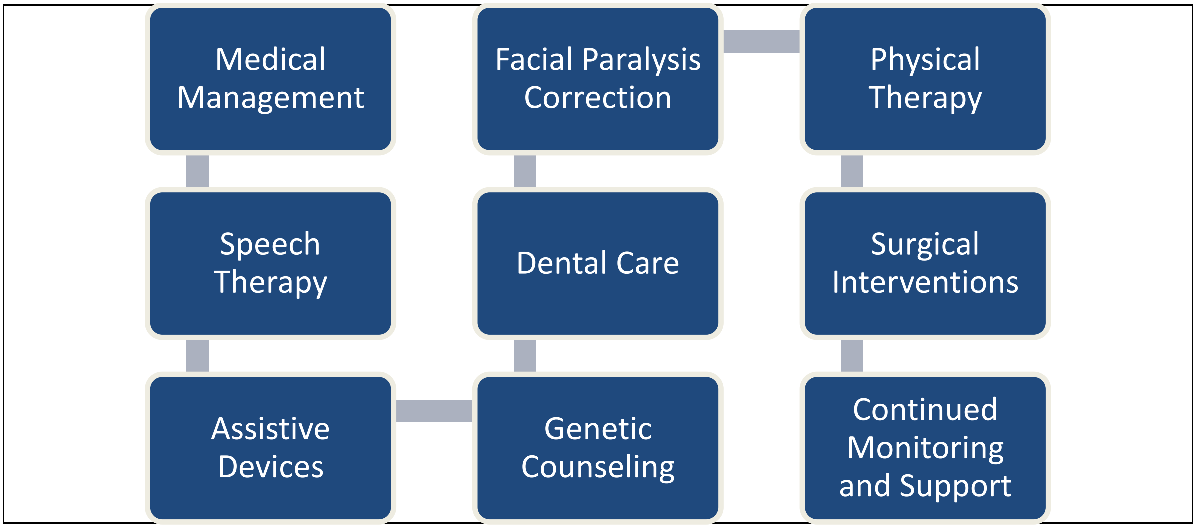
Diagnosis

Moebius syndrome is primarily diagnosed through clinical observation, with hallmark signs including congenital, non-progressive bilateral facial weakness and sixth cranial nerve palsy, typically evident at birth. Affected infants may show an expressionless face, inability to smile or blink, and impaired lateral eye movement. Diagnostic criteria include congenital facial palsy, impaired eye abduction, and absence of neurological progression over time [35,36]. Associated anomalies—such as limb malformations, feeding difficulties, or chest wall defects—support the diagnosis. Although not essential, brain MRI can aid in confirming the diagnosis or excluding other pathologies. Common findings include hypoplasia or absence of cranial nerve nuclei VI and VII, absence of the facial colliculus, and brainstem hypoplasia [36,37]. Electromyography and nerve conduction studies may show reduced motor unit potentials, indicating congenital denervation or myopathy [38]. Genetic testing may identify mutations in genes such as PLXND1 and REV3L, especially in familial cases or those with multiple anomalies [39]. However, most cases are sporadic, and no specific genetic mutation is consistently found. Differential diagnoses include conditions like Duane syndrome, congenital facial palsy, congenital fibrosis of the extraocular muscles, Poland syndrome, and muscular dystrophies. Clinical, radiological, and neurophysiological evaluations help in distinguishing these disorders. Prenatal diagnosis is uncommon but may be pursued in high-risk cases through fetal imaging or genetic testing. However, prenatal findings such as micrognathia or limb anomalies are often non-specific [40].

Treatment

The treatment of Moebius syndrome is complex and highly individualized, typically involving a multidisciplinary team of healthcare professionals. Management is tailored according to the unique combination of symptoms and functional impairments experienced by each patient. The core objective is to improve facial movement, communication, feeding, motor skills, and social integration while addressing any structural or neurological abnormalities. Medical management begins with comprehensive assessment by a team of specialists including pediatricians, neurologists, plastic surgeons, otolaryngologists, orthopedists, dental experts, ophthalmologists, speech therapists, and audiologists. These professionals collaborate to formulate an individualized treatment plan, often initiated early in life to support developmental milestones [41]. Surgical correction of facial paralysis is a key component of treatment for many patients. Procedures such as temporalis tendon transfer, cross-facial nerve grafting, or free muscle transfer (e.g., gracilis muscle) may be employed to restore voluntary facial movements, particularly the ability to smile and close the eyes. These reconstructive surgeries, commonly referred to as smile surgeries, have shown significant improvement in facial symmetry and social communication [41,42]. Physical therapy is recommended to address limb deformities and motor delays.

Therapeutic interventions aim to enhance mobility, strengthen muscle tone, and improve hand-eye coordination. Occupational therapy can further assist in improving fine motor skills and daily functioning, particularly in children with hand or foot malformations. Speech therapy is essential for managing difficulties related to articulation, oral-motor coordination, and swallowing. Many individuals with Moebius syndrome benefit from targeted exercises and adaptive strategies to improve verbal communication and feeding efficiency, especially if they have associated palate abnormalities or tongue dysfunction. Dental care is another important aspect of management. Dental specialists and orthodontists address problems such as enamel hypoplasia, malocclusion, cleft palate, and widely spaced or misaligned teeth. Treatment may include orthodontic appliances, oral surgery, or prosthodontic support to ensure proper jaw alignment and oral hygiene. Surgical interventions may also be necessary to correct other structural anomalies, such as strabismus (crossed eyes), limb malformations, and Poland sequence features involving the chest wall and breast development. Eye muscle surgeries can improve visual alignment and function, enhancing quality of life. Assistive devices, including eye lubricants, corrective lenses, limb braces, or orthotic splints, may be prescribed based on specific physical limitations. These tools support everyday activities and help compensate for deficits in movement, vision, or posture. Genetic counseling plays a valuable role, particularly in familial or syndromic cases. Counseling sessions help patients and their families understand the genetic basis of Moebius syndrome, discuss recurrence risk, and consider implications for future pregnancies. Ongoing follow-up and support are vital components of care. Regular monitoring ensures early identification and management of emerging complications. Additionally, psychosocial support from healthcare teams and advocacy organizations can assist families in navigating the emotional and social challenges posed by the condition. Ultimately, the treatment approach for Moebius syndrome aims to optimize functional independence and social participation. With coordinated, multidisciplinary care and ongoing rehabilitation, many individuals with Moebius syndrome lead fulfilling lives, achieving personal and academic success despite the challenges associated with the condition [42,43].



Discussion

Moebius syndrome is a rare congenital neurological disorder defined by bilateral paralysis of the sixth and seventh cranial nerves, leading to a characteristic lack of facial expression and impaired lateral eye movement. Despite its low prevalence, the syndrome presents a diverse clinical picture with systemic implications that extend beyond cranial nerve dysfunction. The inclusion of limb anomalies, Poland sequence, and orofacial malformations reflects a broader embryological disruption, possibly involving neuroectodermal and mesodermal tissues during early gestation. The etiopathogenesis remains multifactorial, with evidence supporting both genetic and environmental factors. Mutations in genes such as *PLXND1* and *REV3L* suggest a genetic predisposition, although most cases are sporadic. The vascular disruption theory, which proposes transient ischemia in the developing brainstem, offers a compelling explanation for both the cranial and limb defects frequently observed. Management of Moebius syndrome is challenging due to the complexity of symptoms and their impact on essential functions such as communication, feeding, and social interaction. A multidisciplinary approach, involving surgical, therapeutic, and psychological interventions, is essential for improving functional outcomes and quality of life. Early intervention, particularly in speech and physical therapy, can aid in overcoming developmental delays and enhancing social adaptability. Social stigmatization and emotional distress are significant concerns, especially due to the inability to convey facial expressions. Therefore, advocacy, awareness, and educational support are critical. With appropriate care and societal inclusion, many individuals with Moebius syndrome achieve academic and personal success, highlighting the importance of tailored, empathetic, and comprehensive management strategies.

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SALMONELLOSIS: AN OVERVIEW

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Abstract:

Salmonellosis, an infection caused by the bacterium *Salmonella*, continues to be a major global public health challenge. This Abstract: offers an in-depth overview of salmonellosis, highlighting critical aspects such as its epidemiology, microbiological characteristics, clinical features, diagnostic approaches, prevention measures, and treatment options. From an epidemiological perspective, *Salmonella* is widely distributed, with numerous serovars implicated in foodborne disease outbreaks. Understanding the pathogen's transmission routes is vital, as human infection often results from consuming contaminated food items, including raw or improperly cooked eggs, poultry, meat, and unpasteurized dairy products. Microbiologically, *Salmonella* demonstrates significant adaptability, enabling it to persist in diverse environments and infect a broad range of hosts, posing considerable challenges for disease prevention and control. Public health initiatives, including disease surveillance, outbreak investigations, and educational campaigns, are crucial in curbing the incidence of salmonellosis. Most cases are self-limiting and require only supportive care, but severe infections may necessitate antibiotic therapy, underscoring the importance of appropriate antibiotic use to prevent resistance development. In summary, comprehensive knowledge of salmonellosis is imperative for devising effective prevention and control measures. This abstract synthesizes essential information to support researchers, clinicians, and policymakers dedicated to reducing the global burden of *Salmonella* infections.

Keywords: Salmonella Bacterium; Foodborne Disease Outbreaks; Contaminated Eggs; Antibiotic Treatment; Environmental Resilience.

Introduction:

Salmonellosis, a serious infection triggered by the bacterium *Salmonella*, poses a major global health threat, impacting both public health systems and food safety. The disease presents with diverse clinical manifestations, ranging from mild gastrointestinal disturbances to life-threatening systemic complications, affecting millions of people worldwide each year. This introduction delves into the fundamental facets of salmonellosis, detailing its causative organism, modes of transmission, and the varied clinical spectrum it encompasses. It also addresses the socio-economic consequences associated with the disease and highlights the ongoing public health measures aimed at curbing its incidence.

The genus *Salmonella* encompasses a broad range of bacteria, comprising over 2,500 identified serovars, and is noted for its remarkable adaptability to diverse environmental settings. Among these, *Salmonella enterica*—with its many subspecies and serotypes—stands out as the leading cause of human infections. Its capacity to colonize the gastrointestinal tracts of various hosts, including humans, mammals, and birds, highlights its extensive reach and the challenges in controlling its spread. Most commonly, salmonellosis arises from consuming contaminated food, with raw or inadequately cooked eggs, poultry, meat, and unpasteurized dairy products acting as typical transmission sources. Furthermore, practices like poor hygiene and cross-contamination during food handling facilitate the persistence of *Salmonella* within the food supply chain. Therefore, a thorough understanding of its epidemiology and transmission mechanisms is essential for crafting effective control measures and targeted prevention strategies. [1,2].

The clinical presentations of salmonellosis are highly variable, ranging from mild, self-limiting gastroenteritis to serious systemic infections, including bacteremia and complications beyond the gastrointestinal tract. Certain high-risk groups—such as older adults, infants and young children, and those with compromised immune systems—are especially susceptible to severe illness, necessitating extra caution in managing these cases. This clinical diversity adds complexity to the diagnosis and treatment of *Salmonella* infections, highlighting the importance of a thorough understanding of the disease. Beyond its impact on human health, salmonellosis imposes significant economic costs related to medical care, productivity losses, and expenditures associated with investigating foodborne outbreaks. Consequently, controlling and preventing *Salmonella* infections is critical to protecting public health and reducing the financial burden they pose. This introduction lays the groundwork for an in-depth examination of salmonellosis, highlighting the disease's multifaceted nature and the need for ongoing research, monitoring, and coordinated interventions to lessen its prevalence and impact on a global scale.

Imagine a microscopic invader that silently travels through our global food supply, thriving in unsuspecting kitchens, bustling marketplaces, and even seemingly clean farmyards. This stealthy pathogen doesn't wear a crown like viruses or cause alarm like pandemics—but it sickens millions each year, quietly making its mark on global public health. This is Salmonella, the bacterial culprit behind salmonellosis, one of the most common and persistent foodborne illnesses worldwide.

Salmonellosis is far more than a transient episode of diarrhea; it is a complex zoonotic disease that reflects the interconnectedness of human health, animal health, and environmental hygiene. With over 2,500 known serotypes of *Salmonella*, and the capacity to adapt and persist in diverse environments—from livestock intestines to water systems and processed foods—this bacterium poses a continual challenge to food safety authorities and healthcare providers alike.

The disease affects individuals across all age groups but proves especially dangerous for young children, the elderly, and immunocompromised populations. While it often presents as self-limiting gastroenteritis, severe systemic infections and long-term complications like reactive arthritis can also occur. In addition, the rise of antimicrobial resistance in *Salmonella* strains has transformed what was once a treatable condition into a potential threat to modern medicine.

What makes salmonellosis particularly insidious is its invisibility: the contaminated food often looks, smells, and tastes perfectly normal. From a public health perspective, it serves as a biological indicator of deeper systemic issues—unsafe agricultural practices, inadequate food regulation, and gaps in hygiene education.

This chapter delves into the multifaceted world of salmonellosis, exploring its epidemiology, clinical presentation, diagnostic tools, treatment strategies, and, most importantly, the measures needed to control and prevent it. As global food chains grow more complex and antibiotic resistance continues to evolve, understanding and combating salmonellosis becomes not just a medical necessity, but a moral imperative.

Etiology:

Salmonellosis is an infectious disease caused by multiple serovars of the *Salmonella* bacterium, with *Salmonella enterica* being the predominant species implicated in human illness. The disease's etiology reflects the complex interactions between the bacterium, its diverse serotypes, and the routes of transmission that lead to human infection.

1. **Bacterial Agent: Salmonella**

- **Genus:** *Salmonella* is a member of the Enterobacteriaceae family, characterized as a Gram-negative, facultatively anaerobic bacterium.
- **Species:** Among the various species, *Salmonella enterica* is most frequently associated with human disease. Within this species, a large number of serotypes have been identified, each possessing distinct antigenic profiles.

2. **Serovars and Antigenic Diversity**

- **Serovars:** Classification of *Salmonella* into specific serovars relies on differences in surface antigens, particularly the O (somatic) and H (flagellar) antigens. Prominent serovars include *Salmonella Typhimurium*, *Salmonella Enteritidis*, and *Salmonella Newport*, among others.
- **Antigenic Variation:** The broad antigenic diversity among *Salmonella* serovars enhances the bacterium's ability to infect a wide range of hosts and thrive in different environments, thereby complicating the development of universally effective prevention and control measures [3].

3. **Reservoirs and Host Range:**

- **Animal Hosts:** *Salmonella* frequently colonizes the intestines of a wide variety of animals, including mammals, birds, and reptiles. Human infections often originate from contact with contaminated animal products or environments contaminated by animal waste.

- **Zoonotic Nature:** Due to its zoonotic characteristics, *Salmonella* is readily transmitted from animals to humans, typically through the consumption of contaminated food or direct contact with infected animals.

4. **Transmission Pathways:**

- **Foodborne Spread:** The primary route of infection involves consuming contaminated food items. Common sources include raw or inadequately cooked eggs, poultry, meat, and unpasteurized dairy products.
- **Fecal-Oral Route:** Poor hygiene, substandard sanitation, and cross-contamination during food preparation play critical roles in spreading *Salmonella* via the fecal-oral route.
- **Waterborne Spread:** In areas with compromised water quality, contaminated water can also act as a vector for *Salmonella* transmission.

5. **Environmental Persistence:**

- **Survival Capabilities:** *Salmonella* demonstrates remarkable resilience across different environmental conditions, enabling it to survive in water, soil, and on various surfaces. This adaptability allows the bacterium to remain within the food chain, complicating control efforts.[4].

Grasping the underlying causes of salmonellosis is essential for crafting focused preventive approaches, establishing robust food safety protocols, and strengthening public health initiatives to curb the frequency of this prevalent and largely avoidable bacterial disease.

Epidemiology of Salmonellosis

Salmonellosis is a widely occurring zoonotic infection caused mainly by *Salmonella enterica*, and it represents one of the most common foodborne diseases globally. The World Health Organization (WHO) reports that this condition is responsible for nearly **94 million cases of intestinal infection** and around **155,000 deaths** each year.

Global Impact

The occurrence and impact of salmonellosis differ between regions, largely depending on factors such as hygiene practices, quality of drinking water, food production standards, and healthcare infrastructure. In high-income countries, outbreaks are typically linked to contaminated packaged foods or raw vegetables. Conversely, in many low- and middle-income nations, persistent problems like unsafe water supplies and inadequate food safety monitoring contribute to its widespread nature.

Incidence and Prevalence

- In the **United States**, estimates from the Centers for Disease Control and Prevention (CDC) indicate that **1.35 million people** become infected annually, resulting in **over 26,000 hospital admissions** and **more than 400 deaths**.
- Across **Europe**, *Salmonella* is ranked among the top bacterial agents causing foodborne illness, with several thousand confirmed cases each year.

- In **developing regions**, the disease is significantly underreported due to limited access to diagnostic facilities, but it remains a major contributor to illness and death in young children, especially those under five.

Modes of Transmission

The bacteria are primarily spread through the **ingestion of contaminated food or water**. Common sources include:

- Undercooked or raw meat, eggs, and dairy products.
- Contact with infected animals or animal waste, particularly from poultry and reptiles.
- Person-to-person spread, especially in settings with poor sanitation or hygiene, like childcare centers.

Outbreak Scenarios

Salmonellosis outbreaks can occur when:

- Contaminated food products are widely distributed in the supply chain.
- Cooking and food storage practices are inadequate.
- Water supplies become polluted, particularly following natural disasters or flooding.

High-Risk Populations

Certain groups face a greater risk of developing severe or systemic salmonellosis:

- Infants and young children
- Elderly adults
- Immunocompromised individuals (e.g., those with HIV/AIDS, undergoing chemotherapy, or post-transplant)
- People with underlying blood disorders, such as sickle cell anemia

Antibiotic Resistance

A growing concern is the rise of **antibiotic-resistant *Salmonella*** strains, particularly *S. Typhimurium* and *S. Enteritidis*. These strains have shown resistance to several commonly used medications, including ampicillin and trimethoprim-sulfamethoxazole, making treatment more challenging.

Monitoring and Prevention

Surveillance networks like **PulseNet USA** and the **European Food Safety Authority (EFSA)** play a critical role in tracking outbreaks and guiding public health responses. Prevention strategies focus on:

- Enhancing food processing and inspection systems.
- Promoting good hygiene and proper food preparation.
- Raising public awareness about the risks of consuming undercooked or raw animal products.
- Vaccinating livestock in certain regions to reduce transmission

Clinical manifestation:

Salmonellosis exhibits a wide array of clinical presentations, spanning from mild gastrointestinal disturbances to severe systemic infections. The disease's clinical course varies depending on factors such as the patient's age, overall health status, and the specific *Salmonella* serotype involved. The following outlines the typical clinical features of salmonellosis:

1. **Gastroenteritis:**

- **Onset:** Symptoms generally develop within 6 to 72 hours following exposure to the pathogen.
- **Gastrointestinal Symptoms:** The most common presentation is acute gastroenteritis, marked by diarrhea, abdominal pain, nausea, vomiting, and fever.
- **Diarrhea:** Bowel movements are typically watery and may contain mucus or occasionally blood, persisting for several days.
- **Abdominal Pain:** Many patients experience significant abdominal discomfort and cramping, contributing to the disease's overall burden.

2. **Systemic Infections:**

- **Bacteremia:** In certain cases, *Salmonella* can spread to the bloodstream, resulting in bacteremia. This is more frequently seen in vulnerable populations, including the very young, the elderly, and immunocompromised individuals.
- **Extraintestinal Manifestations:** Severe infections can extend beyond the gastrointestinal tract, potentially affecting organs such as the heart, bones, joints, and the central nervous system [5,6].

3. **Typhoid and Paratyphoid Fevers:**

- **Systemic Infections:** Certain *Salmonella* serotypes, notably *Salmonella Typhi* and *Salmonella Paratyphi*, are responsible for causing typhoid and paratyphoid fevers, respectively.
- **Prolonged Febrile Illness:** These systemic infections are characterized by a persistent, high-grade fever accompanied by symptoms such as headache, generalized aches, and an enlarged spleen.
- **Gastrointestinal Involvement:** While primarily systemic, typhoid and paratyphoid fevers can also present with abdominal pain and diarrhea.

4. **Disease Severity in High-Risk Groups:**

- **Children:** Infants and young children may experience more severe disease, with dehydration being a potential complication that requires medical intervention.
- **Older Adults:** Elderly patients, especially those with pre-existing health issues, may develop more intense and prolonged illness.
- **Immunocompromised Individuals:** People with weakened immune systems—such as those with HIV/AIDS or those receiving immunosuppressive therapy—are at increased risk of severe *Salmonella* infections.

5. **Disease Duration and Recovery:**

- **Self-Limiting Nature:** In most cases, symptoms gradually resolve on their own within about a week.

- **Chronic Carrier State:** Some individuals may continue to carry *Salmonella* in their intestines even after clinical recovery, posing a risk of ongoing transmission despite being asymptomatic.

Understanding the wide range of clinical manifestations of salmonellosis is critical for healthcare providers to accurately diagnose and manage cases, particularly among vulnerable populations where the risk of complications is higher. Prompt medical attention is essential in severe cases or when extraintestinal involvement is suspected.

Diagnosis:

The diagnosis of salmonellosis relies on a multifaceted approach, combining clinical evaluation, laboratory analysis, and epidemiological context. Due to its variable clinical manifestations and the need for precise identification, the diagnostic process is thorough. Below are the key components involved in diagnosing salmonellosis:

1. **Clinical Evaluation:**

- **Patient History:** A comprehensive history is essential, focusing on recent dietary intake, travel, and any known exposure to sources of *Salmonella*.
- **Symptom Review:** Key gastrointestinal symptoms—such as diarrhea, abdominal pain, nausea, vomiting, and fever—provide initial diagnostic clues.
- **Systemic Assessment:** For suspected severe or systemic cases, evaluating symptoms like prolonged fever, headaches, and other signs of extraintestinal involvement is critical.

2. **Laboratory Investigations:**

- **Stool Culture:** The gold standard involves isolating *Salmonella* from stool samples through bacterial culture.
- **Selective Media:** Specialized media, such as Salmonella-Shigella agar or xylose-lysine-deoxycholate agar, enhance detection of the pathogen.
- **Biochemical Identification:** Additional tests confirm that the isolated organism is indeed *Salmonella*.
- **Serotyping:** Characterizing the *Salmonella* strain through serotyping pinpoints the specific serovar causing the infection.
- **Antimicrobial Sensitivity Testing:** Assessing the isolate's susceptibility to antibiotics is important for guiding therapy, particularly in severe cases.

3. **Molecular and Immunological Testing:**

- **PCR:** Molecular assays like polymerase chain reaction can rapidly detect *Salmonella* DNA in clinical samples.
- **ELISA:** Immunological methods, including enzyme-linked immunosorbent assays, can identify specific *Salmonella* antigens in stool specimens.

4. **Blood Cultures:**

- **Detection of Bacteremia:** When systemic infection is suspected, blood cultures help identify the presence of *Salmonella* in the bloodstream.

5. **Epidemiological Considerations:**

- **Outbreak Investigations:** When multiple cases occur, epidemiological investigations help trace the infection's source and support public health interventions.
- **Dietary and Travel Histories:** Gathering information on recent food consumption and travel is essential for identifying potential exposure routes.

6. **Differential Diagnosis:**

- **Other Pathogens:** Differentiating *Salmonella* infections from other gastrointestinal pathogens, such as *Campylobacter*, *Shigella*, or *Escherichia coli*, is important due to overlapping symptoms.
- **Non-Infectious Conditions:** Diseases like inflammatory bowel disease or adverse reactions to certain medications may mimic symptoms of salmonellosis, requiring careful clinical evaluation [7].

Timely and accurate detection of salmonellosis is vital for ensuring proper treatment, implementing targeted public health interventions, and controlling disease spread. Healthcare providers should integrate clinical insights with diverse laboratory tests and work closely with public health authorities to manage cases effectively.

Management:

The management of salmonellosis encompasses a combination of supportive measures, fluid therapy, and, when appropriate, antimicrobial treatment. Treatment decisions are guided by the severity of the illness, the patient's age and overall health, and the risk of complications. Below is a summary of the main aspects of salmonellosis management:

1. **Supportive Measures:**

- **Hydration Management:** Ensuring adequate fluid intake is essential, especially in patients experiencing diarrhea and vomiting. This may involve oral rehydration solutions or intravenous fluids to prevent dehydration.
- **Nutritional Care:** A well-balanced diet is recommended to aid recovery. In more severe cases, dietary supplementation might be needed to support overall health.
- **Rest:** Allowing the patient to rest is important to facilitate healing and recovery from the infection.

2. **Antimicrobial Treatment:**

- **Indications for Antibiotics:** In most instances of mild, uncomplicated salmonellosis, antibiotics are not required, as the infection tends to resolve on its own. However, antimicrobial therapy may be necessary in specific cases:
- **Vulnerable Groups:** Antibiotics may be prescribed for high-risk patients, including young children, the elderly, individuals with weakened immune systems, or those experiencing severe illness [8].
- **Systemic Infections:** When the infection spreads beyond the intestines, causing bacteremia or affecting other organs, antibiotic therapy is typically required.

- **Antibiotic Choice:** The selection of antibiotics is guided by the susceptibility profile of the specific *Salmonella* strain. Common options include ciprofloxacin, ceftriaxone, and trimethoprim-sulfamethoxazole. Given the growing issue of antimicrobial resistance, susceptibility testing is essential to inform appropriate therapy.
- **Antibiotic Stewardship:** To minimize the development of resistance, antibiotics should be used judiciously, with decisions based on clinical evaluation and laboratory findings.
- **Monitoring and Follow-Up:**
- **Clinical Monitoring:** Patients should be observed closely to ensure that symptoms—particularly diarrhea and dehydration—are resolving.
- **Follow-Up Assessments:** In some cases, especially among high-risk groups or those with persistent symptoms, additional follow-up may be needed.
- **Preventing Further Spread:**
- **Infection Control:** Individuals infected with *Salmonella* should adhere to strict hygiene practices, including regular handwashing and refraining from preparing food for others while they are symptomatic.
- **Reporting Requirements:** Healthcare professionals are required to notify public health authorities about salmonellosis cases to support outbreak investigations and implement measures to prevent additional cases [9].

3. **Preventive Strategies:**

- **Food Safety Education:** Educating the public on safe food practices—including proper food handling, thoroughly cooking meat, and avoiding raw or undercooked eggs—is vital for reducing the risk of infection.
- **Surveillance and Outbreak Management:** Public health agencies play an essential role in monitoring cases, detecting outbreaks, and implementing appropriate control strategies to contain and prevent the spread of *Salmonella* infections [10].

Managing salmonellosis requires a coordinated approach involving healthcare professionals, public health authorities, and patients themselves. Adapting treatment to individual needs and reinforcing preventive measures are key elements in controlling this disease effectively.

Conclusion:

In summary, salmonellosis continues to pose a serious challenge to global public health, marked by its wide-ranging clinical manifestations—from mild gastrointestinal distress to potentially life-threatening systemic infections. The causative bacterium, *Salmonella*, is highly adaptable, enabling its persistence across diverse environments and among various hosts. Accurate diagnosis requires a comprehensive approach that integrates clinical evaluation, laboratory testing, and epidemiological investigation. While most cases are managed with supportive care and hydration, antimicrobial therapy may be necessary in severe cases. Nonetheless, prevention remains the cornerstone of disease control. Key public health strategies—such as educating the public on safe food practices, maintaining robust surveillance, and responding swiftly to outbreaks—are essential for limiting the impact of *Salmonella* on both individuals and communities. A thorough understanding of salmonellosis, coupled with proactive management, highlights the need for continued research, collaboration, and global health initiatives to reduce the burden of this infection worldwide.

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ROLE OF CLINICAL PHARMACIST IN MANAGING PATIENTS WITH CARDIOVASCULAR DISEASE

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Introduction:

Cardiovascular diseases (CVDs) are among the leading causes of morbidity and mortality worldwide, representing a significant public health challenge. The complexity of CVD management, which often involves polypharmacy and the need for individualized therapy, highlights the critical role of clinical pharmacists in optimizing patient care. Clinical pharmacists possess specialized knowledge in pharmacotherapy and play an integral role in medication management, patient education, and collaborative care with healthcare teams. Their involvement has been associated with improved clinical outcomes, enhanced medication adherence, and reduced healthcare costs [1,2]. This review aims to elucidate the multifaceted role of clinical pharmacists in managing patients with cardiovascular diseases, emphasizing current evidence and future directions.

Cardiovascular Diseases Overview

Cardiovascular diseases encompass a broad range of disorders affecting the heart and blood vessels, including coronary artery disease, heart failure, hypertension, arrhythmias, and stroke. According to the World Health Organization, CVDs account for approximately 17.9 million deaths annually, representing 32% of all global deaths [3]. The pathophysiology of CVDs involves complex interactions between genetic, environmental, and lifestyle factors leading to atherosclerosis, myocardial injury, and vascular dysfunction. Effective management requires a multidisciplinary approach focusing on risk factor modification, pharmacological therapy, and patient-centered care [4,5]. Advances in pharmacotherapy have improved survival rates, but optimal medication use remains challenging due to polypharmacy and adherence issues.

Role of Clinical Pharmacist in Cardiovascular Disease Management

Clinical pharmacists contribute to cardiovascular disease management through multiple functions: medication therapy management, patient education, medication reconciliation, adverse drug reaction monitoring, and participation in multidisciplinary care teams. They ensure appropriate selection, dosing, and monitoring of cardiovascular medications such as antihypertensives, anticoagulants, lipid-lowering agents, and antiarrhythmics [6]. Pharmacists also provide lifestyle counseling, adherence support, and identify potential drug interactions. Their collaboration with physicians and nurses has been shown to improve guideline adherence and optimize therapeutic outcomes in CVD patients [7,8]. Clinical pharmacists contribute significantly to cardiovascular care through various roles, as summarized in Table 1.

Table 1: Roles and Responsibilities of Clinical Pharmacists in CVD Management

Role	Description	Clinical Impact
Medication Review	Assess medication regimens for appropriateness	Reduces adverse drug reactions
Patient Education	Counsel patients on drug use and lifestyle	Improves adherence
Monitoring	Track therapy outcomes and side effects	Enhances therapeutic efficacy
Interdisciplinary Collaboration	Work with healthcare teams	Optimizes care coordination

4. Outcomes of Clinical Pharmacist Involvement in Cardiovascular Disease Management

The inclusion of clinical pharmacists in cardiovascular disease care teams has demonstrated measurable improvements in clinical, humanistic, and economic outcomes. Their interventions contribute to better disease control, patient satisfaction, medication adherence, and healthcare cost reduction.

Multiple randomized controlled trials and systematic reviews have confirmed that clinical pharmacist interventions improve key clinical indicators in CVD management. For example, in hypertension, pharmacist-led interventions were associated with significant reductions in systolic and diastolic blood pressure compared to standard care [9]. Similarly, in heart failure patients, pharmacist-led medication optimization resulted in improved symptom control and reduced hospitalizations [10]. Pharmacists monitor a range of cardiovascular medications, ensuring appropriate dosing and adherence to treatment protocols (Table 2).

Table 2: Common Cardiovascular Medications and Pharmacist Considerations

Medication Class	Example	Monitoring Parameters	Pharmacist Role
ACE Inhibitors	Enalapril	Blood pressure, renal function	Dose adjustment, patient education
Beta-blockers	Metoprolol	Heart rate, BP	Monitoring and titration
Statins	Atorvastatin	Lipid profile, LFTs	Adherence support
Anticoagulants	Warfarin	INR	Dosing, education, INR monitoring

In anticoagulation management, pharmacist-supervised clinics consistently achieve higher time in therapeutic range (TTR) for warfarin users, lowering the risk of thromboembolism and bleeding [11]. For patients on statins or lipid-lowering therapy, pharmacists enhance LDL-cholesterol goal attainment, as shown in trials such as RxACTION [12].

Pharmacist-led interventions have been associated with better adherence to cardiovascular medications, owing to personalized counseling, simplified regimens, and reminder systems [13]. Improved adherence translates into fewer acute cardiovascular events and better long-term disease control.

Patients consistently report high satisfaction with pharmacist services, particularly in areas involving medication counseling, accessibility, and clarity of communication [14]. This trust strengthens the therapeutic alliance and fosters more active patient engagement in self-management.

By reducing adverse drug events, preventing hospital readmissions, and optimizing therapy, pharmacists contribute to decreased healthcare utilization. A systematic review by Chisholm-Burns *et al.* demonstrated that pharmacist interventions in chronic disease management are cost-effective, showing favorable cost-benefit ratios and return on investment [15]. For example, in heart failure, interventions such as pharmacist-led discharge counseling have reduced 30-day readmission rates by up to 25% [16]. Additionally, medication reconciliation during transitions of care lowers the incidence of post-discharge medication errors and associated costs.

Clinical pharmacists support adherence to evidence-based guidelines by ensuring that therapy aligns with current recommendations from organizations such as the ACC, AHA, and ESC. Studies have found that patients under pharmacist-physician collaborative care are more likely to receive recommended therapies such as high-intensity statins, ACE inhibitors, and beta-blockers when indicated [17]. The figure 1 have demonstrated the impact of intervention and its outcome performed by the clinical pharmacist.

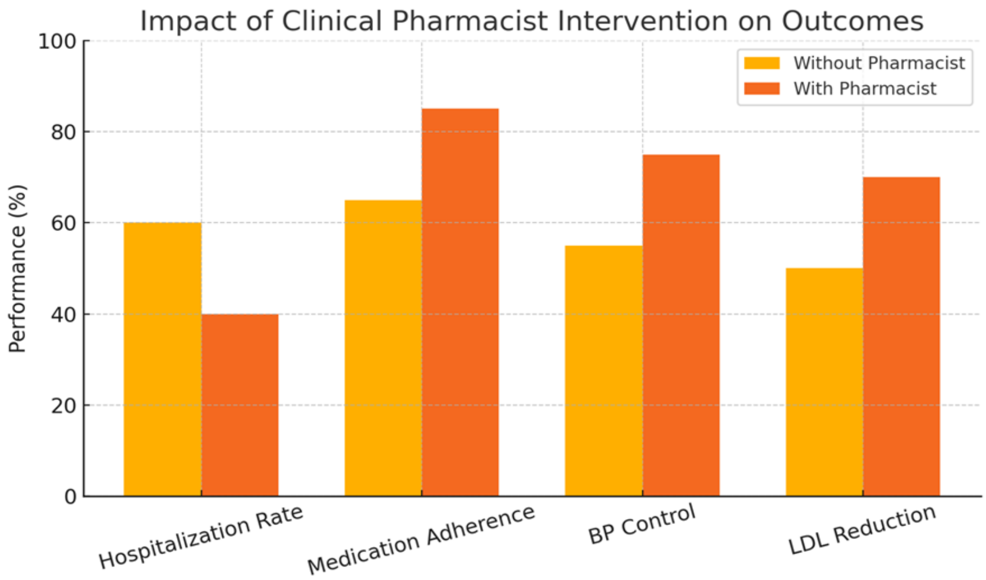

Figure 1: Impact of Clinical Pharmacist intervention on patient health outcome

Through medication reviews, education, and decision support, pharmacists help reduce therapeutic inertia and bridge the gap between guidelines and practice.

5. Challenges and Barriers to Clinical Pharmacist Integration in Cardiovascular Disease Care

While the clinical benefits of pharmacist involvement in cardiovascular care are well-documented, several systemic, professional, and structural barriers hinder their full integration into routine practice. These barriers vary across healthcare systems, but common themes include regulatory restrictions, lack of reimbursement models, limited interprofessional collaboration, and inconsistent role definition.

In many countries, the pharmacist's scope of practice is restricted by regulatory frameworks that do not permit independent prescribing or medication adjustment. Without collaborative practice agreements (CPAs) or prescriptive authority, pharmacists cannot implement treatment changes even when they identify medication-related problems [18]. The absence of a unified global policy on pharmacist roles in clinical settings contributes to inconsistent service delivery. One of the major obstacles to widespread adoption of clinical pharmacist services is the lack of sustainable funding or reimbursement models. In several healthcare systems, pharmacist-provided cognitive services (e.g., patient education, medication review) are not reimbursed adequately, making it challenging for institutions to justify allocating pharmacist time to direct patient care [19].

Despite growing evidence supporting pharmacist-physician collaboration, some healthcare providers remain skeptical about expanding pharmacists' roles. This resistance is often rooted in traditional hierarchies, unclear role boundaries, and concerns about duplication of services [20]. Additionally, variability in training and credentials across regions may lead to inconsistent expectations of clinical pharmacists' competencies.

In many settings, pharmacists face excessive workload demands with limited staffing, reducing their ability to engage in direct patient care. Time constraints, lack of clinical documentation tools, and competing dispensing responsibilities can undermine pharmacists' contributions to CVD management [21]. Moreover, smaller healthcare facilities and rural hospitals may lack access to trained clinical pharmacists entirely.

Although numerous studies demonstrate the benefits of pharmacist interventions, there is a need for standardized metrics to assess their impact across different CVD settings. Without robust health economic evaluations and universally accepted outcome indicators, policymakers may undervalue the contribution of pharmacists [22].

To function effectively in cardiovascular care, pharmacists must possess specialized clinical knowledge. However, in many regions, training programs do not sufficiently emphasize cardiovascular pharmacotherapy, and there may be a lack of continuing education or certification opportunities in this area [23].

6. Future Directions and Recommendations

The growing burden of cardiovascular diseases (CVDs) demands innovative, multidisciplinary approaches to healthcare delivery. As clinical pharmacists continue to demonstrate value in improving outcomes, enhancing medication safety, and reducing healthcare costs, there is a strong rationale to expand their role further within cardiovascular care frameworks. Several strategies and future directions can help overcome current limitations and maximize the impact of clinical pharmacists.

Empowering pharmacists with greater clinical authority—such as independent or collaborative prescribing rights—has shown promising results in several high-income countries. Studies from Canada and the UK demonstrate that pharmacist prescribers can safely and effectively manage hypertension, dyslipidemia, and anticoagulation [24,25]. Expanding this model globally requires policy reform and legislative support.

Future care models should formally embed clinical pharmacists into cardiology departments, heart failure clinics, and primary care teams managing chronic CVDs. Their routine participation in ward rounds, case discussions, and discharge planning should be institutionalized. Evidence suggests that pharmacist integration in multidisciplinary teams leads to better adherence to guidelines, medication optimization, and patient satisfaction [26].

Pharmacy education must adapt to include enhanced training in cardiovascular pharmacotherapy, clinical decision-making, and patient counseling. Postgraduate residencies or board certifications (e.g., BCPS, BCCP) specific to cardiology should be promoted to ensure advanced competence. Continuous professional development through workshops and simulation-based learning is also recommended [27].

Developing and adopting a standardized set of key performance indicators (KPIs) will facilitate robust evaluation of pharmacist-led interventions. These should include clinical (e.g., BP or LDL-C control), economic (e.g., cost savings, readmission rates), and humanistic (e.g., quality of life, satisfaction) outcomes. The establishment of national or international clinical pharmacy registries could help track and benchmark progress [28].

Leveraging digital health tools such as mobile apps, remote monitoring, and teleconsultation platforms can extend the reach of pharmacist-led services, particularly in rural or underserved areas. Telepharmacy models have already shown success in improving medication adherence and chronic disease monitoring remotely [29].

Advocacy is needed to establish dedicated reimbursement pathways for cognitive pharmacy services. Payment-for-performance models that include pharmacists in shared savings programs will incentivize quality care delivery. Policymakers must recognize pharmacists not just as dispensers but as medication therapy experts and care providers [30].

Future research should explore the comparative effectiveness of different pharmacist intervention models in CVDs. Pragmatic trials, cost-effectiveness analyses, and patient-centered outcome research will help tailor services to diverse healthcare settings. Special focus should be given to low- and middle-income countries (LMICs) where pharmacist roles are still underdeveloped [31].

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PRODRUG STRATEGIES TO ENHANCE BIOAVAILABILITY

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Abstract:

Poor bioavailability remains a significant barrier in the successful clinical translation of many therapeutically active compounds. A prodrug is a pharmacologically inactive derivative of a parent molecule designed to undergo biotransformation within the body, resulting in the release of the active drug. This chapter delves into the conceptual basis, design rationale, and pharmacokinetic advantages of prodrugs, particularly focusing on their application to overcome solubility, permeability, and metabolic instability issues. Emphasis is placed on classical and modern prodrug strategies, including ester and amide prodrugs, redox-based systems, enzyme-triggered activation, and carrier-linked prodrugs. Additionally, contemporary approaches such as transporter-targeted prodrugs, self-immolative linkers, and nanocarrier-enabled prodrug delivery are examined for their roles in enhancing site-specific drug release and systemic bioavailability. Regulatory considerations, case studies, and marketed examples are discussed to provide a translational perspective. This chapter aims to equip pharmaceutical scientists with a thorough understanding of how prodrug strategies can be tailored to optimize pharmacokinetics and improve therapeutic efficacy.

Keywords: Prodrug Design, Bioavailability Enhancement, Drug Solubility, Enzyme-Activated Prodrugs, Transporter-Targeted Delivery, Pharmacokinetics

Introduction:

A prodrug is a pharmacologically inactive or significantly less active compound that undergoes chemical or enzymatic transformation within the body to release the active parent drug. This concept is rooted in the principle of bioreversible derivatization, where transient chemical modifications are made to improve one or more undesirable properties of a drug candidate—most notably, its bioavailability. The goal of prodrug design is to circumvent physicochemical and pharmacokinetic limitations that hinder the efficacy of therapeutic agents without compromising their pharmacodynamic potential.

The term "prodrug" was formally introduced in the 1950s, although the underlying concept dates back much earlier. One of the earliest examples is aspirin (acetylsalicylic acid), which serves as a prodrug for salicylic acid. The evolution of prodrug research gained momentum with the increasing understanding of drug metabolism, enzyme specificity, and membrane transport mechanisms. Initially focused on improving oral absorption and masking organoleptic issues such as bitterness or odor, the field has now expanded to include site-specific activation, controlled release, and reduced systemic toxicity.

Modern prodrug design leverages advances in computational modeling, structural biology, and enzyme profiling to achieve targeted activation with enhanced predictability. In addition to classical strategies involving ester or amide linkage hydrolysis, current trends include sophisticated prodrug platforms such as antibody-directed enzyme prodrug therapy (ADEPT), gene-directed enzyme prodrug therapy (GDEPT), and redox-sensitive constructs responsive to the intracellular microenvironment.

Bioavailability is a critical pharmacokinetic parameter that defines the extent and rate at which the active drug ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For orally administered drugs, poor bioavailability is a common reason for clinical failure and development attrition, particularly for compounds that exhibit poor aqueous solubility (Class II) or poor membrane permeability (Class III) as classified by the Biopharmaceutical Classification System (BCS).

Several intrinsic and extrinsic factors influence oral bioavailability:

- Physicochemical properties: molecular weight, lipophilicity (log P), solubility, pKa, and polymorphic form
- Physiological barriers: gastric pH, enzymatic degradation in the GI tract, limited intestinal permeability, and first-pass hepatic metabolism
- Formulation variables: excipient compatibility, dissolution profile, and release kinetics

Drugs with low oral bioavailability often require high doses or alternative routes of administration, leading to increased risk of systemic toxicity, poor patient compliance, and high treatment costs. In such cases, prodrug strategies offer a scientifically sound and clinically validated solution to bypass these hurdles.

Prodrugs may be employed to:

- Enhance solubility (e.g., phosphate ester prodrugs of poorly soluble drugs)
- Improve permeability (e.g., lipophilic derivatives that facilitate transcellular transport)
- Avoid pre-systemic metabolism (e.g., enzyme-resistant linkers or targeted transporters)
- Enable targeted delivery (e.g., enzyme-activated prodrugs at the tumor site)

Moreover, prodrug approaches align with the broader objectives of rational drug design, personalized medicine, and patient-centric therapeutics by enabling the fine-tuning of pharmacokinetic profiles to optimize clinical outcomes.

In summary, prodrug design represents a strategically important and scientifically rigorous method to enhance drug bioavailability. By integrating medicinal chemistry, enzymology, and pharmacokinetics, this approach continues to play a vital role in overcoming the limitations of conventional drug molecules and extending the therapeutic index of promising yet bioavailability-challenged agents.

Challenges in oral bioavailability

Oral drug delivery remains the most favored route of administration due to its convenience and patient compliance. However, the bioavailability of many therapeutic agents is significantly limited by multiple physiological and physicochemical barriers. One of the most prominent issues is poor aqueous solubility, which prevents adequate dissolution of the drug in gastrointestinal fluids, particularly for Biopharmaceutical Classification System (BCS) Class II and IV drugs. In such cases, even highly permeable drugs may not be absorbed in sufficient quantities, rendering them therapeutically ineffective. Incomplete or erratic dissolution often leads to subtherapeutic plasma levels, increased dosing frequencies, and high interpatient variability. In addition to solubility, membrane permeability presents a second major barrier. Large or hydrophilic drug molecules often struggle to cross intestinal epithelial membranes via passive diffusion. This challenge is further complicated by the presence of efflux transporters like P-glycoprotein, which actively expel many xenobiotics back into the intestinal lumen. Furthermore, tight junctions between epithelial cells severely limit paracellular transport, posing difficulties for polar molecules. These factors collectively restrict the fraction of orally administered drug that reaches the systemic circulation intact.

Another critical determinant of bioavailability is the extent of first-pass metabolism. Drugs administered orally are exposed to enzymatic degradation in both the intestinal mucosa and liver before reaching systemic circulation. Enzymes such as cytochrome P450s, carboxylesterases, and UDP-glucuronosyltransferases can metabolize a significant portion of the administered dose, rendering it inactive or, in some cases, forming toxic metabolites. The outcome is reduced plasma concentration and diminished pharmacological response, often necessitating higher doses that may compromise patient safety. Furthermore, the gastrointestinal tract itself presents a hostile environment for many drugs. The acidic pH of the stomach can degrade acid-labile compounds, while proteolytic enzymes in the stomach and intestine can inactivate peptide-based drugs before they are absorbed. Additionally, disease states like Crohn’s disease, celiac disease, or liver dysfunction can alter normal absorption and metabolism patterns, further complicating oral drug delivery. Food effects and intraindividual variability also contribute to unpredictable pharmacokinetics. Changes in gastric emptying time, bile secretion, and intestinal motility due to food intake can substantially alter the absorption profile of many drugs. Consequently, despite the clear advantages of oral dosing, its success is highly dependent on overcoming a variety of biological hurdles. This sets the stage for prodrug design as a powerful tool to circumvent these limitations and enhance oral bioavailability through strategic molecular modification.

Classification of Prodrugs

Prodrugs are broadly classified based on their structural design and site of activation in the body. One of the most common distinctions is between carrier-linked prodrugs and bioprecursor prodrugs. Carrier-linked prodrugs involve the chemical conjugation of the active drug to a promoiety or carrier, which is designed to modify its physicochemical properties such as solubility, lipophilicity, or stability. Upon administration, the carrier is enzymatically or chemically cleaved to release the active drug. These prodrugs are especially useful for enhancing solubility in poorly water-soluble drugs, improving membrane permeability, or masking undesirable organoleptic characteristics such as bitterness. A classic example is valacyclovir, the L-valine ester of acyclovir, which improves oral absorption by utilizing the intestinal PEPT1 transporter. Another notable example is prednisolone phosphate; a water-soluble ester designed for ocular or injectable formulations. In contrast, bioprecursor prodrugs are inactive structural analogs that require metabolic transformation, typically through oxidation, reduction, or hydrolysis, to release the active form. They do not contain a separate promoiety but rather undergo a chemical transformation within the body to regenerate the pharmacologically active parent compound. Levodopa serves as a prototypical example, acting as a precursor to dopamine, which cannot cross the blood-brain barrier in its native form. Another notable example is cyclophosphamide, which is activated via hepatic cytochrome P450 enzymes into its cytotoxic form for cancer therapy. Additionally, mutual prodrugs are a unique subclass where two pharmacologically active drugs are chemically linked to each other. Upon biotransformation, each component is released and contributes to therapeutic action, often with synergistic or complementary effects. For instance, benorylate is a mutual prodrug combining aspirin and paracetamol to offer both analgesic and anti-inflammatory effects. Similarly, sulfasalazine releases 5-aminosalicylic acid and sulfapyridine for localized treatment in inflammatory bowel diseases. A more mechanistic classification, proposed by Stella and colleagues, categorizes prodrugs based on their site of activation into Type I and Type II prodrugs. Type I prodrugs are bioactivated intracellularly, either in target tissues (Type IA) or metabolic organs like the liver (Type IB). Cyclophosphamide exemplifies a Type IB prodrug activated in the liver. Type II prodrugs, on the other hand, are activated extracellularly. These include Type IIA prodrugs activated in the gastrointestinal tract, Type IIB activated in plasma, and Type IIC activated near the site of therapeutic action. Fosphenytoin, activated in plasma, represents a typical Type IIB prodrug, while sulfasalazine, activated in the colon, falls under Type IIA. In summary, the classification of prodrugs into carrier-linked, bioprecursor, mutual, and site-specific types allows for a more rational approach to molecular design. Each class offers distinct advantages based on the intended therapeutic goal and the pharmacokinetic barrier to be overcome. This systematic understanding forms the foundation for the successful translation of prodrugs from laboratory concept to clinical application.

Design Strategies for Prodrugs

The design of a successful prodrug requires a meticulous understanding of the parent drug's pharmacokinetic limitations, the target site of action, enzymatic activation mechanisms, and therapeutic goals. The selection of an appropriate promoiety is critical and must consider not only the chemical compatibility with the parent molecule but also its impact on properties such as solubility, lipophilicity, stability, and permeability. One common strategy involves esterification of hydroxyl or carboxylic acid groups to improve lipophilicity and membrane transport. These ester prodrugs are subsequently hydrolyzed by ubiquitous esterases present in the plasma or tissues, thereby releasing the active compound. This method is widely used because of the high catalytic efficiency and broad substrate specificity of esterases. Another frequently employed approach is the addition of ionizable moieties such as phosphate or sulfonate groups to enhance water solubility, particularly for parenteral formulations or poorly soluble oral drugs. These hydrophilic prodrugs can be rapidly converted in vivo by phosphatases or sulfatases. In some cases, prodrug design leverages site-specific activation using enzymes that are overexpressed in certain tissues or disease states. For instance, tumor-targeted prodrugs can exploit elevated levels of β-glucuronidase or cathepsin B within cancerous tissues to achieve localized activation, thereby reducing systemic toxicity. Targeting transporter proteins is another rational design principle. Conjugation of drugs with nutrient-like moieties (e.g., amino acids, peptides, glucose) enables them to hijack endogenous transport pathways such as PEPT1, LAT1, or GLUT1, resulting in improved oral absorption or blood-brain barrier penetration. This strategy has been particularly successful with drugs like valacyclovir and L-DOPA. Additionally, chemical linkers used in prodrug design must be carefully tailored to ensure appropriate stability during transit and timely release of the active drug upon reaching the desired site. The ideal linker must balance between sufficient metabolic lability and stability to avoid premature activation. Prodrug design also benefits from computational modeling, in silico simulations, and high-throughput screening methods that allow prediction of enzymatic activation, ADMET profiles, and target specificity. These tools facilitate the identification of optimal promoieties and cleavage pathways. Moreover, regulatory considerations must be integrated from the earliest stages, especially when the promoiety itself is novel or may accumulate systemically. Overall, the design of prodrugs is a sophisticated interplay of medicinal chemistry, biochemistry, and pharmacokinetics, guided by the principle of functional optimization to overcome intrinsic drug limitations.

Enzymatic Activation and Bioconversion Mechanisms

The therapeutic efficacy of prodrugs hinges on their successful conversion into the active parent drug via specific enzymatic pathways once they enter the body. Enzymatic activation ensures not only controlled release but also tissue selectivity and reduced systemic toxicity. A profound understanding of the human enzymatic landscape is therefore essential in the rational design of prodrugs. Among the most commonly involved enzymes are hydrolases, oxidoreductases, and transferases. Hydrolases, particularly esterases and peptidases, play a central role in the activation of ester- and amide-linked prodrugs. These enzymes are widely distributed in the gastrointestinal tract, plasma, and intracellular compartments, enabling efficient cleavage of promoieties. For example, ester prodrugs such as enalapril and valacyclovir are activated by carboxylesterases and peptidases, respectively, resulting in rapid liberation of their active forms in systemic circulation. In cases where oxidation or reduction is required, oxidoreductase enzymes such as cytochrome P450 isoforms, alcohol dehydrogenases, and aldehyde oxidases are recruited to facilitate the conversion. These enzymes are primarily localized in hepatic microsomes and play a dominant role in the metabolism of bioprecursor prodrugs. For instance, cyclophosphamide undergoes oxidative activation by CYP2B6 and CYP3A4 in the liver to generate its alkylating metabolites. Similarly, codeine is demethylated by CYP2D6 to form morphine, its pharmacologically active derivative. The expression and activity of these enzymes, however, can be subject to genetic polymorphisms, age, disease conditions, and environmental influences, all of which can impact the efficiency and predictability of prodrug activation. In addition to general systemic enzymes, tissue-specific or disease-associated enzymes can be exploited to achieve site-directed drug release. This strategy is particularly valuable in cancer and inflammatory diseases where certain enzymes are upregulated in the pathological site. For instance, β-glucuronidase is overexpressed in many solid tumors and inflamed tissues, making it an ideal target for the activation of glucuronide-based prodrugs. Similarly, matrix metalloproteinases and cathepsins are elevated in the tumor microenvironment and can be used to selectively trigger drug release from tailored conjugates, thereby minimizing off-target toxicity. Enzymatic bioconversion is not only essential for prodrug activation but also determines the kinetics of drug release, duration of action, and tissue exposure. Therefore, knowledge of the catalytic rate, substrate specificity, and tissue distribution of the activating enzymes is indispensable. Strategies such as enzyme substrate screening, in vitro metabolic studies, and in vivo pharmacokinetic profiling are routinely employed during prodrug development to validate these parameters. Overall, enzymatic activation mechanisms form the cornerstone of prodrug pharmacology and are instrumental in translating a chemically modified drug precursor into a clinically effective therapeutic agent.

Regulatory and Safety Considerations

The development of prodrugs introduces unique regulatory challenges that must be carefully addressed to ensure safety, efficacy, and compliance with international guidelines. Regulatory authorities such as the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and India's Central Drugs Standard Control Organization (CDSCO) recognize prodrugs as new chemical entities (NCEs) when the chemical modification significantly alters pharmacokinetic or pharmacodynamic behavior, even if the parent drug is already approved. As such, prodrugs must undergo comprehensive preclinical and clinical evaluation to establish their safety profiles, bioconversion efficiency, and therapeutic equivalence or superiority to the active drug.

A critical regulatory requirement involves the demonstration of predictable and complete in vivo conversion of the prodrug to its active form. This necessitates detailed characterization of the bioconversion pathway, including identification of the enzymes involved, conversion kinetics, and formation of any potential toxic intermediates. Regulatory authorities often require pharmacokinetic bridging studies to compare plasma exposure of the active moiety between the prodrug and the reference drug. Additionally, the stability of the prodrug in various physiological fluids must be assessed to ensure it does not undergo premature or incomplete activation that could compromise efficacy or safety. Safety assessment extends beyond the prodrug and active drug to include the promoiety and any metabolites generated during activation. If the promoiety is novel or known to accumulate in tissues, dedicated toxicological studies are mandated to determine its pharmacological inactivity, absence of genotoxicity, and lack of adverse immunological effects. In some cases, the promoiety may exhibit pharmacological activity of its own, thus complicating the safety evaluation and labeling requirements. For mutual prodrugs, where both moieties contribute to therapeutic action, regulators assess the pharmacokinetics and safety of both components independently and in combination. Another consideration is the route of administration and site-specific activation. For example, orally administered prodrugs must demonstrate stability in gastric and intestinal fluids, appropriate absorption characteristics, and consistent metabolic activation across diverse populations. For parenteral or topical prodrugs, the risk of local irritation, delayed activation, or depot formation must be evaluated. Regulatory agencies may also require data on enzyme polymorphisms affecting prodrug activation, especially if the metabolism is heavily reliant on genetically variable enzymes such as CYP2D6 or UGT1A1. Population-specific safety risks must be considered in such cases. In addition to scientific evaluation, the prodrug development process must adhere to stringent Good Manufacturing Practices (GMP) and regulatory documentation standards, including submission of Investigational New Drug (IND) applications, Common Technical Documents (CTDs), and New Drug Applications (NDAs). Labeling requirements must clearly describe the nature of the prodrug, the expected metabolic conversion, and any specific contraindications related to enzyme deficiencies or drug interactions. Regulatory guidance documents, such as the FDA's "Safety Testing of Drug Metabolites" and EMA's "Guideline on the Investigation of Bioequivalence," provide frameworks for these evaluations.

Conclusion:

Prodrug strategies have emerged as a transformative approach in modern drug development, offering innovative solutions to long-standing challenges in bioavailability, stability, permeability, and site-specific delivery. By leveraging the principles of medicinal chemistry and enzymatic biotransformation, prodrugs can be systematically engineered to overcome physicochemical and biological barriers that limit the therapeutic efficacy of many active pharmaceutical ingredients. Through judicious selection of promoieties and activation pathways, prodrugs can not only enhance oral absorption but also enable targeted tissue delivery, minimize systemic toxicity, and optimize pharmacokinetic profiles. The diversity of prodrug types ranging from simple ester-based carriers to highly sophisticated enzyme-targeted or transporter-utilizing constructs underscores the adaptability of this strategy across various therapeutic domains. Successful examples such as valacyclovir, enalapril, capecitabine, and fosphenytoin illustrate the clinical relevance and translational potential of prodrugs, having improved patient outcomes through enhanced dosing convenience, reduced side effects, and better therapeutic index. Despite these advances, prodrug design requires careful attention to enzymatic activation mechanisms, safety of released moieties, and interindividual variability arising from genetic polymorphisms. Moreover, the regulatory framework surrounding prodrugs remains intricate, necessitating comprehensive data on bioactivation, pharmacokinetics, toxicity, and clinical efficacy. Future progress in computational modeling, enzyme profiling, and targeted drug delivery technologies is expected to further refine prodrug design and broaden its applicability to complex diseases such as cancer, neurodegeneration, and metabolic disorders.

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THE ROLE OF GUT-SKIN AXIS IN PSORIASIS

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Abstract:

Psoriasis is a chronic immune-mediated inflammatory skin disorder with systemic implications. Emerging evidence implicates the gut–skin axis—a bidirectional communication network linking gastrointestinal microbiota, mucosal immunity, and cutaneous homeostasis—in psoriasis pathogenesis. Dysbiosis, increased gut permeability ("leaky gut"), and aberrant microbial metabolites promote systemic inflammation, skewing T-cell responses and promoting skin plaque formation. Clinical studies reveal altered gut microbiome profiles in psoriatic patients, while interventions like probiotics, prebiotics, dietary modification, and fecal microbiota transplantation (FMT) show promise in modulating disease severity. This chapter critically examines mechanisms underlying gut–skin crosstalk, summarizes preclinical and clinical evidence, and highlights therapeutic strategies targeting gut microbiome to ameliorate psoriasis. Understanding these interactions may pave the way for novel adjunctive treatments.

Keywords: Psoriasis, Gut–Skin Axis, Gut Microbiome, Dysbiosis, Intestinal Permeability, Probiotics, Systemic Inflammation

Introduction

Psoriasis is a common immune-mediated inflammatory skin disease, affecting approximately 2–3% of the global population[1]. It is characterized by hyperproliferative keratinocytes, erythematous plaques, and infiltration of immune cells (notably Th1, Th17, and IL-23-driven pathways) [2]. While genetic predisposition (e.g., HLA-C*06) and environmental triggers (stress, trauma, infection) contribute substantially to its pathogenesis, emerging data highlight the gut–skin axis as an important player[3].

The gut–skin axi**s** refers to bidirectional interactions where gut microbiota and gut-derived products modulate systemic immunity and skin homeostasis, while skin inflammation may affect gut function via neuroimmune and endocrine pathways[4]. In psoriasis, these interactions become maladaptive, exacerbating disease. The gut ecosystem—including bacteria, viruses, fungi, and metabolites—regulates immune cells, epithelial barrier integrity, and endotoxin exposure. Disruptions in this axis— "dysbiosis"—are increasingly linked to psoriasis pathogenesis[5].

This chapter explores:

1. Mechanisms by which gut dysbiosis and increased permeability drive psoriatic inflammation.

2. Clinical and preclinical studies linking microbiome alterations to disease severity.
3. Potential interventions targeting gut microbiota to modulate treatment outcomes.

1. **Mechanistic Framework of the Gut–Skin Axis in Psoriasis**

Gut Dysbosis

Disruption in the normal gut microbial community—referred to as dysbiosis—has emerged as a critical factor in the pathogenesis of autoimmune and inflammatory conditions, including psoriasis[6]. This imbalance is marked by a decline in beneficial microbes, an overgrowth of pathogenic species, and a general reduction in microbial diversity, all of which weaken immune defenses and disturb systemic equilibrium. In individuals with psoriasis, unique alterations in gut microbiota have been observed compared to healthy controls. For example, there is a notable decrease in Firmicutes, including the butyrate-producing Faecalibacterium prausnitzii, a microbe with recognized anti-inflammatory functions[7]. This bacterium helps preserve the intestinal barrier and encourages the development of regulatory T cells (Tregs), which are essential for preventing inappropriate immune activation. In contrast, increased levels of pro-inflammatory bacteria such as Escherichia coli, Ruminococcus gnavus, and Enterococcus faecalis have been consistently reported[8]. These pathogens can produce harmful metabolites, weaken the gut lining, and trigger inflammatory responses via immune receptor engagement.

Several pathways illustrate how dysbiosis may influence psoriasis. First, altered microbial metabolite profiles—particularly a reduction in short-chain fatty acids (SCFAs) like butyrate, acetate, and propionate—play a key role. In a healthy gut, these SCFAs are generated through the fermentation of dietary fibers and exert regulatory effects on immune responses by activating specific G-protein-coupled receptors (GPR43, GPR109A) and modulating epigenetic activity through histone deacetylase inhibition[9]. This activity enhances Treg differentiation and IL-10 production, which are essential for suppressing inflammation. In psoriasis, the loss of SCFA-producing bacteria reduces these beneficial signals, promoting Th17-mediated immune activation—a major contributor to psoriatic pathology[10].

Second, an overrepresentation of Gram-negative bacteria increases systemic exposure to lipopolysaccharide (LPS), an inflammatory endotoxin. LPS can cross a weakened gut barrier and interact with Toll-like receptor 4 (TLR4) on immune cells, thereby activating the nuclear factor kappa B (NF-κB) pathway and promoting pro-inflammatory cytokine production, including TNF-α, IL-1β, and IL-6[11]. These cytokines are directly implicated in psoriasis and serve as targets for current biologic therapies. Elevated serum levels of LPS-binding protein (LBP) in psoriatic patients further support the role of gut-derived endotoxins in disease amplification.

Third, dysbiosis alters tryptophan metabolism, limiting the production of beneficial indole derivatives such as indole-3-aldehyde (IAld) and indole-3-propionic acid (IPA). These compounds activate the aryl hydrocarbon receptor (AhR), a nuclear receptor found on keratinocytes and immune cells that modulates skin barrier integrity and cytokine balance, including IL-22[12]. Reduced AhR activation due to lower indole availability can weaken the skin barrier and shift immunity toward Th17/Th22 dominance, both central to psoriasis development.

Additionally, research now recognizes the roles of the gut virome and mycobiome. Viral nucleic acids may trigger immune signaling, while fungal cell wall components like β-glucans from Candida or Malassezia species can drive innate immune responses and favor Th17 polarization. These microbial kingdoms add further complexity and may open doors for novel treatment targets.

In summary, dysbiosis disrupts immune regulation, compromises intestinal and skin barriers, and promotes systemic inflammation, all of which reinforce psoriasis as a systemic disease. Therefore, therapeutic restoration of a balanced gut microbiome could play a valuable role in holistic psoriasis care.

Intestinal Barrier Dysfunction ("Leaky Gut")

A properly functioning intestinal barrier is essential for maintaining immunological equilibrium by limiting the entry of microbial elements, antigens, and toxins from the intestinal lumen into the bloodstream. This barrier system consists of epithelial tight junctions, mucosal secretions, antimicrobial proteins, and resident immune cells. In individuals with psoriasis, this defense mechanism is frequently impaired—a condition commonly described as "leaky gut." Numerous studies have shown that essential tight junction proteins, including claudin-1, occludin, and zonula occludens-1 (ZO-1), are significantly reduced in those affected by psoriasis[13]. These proteins are crucial for preserving the selective permeability of the intestinal lining. Their diminished expression leads to compromised mucosal integrity, allowing the systemic absorption of microbial fragments, dietary antigens, and environmental toxins.

The resulting intestinal permeability facilitates the development of metabolic endotoxemia—a condition characterized by increased levels of lipopolysaccharide (LPS), an inflammatory component derived from Gram-negative bacterial membranes. Elevated serum concentrations of LPS-binding protein (LBP) observed in psoriatic individuals support the presence of heightened microbial translocation[14]. Once LPS enters the circulation, it binds to Toll-like receptor 4 (TLR4) expressed on innate immune cells, such as macrophages and dendritic cells. This ligand-receptor interaction initiates intracellular signaling cascades, most notably the activation of the nuclear factor kappa B (NF-κB) pathway, culminating in the production and release of pro-inflammatory mediators like tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-23 (IL-23).

These cytokines play a pivotal role in psoriasis pathogenesis. IL-23 is especially important for supporting Th17 cell differentiation and survival. Th17 cells secrete IL-17A, a cytokine that drives keratinocyte hyperproliferation and the recruitment of neutrophils, resulting in the formation of characteristic psoriatic plaques[15]. Continued stimulation of this inflammatory circuit perpetuates a feedback loop in which gut barrier compromise enhances systemic inflammation, which in turn worsens skin pathology and impairs epidermal function.

Moreover, systemic endotoxemia caused by a disrupted gut barrier may also contribute to various comorbidities commonly associated with psoriasis, such as insulin resistance, cardiovascular disease, and non-alcoholic fatty liver disease. This adds further weight to the idea that gastrointestinal health is intricately linked to psoriasis progression and severity.

Restoring the integrity of the gut lining has emerged as a promising therapeutic strategy. Potential interventions include the administration of short-chain fatty acids (SCFAs), L-glutamine supplementation, probiotic therapy, and targeted dietary changes. These strategies aim to reinforce mucosal defenses, reduce systemic inflammation, and potentially improve clinical outcomes in individuals suffering from psoriasis.

Immune Polarization: Th17/Treg Balance

The dynamic interplay between gut microbiota and the host immune system is a major determinant of immune responses beyond the gastrointestinal tract, including those that affect the skin. A crucial aspect of this interaction is the regulation of T-helper (Th) cell subsets—specifically, the balance between pro-inflammatory Th17 cells and anti-inflammatory regulatory T cells (Tregs). This Th17/Treg axis is particularly relevant in the immunopathology of psoriasis.

In a balanced gut ecosystem, commensal microbes' ferment dietary fibers into short-chain fatty acids (SCFAs) such as butyrate, acetate, and propionate. These metabolites support the development and expansion of Tregs by inhibiting histone deacetylases and activating specific G-protein-coupled receptors (GPR43 and GPR109A)[10]. Tregs function as immunological gatekeepers by maintaining tolerance and suppressing inappropriate inflammatory responses.

When dysbiosis occurs—marked by a decline in SCFA-producing bacteria—there is a consequential reduction in both the quantity and efficacy of Tregs. This disruption favors Th17 cell predominance, which plays a central role in driving the inflammatory cascade observed in psoriatic pathology. Moreover, dysbiosis elevates the levels of gut-derived cytokines like interleukin-6 (IL-6) and interleukin-23 (IL-23), both of which are essential for the differentiation and persistence of Th17 cells. These Th17 cells secrete pro-inflammatory cytokines such as IL-17A and IL-22, which activate keratinocytes, promote their proliferation, and stimulate the release of other inflammatory mediators—features that typify psoriatic plaques.

Beyond this cytokine-driven imbalance, microbial disruption can also induce the production of type I interferons. These signaling molecules activate plasmacytoid dendritic cells (pDCs), which further potentiate Th1 and Th17 immune pathways through enhanced antigen presentation and pro-inflammatory cytokine secretion[16]. This sequence of events reinforces a chronic inflammatory loop that links intestinal dysbiosis with skin-directed autoimmune responses.

In essence, the gut microbiome influences systemic immunity by orchestrating the balance between regulatory and inflammatory T cells. The skewing of this balance towards Th17 dominance underpins the systemic inflammatory nature of psoriasis and emphasizes the significance of targeting gut-immune crosstalk in disease management.

Gut-Skin Neural and Endocrine Crosstalk

In addition to its immunological impact, the gut–skin axis engages intricate neural and hormonal signaling pathways that contribute substantially to the pathogenesis of psoriasis. The enteric nervous system (ENS), often dubbed the "second brain," communicates closely with the central nervous system (CNS) via the gut-brain axis, primarily through the vagus nerve. Current research suggests that disturbances in the gut microbiome can impair vagal function, disrupting the flow of regulatory neural signals between the gut and the brain, as well as to peripheral organs. This disruption is particularly relevant under chronic stress, as the vagus nerve regulates the hypothalamic-pituitary-adrenal (HPA) axis. Malfunction of this system results in increased secretion of cortisol—a glucocorticoid stress hormone known to affect immune regulation and the integrity of the skin barrier. Persistent psychological stress elevates the levels of inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), both of which are implicated in worsening psoriatic inflammation[17].

Beyond neural mechanisms, the gut microbiota also plays a role in hormone metabolism. It contributes to the biotransformation and recycling of hormones such as insulin, estrogens, and glucocorticoids through enterohepatic circulation. When gut microbial balance is disrupted, this hormonal regulation can be impaired. In patients with psoriasis—who often present with metabolic comorbidities such as insulin resistance or metabolic syndrome—dysbiosis may exacerbate systemic low-grade inflammation and adipokine imbalances, thereby worsening skin symptoms[18]. Additionally, gut-derived metabolites, such as secondary bile acids, interact with endocrine receptors like the farnesoid X receptor (FXR) and TGR5. These receptors influence glucose and lipid metabolism and play roles in modulating inflammatory pathways.

Altogether, these insights illustrate the multifaceted role of the gut–skin axis. Microbiome-driven changes in neural signaling can alter the body's stress response, while hormonal interactions shaped by gut microbes can affect systemic inflammation and metabolic balance—factors that collectively influence the progression and severity of psoriasis. Consequently, therapeutic strategies that aim to restore gut microbial health, improve vagal tone (e.g., via meditation, vagus nerve stimulation, or biofeedback), and normalize metabolic functions may offer valuable adjunctive options in managing chronic inflammatory skin disorders such as psoriasis.

2. **Preclinical and Clinical Evidence**

Animal and Cell-Line Studies

Preclinical models have significantly advanced our understanding of the gut–skin axis in psoriasis by demonstrating the functional impact of microbial changes on skin inflammation. In one notable experiment, germ-free mice—raised in sterile conditions without exposure to microbes—were colonized with gut microbiota from patients with psoriasis. These mice developed significantly more severe skin inflammation when subjected to Imiquimod-induced dermatitis, a well-established model that mimics psoriatic plaque formation[24]. This finding strongly supports the causal role of microbiota in exacerbating psoriatic inflammation.

Moreover, supplementation with short-chain fatty acids (SCFAs) in mouse models has demonstrated protective effects. SCFAs such as butyrate and propionate were shown to reduce epidermal thickening, diminish immune cell infiltration, and downregulate IL-17A expression in inflamed skin[25]. These results suggest that the loss of SCFA-producing bacteria in dysbiosis contributes directly to the propagation of psoriatic inflammation and that replenishing these metabolites may offer therapeutic benefit.

In vitro studies have further elucidated the role of gut-derived microbial components on skin cells. For instance, keratinocytes exposed to lipopolysaccharide (LPS)—a pro-inflammatory endotoxin derived from Gram-negative bacteria—exhibited upregulated expression of inflammatory cytokines, notably IL-36γ and TNF-α[26]. These cytokines are key mediators in psoriatic plaque formation and epithelial activation. The ability of LPS to directly induce such responses in keratinocytes underscores the significance of gut-sourced endotoxins in driving systemic and cutaneous inflammation.

Human Microbiome and Correlational Studies

Numerous clinical investigations have analyzed the fecal microbiota profiles of individuals with psoriasis, revealing significant differences in microbial diversity and composition compared to healthy individuals. For example, a study conducted by Huang *et al.* (2019) observed a marked decrease in the abundance of beneficial gut bacteria, particularly Faecalibacterium prausnitzii and Akkermansia muciniphila, in psoriasis patients. Importantly, lower levels of these microbes were found to negatively correlate with Psoriasis Area and Severity Index (PASI) scores, suggesting a potential link between microbial depletion and disease intensity[27].

In a separate study, Eppinga *et al.* (2017) documented increased levels of Ruminococcaceae alongside a reduction in Prevotella species in the gut microbiota of psoriatic individuals, highlighting a distinct dysbiotic pattern that may be characteristic of the disease[28]. Additionally, research by Scher *et al.* (2015) reported a positive association between altered microbial communities and increased concentrations of fecal calprotectin—a marker widely recognized for indicating gut inflammation. This finding reinforces the hypothesis that gastrointestinal immune dysregulation may contribute to the systemic and dermatological manifestations observed in psoriasis[29].

Beyond microbiome composition, markers indicative of impaired intestinal barrier function have also been identified in psoriasis patients. Elevated serum levels of proteins such as zonulin and claudin-3—both involved in maintaining epithelial tight junctions—have been documented[30]. These increases signal a breakdown in gut barrier integrity, supporting the theory that heightened intestinal permeability ("leaky gut") facilitates systemic immune activation and exacerbates psoriatic disease processes.

Interventional Trials

Emerging clinical trials aimed at modulating the gut microbiota have yielded encouraging, though preliminary, findings that support the potential of microbiome-targeted therapies in the management of psoriasis. Several studies have examined the effects of probiotics and prebiotics in small patient populations. For instance, a randomized controlled trial by Navarro-López *et al.* (2019), which enrolled 90 individuals, assessed the impact of a 12-week regimen containing Lactobacillus and Bifidobacterium strains. Participants receiving this probiotic combination experienced notable reductions in both Psoriasis Area and Severity Index (PASI) scores and serum levels of C-reactive protein (CRP), indicating improvements in both clinical symptoms and systemic inflammation[31]. In another trial, Naldi *et al.* (2021) investigated the use of prebiotic fiber supplements and reported improvements in cutaneous features such as erythema and scaling, although the overall effect on PASI scores was modest[32]. These outcomes suggest that rebalancing gut flora using probiotic and prebiotic approaches may offer supportive benefits in treating psoriasis.

Nutritional strategies aimed at reshaping the intestinal microbiome have also shown promise. Pilot investigations have demonstrated that diets low in gluten and rich in anti-inflammatory components are associated with significant clinical improvement. Some individuals reported reductions in PASI scores exceeding five points[33]. Such dietary interventions are believed to mitigate intestinal inflammation, enhance gut barrier function, and support microbial diversity. Furthermore, consistent adherence to the Mediterranean diet—which is abundant in plant-based fiber, omega-3 fatty acids, and polyphenols—has been linked to favorable shifts in gut microbial composition, decreased systemic inflammation, and reduced psoriasis severity[33].

Fecal microbiota transplantation (FMT) is another promising avenue, albeit still in the early stages of dermatologic research. Initial case reports have indicated substantial clinical improvement in psoriatic symptoms following FMT, with observed decreases in PASI scores. These findings imply that transferring a healthy microbial community from a donor may help re-establish immune homeostasis in affected individuals[34]. However, to confirm its clinical utility, large-scale randomized trials are needed to examine the durability of therapeutic effects, assess safety profiles, and determine optimal donor-recipient compatibility.

Collectively, these intervention-based studies reinforce the therapeutic potential of targeting the gut–skin axis. Whether through microbial supplementation, specific dietary practices, or advanced therapies like FMT, altering the gut microbiome presents an exciting and evolving approach to managing psoriasis and enhancing treatment outcomes.

3. **Therapeutic Implications**

Microbiota-Modulating Therapies

Interventions aimed at modulating the gut microbiota have garnered attention as supportive treatments for psoriasis. Among these, probiotics and prebiotics are the most extensively studied and have demonstrated beneficial effects in several small clinical trials. Specific strains such as Lactobacillus paracasei and Bifidobacterium longum have been linked with improvements in PASI scores and reductions in circulating inflammatory markers like C-reactive protein (CRP)[31]. These therapeutic effects are thought to result from multiple mechanisms, including reinforcement of intestinal barrier integrity, enhancement of short-chain fatty acid (SCFA) production, and suppression of pro-inflammatory cytokine activity.

Prebiotics—comprising indigestible carbohydrates like inulin and fructooligosaccharides—work by selectively nourishing beneficial gut microbes, especially those that produce butyrate. Supplementation with prebiotics has been shown to elevate SCFA levels, enhance expression of tight junction proteins, and reduce intestinal permeability. These changes can contribute to dampening systemic and skin-associated inflammation[32]. While these findings are promising, they require further confirmation through large-scale, long-duration studies to ensure reproducibility and safety across broader patient groups.

Fecal microbiota transplantation (FMT), the process of introducing stool from a healthy donor into a recipient's gastrointestinal tract, is another emerging approach under exploration for psoriasis. Although still in the investigational stage for dermatologic conditions, early reports indicate that FMT may reduce disease severity and lower systemic inflammatory markers. However, to establish its place in clinical practice, well-designed randomized controlled trials are necessary to evaluate its long-term effectiveness, safety considerations, and donor screening protocols.

Another innovative therapeutic category gaining interest is postbiotics, which include non-living microbial derivatives such as butyrate and indole compounds. These molecules retain the bioactivity of live organisms but with fewer risks. They have demonstrated anti-inflammatory and immunomodulatory effects in preclinical settings, suggesting their potential as future treatments that avoid the challenges of administering live bacteria.

Dietary Patterns Diet

Nutrition plays a pivotal role in shaping gut microbial communities and can significantly influence inflammatory processes in individuals with psoriasis. One of the most studied dietary approaches is the Mediterranean diet, which focuses on high intake of plant-derived foods, dietary fiber, omega-3 fatty acids, and antioxidant-rich polyphenols. This diet has been associated with greater microbial diversity and reduced markers of systemic inflammation[33]. Its beneficial effects are likely mediated through enhanced populations of SCFA-producing bacteria and modulation of immune responses, contributing to decreased psoriasis activity.

Another dietary approach of interest is the low-gluten diet, particularly for individuals who exhibit increased levels of zonulin or have non-celiac gluten sensitivity. Restricting gluten intake in these patients may help reduce gut permeability and dampen immune activation, potentially leading to improvement in psoriatic symptoms[33]. Nonetheless, further high-quality studies are necessary before such a dietary modification can be recommended universally.

The specific carbohydrate diet (SCD), which eliminates complex carbohydrates, processed foods, and grains, has also been explored in the context of psoriasis. Case reports have shown reductions in PASI scores and improvements in gastrointestinal health among adherent patients. However, the lack of randomized controlled trials and challenges in dietary compliance limit its broader clinical application[35].

Overall, dietary strategies tailored to an individual's gut microbiota profile, metabolic health, and immune status may offer valuable adjunctive benefits in psoriasis care. Personalized nutritional interventions could support conventional therapies and improve patient outcomes through microbiome-mediated effects.

Complementary to Immunotherapy

There is growing interest in the potential for gut-directed therapies to enhance the efficacy of conventional systemic treatments, particularly biologics. Treatments that target IL-17 and IL-23 pathways, such as secukinumab and ustekinumab, may be more effective in patients with intact gut barrier function and reduced systemic endotoxemia. By minimizing immune triggers derived from the gut, microbiota-based therapies may allow better disease control with lower immunosuppressive burden.

Additionally, improving gut health through microbiota modulation may reduce the risk of adverse effects associated with systemic immunomodulators, including gastrointestinal infections and dysbiosis-related complications[36]. The synergistic use of diet, probiotics, and microbiome-restoring therapies alongside biologics holds the potential to improve therapeutic outcomes and quality of life in psoriasis patients.

Future Directions and Limitations

Despite significant advances, several challenges remain in integrating gut-skin axis insights into standard psoriasis management. One major limitation is the variability in microbiome composition due to external factors such as diet, antibiotic use, stress, geography, and medication, all of which act as potential confounders in clinical studies. Accurate fecal microbiome profiling requires standardization in sample collection, sequencing methods, and bioinformatic analysis to allow for reproducible and clinically meaningful interpretations.

Furthermore, disease heterogeneity within psoriasis, including differences in onset, severity, genetic background, and comorbid conditions, complicates the generalization of microbiome-related findings. Some patients may exhibit a stronger gut-skin connection than others, emphasizing the need for microbiome-based phenotyping and stratification in future studies.

Personalized medicine approaches that categorize patients based on microbiota signatures, intestinal permeability markers, or immune profiles could enable more targeted therapeutic interventions.

Key research priorities include the development of large-scale, multicenter, randomized controlled trials to validate the clinical efficacy of gut-modulating therapies. Such studies should assess long-term safety, durability of treatment effects, and the influence of patient-specific variables such as age, gender, diet, and concurrent medications. Mechanistic studies investigating specific bacterial taxa, such as Akkermansia muciniphila and Faecalibacterium prausnitzii, and their associated metabolites, will be crucial in identifying therapeutic targets and designing next-generation probiotics or postbiotics.

In addition, the discovery of biomarkers to predict therapeutic response is a promising direction. Candidates such as fecal zonulin, calprotectin, circulating microbial DNA, and gut-derived microRNAs may help in selecting patients most likely to benefit from microbiota-focused strategies. These markers could also serve as early indicators of treatment success or relapse risk, paving the way for precision medicine in dermatology.

In conclusion, while the therapeutic potential of the gut–skin axis in psoriasis is increasingly recognized, further research is essential to overcome current limitations and translate these findings into routine clinical practice.

Conclusion:

The gut–skin axis serves as a critical, dynamic interface in psoriasis pathogenesis, with gut dysbiosis, barrier dysfunction, and altered metabolites contributing to systemic and cutaneous inflammation via immune dysregulation. Both preclinical and clinical studies support the notion that modulating the gut microbiota through probiotics, prebiotics, dietary interventions, or FMT may reduce disease severity and enhance existing therapies. However, rigorous, well-controlled trials are required to standardize treatment regimens, evaluate long-term safety and efficacy, and personalize interventions. A deeper understanding of gut-derived mechanisms, immune signaling, and microbial-host interactions holds promise for novel adjunctive management strategies in psoriasis.

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BEYOND ALBINISM:
THE MULTISYSTEMIC CHALLENGE OF HERMANSKY-PUDLAK SYNDROME

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Abstract:
Hermansky-Pudlak Syndrome (HPS) is an uncommon autosomal recessive disorder affecting multiple systems and marked by a combination of oculocutaneous albinism, a bleeding tendency due to platelet abnormalities, and progressive scarring of the lungs (pulmonary fibrosis). This syndrome is caused by mutations in at least 11 identified HPS-related genes, which disrupt the formation and movement of lysosome-related organelles, including those critical for pigmentation and platelet function. Clinically, patients commonly exhibit reduced pigmentation in the skin, hair, and eyes, leading to visual difficulties and a higher risk of bruising. As the disease progresses, some individuals may develop inflammatory bowel disease (granulomatous colitis) and lung scarring, both of which contribute to significant health issues and can reduce lifespan. Prompt diagnosis, utilizing detailed clinical evaluation, genetic testing, and specialized lab studies, is essential for effective management and patient counseling. Treatment primarily centers on symptom control, including managing bleeding risks, ensuring sun protection, and monitoring lung health. Ongoing research into gene therapy and antifibrotic medications holds promise for more targeted treatments in the future.

Keywords: Hermansky-Pudlak Syndrome; Oculocutaneous Albinism; Platelet Storage Pool Deficiency; Lysosome-Related Organelles; Autosomal Recessive; Pulmonary Fibrosis; Bleeding Diathesis; HPS Gene Mutations; Colitis; Supportive Care.

Introduction:

Hermansky-Pudlak Syndrome (HPS) is a rare, inherited disorder that exemplifies the complexity of conditions involving lysosome-related organelle dysfunctions (LRODs). First described in 1959 by Drs. Hermansky and Pudlak among Puerto Rican patients exhibiting oculocutaneous albinism and a bleeding tendency, HPS is now recognized worldwide, although its prevalence varies by genetic subtype and region. Certain populations, such as those in northwestern Puerto Rico, exhibit a higher carrier frequency due to founder effects.[1]

The classic clinical presentation of HPS includes oculocutaneous albinism—manifesting as decreased pigmentation of the skin, hair, and eyes—and a bleeding tendency caused by defects in platelet dense body storage, which impairs normal clotting. Some genetic subtypes of HPS are also associated with progressive lung scarring (pulmonary fibrosis), which can significantly impact lifespan. Other systemic features may include granulomatous colitis, renal issues, and, in some cases, immune system abnormalities.

At the molecular level, HPS is caused by mutations in at least eleven different genes (HPS1 through HPS11). These genes code for proteins essential to the formation, trafficking, and function of LROs, including melanosomes (responsible for pigmentation), platelet dense bodies (critical for clotting), and lamellar bodies in lung cells (important for surfactant storage). Mutations disrupt these processes, resulting in the hallmark features of the disorder. Hypopigmentation arises from defective melanosome formation, while a deficiency in platelet dense bodies accounts for the bleeding tendency, as platelets cannot properly release mediators essential for hemostasis. In the lungs, defective lamellar body function can lead to surfactant abnormalities and interstitial lung disease, particularly in subtypes 1 and 4.

Clinically, HPS often presents in infancy or early childhood with symptoms such as nystagmus, light sensitivity, and poor vision due to the albinism component. Easy bruising and mucosal bleeding are also common, though severe bleeding is infrequent. Pulmonary fibrosis typically develops in early adulthood, necessitating regular monitoring of lung function. Additionally, some patients develop granulomatous colitis, which can mimic inflammatory bowel disease and complicate management.

Accurate diagnosis relies on a combination of clinical assessment, laboratory tests (including platelet aggregation studies and electron microscopy to evaluate platelet dense bodies), and genetic testing to identify the causative gene. Recognizing the specific genetic subtype can guide prognosis and management, as risks for systemic complications vary. Current treatment is largely supportive, focusing on symptomatic management of bleeding—often with desmopressin—alongside strict sun protection and lung monitoring. Hematopoietic stem cell transplantation is not recommended at present, but research into gene therapy and antifibrotic therapies is ongoing and may offer new treatments in the future.

In conclusion, Hermansky-Pudlak Syndrome is a complex disorder with significant clinical variability. Early recognition and a coordinated, multidisciplinary approach are essential to optimize care and improve quality of life for affected individuals.

Epidemiology

Hermansky-Pudlak Syndrome (HPS) is an extremely rare genetic disorder inherited in an autosomal recessive manner, with an estimated global prevalence ranging from 1 to 9 cases per million people. The condition demonstrates significant geographic and ethnic clustering, largely due to founder mutations and high rates of consanguinity in certain regions.[2]

High Prevalence in Puerto Rico

The highest known prevalence of HPS occurs in the northwest region of Puerto Rico, where approximately 1 in every 1,800 individuals is affected, and the carrier rate is estimated at around 1 in 21. This strikingly high frequency is attributed to a founder mutation in the **HPS1 gene**. The unique genetic landscape of this region has allowed for extensive research into HPS and facilitated the identification of numerous cases.

Other Affected Populations

Beyond Puerto Rico, HPS has been reported in several other regions, though at substantially lower frequencies. Cases have been documented in Japan, Northern Europe, and parts of the Middle East. For instance, mutations in the **HPS3 gene** have been identified in Ashkenazi Jewish and select European populations, although carrier rates are much lower than those seen in Puerto Rico. Additionally, sporadic cases continue to be recognized worldwide, largely due to improved genetic testing.

Genetic Subtypes and Variability

To date, researchers have identified eleven genetic subtypes of HPS (designated HPS1 through HPS11), each with its own spectrum of prevalence and clinical features. Notably, HPS1 and HPS4 subtypes are most frequently linked to severe complications like lung fibrosis and inflammatory bowel disease, both of which significantly impact patient outcomes. The rarer subtypes are less well understood, given their scarcity and the challenges of molecular diagnostics in very small patient populations.

Demographic Characteristics

HPS affects both males and females equally, consistent with its autosomal recessive inheritance. Symptoms often manifest during infancy or early childhood, usually beginning with hypopigmentation and a tendency to bruise easily. Complications such as pulmonary fibrosis typically develop later in adulthood.

Underdiagnosis and Clinical Awareness

Given its rarity and its clinical similarities to other conditions that cause albinism and bleeding disorders, HPS is likely underrecognized, especially in areas where genetic and specialized hematologic testing are less accessible. Nonetheless, increased clinical awareness and advances in molecular diagnostic tools are gradually improving detection rates and contributing to a better understanding of the disease's distribution.

Etiology

Hermansky-Pudlak Syndrome (HPS) is a genetically diverse condition arising from mutations in at least eleven genes (designated HPS1 through HPS11), each of which plays a role in the formation, transport, and function of lysosome-related organelles (LROs). These specialized cellular structures include melanosomes (which contribute to pigmentation), platelet dense granules (necessary for blood clotting), and lamellar bodies within lung alveolar cells (responsible for surfactant production).[3] Mutations in these genes lead to a complex disorder characterized by varying degrees of albinism, bleeding tendencies, and, in some cases, pulmonary fibrosis and inflammatory bowel disease.

1. Genetic Background and Inheritance Patterns

HPS is inherited in an **autosomal recessive** fashion, meaning individuals must inherit mutations from both parents to exhibit symptoms, while carriers typically remain unaffected.

- **HPS1 (located on chromosome 10q23.1–q23.3)** is the most commonly mutated gene, particularly among Puerto Rican patients where a founder mutation contributes to high disease prevalence. This gene encodes a subunit of the biogenesis of lysosome-related organelles complex-3 (BLOC-3), critical for LRO function.
- **HPS2 (AP3B1 gene)** mutations impact the adaptor protein complex-3 (AP-3), and can lead to immune deficiencies in addition to the classic HPS features.
- Mutations in **HPS3 through HPS11** involve various components of BLOC complexes and related pathways essential for LRO formation and trafficking. Each of these genes encodes a protein that helps assemble or regulate these organelles; disruptions lead to a cascade of problems, including defective melanosomes (causing albinism), absent or poorly formed platelet dense bodies (resulting in bleeding diathesis), and abnormal lamellar bodies in the lungs (contributing to interstitial lung disease in certain subtypes).

2. Mechanisms of Pathogenesis

- **Melanosome Dysfunction:**
  Mutations impair the proper assembly and movement of melanosomes, leading to decreased melanin synthesis and uneven distribution in the skin, hair, and eyes.
- **Platelet Dense Body Deficiency:**
  Platelets lack the dense granules that store and release important molecules needed for platelet aggregation and clot formation, resulting in a bleeding tendency.
- **Lamellar Body Impairment:**
  Particularly in HPS1 and HPS4, defects in lamellar bodies of type II lung alveolar cells disrupt surfactant storage and secretion, leading to progressive lung scarring.
- **Granulomatous Colitis:**
  Although not fully understood, this may stem from immune dysregulation or impaired organelle trafficking in immune cells.

3. Additional Genetic Considerations

Some HPS subtypes, such as HPS2 (linked to AP3B1 mutations), can present with immune deficiencies due to abnormal protein trafficking within immune cells. Rare mutations in genes like **PGM3, ZNF341, and CARD11** may produce symptoms that overlap with HPS but may not meet strict diagnostic criteria.

Pathophysiology

Hermansky-Pudlak Syndrome (HPS) arises from disrupted formation, transport, and function of lysosome-related organelles (LROs), a consequence of mutations in at least eleven genes (HPS1–

HPS11). These LROs encompass melanosomes in pigment-producing cells, dense granules in platelets, and lamellar bodies in lung alveolar cells.[4] Malfunction of these organelles underlies the characteristic features of HPS, including albinism, bleeding disorders, and, in certain subtypes, pulmonary fibrosis and gastrointestinal inflammation.(See in Figure 1)

- **Melanosome Dysfunction and Albinism**

Melanosomes are specialized cellular compartments responsible for producing and storing melanin within melanocytes. Genetic mutations in HPS compromise the development and transport of these organelles, leading to reduced melanin synthesis and distribution. Clinically, this presents as hypopigmentation of the skin, hair, and eyes, often accompanied by light skin tone, pale hair, involuntary eye movements (nystagmus), and decreased visual acuity. The lack of melanin also heightens sensitivity to ultraviolet (UV) radiation, increasing the risk of sunburn and skin damage.

- **Deficiency of Platelet Dense Granules and Bleeding Diathesis**

Dense granules (δ-granules) in platelets are key storage sites for molecules like adenosine diphosphate (ADP), serotonin, and calcium, all of which are essential for normal platelet aggregation and clotting. In HPS, defective biogenesis of these granules prevents the proper release of these mediators at sites of vascular injury. As a result, patients exhibit a bleeding tendency characterized by prolonged bleeding time, frequent bruising, mucosal bleeding, and increased bleeding risk following surgery or trauma.

- **Lamellar Body Defects and Lung Fibrosis**

Particularly in subtypes HPS1 and HPS4, lamellar bodies within type II alveolar cells are affected. These organelles are crucial for storing and releasing surfactant, a substance that maintains alveolar stability. When lamellar bodies malfunction, surfactant balance is disrupted, leading to chronic inflammation, alveolar damage, and eventually, scarring of lung tissue (pulmonary fibrosis). Clinically, this presents as progressive shortness of breath, persistent cough, and respiratory decline, usually starting in early to middle adulthood.

4. Immune Dysfunction and Gastrointestinal Inflammation

Some subtypes, especially those involving HPS1 and HPS4, are linked to granulomatous colitis, an inflammatory bowel-like condition. Although the precise mechanism is unclear, it may involve faulty trafficking of lysosomes in immune cells, resulting in abnormal immune responses and chronic inflammation of the gut. Symptoms often include abdominal pain, diarrhea, and occasional rectal bleeding.

- **Broader Immune System Involvement**

In certain forms of HPS, notably HPS2 due to AP3B1 gene mutations, additional immune issues arise, such as increased susceptibility to infections and impaired natural killer (NK) cell function. These immune complications are related to defects in the AP-3 complex, which is critical for transporting proteins within immune cells.

- **Molecular Mechanisms**

The proteins encoded by HPS genes are integral components of large intracellular complexes, including the biogenesis of lysosome-related organelles complexes (BLOCs) and the AP-3 complex. When these complexes malfunction, it leads to improper trafficking or incomplete assembly of LROs across multiple cell types. Consequently, these organelles do not develop or function as intended, giving rise to the diverse symptoms seen in HPS.

Conclusion:

In summary, Hermansky-Pudlak Syndrome results from genetic mutations that disrupt the formation and function of key intracellular organelles, including melanosomes, platelet dense granules, and lamellar bodies. These organelle defects collectively produce the hallmark features of the disease: oculocutaneous albinism, a bleeding tendency, lung fibrosis, and gastrointestinal inflammation.

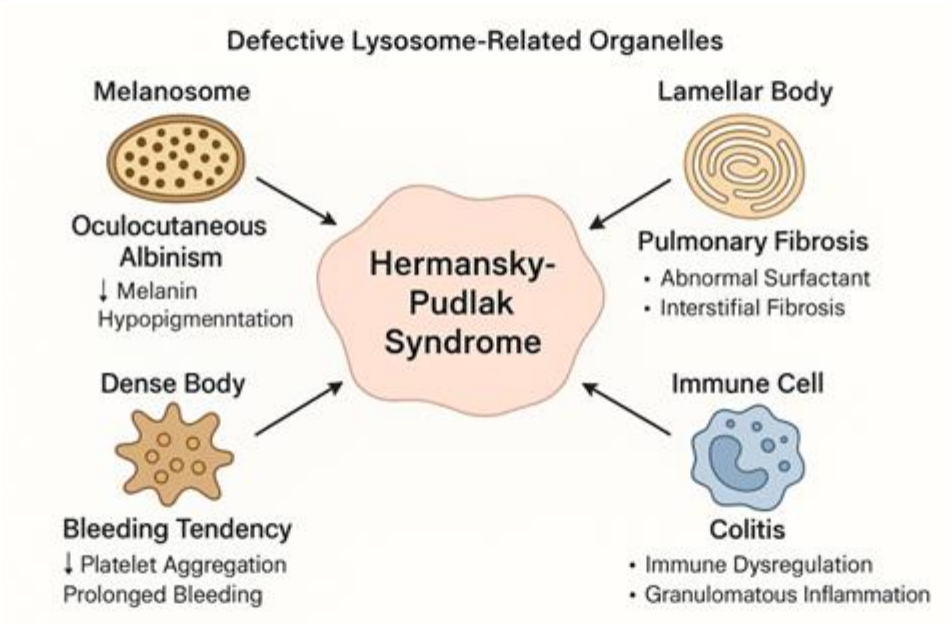

Figure 1: Pathophysiology of Hermansky-Pudlak Syndrome (HPS)

Clinical presentation

Hermansky-Pudlak Syndrome (HPS) is a multisystem condition that typically manifests in infancy or early childhood, although the timing and severity of symptoms can vary depending on the genetic subtype involved. The syndrome's diverse features stem from defective lysosome-related organelles (LROs) affecting the function of melanocytes, platelets, and lung epithelial cells.[5] The key clinical features include albinism, a bleeding tendency, and—in certain subtypes—progressive lung fibrosis and gastrointestinal inflammation.

1. Oculocutaneous Albinism

- **Skin and Hair Pigmentation:**

  Individuals often have lighter-than-normal skin and hair because of reduced melanin production.

- **Ocular Manifestations:**

  Common issues include involuntary eye movements (nystagmus), sensitivity to light (photophobia), eye misalignment (strabismus), and reduced visual acuity.

  Eye exams may reveal iris transillumination and underdeveloped central retinal structures (foveal hypoplasia).

2. Bleeding Tendency

- **Platelet Function Abnormalities:**

  Due to missing or poorly developed platelet dense granules, patients are prone to easy bruising, prolonged bleeding after even minor injuries, and mucosal bleeding (such as frequent nosebleeds and heavy menstrual bleeding).

- **Surgical Considerations:**

  There is a heightened risk of excessive bleeding during and after surgical or dental procedures.

3. Pulmonary Involvement

- **Progressive Lung Fibrosis:**

  Interstitial lung disease mainly affects individuals with HPS1 and HPS4 subtypes.

  Symptoms often emerge in early adulthood (usually in the 30s to 40s) and include shortness of breath with activity, a dry cough, and eventual respiratory failure.

  On examination, clinicians may detect fine crackles with inhalation and clubbing of the fingers in advanced cases.

4. Gastrointestinal Complications

- **Granulomatous Colitis:**

  Found in some subtypes (notably HPS1 and HPS4), presenting with symptoms similar to Crohn's disease, such as abdominal pain, diarrhea, and occasional rectal bleeding.

  Chronic cases may cause anemia and other nutritional deficiencies.

5. Additional Clinical Features

- **Skin Sensitivity:**

  Reduced melanin increases susceptibility to sunburn and potentially raises the risk of skin cancer.

- **Immune Abnormalities:**

  Some subtypes, particularly HPS2, may involve immune system dysfunction, leading to increased infections and issues with natural killer (NK) cell activity.

- **Other Organ Involvement:**

  Rarely, affected individuals may experience mild kidney or liver abnormalities, depending on the genetic variant.

Pharmacological treatment

There is currently no cure for Hermansky-Pudlak Syndrome (HPS). As such, treatment is mainly supportive, aiming to control symptoms and prevent complications. Pharmacological approaches address the primary clinical challenges of HPS, namely bleeding tendencies, lung fibrosis, and related complications.[6]

1. Managing Bleeding Tendencies

- **Desmopressin (DDAVP):**

  Can be administered before minor surgical or dental procedures to improve platelet function by stimulating the release of von Willebrand factor and factor VIII from endothelial cells.

  Particularly beneficial for managing mild bleeding episodes.

- **Antifibrinolytic Drugs:**

  Medications like tranexamic acid or aminocaproic acid can be prescribed to reduce mucosal bleeding, such as nosebleeds or heavy menstrual bleeding.

- **Platelet Transfusions:**

  Used only for severe bleeding events or as preparation for major surgery, since HPS-related platelet dysfunction (due to absent dense granules) limits normal clot formation.

2. Managing Pulmonary Fibrosis

- **Antifibrotic Medications:**

  Drugs such as pirfenidone and nintedanib are under investigation for their potential to slow lung scarring in HPS patients.

  These treatments are still experimental in HPS and should be considered within specialized centers or clinical research trials.

- **Supportive Measures:**

  Oxygen therapy for patients with low blood oxygen levels.

  Pulmonary rehabilitation to maintain breathing capacity and overall fitness.

  Lung transplantation may be an option in advanced cases, though bleeding risks and donor availability complicate the process.

3. Managing Colitis

- **Anti-Inflammatory and Immunosuppressive Drugs:**

  For granulomatous colitis, medications commonly used for Crohn’s disease, like corticosteroids or mesalamine, may help control gut inflammation.

  In more severe cases, immunosuppressants such as azathioprine may be necessary.

- **Nutritional Support:**

  Iron supplementation can help address anemia, and vitamins or minerals should be adjusted as needed.

4. Additional Symptom Management

- **Sun Protection:**
  Patients should use broad-spectrum sunscreens and protective clothing to reduce the risk of sunburn and skin cancer.
- **Infection Management:**
  Prompt use of antibiotics for bacterial infections, especially in those HPS subtypes associated with impaired immune function.

5. Genetic Counseling and Ongoing Care

- While not a medication, genetic counseling is crucial for family planning and helping families understand the disease.
- Regular assessments and close collaboration with a multidisciplinary care team are vital to adapt treatment plans as the disease progresses.

Non-pharmacological management

Although medications can alleviate some symptoms of Hermansky-Pudlak Syndrome (HPS), comprehensive care also requires a variety of non-drug strategies. These interventions aim to prevent complications, support daily living, and enhance overall well-being.[7]

1. Skin Care and Sun Protection

- **Avoiding Sun Exposure:**
  Because of light skin and photosensitivity, patients should minimize direct sun exposure.
  The use of broad-spectrum sunscreens (SPF 30 or higher), protective hats, sunglasses, and UV-protective clothing is vital to lower the risk of skin damage and skin cancer.
- **Dermatologic Surveillance:**
  Regular skin exams are important to detect early signs of skin cancer or other sun-induced issues.

2. Reducing Bleeding Risks

- **Injury Prevention:**
  Patients should be taught to avoid activities with a high chance of injury that might lead to significant bleeding.
- **Oral Health:**
  Routine dental visits and gentle brushing habits can help prevent gum disease and bleeding.
  Dental practitioners should be informed about the bleeding risk to ensure proper precautions during procedures.

3. Pulmonary Support

- **No Smoking:**
  Avoidance of tobacco use is strongly recommended to slow the progression of lung scarring.

- **Environmental Controls:**
  Limiting exposure to airborne pollutants, dust, and irritants helps protect lung function.
- **Breathing and Exercise Therapy:**
  Supervised rehabilitation can maintain lung capacity and support quality of life.
- **Vaccinations:**
  Annual flu shots and pneumococcal vaccines can help prevent respiratory infections.

4. Gastrointestinal Health

- **Dietary Management:**
  For patients with colitis, dietitians can advise on proper nutrition, fiber intake, and ways to manage diarrhea or nutrient absorption problems.
- **Anemia Monitoring:**
  Regular checks for iron deficiency or anemia are recommended due to the risk of chronic blood loss from colitis.

5. Visual and Educational Support

- **Vision Aids:**
  Glasses, magnifying devices, and other assistive tools can help patients make the most of their vision.
- **School Support:**
  Children often need individualized education plans that accommodate vision issues and other needs.

6. Genetic Counseling and Psychosocial Support

- **Family Planning:**
  Genetic counseling helps families understand inheritance patterns, carrier testing, and available prenatal diagnostic options.
- **Emotional Support:**
  Support groups and counseling services can help families and patients cope with the long-term challenges of living with HPS.[8]

7. Coordinated Multidisciplinary Care

- **Collaborative Approach:**
  Dermatologists, lung specialists, eye doctors, blood specialists, gastrointestinal experts, and genetic counselors should work together to manage all aspects of the disease.
  Regular appointments are essential to monitor disease progression and adjust care plans.

Conclusion:

Hermansky-Pudlak Syndrome (HPS) is a rare, multisystem genetic condition defined by the combination of oculocutaneous albinism, a bleeding tendency, and—depending on the subtype—progressive lung fibrosis and inflammatory bowel disease. The disorder stems from mutations in genes essential for the development and function of lysosome-related organelles, affecting structures like melanosomes, platelet dense bodies, and lamellar bodies in lung cells.[9] Early clinical suspicion and genetic confirmation are crucial for timely intervention and family counseling.

Although no definitive cure is available, optimal management relies on a comprehensive, team-based approach that integrates both pharmacologic and non-pharmacologic measures. Pharmacological options—such as desmopressin for bleeding, antifibrinolytic drugs, and investigational antifibrotics—address the most pressing symptoms and complications. Non-drug strategies, including sun protection, pulmonary care, dietary guidance, and education, complement medical therapies and support overall quality of life.

Looking ahead, ongoing research into gene therapy and targeted antifibrotic medications offers hope for more effective treatments. Until such therapies become available, a coordinated, multidisciplinary model of supportive care remains the cornerstone of management—empowering patients and families while aiming to reduce complications and enhance outcomes in this challenging disease.[10]

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STRATEGIES TO OVERCOME FIRST PASS METABOLISM

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Abstract:

First-pass metabolism, also known as presystemic metabolism, significantly reduces the bioavailability of many orally administered drugs, posing a major challenge in pharmaceutical development. This chapter explores the physiological basis and impact of first-pass metabolism, primarily occurring in the liver and gastrointestinal tract. Various strategies to overcome this barrier are critically reviewed, including alternative routes of administration (such as sublingual, transdermal, and rectal), use of prodrugs, enzyme inhibitors, nanoparticle-based delivery systems, and targeted drug delivery techniques. Emphasis is placed on recent advances in formulation science and nanotechnology that enhance drug stability and absorption. The chapter also discusses case studies of successful drug products and the regulatory considerations surrounding these approaches. By addressing both established and emerging methods, this chapter provides a comprehensive guide for improving drug bioavailability and therapeutic efficacy through mitigation of first-pass effects.

Keywords: Presystemic Metabolism, Novel Approaches, Nanotechnology, Improved Bioavailability

Introduction:

First-pass metabolism, also known as first-pass effect or presystemic metabolism, refers to the initial metabolism of a drug that occurs before it reaches systemic circulation. This process primarily takes place in the liver and intestinal wall after oral administration. When a drug is taken orally, it is absorbed through the gastrointestinal (GI) tract and transported via the portal vein to the liver, where enzymes may chemically alter or degrade the drug. As a result, a significant portion of the active drug may be inactivated or transformed into metabolites before it enters the bloodstream, thereby reducing its bioavailability[1,2].

First-pass metabolism plays a critical role in determining the efficacy, dosage, and route of administration of many pharmaceutical drugs. Its significance in drug delivery lies in its direct impact on drug bioavailability, which is essential for achieving desired therapeutic effects. Key aspects of first pass metabolism are explained underneath[3,4]:

1. **Reduction in Bioavailability**
    - Drugs with high first-pass metabolism have significantly reduced concentrations in systemic circulation after oral administration.

- This can lead to sub-therapeutic levels, requiring dose adjustments or alternative delivery routes.

2. **Influence on Route of Administration**
   - Drugs susceptible to first-pass metabolism often need to be delivered via non-oral routes such as sublingual, transdermal, rectal, or parenteral to bypass the liver.
3. **Formulation Challenges**
   - Designing oral formulations for drugs with high first-pass metabolism demands innovative strategies like prodrugs, enzyme inhibitors, or protective carriers.
4. **Variability in Patient Response**
   - Individual differences in liver enzyme activity, age, diet, and genetic factors can cause variability in drug metabolism, making dosing complex.
5. **Drug Safety and Toxicity**
   - In some cases, first-pass metabolism may convert a drug into toxic metabolites, impacting safety profiles and requiring careful monitoring.
6. **Pharmacokinetic Optimization**
   - Understanding the extent of first-pass effect is essential for optimizing pharmacokinetics (absorption, distribution, metabolism, excretion) and improving therapeutic outcomes.

First-pass metabolism is a major consideration in drug development and clinical pharmacology. Overcoming or minimizing this effect is essential for improving drug effectiveness, enhancing patient compliance, and ensuring safety and predictability in treatment.

Mechanism of First-Pass Metabolism

First-pass metabolism, or presystemic metabolism, occurs before a drug reaches systemic circulation, primarily through metabolic processes in the gastrointestinal (GI) tract and liver. The mechanism involves enzymatic degradation that can significantly reduce the amount of active drug available for therapeutic action[5,6].

Step-by-Step Mechanism:

1. **Oral Administration**
   - The drug is ingested and travels through the stomach to the small intestine, where it is absorbed into the bloodstream.
2. **Absorption into the Portal Circulation**
   - From the intestinal lumen, the drug is absorbed by intestinal epithelial cells and enters the hepatic portal vein, which carries it directly to the liver.
3. **Metabolism in the Intestinal Wall (Enteric First-Pass Effect)**
   - Some drugs are partially metabolized in the enterocytes (intestinal cells) by enzymes such as cytochrome P450 (CYP3A4) and esterases.

- Efflux transporters like P-glycoprotein can also reduce absorption by pumping the drug back into the intestinal lumen.

4. **Hepatic Metabolism (Hepatic First-Pass Effect)**
    - Upon reaching the liver, the drug undergoes extensive biotransformation by liver enzymes, primarily cytochrome P450 enzymes (e.g., CYP3A4, CYP2D6).
    - The liver may convert the drug into:
        - Inactive metabolites (reducing therapeutic effect)
        - Active metabolites (sometimes with therapeutic or toxic effects)
        - Highly polar compounds for easier excretion
5. **Entry into Systemic Circulation**
    - Only the fraction of the drug that escapes metabolism enters the systemic circulation, becoming available for therapeutic action.

Challenges Posed by First-Pass Metabolism

First-pass metabolism presents significant barriers to effective drug delivery, especially for orally administered drugs. These challenges affect not only the bioavailability and therapeutic efficacy of a drug but also influence its formulation, dosage, and route of administration[7,8].

1. Reduced Bioavailability

- A substantial portion of the drug is metabolized before entering systemic circulation, leading to low therapeutic concentrations.
- This often necessitates higher doses, which may increase the risk of side effects or toxicity.

Example:

- Propranolol undergoes extensive first-pass metabolism, resulting in only ~25% bioavailability after oral administration.

2. Variable Drug Response

- Individual differences in metabolic enzyme activity (due to genetics, age, disease states, or drug interactions) can cause unpredictable plasma levels and therapeutic variability.
- This may lead to underdosing or overdosing, especially for drugs with a narrow therapeutic index.

3. Complicated Drug Formulation and Design

- Drugs susceptible to high first-pass metabolism often require complex delivery systems (e.g., nanoparticles, prodrugs, or enzyme inhibitors) to enhance their effectiveness.
- This increases development time, cost, and regulatory challenges.

4. Limited Oral Drug Options

- Many promising drug candidates are abandoned during development due to poor oral bioavailability caused by first-pass effect.

- This restricts route-of-administration flexibility, potentially affecting patient compliance (e.g., injectable-only drugs).

5. Potential Formation of Toxic Metabolites

- Some drugs are converted into harmful metabolites during first-pass metabolism, which can lead to hepatotoxicity **or** gastrointestinal damage**.**

Example*:*

- Acetaminophen (paracetamol) in high doses forms a hepatotoxic metabolite during hepatic metabolism.

6. Inefficient Drug Delivery

- Drugs affected by first-pass metabolism often show delayed or inconsistent onset of action, which is problematic in acute or emergency treatments.

7. Increased Dosing Frequency

- Due to poor bioavailability, such drugs may require frequent administration, which can reduce patient adherence **and** treatment effectiveness**.**

First-pass metabolism poses formidable obstacles in drug development, affecting efficacy, safety, and patient compliance. Addressing these challenges requires innovative formulation strategies and alternative delivery routes to ensure optimal therapeutic outcomes.

Strategies to Overcome First-Pass Metabolism

Overcoming first-pass metabolism is essential to improve the bioavailability**,** efficacy, and therapeutic consistency of many drugs. Multiple pharmaceutical and formulation strategies have been developed to bypass or minimize the presystemic metabolism that occurs primarily in the liver and intestinal wall[9-12]**.**

1. Alternative Routes of Drug Administration

By avoiding the gastrointestinal tract and liver, these routes reduce or bypass first-pass metabolism entirely.

- **Sublingual and Buccal Routes**
  - Absorption through the mucosa under the tongue or cheek directly into systemic circulation.
  - Example*:* Nitroglycerin tablets
- **Transdermal Delivery**
  - Drugs are absorbed through the skin into the bloodstream.
  - Example*:* Fentanyl patches
- **Rectal Administration**
  - Partially bypasses the liver via the lower rectal veins.
  - Useful when oral administration isn't feasible.
- **Intravenous (IV), Intramuscular (IM), and Subcutaneous (SC) Injections**

  - Deliver the drug directly into systemic circulation, completely avoiding first-pass effect.
- **Nasal and Pulmonary Routes**
  - Rapid absorption with minimal hepatic metabolism.
  - Example*:* Nasal sprays (sumatriptan), inhalers (salbutamol)

2. Prodrug Design

- A prodrug is an inactive compound that is metabolized in the body to release the active drug.
- Prodrugs can be designed to bypass first-pass metabolism and activate after absorption or outside the liver**.**
- Example*:* Enalapril (converted to enalaprilat)

3. Enzyme Inhibitors

- Co-administration of metabolism inhibitors (e.g., CYP450 or esterase inhibitors) can reduce the metabolic breakdown of drugs.
- This increases the amount of active drug reaching systemic circulation.
- Example*:* Ritonavir used to boost the levels of protease inhibitors in HIV treatment.

4. Nanotechnology-Based Drug Delivery Systems

Advanced carriers protect the drug from enzymatic degradation and enhance absorption.

- Liposomes
- Solid Lipid Nanoparticles (SLNs)
- Polymeric Nanoparticles
- Niosomes

These systems can target absorption sites**,** enhance permeability**,** and control drug release**,** thereby minimizing first-pass effect.

5. Targeted Drug Delivery Systems

- Use of ligands**,** receptors**,** or carriers to direct the drug to a specific site, reducing systemic metabolism.
- These systems increase the efficiency and reduce the need for high systemic drug levels.

6. Controlled-Release Formulations

- Sustained or controlled-release dosage forms can be designed to:
  - Bypass initial metabolism
  - Release the drug in parts of the GI tract with less enzymatic activity

7. Use of Absorption Enhancers

- Certain excipients or formulation additives can increase permeability of the intestinal membrane or inhibit efflux transporters**.**
- *Example:* Bile salts, surfactants, or fatty acids

Overcoming first-pass metabolism requires a multidisciplinary approach combining pharmacokinetics, drug design, and advanced formulation techniques. By selecting appropriate strategies, drug developers can significantly improve bioavailability, reduce dosing frequency, and enhance patient outcomes.

Formulation Approaches

Formulation strategies are critical in enhancing the bioavailability of drugs that undergo extensive first-pass metabolism. These approaches are designed to modify the physicochemical properties, alter the site of absorption, or protect the drug from metabolic degradation in the liver and intestinal tract[13-15].

1. Prodrug Formulation

- A prodrug is an inactive or less active compound that is converted into the active drug form after absorption.
- Formulating a prodrug allows the molecule to bypass liver metabolism and be activated in the systemic circulation or at the target site.

Example:

- Valacyclovir → converted to acyclovir after absorption, enhancing oral bioavailability.

2. Use of Enzyme Inhibitors in Formulations

- Co-formulating drugs with enzyme inhibitors can reduce metabolism by blocking hepatic or intestinal enzymes (e.g., CYP450, esterases).
- This increases the concentration of active drug reaching systemic circulation.

Example:

- Ritonavir as a booster in HIV therapy to inhibit CYP3A4 metabolism of co-administered drugs.

3. Nanocarrier Systems

- Nanotechnology-based formulations enhance absorption and protect the drug from enzymatic degradation.

Types:

- Liposomes
- Solid Lipid Nanoparticles (SLNs)
- Nanostructured Lipid Carriers (NLCs)
- Polymeric nanoparticles

Advantages:

- Controlled release
- Targeted delivery
- Bypass of hepatic metabolism

4. Mucoadhesive Drug Delivery Systems

- These systems adhere to the mucosal lining (e.g., buccal, nasal, rectal) and allow drug absorption directly into the bloodstream, bypassing the liver.

Formulations Include:

- Buccal tablets
- Gels and films
- Patches

5. Gastroretentive Drug Delivery Systems (GRDDS)

- These are designed to prolong the retention time of a drug in the stomach or upper GI tract to maximize absorption before metabolism occurs.

Techniques*:*

- Floating tablets
- Swelling systems
- Bioadhesive systems

6. Lipid-Based Formulations

- Using lipids or surfactants in formulations can enhance solubility, lymphatic absorption, and reduce metabolism.

Examples*:*

- Self-emulsifying drug delivery systems (SEDDS)
- Self-microemulsifying systems (SMEDDS)

Benefit*:*

These bypass the portal vein and **promote lymphatic transport**, reducing hepatic metabolism.

7. pH Modifiers and Buffer Systems

- Including **pH modifiers** in a formulation can:
    - Stabilize the drug
    - Alter local GI conditions to reduce degradation
    - Improve solubility and absorption

8. Co-crystals and Complexes

- Drugs may be formulated as co-crystals**,** inclusion complexes (e.g., cyclodextrins)**,** or salts to improve solubility and reduce enzymatic exposure.

Formulation approaches play a pivotal role in minimizing first-pass metabolism by enhancing drug stability**,** altering absorption sites**,** or redirecting drug transport. These strategies are essential in designing effective oral formulations and enabling the success of drugs with poor systemic bioavailability.

Regulatory and Safety Considerations

Developing drug formulations or delivery systems to overcome first-pass metabolism requires careful attention to regulatory standards and safety protocols. Regulatory agencies such as the

FDA (U.S. Food and Drug Administration) and EMA (European Medicines Agency) closely evaluate the safety, efficacy, and quality of such drug products due to their altered pharmacokinetics and novel delivery mechanisms[16-18].

1. Regulatory Approval Pathways

- Novel Formulations: Drugs formulated using nanotechnology, prodrugs, or alternative delivery systems often fall under New Drug Applications (NDAs) or Investigational New Drug (IND) categories.
- **Drug-Device Combinations**: Transdermal patches, nasal sprays, and implantable systems require assessment as combination products, evaluated for both pharmaceutical and device safety.
- **Bioequivalence Studies**: For modified-release or alternate route formulations (e.g., sublingual), bioavailability and bioequivalence data are mandatory.
- **GRAS Status (**Generally Recognized as Safe**)**: Any novel excipients or absorption enhancers used to bypass first-pass metabolism must have toxicological safety data or GRAS designation.

2. Safety Evaluation

- **Toxicity of Metabolites**: Metabolic profiling is essential to ensure that bypassing first-pass metabolism does not lead to accumulation of harmful active or inactive metabolites.
- **Enzyme Inhibition Risks**: Use of metabolic enzyme inhibitors (e.g., CYP450 inhibitors) must be evaluated for drug-drug interactions and potential systemic side effects.
- **Systemic Exposure Monitoring**: Non-oral routes may increase plasma drug concentrations, necessitating careful dose titration to avoid toxicity.
- **Immune and Hypersensitivity Reactions**: Novel carriers such as liposomes or nanoparticles must be assessed for immunogenicity and biocompatibility.

3. Manufacturing and Quality Control

- **Reproducibility and Stability**: Formulations that bypass first-pass metabolism (e.g., nanoparticles, prodrugs) must demonstrate batch-to-batch consistency and shelf stability.
- **Sterility and Cleanroom Standards**: Injectable or nasal formulations require adherence to strict sterility protocols during manufacturing.
- **Device Regulations**: Delivery systems (like inhalers or patches) must comply with medical device standards and undergo human factor testing.

4. Post-Market Surveillance

- **Pharmacovigilance**: Continuous monitoring for adverse drug reactions (ADRs) is essential, especially when bypassing first-pass metabolism alters the safety profile.
- **Real-world Evidence (RWE)**: Regulators may require ongoing studies to gather data on the long-term safety and effectiveness of the novel formulation or delivery system.

Regulatory and safety considerations are central to the successful development and approval of drug products designed to overcome first-pass metabolism. Developers must present comprehensive data on pharmacokinetics, toxicology, manufacturing quality, and patient safety to meet global regulatory requirements and ensure effective and safe therapy.

Future Perspectives and Emerging Trends

With growing interest in personalized medicine and advanced drug delivery systems, the pharmaceutical industry is actively exploring innovative technologies and scientific advancements to bypass or minimize first-pass metabolism. These developments aim to improve bioavailability, target specificity, therapeutic efficacy, and patient compliance[19,20].

1. Personalized Drug Delivery

- Pharmacogenomics is increasingly being used to tailor drug therapy based on an individual's genetic profile, especially variations in liver enzymes like CYP450.
- Personalized formulations could minimize first-pass effects by adjusting drug doses or selecting alternative delivery routes for specific populations.

2. Advanced Nanotechnology-Based Systems

- Smart nanocarriers with stimuli-responsive features (e.g., pH, temperature, or enzyme-triggered release) are under development to target absorption sites and avoid hepatic metabolism.
- Emerging systems:
    - Dendrimers
    - Exosome-inspired vesicles
    - Hybrid lipid-polymer nanoparticles

3. Lymphatic Drug Delivery Targeting

- Formulations designed to exploit intestinal lymphatic transport (especially lipid-based systems) are gaining interest for delivering drugs directly into the lymphatic system, bypassing the portal vein and liver.

Example:

- Lipophilic drugs in Self-emulsifying Drug Delivery Systems (SEDDS) or SMEDDS

4. 3D Printing of Personalized Dosage Forms

- 3D printed tablets or films allow precise control **of** drug layering, release kinetics, and geometry, offering ways to:
    - Protect the drug from enzymatic degradation
    - Deliver drugs directly to absorption sites
    - Combine multiple drugs with staggered release

5. Oral Biologic Delivery

- Biologics (e.g., peptides, proteins) are highly sensitive to first-pass metabolism and enzymatic degradation.

- Cutting-edge approaches involve:
  - Permeation enhancers
  - Enzyme inhibitors
  - Mucoadhesive hydrogels
  - Oral delivery capsules with microneedles or self-injecting mechanisms (e.g., MIT's ingestible robotic capsule)

6. Artificial Intelligence in Drug Design

- AI and machine learning are being applied to predict:
  - Drug metabolism pathways
  - Formulation performance
  - Optimal excipients and routes of administration
- This accelerates the development of formulations that avoid first-pass metabolism.

7. Gene Therapy and RNA-Based Drugs

- Non-oral delivery systems for mRNA, siRNA, and gene-editing tools (like CRISPR-Cas9) are evolving rapidly.
- These therapies inherently avoid first-pass metabolism but require precise delivery mechanisms to target tissues effectively.

8. Regulatory Framework Evolution

- Regulatory bodies are updating guidance for complex generics, novel delivery systems, and bioequivalence assessments involving first-pass metabolism.
- Emphasis on real-world data and patient-centered outcomes is shaping future approval pathways.

The future of overcoming first-pass metabolism lies in the integration of biology, engineering, and data science. With continuous innovation in drug formulation, delivery systems, and personalized medicine, the limitations posed by first-pass metabolism are becoming increasingly surmountable, opening new horizons for efficient and patient-friendly therapies.

Conclusion:

First-pass metabolism remains a major obstacle in achieving optimal therapeutic outcomes, particularly for drugs administered orally. This presystemic metabolic process, primarily occurring in the liver and gastrointestinal tract, can significantly reduce drug bioavailability, alter pharmacokinetics, and introduce variability in patient response. Overcoming this challenge requires a comprehensive understanding of the mechanism of first-pass metabolism and the implementation of strategic approaches in drug design, formulation, and delivery.

Through alternative administration routes, prodrug development, nanocarrier systems, and enzyme inhibition techniques, it is possible to minimize or bypass first-pass metabolism, thereby enhancing drug absorption and efficacy. Additionally, formulation innovations, regulatory compliance, and safety evaluations play a vital role in ensuring that such approaches are both effective and patient-safe.

Looking forward, the emergence of personalized medicine, advanced nanotechnology, 3D printing, and AI-driven formulation design promises to further revolutionize the way drugs are developed to circumvent first-pass metabolism. These innovations will not only improve drug performance but also contribute to more individualized, effective, and accessible therapies.

In summary, addressing first-pass metabolism is not just a scientific challenge but an opportunity to enhance the quality of pharmaceutical care. Continued research, technological advancement, and interdisciplinary collaboration will be key to unlocking the full therapeutic potential of drugs affected by this metabolic barrier.

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MICROBIOME TARGETED DRUG DELIVERY SYSTEMS

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Abstract:
The human microbiome plays a pivotal role in health and disease, influencing metabolic functions, immune responses, and drug metabolism. As our understanding of the microbiome deepens, it has become a promising target for precision therapeutics. Microbiome-targeted drug delivery systems are innovative strategies designed to deliver therapeutic agents directly to or via the microbiota, maximizing efficacy while minimizing systemic side effects. These systems utilize the unique features of microbial communities such as localized enzyme activity, pH gradients, and site-specific colonization to activate or release drugs in a controlled and targeted manner. Approaches include microbiota-responsive polymers, probiotics as delivery vehicles, synbiotics, and smart nanocarriers that interact selectively with gut microbes. These delivery platforms are being explored for a wide range of conditions, including inflammatory bowel disease, metabolic disorders, infections, and cancer. This chapter explores the design principles, technological platforms, current applications, and regulatory challenges associated with microbiome-targeted drug delivery. It also highlights emerging trends and the integration of omics data and artificial intelligence to enhance microbiome-based precision medicine. Overall, microbiome-targeted systems represent a frontier in drug delivery science, promising more personalized, effective, and sustainable treatments.

Keywords: Microbiome, Probiotic Delivery System, Prebiotics and Synbiotics, Microbiota-Responsive Polymers, Precision Medicine, Smart Drug Delivery

1. Introduction:

The human microbiome encompasses trillions of microorganisms, including bacteria, fungi, viruses, and protozoa, residing primarily in the gastrointestinal tract but also found on the skin, in the oral cavity, and other mucosal surfaces. These microbial communities are not passive bystanders; rather, they actively engage in numerous physiological processes that are essential for host health, such as digestion, immune modulation, and vitamin synthesis. The gut microbiota alone comprises over 1,000 species, with the composition and function varying significantly between individuals based on factors such as diet, genetics, environment, and age. The microbial genome (microbiome) collectively encodes vastly more genes than the human genome, making it a dynamic and adaptable metabolic organ. Advances in metagenomics and next-generation sequencing have revealed the immense diversity and complexity of the microbiome and its crucial role in maintaining homeostasis and preventing disease. The microbiota can significantly influence drug pharmacokinetics and pharmacodynamics through mechanisms such as biotransformation, modulation of host enzyme activity, and alteration of gut barrier function. Certain microbial enzymes are known to activate or inactivate drugs, impacting their efficacy and safety. For example, bacterial β-glucuronidase can reverse hepatic detoxification of irinotecan, leading to gastrointestinal toxicity [1,2]. Conversely, some prodrugs are converted into their active forms only in the presence of specific microbial enzymes. The microbiome also interacts with the immune system, playing a role in immune-related diseases and influencing responses to immunotherapies and vaccines. Dysbiosis, or imbalance in microbial composition, has been linked to a wide range of diseases, including inflammatory bowel disease (IBD), obesity, type 2 diabetes, cancer, and neurodegenerative disorders. These insights have highlighted the microbiome not only as a modulator of disease processes but also as a promising target for therapeutic intervention [3].

Given the profound impact of the microbiota on health, disease, and drug metabolism, there is a compelling rationale for the development of microbiome targeted drug delivery systems. These strategies aim to either modulate the microbiota to restore balance or exploit microbial characteristics such as enzymatic activity or specific colonization sites, to enhance drug delivery and efficacy. Traditional drug delivery systems often fail to account for the influence of the gut microbiota, resulting in suboptimal therapeutic outcomes or adverse effects. Microbiome-targeted systems offer solutions by ensuring localized, controlled release in response to microbial cues such as pH, enzyme activity, or redox gradients. These systems can be tailored to release drugs at specific sites within the gastrointestinal tract or interact selectively with microbial communities to restore eubiosis. The growing field of microbiome therapeutics, which includes probiotics, prebiotics, synbiotics, postbiotics, and microbial consortia, opens new avenues for treating diseases in a more personalized and sustainable way. This chapter explores the principles, technologies, and applications behind microbiome-targeted drug delivery, highlighting its potential to revolutionize precision medicine [4,5].

2. Principles of microbiome-targeted drug delivery

Microbiome-targeted drug delivery represents a strategic approach that leverages the unique features of the gut microbiota and its surrounding environment to achieve site-specific, controlled, and efficient therapeutic outcomes. The design of such systems is guided by specific physiological and biochemical markers associated with microbial populations. Unlike conventional drug delivery, which relies largely on passive mechanisms, microbiome-targeted delivery systems utilize active microbial cues such as enzymes, pH gradients, and redox conditions to trigger drug release at desired locations. These approaches aim to improve therapeutic efficacy, minimize systemic side effects, and enhance patient compliance by ensuring that drugs are released precisely where they are most needed often in the colon or regions of microbial dysbiosis [6]. By integrating microbiological, biochemical, and pharmaceutical knowledge, these systems embody a modern, precision-based approach to therapy.

2.1 Microbial biomarkers and enzyme triggers

One of the core principles in microbiome-targeted drug delivery is the exploitation of microbial biomarkers and enzymes as site-specific release triggers. The gut microbiota produces a variety of enzymes, such as azoreductases, nitroreductases, β-glucuronidases, and glycosidases, which are either absent or present at very low levels in human tissues. These microbial enzymes can be used to cleave specific bonds in drug carriers or prodrugs, thereby initiating drug release only in regions with active microbiota, such as the colon. For instance, azoreductase-sensitive azo bonds are commonly used in colon-targeted prodrugs, where the intact compound passes through the stomach and small intestine unaltered but is cleaved by microbial enzymes in the colon to release the active drug. β-glucuronidase is another widely studied enzyme that can activate glucuronide prodrugs at microbial-rich sites. This enzyme-based activation ensures minimal degradation in the upper GI tract and selective delivery to microbial niches, reducing off-target effects and enhancing therapeutic precision [7].

2.2 pH and redox gradients in microbial niches

The gastrointestinal tract exhibits distinct pH and redox gradients along its length, many of which are influenced or maintained by microbial activity. These gradients provide valuable cues for designing responsive drug delivery systems. For example, the pH progressively increases from the acidic environment of the stomach (pH 1–3) to the mildly alkaline conditions in the colon (pH 6.5–7.5), offering a basis for pH-sensitive coatings that remain intact in the upper GI tract and dissolve only upon reaching the colon. Additionally, microbial fermentation generates a reducing environment in the colon, characterized by elevated levels of reducing agents such as glutathione and short-chain fatty acids. This enables the use of redox-sensitive polymers or disulfide bonds in drug carriers, which remain stable in oxidative conditions but break down in the reductive colon milieu. By leveraging these physiological differences, drug formulations can be engineered to release their payloads specifically in microbial-dense regions, improving local bioavailability and reducing systemic toxicity [8].

2.3 Spatial and temporal targeting within the gut

Another fundamental concept in microbiome-targeted drug delivery is spatial and temporal targeting within the gastrointestinal tract. Spatial targeting refers to directing the drug to a specific anatomical location such as the ileum, colon, or cecum where microbial populations are dense or where disease activity is localized. This is particularly important for treating conditions like inflammatory bowel disease (IBD), colorectal cancer, or microbial dysbiosis.

Temporal targeting involves controlling the timing of drug release, ensuring that the drug is released only after a predetermined lag time or upon exposure to a specific environmental cue. This can be achieved through the use of time-dependent coatings, multi-layered systems, or polymer matrices that degrade at defined rates. The integration of both spatial and temporal cues enhances the precision of drug release, reduces premature degradation, and supports synchronized therapeutic actions especially important in chronotherapy or diseases with fluctuating microbial activity. By understanding and exploiting these principles, researchers can design sophisticated microbiome-responsive systems that align with the dynamic nature of the human gut and the diverse roles of its resident microbiota [9,10].

3. Types of microbiome-targeted delivery systems

Advances in drug delivery science have enabled the development of innovative systems specifically designed to interact with, target, or modulate the microbiome. These delivery systems go beyond conventional pharmaceutical approaches by integrating the dynamic and complex nature of microbial populations into their design. Depending on the therapeutic goal whether to modulate microbial composition, exploit microbial enzymes for drug release, or selectively deliver drugs to the colon different strategies are employed. These include using live microorganisms as delivery agents, designing polymeric systems that respond to microbial stimuli, incorporating microbiota-specific release mechanisms, and engineering nanocarriers that improve stability, targeting, and bioavailability [11]. Each type of system offers unique advantages and presents specific challenges in terms of formulation, stability, and scalability.

3.1 Probiotic-based delivery vehicles

They live microorganisms that confer health benefits have emerged as not only therapeutic agents but also potential carriers for drug delivery. In microbiome-targeted strategies, genetically engineered probiotic strains such as Lactobacillus, Bifidobacterium, or Escherichia coli Nissle 1917 can be used to produce and release therapeutic proteins, peptides, or enzymes directly at the site of action. These living systems are particularly advantageous for conditions affecting the gastrointestinal tract, as they can colonize specific regions and interact with host tissues and resident microbiota. For instance, probiotics have been engineered to secrete anti-inflammatory cytokines in IBD or to deliver antigens for mucosal vaccines. Moreover, their innate ability to survive in hostile gut conditions and adhere to intestinal mucosa makes them suitable candidates for sustained delivery. However, challenges such as genetic stability, immune tolerance, and regulatory concerns regarding genetically modified organisms (GMOs) must be carefully addressed [12].

3.2 Synbiotics and prebiotic-enhanced systems

Synbiotics are formulations that combine probiotics with prebiotics non-digestible food components like inulin, fructooligosaccharides (FOS), or galactooligosaccharides (GOS) which selectively promote the growth and activity of beneficial microorganisms. In the context of drug delivery, synbiotics can be tailored to enhance microbial colonization, improve drug metabolism, and restore microbial balance in dysbiotic conditions. Prebiotics can also serve as drug carriers or matrix materials that degrade only upon fermentation by specific microbial enzymes. For example, formulations incorporating inulin or guar gum remain intact in the upper GI tract but undergo enzymatic breakdown in the colon, releasing the active drug at the target site. This approach allows for site-specific, microbiota-dependent release, particularly useful in treating colonic disorders or delivering drugs influenced by microbial fermentation. Combining prebiotics with other smart materials enhances formulation stability and therapeutic effectiveness [13,14].

3.3 Microbiota-responsive Polymers

These polymers are intelligent materials designed to undergo structural changes such as swelling, degradation, or dissolution upon interaction with microbial enzymes or metabolic byproducts. These polymers are critical for developing colon-targeted drug delivery systems that release their payload only in the presence of specific microbial signatures.

Common strategies include incorporating azo bonds, β-glucuronide linkers, or polysaccharide backbones (e.g., pectin, chitosan, xanthan gum) into the polymer matrix, which are cleaved by colonic bacteria to trigger drug release. These polymers can be used to coat tablets, capsules, or microparticles, ensuring protection of the drug during transit through the stomach and small intestine. This enzymatically-triggered degradation improves drug stability, reduces systemic exposure, and ensures maximum efficacy at the site of inflammation or microbial dysbiosis.

The design flexibility of these polymers also allows for tuning of drug release profiles based on enzyme concentration or microbial activity, offering precision in both timing and location of drug delivery [15].

3.4 Nanoparticle and liposome-based systems

Nanoparticles and liposomes are advanced drug delivery platforms that offer enhanced solubility, stability, and targeting capabilities. When designed for microbiome interaction, these carriers can be modified to respond to microbial enzymes, pH gradients, or redox conditions unique to the gut environment. For example, polymeric nanoparticles composed of pH-sensitive or enzyme-degradable materials can remain intact in the upper GI tract and release drugs only in the colon. Liposomes, which are vesicles composed of lipid bilayers, can be surface-modified with microbiota-specific ligands or designed to carry prebiotics or probiotics along with the active pharmaceutical ingredient. These systems can encapsulate hydrophobic or hydrophilic drugs, protect them from enzymatic degradation, and deliver them to microbial-rich regions in a controlled manner [16]. Nanocarriers are particularly useful in delivering poorly bioavailable or sensitive drugs, such as peptides, proteins, and nucleic acids. Additionally, they can be designed to co-deliver antibiotics and microbiome modulators, offering a multifaceted approach to infection control and microbiome restoration. The small size and surface tunability of nanoparticles also allow for mucus penetration, cellular uptake, and targeted delivery, making them highly versatile for gastrointestinal and systemic applications influenced by the microbiota [17].

4. Applications in disease treatment

Microbiome-targeted drug delivery systems have unlocked novel therapeutic opportunities by addressing diseases where the microbiota plays a central or contributory role. By precisely targeting microbial populations or using them as tools for localized drug activation, these delivery platforms enable more effective, patient-specific treatments with reduced systemic toxicity. Several chronic and complex conditions including inflammatory, neurological, metabolic, infectious, and oncologic disorders are now being explored through the lens of microbiome interactions [18]. With the ability to manipulate microbial composition, function, and signaling, microbiome-focused drug delivery offers a paradigm shift toward more personalized and responsive medicine.

4.1 Inflammatory Bowel Disease (IBD) and Colitis

IBD including Crohn's disease and ulcerative colitis, is among the most extensively studied conditions for microbiome-targeted drug delivery due to the strong link between dysbiosis and gut inflammation. IBD is characterized by immune dysregulation, epithelial barrier dysfunction, and alterations in microbial diversity. Microbiota-targeted approaches such as bacteria-responsive drug carriers, probiotic therapies, and microbiota-activated prodrugs are being developed to achieve site-specific treatment of inflamed colonic tissues. For instance, azo-bonded prodrugs like sulfasalazine are cleaved by colonic bacteria to release anti-inflammatory agents at the disease site, minimizing systemic side effects. Likewise, polymeric systems using pectin or chitosan degrade selectively in the presence of colonic enzymes, allowing localized drug delivery. Probiotic-based systems, especially those engineered to express anti-inflammatory cytokines (e.g., IL-10), show promise in modulating the local immune response. These technologies collectively offer a tailored and minimally invasive strategy for long-term IBD management [19].

4.2 Gut-brain axis and neurological disorders

Emerging evidence underscores the critical role of the gut-brain axis the bidirectional communication pathway between the gut microbiota and central nervous system in the pathogenesis of various neurological and psychiatric conditions, including depression, anxiety, autism spectrum disorders, Parkinson's disease, and Alzheimer's disease. Microbiome-targeted therapies aim to modulate this axis to alleviate disease symptoms and restore neurochemical balance. Strategies include probiotic delivery systems that influence neurotransmitter production (e.g., GABA, serotonin), and prebiotic-enhanced carriers that promote the growth of beneficial microbes linked to neuroprotection. Some systems utilize nanocarriers to deliver psychobiotics (microbes with mental health benefits) or drugs that modulate microbial metabolites affecting neural pathways. Additionally, oral formulations targeting short-chain fatty acid (SCFA) production have shown promise in reducing neuroinflammation and oxidative stress. These interventions are opening new frontiers in the treatment of neurodegenerative and mood disorders by leveraging the therapeutic potential of the gut microbiome [20].

4.3 Cancer therapy and immunomodulation

The microbiome has a profound influence on the efficacy and toxicity of cancer therapies, particularly immunotherapies and chemotherapeutics. Certain gut bacteria enhance the effectiveness of immune checkpoint inhibitors by modulating systemic immunity, while others can mediate resistance or toxicity. Microbiome-targeted delivery systems are being explored to either modulate the microbial ecosystem to favor treatment response or to deliver anti-cancer agents directly to the tumor microenvironment via microbiota-responsive triggers. For example, enzyme-sensitive nanocarriers have been developed to release cytotoxic drugs in response to bacterial enzymes overexpressed in tumor-associated microbiomes. Moreover, probiotic vectors are being engineered to express immunomodulatory molecules, directly influencing the tumor milieu. Synbiotic formulations may also support immune reconstitution following chemotherapy-induced dysbiosis. By integrating microbial modulation with targeted drug release, these systems enhance precision and reduce off-target effects in cancer therapy [21].

4.4 Antibiotic stewardship and infection control

Overuse and misuse of antibiotics have led to global concerns regarding antimicrobial resistance (AMR) and microbiota disruption, prompting the need for more selective and controlled antimicrobial delivery strategies. Microbiome-targeted systems offer a promising avenue to optimize antibiotic use by focusing on localized and responsive delivery, thereby reducing systemic exposure and preserving beneficial microbes. Innovations include bacteria-triggered antibiotic release systems, where the drug is activated only in the presence of pathogenic bacteria or their toxins. Smart polymers can be designed to release antibiotics based on pH shifts or enzymatic signals indicative of infection sites, such as in the colon or oral cavity. Additionally, bacteriophage-loaded nanocarriers and CRISPR-based antimicrobials are being explored to precisely target pathogenic strains without disturbing the native microbiota.

These approaches support more responsible antibiotic use, enhance therapeutic outcomes, and minimize the emergence of resistance aligning with the goals of global antimicrobial stewardship programs [22].

5. Technological innovations and approaches

Advances in technology are revolutionizing the design, evaluation, and application of microbiome-targeted drug delivery systems. The integration of cutting-edge tools such as high-throughput sequencing, computational biology, artificial intelligence (AI), and advanced materials science is enabling deeper insight into host–microbiome interactions and more precise formulation of drug delivery systems [23]. These innovations allow for personalized therapeutic strategies, better predictability of drug-microbiome interactions, and improved site-specific targeting. This section highlights the key technological enablers driving this emerging field forward.

5.1 Metagenomics and microbiome profiling

Metagenomics, the study of genetic material recovered directly from microbial communities, has become an essential tool in microbiome research. Through next-generation sequencing (NGS), researchers can analyze the composition, diversity, and functional capacity of the microbiota without the need for culturing individual species. This approach enables the identification of specific microbial biomarkers, enzyme profiles, and metabolic pathways that can be targeted by drug delivery systems. In the context of drug delivery, metagenomic data help inform formulation design by revealing which microbial enzymes or environmental conditions are present at target sites (e.g., colon-specific β-glucuronidase or azoreductase activity). Furthermore, personalized microbiome profiling can guide the customization of microbiome-targeted therapeutics based on an individual's microbial composition, paving the way for precision medicine. These insights are also valuable in monitoring changes in the microbiome during and after treatment, supporting real-time adjustments to therapy [24].

5.2 AI and computational modeling in microbiome-drug design

AI and ML are increasingly being applied to model complex microbiome-host-drug interactions and to predict therapeutic outcomes. These tools process vast datasets from metagenomic studies, clinical trials, and drug screening to uncover hidden patterns and correlations that inform the rational design of microbiome-targeted therapeutics. Computational tools also enable virtual screening of drug–microbiome interactions, helping researchers identify potential adverse effects or therapeutic synergies early in the development process [25,26]. By integrating systems biology with AI, researchers can design more effective and personalized microbiome-targeted delivery systems that are robust and clinically translatable.

AI algorithms can be used to:

- Predict microbial metabolic pathways affected by drugs.
- Model the impact of microbiome composition on drug absorption, distribution, metabolism, and excretion (ADME).
- Optimize nanoparticle surface properties for targeted microbial interactions.
- Simulate drug release profiles under varying microbiota conditions [27].

5.3 Controlled release and site-specific activation

A cornerstone of microbiome-targeted drug delivery is the ability to achieve controlled release and precise activation at specific sites within the gastrointestinal tract. This is accomplished through smart formulation strategies that respond to microbial stimuli, such as enzymes, pH, or redox conditions. For example, polymeric carriers with azo bonds are stable in the upper GI tract but cleaved by bacterial azoreductases in the colon to release the active drug. These technologies enable spatial and temporal control of drug delivery, ensuring that the therapeutic agent is released exactly when and where it is needed. This not only enhances therapeutic efficacy but also minimizes systemic side effects, drug degradation, and off-target interactions. Such precision is particularly critical in treating conditions like IBD, colorectal cancer, and microbial dysbiosis. Other innovations include:

- Redox-sensitive nanoparticles that disassemble in the reducing environment of the colon.
- pH-sensitive coatings that dissolve at specific GI tract pH values.
- Enzyme-responsive hydrogels that swell or degrade in the presence of microbial enzymes.
- Multi-layered capsules that delay drug release until reaching specific anatomical locations [28].

6. Future perspectives and challenges

The future of microbiome-targeted drug delivery lies in the convergence of personalized medicine, systems biology, and translational innovation. As research continues to unveil the complexity and individuality of the human microbiome, there is growing potential to develop personalized microbiome-based therapies tailored to an individual's unique microbial profile, disease state, and genetic background. By integrating multi-omics approaches including genomics, metagenomics, metabolomics, and proteomics with systems biology frameworks, researchers can create comprehensive models that capture host-microbiota-drug interactions in unprecedented detail. This integration enables the identification of new microbial biomarkers, druggable pathways, and predictive signatures for treatment response. Despite these advances, significant challenges remain in translating microbiome-based systems to clinical practice, including standardization of methods, inter-individual variability in microbial composition, and regulatory hurdles surrounding the use of live biotherapeutics and complex biologically responsive systems [29]. Clinical trials designed to evaluate microbiome-targeted formulations must adopt robust, reproducible protocols and account for dynamic microbiota changes over time. Moreover, ensuring scalability, manufacturing consistency, and safety will be key to advancing these systems from bench to bedside. Overall, the future of microbiome-targeted drug delivery holds great promise in reshaping therapeutic paradigms, offering more effective, sustainable, and patient-centric solutions for a wide range of diseases.

Conclusion:

The exploration of microbiome-targeted drug delivery systems marks a significant advancement in the field of pharmaceutics, offering a novel and personalized approach to disease treatment and prevention. By harnessing the unique biochemical and physiological characteristics of the human microbiota, such as enzymatic activity, pH gradients, and localized metabolic functions, these systems enable precise, site-specific, and responsive therapeutic delivery. Innovations including probiotic-based vehicles, microbiota-sensitive polymers, synbiotics, and smart nanocarriers are transforming the way we approach complex diseases like inflammatory bowel disease, cancer, neurological disorders, and antibiotic-resistant infections. Supported by emerging tools in metagenomics, artificial intelligence, and multi-omics integration, microbiome-based drug delivery is not only enhancing drug efficacy and safety but also paving the way for more ethical and sustainable alternatives to conventional therapies. Despite the promise, challenges remain in terms of clinical translation, regulatory frameworks, and inter-individual microbiome variability. However, with continued interdisciplinary research, technological refinement, and patient-centric design, microbiome-targeted systems are poised to become a cornerstone of future pharmaceutical development, aligning modern therapeutics with the intricate biology of the human host.

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IN-VITRO AND EX-VIVO MODELS AS ALTERNATIVES TO ANIMAL TESTING

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Abstract:
The growing ethical concerns, regulatory constraints, and scientific limitations of animal testing have accelerated the development and adoption of alternative models in pharmaceutical and biomedical research. Among these, in-vitro and ex-vivo models have emerged as powerful and reliable tools for evaluating drug efficacy, toxicity, pharmacokinetics, and disease mechanisms, without the ethical complications associated with animal experimentation. In-vitro models, including 2D and 3D cell cultures, organoids, and tissue-engineered constructs, offer controlled environments to study cellular responses and molecular interactions. Ex-vivo models, derived from freshly isolated organs or tissues, provide physiologically relevant systems that preserve native architecture and function, making them highly suitable for studying organ-specific pharmacodynamics and toxicology. These models not only reduce the need for animal use but also enable high-throughput screening, improved reproducibility, and human-relevant data generation. Technological advancements in microfluidics, organ-on-chip platforms, and imaging techniques have further enhanced the accuracy and complexity of these systems. This chapter explores the types, advantages, limitations, and current applications of in-vitro and ex-vivo models in drug development, alongside regulatory perspectives and future directions. By highlighting these innovations, the chapter underscores the potential of alternative testing methods to replace or significantly reduce animal testing, promoting more ethical and predictive pharmaceutical research.

Keywords: In-vitro Models, Organ-On-Chip, 3D Cell Culture, Microfluidics, Personalised Medicine

1. Introduction:

Animal testing has long been a cornerstone of biomedical and pharmaceutical research, providing essential insights into the safety, efficacy, and biological interactions of drug candidates. However, growing ethical concerns, scientific limitations, and regulatory pressures have fueled the search for alternative methods. The 3Rs principle as Replacement, Reduction, and Refinement, introduced by Russell and Burch in 1959, remains a foundational concept encouraging the scientific community to seek alternatives that either replace animals, reduce the number used, or refine procedures to minimize suffering [1]. Despite their historical significance, animal models often fail to predict human responses accurately due to interspecies differences in physiology, metabolism, and genetic expression. Such discrepancies can lead to false positives or negatives in drug development, contributing to high attrition rates during clinical trials. Moreover, the financial and time costs associated with animal experiments are substantial, prompting the need for more cost-effective and efficient platforms. In this context, in-vitro (cell/tissue culture-based) and ex-vivo (isolated tissue/organ-based) models have emerged as promising alternatives. These systems not only provide human-relevant data but also enable high-throughput screening, better control over experimental variables, and reduced ethical concerns. Their adoption can accelerate early-stage drug discovery while improving the reproducibility and translational value of preclinical studies [2].

The ethical debate surrounding animal testing has intensified over the past few decades, with advocacy groups, regulatory bodies, and the public demanding more humane approaches to scientific research. Animals used in testing may endure pain, stress, or long-term harm, leading to increased scrutiny under institutional and international ethical review boards. In response, governments and regulatory agencies worldwide have strengthened laws and policies to promote alternative methods. The European Union, for instance, has banned animal testing for cosmetics and enforces strict regulations for animal use in pharmaceuticals through REACH and Directive 2010/63/EU [3]. From a scientific perspective, in-vitro and ex-vivo models offer several advantages over traditional animal testing. In-vitro systems such as 3D cultures, organoids, and microfluidic chips allow researchers to replicate human tissue architecture and function in a controlled environment, thus providing more relevant data. Ex-vivo models, like precision-cut tissue slices or perfused organs, retain the native structure and physiological characteristics of the tissue, making them ideal for studying organ-specific drug responses and toxicity [4]. Regulatory agencies such as the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and Organisation for Economic Co-operation and Development (OECD) are increasingly recognizing the value of alternative testing models. Several validated in-vitro assays are now part of regulatory guidelines for toxicity and safety evaluation, and new frameworks continue to evolve to accommodate emerging technologies. Together, ethical imperatives, scientific advancements, and supportive regulatory landscapes are converging to redefine the future of preclinical testing shifting the focus from animal-based methods to more predictive, humane, and efficient alternatives [5,6].

2. Overview of In-vitro models

In-vitro models serve as foundational tools in pharmaceutical and biomedical research, providing controlled, reproducible platforms for studying cellular behavior, drug responses, and disease mechanisms. These models are developed by cultivating cells outside their natural environment under laboratory conditions, allowing researchers to simulate physiological or pathological scenarios with high precision. Over time, in-vitro techniques have evolved from simple monolayer (2D) cultures to more complex and physiologically relevant three-dimensional (3D) systems such as organoids, spheroids, and microfluidic platforms. Their relevance has been amplified by their ability to reduce reliance on animal models while offering cost-effective, ethical, and scalable alternatives that often yield human-specific data [7].

2.1 2D and 3D cell cultures

Two-dimensional (2D) cell cultures involve growing cells in a flat monolayer, usually on plastic or glass surfaces. This traditional technique has been widely used for decades due to its simplicity, low cost, and ease of handling. While 2D models are suitable for studying basic cellular processes such as proliferation, cytotoxicity, and gene expression, they often fail to replicate the complex cell-cell and cell-matrix interactions found in living tissues [8].

To address these limitations, three-dimensional (3D) cell cultures have been developed, where cells are grown within a scaffold or matrix that mimics the extracellular environment. These models support more realistic cellular architecture and behavior, allowing for better modeling of in-vivo tissue function, drug penetration, and resistance mechanisms. Common methods for 3D culture include hydrogel-based scaffolds, hanging drop techniques, and matrix-free spheroid formation. 3D cultures are especially useful in cancer research, tissue engineering, and regenerative medicine [9].

2.2 Organoids and Spheroids

Organoids are self-organizing 3D structures derived from stem cells or progenitor cells that replicate key features of their organ of origin. They can mimic organ-specific architecture, function, and even disease phenotypes. Organoids have been successfully developed from tissues such as the intestine, liver, pancreas, brain, and kidney, making them powerful models for drug screening, toxicology testing, and studying developmental biology and genetic diseases [10].

Spheroids, on the other hand, are simpler aggregates of cells that form spherical masses through spontaneous cell-cell interactions. Tumor spheroids, in particular, are widely used in oncology research to study cancer cell behavior, hypoxia, and drug resistance in a 3D context. While organoids offer more structural and functional complexity, spheroids are easier to produce and standardize for high-throughput applications. Both organoids and spheroids bridge the gap between traditional 2D cultures and complex animal models by providing human-relevant, scalable systems for investigating tissue-specific drug responses and disease mechanisms [11].

2.3 Human Cell-Based Assays

These assays utilize primary cells, immortalized cell lines, or induced pluripotent stem cells (iPSCs) to investigate pharmacological, toxicological, and physiological endpoints. These assays are increasingly favored over animal-derived cell models due to their ability to provide more predictive data regarding human responses. Primary human cells, isolated directly from donor tissues, retain many of their native characteristics but are limited in availability and lifespan. Immortalized cell lines, such as HeLa or Caco-2, offer reproducibility and ease of culture but may lack certain physiological features. iPSC-derived cells represent a cutting-edge alternative, as they can be reprogrammed from adult cells and differentiated into various cell types, enabling disease modeling and personalized medicine [12]. Human cell-based assays are widely applied in evaluating cytotoxicity, metabolic activity, receptor binding, inflammation, and genotoxicity. They also support the development of personalized therapies by enabling testing on patient-derived cells, thus aligning with the goals of precision medicine.

2.4 High-Throughput Screening Systems (HTS)

HTS is a powerful technique that allows researchers to rapidly assess thousands of compounds for biological activity using automated in-vitro systems. HTS integrates robotics, data processing software, and miniaturized assays to evaluate multiple endpoints such as viability, enzyme activity, or receptor binding in a time- and cost-efficient manner. HTS platforms commonly use microplate formats (96-, 384-, or 1536-well plates) combined with fluorescence, luminescence, or colorimetric readouts. These systems are especially valuable in early-stage drug discovery, where they help identify lead compounds, assess toxicity profiles, and explore mechanisms of action. Recent advancements have enabled high-content screening (HCS), which combines HTS with automated imaging and multiparametric analysis. This allows for detailed phenotypic characterization of cells in response to compounds, enhancing the depth of data generated. When integrated with 3D cultures and human-derived cells, HTS systems become even more predictive of in-vivo outcomes, helping to further reduce reliance on animal models [13].

3. Overview of Ex-vivo Models

Ex-vivo models are biological systems derived from living tissues or organs that are maintained and studied outside the organism under controlled conditions. These models offer a valuable bridge between in-vitro systems and in-vivo animal testing, preserving the complex architecture, cell–cell interactions, and physiological responses of native tissues. Unlike in-vitro models, which often use isolated or cultured cells, ex-vivo systems retain the structural and functional integrity of whole tissues or organs, allowing for more physiologically relevant insights into drug absorption, metabolism, toxicity, and disease mechanisms. Their application is especially valuable in pharmacokinetic and pharmacodynamic studies, organ-specific toxicity evaluation, and validation of drug targets under near-natural conditions [14,15].

Tissue and Organ Explants

Tissue and organ explants are small sections of freshly isolated tissues or intact organ segments obtained from human donors or animal models. These are typically maintained in specialized culture media under sterile conditions to preserve viability and function for short-term experimental use. Explants can be derived from various organs such as the liver, kidney, skin, brain, or intestine, and are often used to study localized responses to drugs, pathogens, or toxicants. One key advantage of explants is the preservation of the original microenvironment, including the extracellular matrix, vascular architecture, and multiple interacting cell types, which collectively influence tissue function. This makes them ideal for assessing tissue-specific effects such as inflammatory responses, enzyme activity, or metabolic changes. For instance, human skin explants are used for dermatological testing and transdermal drug delivery studies, while intestinal explants are valuable for permeability and absorption assessments [16].

3.1 Precision-Cut Tissue Slices (PCTS)

PCTS represent a refined ex-vivo technique involving the generation of uniformly thin slices (typically 100–300 µm) from freshly harvested organs using specialized equipment such as a vibratome or microtome. These slices maintain cellular heterogeneity and spatial organization while allowing for uniform exposure to experimental compounds. PCTS are widely used in liver, lung, kidney, and brain studies for toxicological screening, metabolism assays, and mechanistic investigations. Precision-cut liver slices (PCLS), for example, are extensively utilized for evaluating hepatotoxicity, drug metabolism (via cytochrome P450 enzymes), and inflammation. Similarly, precision-cut lung slices (PCLS) allow researchers to study bronchoconstriction, airway inflammation, and pulmonary toxicology in a structurally intact lung matrix. The ability to prepare multiple slices from a single organ sample allows for parallel experiments with minimal biological variability, making PCTS suitable for high-throughput and reproducible testing. Their use also supports the 3Rs principle by reducing the number of animals needed for experimentation [17].

3.2 Isolated Perfused Organ Systems (IPOS)

IPOS are ex-vivo setups where an intact organ, such as a liver, kidney, heart, or lung, is maintained viable by continuously supplying it with oxygenated nutrient-rich perfusate under physiological pressure and temperature. These systems simulate in-vivo conditions more closely than static tissue cultures, enabling dynamic studies of organ function, drug metabolism, and real-time physiological responses. The isolated perfused liver (IPL) is commonly used for studying hepatic clearance, bile secretion, and metabolic pathways of drugs. Similarly, isolated perfused lungs (IP Lung) facilitate research on pulmonary absorption, gas exchange, and respiratory toxicology. These systems offer critical insights into pharmacokinetics and organ-specific toxicity without systemic interferences from other tissues or organs [18]. One major benefit of IPOS is the ability to precisely control experimental variables such as perfusate composition, flow rate, and oxygen levels, allowing detailed analysis of time-dependent responses. Advanced setups can include sensors and imaging systems to monitor physiological parameters in real time. Although technically demanding and limited by tissue viability over time, isolated perfused organ models remain invaluable for bridging in-vitro findings with in-vivo relevance, and they continue to play a critical role in validating new drug candidates while minimizing animal use [19].

4. Advanced technologies supporting In-vitro and Ex-vivo systems

In-vitro and ex-vivo models have undergone a dramatic transformation in recent years, owing to the integration of advanced technologies that enhance physiological relevance, scalability, and data quality. Cutting-edge platforms such as organ-on-chip, 3D bioprinting, and real-time imaging systems have significantly improved the functional complexity and analytical capabilities of these models. These innovations not only replicate native tissue architecture and microenvironments more faithfully but also enable dynamic monitoring of biological responses at the cellular and molecular levels. As a result, they play a pivotal role in improving the translational value of preclinical research and reducing reliance on animal models [20].

4.1 Organ-on-Chip and Microfluidics

Organ-on-chip technology, a subset of microfluidics, involves the use of small, engineered devices that simulate the structural and functional units of human organs. These chips are typically composed of transparent polymers containing microchannels lined with living human cells from specific tissues. By mimicking physical and chemical cues such as fluid shear stress, mechanical strain, and biochemical gradients, organ-on-chip devices provide a more accurate representation of the in-vivo microenvironment than traditional static cultures [21]. Examples include lung-on-chip for modeling air–blood barrier functions, liver-on-chip for drug metabolism and hepatotoxicity studies, and gut-on-chip to investigate nutrient absorption and microbiome interactions. These platforms allow researchers to observe real-time responses to drugs or toxins and are compatible with high-resolution imaging and biosensing tools. Furthermore, multi-organ chips, or "body-on-chip" systems, are being developed to simulate interconnected organ interactions, providing holistic insights into systemic pharmacokinetics and toxicity. Organ-on-chip models are increasingly being recognized by regulatory agencies as valid preclinical tools, and their potential for personalized medicine is vast, especially when combined with patient-derived cells [22].

4.2 3D Bioprinting

It is a revolutionary technology that enables the fabrication of complex, tissue-like structures by precisely depositing bioinks composed of living cells, biomaterials, and growth factors layer by layer. This approach allows for the creation of physiologically relevant 3D tissue constructs that replicate native tissue architecture, heterogeneity, and function with remarkable precision. In pharmaceutics, 3D bioprinting is being applied to create engineered tissues such as liver, skin, kidney, and vascular structures for use in drug testing, toxicity studies, and disease modeling. For example, bioprinted liver tissues can assess hepatotoxicity, while printed skin models are useful for dermatological and transdermal drug evaluations. Unlike traditional scaffold-based models, bioprinted tissues offer customizable geometries and cell arrangements, enabling better control over microenvironmental conditions. Additionally, 3D bioprinting supports personalized medicine by allowing the generation of patient-specific tissue models using cells derived from individuals, making it a powerful tool for individualized drug screening and therapy optimization [23].

4.3 Imaging and Biosensing Technologies

Advanced imaging and biosensing technologies have become indispensable for monitoring and analyzing in-vitro and ex-vivo models in real time. These technologies allow researchers to visualize structural changes, measure dynamic biological processes, and quantify functional endpoints with high sensitivity and specificity. Live-cell imaging using fluorescence, confocal, and two-photon microscopy enables the observation of cellular responses such as proliferation, apoptosis, and migration within 3D cultures and organoids. Label-free techniques like phase contrast and holographic imaging offer non-invasive monitoring of tissue health and morphology. Biosensors, including electrochemical, optical, and piezoelectric devices, are used to detect biomarkers, metabolites, pH changes, oxygen levels, and enzymatic activity within culture systems. Integrated biosensor chips embedded in organ-on-chip platforms allow continuous, real-time monitoring of tissue viability, drug response, and toxicity, significantly enhancing the temporal resolution of data collection. The convergence of imaging and biosensing with AI-powered data analysis tools further boosts the ability to extract actionable insights, supporting high-content screening and predictive modeling in pharmaceutical research [24].

5. Applications in Drug Discovery and Development

The use of in-vitro and ex-vivo models in pharmaceutical research has expanded rapidly due to their ability to simulate human physiology with greater precision, reproducibility, and ethical compliance than traditional animal models. These systems are now integral to various stages of drug discovery and development, including early compound screening, mechanism-of-action studies, safety profiling, pharmacokinetics, and target validation. The integration of advanced platforms such as organoids, organ-on-chip devices, and high-throughput screening systems has further enhanced the relevance of these models [25]. As regulatory agencies and the pharmaceutical industry move toward human-centric models, in-vitro and ex-vivo systems are becoming essential tools to streamline development pipelines, reduce failure rates, and improve translational outcomes.

5.1 Toxicity and Safety Testing

One of the most critical applications of in-vitro and ex-vivo models is in toxicity and safety evaluation, a key requirement in preclinical drug development. Conventional animal models often fail to accurately predict human-specific toxicities due to interspecies differences in metabolism and immune response. In contrast, human cell-based in-vitro systems and tissue explants offer more relevant platforms for assessing cytotoxicity, genotoxicity, hepatotoxicity, nephrotoxicity, cardiotoxicity, and neurotoxicity. For instance, hepatocyte cultures and PCLS are widely used to assess liver injury and metabolic enzyme induction. Similarly, cardiac microtissues and iPSC-derived cardiomyocytes are utilized for evaluating QT prolongation and other cardiac risks. Ex-vivo systems such as isolated perfused organs provide real-time insights into tissue-specific effects under near-physiological conditions. These models support both acute and chronic toxicity testing and allow for mechanistic investigations of adverse drug reactions, thereby improving early risk identification and decision-making in development programs [26,27].

5.2 Pharmacokinetics and ADME Studies

Understanding the absorption, distribution, metabolism, and excretion (ADME) properties of drug candidates is fundamental to ensuring therapeutic efficacy and safety. In-vitro and ex-vivo platforms play a vital role in generating this pharmacokinetic data early in the development process, often before in-vivo testing is initiated. Caco-2 cell monolayers are commonly used as an in-vitro model of the intestinal barrier to predict oral drug absorption. Hepatocyte cultures, microsomes, and recombinant enzyme systems are employed to study drug metabolism, enzyme induction, and drug–drug interactions. Human kidney cell models and tissue slices aid in the evaluation of renal clearance and nephrotoxicity [28,29]. Ex-vivo systems such as isolated perfused organs, particularly the liver and kidney, enable dynamic studies of drug clearance, biliary excretion, and metabolite profiling under controlled conditions. These models offer insight into first-pass metabolism and tissue-specific drug accumulation, helping to predict human pharmacokinetics more accurately than traditional animal models. Additionally, the incorporation of organ-on-chip platforms provides a fluidically connected, multi-tissue approach to simulate systemic drug distribution and interactions [30].

5.3 Disease Modeling and Target Validation

In-vitro and ex-vivo models are increasingly used to replicate disease-specific conditions for the purposes of mechanistic study, target identification, and validation of drug efficacy. Advanced systems such as patient-derived organoids, 3D tumor spheroids, and genetically engineered cell lines can mimic the pathophysiological features of diseases including cancer, neurodegenerative disorders, inflammatory diseases, and viral infections. For example, tumor organoids derived from patient biopsies retain the heterogeneity and microenvironmental context of the original tumor, allowing for personalized oncology drug testing. In neurological research, brain organoids and neuron-glia co-cultures are used to study disorders like Alzheimer's, Parkinson's, and epilepsy [31]. These systems allow for high-content screening of therapeutic candidates and enable exploration of disease progression and response at the molecular level. Ex-vivo tissues from diseased human organs can also be used to study drug effects in a native pathological context. For instance, lung explants from COPD or asthma patients serve as valuable models for evaluating anti-inflammatory agents or bronchodilators. These disease models are especially critical for validating novel therapeutic targets, optimizing drug dosing regimens, and predicting patient-specific responses [32,33].

6. Advantages and limitations of In-vitro and Ex-vivo models

In-vitro and ex-vivo models have become indispensable in modern pharmaceutical research and development due to their ability to offer human-relevant insights with greater ethical acceptability. These systems provide advanced platforms for evaluating drug efficacy, toxicity, and mechanisms of action under controlled conditions. However, despite their advantages, they also have limitations in terms of complexity, scalability, and regulatory acceptance [34, 35]. Understanding both the benefits and constraints is essential for selecting the most appropriate model system for specific research objectives and for interpreting data in a translational context in Table 1.

Table 1: Comparative overview of In-vitro, Ex-vivo, and animal models

Criteria	In-vitro models	Ex-vivo models	Animal models
Physiological Relevance	Moderate (improved in 3D/organoid systems)	High (native tissue architecture reserved)	High (whole-body systemic responses)
Species Specificity	Human-specific (if human cells are used)	Human or animal-derived (depending on source)	Non-human (species differences may limit relevance)
Ethical Concerns	Minimal	Minimal to moderate	High (animal welfare issues)
Complexity	Low to moderate	Moderate to high	High
Duration of Experiment	Suitable for short to medium term	Short-term only (limited tissue viability)	Short- and long-term possible
Cost and Throughput	Low cost, high-throughput capability	Moderate cost, limited scalability	High cost, lower throughput
Reproducibility	High (standardized cell lines), may vary with complexity	Moderate (depends on donor variability and tissue prep)	Variable (biological variability among animals)
Systemic Interaction	Absent or limited	Absent	Present (whole-body interactions)
Regulatory Acceptance	Increasing (for toxicity and screening)	Limited but growing	Well-established (still gold standard for many tests)

Conclusion:

The growing adoption of in-vitro and ex-vivo models mark a transformative shift in pharmaceutical research, driven by the need for more ethical, human-relevant, and predictive testing strategies. Over the past decade, remarkable progress has been made in developing sophisticated in-vitro systems such as 3D cell cultures, organoids, and organ-on-chip technologies, as well as advanced ex-vivo approaches that preserve native tissue architecture and function. These models not only minimize ethical concerns associated with animal testing but also offer enhanced experimental control, reproducibility, and the ability to generate human-specific data. While challenges related to standardization, scalability, and systemic integration remain, continuous technological innovations and interdisciplinary collaborations are steadily addressing these limitations. Regulatory agencies are increasingly recognizing the validity of alternative testing methods, signaling a broader shift toward their acceptance in drug development pipelines. Looking ahead, the integration of patient-derived models, artificial intelligence, and high-throughput screening technologies is expected to further refine these platforms, paving the way for personalized, data-driven, and mechanistically informed drug discovery. Ultimately, in-vitro and ex-vivo models represent a crucial step toward an ethical and scientifically robust future in pharmaceutics one that prioritizes both human safety and compassionate research practices.

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SMART CONTACT LENSES FOR SUSTAINED OCULAR DRUG RELEASE

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Abstract:

Smart contact lenses represent a rapidly evolving platform in ocular drug delivery, offering a promising solution to the long-standing challenges of poor drug bioavailability and patient non-compliance associated with traditional eye drop formulations. These advanced lenses are engineered not only to correct vision but also to function as sustained-release drug delivery systems that enhance therapeutic efficacy while minimizing side effects. Incorporating technologies such as nanocomposites, hydrogels, micro-reservoirs, stimuli-responsive materials, and electronic sensors, smart contact lenses can provide controlled, prolonged drug release directly to the ocular surface. This targeted delivery circumvents rapid precorneal clearance and improves drug retention in ocular tissues. Recent innovations also include integration with biosensors for real-time monitoring of intraocular pressure, glucose levels, and tear composition, enabling personalized treatment strategies for chronic ocular conditions such as glaucoma, dry eye disease, and diabetic retinopathy. This chapter explores the fundamental design principles, drug loading and release mechanisms, current applications, regulatory considerations, and future directions of smart contact lenses as next-generation ocular drug delivery systems.

Keywords: Smart Contact Lenses, Ocular Drug Delivery, Sustained Release, Hydrogel-Based Lenses, Glaucoma Treatment, Nanotechnology in Ophthalmology, Tear Film Retention, Stimuli-Responsive Lenses

1. Introduction:

The delivery of therapeutic agents to ocular tissues poses a formidable challenge in pharmaceutical science due to the eye's complex anatomy and dynamic physiological barriers. Conventional methods, particularly topical eye drops, remain the most widely used form of ocular drug delivery. However, they are inherently limited by poor bioavailability, rapid tear turnover, blinking, nasolacrimal drainage, and limited corneal permeability. These factors result in less than 5% of the administered dose reaching intraocular tissues, necessitating frequent dosing that compromises patient compliance and increases the risk of side effects. Given the growing prevalence of chronic ocular diseases such as glaucoma, dry eye syndrome, and diabetic retinopathy, there is a compelling need for innovative strategies that can provide sustained, controlled, and patient-friendly drug delivery to ocular targets.

Smart contact lenses have emerged as a next-generation platform that addresses many of the limitations associated with traditional ocular drug delivery systems. Unlike conventional lenses, which primarily serve corrective optical functions, smart lenses are designed to integrate drug delivery mechanisms, biosensors, and electronic components within a single, biocompatible platform. This dual-functionality allows for vision correction and localized, sustained therapeutic release directly to the ocular surface, thereby enhancing therapeutic efficacy while reducing systemic exposure and patient burden. Furthermore, smart lenses can be engineered to respond to external or internal stimuli—such as temperature, pH, enzyme activity, or electromagnetic signals—to achieve precise, on-demand drug release (1).

1.1 Limitations of Conventional Ocular Drug Delivery

Topical administration in the form of eye drops is plagued by low bioavailability and transient drug residence on the ocular surface. The protective mechanisms of the eye, including blinking, tear secretion, and nasolacrimal drainage, are designed to rapidly eliminate foreign substances, resulting in most of the instilled drug being lost within minutes. In addition, the corneal epithelium presents a formidable lipophilic barrier that restricts the passage of hydrophilic drugs, while the stroma impedes the diffusion of lipophilic agents. As a result, frequent instillations are required to maintain therapeutic drug concentrations, often leading to poor adherence, particularly among elderly or pediatric patients with chronic diseases (2).

Other routes of administration—such as systemic delivery, subconjunctival injection, and intravitreal injection—are associated with their own limitations, including invasive procedures, systemic toxicity, and risks of infection or retinal detachment. These shortcomings highlight the urgent need for non-invasive systems capable of delivering therapeutics in a sustained and controlled manner, directly to the ocular surface or internal structures, without compromising patient comfort or safety.

1.2 Emergence of Smart Contact Lenses

The concept of using contact lenses for ocular drug delivery is not new; however, early iterations were largely passive systems that relied on soaking lenses in drug solutions. These methods suffered from burst release, short duration of action, and inconsistent dosing. Recent advances in materials science, nanotechnology, and bioelectronics have transformed the landscape, enabling the development of smart contact lenses capable of prolonged drug retention, controlled release, and real-time monitoring of ocular parameters.

Smart lenses can be fabricated from hydrogel-based polymers such as silicone hydrogel and poly(2-hydroxyethyl methacrylate) (pHEMA), which offer excellent biocompatibility, oxygen permeability, and mechanical stability. Drug molecules can be incorporated into these lenses using diverse strategies including molecular imprinting, nanoparticle embedding, and micro-reservoir encapsulation. Additionally, smart lenses can be functionalized with stimuli-responsive materials that modulate drug release in response to physiological cues such as tear composition or intraocular pressure (3).

One of the most promising aspects of smart contact lenses lies in their ability to integrate electronic components such as biosensors, microprocessors, wireless communication modules, and microbatteries. These technologies allow lenses not only to release drugs in a programmed or responsive fashion but also to continuously monitor ocular conditions such as glucose levels in tears or fluctuations in intraocular pressure. Such feedback-responsive systems open the door to personalized ocular therapy, where drug release can be tailored in real-time based on patient-specific needs.

In summary, the emergence of smart contact lenses represents a paradigm shift in ocular drug delivery, combining therapeutic functionality with diagnostic capability in a single, wearable platform. These innovations promise to significantly enhance treatment outcomes, particularly for chronic and progressive ocular diseases where conventional delivery systems fall short.

2. Design Principles of Smart Contact Lenses

The successful development of smart contact lenses for sustained ocular drug delivery hinges on a careful balance between material science, mechanical functionality, biocompatibility, and optical clarity. These lenses must perform the primary function of vision correction while simultaneously supporting drug encapsulation, sustained release, and, in some cases, sensor integration or electronic circuitry. Each of these requirements introduces complex design considerations, necessitating a multidisciplinary approach that draws from polymer chemistry, nanotechnology, bioengineering, and ophthalmology. This section outlines the essential parameters and functional criteria that govern the design of smart contact lenses.

2.1 Material Requirements and Biocompatibility

The base material of smart contact lenses must fulfill several fundamental criteria: high oxygen permeability to support corneal health, adequate water content for comfort and hydration, mechanical flexibility for ease of wear, and the ability to accommodate drug loading without compromising transparency or structural integrity. Traditional contact lenses are fabricated from hydrogel-based polymers such as poly(2-hydroxyethyl methacrylate) (pHEMA), silicone hydrogels, or polyvinyl alcohol (PVA). Among these, silicone hydrogels have gained prominence for smart lens applications due to their superior oxygen permeability and robust mechanical properties.

Biocompatibility is paramount in ocular applications, as the lens interfaces directly with the delicate tissues of the cornea and conjunctiva. The material must not induce toxicity, inflammation, or allergic reactions. Additionally, the lens surface must resist protein and lipid deposition from the tear film, which could impede drug release or sensor function over time. Surface modifications, such as plasma treatment or incorporation of antifouling polymers like polyethylene glycol (PEG), are often employed to enhance biocompatibility and reduce biofouling.

From a pharmaceutical standpoint, the material must possess appropriate swelling behavior and porosity to facilitate controlled diffusion of therapeutic agents. Hydrogels offer tunable mesh sizes and swelling characteristics, allowing modulation of drug release kinetics by adjusting cross-link density, polymer composition, and degree of hydrophilicity. Furthermore, smart lenses must maintain their structural integrity and performance under physiological conditions—temperature, pH, tear osmolarity—throughout the intended duration of wear.

For lenses incorporating nanoparticles or micro-reservoirs, the polymer matrix must also prevent premature drug leakage, degradation of encapsulated agents, or interference with embedded electronic components. Careful selection and engineering of materials are thus essential to ensure multifunctionality without compromising ocular safety or patient comfort (4).

2.2 Optical and Mechanical Considerations

In addition to material selection, the optical and mechanical properties of smart contact lenses must be rigorously optimized to meet the dual demands of vision correction and advanced functionality. Optical clarity is non-negotiable for contact lens users; thus, any incorporated drug delivery or electronic components must be either transparent, confined to the lens periphery, or minimally scattering. Nanoparticles embedded within the lens matrix must be of sub-wavelength dimensions (<200 nm) to avoid light scattering and haze. For sensor-embedded designs, transparent conductors such as graphene, indium tin oxide (ITO), or silver nanowires are commonly employed to ensure electrical conductivity without sacrificing visual acuity (5).

The refractive index of the lens must be tailored to match that of the cornea to provide effective correction of myopia, hyperopia, or astigmatism. This requirement imposes additional constraints on the selection and modification of lens materials and embedded components. Any structural asymmetry or heterogeneity in the lens matrix, especially near the optical center, can lead to vision distortion or discomfort.

Mechanically, the lens must be soft and flexible enough to conform to the corneal curvature without causing irritation or compromising tear exchange. However, it must also possess sufficient tensile strength and elasticity to withstand handling, blinking, and prolonged wear. For lenses incorporating electronics or drug reservoirs, mechanical robustness is especially important to avoid component failure or deformation under normal usage.

Furthermore, the dynamic movement of the lens during blinking, tear flow, and ocular rotation necessitates a stable drug release profile that is unaffected by mechanical stress. In some designs, microfabricated channels or stimuli-responsive hydrogels are integrated to maintain consistent drug delivery despite changes in tear film dynamics or lens position (6).

The integration of energy sources, such as micro-batteries or wireless power receivers, introduces further mechanical complexity. These components must be thin, flexible, and lightweight to avoid altering the lens curvature or increasing wearer discomfort. Innovations such as stretchable electronics and wireless energy harvesting technologies are increasingly being explored to address these challenges.

3. Mechanisms of Drug Loading and Release

The efficiency and therapeutic potential of smart contact lenses as drug delivery systems are critically dependent on their ability to load, retain, and release pharmaceutical agents in a sustained and controlled manner. Several advanced techniques have been developed to incorporate drugs into the lens matrix or its associated compartments, each offering unique advantages in terms of drug release kinetics, capacity, and adaptability to various classes of molecules. The ideal method achieves high drug loading while preserving the optical clarity, biocompatibility, and mechanical integrity of the lens. In this section, we describe the major mechanisms employed in smart contact lenses for drug incorporation and release, with emphasis on sustained and responsive delivery strategies.

3.1 Soaking, Molecular Imprinting, and Incorporation Methods

The most straightforward approach to drug loading involves soaking preformed contact lenses in a drug solution, allowing the drug to diffuse into the polymer matrix. This technique is compatible with many hydrophilic drugs and is widely used due to its simplicity and minimal processing. However, soaking often results in a burst release effect, where a significant portion of the drug is rapidly eluted upon application, followed by a sharp decline in therapeutic levels. The poor retention and lack of sustained release have limited the clinical translation of soaking as a standalone strategy (7).

To address these limitations, molecular imprinting has been introduced as a method to create drug-specific cavities within the polymer matrix. During lens synthesis, the drug (template molecule) is mixed with the monomers and crosslinkers; after polymerization, the drug is removed, leaving behind molecular-scale recognition sites. These sites exhibit a high affinity for the original molecule, enabling prolonged retention and more controlled release. Molecularly imprinted lenses show improved drug binding specificity and release duration compared to non-imprinted counterparts, particularly for small-molecule therapeutics.

Other incorporation techniques involve embedding drug-loaded carriers, such as microparticles or dendrimers, directly into the hydrogel network. These hybrid systems allow for modulation of drug release profiles by varying particle composition, size, or degradation rate. For example, cyclodextrin inclusion complexes embedded in the lens matrix can encapsulate hydrophobic drugs and release them gradually over days to weeks, depending on environmental factors.

3.2 Nanoparticle-Embedded and Reservoir-Based Designs

To overcome the burst release associated with soaking and to enhance drug loading capacity, nanoparticle-embedded systems have emerged as a sophisticated approach. In these designs, biodegradable nanoparticles—typically composed of polymers like poly(lactic-co-glycolic acid) (PLGA), chitosan, or lipid-based materials—are loaded with drugs and then uniformly dispersed within the lens matrix. The nanoparticles act as drug depots, slowly releasing the encapsulated payload as they degrade or as the drug diffuses through the polymer shell. This system allows for better control over release kinetics, extends the duration of drug availability, and minimizes the risk of ocular irritation.

Reservoir-based lenses represent another innovation in smart lens technology. These lenses contain micro-reservoirs or multi-layered compartments within their structure that physically store a concentrated drug solution or gel. These reservoirs are surrounded by diffusion barriers or membranes that regulate the rate at which the drug is released into the tear film. The design can be tailored to accommodate different drugs, release durations, and dosing frequencies, offering flexibility and precision. In some configurations, the reservoirs can be refilled or reactivated via external stimuli such as light or heat (8).

Importantly, these compartmentalized systems allow for spatial segregation of the drug from the optical zone of the lens, preserving vision clarity while delivering therapeutics through the peripheral or posterior sections. Such modular architectures also facilitate the co-delivery of multiple agents, such as anti-inflammatory drugs and antibiotics, in a single platform.

3.3 Stimuli-Responsive Release Systems

Stimuli-responsive or "smart" drug delivery systems represent the most advanced frontier in contact lens-based therapeutics. These systems are designed to modulate drug release in response to specific internal or external cues, enabling dynamic, on-demand therapy that aligns with the patient’s physiological state.

pH-responsive hydrogels are one example, wherein drug release is triggered or accelerated in response to changes in tear pH, which may occur in pathological conditions such as dry eye or allergic conjunctivitis. These materials undergo reversible swelling or deswelling, thereby controlling the diffusion of drugs embedded within their matrix.

Enzyme-responsive systems utilize hydrogel components or crosslinkers that are selectively degraded by enzymes present in the tear film or elevated during infection or inflammation. This approach offers targeted drug release at sites of disease activity and can reduce the exposure of healthy tissues to unnecessary medication.

Temperature-sensitive polymers, such as poly(N-isopropylacrylamide) (PNIPAAm), respond to ocular surface temperature changes by altering their swelling behavior and releasing drugs accordingly. These materials can be engineered to remain in a collapsed state at room temperature and expand upon insertion into the eye, initiating drug release only during wear (9).

Perhaps most innovatively, electrically or light-responsive lenses integrate micro-electronic components or photoreactive materials that release drugs upon receiving a specific signal. Wireless activation allows for external control of dosing schedules and has shown promise in the treatment of glaucoma, where intraocular pressure fluctuations can be monitored and addressed in real time.

The integration of stimuli-responsive mechanisms offers unparalleled precision and adaptability, enabling a truly personalized ocular therapy platform. However, these systems also introduce complexity in terms of fabrication, regulatory approval, and cost, which must be addressed for widespread clinical implementation.

4. Technological Advancements

The evolution of smart contact lenses from passive therapeutic platforms to dynamic, multifunctional biomedical devices has been fueled by breakthroughs in materials science, bioelectronics, microfabrication, and wireless communication technologies. These advancements have enabled the seamless integration of sensors, circuits, and drug reservoirs within soft, flexible, and transparent contact lens matrices—paving the way for real-time monitoring, controlled drug release, and personalized therapy. This section highlights the major technological innovations underpinning smart contact lenses, focusing on their sensing capabilities, energy management systems, and self-regulated therapeutic functionalities.

4.1 Integration with Electronics and Sensors

One of the most transformative aspects of smart contact lenses is their ability to incorporate biosensors that monitor physiological parameters from tear fluid in a non-invasive and continuous manner. Tear fluid contains a wealth of biomarkers—such as glucose, lactate, electrolytes, cytokines, and pH—making it an ideal medium for ocular diagnostics and disease monitoring (10).

Electrochemical sensors are the most commonly integrated sensing modality. These sensors consist of electrodes embedded within the lens that can detect specific analytes through redox reactions, changes in impedance, or ion-selective potentiometry. For example, glucose sensors based on glucose oxidase immobilized on platinum electrodes have been developed to monitor tear glucose levels in diabetic patients. The data obtained can be wirelessly transmitted to an external device for real-time monitoring and therapeutic adjustment.

Optical sensors offer another approach, using colorimetric or fluorescence-based detection of analyte concentrations. These systems can be engineered to change color or intensity in response to specific biomarkers, providing a visual indication of disease status. Advances in nanophotonic structures, such as plasmonic nanostructures or photonic crystals, have further enhanced the sensitivity and miniaturization of these optical components.

To ensure that sensors do not impair visual acuity, most electronics are positioned outside the central optical zone, typically near the periphery of the lens. The use of transparent conductors, such as graphene or silver nanowires, also allows for inconspicuous sensor integration without compromising optical clarity. These developments mark a significant step toward contact lenses that function as wearable diagnostic laboratories, enabling continuous health surveillance and therapeutic feedback.

4.2 Wireless Powering and Data Transmission

Embedding electronics in a soft, curved, and hydrated environment such as a contact lens necessitates innovative approaches to energy management. Traditional batteries are impractical due to their bulk, rigidity, and potential toxicity. As a result, wireless power transfer technologies have become central to smart lens development.

Radiofrequency (RF) energy harvesting is one of the most commonly employed techniques. In this approach, a miniature antenna embedded in the lens receives energy transmitted from an external RF source—such as a smartphone or specialized transmitter—and converts it into electrical power to operate sensors, microprocessors, and drug release mechanisms. Inductive coupling, which relies on the mutual inductance between coils in the lens and the transmitter, provides an efficient and biocompatible method for power transfer at short ranges (11).

Photovoltaic cells represent another option, harnessing ambient or directed light to generate electricity. These systems are particularly attractive for daytime use and can be integrated into the lens periphery or outer surface.

Wireless data communication is typically achieved via Bluetooth Low Energy (BLE), near-field communication (NFC), or custom RF protocols. The integration of wireless modules allows for bidirectional data exchange between the lens and external devices, enabling real-time feedback, cloud-based analytics, and remote monitoring by clinicians.

Flexible, stretchable electronics have made it feasible to embed these components without compromising the lens's comfort or function. Advanced microfabrication techniques, including transfer printing and soft lithography, allow for the precise patterning of circuits and sensors on curved, deformable substrates. Collectively, these innovations ensure that smart lenses can operate autonomously while maintaining user safety and comfort.

4.3 Self-Regulated Drug Delivery Systems

Perhaps the most exciting frontier in smart contact lens technology is the development of self-regulated drug delivery systems—devices that can autonomously adjust the rate, timing, and dosage of therapeutic release in response to real-time physiological feedback.

In these systems, biosensors continuously monitor specific biomarkers (e.g., intraocular pressure, glucose, or inflammatory cytokines) and relay this data to an onboard processing unit. Upon detecting a critical threshold or pathological change, the system activates a drug release mechanism, which may involve the degradation of a polymer membrane, triggering of a micro-pump, or electrostimulation of a responsive hydrogel. For instance, smart lenses designed for glaucoma management can monitor intraocular pressure using piezoresistive sensors or strain gauges embedded within the lens. If pressure exceeds a set threshold, an actuator may be triggered to release an anti-glaucoma drug from a micro-reservoir, thereby preventing disease progression without patient intervention.

Light-activated systems represent another avenue, wherein specific wavelengths of light are used to trigger drug release from photoresponsive carriers. This strategy offers external control over dosing and has shown promise in experimental models of retinal disease and ocular inflammation. While these self-regulated systems remain in early stages of development, they exemplify the convergence of diagnostics and therapeutics—termed theranostics—in a single wearable platform. Such integration holds immense potential for managing chronic ocular diseases with unprecedented precision, minimizing patient burden, and enhancing compliance.

5. Applications in Ocular Diseases

Smart contact lenses have demonstrated significant therapeutic potential across a broad spectrum of ocular pathologies. Their ability to combine sustained, targeted drug delivery with real-time disease monitoring enables not only improved treatment outcomes but also the potential for early detection and disease prevention. This section discusses the major disease categories for which smart contact lenses have been explored, emphasizing the pathophysiological rationale, clinical relevance, and technological adaptations specific to each application.

5.1 Glaucoma

Glaucoma is a leading cause of irreversible blindness worldwide and is primarily characterized by elevated intraocular pressure (IOP) leading to progressive optic nerve damage. Management of glaucoma typically involves long-term topical administration of intraocular pressure-lowering drugs such as prostaglandin analogs, beta-blockers, and carbonic anhydrase inhibitors. However, poor patient compliance and limited ocular bioavailability significantly reduce treatment efficacy.

Smart contact lenses offer a dual-functional approach in glaucoma therapy: continuous IOP monitoring and responsive or sustained drug delivery. Several prototypes have been developed that incorporate pressure-sensitive strain gauges, microfluidic channels, or piezoresistive sensors to non-invasively monitor IOP fluctuations throughout the day. Coupled with wireless communication systems, these lenses can transmit real-time data to clinicians, enabling timely intervention (12).

Drug-eluting smart lenses loaded with agents such as latanoprost or timolol maleate have shown promise in preclinical studies, maintaining therapeutic drug levels for days to weeks. Some models are also equipped with actuated micro-reservoirs that release medication when elevated IOP is detected. This convergence of diagnostics and therapeutics has the potential to greatly enhance disease control and mitigate the progression of vision loss in glaucoma patients.

5.2 Dry Eye Syndrome

Dry eye disease (DED) is a multifactorial disorder characterized by tear film instability, ocular surface inflammation, and neurosensory abnormalities. The chronic nature of DED often necessitates frequent application of artificial tears, anti-inflammatory drugs (e.g., cyclosporine), or corticosteroids, leading to reduced adherence and suboptimal therapeutic efficacy.

Smart contact lenses offer a means of restoring tear film homeostasis while simultaneously delivering anti-inflammatory and lubricating agents in a sustained manner. Hydrogel-based lenses with embedded nanoparticles or liposomes can encapsulate drugs such as cyclosporine A and release them gradually over extended periods. This improves drug residence time and therapeutic outcomes compared to conventional eye drops (13).

Some smart lenses are also engineered to retain moisture and reduce tear evaporation, offering both therapeutic and mechanical protection to the ocular surface. Additionally, sensors that monitor tear osmolarity or protein content may provide real-time feedback on disease status, allowing for personalized treatment adjustments.

5.3 Diabetic Retinopathy

Diabetic retinopathy (DR) is a microvascular complication of diabetes that remains a major cause of vision impairment globally. Although DR primarily affects the posterior segment of the eye, early biomarkers such as glucose levels and inflammatory cytokines are detectable in tear fluid, offering an opportunity for early diagnosis and intervention.

Smart contact lenses equipped with electrochemical glucose sensors have been developed to non-invasively monitor tear glucose levels in real time. These lenses can transmit glucose readings to external devices, alerting patients to hyperglycemic episodes and enabling better glycemic control—an essential factor in slowing DR progression.

While drug delivery to the posterior segment via contact lenses is inherently challenging due to anatomical barriers, recent efforts have focused on enhancing drug penetration using permeation enhancers, iontophoresis, or nanocarrier systems. These approaches could potentially enable anterior-to-posterior drug delivery for conditions such as DR, especially in its early stages.

5.4 Post-Surgical Recovery

Ocular surgeries, including cataract extraction, LASIK, and vitrectomy, often necessitate prolonged courses of anti-inflammatory, antibiotic, and corticosteroid eye drops to prevent infection and support healing. However, postoperative adherence is frequently suboptimal, especially among elderly patients or those with limited dexterity.

Smart contact lenses have been investigated as post-surgical therapeutic platforms capable of providing sustained delivery of drugs such as dexamethasone, prednisolone, or moxifloxacin. By maintaining therapeutic concentrations at the surgical site and reducing dosing frequency, these lenses can improve patient compliance and reduce the risk of complications such as endophthalmitis or cystoid macular edema (14).

Furthermore, the transparent and conformal nature of contact lenses offer mechanical protection to the healing corneal epithelium, reducing discomfort and photophobia during the recovery period. Some designs also incorporate fluorescence-based sensors to detect infection or inflammation, enabling early clinical intervention.

Conclusion:

Smart contact lenses represent a transformative innovation in the field of ocular therapeutics, bridging the gap between traditional drug delivery limitations and the growing need for precision medicine in ophthalmology. By leveraging advances in polymer science, nanotechnology, biosensing, and wireless communication, these lenses offer a unique combination of sustained drug release, real-time diagnostics, and patient-centered convenience. Unlike conventional eye drops, which suffer from poor bioavailability and compliance issues, smart lenses provide continuous and localized delivery of therapeutics directly to the ocular surface, significantly enhancing pharmacological efficacy while minimizing systemic exposure.

The versatility of smart lenses is evident in their broad applicability to a range of ocular diseases, including glaucoma, dry eye syndrome, diabetic retinopathy, and postoperative care. Their ability to integrate sensors capable of monitoring tear biomarkers, intraocular pressure, or inflammation markers introduces the possibility of theranostic systems—devices that not only treat but also diagnose and adapt to disease states in real-time. This feedback-responsive functionality aligns with the paradigm shift toward personalized medicine and holds potential for revolutionizing the management of chronic eye conditions.

Despite their promise, smart contact lenses face several translational challenges, including scalability of manufacturing, long-term biocompatibility, and regulatory approval for multifunctional medical devices. Continued interdisciplinary research is required to refine lens architecture, enhance power efficiency of embedded electronics, and validate safety and efficacy through extensive preclinical and clinical studies. Nevertheless, the trajectory of innovation in this domain is encouraging, with early prototypes demonstrating feasibility and growing interest from both academia and industry. In the near future, smart contact lenses are poised to become a cornerstone technology in ocular drug delivery and diagnostics, offering a paradigm shift in how we approach the treatment and management of eye diseases.

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PHYTOCHEMICALS AS ADJUNCTIVE AGENTS IN CHRONIC OBSTRUCTIVE AIRWAY DISEASE: MECHANISMS AND APPLICATIONS

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Chronic obstructive airway disease (COAD) is a long-term, progressive condition characterized by inflammation in the lung tissue and small airways. This persistent inflammation causes airway blockage, denser within the bronchial walls and airway walls due to increased proliferation of mesenchymal cells and accumulation of extracellular matrix components, and narrowing of the airways through fibrosis. These alterations gradually result in reduced lung function. [1]

COAD has no cure, only symptom management, and current drugs like bronchodilators and steroids only help relieve symptoms and reduce exacerbations. They have limited effect on inflammation, particularly in severe cases, and may not be effective in certain patient subgroups. Long-term therapy can have side effects like oral candidiasis, osteoporosis, and pneumonia. Exacerbations can cause hospitalizations and worsen lung function, and current therapies do not directly address oxidative stress, which is central to COAD pathogenesis. Current therapies cannot repair or regenerate damaged alveolar and airway structures. Comorbid conditions are often untreated, and current treatments are "one-size-fits-all." There is also a lack of personalized medicine and poor patient adherence due to complex inhaler regimens and poor inhaler technique.[2,3]

Therapeutic Uses of Phytochemicals in the Management of COAD

i) Apigenin

Apigenin exerts its pharmacological effects through several key mechanisms. Apigenin inhibits NF-κB and AP-1, leading to reduced pro-inflammatory cytokine production and overall suppression of inflammation.[4] Additionally, apigenin demonstrates potent antioxidant properties by intiating the Nrf2 signaling, which enhances the expression of various cytoprotective and detoxifying enzymes. This dual anti-inflammatory and antioxidant action makes apigenin particularly beneficial in inflammatory diseases. Furthermore, apigenin has shown potential in improving glucocorticoid sensitivity, particularly in the context of steroid-resistant chronic obstructive plumonary disease (COPD), suggesting its role in enhancing the efficacy of existing treatments.[5]

In terms of dosing, animal studies have typically used oral doses ranging from 100 to 200 mg/kg/day. In human clinical settings, doses between 500 and 2000 mg per day of standardized apigenin extract have been investigated. To address this, formulations incorporating piperine or delivery systems such as liposomes are often used to enhance absorption and therapeutic effectiveness.[6]

ii) Quercetin

Quercetin, a flavonoid, exhibits potent anti-inflammatory and antioxidant properties that are particularly beneficial in respiratory health. Quercetin inhibits key inflammatory signaling pathways like MAPK and NF-κB, and also suppresses the expression of pro-inflammatory cytokines and mediators. Furthermore, quercetin combats oxidative stress by scavenging ROS, thus protecting against the oxidative lung damage. Also, it enhances the integrity and function of the lung epithelial barrier, providing a protective role against environmental insults and pathogens. [8,9]

In terms of dosing, animal studies have reported efficacy at oral doses ranging from 10 to 50 mg/kg/day. In human clinical trials, oral supplementation with quercetin at doses between 500 and 1000 mg/day has demonstrated beneficial outcomes with good tolerability. These findings support the quercetin as a dietary supplement for inflammatory lung conditions and general respiratory support. [10,11]

iii) Gallic acid

Gallic acid, shown antioxidant and anti-inflammatory effects, significantly reducing lung inflammation and emphysema in COAD mouse models. This was due to its ability to suppress neutrophil infiltration, decrease myeloperoxidase activity, and lower levels of pro-inflammatory cytokines. Gallic acid also reestablished redox balance in the lungs, normalizing markers like ROS, GSH, MDA, and protein carbonyls.[12,13] It also provided protection against exacerbations by reducing inflammatory cell infiltration and oxidative stress. Gallic acid's mechanisms of action include inhibiting NF-κB pathway, increasing Nrf2 protein levels, and modulating matrix metalloproteinase (MMP) activity. These actions suggest that gallic acid may have potential benefits in treating COAD and other lung conditions. [14,15]

A key preclinical study in COPD mouse models used gallic acid at 200 mg/kg/day, administered from 7 days before elastase exposure through the lung injury and exacerbation phases. The study reported significant reductions in lung inflammation, oxidative stress, and pro-inflammatory cytokines at this dose.[16]

iv) Resveratrol

Resveratrol**,** has potential in addressing COAD through anti-inflammatory, antioxidant, and mitochondrial-enhancing mechanisms. It suppresses NF-κB, a central regulator of pro-inflammatory cytokines, thereby decreasing both lung and systemic inflammation. It also suppresses macrophage activation and cytokine release more effectively than corticosteroids in COAD models.[17,18] Resveratrol reduces oxidative stress by diminishing MDA concentrations and promoting SOD enzyme activity in pulmonary tissue. It counters cigarette smoke-induced oxidative damage by activating antioxidant pathways. It also enhances mitochondrial biogenesis and function in skeletal and respiratory muscles, improving respiration and oxidative metabolism, addressing muscle wasting common in COAD. Additionally, it modulates autophagy via SIRT1-FOXO3 signaling, potentially mitigating protein degradation in muscles and lungs. However, clinical evidence remains limited.

In rat models of COAD, administration of resveratrol at 50 mg/kg led to notable improvements, including reduced alveolar damage, diminished infiltration of inflammatory cells. Similarly, human COAD macrophages exposed to resveratrol exhibited a substantial decrease in inflammatory mediator production, with IL-8 levels reduced by 88–94% and Colony-Stimulating Factor 2 lowered by 76–79%. by restoring SOD activity and normalizing MDA levels in lung tissue. [19,20]

v) Berberine

Berberine shows promise as a supportive treatment for COAD due to its multiple beneficial effects. It is marked by persistent airway inflammation, and berberine has been found to inhibit key pro-inflammatory cytokines and central regulator of inflammation. [21]

The increased TNF-α levels, which are linked to airway inflammation, mucus overproduction, emphysema, and airway remodeling. Berberine's suppression of TNF-α reduces inflammatory cell infiltration, airway epithelial thickening, and mucus production in COAD models.[22]

In addition to its anti-inflammatory properties, berberine exhibits antioxidant activity by enhancing the function of enzymes (SOD and GSH-Px), which help reduce oxidative stress, a major contributor to lung tissue damage in COAD. It also activates the network of AMPK, improving mitochondrial function and further mitigating inflammation and oxidative damage. Moreover, some studies suggest that berberine can reduce mucus hypersecretion, a common and problematic symptom in COAD. Its antimicrobial effects may also help lower the frequency of respiratory infections, which are a leading cause of COAD exacerbations. Together, these actions highlight berberine's potential as a multi-targeted approach to managing COAD symptoms and progression. [23]

vi) Curcumin

Curcumin, a proven anti-inflammatory agent, including inhibiting the NF-κB signaling pathway and modulating PPARγ-NF-κB interactions, which are central to the inflammatory cascade in chronic obstructive airway disease. It also downregulates key pro-inflammatory cytokines, attenuating inflammation in the airways. Curcumin enhances the expression of gene responsible for antioxidant effect, and reducing oxidative stress in lung tissues.[24,25] It promotes autophagy and cell protection, preserving lung cell viability and preventing apoptosis under stress conditions commonly found in COAD. Curcumin also restores the expression of histone deacetylase 2, which is often diminished in COAD patients, which can suppress chemokine production and improve corticosteroid sensitivity, offering a potential avenue to overcome steroid resistance in severe COAD.[26,27]

vii) Luteolin

Luteolin, has shown promising therapeutic potential in the management of COAD.

Luteolin alleviates inflammation and oxidative stress in COAD, primarily by inhibiting the NOX_4-mediated NF-κB signaling pathway. In both animal and cell models of cigarette smoke-induced COAD, luteolin was found to decrease levels of pro-inflammatory cytokines and oxidative stress markers, while SOD and CAT. [28] Luteolin downregulates TRPV1 and CYP2A13, upregulates SIRT6 and NRF2, and diminished calcium influx within cell and ROS production, which are key factors in cigarette smoke-induced lung damage. [29,30]

viii) Bromelain

Bromelain is an enzyme extract derived from pineapples, commonly used as a dietary supplement for its potential anti-inflammatory and mucolytic (mucus-thinning) activity.

Bromelain may help thin phlegm and mucus, which could be beneficial for people with COAD who often struggle with thick respiratory secretions. Animal studies have shown that bromelain can lowering the number of inflammatory cells (such as T lymphocytes and eosinophils) and decreasing inflammatory cytokines like IL-13 in the lungs. These effects suggest a possible benefit in reducing airway inflammation in COAD, although most evidence comes from asthma or allergy models, not COAD-specific studies. [31-33]

xi) Naringenin

Naringenin an orally administered drug, has been shown to reduce inflammation in the lungs and decrease myeloperoxidase activity, resulting in less tissue injury. It also suppresses the production of pro-inflammatory cytokines, and NF-κB factor are associated with COAD severity and exacerbations.[34] It also modulates chemokines, such as MCP-1 and MIP-1α, which recruit inflammatory cells to the lungs. It also has antioxidant effects, decreasing reactive oxygen species levels and increasing antioxidant enzyme activity. Naringenin also regulates mucus by downregulating the NF-κB pathway and improving mucus clearance.[35-37]

x) Baicalin

Baicalin reduces inflammation in COAD through multiple, well-documented mechanisms, primarily by targeting key inflammatory signaling pathways and modulating immune responses along suppression of NF-κB pathway, a central regulator of inflammation in COAD. This leads to decreased production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which are typically elevated in COPD patients. [38]

It downregulates TLR2 and MYD88 pathway, further reducing NF-κB activation and subsequent inflammatory responses. This mechanism has been confirmed in COAD animal models, where baicalin treatment led to improved lung function and reduced inflammatory markers.

Baicalin increases the activity of histone deacetylase 2 (HDAC2), which is often reduced in COAD. Enhanced HDAC2 activity contributes to the suppression of NF-κB-driven inflammation. [39,40]

Baicalin enhances antioxidant defenses which helps mitigate oxidative damage that exacerbates inflammation in COAD.

By decreasing the expression of inflammatory mediators and remodeling markers (such as TNF-α and IFN-γ), baicalin limits airway wall thickening and collagen deposition, both of which contribute to airflow limitation in COAD. [41,42]

xi) Fisetin

Fisetin, has anti-inflammatory and senolytic actions benefiting in COAD. It suppresses inflammation by inhibiting the TNF-α/NF-κB pathway via binding to PKCδ, thereby reducing NF-κB activation. Fisetin reduces pro-inflammatory cytokines like IL-8, limits inflammatory cell infiltration, mucus overproduction, and airway inflammation. It also lowers cytokine levels in lung tissue and serum and modulates immune responses by decreasing co-stimulatory molecule expression on airway dendritic cells, thereby reducing airway hyperresponsiveness and chronic inflammation. Finally, it suppresses MyD88 and TLR signaling, leading to reduced activation of NF-κB and decreased secretion of inflammatory mediators. [43- 45]

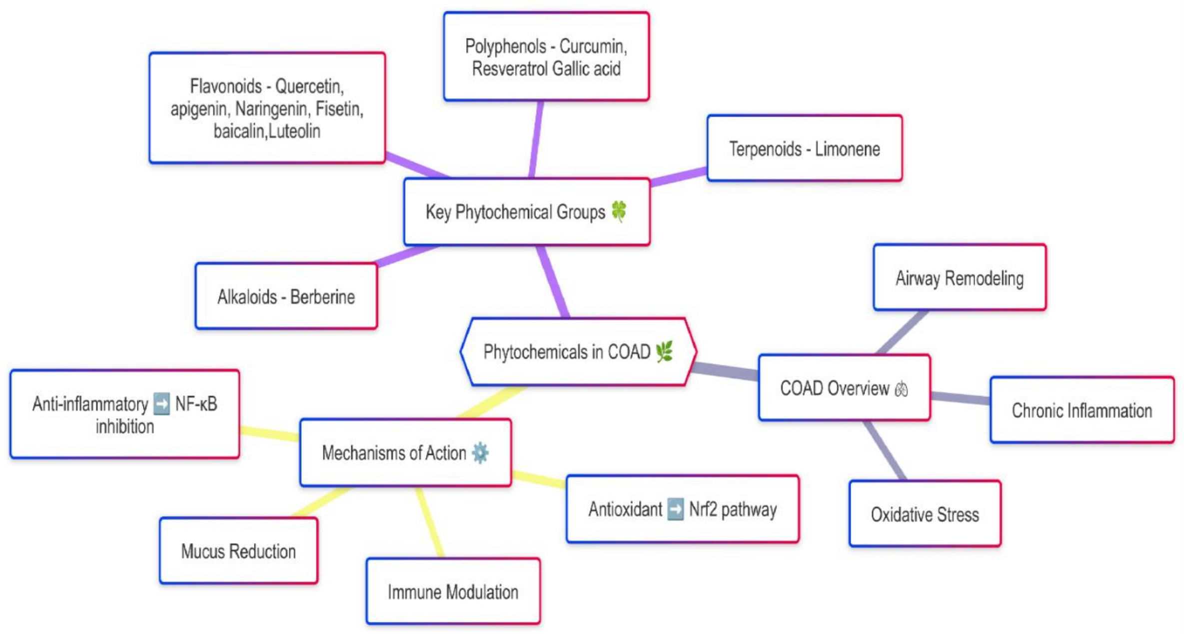

Figure 1: Mechanism of Action of various phytochemical in COAD

Conclusion:

Phytochemicals are promising for COAD management by targeting inflammation and oxidative stress. Early evidence supports their benefits when combined with conventional treatments and lifestyle changes. However, more rigorous clinical trials are needed to confirm their safety, effectiveness, and optimal use in conjunction with conventional therapies, despite moderate overall strength of evidence.

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ROLE OF BIODEGRADABLE POLYMERS IN 3D PRINTING OF PHARMACEUTICALS

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Abstract:
The integration of biodegradable polymers in 3D printing technology represents a transformative advancement in the field of pharmaceutical sciences. This chapter explores the critical role these polymers play in the development of personalized, patient-specific drug delivery systems. Biodegradable polymers offer distinct advantages, such as biocompatibility, controlled degradation, and reduced environmental impact, making them ideal for use in pharmaceutical applications. The chapter begins with an overview of 3D printing techniques and their relevance to pharmaceutics, followed by a detailed examination of various biodegradable polymers commonly used in additive manufacturing—such as polylactic acid (PLA), polycaprolactone (PCL), and poly(lactic-co-glycolic acid) (PLGA). Key formulation and processing considerations, including drug-polymer interactions, mechanical properties, and printability, are also discussed. Furthermore, the chapter highlights current applications, recent advancements, and notable case studies demonstrating the efficacy of biodegradable polymers in producing customized drug dosage forms, sustained-release systems, and complex multi-drug platforms. Regulatory challenges, ethical concerns, and future prospects for sustainable pharmaceutical manufacturing are also addressed. Overall, this chapter emphasizes the growing importance of biodegradable polymers in advancing the safety, efficacy, and sustainability of pharmaceutical 3D printing.

Keywords: Biodegradable Polymers, 3D Printing Technology, Personalized and Patient-Specific Drug Delivery Systems, Sustainability of Pharmaceuticals

Introduction:

3D printing, also known as additive manufacturing, has emerged as a groundbreaking technology in the pharmaceutical industry, enabling the precise fabrication of complex and personalized drug delivery systems. Unlike traditional manufacturing methods, 3D printing builds dosage forms layer by layer from digital designs, allowing for unprecedented control over drug release profiles, geometry, and dosage customization. This technology supports the creation of multi-drug combinations, tailored therapies for individual patients (such as paediatric or geriatric populations), and on-demand production of medications. With various printing techniques like fused deposition modelling (FDM), inkjet printing, and stereolithography (SLA), 3D printing offers flexibility in formulation and design, paving the way for a new era of precision medicine [1,2].

Biodegradable polymers play a vital role in pharmaceutical applications due to their ability to safely degrade within the body into non-toxic byproducts, eliminating the need for surgical removal and reducing long-term side effects. In the context of 3D printing, these polymers enable the development of biocompatible, customizable drug delivery systems that align with the principles of personalized medicine and environmental sustainability. Their tunable mechanical, thermal, and degradation properties allow for controlled drug release, enhanced therapeutic efficacy, and improved patient compliance. Moreover, biodegradable polymers contribute to reducing pharmaceutical waste and support the growing demand for greener, more sustainable healthcare solutions [3,4].

Fundamentals of 3d printing in pharmaceuticals

Additive Manufacturing Techniques in 3D Printing

Additive manufacturing in 3D printing refers to the process of creating objects by adding material layer by layer based on a digital design. In pharmaceutical applications, several techniques are used to fabricate precise and personalized drug delivery systems [5,6]:

1. **Fused Deposition Modelling (FDM):** One of the most common methods, FDM involves heating and extruding thermoplastic polymers through a nozzle to build the object layer by layer. It is suitable for producing solid oral dosage forms using biodegradable polymers like PLA and PCL, allowing for controlled drug release.
2. **Inkjet Printing:** This technique uses droplets of drug-containing ink, deposited onto a substrate in a precise pattern. It is ideal for low-dose medications, fast-dissolving films, and polypills. It supports heat-sensitive drugs due to its non-thermal process.
3. **Stereolithography (SLA):** SLA utilizes a UV laser to cure photosensitive liquid resins into solid forms. It provides high resolution and accuracy, making it suitable for intricate drug delivery devices, though it is limited by the availability of biocompatible resins.
4. **Selective Laser Sintering (SLS):** SLS involves using a laser to sinter powdered material into solid structures. It enables solvent-free production and the creation of porous matrices for modified drug release, but typically requires advanced equipment and post-processing.
5. **Binder Jetting:** In binder jetting, a liquid binding agent is selectively deposited to join powder particles layer by layer. It allows for high-speed production and complex geometries but often requires post-processing to enhance mechanical strength.

These techniques offer flexibility in formulation design, enabling the production of personalized, multi-drug, and controlled-release pharmaceutical products with high precision and functionality.

Types of 3D Printers Used in Pharmaceutics

Several types of 3D printers are utilized in pharmaceutical applications, each tailored to specific materials, drug properties, and desired dosage forms. The most common types include [7,8]:

1. **Fused Deposition Modeling (FDM) Printers:** These printers use thermoplastic filaments (e.g., PLA, PCL) that are melted and extruded through a heated nozzle to form layers. FDM is widely used for fabricating tablets, implants, and scaffolds with controlled-release properties.
2. **Inkjet Printers:** Inkjet 3D printers deposit precise droplets of drug-laden liquid onto a substrate. They are suitable for low-dose medications, rapid-dissolving films, and multi-drug layered structures, especially when processing heat-sensitive drugs.
3. **Stereolithography (SLA) Printers:** SLA printers use UV lasers to cure photosensitive liquid resins into solid forms. They offer high resolution and are ideal for creating intricate drug delivery devices and prototypes, although their use is limited by the need for biocompatible resins.
4. **Selective Laser Sintering (SLS) Printers:** SLS printers sinter powdered materials using a high-powered laser to form solid structures. They are suitable for producing porous dosage forms and implantable devices without the use of solvents, allowing for customizable drug release profiles.
5. **Binder Jet Printers:** These printers deposit a liquid binding agent onto powder beds to create solid objects. Binder jetting supports complex geometries and is being explored for high-throughput production of pharmaceutical tablets.

Each printer type has specific advantages depending on the formulation requirements, drug stability, and desired performance of the final dosage form, making them valuable tools in the advancement of personalized and precision medicine.

Advantages over Conventional Methods

3D printing offers several key advantages over traditional pharmaceutical manufacturing techniques [9,10]:

1. **Personalized Medicine:** 3D printing enables the creation of patient-specific dosage forms tailored to individual needs, such as age, weight, genetic profile, and disease condition—something not possible with mass production methods.
2. **Complex Dosage Forms:** It allows for the fabrication of complex geometries and multi-layered or multi-drug systems, which can achieve controlled, sustained, or targeted drug release patterns with high precision.
3. **On-Demand Manufacturing:** Drugs can be printed as needed, reducing storage requirements, minimizing waste, and ensuring fresher products with better shelf-life control.

4. **Material Efficiency:** Additive manufacturing uses only the required amount of material, minimizing waste and making it a more sustainable option.
5. **Rapid Prototyping and Innovation:** New drug formulations and delivery systems can be quickly prototyped and tested, accelerating research and development timelines.
6. **Improved Patient Compliance:** Customized shapes, flavours, and drug combinations can enhance the acceptability of medications, especially for paediatric and geriatric patients.
7. **Integration of Biodegradable Polymers:** 3D printing supports the use of biodegradable materials for eco-friendly, implantable, and resorbable drug systems that are not easily achievable through conventional methods.

These advantages highlight the transformative potential of 3D printing in creating more effective, sustainable, and patient-centred pharmaceutical products.

Biodegradable polymers: an overview

Biodegradable polymers are materials that can break down into biologically harmless byproducts such as water, carbon dioxide, and biomass through natural processes involving enzymes or microorganisms. In pharmaceuticals, these polymers are highly valued for their biocompatibility, controlled degradation, and minimal environmental impact. They play a critical role in drug delivery systems, especially in applications where temporary function is required, such as implants, scaffolds, and controlled-release formulations [11].

Biodegradable polymers can be broadly classified into **natural** (e.g., chitosan, gelatine, alginate) and **synthetic** (e.g., polylactic acid [PLA], polycaprolactone [PCL], poly (lactic-co-glycolic acid) [PLGA]) types. Natural polymers are often favoured for their inherent biological compatibility, while synthetic ones offer better tunability in terms of mechanical strength, degradation rate, and processability—especially important in 3D printing.

These polymers must possess specific properties for pharmaceutical use, such as non-toxicity, suitable mechanical strength, printability, and predictable degradation profiles. When used in 3D printing, they enable the fabrication of personalized, implantable, or ingestible drug delivery systems that degrade after fulfilling their function, thus reducing the need for surgical removal or long-term maintenance.

The use of biodegradable polymers in pharmaceutical 3D printing supports the development of advanced, patient-friendly therapies and aligns with global goals for sustainable and environmentally responsible healthcare solutions.

Common biodegradable polymers used in 3D printing

A variety of biodegradable polymers are commonly employed in pharmaceutical 3D printing due to their biocompatibility, processability, and tunable degradation profiles. These materials enable the production of customized drug delivery systems with specific release kinetics and structural properties. Below are some of the most widely used biodegradable polymers [12,13]:

1. **Polylactic Acid (PLA):** PLA is a thermoplastic aliphatic polyester derived from renewable sources like corn starch. It is one of the most commonly used polymers in Fused Deposition Modelling (FDM) due to its excellent printability, mechanical strength, and slow degradation rate. PLA is suitable for producing oral tablets and implantable devices.
2. **Polycaprolactone (PCL):** PCL is a semi-crystalline polymer with a low melting point and slow degradation profile, making it ideal for long-term drug delivery systems and implants. It exhibits good thermal stability and flexibility, which is advantageous for 3D printing, especially in fabricating scaffolds and sustained-release systems.
3. **Poly (lactic-co-glycolic acid) (PLGA):** PLGA is a copolymer of lactic acid and glycolic acid and offers customizable degradation rates by varying the monomer ratio. It is widely used in drug delivery due to its FDA approval and predictable biodegradation. PLGA is particularly effective for controlled-release applications.
4. **Polyhydroxyalkanoates (PHAs):** PHAs are bacterial polyesters that degrade naturally and are biocompatible. They are being explored for use in biomedical 3D printing due to their good mechanical properties and safe degradation products.
5. **Chitosan:** A natural polymer derived from chitin, chitosan is biodegradable, biocompatible, and has intrinsic antibacterial properties. It is suitable for printing mucoadhesive drug delivery systems and wound-healing materials, although its printability can be limited without modification.
6. **Gelatine:** Derived from collagen, gelatine is widely used in bioprinting for its cell-friendly environment and biodegradability. It is suitable for soft tissue engineering and the development of fast-dissolving drug films or scaffolds.
7. **Alginate:** Extracted from brown seaweed, alginate is a natural polysaccharide used for hydrogel-based drug delivery systems. It forms gels in the presence of calcium ions and is useful in bio-ink formulations for 3D printing soft, biocompatible structures.

These biodegradable polymers, individually or in combination, provide a versatile platform for creating advanced pharmaceutical products via 3D printing, allowing for tailored drug release, improved patient outcomes, and reduced environmental impact.

Formulation and processing considerations

In 3D printing of pharmaceuticals using biodegradable polymers, careful attention must be given to formulation and processing parameters to ensure the safety, functionality, and performance of the final dosage form. These considerations directly influence printability, drug stability, mechanical integrity, and drug release characteristics [14].

1. **Polymer Selection:** The choice of polymer depends on the desired degradation rate, mechanical strength, thermal properties, and compatibility with the active pharmaceutical

ingredient (API). For instance, PLA and PLGA are ideal for sustained-release systems, while gelatine and chitosan suit fast-release or mucoadhesive formulations.

2. **Drug-Polymer Compatibility:** Drug stability during processing is critical, especially when using thermal methods like FDM. The API must be thermally stable and chemically compatible with the polymer to prevent degradation or inactivation during printing.
3. **Melt Rheology and Viscosity:** For FDM, the polymer must have appropriate melt flow properties to ensure smooth extrusion. Too high a viscosity can lead to nozzle clogging, while too low can affect the mechanical strength of the printed product.
4. **Solvent Use (in Inkjet or SLA):** In liquid-based printing techniques, solvents must be pharmaceutically acceptable and should not react with the drug or alter its activity. The solvent system must ensure appropriate viscosity, surface tension, and evaporation rate for reliable printing.
5. **Print Parameters:** Factors like nozzle temperature, bed temperature, print speed, and layer height must be optimized based on the material and the design. Improper settings can lead to warping, poor adhesion between layers, or uneven drug distribution.
6. **Drug Loading and Distribution:** Uniform distribution of the drug within the polymer matrix is essential for consistent dosing. Techniques such as hot-melt extrusion, solvent casting, or direct blending are used to incorporate drugs into the polymer.
7. **Post-Processing Requirements:** Some printed products may require additional steps such as drying, crosslinking, or sterilization. These processes must not compromise the drug's stability or the polymer's integrity.
8. **Storage Stability:** Printed dosage forms must maintain their physical structure, drug content, and release properties over time. This requires careful formulation to resist moisture uptake, temperature sensitivity, or chemical degradation.

By optimizing this formulation and processing parameters, pharmaceutical 3D printing with biodegradable polymers can produce safe, effective, and reproducible dosage forms tailored to specific therapeutic needs.

Applications in drug delivery systems

The integration of biodegradable polymers in 3D printing has unlocked a wide range of innovative applications in drug delivery systems. These applications focus on improving therapeutic efficacy, patient compliance, and personalization of treatment through precise control over drug release profiles and dosage form design [15,16].

1. **Personalized Dosage Forms:** 3D printing allows the production of individualized medications based on patient-specific parameters such as age, weight, and disease condition. Biodegradable polymers enable the creation of custom-tailored tablets or capsules with adjustable drug loads and release kinetics.

2. **Controlled and Sustained Release Systems:** By selecting appropriate biodegradable polymers like PLGA or PCL, drug release can be modulated over hours, days, or even weeks. These systems maintain therapeutic drug levels over extended periods, reducing dosing frequency and improving compliance.
3. **Multi-Drug Delivery Platforms:** 3D printing enables compartmentalized or layered dosage forms that can carry multiple drugs with distinct release profiles. This is particularly useful for polypharmacy in chronic diseases, allowing for simplified regimens and reduced drug interactions.
4. **Paediatric and Geriatric Formulations:** Taste-masked, chewable, or fast-dissolving dosage forms can be printed to suit the preferences and swallowing abilities of paediatric and elderly patients. Biodegradable polymers ensure safety and ease of metabolism in these vulnerable populations.
5. **Implantable Drug Delivery Devices:** Biodegradable implants printed via FDM or SLS can provide site-specific, long-term drug delivery for applications such as cancer therapy, pain management, or hormone replacement. These implants degrade naturally after drug release, eliminating the need for surgical removal.
6. **Wound Healing and Local Delivery:** Polymers like chitosan and gelatine are used to print bioactive films, scaffolds, and hydrogels that release antibiotics, growth factors, or anti-inflammatory agents directly at the wound site, promoting healing and reducing infection.
7. **Oral Thin Films and Buccal Patches:** Soluble biodegradable polymers such as alginate or gelatine are used to fabricate thin films that rapidly dissolve in the mouth, delivering drugs through the oral mucosa for rapid onset of action.
8. **Transdermal and Microneedle Systems:** 3D-printed microneedles made from biodegradable materials can be used for painless, minimally invasive drug delivery through the skin, with applications in vaccines, insulin delivery, and cosmetics.

These diverse applications demonstrate the versatility and potential of biodegradable polymers in advancing 3D-printed drug delivery systems that are efficient, patient-centric, and environmentally friendly.

Recent advances and case studies

In recent years, significant progress has been made in the application of biodegradable polymers in 3D printing for pharmaceutical use. These advances highlight the technology's potential to revolutionize drug delivery, offering personalized therapies and improved patient outcomes [17,18].

1. FDA-Approved 3D-Printed Drug – Spritam®

Although not based on biodegradable polymers, the approval of *Spritam®* (levetiracetam) in 2015 marked a pivotal moment for 3D-printed pharmaceuticals. It demonstrated the feasibility of producing high-dose, fast-dissolving tablets using ZipDose® technology, paving the way for future applications using biodegradable materials.

2. Personalized Polypills

Researchers have successfully developed 3D-printed polypills using biodegradable polymers like PLA and PCL to combine multiple drugs into a single dosage form. These tablets feature separate compartments or layers to control release timing, enabling simplified regimens for patients with chronic diseases such as hypertension or diabetes.

3. Paediatric and Geriatric Formulations

Custom-designed chewable tablets and fast-dissolving films tailored for children and the elderly have been developed using natural biodegradable polymers like gelatine and chitosan. These dosage forms improve compliance by enhancing palatability and ease of administration.

4. Implantable Drug Delivery Devices

Studies have shown successful use of PLGA and PCL in 3D-printed biodegradable implants for localized delivery of chemotherapeutic agents and antibiotics. These implants provide sustained release directly at the disease site and degrade over time, avoiding the need for surgical removal.

5. Biodegradable Microneedles

Recent work has focused on printing microneedle patches from biodegradable polymers for painless transdermal drug delivery. These systems offer minimally invasive delivery of vaccines, insulin, or pain medications with high patient acceptability.

6. Smart Drug Delivery Systems

Advanced designs have incorporated stimuli-responsive biodegradable materials that alter drug release in response to pH, temperature, or enzymes. For example, chitosan-based hydrogels have been 3D printed to release drugs specifically in the gastrointestinal tract.

7. Scaffold-Based Tissue Engineering with Drug Release

Biodegradable scaffolds printed from PLA or PCL have been used to simultaneously support tissue regeneration and deliver bioactive molecules like antibiotics or growth factors, showing promise in wound healing and orthopaedic applications.

These case studies demonstrate how combining 3D printing with biodegradable polymers can lead to highly functional, targeted, and patient-specific pharmaceutical products. Continued interdisciplinary research is expected to expand these applications and improve clinical translation.

Regulatory and ethical considerations

The integration of biodegradable polymers in 3D printing for pharmaceutical applications presents unique regulatory and ethical challenges. Regulatory bodies like the FDA and EMA must establish clear guidelines for the approval of 3D-printed drug products, ensuring consistent quality, safety, and efficacy. This includes evaluating factors such as material biocompatibility, drug-polymer interactions, manufacturing reproducibility, and product stability. Ethical considerations revolve around ensuring equitable access to personalized medicines, protecting patient data used in digital design, and preventing misuse of on-demand drug fabrication. Moreover, quality control in decentralized or point-of-care production settings requires robust validation to maintain public trust and ensure therapeutic reliability. As the technology advances, collaborative efforts among scientists, manufacturers, and regulators are essential to address these concerns and support safe, ethical implementation [19,20].

Future perspectives

The future of 3D printing with biodegradable polymers in pharmaceuticals is poised to transform personalized medicine, offering unprecedented control over drug release, dosage customization, and site-specific delivery. Advancements in printable biomaterials, smart polymers, and bio-inks will expand the range of compatible drugs and dosage forms, including tissue-engineered implants and multifunctional drug-device hybrids. Integration with artificial intelligence and digital health technologies will enable automated, patient-tailored formulation design and real-time treatment optimization. Regulatory frameworks are expected to evolve to accommodate decentralized, on-demand manufacturing models such as hospital-based printing. As research continues to bridge the gap between laboratory innovation and clinical application, 3D printing with biodegradable polymers holds the potential to make drug therapy more precise, accessible, and environmentally sustainable [21,22].

Conclusion:

The use of biodegradable polymers in 3D printing represents a ground-breaking advancement in pharmaceutical science, enabling the creation of personalized, eco-friendly, and therapeutically effective drug delivery systems. By combining the precision of additive manufacturing with the versatility of biodegradable materials, it is now possible to fabricate complex dosage forms tailored to individual patient needs, improving treatment outcomes and adherence. Despite challenges related to formulation, regulation, and large-scale implementation, ongoing research and technological progress continue to push the boundaries of what is possible. As the field matures, biodegradable polymer-based 3D printing is expected to become an integral part of the future of medicine, offering solutions that are not only innovative but also sustainable and patient-centered.

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AN OVERVIEW OF FATTY ACID OXIDATION DISORDER

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Abstract:
Inherited metabolic abnormalities known as fatty acid oxidation disorders (FAODs) occur when either mitochondrial β-oxidation or the carnitine transport route for fatty acids is disrupted. Different FAODs will manifest in different ways, but they all have certain symptoms and, in the end, need the same treatment. During the newborn era, cardiomyopathy is one of the first severe signs of FAODs. In infancy and childhood, hypoketotic hypoglycemia and liver dysfunction are prevalent. The majority of FAODs manifest during or after puberty, but intermittent rhabdomyolysis is more common in this age group. Avoiding fasting, aggressive therapy during illness, and carnitine supplementation, if needed, are all part of the treatment for FAODs. In contrast, long-chain FAODs necessitate a fat-restricted diet in addition to medium chain triglyceride oil and, in many cases, docosahexaenoic acid (DHA), an important fatty acid that is vital for the immune system, brain, and vision as well as for preventing fat-soluble vitamin shortages. Although the FAOD are a cluster of hereditary diseases that cause a lot of illness and death, things are looking good because to newborn screening (NBS) and the fact that therapy can start sooner rather than later. Randomized, controlled therapeutic trials and other forms of clinical research are necessary for the ongoing evaluation of existing knowledge and the development of new treatments.

Keywords: Fatty Acid Oxidation Disorders, Mitochondria, Carnitine, Oxidation

1. Introduction:

1.1 The Role of Fatty Acids in Production of Energy

The mitochondria are where β-oxidation happens, which is how fatty acids give the myocardium, skeletal muscle, and liver a lot of energy. Short-chain and medium-chain fatty acids can go straight into the mitochondria, but long-chain fatty acids (LCFAs) need to be moved in with the help of carnitine and three enzymes/transporters [1]. In the mitochondrial matrix, β-oxidation happens in a cycle of four steps. These phases break off 2-carbon acetyl-coenzyme A (CoA) from the fatty acid chain and move electrons to the respiratory chain to make adenosine triphosphate (ATP). Acetyl-CoA can serve as a substrate in the tricarboxylic acid (TCA) cycle to provide additional reducing equivalents for the electron transport chain, or it can be employed in ketone production, an alternative energy source for the brain, heart, muscle, kidney, and other tissues [2]. This energy is really important while you are fasting and can't get glucose, as well as when you are under a lot of stress. The metabolism of LCFAs to support energy production centers on the oxidation of acetyl-CoA inside the mitochondrial TCA cycle. For the TCA cycle to work right, the intake of substrates (anaplerosis) must be equal to the outflow (cataplerosis). Anaplerosis is the process of constantly adding intermediates to keep the TCA cycle going and make ATP. Cataplerosis removes additional intermediates to start gluconeogenesis and lipogenesis. This balance is very important for keeping energy homeostasis [3].

There are two types of fatty acids: even-chain and odd-chain. The number of carbons in the α-carbon backbone determines which type it is. Fatty acids with an odd number of carbon atoms are not very common in the body. Most of the time, they are found in diet and tissue storage as 16- and 18-carbon species [4]. Odd-chain fatty acids undergo oxidation in the same manner as even-chain fatty acids, with the exception that the last stage of β-oxidation yields one molecule each of acetyl-CoA and anaplerotic propionyl-CoA. The formation of propionyl-CoA is unique to odd-carbon fatty acids, resulting in their anaplerotic characteristics. Medium odd-chain fatty acids can help the heart and skeletal muscles work better and make more energy until odd-chain substrates run out. This is not a problem when anaplerotic odd-chain fats are used [5].

When cell glycogen is in short supply, the mitochondrial beta-oxidation of fatty acids (FAO) steps in to provide energy. Through a series of processes facilitated by enzymes such as 3-ketoacyl-CoA thiolases, 2 - hydroxyacyl-CoA dehydrogenases that are dependent on NAD, 2-enoyl-CoA hydratases, and FAD-dependent acyl-CoA dehydrogenases, this oxidative catabolic pathway converts acyl-CoA esters into acetyl-CoA. The mitochondrial membrane can be crossed directly by medium-chain (C6-10) and short-chain (C4-6) fatty acids, Carnitine must be conjugated with fatty acids that have twelve or more carbon atoms [6].

With an estimated overall prevalence of 1:9000, fatty acid oxidation deficiencies (FAODs) are a category of common inborn metabolic abnormalities. These hereditary disorders cause FAO-related transport proteins or enzymes to be insufficient. Because of this, individuals might show a wide range of symptoms, from a moderate late-onset variant to a more severe newborn phenotype characterized by multi-organ failure. Because of their heightened reliance on fatty acids for energy, the liver, skeletal muscles, and cardiac muscles are particularly vulnerable. Hepatopathy, rhabdomyolysis, cardiomyopathy, and skeletal myopathy are typical findings in these illnesses. Hypoglycemic events can cause significant brain damage in FAODs, which is seen as seizures, hypotonia, lethargy, and gradual neurologic deterioration. This is because FAODs have reduced gluconeogenesis and increased tissue glucose uptake. Because of their fast metabolic rate and limited glycogen reserves, neonates might die suddenly from FAODs if they are not treated quickly enough [7].

From a biochemical standpoint, excess l-carnitine derivatives of distinctive fatty acids build up in patient tissues, which has a harmful effect on cells and exacerbates symptoms. Whenever there is a greater as fatty acids are drawn out of adipose tissue, as happens during fasting or lengthy periods of exercise, metabolic acidosis, hypoglycemia, and acute episodes of hyperammonemia are more likely to occur, and their concentrations are higher as well. Various FAODs fall into three categories: There are three issues that need to be addressed: first, the transportation of fatty acids with long and very long chains into the mitochondria; second, the oxidation of fatty acids with medium and short chains; and third, the transfer of electrons from mitochondrial β-oxidation to the respiratory chain. In clinical practice, the most prevalent FAODs are deficits in medium-chain acyl-CoA dehydrogenase (MCAD), long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), and very long-chain acyl-CoA dehydrogenase (VLCAD) [8].

Therefore, mitochondrial malfunction can impair oxidative phosphorylation and, by extension, ATP synthesis, which is particularly detrimental to tissues like muscles, the heart, and the brain that rely on energy for their functional capability. The energy deficit that patients experience can be exacerbated when toxic lipides and their metabolites build up in FAODs and disturb mitochondrial homeostasis [9].

2. Fatty acid oxidation disorders (FAOD)

2.1 Medium-chain acyl-CoA dehydrogenase deficiency (MCADD)

The most frequent FAOD is MCADD (12). When NBS was first introduced, the mortality rate for MCADD was at least 20%. However, since therapy can be started as soon as possible after diagnosis, both mortality and morbidity have decreased below 5%. Dehydration, lethargy, hypoketotic hypoglycemia, and vomiting are symptoms of MCADD, which can develop in infants and toddlers as a result of infections. Clinical manifestations of liver disease can resemble those of Reye syndrome. Hyperammonemia and cerebral edema, which can develop from untreated, undiagnosed sickness, can cause mortality in people of any age due to its progressive nature [10].

Patients lacking MCAD may not exhibit any symptoms at all, or they may exhibit a severe phenotype that, when triggered by fasting or catabolic stress, generates metabolic acidosis, latic acidemia, hypoketotic hypoglycemia, nausea, vomiting, convulsions, and weakness; at its most severe, this phenotype can cause coma or sudden infant mortality. A breakdown in the Krebs cycle substrate conversion of fatty acids to acetyl-CoA, may underlie some of these symptoms. In addition to MCAD deficiency, hepatomegaly and hyperammonemia are seen in individuals, which can affect brain functioning and lead to encephalopathy. Acute bouts often include several symptoms such as myopathy, hypotonia, persistent muscular weakness, and rhabdomyolysis. People of any age can develop MCAD deficiency eventually [11].

Neonatal screening for MCAD deficiency using LC/MS/MS analysis of acylcarnitines present in the blood of suspected persons can achieve a fair prognosis when the disease is detected early. Patients have elevated levels of GC/MS-detectable glycine derivatives (hexanoyl-, suberyl-, and phenylpropionylglycine) in their urine in addition to blood octanoylcarnitine (OC) buildup. Pathogenic mutations in the ACADM gene can also be identified, hence confirming the diagnosis [12].

A frequent oral or intravenous feeding of highly caloric carbohydrates is the foundation of the treatment of MCAD deficiency, which aims to prevent fasting by blocking FAO. To further help patients avoid cardiac changes, a diet low in fat might also be recommended. Because it aids in the elimination of aberrant acylcarnitines, prevents secondary free carnitine deficiency, and restores the crucial acylCoA/CoA ratio for mitochondrial activities, l-Car supplementation may be useful in MCAD deficiency. Though l-Car has decreased metabolic decompensation in some individuals and improved their symptoms, there is still no definitive agreement on its usage in MCAD deficiency. Numerous studies have shown that l-Car has antioxidant and antiperoxidative capabilities; they may serve as an extra benefit. By activating octanoyl-CoA dehydrogenase in lymphocytes, riboflavin, like l-Car, appears to enhance the biochemical profile of MCAD-defcient individuals [13].

2.2 Very Long-Chain Acyl-CoA Dehydrogenase Deficiency

A genetic abnormality in the ACADVL gene, which codes for the VLCAD enzyme, leads to VLCAD deficiency. This enzyme is responsible for the inner mitochondrial membrane dehydrogenation of 12- to 18-carbon long-chain acyl-CoA esters. The energy acquisition is hindered, particularly during extended fasting, viral diseases, or physical over-exercise, in the severely life-threatening autosomal recessive disorder VLCAD deficiency, which affects an estimated 1 in 30,000 to 1 in 100,000 neonates [14].

People of all ages and stages of severity might experience the varied symptoms of a VLCAD deficiency, which primarily impacts the heart, liver, and skeletal muscles. In children, VLCAD deficiency manifests itself in two main ways. The first is associated with a high newborn death rate and is characterized by hypoketotic hypoglycemia, rhabdomyolysis, cardiomyopathy, liver failure, and abrupt bouts of metabolic acidosis. The second phenotype is seen in older children who have hypoketotic hypoglycemia episodes more frequently, but they tend to have a better prognosis in the long run because cardiomyopathy is less common. The later-onset phenotype of VLCAD deficiency is more commonly associated with muscle injury (rhabdomyolysis) and metabolic decompensation, which are caused by exercise and catabolic circumstances (fever and hunger, respectively). Because of the documented genotype-phenotype connections in VLCAD deficiency, the most severe forms of the disease, in which there is no residual enzyme activity, have been associated with homozygosity or compound heterozygosity for null variants [15].

One treatment for very low cholesterol is a low-fat diet that includes medium-chain triglycerides (MCT). These triglycerides can be completely oxidized in the mitochondrial β-oxidation pathway and have shown great effectiveness in preventing and treating heart conditions like cardiomyopathy and skeletal myopathy. The same holds true for fatty acid oxidation diseases (FAODs): avoiding buildup requires regular meals and the rapid treatment of fever and other diseases. Because it can lead to the increase of toxic acylcarnitines, the use of L Car, even at modest levels, is contentious when it comes to preventing secondary carnitine deficiency. Some other medicinal substances, such as the medium odd-chain fatty acid triheptanoin and the muscular relaxant bezafbrate, have improved the cardiac and skeletal muscle functioning of patients [16].

2.3 Long-Chain 3-hydroxyacyl-CoA Dehydrogenase Deficiency

At the inner mitochondrial membrane, you'll find the mitochondrial trifunctional protein (MPT) complex, which includes long-chain 3-hydroxy-acyl CoA dehydrogenase, which catalyzes the third step in the oxidation of long-chain fatty acids. The α-subunit of the MPT complex, which is encoded by the HADHA gene, is mutated in 1:250,000 newborns worldwide, causing LCHAD deficiency, which is passed down through an autosomal recessive inheritance pattern. When people fast or exercise for lengthy periods of time, their bodies produce less energy, have less acetyl-CoA available, and experience hypoketosis. They also build up LC3HFA and LC3-hydroxyacylcarnitines in their tissues [17].

The clinical manifestations of LCHAD, a serious condition, can vary greatly. In the neonatal period, the majority of patients experience a severe phenotype that can be fatal. This phenotype is marked by problems with the heart and liver, problems with the nervous system, possible metabolic decompensation crises, hypoketotic hypoglycemia, lactic acidemia, skeletal myopathy, hypotonia, and metabolic acidosis, with potentially more severe consequences. Clinical signs such as hypotonia, seizures, mental retardation, cardiomyopathy, peripheral neuropathy, and retinopathy are milder in patients with late-onset variants [18].

Patients with suspected LCHAD deficiency should undergo mass spectrometry testing to confirm the presence of 3-hydroxytetradecanoic, 3-hydroxyhexadecanoic, 3-hydroxyoctadecanoic, 3-hydroxysebacic, 3-hydroxydehydrosebacic, 3-hydroxydodecanedioic, and their carnitine derivatives in their blood or urine. Although newborn screening (NBS) can discover LCHAD or MPT deficiencies early by long-chain 3-hydroxyacylcarnitines analysis, molecular analysis and measurement of fibroblast enzyme activity are often necessary for confirming a diagnosis [19].

3. Carnitine transport disorders

Carnitine is essential for the translocation of long-chain fatty acids through the inner membrane of mitochondria. A sodium-dependent carnitine transporter moves the acyl-CoA-linked carnitine across the inner mitochondrial membrane in the first of these three steps, and a second transferase removes the acyl-CoA-linked carnitine from the first.

3.1 Carnitine palmitoyltransferase type 1 deficiency (CPT1D)

Only CPT1A deficiency, which manifests in the kidneys and liver, has been documented, although three distinct isoforms of the CPT1 enzyme are encoded by separate genes. Hypoketotic hypoglycemia, liver dysfunction, and quick development to liver failure are early pediatric manifestations of CPT1D. Skeletal myopathy in adults is uncommon, and hypoglycemia in neonates is even rarer. It has been reported that epidoses of acute decompensation can cause renal tubular acidosis. Laboratory results show lower levels of long-chain acylcarnitines and higher levels of free plasma carnitine; NBS for CPT1D is accessible in most states. The specificity of NBS is enhanced by an aberrant ratio of C0/(C16+C18). The CPT1A gene or the activity of the fibroblast enzyme can be sequenced genetically. There may be a correlation between the greater rates of newborn mortality and impaired fasting intolerance in Arctic populations and the milder phenotype of CPT1D [20].

3.1 Carnitine-acylcarnitine translocase deficiency (CACTD)

The worst case scenario for congenital arterial coronary disease (CACTD) is a newborn with severe cardiomyopathy, irregular heartbeats, low blood sugar, high levels of ammonemia, or sudden death. Symptoms that may be experienced by older patients include moderate hypertrophic cardiomyopathy, vomiting, mild hypoglycemia, mild chronic hyperammonemia, and severe skeletal myopathy. Seizures, significant developmental delay, and other complications may still befall many patients even after early diagnosis with NBS and treatment [21]. Although the degree of illness does not always correlate with its severity, some patients may have a lesser version of the disease with increased enzyme activity. Because CPT2D is caused by identical acylcarnitine profiles in both NBS and plasma, it is crucial to confirm NBS results and diagnoses based on plasma acylcarnitines using DNA sequencing of SLC25A20. Even with NBS, patients still face a poor prognosis and a low probability of survival. Treatment does not eliminate the risk of seizures and significant developmental delay in children [22]. The worst case scenario for congenital arterial coronary disease (CACTD) is a newborn with severe cardiomyopathy, irregular heartbeats, low blood sugar, high levels of ammonemia, or sudden death. Symptoms that may be experienced by older patients include moderate hypertrophic cardiomyopathy, vomiting, mild hypoglycemia, mild chronic hyperammonemia, and severe skeletal myopathy. Seizures, significant developmental delay, and other complications may still befall many patients even after early diagnosis with NBS and treatment. Although the degree of illness does not always correlate with its severity, some patients may have a lesser version of the disease with increased enzyme activity. Because CPT2D is caused by identical acylcarnitine profiles in both NBS and plasma, it is crucial to confirm NBS results and diagnoses based on plasma acylcarnitines using DNA sequencing of SLC25A20. Even with NBS, patients still face a poor prognosis and a low probability of survival. Treatment does not eliminate the risk of seizures and significant developmental delay in children [23].

4. Inherited disorders of fatty acid oxidation

There have been 17 reported hereditary abnormalities in proteins that impact the process of β-oxidation or the carnitine dependent transport of long chain fatty acids. Even though ACAD9, ACAD10, and ACAD11 are all long chain acyl-CoA dehydrogenases that have been identified, little is known about how they contribute to the pathogenesis of human disease [24].

4.1 Inadequate supply of energy:

While fasting, the liver draws fatty acids from adipose tissue and uses them to make ketone bodies. These ketone bodies drive the extra hepatic tissue and have the added benefit of "sparing" glucose for other important tissues, particularly the brain. There is a high proportionate glucose utilisation in cerebral tissue in babies, making this "glucose sparing effect" all the more crucial. Hypoglycemia occurs when the body is unable to maintain normal blood sugar levels due to depleted glycogen stores and a lack of ketones, which prevents the gluconeogenic pathways from producing enough glucose [25].

Gluconeogenesis in the liver and ketone body production in the extrahepatic tissues work together to supply energy during fasting. A continual supply of acetyl-CoA, NADH+H+, and ATP from fat oxidation sustains hepatic gluconeogenesis, which uses amino acids as its primary substrate. Hypoglycemia emerges when gluconeogenesis is hindered due to an inconsistent supply of these molecules.

Even in the fed condition, a considerable amount of energy is derived by skeletal and cardiac muscle from the β-oxidation of long chain fatty acids. In patients with long-chain abnormalities, myocardial fat oxidation is significantly reduced, and these fatty acids are likely moved to a compartment with sluggish turnover, where they mostly undergo esterification to triglycerides. Hypertrophy of the myocardial seems to be the end outcome of a long-term, highly-understood remodeling brought about by the myocardium's forced increased dependence on glucose, which is mediated by significant changes in gene expression. Muscle weakness, exercise intolerance, and persistent hypotonia are symptoms of skeletal muscle receiving an inadequate amount of energy. Similarly, hyperammonaemia and encephalopathy caused by a malfunctioning urea cycle are common outcomes of a decrease in the availability of hepatic ATP for the essential and diverse metabolic processes taking place within the hepatocyte [26].

4.2 Accumulation of toxic metabolites

The missense type accounts for about two-thirds of all disease-associated gene variants; these changes can cause misfolding to lead to aberrant protein conformations. Several cellular variables determine the harmful effects of aberrant proteins on the hypothesized fatty acid oxidation metabolone.

The process of beta-oxidation Some mitochondrial defects, such as octanoyl-CoA in medium chain acyl-CoA dehydrogenase deficiency (MCADD), are known to produce short, medium, and long chain acyl-CoA intermediates, depending on the specific defect. Some of these intermediates have been found to be extremely hazardous. After leaving the mitochondria, these intermediates undergo βoxidation and/or ʊ-oxidation in the peroxisomal pathway, resulting in various carboxylic and dicarboxylic acids ranging from C4 to C16, as well as certain unsaturated species. The mitochondria can once again oxidize dicarboxylic and short- and medium-chain carboxylic acids. Having said that, there have been reports of harmful effects from carboxylic acid derivatives, specifically C8-C10 and 3-hydroxy C12-C16 [27].

4.3 Sequestration of vital components

There is a limited supply of coenzyme A in the mitochondria, and it cannot pass the mitochondrial membrane. Sequestration of coenzyme A as acyl-CoA intermediates results from β-oxidation defects. With the exception of CPT1 deficiency, all primary abnormalities of fatty acid oxidation lead to either a decrease in total plasma L-carnitine concentration or an increase in the acyl: free L-carnitine ratio. In order to free up coenzyme A, free L-carnitine helps remove unmetabolized acyl groups from the mitochondria. When total Lcarnitine levels drop, the kidneys excrete acylcarnitine instead. The depletion of L-carnitine is worsened by acylcarnitines because they block the renal tubule's carrier-mediated reabsorption of L-carnitine. Many fatty acid oxidation disorders involve a mix of energy deficit, potentially harmful metabolites, and sequestration of essential components, making it difficult to assess the role of toxic metabolites in the pathophysiology of disease in humans [28].

4.4 Altered enzyme product:

Acute respiratory distress syndrome (ARDS) has been reported in both newborns and older patients with mitochondrial trifunctional protein (MTP) deficiency and isolated long chain 3-hydroxyacyl-CoA dehydrogenase (LCHADD) deficiencies. The lung is the site of expression for the MTP complex and the long chain acyl CoA dehydrogenase LCAD. Mutations in MTP/LCHAD may increase the risk of acute respiratory distress syndrome (ARDS) through a variety of pathways, including aberrant surfactants and mitochondrial malfunction. Patients with LCHAD/MTP abnormalities may have the surfactant's phospholipid components changed and its function impaired due to the accumulation of fatty acid metabolites. The absence of LCAD has been associated with one episode of respiratory distress. Since surfactant includes a number of lipid components, including palmitoyl myristoyl phosphatidylcholine, this may indicate that LCAD and MTP protein play a role in substrate modification during surfactant formation. Fatty acid chain shortening would be required for myristic acid synthesis [29].

4.5 Loss of protein-protein interaction

Hypoglycemia caused by an excess of insulin is a symptom that patients with SCHAD deficiency (short chain 3-hydroxyacyl-CoA dehydrogenase) sometimes experience. It has been demonstrated that this is caused by the SCHAD protein losing its ability to inhibit glutamate dehydrogenase. This protein is unique in that it can work as an enzyme and also interact directly with other proteins.

5. Phenotypic diversity in fatty acid oxidation disorders

Fatty acid oxidation disorders cause a broad variety of medical conditions. Homozygous MCADD, for example, can manifest as hypoketotic hypoglycemia in infants or adults, or as neonatal ketoacidosis with encephalopathy in newborns, even if the mutation is present in all three. Even while we still don't fully understand how this variety occurs, new information on the metabolome-dictating multiple gene expression is giving us a better idea [30]. Several FAODs, such CPT2, very long chain acyl-CoA dehydrogenase (VLCAD), and multiple acyl-CoA dehydrogenase (MAD) deficiency, do exhibit a strong genotype/phenotype connection, especially when comparing the severe phenotypes to the milder ones. Nevertheless, in a number of diseases, such as MCADD and CTD, the association is significantly weaker or nonexistent. The phenotype is known to be affected by a wide range of variables, including but not limited to: the amount and duration of exercise, the frequency and duration of fasting, the presence or absence of intercurrent infections, the energy substrate type (fat vs. carbohydrates), the amount and duration of drug exposure, and the protective effects of antioxidants and co-factors. It is still a mystery to us why some LCHADD patients reach adulthood with just minor retinal alterations as an indication of clinical illness, while others experience considerable morbidity, chorioretinopathy, and neuropathy—even in cases when the condition is generally well-controlled [31]. Many genes involved in intermediate metabolism have their functional activity influenced by variations in single nucleotide polymorphisms (SNPs), which is being better understood. The regulatory processes that impact this phenotypic diversity may be better understood with the recent explanation of the peroxisome proliferators-activated receptor gamma-Co-activator-1α (PGC-1α) transcriptional complexes regulated through the silent information regulator; ortholog of mammalian sirtuin (SIRT1) pathways [32].

6. Therapies under investigation

6.1 Triheptanoin

Triheptanoin, a triglyceride composed of three seven-carbon fatty acids, has been studied for potential usage as an alternate fuel. Once hydrolyzed in the small intestine to three molecules of heptanoic acid, the acid undergoes β-oxidation to generate acetyl-CoA and propionylCoA. These byproducts can subsequently be introduced into the citric acid cycle. In the liver, pentanoyl-CoA can act as a substrate for anaplerotic reactions and produce 5-carbon ketone bodies (β-hydroxypentanoate and β-ketopentanoate) that peripheral tissues can use. It is in the realm of possibility that triheptanoin inhibits lipolysis and the buildup of harmful metabolites in LCFAODs [33].

Three VLCADD patients who had anaplerotic treatment with triheptanoin reported relief from cardiac symptoms, muscular weakness and exhaustion, hypoglycemia, and hepatomegaly during the initial month of treatment. No improvement in rhabdomyolysis was noted. Despite no improvement in LCHADD-associated retinopathy, subsequent investigations demonstrated comparable results in TFPD, CPT2D, and CPT1D. Other clinical trials, such as a Phase II FDA study with double-blind participants, are currently in progress. Longitudinal randomized clinical trials comparing triheptanoin efficacy to that of MCT oil standard therapy are now under way [34].

6.2 Gene transcription activation

Some studies have suggested using bezafibrate, a medicine already used to treat hyperlipidemia, to raise HDL levels while decreasing LDL and triglyceride levels. The PPAR agonist bezafibrate increases gene transcription for numerous targets, including CPT2D and VLCADD. Results from clinical trials with patients with CPT2D and VLCADD have been mixed, with some reporting improvements in quality of life and a decrease in rhabdomyolysis episodes and creatine kinase levels, while others found no improvement in clinical symptoms or fatty acid oxidation during exercise [35]. Quality of life scores improved consistently, whereas creatine kinase levels and plasma acylcarnitine levels increased and reduced, myopathic attacks decreased, and plasma acylcarnitine levels increased, in a recent open label trial including individuals with VLCADD and CPT2D. The development of this possible medicine certainly needs additional clinical trials.

7. Conclusions

Significant morbidity and death are linked with the FAOD category of autosomal recessive illnesses; however, results are improving with early diagnosis on NBS and treatment beginning. Possible benign features, chronic skeletal myopathy, or even fatal newborn cardiomyopathy can be among the many clinical manifestations of these diseases. Nutritional therapy with a low-fat diet, supplementation with medium-chain triglycerides (MCTs), intensive treatment when sick, and maybe carnitine are all parts of the current treatment plan. Symptoms, particularly rhabdomyolysis and cardiomyopathy, continue to pose a serious threat despite the considerable progress achieved thus far. Randomized, controlled therapeutic trials and other forms of clinical research are necessary for the ongoing evaluation of existing knowledge and the development of new treatments.

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EVALUATION STUDY OF UV AND HPLC METHODS FOR ANTI-DIABETIC DRUGS IN COMPARISON

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Abstract:

Accurate medication quantification is crucial for treatment effectiveness and safety in diabetes mellitus, a chronic metabolic disease marked by persistent hyperglycemia that requires ongoing pharmacological control. Among analytical techniques, High-Performance Liquid Chromatography (HPLC) and Ultraviolet-Visible (UV-Vis) spectrophotometry are widely used for anti-diabetic medication analysis. Their concepts, uses, benefits, and drawbacks are examined in this comparative analysis. Regular quality control of single-component formulations can benefit from UV-Vis spectrophotometry simplicity, affordability, speed of analysis, and ease of use. However, because to matrix interferences and overlapping spectra, its low specificity and moderate sensitivity restrict its application in complicated mixes. On the other hand, even in complicated matrices, HPLC effectively separates and quantifies various pharmacological components due to its great sensitivity, specificity, and adaptability. Rigid pharmaceutical analysis benefits from HPLC's automation and repeatability despite its increased expense, technical complexity, & solvent use. While HPLC is excellent in simultaneous multi-drug quantification, including metformin combos and more recent anti-diabetics, studies show that UV techniques are effective at estimating medications like repaglinide and metformin. Sample complexity, needed sensitivity, specificity, resource availability, & throughput requirements all influence which of these approaches is best. All things considered, HPLC and UV are still essential to the examination of anti-diabetic drugs, with HPLC being chosen for thorough, accurate pharmacological evaluations and UV for ease of use and cost considerations.

Keywords: HPLC, UV-Spectrophotometry, Anti-Diabetic,

Introduction:

The hallmark of diabetes mellitus, a chronic metabolic disease, is persistent hyperglycemia brought on by deficiencies in either insulin action or secretion, or both. Pharmacological therapies are necessary for the lifetime management of this chronic metabolic disease. Pharmaceutical development & therapeutic monitoring depend heavily on the measurement & quality control of anti-diabetic medications. It is often divided into gestational diabetes, type 2 diabetes (insulin resistance with relative insulin shortage), type 1 diabetes, and other particular kinds [1]. According to the World Health Organization (WHO), 422 million persons worldwide were predicted to have diabetes in 2014; this number is expected to climb sharply over the next several decades [2]. Diabetes-related chronic hyperglycemia has been connected to long-term harm to the kidneys, heart, blood vessels, nerves, and eyes [3]. Because of their sensitivity and dependability, High-Performance Liquid Chromatography (HPLC) and Ultraviolet (UV) spectrophotometry are often used among the various analytical techniques available. The concepts, benefits, drawbacks, and uses of UV and HPLC methods for the investigation of anti-diabetic medications are compared in this chapter.

Antidiabetic Drugs

Pharmacological medicines known as anti-diabetic medications are used to help diabetic patients reach & maintain normal blood glucose levels. Among these agents are:

Oral Insulins for Diabetes

- Biguanides, including metformin, are known to improve insulin sensitivity and reduce the synthesis of glucose in the liver.
- Glibenclamide is one example of a sulfonylurea, which stimulates the pancreatic β-cells to secrete insulin.
- Thiazolidinediones: increase peripheral insulin sensitivity (e.g., pioglitazone).
- The incretin impact is heightened by dipeptidyl peptidase-4 (DPP-4) inhibitors, such as sitagliptin.
- Canagliflozin and other SGLT2 inhibitors decrease the kidneys' ability to reabsorb glucose.
- When oral medications are inadequate, especially in type 1 diabetes, insulin and its analogues are used.
- Repaglinide and nateglinide are meglitinides.
- Alpha-glucosidase inhibitors include voglibose, miglitol, and acarbose.
- Exenatide, liraglutide, dulaglutide, and semaglutide are examples of GLP-1 receptor agonists.

Injectable Antidiabetic Drugs:

- GLP-1 receptor agonists, such as exenatide, liraglutide, dulaglutide, and semaglutide, are injectable antidiabetic medications.
- Dual GLP-1/GIP receptor agonists are a novel family of type 2 diabetes drugs.
- Pramlintide is an analogue of amylin.

For therapeutic efficacy & safety, analytical techniques for figuring out the concentration & purity of these medications in biological samples and pharmaceutical formulations are essential. Because of their dependability and versatility across several drug classes, UV spectrophotometry & HPLC are two of the most commonly employed of these [4,5].

UV- Spectroscopy:

In pharmaceutical sciences, ultraviolet-visible (UV-Vis) spectrophotometry is a commonly used analytical method, especially for the quantitative identification of active pharmaceutical ingredients. Its simplicity, affordability, and quick analytical capabilities are the main reasons for its appeal. Compounds with chromophores that absorb light in the UV-Vis range, which is often between 200 and 800 nm, respond very well to UV-Vis spectrophotometry. In quality control labs, this technique is often used to analyse different pharmaceutical formulations [6].The core idea of UV-Vis spectrophotometry is based on the Beer-Lambert law, which says that the molar absorptivity (ε) of the compound, the path length (l) of the sample cell, and the concentration (c) of the absorbing species all directly affect the absorbance (A) of a solution: $A = \varepsilon lc$. Electronic transitions between molecular orbitals occur when a UV or visible light beam travels through a solution and is absorbed by a particular wavelength. It is possible to precisely ascertain the analyte concentration in the solution by measuring the absorbance at particular wavelengths [7]. There are a number of benefits to using UV-Vis spectrophotometry in pharmaceutical analysis. It is a non-destructive method that yields results quickly and requires very little sample. Because the equipment is user-friendly and reasonably priced, it may be used for routine analysis. Furthermore, the approach is flexible, suitable for both qualitative & quantitative investigations, and applicable to a broad variety of substances. Its great sensitivity makes it possible to identify analyte concentrations that are low, which is essential for stability and quality control investigations. UV-Vis spectrophotometry has several drawbacks despite its benefits. For complicated mixes, the method is less successful since overlapping absorption bands might make precise measurement difficult. Additionally, it is restricted to substances having chromophores that absorb in the UV-Vis range; derivatization is required to analyse non-absorbing substances. Furthermore, the analysis may become more difficult if there are contaminants or degradation products present that have overlapping spectra. The accuracy & precision of the data may also be impacted by matrix effects & solvent interferences [8].

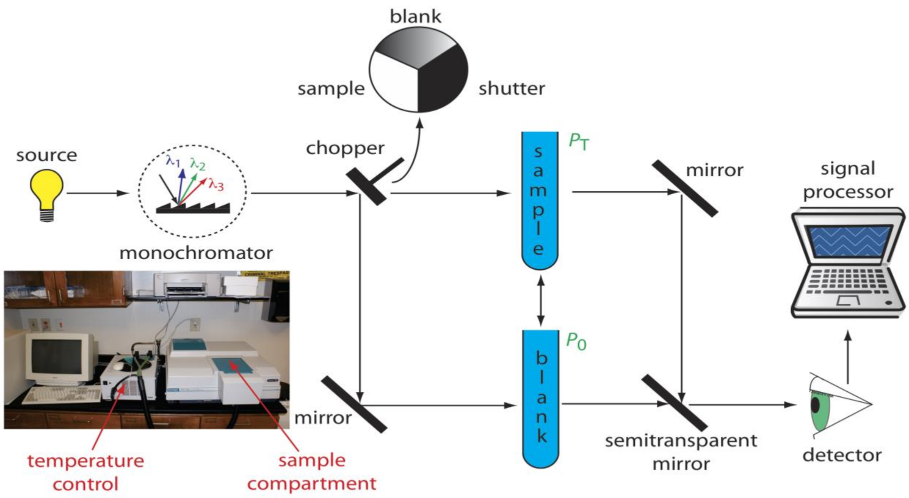

Figure 1: UV Spectrophotometer

HPLC:

The advanced analytical method known as High-Performance Liquid Chromatography (HPLC) is often used in biological, environmental, and medicinal studies. It makes it possible to separate, identify, and measure the constituents of intricate mixes. The technique is essential for guaranteeing the efficiency and quality of pharmaceutical items, especially anti-diabetic medications, because to its high resolution, sensitivity, as well as adaptability. HPLC's place in contemporary analytical labs has been cemented by its versatility in handling different sample matrices and detection techniques [9]. The differential partitioning across a mobile phase & a stationary phase is the basis for HPLC's operation. After passing through a column filled with a stationary phase, a liquid sample is added to a stream of solvent (the mobile phase). The components of the sample interact differently with the stationary phase as it moves through the column, causing them to separate according to variations in polarity, molecule size, or affinity. Usually, mass spectrometry, fluorescence, or UV-Vis spectrophotometry are used for detection, yielding both qualitative and quantitative information on the analytes [10]. A popular method in analytical labs, High-Performance Liquid Chromatography (HPLC) has several noteworthy benefits. Its excellent sensitivity & specificity, which allow for the accurate detection and measurement of even the smallest analyte concentrations, are among its main advantages. In pharmaceutical analysis, where precise measurements are essential, this is especially crucial. Furthermore, HPLC has exceptional adaptability, working with a broad range of chemical substances, including those that are non-volatile or thermally unstable—properties that make it appropriate for examining intricate medication formulations. Because it enables quick component separation with great resolution, the technology is also known for its speed & efficiency, which supports high-throughput operations in quality control and research contexts. Reproducibility and automation are other benefits. HPLC systems may be connected with automated data processing and sample handling, which reduces human error and guarantees reliable findings. Last but not least, the approach provides quantitative precision, producing accurate and repeatable data that is necessary for strong quality assurance procedures and regulatory compliance. High-Performance Liquid Chromatography (HPLC) has a number of drawbacks that should be taken into account when choosing an analytical method, despite its many advantages. The high cost of the original investment and continuing operating costs is one major disadvantage. HPLC is a somewhat costly choice for regular analysis, particularly in smaller or resource-constrained laboratories, due to its complex apparatus and need for high-purity consumables like columns and solvents. Furthermore, because of the technique's technological complexity, labour and training expenses may rise as skilled workers are required for system operation, maintenance, & method development. The widespread usage of organic solvents, many of which are poisonous, combustible, or harmful to the environment, is another issue. This presents environmental issues with relation to solvent disposal & sustainability in addition to safety hazards in the lab. Additionally, HPLC sample preparation is frequently complex and time-consuming. Filtration, dilution, & the elimination of any interferences may be necessary to prevent column damage and guarantee precise, repeatable findings. These actions can slow down analysis and decrease workflow efficiency in general, especially in high-throughput settings [11].

Figure 2: HPLC

Application of HPLC and UV Spectrophotometry Methods for Analyzing Anti-diabetic Drugs

For pharmaceutical formulations to be safe and effective, precise measurement of anti-diabetic medications is essential. High-Performance Liquid Chromatography (HPLC) and UV spectrophotometry are two analytical methods that are often used in this field.

An easy, quick, and affordable technique for routinely analyzing anti-diabetic medications in tablet and bulk form is UV Spectrophotometry. For example, a study by Patel *et al.* created and verified UV spectrophotometric techniques for repaglinide measurement in tablets, showing exceptional linearity, accuracy, and precision. The usefulness of a UV spectroscopic approach for the simultaneous measurement of metformin hydrochloride and empagliflozin in pharmaceutical dosage forms and bulk was also highlighted by Munde *et al.* [12].

However, when examining complicated mixes or formulations with overlapping spectra, UV spectrophotometry may encounter difficulties. Derivative spectrophotometric techniques have been used to address this. For instance, a research group created green UV derivative spectrophotometric techniques that successfully resolved overlapping spectra and improved method selectivity for the simultaneous measurement of metformin & remogliflozin from formulations [13,14].

Because of its increased sensitivity, specificity, and adaptability, High-Performance Liquid Chromatography (HPLC) is a good choice for analyzing complicated matrices and many components. Gedawy *et al.* created and verified an HPLC technique for the simultaneous measurement of gliclazide and metformin in approved goods and bulk, proving its usefulness in combination therapy analysis. Similar to this, Naseef *et al.* published a quick and sensitive HPLC approach that was verified in accordance with FDA and ICH requirements for assessing alogliptin benzoate in pharmaceutical dosage forms and bulk [15].

Additionally, HPLC techniques have been refined for the simultaneous measurement of many anti-diabetic medications. To demonstrate its usefulness in quality control and pharmacokinetic studies, Chaudhary *et al.* created an HPLC method for the simultaneous analysis of six important anti-diabetic medications in pharmaceutical formulations: metformin, sitagliptin, dapagliflozin, linagliptin, empagliflozin, & vildagliptin, [16,17].

Evaluation of UV and HPLC in Comparison

Table 1: Comparative Analysis

Parameter	UV Spectrophotometry	HPLC
Sensitivity	Moderate	High
Specificity	Low (in mixtures)	High
Cost	Low	High
Sample Preparation	Simple	Moderate to complex
Analysis Time	Short	Moderate
Suitability for Complex Matrices	Poor	Excellent
Method Development	Quick	Time-consuming

To sum up, HPLC and UV spectrophotometry are both useful analytical methods for identifying anti-diabetic medications. The sample matrix's complexity, the requirement for sensitivity or specificity, and the resources at hand all influence which option is best.

Conclusion:

Both High-Performance Liquid Chromatography (HPLC) and Ultraviolet (UV) spectrophotometry are crucial analytical methods for antidiabetic medication analysis, and each has unique advantages. Because UV spectrophotometry is quick, easy, and affordable, it may be used for regular quality control of bulk materials and single-component medications, particularly in environments with limited resources. However, because of overlapping spectra and decreased specificity—problems that derivative UV approaches only partially address—its efficacy decreases with complex mixes. On the other hand, HPLC provides exceptional sensitivity, specificity, and adaptability, making it possible to precisely separate and measure many medications in intricate formulations and biological materials. HPLC provides dependable and legally valid results, which are essential for sophisticated pharmaceutical analysis, despite its greater price and technical requirements. Thus, sample complexity, sensitivity requirements, and available resources determine which method is best; HPLC is favoured for in-depth, high-precision studies, whereas UV is appropriate for simpler applications. Therapeutic monitoring and medication quality assurance can be maximized by combining the two approaches.

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GREEN SYNTHESIS IN PHARMACY

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Abstract:
Green synthesis in pharmacy represents a transformative approach that integrates the principles of green chemistry into drug discovery, development, and manufacturing. With the growing need for sustainable and environmentally responsible pharmaceutical practices, Green synthesis seeks to encourage the use of renewable raw materials, minimize or completely eradicate the use of harmful compounds, and lower energy usage. Based on the twelve green chemistry principles put forward by Anastas and Warner, this approach facilitates the creation of safer and more efficient chemical processes without compromising therapeutic efficacy. In pharmaceutical applications, green synthesis promotes the use of non-toxic solvents, biodegradable excipients, techniques that use less energy, such as microwave-assisted synthesis & renewable feedstocks. It has shown particular promise in the green production of nanoparticles, biocatalysis, and solvent-free reactions, making it highly relevant in the development of advanced drug delivery systems. Furthermore, it aligns well with regulatory frameworks that encourage sustainable manufacturing, offering both environmental and economic benefits. The future of green synthesis in pharmacy is expected to be driven by advancements in artificial intelligence, machine learning, biorefineries, and green analytical methods. Integration of these technologies will allow for the optimization of synthesis pathways and further reduce the environmental footprint of pharmaceutical production. As the pharmaceutical industry increasingly embraces sustainability, green synthesis is poised to become a foundational strategy in building a cleaner, safer, and more innovative healthcare system.

Keywords: Green Chemistry, Sustainable Pharmacy, Drug Formulation, Eco-Friendly Synthesis, Biocatalysis

Introduction:

Green synthesis, also referred to as environmentally benign or sustainable synthesis, is a transformative concept in pharmaceutical sciences that aligns closely utilizing the green chemistry principles. It involves designing of chemical process/products in a manner which significantly reduces/eliminates the usage of hazardous substances. As the pharmaceutical industry faces increasing pressure from environmental regulations, resource scarcity, and the global movement toward sustainability, green synthesis has emerged as a key strategy to create safer, more efficient, and eco-friendly drug development processes. Paul Anastas and John

Warner formally developed the concept of green chemistry, the cornerstone of green synthesis, in 1998. Twelve guiding principles that offer a scientific basis for creating chemical processes that are environmentally responsible were proposed by them [1]. These guidelines place a strong emphasis on energy efficiency, atom economy, using renewable feedstocks, and creating safer chemicals and solvents. The aim is not merely to reduce environmental impact but to fundamentally reimagine chemical manufacturing to be inherently safer and more environmentally friendly right from the start.

In pharmaceutical context, green synthesis plays a vital role in several areas, including drug discovery, formulation, production, and waste management. It permits the use of safe substitutes like water, ethanol, or hypercritical fluids in place of hazardous solvents and promotes catalytic over stoichiometric reagents to minimize waste. Additionally, green synthesis enables the development of one-pot reactions, microwave-assisted synthesis, and biocatalytic processes that are less energy-intensive and more resource-efficient. One of the most notable advantages of green synthesis is its compatibility with the principles of QbD (quality by design) & PAT (process analytical technology), which are increasingly used in modern pharmaceutical manufacturing. These methodologies facilitate monitoring and managing production operations in real time, ensuring that product quality is maintained while environmental impact is minimized. Green synthesis also holds promise in the preparation of nanoparticles and drug delivery systems, providing a sustainable substitute for traditional physical and chemical synthesis techniques. Biological entities such as plant extracts, bacteria, fungi, and enzymes have been successfully used to synthesize metallic and polymeric nanoparticles, providing a biocompatible and non-toxic route for advanced drug formulations. Moreover, embracing green synthesis can significantly reduce costs, improve safety, and enhance regulatory compliance, making it both an environmentally and economically sound strategy. The incorporation of life cycle assessment (LCA) further helps evaluate the environmental footprint of pharmaceutical products from synthesis to disposal, enabling more informed decision-making. A paradigm change in pharmaceutical chemistry is represented by green synthesis. By integrating sustainability into every stage of the drug development lifecycle, it not only addresses environmental and regulatory challenges but also paves the way for more innovative, safe, and responsible healthcare solutions.

Foundations of Green Chemistry

The twelve principles of green chemistry, put forth by Anastas and Warner in 1998, regulate green synthesis in the pharmaceutical industry. Waste reduction, atom economy, better solvent and reaction conditions, energy efficiency, renewable feedstocks, and the creation of less hazardous and biodegradable chemical products are some of these concepts[2]. Application of these principles minimizes harmful impacts during drug development and manufacturing.

Green Chemistry's 12 Principles:

1. Prevention

First principle emphasizes prevention of waste rather than waste treatment. In pharmacy, this involves designing processes that inherently generates minimal amount of waste rather than after creating waste. For example, choosing atom-efficient reactions during the manufacture of APIs (Active Pharmaceutical Ingredients) might stop byproducts from being produced [3].

2. Atom Economy

Atom economy refers to designing synthetic methods to ensure that every material utilized during the process is fully incorporated into the finished product. This minimizes raw material use & waste generation. The usage of catalytic hydrogenation in place of stoichiometric reagents is a practical application in synthesis of NSAIDs [4].

3. Reduced Toxic Chemical Manufacturing

Substances with low or no toxicity should be used and produced using synthetic processes.

In pharmacy, this means replacing harmful reagents like phosgene or cyanide with safer alternatives, thus reducing occupational and environmental risks [5].

4. Designing Safer Chemicals

Pharmaceutical compounds shall be effectively designed so to reduce toxicity. Medicinal chemistry increasingly involves structural modifications that retain pharmacological activity while minimizing side effects and environmental persistence. For example, prodrug development can target specific tissues, reducing toxicity (systemic)[6].

5. Safer Solvents & Auxiliaries

Solvent contribution significantly to the environmental burden of pharmaceutical processes. Green chemistry promotes usage of water, ethanol, supercritical CO_2, or ionic liquids instead of volatile organic solvents like chloroform or benzene [7]. In solid-phase peptide synthesis, less toxic solvents such as dimethyl carbonate are gaining acceptance.

6. Design for Energy Efficiency

To save energy, reactions should be carried out at room temperature and pressure whenever feasible. Techniques like microwave-assisted synthesis and ultrasound-promoted reactions are being employed in pharmaceutical labs for faster, energy-efficient reactions [8].

7. Utilizing Sustainable Feedstocks

Renewable raw resources ought to take the place of non-renewable ones wherever it is both technically and financially possible. Examples in pharmacy include using plant-based precursors for alkaloids, steroids, and other natural product-derived drugs [9].

8. Cut Down on Derivatives

Blocking, protection/deprotection, and temporary alteration are examples of unnecessary derivatization actions that should be avoided. These procedures frequently produce waste and need for more reagents. Simplifying synthesis lowers expenses, environmental effect, and reaction stages.

9. Catalysis

Catalyst whether chemical or biological are preferred over stoichiometric reagents. Catalysts offer the advantage of being used in smaller quantities and reused, often with improved selectivity and lower energy demands. In pharmaceutical chemistry, metal catalysts like palladium or enzymatic catalysts are widely used for chiral synthesis [10].

10. Design for Degradation

Products should break down into non-toxic substances in the environment. In pharmaceuticals, designing biodegradable drugs and excipients ensures that drug residues in wastewater do not accumulate or disrupt ecosystems [11].

11. Real-Time Analysis for Pollution Prevention

Analytical methodologies should allow for real-time monitoring to prevent the formation of hazardous substances. Process Analytical Technology (PAT) is employed in modern pharmaceutical manufacturing to ensure product quality and minimize waste in real-time [12].

12. Inherently Safer Chemistry for Accident Prevention

Chemical processes should be designed to minimize the potential for explosions, fires, and accidental releases. This includes choosing reagents with low flammability or toxicity and avoiding pressurized conditions. Aqueous-phase reactions are examples of inherently safer conditions in pharmaceutical synthesis [13].

Role of Green Synthesis in Drug Formulation:

Beyond synthesis, green chemistry principles are applied in drug formulation processes. For example, using biodegradable and biocompatible excipients in dosage forms ensures safer degradation. Solid lipid nanoparticles, liposomes, and polymeric nanoparticles formulated through green methods provide controlled drug release with minimal side effects [14]. Green synthesis, grounded in the principles of green chemistry, is an environmentally conscious approach to drug formulation that emphasizes sustainability, safety, and efficiency. The role of green synthesis in drug formulation spans across all stages of pharmaceutical development—from the selection of raw materials to the final dosage form—integrating eco-friendly practices without compromising therapeutic efficacy. With the increasing demand for sustainable pharmaceutical practices, green synthesis offers a viable alternative to conventional formulation methods that are often energy-intensive and reliant on toxic solvents or hazardous intermediates.

1. Green Excipients and Biodegradable Materials

A key aspect of green drug formulation is the selection of sustainable excipients—substances used to aid the manufacturing and delivery of active pharmaceutical ingredients (APIs). Natural, biodegradable polymers such as chitosan, alginate, pectin, and cellulose derivatives are widely used for their non-toxic nature and favorable pharmacokinetics. These materials degrade harmlessly in biological and environmental systems and do not accumulate as persistent pollutants [15]. For example, chitosan, derived from the exoskeletons of crustaceans, exhibits mucoadhesive and controlled-release properties and is biodegradable and biocompatible [2]. Such materials help in developing oral, topical, and injectable formulations with reduced environmental impact.

2. Use of Green Solvents in Formulation

Traditional pharmaceutical formulations often use volatile organic solvents (VOCs) such as methanol, chloroform, or dichloromethane, which pose significant environmental and health hazards. Green synthesis promotes the use of green solvents—such as water, ethanol, ethyl lactate, ionic liquids, and supercritical fluids—that offer similar or better solubility and reactivity without adverse effects [16]. Supercritical carbon dioxide ($scCO_2$) is particularly promising. It is non-toxic, non-flammable, and recyclable, and is used in particle size reduction and encapsulation technologies [17]. Solvent substitution in formulations, especially for parenteral preparations, enhances patient safety and manufacturing sustainability.

3. Microwave and Ultrasound-Assisted Formulations

Energy-intensive processes in formulation can be replaced with microwave-assisted and ultrasound-assisted techniques. These methods allow rapid heating and molecular activation, thereby reducing reaction time, solvent use, and energy consumption. In the synthesis of nanoparticles and emulsions, these technologies enhance homogeneity, reduce aggregation, and minimize solvent residues [18]. For instance, microwave-assisted synthesis of solid lipid nanoparticles (SLNs) has shown reduced reaction times and better control over particle size distribution, improving bioavailability and formulation efficiency [19].

4. Plant-Mediated Nanoparticle Formulations

Green synthesis is pivotal in the eco-friendly production of nanoparticles used in targeted drug delivery. Plant extracts, containing phytochemicals like flavonoids and polyphenols, act as natural reducing and capping agents for nanoparticle synthesis. This eliminates the need for toxic chemicals like hydrazine or sodium borohydride. Silver and gold nanoparticles synthesized using plant extracts (e.g., *Azadirachta indica*, *Ocimum sanctum*) have demonstrated antimicrobial and anticancer properties and are explored in transdermal and injectable formulations [20]. These biologically synthesized nanoparticles are more biocompatible and safer for clinical applications.

5. Supercritical Fluid Technology in Formulation

Supercritical fluids, particularly CO_2 above its critical temperature and pressure, are used in drug formulation to solubilize and encapsulate poorly water-soluble drugs. This is crucial in enhancing drug bioavailability, especially for lipophilic compounds. The Rapid Expansion of Supercritical Solutions (RESS) and Supercritical Anti-Solvent (SAS) techniques allow solvent-free particle generation [21]. Drugs like paclitaxel, itraconazole, and curcumin have been successfully formulated using $scCO_2$, yielding nano- or microparticles with improved dissolution and reduced toxicity [22].

6. Green Polymers in Controlled Drug Release

Controlled release formulations benefit significantly from green polymer technologies. Polymers such as polylactic acid (PLA), polyglycolic acid (PGA), and polycaprolactone (PCL) are derived from renewable resources and degrade into non-toxic by-products [23]. These are used in transdermal patches, implants, and injectable depots. For example, PLGA microspheres are widely employed in injectable sustained-release formulations, such as Lupron Depot, an FDA-approved product. The polymer matrix degrades into lactic and glycolic acids, which are metabolized via the Krebs cycle [24].

7. Green Analytical and Quality Control Approaches

Green synthesis also includes adopting real-time analytical technologies during formulation development. Tools such as Process Analytical Technology (PAT) and Quality by Design (QbD) support continuous monitoring of critical formulation parameters like particle size, dissolution, and pH. These methods eliminate the need for destructive sampling and reduce resource wastage, ensuring consistent product quality and regulatory compliance [25].

8. Solvent-Free and Dry Processing Techniques

Techniques like hot-melt extrusion (HME) and compression molding enable formulation of solid dosage forms without solvents. These are particularly useful in the development of orally disintegrating tablets (ODTs) and drug-loaded films, where uniform dispersion and stability are critical. The HME process is compatible with thermolabile drugs and biodegradable polymers, aligning with the green synthesis ethos [26].

9. Green Extraction in Herbal Drug Formulation

In the formulation of herbal drugs and nutraceuticals, green synthesis emphasizes the use of green extraction methods, including microwave-assisted extraction (MAE), ultrasound-assisted extraction (UAE), and supercritical fluid extraction (SFE). These methods improve yield, reduce solvent usage, and preserve the phytochemical profile of plant materials [14]. For example, MAE has been used to extract high-purity curcumin from turmeric (*Curcuma longa*) for incorporation into anti-inflammatory and antioxidant formulations [27].

10. Regulatory and Environmental Benefits

Pharmaceutical industries adopting green synthesis gain strategic advantages in terms of regulatory acceptance, eco-certification, and market differentiation. Reduced toxic solvent residues and lower carbon emissions align with global environmental regulations such as the REACH directive and Good Manufacturing Practice (GMP) guidelines [28]. Moreover, consumer awareness of eco-friendly and clean-label pharmaceuticals further motivates the integration of green synthesis into drug formulation.

Benefits of Green Synthesis:

The advantages of green synthesis in pharmacy include:

- Environmental Safety: Reduces toxic emissions, waste, and effluents.
- Cost-Efficiency: Minimizes raw material and energy consumption.
- Regulatory Compliance: Meets stringent environmental standards.
- Improved Safety: Safer working conditions for scientists and reduced patient risk.
- Innovation and Sustainability: Encourages research into renewable resources and cleaner technologies [29].

Challenges and Limitations:

Despite its benefits, green synthesis faces several challenges in pharmaceutical application:

- Scalability: Lab-scale green processes may not be easily scaled to industrial production.
- Cost of Green Catalysts: Some biocatalysts and green reagents are expensive.
- Lack of Awareness: Limited training and awareness among researchers.
- Regulatory Gaps: Absence of uniform guidelines on green synthesis practices [30].
- Economic Constraints: Initial costs for green technologies may be high.
- Technological Limitations: Not all green alternatives are efficient or scalable.
- Resistance to Change: Traditional methods are deeply entrenched in pharmaceutical manufacturing [31].

Nonetheless, ongoing research and technological advancements are addressing these barriers, making green synthesis increasingly viable.

Case Studies

Case 1: Green Synthesis of Ibuprofen

A BHC Company process redesigned the synthesis of ibuprofen using a catalytic process instead of traditional six-step synthesis. This method significantly reduced waste and increased yield, embodying atom economy and waste prevention [32].

Case 2: Plant-Mediated Nanoparticles

Green synthesis of gold nanoparticles using *Ocimum sanctum* (holy basil) has demonstrated enhanced therapeutic efficacy in drug delivery applications, particularly for anti-inflammatory and anticancer treatments [33].

Future Prospects:

The future of green synthesis in pharmaceutical sciences is poised for significant growth, driven by technological innovation, environmental imperatives, and evolving global regulations. As the pharmaceutical industry shifts towards more sustainable practices, green synthesis is expected to play a pivotal role in transforming drug development, formulation, and manufacturing. One of the most promising future directions is the integration of artificial intelligence (AI) and machine learning (ML) to optimize green chemical pathways. AI can facilitate the prediction of reaction outcomes, optimize synthetic routes for atom economy, and reduce the trial-and-error approach in formulation development. Machine learning algorithms, when applied to green chemistry databases, can suggest the most efficient, least toxic, and cost-effective synthetic methods, saving both time and resources [34]. Additionally, AI-driven modeling tools can be used to design and evaluate green solvents and catalysts, significantly improving reaction efficiency and reducing environmental impact. Another emerging area is the development of biorefineries, which utilize renewable biological resources such as agricultural waste, lignocellulosic biomass, and algae to produce pharmaceutical intermediates and active pharmaceutical ingredients (APIs). These systems not only reduce reliance on petrochemical feedstocks but also contribute to waste valorization, promoting a circular economy [35]. For instance, algae-based platforms are being explored for producing lipids, proteins, and other bioactive compounds suitable for pharmaceutical use, offering high yields with minimal ecological footprint [36]. Green analytical chemistry is also expected to gain momentum in pharmaceutical quality control and research. Techniques such as solvent-free sample preparation, microextraction, and the use of environmentally benign mobile phases in chromatography will help minimize solvent consumption and hazardous waste generation. The miniaturization of analytical systems and the adoption of point-of-care green diagnostics could further enhance sustainability in pharmaceutical analysis [37]. In sourcing raw materials, future pharmaceutical manufacturing will increasingly rely on sustainable resources, such as agro-industrial by-products, marine organisms, and biodegradable polymers. These alternatives are not only renewable and biodegradable but also often possess inherent biological activity, providing dual functionality in drug delivery systems [38]. Pharmaceutical companies are also anticipated to adopt green certifications and sustainability labels as part of their corporate social responsibility (CSR) initiatives. Certifications such as ISO 14001 for environmental management and LEED for green manufacturing facilities demonstrate commitment to sustainable practices and enhance brand value. Investors and consumers are increasingly favoring environmentally responsible companies, and green synthesis will become a competitive advantage in this context [39]. Furthermore, future policies are likely to mandate eco-design in pharmaceutical product development. International regulatory bodies may introduce guidelines and incentives that support green synthesis, including tax benefits, fast-track approvals, or public funding for green R&D initiatives.

Conclusion:

Green synthesis has emerged as a transformative paradigm in pharmaceutical sciences, steering the discipline toward sustainability, safety, and environmental responsibility. Rooted in the principles of green chemistry—as outlined by Anastas and Warner in 1998—this approach advocates for minimizing waste, reducing toxicity, and designing energy-efficient, resource-conscious processes and products [40]. These principles serve not only as scientific guidelines but also as a roadmap for aligning pharmaceutical innovation with global environmental and ethical standards. In the context of drug formulation and manufacturing, green synthesis entails the use of biodegradable excipients, non-toxic and renewable solvents like water and ethanol, and innovative methods such as biocatalysis, microwave-assisted synthesis, and supercritical fluid extraction. These techniques reduce harmful emissions, lower energy consumption, and eliminate the need for hazardous reagents—contributing significantly to both product safety and environmental conservation [42]. Additionally, plant-mediated synthesis of nanoparticles and other green nanotechnologies have shown great promise in the development of eco-friendly drug delivery systems with improved efficacy and biocompatibility. From an economic and regulatory standpoint, green synthesis provides a dual benefit. It reduces the costs associated with waste management and toxic waste disposal, while also facilitating smoother compliance with stringent environmental and pharmaceutical regulations. As consumer awareness grows and demand for sustainable products rises, pharmaceutical companies that adopt green synthesis are better positioned to meet both market and compliance expectations [43]. However, the widespread implementation of green synthesis still faces several challenges. Issues such as scalability, standardization of green reagents, and regulatory gaps need to be addressed through focused research, interdisciplinary collaboration, and international policy support[44,45]. Moreover, there is a pressing need to incorporate green chemistry principles into pharmaceutical education to equip the next generation of scientists and formulators with the tools and mindset necessary for sustainable innovation. Future efforts should also emphasize the development of green technologies such as AI-assisted synthesis route prediction, green solvents databases, and automated environmentally conscious synthesis systems. Policy interventions, including incentives for green manufacturing and sustainability certifications, will further accelerate the adoption of green synthesis practices across the pharmaceutical value chain.

In conclusion, green synthesis in pharmacy is not merely a technical advancement but a holistic, ethical, and scientific imperative. It offers a sustainable alternative to conventional practices by harmonizing drug development with ecological preservation and public health[46]. As environmental challenges intensify and healthcare systems seek more sustainable solutions, green synthesis stands out as a vital cornerstone of a resilient, responsible, and forward-looking pharmaceutical industry.

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ENHANCING MEDICATION ADHERENCE: INNOVATIVE STRATEGIES FOR PATIENT ENGAGEMENT AND EDUCATION

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Abstract:
The issue of medication adherence presents a significant obstacle in the pursuit of optimal health outcomes, particularly among individuals with enduring medical conditions. This review, grounded in scholarly sources, delves into novel patient-centric methodologies aimed at bolstering adherence by means of active involvement and education, with a focus on innovative technological, individualized, and interdisciplinary approaches. Advancements in the realm of digital health, including the integration of AI-driven conversational agents like ChatGPT, customized alert mechanisms, and prognostic analytics, are being assimilated into healthcare frameworks to promote adherence, monitor health indicators, and furnish bespoke medication prompts. Tailored communication tactics steered by AI and electronic health records have demonstrated marked enhancements in patient contentment, adherence to treatment regimens, and a decrease in hospital readmissions. Coordinated care paradigms, particularly those involving clinical pharmacists, augment adherence through the provision of comprehensive, real-time, and patient-tailored interventions. Telemedicine and remote monitoring modalities have proven notably efficacious amid the COVID-19 crisis, heightening medication adherence and healthcare accessibility while mitigating emergency department visits. Evidence from diverse medical disciplines, encompassing gastroenterology, congestive heart failure, and the management of alcohol use disorders, substantiates the efficacy of digital interfaces in chronic disease oversight. Furthermore, specialized technologies tailored for distinct demographic groups, such as diabetic patients in resource-scarce regions, underscore the promise of equitable digital interventions. Nevertheless, ethical, legal, and confidentiality considerations endure, accentuating the imperative for regulatory supervision and secure deployment. Subsequent strategies should center on surmounting these obstacles and expanding patient-centered digital innovations to ensure enduring enhancements in medication adherence.

Keywords: Medication Adherence, Patient Engagement, Artificial Intelligence, Telemedicine, Digital Health, Personalized Communication, Chronic Disease Management, Clinical Pharmacy, Remote Monitoring, Healthcare Technology.

Introduction:

The issue of medication adherence poses a significant challenge within the realm of healthcare provision, impacting patient outcomes, healthcare expenditure, and the overall quality of care.

Despite advancements in medical interventions, inadequate adherence to medication remains a barrier to achieving desired therapeutic outcomes in various chronic illnesses. This exhaustive review of literature explores novel methodologies aimed at improving medication adherence by fostering patient engagement and education, with a specific emphasis on evolving technologies and individualized approaches. The healthcare domain has experienced a shift towards patient-centric care paradigms, recognizing the pivotal role of active patient involvement in effective disease management. Patient-focused strategies encompass mechanisms to facilitate efficient communication, collaboration, and health education, all of which are fundamental constituents of high-quality healthcare provision. In the sphere of medication adherence, these components acquire heightened significance as they significantly impact patients' comprehension of and dedication to their prescribed treatment protocols [1].

Digital Technologies for Enhancing Medication Adherence

AI-Powered Chatbots and Conversational Agents

Artificial intelligence, notably in the guise of chatbots and conversational agents, has emerged as a promising asset for enhancing adherence to medication regimens. An example of this is seen in ChatGPT, which leverages natural language processing to comprehend user input and provide relevant responses, thereby serving as a valuable resource for individuals seeking information or educational opportunities. ChatGPT, an AI-driven chatbot, demonstrates a versatile scope that extends across various domains, including science, technology, entertainment, and current affairs. Within healthcare environments, it offers tailored suggestions based on user preferences and interests, assists in task organization such as setting reminders, scheduling appointments, and making reservations, and provides guidance on health, wellness, financial management, and professional development. These features underscore the potential benefits of AI-driven chatbots for improving medication adherence. The capacity of ChatGPT to transform the healthcare industry is evident through its wide array of services. These services encompass diagnostics, patient health surveillance, pharmaceuticals, patient involvement, healthcare provision, and health research. ChatGPT also offers assistance to individuals facing mental health challenges such as anxiety and depression by providing help with stress reduction, mindfulness techniques, and relaxation methods. Notable applications include the use of chatbots in suicide prevention and cognitive-behavioral therapy, potentially offering virtual therapeutic interventions for those reluctant to engage in direct therapy sessions. To enhance patient involvement, ChatGPT provides personalized health recommendations and motivational prompts to encourage healthy behaviors. This empowers patients to take an active role in managing their health and improving their well-being. Additionally, ChatGPT assists patients in managing chronic conditions like diabetes, hypertension, stroke, cardiovascular diseases, cancer, dermatological conditions, and neurological disorders. It achieves this by offering information and personalized advice on medications and lifestyle adjustments, aiding in symptom control and enhancing their quality of life. Regarding medication management specifically, ChatGPT provides insights on prescription medications, their uses, and potential side effects. It also facilitates medication monitoring and timely reminders to promote adherence. Furthermore, ChatGPT supports patients in health monitoring by tracking essential parameters like blood pressure, heart rate, and blood glucose levels, enabling data sharing with healthcare providers to facilitate informed clinical decisions. Despite the manifold advantages, a noteworthy 96.7% of scrutinized literature raises apprehensions regarding the use of ChatGPT, citing concerns encompassing ethical considerations, copyright infringement, transparency and legal issues, biases, plagiarism risks, content inaccuracies with the potential for inducing hallucinations, limited expertise, citation inaccuracies, cybersecurity vulnerabilities, and the peril of information epidemics. These apprehensions underscore the imperative for judicious integration and oversight of AI-powered tools in healthcare environments [2,3].

Notification Scheduling Systems

Notification scheduling systems represent a notable technological strategy aimed at improving medication adherence within healthcare settings. These systems have been pivotal in augmenting patient outcomes by ensuring the timely delivery of alerts, reminders, and notifications to patients, healthcare providers, and caregivers. The primary goal of this approach is to enhance medication adherence, reduce instances of hospital readmissions, and foster increased patient engagement. Within the realm of healthcare, notification scheduling plays a critical role in optimizing patient care and outcomes by facilitating personalized and timely communication with individuals. The efficacy of these systems is heavily reliant on their design and execution, requiring a meticulous calibration of notification strategies that are unobtrusive while accurately informing users. Such strategies must encompass the optimization of personalized content, timing, and frequency. The evolution of artificial intelligence (AI) and machine learning technologies has further bolstered notification scheduling systems by integrating predictive analytics and tailored notifications. The advancements in healthcare information systems, particularly electronic health records and clinical decision support systems, have shown substantial potential in reducing medication errors, improving chronic disease management, and enhancing preventive care. These technologies help clinicians access comprehensive patient data, flag potential drug interactions, and facilitate personalized treatment plans, thereby improving clinical outcomes and patient safety. However, these benefits come with important concerns regarding patient confidentiality and data security. The use of digital systems creates vulnerabilities where unauthorized access or data breaches could expose sensitive health information. To mitigate these risks, strict adherence to regulatory frameworks like the Health Insurance Portability and Accountability Act (HIPAA) in the United States and the General Data Protection Regulation (GDPR) in the European Union is critical. These regulations establish standards for protecting patient data privacy and security throughout its lifecycle, including collection, transmission, and storage. In addition to regulatory compliance, technical safeguards are essential. Employing end-to-end encryption ensures that data remains secure during transmission between healthcare providers, preventing interception or tampering. Likewise, encrypting data at rest protects patient information stored in databases or servers from unauthorized access, even in the event of physical theft or hacking attempts. Together, these encryption methods form a vital security layer, ensuring that sensitive health data maintains confidentiality and integrity in both transit and storage, thereby supporting trust in digital healthcare solutions [4].

Personalized Communication Approaches

Tailored communication has emerged as a pivotal strategy in improving adherence to medication regimens. Effective healthcare communication plays a crucial role in patient engagement, treatment compliance, and overall health enhancement. Conventional medical communication methods that deliver generic messages and reminders often fail to resonate with patients, leading to suboptimal adherence to prescribed medications, decreased response rates, and increased hospital readmissions. Recent studies have delved into the impact of personalized healthcare messages driven by artificial intelligence on health outcomes. These systems generate personalized health messages for individual patients by combining Natural Language Processing (NLP), Machine Learning (ML), and Electronic Health Records (EHR) integration. The effectiveness of such tailored approaches has been substantial. In a study involving a sample of 500 individuals divided into two cohorts (250 receiving conventional communication methods and 250 receiving customized messages from artificial intelligence), the group receiving personalized messages exhibited significantly higher response rates (82.5% vs. 55.3%), medication adherence (89.4% vs. 67.8%), and patient satisfaction scores (8.9 vs. 6.7 out of 10). Moreover, hospital readmissions decreased from 21.4% (standard) to 12.3% (personalized), and missed appointments reduced from 18.5% to 8.2%. These results suggest that tailored healthcare messaging facilitated by artificial intelligence substantially enhances patient engagement, promotes adherence to treatment regimens, and leads to cost savings in healthcare. Nevertheless, ethical considerations, challenges related to data security, and the scalability of the system are also addressed in the study. It underscores the necessity of achieving a balance in healthcare communication between artificial intelligence-driven approaches and human oversight [5].

Integrated Care Models and Multidisciplinary Approaches

Integrated care models that engage a variety of healthcare professionals have demonstrated potential in improving adherence to medications. The management of hypertension within Federally Qualified Health Centers (FQHCs), for instance, necessitates novel and thorough approaches that go beyond conventional methodologies. Research has investigated cooperative strategies by integrating clinical pharmacists into the healthcare team and employing Electronic Medical Record (EMR) systems. These frameworks tackle both medical and non-medical determinants of health, providing comprehensive care for marginalized populations irrespective of their financial capabilities. The incorporation of clinical pharmacists is posited to enhance and maintain blood pressure regulation, leading to a higher proportion of patients achieving their desired health outcomes. As members of interdisciplinary teams, clinical pharmacists identify, monitor, and evaluate patient data, oversee medication therapies through collaborative practice agreements, and collaborate with other healthcare professionals to ensure uninterrupted care. By utilizing the data management and patient monitoring features of EMRs, clinical pharmacists utilize real-time data to customize medication regimens, provide timely interventions, and conduct follow-up sessions every 2 to 4 weeks via telehealth or in-person visits until patients attain their targets. This method enhances patient involvement and medication adherence, which are critical for effective blood pressure control and cost containment. Moreover, it supports individualized care that addresses medical requirements, lifestyle factors, and socioeconomic aspects influencing patient well-being. Early findings from a 2024 study revealed that among 327 patients, 58% received a minimum of 2 consultations with a clinical pharmacist. Within this cohort, 46% achieved blood pressure control below 140/90 mmHg, while 27% displayed progress towards their objectives. This quality-focused and outcome-oriented strategy raises the benchmarks for hypertension management, diminishes health disparities, and improves healthcare provision within FQHCs [6].

Telemedicine and Remote Monitoring Solutions

Telemedicine has emerged as a crucial tool in improving medication adherence, particularly amidst the COVID-19 pandemic. It involves the utilization of electronic communication technologies to deliver healthcare services remotely. Patient satisfaction and engagement are fundamental metrics for healthcare facilities and providers aiming to enhance the continuum of care and ensure ongoing quality enhancement within healthcare systems. Telemedicine has played a pivotal role in patient connectivity for consultations and follow-up, particularly during the pandemic. Studies have indicated a notable increase in patient satisfaction levels and a positive shift in patient attitudes towards telemedicine. Additionally, improvements in parameters such as medication adherence, reduced readmission rates, and decreased emergency department utilization times have been noted. Clinical outcomes have been documented, revealing a strong correlation ($r = 0.9$) between readmission rates and medication adherence. The statistical analysis has shown a highly significant p-value concerning the reductions in emergency department visits, readmission rates, and medication adherence. In the treatment of alcohol use disorder (AUD), innovative strategies are crucial for improving the accessibility and engagement of patients, as AUD treatment remains underutilized. The Ria Treatment Platform (RTP) is a patient-centered telemedicine program designed for the treatment of AUD and can be accessed through a smartphone application. This program includes teleconsultations with physicians, prescription management for AUD medications, support from a recovery coach via text and phone, video monitoring of medication adherence, and Bluetooth-enabled breathalyzer monitoring of alcohol consumption. An evaluation of the RTP demonstrated a 55% retention rate in treatment at the 90-day mark. Analysis of blood alcohol content data showed that among patients who were actively involved for 90 days, the average levels decreased by around 50% (from.091 to.045) from the baseline to day 90. These results provide initial evidence of substantial reductions in alcohol intake among individuals using the RTP, a novel telemedicine intervention accessible via smartphones. While other alcohol reduction apps have shown promise in scientific evaluations, the RTP distinguishes itself as the only application that combines physician-prescribed medications with the support of a recovery coach [7,8]. The COVID-19 pandemic significantly increased the adoption and availability of telehealth services in outpatient settings. While telehealth has been extensively validated across various medical fields, its application in gastroenterology, particularly for chronic diseases like inflammatory bowel disease (IBD), has not been thoroughly explored. Research has aimed to assess the effectiveness of telehealth in gastroenterology by comparing medication adherence rates between patients using telehealth and those attending traditional in-person consultations for various gastrointestinal (GI) conditions. A study found that the medication fulfillment rate was 98.2% for patients engaged in telehealth consultations compared to 89.1% for those attending in-person visits (P = 0.004). Furthermore, patients utilizing telehealth services were 6.8 times more likely to adhere to prescribed medications than those attending face-to-face appointments (OR 6.82, CI 1.51 – 30.68, P = 0.004). Excluding biologic therapies, the prescription fill rate for the telehealth group was 94.7% versus 81.4% for the in-person group (OR 4.11, CI 0.88 – 19.27, P = 0.056). These findings collectively suggest that medication adherence rates were higher for telehealth patients, highlighting the potential of telehealth as a valuable option for outpatient management, especially for individuals managing persistent GI conditions such as IBD. In the context of heart failure (HF), a widespread global health issue marked by increased morbidity, mortality, and healthcare utilization rates, traditional in-person care models face difficulties in ensuring continuous monitoring and timely interventions. Telemedicine has emerged as a promising solution to address these challenges in HF management. Evidence from randomized controlled trials and meta-analyses indicates that telemedicine interventions can improve the implementation of guideline-directed medical therapies, reduce hospitalization rates, enhance patient engagement, and potentially lower mortality rates among HF patients. Remote monitoring systems, capable of tracking vital signs, symptoms, and medication adherence, enable early detection of clinical deterioration, facilitating prompt interventions before decompensation occurs. Despite these benefits, the implementation of telemedicine encounters obstacles such as technological limitations, reimbursement complexities, variations in digital literacy, and challenges in integrating workflows. Future strategies include developing standardized protocols, creating patient-centered technological solutions, and establishing hybrid care models that combine virtual and in-person modalities. As healthcare systems globally seek more effective and efficient approaches to managing the growing population of HF patients, telemedicine emerges as a viable strategy with the potential to significantly improve patient outcomes and quality of life [9,10].

Digital Health Technologies for Specific Populations

Digital health technologies have been increasingly tailored to meet the specific needs of patient populations, especially those suffering from chronic diseases such as diabetes. In the Asian and Western Pacific regions, diabetes prevalence has risen dramatically, posing a significant global health challenge. Effective diabetes management in these regions heavily depends on patients' self-care behaviors such as monitoring blood glucose, maintaining physical activity, and following dietary recommendations. Unfortunately, achieving optimal glycemic control remains difficult, particularly in developing countries where healthcare resources are limited. A shortage of healthcare providers and insufficient healthcare funding exacerbate these challenges, making regular clinical follow-ups and patient education less accessible to large portions of the population. Digital health technologies offer promising solutions by promoting patient engagement and improving adherence to therapy, effectively bridging gaps in healthcare access. For example, mobile health applications provide patients with tools for tracking their physical activity, dietary intake, and glucose levels, empowering individuals to better manage their condition. Telemedicine platforms facilitate remote consultations with healthcare providers, which is crucial in areas where specialist access is scarce. Electronic health records (EHR) enable streamlined management of patient data, improving continuity of care and reducing fragmentation. These technologies collectively help tailor diabetes management to individual patient needs, potentially improving outcomes where traditional healthcare infrastructure is insufficient. Despite their benefits, several barriers impact the adoption of digital health in diabetes care. Infrastructure limitations, such as poor internet connectivity in rural areas, limit the use of mobile and telemedicine platforms. Regulatory barriers, including inconsistent policies for digital health products and unclear data governance frameworks, hinder widespread implementation. Data security and privacy concerns also reduce patient trust in digital systems, discouraging usage. To address these issues, many Asian countries have launched national digital health strategies and created regulatory frameworks to guide the development and deployment of digital tools. For instance, countries like Singapore and South Korea have invested heavily in digital health infrastructure and policy development, promoting wider adoption. Nevertheless, disparities in digital health readiness persist across the region, with lower-middle-income countries lagging behind developed nations. To ensure successful implementation, efforts must focus on strengthening digital infrastructure, developing user-friendly and culturally appropriate app interfaces, and ensuring compliance with regulatory requirements concerning data protection and quality standards. Validating the clinical effectiveness of digital health interventions through rigorous studies is essential to build confidence among patients and providers. Looking forward, integrating advanced technologies such as machine learning and artificial intelligence within diabetes digital interventions offers new possibilities. AI-driven tools can provide personalized recommendations, predict disease progression, and optimize treatment plans in real-time. However, these innovations must be accompanied by equitable access initiatives to avoid widening the digital divide in healthcare. Prioritizing the validation and usability of digital health tools will be key to maximizing their potential in improving diabetes care in Asia and the Western Pacific [11].

Peer Support and Community Health Worker Approaches

HCV transmission is predominantly driven by intravenous drug use, leading to concentrated epidemics in rural areas where healthcare access is limited. This has necessitated innovative service delivery models that incorporate peer support and community health workers to overcome structural barriers such as stigma, transportation, and lack of specialized providers. Peer support strategies in HCV care often include community-based screening, patient navigation through pre-treatment evaluation steps, linkage to telemedicine services, and ongoing medication adherence support. Peers who have lived experience with HCV and/or substance use provide culturally competent guidance, enhance trust, and reduce disengagement from care. This approach yields high sustained virological response (SVR) rates, meaning successful treatment completion and viral clearance in these populations. Notably, interventions embedding peers have demonstrated not only improved clinical outcomes but also reductions in risky behaviors associated with HCV transmission, illustrating a dual benefit of individual and public health impact. Telemedicine integration is pivotal for rural populations, enabling remote specialist care access that otherwise would be unavailable. Simplified testing and treatment protocols facilitate patient adherence and outcome monitoring, especially when combined with the support roles of peers, who may assist in medication reminders and addressing social determinants that threaten adherence. Community health worker interventions have also proven highly effective in managing other chronic diseases, offering valuable lessons relevant to HCV. For instance, a large-scale community health worker-led program in Argentina targeted hypertension management in low-income adults. The intervention involved comprehensive training for both patients and families, supplemented by frequent home visits and behavior change communication through in-person contact and text messages. This resulted in a significant reduction of systolic blood pressure by 6.6 mm Hg and diastolic pressure by 5.4 mm Hg compared to usual care, with a 21% absolute increase in controlled blood pressure rates (73% intervention vs. 52% standard care). The multipronged approach entailed training physicians to adopt stepped-care treatment strategies, highlighting the importance of coordination across the care continuum facilitating sustained outcomes. This robust evidence underscores that community-centered, culturally tailored interventions that address social, behavioral, and healthcare system factors can markedly improve chronic disease outcomes. Their success in hypertension management suggests potential translatability to HCV treatment adherence programs, particularly in rural or marginalized communities. In conclusion, integrating peer support experts and community health workers with telemedicine and streamlined care pathways holds promise for improving HCV treatment adherence and outcomes in rural PWUD populations. The success of CHWs in managing hypertension further supports the scalability and adaptability of such interventions to HCV and other chronic health conditions requiring sustained patient engagement [12, 13].

Challenges and Limitations

Despite the progress made in improving medication adherence through various strategies, several persistent challenges and limitations remain. For instance, while notification scheduling systems offer advantages, they also pose risks concerning patient confidentiality and data protection [4]. Similarly, AI-based tools like ChatGPT present ethical concerns, copyright issues, transparency challenges, legal implications, potential biases, plagiarism risks, lack of originality, inaccurate information leading to potential misconceptions, limited knowledge base, incorrect referencing, cybersecurity vulnerabilities, and the threat of spreading misinformation [3]. Studies focusing on AI-driven chatbots have identified worries regarding accuracy, cybersecurity, and the incapability of AI systems to empathize [14]. The results from the survey revealed a moderate level of acceptance (67%) towards AI-powered chatbots, demonstrating a significant inverse relationship with perceived low IT proficiency (OR = 0.32 [CI95%: 0.13–0.78]), disinclination to engage with computers (OR = 0.77 [CI95%: 0.60–0.99]), and a substantial positive association with perceived utility (OR = 5.10 [CI95%: 3.08–8.43]), positive attitudes (OR = 2.71 [CI95%: 1.77–4.16]), and perceived dependability (OR = 1.92 [CI95%: 1.13–3.25]). Although a majority of online users demonstrate a willingness to utilize healthcare chatbots, concerns surrounding this technology may impede its acceptance. To overcome these challenges, developers of AI-driven healthcare chatbots should implement user-centric and theory-driven approaches to address patient reservations and improve user experiences to promote optimal acceptance and utilization. It is imperative to take into account patients' perspectives, incentives, and competencies in the development and assessment of the effectiveness of healthcare chatbots [14]. The implementation of telemedicine encounters various obstacles, such as technological constraints, reimbursement challenges, disparities in digital literacy, and difficulties in workflow integration [10]. Likewise, digital health technologies encounter hurdles to widespread adoption, including limitations in infrastructure, regulatory obstacles, and concerns regarding data security [11]. Personalized healthcare messaging strategies also confront difficulties related to ethical considerations, data security issues, and system scalability [5]. Striking a balance between artificial intelligence and human oversight is essential in healthcare communication [5].

Future Directions

The future of enhancing medication adherence strategies relies on the amalgamation of diverse methodologies and the continuous advancement of individualized, technology-oriented interventions. Prospective avenues for telemedicine encompass the formulation of standardized protocols, the development of patient-centric technologies, and the establishment of blended care modalities amalgamating virtual and face-to-face approaches [10]. Regarding digital health technologies, forthcoming endeavors should concentrate on emphasizing app adoption and effectiveness, as well as integrating artificial intelligence and machine learning-driven digital solutions [11]. Tools such as ChatGPT and analogous AI applications can significantly contribute to health investigations through facilitating data aggregation, analysis, and interpretation. They can create an unidentified database by gathering information from patients while safeguarding their anonymity, healthcare professionals, and researchers regarding diverse health-related subjects, including medication adherence and disease prevalence. This dataset can be utilized to recognize trends, regularities, and potential health condition risk factors, inform research investigations, and enhance healthcare results. Furthermore, it can be employed to accumulate patient-reported outcomes, aiding researchers in gaining deeper insights into the patient journey [2]. Insight from studies on personalized healthcare messaging underscores that AI and natural language processing-powered messaging platforms could revolutionize contemporary healthcare delivery, heralding a more adaptable and patient-centered communication conduit [5]. Clinical pharmacists have demonstrated their irreplaceable role within the healthcare team, with upcoming research endeavors aiming to provide pragmatic perspectives and tactics for healthcare practitioners to implement akin models, thereby shaping the future landscape of hypertension care [6]. Further investigations that integrate random allocation and robust comparison cohorts are imperative to more thoroughly assess promising interventions such as telehealth platforms for treating alcohol use disorder [8].

Conclusion:

Improving medication adherence through novel methods of patient engagement and education is a crucial focus of healthcare research and practice. This review has outlined several promising strategies, such as AI-driven chatbots, notification systems, personalized communication, integrated care models, telemedicine, remote monitoring, digital health technologies for specific demographics, and peer support. Each strategy presents distinct benefits and challenges. An optimal approach to boosting medication adherence likely involves a blend of these strategies, customized to individual patient needs and healthcare contexts. Future research should concentrate on overcoming the identified challenges, particularly concerning privacy, data security, ethics, and technical obstacles. Furthermore, more comprehensive studies with larger participant pools and extended observation periods are necessary to determine the sustained efficacy of these innovative interventions. With advancing technology and a growing emphasis on patient-centered care, the field of medication adherence stands to make significant progress. By harnessing the strengths of diverse methods and mitigating their weaknesses, healthcare providers can design more efficient strategies to improve medication adherence, leading to better patient outcomes and reduced healthcare expenses.

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MODERN PERSPECTIVES IN PHARMACY PRACTICE: CURRENT TRENDS AND FUTURE DIRECTIONS

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Abstract:
Contemporary Perspectives on Pharmacy Practice: Present Patterns and Future Prospects" delves into the changing functions of pharmacists within the intricate healthcare environment of today. The profession has transitioned from a focus on products to a lively, patient-centered approach that highlights clinical duties, interdisciplinary teamwork, and technological fusion. This shift has its origins in a lengthy progression, notably in community pharmacy practice, which has traversed various historical stages. Presently, pharmacists are acknowledged worldwide as essential components of healthcare teams, influenced by factors like polypharmacy, elderly demographics, and an increased emphasis on patient results. Noteworthy developments encompass the acceptance of patient-centered care strategies, where pharmacists provide services like medication therapy management (MTM), chronic disease oversight, and public health guidance. Cooperative practice schemes have also gained traction, embedding pharmacists into diverse care environments such as primary care facilities and telehealth systems. The emergence of specialized roles, for instance, in cardiology and critical care, underscores the escalating intricacy and clinical significance of pharmacy practice. Moreover, the redefinition of pharmacy technicians' roles aims to afford pharmacists more opportunities for direct patient care, albeit with regional variability in implementation. Advancements in technology, encompassing digital health resources and telepharmacy, are further transforming pharmacy services, enhancing medication monitoring, patient involvement, and care provision. These advancements underscore the profession's progressive trajectory and the necessity for continual adjustment to address forthcoming healthcare obstacles.

Keywords: Pharmacy Practice, Clinical Pharmacy, Patient-Centered Care, Medication Therapy Management, Interdisciplinary Collaboration, Specialized Pharmacy Roles, Pharmacy Technicians, Healthcare Transformation, Telepharmacy, Digital Health Integration.

Introduction:

The field of pharmacy has experienced a significant transformation in recent decades, transitioning from a focus on product dispensing to a holistic, patient-centered healthcare approach. Since the 1960s, there has been notable progress in the incorporation of clinical pharmacists into healthcare teams, aimed at enhancing drug therapy, fostering wellness, and preventing illnesses. This shift represents a substantial paradigm change, redefining the pharmacist's role within the healthcare system. The evolution of community pharmacy in the United States from the 1920s has been characterized by gradual advancements towards greater professional recognition through modifications in pharmacy education and practice. The history of American community pharmacy in contemporary times can be segmented into four distinct periods: 1920–1949 (Soda Fountain Era), 1950–1979 (Lick, Stick, Pour and More Era), 1980–2009 (Pharmaceutical Care Era), and 2010–present (Post-Pharmaceutical Care Era). This historical context forms the basis for comprehending the present status and direction of modern pharmacy practice. The current landscape of pharmacy is defined by the increasing acknowledgment of pharmacists as essential healthcare providers. Clinical pharmacists are in high demand globally and are now acknowledged as vital members of healthcare teams. This acknowledgment has been hastened by various factors, including the rising complexity of medication regimens, an aging population with multiple concomitant conditions, and the growing emphasis on patient safety and outcomes-focused healthcare.[1,2]

Current Trends in Modern Pharmacy Practice

Patient-Centered Care and Clinical Responsibilities

The prevailing trend in contemporary pharmacy practice entails a notable transition towards patient-centered care paradigms. Pharmacists have seen a gradual increase in their clinical duties, embracing a more individual-focused approach and experiencing heightened participation in healthcare teams across various environments. This evolution surpasses conventional dispensing functions to encompass thorough medication therapy management, patient education, and clinical decision-making. In Indonesia, community pharmacy practice has pivoted towards a patient-centered model, offering a spectrum of services such as therapeutic guidance, chronic illness management, and public health advocacy. This transformation is advantageous for individuals seeking initial healthcare assistance at community pharmacies, highlighting the global implementation of patient-centered strategies with these pharmacies serving as convenient primary healthcare points. The broadening of clinical obligations is notably evident in medication therapy management (MTM) services. Within community pharmacy settings, pharmacists have long been delivering clinical services through MTM and other advanced services that prioritize high-quality care. This article will delineate the evolution of pharmacists' roles in patient management through MTM, present evidence of favorable patient care outcomes resulting from pharmacist-led services in community-based settings, and offer suggestions for U.S. payers to recognize and enhance reimbursement for pharmacist-led services.[3-5]

Collaborative Practice and Interdisciplinary Integration

Current trends in pharmacy practice highlight a shift towards collaborative care models that involve the integration of pharmacists within multidisciplinary healthcare teams. Collaborating with other healthcare professionals is essential for enhancing patient outcomes. This collaborative approach transcends conventional hospital settings and extends to various healthcare settings such as primary care clinics, specialty practices, and telehealth platforms. The growing recognition of pharmacists as medication experts has led to a global push for the adoption of clinical pharmacy practice, which refers to any pharmacist, regardless of the setting, who delivers direct patient care. While the pharmacy profession in Bangladesh traditionally focused on the pharmaceutical industry, there is a gradual emergence of pharmacists assuming direct patient care responsibilities in community and hospital settings. The effectiveness of collaborative drug therapy management (CDTM) has been validated in diverse healthcare systems. Several providers, legislators, and some insurers now acknowledge the critical role of pharmacists, given their education, training, and expertise in therapy. They are increasingly being positioned to take on additional responsibilities in patient care and provide services that can significantly impact outcomes. Programs led by the U.S. Public Health Service, armed forces, Veterans Administration, and 38 states actively support pharmacist involvement in CDTM. Pharmacists working within an interdisciplinary framework alongside physicians and other healthcare professionals have demonstrated improvements in effectiveness, efficiency, and safety, emphasizing the importance of integrating this valuable skill as a fundamental component of modern healthcare service delivery.[1,6,7]

Specialized Practice Areas and Advanced Roles

The evolution of specialized pharmacy practice areas is a significant contemporary trend within the field of pharmacy. Pharmacists are increasingly specializing in specific disease states and patient populations, leading to the development of specialized roles in various therapeutic areas. In Saudi Arabia, pharmacy practice has notably advanced in the last twenty years, with the field of cardiology pharmacy experiencing substantial progress. This advancement has been facilitated by the introduction of several cardiology residency programs, contributing to the growth of cardiology pharmacy practice. An illustrative example of the progression of specialized pharmacy practice can be observed in the intensive care unit (ICU) setting. The evolving role of pharmacists in this specialized area signifies a transformation from traditional drug dispensing tasks to becoming integral members of multidisciplinary clinical teams dedicated to enhancing healthcare outcomes. Particularly crucial in the ICU setting, where patients often present with critical illness, multiorgan dysfunction, metabolic imbalances, preexisting comorbidities, and complex therapeutic interventions, pharmacists play a vital role in managing the intricate effects of drug pharmacokinetics and pharmacodynamics. Research consistently demonstrates the valuable contributions of ICU pharmacists in mitigating adverse drug effects resulting from suboptimal prescribing and administration practices, improving patient outcomes, and reducing healthcare expenditures. ICU pharmacists serve as essential resources for medical and nursing staff, providing expert guidance and oversight on drug management, especially in situations where evidence-based dosing guidelines may be limited or insufficient.[8,9]

Workforce Evolution and Role Differentiation

The field of pharmacy has undergone notable transformations in the distribution of roles and duties among its workforce. Pharmacy personnel, encompassing both fully trained pharmacists and pharmacy technicians, are licensed professionals. Recent patterns suggest a shift towards the utilization of pharmacy technicians to allow pharmacists to concentrate on clinical responsibilities. Nevertheless, the integration of this role diversification has encountered hurdles in certain areas. Despite the publication of professional practice guidelines supporting clinical functions for pharmacy technicians, these roles are rarely carried out. Measures are necessary to overcome the obstacles hindering the expansion of clinical responsibilities for hospital pharmacy technicians. This discovery indicates that although the conceptual framework for role diversification is in place, practical execution demands continuous attention and methodical intervention.[4,10]

Technology and Digital Health Integration

Digital Health Revolution in Pharmacy

The incorporation of digital health technologies has emerged as a significant transformative trend within contemporary pharmacy practice. This integration has significantly altered patient care and medication management, introducing a new era of convenient, accessible, and personalized healthcare services. This comprehensive analysis delves into the advancing role of digital health within the pharmacy sector, emphasizing emerging trends and their effects on patients. Digital health tools such as telepharmacy services, mobile health apps, and virtual consultations have revolutionized the conventional pharmacy framework by overcoming geographical limitations and broadening healthcare service availability. Pharmacists are now able to interact with patients from a distance, delivering medication guidance, monitoring, and adherence assistance through digital platforms. These advancements not only enhance patient convenience but also empower individuals to assume more responsibility for their health, ultimately leading to improved health outcomes.[11]

Artificial Intelligence and Data Analytics

The integration of artificial intelligence (AI) and advanced data analytics in pharmacy practice signifies a transformative shift towards precision medicine and intelligent decision-making. In addition, digital health solutions utilize sophisticated technologies such as AI and data analytics to enhance medication therapy and individualize patient care. By employing AI-powered algorithms to analyze patient data, patterns can be identified, health outcomes predicted, and medication regimens optimized, resulting in more efficient treatment strategies and reduced medication errors. The concept of pharmacointelligence has emerged as a holistic approach to integrating AI into pharmacy practice. Leading this progression is AI-driven pharmacy practice (IDPP), which merges data science and technology to augment pharmacists' capabilities. This forward-looking discussion introduces the notion of pharmacointelligence, a groundbreaking transformation that harmonizes AI, data integration, clinical decision support systems (CDSS), and pharmacy informatics to refine medication-related procedures.[11,12]

Knowledge, Attitudes, and Implementation Challenges

The integration of artificial intelligence (AI) and digital technologies in pharmacy practice encounters notable obstacles despite their potential advantages. A large percentage (92.6%) of participants acknowledged awareness of AI technology in their field, yet only a minority (39.5%) demonstrated a proficient comprehension of its principles. The collective knowledge level regarding AI among the research subjects was assessed as moderate, with an average knowledge score of 42.3 ± 21.8 out of 100, indicating that students possessed a notably higher knowledge score compared to faculty members. An overwhelming majority (96.2%) of respondents expressed confidence in the capacity of AI to enhance patient care and pharmacy services. Nevertheless, a small fraction (18.6%) reported having undergone formal education or training on AI technology. These results imply that while awareness of AI technology is on the rise among pharmacy professionals in the Middle East and North Africa (MENA) region, there are conspicuous deficiencies in both understanding and embracing AI within pharmacy practice.[13]

Telemedicine Integration

The incorporation of telemedicine into clinical pharmacy services has experienced a substantial surge, particularly in the aftermath of the COVID-19 pandemic. Telemedicine utilizes information and communication technologies to facilitate healthcare delivery at a distance, effectively overcoming geographical barriers. The amalgamation of clinical pharmacy and telemedicine plays a crucial role in contemporary healthcare frameworks, especially in the care of patients with chronic conditions. Amid the recent global COVID-19 crisis, telemedicine has flourished as an essential tool for enhancing the management of individuals who are isolated due to lockdown measures or shielding protocols, particularly those with hypertension. An optimal model for managing hypertension through telemedicine should encompass the monitoring and remote transmission of vital signs, notably blood pressure readings, assessment of medication adherence, provision of educational resources on lifestyle risk factors, and the option for video consultations. Implementing a blended approach that incorporates automated feedback mechanisms and the oversight of a multidisciplinary clinical team comprising physicians, nurses, and pharmacists represents the most effective strategy for hypertension management within the realm of telemedicine.[14,15]

Medication Safety and Quality Improvement

Emerging Themes in Medication Safety

The enhancement of medication safety holds a prominent position within contemporary pharmacy practice, with recent developments highlighting the integration of technology and systematic strategies to prevent errors. Medication safety stands as a pivotal concern in the realm of healthcare, seeking to diminish adverse drug events and ensure optimal patient results. Despite progress in pharmacy operations, medication inaccuracies endure as a noteworthy global impediment, underscoring the need for a comprehensive comprehension of the progressing trends in this domain. The findings underscore a notable emphasis on critical topics such as medication safety, medication inaccuracies, patient safety, and the incorporation of technology in pharmacy practice. Key terms like "medication safety" and "patient safety" were prevalent in the literature, indicating sustained endeavors to enhance healthcare protocols and mitigate medication-linked hazards.[16,17]

Technology-Enhanced Safety Systems

The significance of technology in improving medication safety has gained prominence in recent years. An examination highlights the growing importance of digital resources such as electronic health records and clinical decision support systems in bolstering medication safety. This bibliometric assessment emphasizes the changing nature of medication safety studies, underscoring the contributions of pharmacists and technology in mitigating medication mistakes. Furthermore, digital health tools promote enhanced cooperation and information exchange among healthcare professionals, facilitating smooth care coordination and better patient results. By utilizing secure electronic health records and compatible systems, pharmacists are able to retrieve comprehensive patient data, thereby aiding in well-informed decision-making and improved patient safety.[11,16]

Global Perspectives and Challenges

International Variations in Practice Development

The advancement of clinical pharmacy practice exhibits notable disparities among nations and healthcare infrastructures. The progression and transformation of clinical pharmacy practice within each nation are contingent upon a spectrum of facilitators and impediments that are diverse and closely tied to the specific context. This diversity presents challenges and avenues for the dissemination of knowledge and optimal practice integration. Key determinants for the enhancement of clinical pharmacy practice encompass aspects linked to the healthcare and political environment, including reimbursement mechanisms, leadership qualities, and the inclination and preparedness for change. Additionally, identified success factors are intricately associated with the pharmacist, such as the application of reflective methods and the level of professional drive.[3]

Emerging Markets and Practice Evolution

In developing nations, the evolution of pharmacy practice is marked by distinct opportunities and obstacles. In Nigeria, pharmacists have spearheaded extensive research endeavors focusing on natural product development. More than 200 native plant species are currently under systematic scrutiny for their potential therapeutic properties. The engagement of Nigerian pharmacists in clinical trials has surged by 45% since 2015, particularly concentrating on infectious diseases and chronic ailments. Pharmacists have also initiated implementation science projects that have notably enhanced medication adherence rates by 30-40% and improved outcomes in managing chronic illnesses. Meanwhile, in Mexico, clinical pharmacy is an emerging discipline, lacking a dedicated service for monitoring that applies pharmacokinetic principles. It is imperative to advocate for the involvement of hospital clinical pharmacists in tailoring pharmacological treatments to individual patients and to recognize the manifold benefits that this integration can yield.[17,18]

Regulatory and Economic Considerations

The evolution of pharmacy practice is notably shaped by economic determinants and regulatory structures. While regulations demand extensive services, a substantial portion of pharmacists currently operate without compensation for their offerings. Anticipated influences on forthcoming practices stem from economic considerations and novel service provision methods, including telepharmacy and internet-based procurement. These developments are poised to augment the pharmacist's involvement in managing chronic illnesses and other health maladies.[4]

Future Directions and Emerging Opportunities

Precision Medicine and Pharmacogenomics

Pharmacy practice is advancing towards precision medicine, with a specific focus on integrating pharmacogenomics. Precision pharmacotherapy involves monitoring drug levels, assessing hepatic and renal function, genetic analysis, considering environmental factors, lifestyle influences, and other individual patient or disease traits to inform drug choice and dosage. This study highlights practical clinical uses of precision pharmacotherapy, concentrating on the developing area of clinical pharmacogenomics. The field of precision pharmacotherapy is progressing swiftly, and clinical pharmacists are increasingly essential in applying pharmacogenomics in clinical settings, educating others, and conducting research in this area.[19]

Advanced Manufacturing and Personalized Medicine

The incorporation of cutting-edge manufacturing technologies, notably 3D printing, offers a substantial potential for tailored pharmaceutical interventions. The rising need for personalized medications and medical tools has led to a heightened utilization of additive manufacturing in recent times. 3D printing has emerged as a groundbreaking tool enabling the precise fabrication of custom dosage forms, advancements in tissue engineering, and disease simulation. Noteworthy accomplishments encompass the development of multifaceted drug delivery systems with enhanced release profiles, customizable implants and phantoms tailored to individual anatomical features, as well as bioengineered materials for regenerative medicine applications.[20]

Expanded Clinical Services and Primary Care Integration

Anticipated developments in pharmacy practice suggest a trend towards greater integration into primary healthcare settings and an expansion of clinical services. Foreseen advancements include the implementation of a collaborative multidisciplinary approach in practice, the broadening scope of clinical pharmacy services, and the provision of clinical pharmacy services within primary care contexts. This progression is driven by factors such as the rising prevalence of medications due to an aging population, coupled with an escalating need for clinical intervention by pharmacists in response to the increasingly intricate and costly pharmacotherapies used in the management of chronic diseases. Furthermore, as healthcare spending shifts towards medications and the healthcare system in the United States transitions towards community-centered care, there is a mounting requirement for pharmacists capable of delivering advanced clinical care services to meet the expanding demand.[3,21]

Translational Science Integration

The incorporation of translational science into the field of pharmacy offers pharmacists a growing avenue to participate in the continuum of drug development. Translational science serves as a critical link between basic research conducted in laboratories and its practical application in clinical settings, with pharmacists assuming an increasingly crucial function within this process. This analysis delves into the progressing landscape of translational science as observed in Nigerian pharmacy practice, outlining notable advancements, obstacles, and potential trajectories. Despite facing constraints related to infrastructure and financial resources, Nigerian pharmacists have demonstrated notable headway in the realm of translational science. Prospective areas ripe for further advancement include the implementation of precision medicine, the integration of artificial intelligence in drug discovery processes, and expanded responsibilities in the design and oversight of clinical trials.[17]

Educational Transformation and Competency Development

Competency-Based Education Models

The advancement of pharmacy practice has prompted adjustments in educational methodologies to align with contemporary requirements. Current pharmacy education emphasizes a competency-based approach that delineates specific expected accomplishments for graduates, conforming to established professional benchmarks. This educational framework equips students to thrive in the dynamic landscape of healthcare delivery, ultimately enhancing patient outcomes and streamlining healthcare services. Essential competencies for a clinical pharmacist encompass patient care, clinical knowledge, interprofessional teamwork, ethical conduct, provision of high-quality care, and promotion of medication safety. These proficiencies mirror the intricate demands of contemporary pharmacy practice and underscore the necessity for comprehensive skill acquisition.[1]

Continuing Education and Professional Development

The dynamic evolution of pharmacy practice necessitates continuous professional growth and adjustment. Consequently, pharmacy education needs to be reformed to emphasize clinical competencies, integrated professional instruction, and career advancement opportunities. Issues like regulatory frameworks, practice variations, and inadequate acknowledgment should be tackled through cooperative efforts involving healthcare stakeholders, educators, and policymakers.[1]

Challenges and Barriers to Implementation

Regulatory and Recognition Issues

Despite the considerable progress in pharmacy practice advancements, challenges persist in regulatory structures and professional acknowledgment. The integration of digital health in pharmacy introduces obstacles such as privacy issues, intricate regulations, and variations in patient digital literacy levels. Overcoming these hurdles is vital for the ethical and efficient integration of digital health technologies in pharmacy practice.[11]

Economic and Reimbursement Barriers

Financial considerations pose a substantial impediment to the complete integration of advanced pharmacy services. The incongruity between the broadening scope of pharmacy practice and suitable reimbursement structures persists as a fundamental obstacle to the development of the profession. This economic constraint impacts the viability of services and the capacity to showcase their worth within healthcare frameworks.

Infrastructure and Resource Limitations

Numerous healthcare systems encounter constraints in their infrastructure that hinder the complete utilization of the potential of contemporary pharmacy practices. These constraints encompass deficiencies in technological systems, inadequacies in staffing strategies, and insufficiency in physical facilities for patient care endeavors.

Impact of Global Health Crises

COVID-19 as a Catalyst for Change

The emergence of the COVID-19 pandemic has been a major driver for the transformation of pharmacy practice. Over the past few decades, there has been a notable shift in the role of pharmacies from primarily dispensing products to offering patient-centered services. Pharmacies have evolved from being compounding centers focused on preparing medicinal substances to becoming clinical pharmacies that are integral parts of healthcare networks, providing a wide range of non-prescription services. The responsibilities and functions of pharmacists have expanded gradually to encompass new skills that address the evolving demands and complexities of the profession. The pandemic has highlighted the essential role that pharmacists play in healthcare, underscoring the importance of integrated and collaborative efforts across sectors and professions to effectively manage public health crises. There are indications that a new era in pharmacy practice, characterized by a heightened professional status for pharmacists as frontline healthcare workers, has commenced in the aftermath of COVID-19.[22]

Conclusion:

The contemporary landscape of pharmacy practice is undergoing a rapid evolution characterized by the integration of technology, expanded clinical duties, and the growing recognition of pharmacists as crucial healthcare providers. This evolution is paving the way for a promising future in clinical pharmacy, where pharmacists are assuming pivotal roles in patient care through the application of advanced technology and personalized medicine. The transition in pharmacy practice from conventional product-centric models to more intricate, patient-centered healthcare services is evident in current trends. The incorporation of digital health technologies, artificial intelligence, and precision medicine strategies is positioning pharmacists at the forefront of healthcare innovation. Nonetheless, the successful implementation of these advancements necessitates addressing substantial challenges pertaining to education, regulation, economic frameworks, and professional acknowledgment. The advancement of clinical pharmacy practice hinges on a multitude of factors, as identified in this study, which sheds light on both the key success factors and potential future directions of clinical pharmacy. This analysis can serve as a catalyst for the advancement of the pharmacy profession at local, regional, and global levels. The future progression of pharmacy practice will rely on the profession's capacity to demonstrate its value, adapt to technological progress, and uphold a focus on patient outcomes amid intricate healthcare environments. The integration of digital health technologies into contemporary pharmacy practices represents a transformative shift in patient care delivery, offering unparalleled prospects to enhance access, efficacy, and quality of care. By embracing emerging digital health trends, pharmacists have the potential to revolutionize medication management, enhance patient involvement, and ultimately contribute to improved health outcomes for individuals and communities. The metamorphosis of pharmacy practice from mere dispensing to active clinical care signifies not only a professional evolution but a fundamental redefinition of the pharmacist's role in healthcare provision. As the profession progresses, success will be gauged not solely by the adoption of technology but by the tangible enhancements in patient outcomes and healthcare system efficiency enabled by these changes.

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REDEFINING DRUG CARE DELIVERY: TELEPHARMACY IN THE DIGITAL LANDSCAPE

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Abstract:

Telepharmacy, a specialized branch of telemedicine, utilizes digital communication technologies to provide pharmaceutical services remotely, helping to address disparities in access—especially in rural and underserved communities. Through this model, pharmacists can perform essential functions such as prescription verification, medication therapy management, patient counseling, and monitoring for potential drug interactions from a distance. Successful implementations, such as those led by the U.S. Department of Veterans Affairs, highlight scalable models like remote pharmacist support and collaborative telehealth teams. These initiatives have demonstrated positive outcomes, including better medication adherence, improved management of chronic conditions, and increased operational efficiency. In rural areas with limited pharmacy access, telepharmacy not only fills critical service gaps but also proves to be economically beneficial by reducing the risk of adverse drug events. The integration of artificial intelligence (AI) and machine learning (ML) has further enhanced telepharmacy by aiding clinical decision-making, automating routine tasks, and enabling real-time patient monitoring. Still, the field faces notable barriers, including inconsistent reimbursement policies, digital infrastructure limitations, and regulatory variability across jurisdictions. Adoption success also depends on healthcare providers' readiness and openness to new technology, with research indicating strong support among younger pharmacists. Looking ahead, embedding telepharmacy into broader healthcare frameworks—particularly through AI-driven medication therapy management—has the potential to revolutionize pharmaceutical care. However, achieving this will require solid regulatory backing, greater digital inclusivity, and continued evidence of clinical and economic value. As such, telepharmacy emerges as a key innovation in delivering accessible, efficient, and patient-focused care in an increasingly digital healthcare landscape.

Keywords: Telepharmacy, Digital Health, Artificial Intelligence, Machine Learning, Digital Healthcare.

Introduction:

Telepharmacy is a transformative innovation in healthcare that leverages digital and telecommunication technologies to deliver pharmaceutical services to patients without direct access to a pharmacist. As a focused subset of telemedicine, it enables remote provision of pharmaceutical care—including medication dispensing, therapeutic drug monitoring, and patient counseling—via virtual platforms. This approach is especially crucial for improving healthcare access in rural, remote, and underserved areas where pharmacist shortages are common. Telemedicine broadly refers to technology-enabled, real-time communication between healthcare professionals and patients at different locations. Within this framework, telepharmacy allows pharmacists to deliver services traditionally offered in person, such as prescription review, medication therapy management (MTM), adherence monitoring, patient education, and consultations on drug interactions and adverse reactions. The development of telepharmacy is largely driven by the uneven distribution of healthcare providers. In countries like the United States and India, rural populations often face limited access to pharmacists and primary care professionals. Telepharmacy helps close this gap by ensuring that patients in these areas receive quality pharmaceutical care comparable to urban settings. It also presents a valuable opportunity for pharmacists to play a larger role in managing chronic diseases such as hypertension, diabetes, asthma, and hyperlipidemia. Implementation models vary. One common approach involves pharmacy technicians at remote sites preparing prescriptions, which are then verified and approved by a pharmacist at a central location. Another model features live video consultations between patients and pharmacists for counseling, disease management, and addressing medication-related concerns. Additionally, telepharmacy may involve automated dispensing systems, remotely supervised to ensure timely and accurate medication delivery. As digital healthcare continues to evolve, the role of telepharmacy is expanding. It enhances medication safety, improves adherence, reduces costs, and minimizes the need for patients to travel long distances for care. By streamlining access and offering personalized, real-time support, telepharmacy contributes to better health outcomes and more equitable service delivery. In summary, telepharmacy is becoming a cornerstone of modern healthcare systems. It demonstrates how technology can extend pharmaceutical expertise, improve patient involvement, and break down long-standing barriers to care. With continued innovation in digital health, telepharmacy is well-positioned to become a mainstream, patient-centered solution for accessible and efficient medication management.[1,2]

Models and Implementation of Telepharmacy

Telepharmacy has become a transformative solution for expanding pharmaceutical care, particularly within healthcare systems serving rural or underserved communities. By harnessing telecommunication technologies, it extends the reach of pharmacists, ensuring high-quality, continuous care in areas lacking sufficient healthcare professionals. Various implementation strategies have emerged to meet diverse healthcare needs, with the U.S. Department of Veterans Affairs (VA) standing out as a pioneer in large-scale telepharmacy adoption. In 2014, the VA established a regional Telehealth Hub at the Boise VA Medical Center in Idaho, enabling clinical pharmacy specialists to deliver remote services to 16 VA clinics. This initiative exemplifies the adaptability and scalability of telepharmacy within integrated health systems and demonstrates how pharmacists can support chronic disease management through virtual, team-based care. The VA has developed two key telepharmacy models. The first is a team-based approach where pharmacists collaborate with remotely located primary care teams—including physicians, nurses, social workers, and psychologists—to conduct virtual consultations with veterans. On-site nursing staff assist during these sessions, facilitating comprehensive care and expanding pharmacists' roles in managing complex medication regimens for rural patients. The second model involves remote pharmacist coverage, allowing pharmacists located off-site to participate in live clinical consultations. This model ensures continuity of care during staff absences and supports medication management in real time, particularly for chronic or high-risk conditions. These models have yielded significant clinical and operational benefits. Since the Boise Telehealth Hub's launch, pharmacists have managed care for over 1,200 veterans with chronic conditions like diabetes, hypertension, and hyperlipidemia. These services have improved patient outcomes and optimized medication use. Operationally, facilities reported faster processing of medication orders and a rise in pharmacist-led interventions—including chart reviews, dose adjustments, patient education, discharge counseling, and anticoagulant (e.g., warfarin) monitoring. Additionally, the implementation of telepharmacy has enhanced collaboration across disciplines, with increased nurse satisfaction and more efficient clinical workflows. In summary, the VA's successful use of telepharmacy showcases its ability to improve both patient care and system performance. As healthcare continues to evolve toward more decentralized and technology-driven models, telepharmacy is poised to become a vital part of routine pharmaceutical practice, ensuring broader access and better outcomes across diverse populations.[3,4]

Telepharmacy in Rural and Underserved Areas

Rural populations face distinct barriers to accessing pharmacy services, making them ideal candidates for telepharmacy solutions. In a study involving over 3 million patients, only 23.4% (711,348 individuals) received clinical pharmacy services. Utilization varied significantly based on both geographic location and healthcare setting: 24.9% in urban areas versus 19.7% in rural areas, and 25.9% in medical centers compared to 22.5% in urban clinics and just 17.6% in rural clinics. These figures underscore the disparity in pharmacy service access between urban and rural populations. Further analysis revealed that these differences were more closely linked to the type of healthcare facility than to patient residence alone, indicating that access to pharmacy services depends heavily on the resources and infrastructure available at care sites. Telepharmacy has emerged as a promising strategy to bridge these gaps. Within the Veterans Affairs (VA) healthcare system, nearly half of patients who received clinical pharmacy services engaged in telehealth visits. Although video-based telehealth remains rare (less than 0.2% of cases), it was significantly more common in rural clinics than in medical centers, with an odds ratio of 9.7 (95% CI: 9.0–10.5). This suggests that when available, rural patients are more likely to take advantage of video-based telepharmacy services. Beyond improving access, telepharmacy—particularly when integrated with machine learning (ML) and artificial intelligence (AI)—is helping to address more complex challenges in rural healthcare. These include limited medication availability and the increasing need for continuous care in managing chronic diseases. The use of AI and ML enhances telepharmacy's effectiveness by enabling better decision support, proactive patient monitoring, and optimized medication management.

Telepharmacy also brings substantial economic benefits. One study projected cost savings exceeding $1.4 million USD through reductions in adverse drug reactions and their associated treatment costs. The research also examined how AI-driven telepharmacy is evolving, highlighting successful case studies, current trends, and barriers to wider adoption. These financial advantages further strengthen the case for deploying telepharmacy in underserved rural areas where resources are limited.[4,5]

Clinical Applications and Outcomes of Telepharmacy

Telepharmacy has been applied across various clinical domains, with a strong emphasis on chronic disease management. While studies have explored its use in treating conditions such as hypertension, diabetes, asthma, depression, and anticoagulation, robust evidence supporting its effectiveness is still limited by condition. Notably, only two randomized controlled trials with adequate sample sizes have shown significant benefits of combining telemonitoring with pharmacist-led interventions specifically for hypertension management. One well-documented success involves the use of telepharmacy in controlling high blood pressure. In a cluster-randomized clinical trial, patients in the intervention group used home-based blood pressure monitors to send data to pharmacists, who then adjusted their treatment regimens accordingly. The results were significant: at both 6 and 12 months, blood pressure was under control in 57.2% of patients receiving the intervention (95% CI: 44.8%–68.7%), compared to just 30.0% in the usual care group (95% CI: 23.2%–37.8%, P =.001). Even 6 months after the intervention ended, control rates remained higher in the intervention group (71.8%) versus the usual care group (57.1%, P =.003). These findings highlight both the short- and long-term benefits of pharmacist-led telemonitoring programs. Telepharmacy has also had a measurable impact on medication safety. In a one-year study, a telepharmacist reviewed over 218,000 medication orders, flagging 2,292 problematic prescriptions that included 16,224 distinct medication-related issues. The most common concerns were drug allergies (31.2%) and incorrect dosages requiring adjustment for kidney or liver function (24.1%). Additionally, several issues were related to high-alert medications, such as insulins and heparinoids, which are known to carry greater risk of patient harm if used incorrectly. These findings emphasize telepharmacy's critical role in preventing medication errors and improving patient safety. By providing continuous oversight—especially in settings lacking an on-site pharmacist—telepharmacists ensure ongoing clinical review and intervention, maintaining a consistent standard of care. This 24/7 service capability is one of telepharmacy's key strengths, helping to safeguard patients and support safe medication use even in resource-limited environments.[1,4,6,7]

Technology Integration in Telepharmacy

The advancement of telepharmacy is deeply connected to the ongoing progress in digital technology. Today's healthcare landscape relies on a wide array of communication tools—ranging from mobile phones and smartphones to interactive voice systems, SMS, email, video conferencing, webcams, two-way smartphone cameras, personal monitoring devices, kiosks, digital dashboards, personal health records, web portals, and even social media and secure online forums. These tools collectively offer a broad foundation for delivering telepharmacy services across different settings. Artificial intelligence (AI) and machine learning (ML) are playing an increasingly important role in enhancing the scope and effectiveness of telepharmacy. As the demand for remote care grows, AI and ML technologies are helping to improve efficiency, personalize treatment, and drive better patient outcomes. These systems support complex functions such as automated prescription verification, inventory management, and drug interaction analysis. Predictive algorithms analyze individual patient data to recommend optimal treatment plans, reducing the risk of medication errors and strengthening clinical decision-making. Machine learning tools also allow for real-time tracking of medication adherence, providing pharmacists and healthcare providers with actionable insights into patient behavior. This enables earlier, more targeted interventions—particularly valuable in managing chronic illnesses. AI-driven tools like virtual assistants and chatbots offer around-the-clock support by responding to routine questions, monitoring medication schedules, and helping patients stay on track with their treatment. By automating these repetitive tasks, pharmacists can dedicate more time to complex clinical care. Despite these technological gains, key challenges persist. Ensuring patient data privacy, complying with regulatory standards, and achieving equitable access to digital health resources remain major concerns. Addressing these issues is essential for fully unlocking the potential of AI- and technology-enabled telepharmacy services.[2,8]

Attitudes, Perceptions, and Adoption of Telepharmacy

The success of telepharmacy largely hinges on the perspectives and acceptance of healthcare professionals, particularly pharmacists. A study conducted in Indonesia aimed to assess the knowledge, attitudes, and perceptions of young pharmacists regarding the real-world application of telepharmacy. Utilizing a cross-sectional observational design with a quantitative descriptive method, the research involved non-probability accidental sampling of participants from various locations in the Special Region of Yogyakarta. Data was gathered through a structured questionnaire covering participants' understanding and views on telepharmacy. The study revealed that while knowledge levels were moderate—with an average score of 69.92%—attitudes toward telepharmacy were overwhelmingly positive. Approximately 79.47% of respondents strongly supported its implementation, and 82.83% expressed favorable perceptions overall. In essence, despite having only moderate technical understanding, young Indonesian pharmacists demonstrated a strong willingness to adopt and engage with telepharmacy services. These results underscore the potential for successfully expanding telepharmacy in Indonesia, especially in remote and underserved regions. The enthusiasm among the younger generation of pharmacists highlights the importance of enhancing education, training, and infrastructure to fully realize the benefits of telepharmacy.

In addition to provider readiness, the expansion of telepharmacy also relies heavily on regulatory support. While the National Association of Boards of Pharmacy (NABP) has included telepharmacy in its model pharmacy practice act, many U.S. state pharmacy boards are still in the early stages of establishing formal telepharmacy regulations. The model act supports cross-state pharmacy practice, and most state board directors agree that pharmacists should be licensed in the state where services are provided. However, regulatory requirements vary by state, particularly in terms of whether pharmacists must be physically present in a licensed facility and how much time they are required to be onsite. Some states have implemented hospital-based telepharmacy models that allow pharmacists to supervise pharmacy technicians remotely. These models differ depending on regional needs, legal frameworks, facility ownership, size, and the volume of prescriptions processed. [9,10]

Barriers and Challenges to Telepharmacy Implementation

Although telepharmacy holds significant promise, several obstacles hinder its broader implementation. One major challenge is the limited and methodologically weak research supporting pharmacist-led telemedicine models. Many existing studies lack strong internal and external validity, making it difficult to draw definitive conclusions about their effectiveness. This gap in high-quality evidence poses a barrier to broader acceptance and integration of telepharmacy services, particularly when it comes to securing reimbursement. Reimbursement remains a key hurdle. Without clear and consistent financial support, pharmacists may be discouraged from offering services via telemedicine platforms. The absence of reimbursement mechanisms also makes it less likely that healthcare organizations will invest in the infrastructure and personnel required to sustain telepharmacy programs. Another significant concern is the digital divide. While improved internet access can help overcome barriers related to geography, time, and cultural differences, persistent inequalities in digital access risk deepening healthcare disparities. Vulnerable populations—such as those with low income, limited digital literacy, or poor connectivity—may face new obstacles in accessing remote pharmacy care. This highlights the dual potential of telepharmacy: it can either enhance healthcare equity or unintentionally widen existing gaps, depending on how it is deployed. Regulatory issues further complicate implementation. The adoption of telepharmacy in rural hospitals across the U.S. varies widely, with many states lacking comprehensive or consistent regulations to guide its use in hospital settings. This lack of standardized regulatory frameworks can delay the integration and scaling of telepharmacy services, making widespread adoption more difficult.[1,8,10,11]

Future Directions and Opportunities

The future of telepharmacy holds great potential to improve access to pharmaceutical care, particularly as healthcare continues to evolve toward digital and remote interactions. As patient engagement increasingly occurs outside of traditional in-person visits, it becomes necessary to redefine and update how healthcare access is measured. Existing frameworks often fall short in capturing the dynamics of virtual care delivery, presenting a unique opportunity to create new models that reflect the realities of digital healthcare. Integrating telepharmacy into broader healthcare delivery systems offers a valuable opportunity to strengthen care in underserved areas. One study examined how pharmacists could be better utilized in rural settings to address shortages of physicians and other providers, while also considering future reductions in public funding and shifts in the pharmacy workforce. The findings emphasized the potential of pharmacists to play a larger role through medication therapy management (MTM), especially when delivered via telepharmacy. Telepharmacy enables the scalable delivery of MTM services, which are particularly beneficial for rural patients managing multiple complex medications. This model not only supports better patient outcomes but also offers a cost-effective—and potentially cost-saving—strategy by integrating pharmacists into the primary care team. Looking ahead, the incorporation of AI and ML into telepharmacy offers exciting advancements. Research has explored how these technologies are currently being applied, what benefits they offer, and what barriers exist to broader adoption. With deeper understanding and strategic implementation, AI and ML can enhance telepharmacy's role in transforming remote pharmaceutical care, improving efficiency, and reducing disparities in healthcare access.[2,8,11]

Conclusion:

Telepharmacy marks a major advancement in the provision of pharmaceutical care, especially for populations in rural and underserved areas. The literature highlights a range of implementation models, demonstrating positive clinical outcomes in areas such as chronic disease management and medication safety. The integration of technologies like AI and ML is further enhancing the scope and efficiency of telepharmacy services. However, significant challenges remain, including limited high-quality evidence, reimbursement limitations, regulatory inconsistencies, and digital access disparities. Within the U.S. Department of Veterans Affairs healthcare system, telepharmacy has proven to be both cost-effective and well-received, particularly in delivering pharmacy services to rural patients. These successes suggest that similar models could be replicated in other healthcare settings. To support broader adoption, future research should aim to strengthen the evidence base for telepharmacy, establish standardized implementation guidelines, address regulatory obstacles, and promote equitable access to digital care. A notable disparity persists in access to clinical pharmacy services between rural and urban populations—largely due to rural patients relying more on community clinics rather than larger medical centers. Further investigation is needed to determine whether organizational changes, such as improved telehealth infrastructure and increased pharmacist integration into primary care teams, can help close this gap. Additionally, exploring the extent to which the VA's telepharmacy model can be adapted to other healthcare systems is essential.As the healthcare landscape continues to embrace digital transformation, telepharmacy is well-positioned to expand access, enhance medication management, and improve patient outcomes. By addressing existing barriers and leveraging technological innovation, telepharmacy has the potential to close service gaps and contribute to a more equitable and effective healthcare system.

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MILLETS AS A SOURCE OF NUTRITION AND THEIR IMPACT ON HUMAN HEALTH

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Abstract:
The world is confronted with nutritional and agricultural crises. We need to shift our focus to dry areas if we want to further expand grain output; we have already used up all the agricultural land with irrigation systems. Using arid areas to produce enough high-quality grains is difficult because of poor fertility. When compared to other grains, such as wheat and rice, millets, which are climate change compliant, have superior nutritional content and require less water during growth. These nutri-cereals contain antioxidants, phyto-chemicals, vitamins, minerals, vital fatty acids, and phyto-nutrients, all of which can aid in the eradication of many ailments caused by nutritional deficiencies. Cultivating millets is one way to maintain the productivity of drylands and secure our food and nutrition in the future. In addition to providing supplemental nourishment in the form of minerals and vitamins, millets also include phytochemicals and specialized compounds with therapeutic benefit, such as antioxidant-potential components like flavonoids, phenolics, anthocyanidins, and others. Phytochemicals in millets help cure lifestyle issues and prevent diseases like carcinogenesis; they are low on the glycemic index and don't contain any gluten. As an added bonus, it can help treat anemia and calcium deficits, which are common in pregnant women and tiny children. The pharmaceutical sector can benefit from the identification of compound-specific genotypes in millets made feasible by advancements in analytical technologies for detecting various substances. The demand can be met by breeding genotypes that are specific to their end use. Due to their resilience to climate change, millets have the potential to improve human health and the environment via the efficient use of natural resources.

Keywords: Nutrition, Nutri-Cereals, Millets, Micronutrient Deficiency, Dry Lands

Introduction:

There has been a recent uptick in the popularity of whole, natural foods, and millets are a great example of this trend. The small-seeded cereal grains known as millets have a long history of cultivation, with a focus on Asia and Africa. More popular grains, such as rice and wheat, get all the attention when it comes to health advantages, but millets are starting to make a comeback.

Among their many health benefits are the fact that millets are naturally gluten-free and packed with important nutrients including protein, fiber, vitamins, and minerals. It is well-known that they facilitate digestion, promote heart health, assist in controlling blood sugar levels, and aid in

weight management. Their ability to fight oxidative stress and lessen the likelihood of chronic diseases is further enhanced by their strong antioxidant content.
Millet is showing to be more than simply an old grain; it's also a contemporary and wise dietary option in light of rising worries about lifestyle-related diseases and a resurgence of interest in sustainable and nutrient-dense foods.[1]

Millets are versatile cereals with small grains that have medical potential due to the presence of bioactive chemicals, minerals, and vitamins that help people recover and stay healthy. Nutri cereals is another name for these ancient grains that have a high nutritional value. Sorghum, pearl, and finger millet are main millets, whereas foxtail, little, kodo, proso, brown top, fonio, teff, and barnyard millet are minor millets. The outer layers of grain in minor millets need to be gently removed during primary processing in order to make room for the numerous antioxidants that are present in the harvested and cleaned major millets. More and more people are learning about the health benefits of millets, which has led to a surge in demand for these grains in both their raw and processed forms.[2] There are around 65–75% carbs, 7–12% protein, 2–5% fat, and 8–15% fiber in millets. Prolaminin millets improve protein digestion and contain more important amino acids than regular grains. The nutritional benefits of millets have just come to light thanks to information exchange, but the medicinal potential of millets is still underexplored.
Consumption of millets is associated with better glycemic management, a lower body mass index (BMI), and a reduced risk of atherosclerotic cardiovascular disease, according to strong scientific evidence.[3] Millets' high levels of resistant starch (RS) and slowly digested starch (SDS) reduce insulin and postprandial glucose excursions. People with celiac disease often choose millets as a gluten-free food option. Weaning and health-conscious food companies are seeing increased demand for millets as a result of their high nutritional content. Millets' grain and bran include phytochemicals such proanthocyanidins, which induce fullness and so have anti-obesity properties. Wellness, preventative, and therapeutic millet foods and products have been around for a long time, but they still have a lot of room to grow around the globe. In this overview, we will go over the history of millets in traditional medicine, as well as their various medicinal and therapeutic properties that can help prevent and cure lifestyle issues, specific diseases, and maladies. [4]

Agrarian Importance of Millets

As the global population rises, so will the demand for food. Cereals currently provide half of the calories consumed worldwide.[5] The three most common cereal grains are rice, wheat, and corn, with sorghum and millets playing a smaller role. According to Sharma,[6] there has been a 0.009% increase in the distance between ground level and the ground water table, which is roughly the same as a loss of 7191 L of ground water per hectare. This increase is due to the expansion of water-intensive crops such as rice, sugarcane (Saccharum officinarum), and cotton (Gossypium). The world is already confronted with the issues of increasing dry land and deepening ground water levels, thus there is less chance of boosting production of main basic grains.[7] Half of the net planted area will still be rainfed after the entire irrigation capacity is realized, according to the National Rainfed Area Authority (NRAA) report. This highlights the urgent need to find substitutes for commonly used cereals. [8]

The cultivation of millets, which thrive on soils with pH levels ranging from slightly acidic 4.5 to slightly basic 8.0, could provide an answer to this dilemma. In areas where the soil is acidic, millets can be a suitable substitute for wheat. If the soil is more than 3dS/m salty, the rice won't grow or harvest well because the plant is so sensitive to salt. Finger millet and pearl millet (Pennisetum glaucum) are two examples of millets that can withstand soil salinity levels of 11-12 dS/m. Both the total amount of water needed during growth and the amount of water needed during the specific growing period are quite minimal for millets. Some millets, such as proso millet (Panicum miliaceum) and pearl millet (Panicum miliaceum), have a far lower rainfall requirement than rice, which typically requires 120–140 cm of rain.[9] Because they reach maturity within 60 to 90 days of planting, millets are an excellent crop for reducing water use. Among millets, barnyard millet (Echinochloa frumentacea) takes the shortest amount of time to mature (45–70 days), somewhat longer than rice (120–140 days). As a type of cereal, millets are classified as C4. Because of their low input requirements, excellent water efficiency, and increased ability to absorb and convert atmospheric carbon dioxide to oxygen, C4 cereals are better for the environment than other types of cereals. Therefore, millets can contribute to lowering atmospheric carbon dioxide and phasing out climate uncertainties, which in turn can help mitigate climate change.[10]

Nutritional Profile of Millets

Among cereals, millets stand out for the abundance of protein, antioxidants, and dietary fiber they provide. While millet does contain some protein, fat, and fiber, the majority of its nutritional value comes from the carbs it contains. The majority of millet's weight is carbohydrates, though this varies across varieties.[11] Starch, the main component of grains, regulates digestion and the body's reaction to sugar. In addition to dietary fibers and small amounts of free sugars such as glucose and sucrose, the main components of grain starch include amylose and amylopectin.[12] Foxtail millet and proso millet have the highest protein levels, ranging from 6 to 13%. Compared to other cereal grains, millet has a higher concentration of important amino acids such cysteine, lysine, and methionine.[13]. As the millet grain with the highest concentration of lipids, pearl millet grains contain 2 to 8 percent by weight. Millet fats are more beneficial to health and have more nutritional value because they contain unsaturated fatty acids like linoleic acid and oleic acid.[14,15]

Millet has a similar amount of dietary fiber to whole wheat and nearly twice as much as rice. Millet contains soluble and insoluble components that make up its dietary fiber.[16] Soluble components include glucans, arabinoxylans, and pectins. Insoluble components include cellulose and hemicellulose. Two types of millet, pearl and finger, are particularly high in fiber. In addition to being an excellent source of calcium (10-348 mg/100 g), iron (2.2-17.7 mg/100 g), zinc (0.4-2.8 mg/100 g), and phosphorus (189-293 mg/100 g), millets are also an excellent source of vitamins including thiamine (0.15-0.60 mg/100 g), niacin (0.89-4.6 mg/100 g), and riboflavin (0.9-0.28 mg/100 g).[17-19] Iron level ranges from 5-6.5 mg/100g in pearl millet, making it the highest. With 300–350 mg/100 g, finger millet is about ten times more calcium-rich than wheat, making it one of the most abundant vegetarian sources of this mineral. Antioxidants phytosterols, policosanols, and phenolics (including phenolic acids, flavonoids, and tannins) are some of the millets' secondary metabolites. When compared to wheat and rice, millets have a higher concentration of the B-group vitamins, including thiamine and riboflavin. The nutritional density of sorghum grain suggests it may have medicinal and health benefits.[20]

The metabolic problems can be prevented and lifestyle disorders can be corrected by consuming millets. Because they are given in a dietary form, they are more easily absorbed and have a higher bioavailability. Positive effects on health and performance have been observed in dietary experiments supplementing with millet. Dietary supplementation with millets has shown encouraging results in trials, with health and performance benefits including anemia being one of them.[21] The anthropometric indices of primary school students in India increased when they were regularly supplemented with a multi-millet health mix, which includes kodo millet, small millet, foxtail millet, finger millet, wheat, and pulses.[22] Preschoolers who had malted millet mixes supplemented with amylase for four months saw a considerable improvement in their body mass index (BMI), according to research by Khader and Maheswari.[23] Adolescent girls' mean haemoglobin (Hb) levels increased significantly in a randomized clinical trial program that used a food-based approach and pearl millet ladoo, an Indian dessert.[24] Feminine millet porridge, when added to the diets of teenage schoolgirls, raised their hemoglobin levels.[25]

Role of Millets in Correcting Diseases and Lifestyle Disorders

As a result of impaired or nonexistent insulin activity, the hallmark symptom of the global epidemic known as diabetes is a steady increase in blood sugar levels. Many have described the underlying mechanisms that make millets an ideal meal for managing diabetes. Millets have a hypoglycemic effect due to a number of factors, including a high concentration of indigestible starch, phenolics' ability to limit carbohydrate digestion, an increase in the abundance of probiotic bacteria, an increase in the amount of reactive oxygen species (ROS), enzyme activation and inhibition, and the regulation of different signaling pathways.[26–29]

Research on both rodents and humans has shown that diabetic rats can reduce their blood glucose levels by eating a diet high in kodo and finger millet.[30] Glycation of tail-end collagen was suppressed, resulting in reduced glycemic and oxidative stress, as evidenced by low levels of lipid peroxidation in rats fed millet compared to control rats. By blocking hepatic gluconeogenesis, an ethanolic extract of sorghum and foxtail millet had hypoglycemic effects in diabetic rats comparable to those of anti-diabetic medication.[31] Dietary preparations containing millet (due to the millet's high dietary fiber content[32], peptides[33] and starch[34] decreased the glycemic response in rat models associated with diabetes. Glucose metabolism, abnormal lipid levels, and poor glucose tolerance were all improved in diabetic rats that received foxtail millet starch and protein components.[35] Mice with diabetes were able to experience some relief after ingesting Japanese barnyard millet protein.[36] In rats with diabetes, a diet rich in millet bran decreased polyuria, water consumption, and hemoglobin A1c levels.[37]

A number of diabetic problems, including cataracts, skin sores, fatty liver, etc., were successfully treated with millets. Diabetic rats given finger millet healed their skin wounds more quickly[38] via means of changes in the functions of antioxidant enzymes, upregulation of nerve growth factor (NGF) expression, upregulation of collagen synthesis, and activation of mast cells and fibroblasts. Phenolic compounds in finger millet seeds slowed the development of cataracts in diabetic rats by reducing levels of serum advanced glycation end products, blood glycosylated hemoglobin, and lens aldose reductase (AR) activity.[39]

Clinical studies found that the average fasting blood glucose and 2-hour glucose levels were both decreased with increasing foxtail millet consumption. A significant increase in blood leptin (a crucial hormone that controls hunger and normalizes hyperglycemia) occurred, along with a decrease in insulin resistance and inflammation. A millet-based diet was associated with better glycemic control, less hyperinsulinemia, and lower plasma lipid contents in type 2 diabetic individuals.[40] Chronic kidney damage is an additional consequence of long-term diabetes; nevertheless, consuming fermented and germinated foxtail millet helped relieve this condition.[41] Millets improve postprandial blood glucose and HbA1c levels in adults when consumed regularly[42] Compared to non-millet diets, millet (including foxtail millet, finger millet, and sorghum) diets helped diabetic individuals control their blood sugar levels more effectively.[43] In a breakfast consumption testing, participants' reactions were comparable to those to both Pearl millet porridge (PMP) and the more popular Scottish oats porridge (SOP). Nevertheless, PMP exhibited a greater incremental area under the curve (iAUC) and reduced glucose-dependent insulinotropic polypeptide (GIP) responses in relation to gastric volume compared to SOP.[44]

Millets for Cardiovascular Diseases

According to WHO, cardiovascular disorders account for the majority of deaths worldwide. Millets inhibit the production of cholesterol due to their high concentration of sterols and pinacosanols. Studies on animals have shown that hamsters given sorghum have decreased levels of non-HDL cholesterol.[45] In their study on obese mice, Yin et al.[46]] found that both millet bran oil (MBO) and refined millet bran oil (MRO) had a beneficial impact on lipid metabolism. Dyslipidemia, brown and white fat hypertrophy, and hepatic lipid accumulation were all ameliorated by MBO. It expanded the population of certain harmless bacteria, such as Akkermansia and Prevotellaceae, and reduced oxidative stress in the liver, plasma, and lipids.

Blocking LDL cholesterol and liposome oxidation was successfully accomplished by the phenolic extract of kodo millet. Incorporating sorghum into your diet can help lower your risk of cardiovascular illnesses like atherosclerosis and stroke because of its high fiber content, which binds bile acids in the small intestine and keeps them out of your bloodstream. Multiple in vitro and animal studies found that sorghum's phenolic and lipidic fractions modulate dyslipidemia risk factors and cardiovascular disease risk factors due to the activity of phenolic chemicals, policosanols, and phytosterols. Studies have demonstrated that DDGS (Dried Distillers Grains with Solubles), a byproduct of grain sorghum lipids, can promote cardiovascular health by lowering levels of hepatic cholesterol and plasma low-density lipoprotein (LDL) at varying dosages. Millets are beneficial to your health since they reduce the risk of insulin resistance, glycemic control, non-HDL cholesterol, hypertension, and atherosclerotic cardiovascular disease[47,48]

Anti-Hypertensive Properties of Millets

An epidemic proportion of hypertension has emerged as a key public health concern among today's youth. Ignored and mistreated, it might progress to a fatal sickness. To relieve the problem, dietary treatments are suggested. Dietary fiber, protein, calcium, and other phytochemicals included in millets make them an attractive option for people with hypertension, according to studies. In rats that developed hypertension on their own, researchers discovered that using foxtail millet protein hydrolysates to treat the condition reduced the risk of cardiovascular complications. The treated rats exhibited a marked decrease in levels of angiotensin II and activity of serum ACE (Angiotensin I Converting Enzyme), two critical components in the development of hypertension.[49] Ethanol extracts from finger millet were also discovered to modulate the renin-angiotensin system, which led to antihypertensive effects in rats.[50] Natural ACE inhibitors may be found in foxtail millet bran glutelin-2 peptide fractions, according to in silico research.[51] One group of sorghum-kafirins was found to lower blood pressure by blocking angiotensin I converting enzyme activity.[52] Mildly hypertensive individuals showed a marked decrease in both systolic and diastolic blood pressure when they had a meal of whole foxtail millets.[53]

Millets for Thyroid Gland Function and Combating Obesity

The balanced production of thyroid hormones promotes weight loss by controlling fat metabolism, and sorghum, a high source of manganese, aids in this process. People with diabetes and obesity can benefit from the resistant starch found in sorghum grain, which has 1.2 times the amylose of other fine cereals. There is evidence that sorghum with a high tannin content can assist animals maintain a healthy weight by reducing their calorie intake through the creation of complexes with starch. Sorghum polymeric tannins spontaneously alter starch by creating resistant starch through strong interactions with amylose. This starch is then able to bypass small intestine digestion and travel to the large intestine, where it imparts the health advantages of dietary fiber[54-56]

Effect of Millets on Gut Microbiome

A large portion of the millet bran component is indigestible dietary fiber. The fiber component is thus greatly diminished due to the removal of the bran section during decortication/dehulling. The amount of nutritious fiber lost when millet grains are dehulled exceeds 30%, according to reports. It is crucial to control the amount of dehulling to maximize fiber content in millets as they are mostly eaten in their decorticated state. The milled fraction of foxtail millet had less insoluble dietary fiber than whole millet flour, according to an analysis of the milling effect on the fiber components of foxtail millet. On the other hand, the fiber content of foxtail millet increased dramatically with longer germination times.[57,58]

Conclusion:

The complex chemical composition of millet grains makes them an ideal dietary supplement. They contain a lot of protein, essential amino acids, fiber, vitamins, minerals, phytochemicals, and antioxidants. Due to its hypoglycemic, anti-proliferative, anti-atherosclerogenic, antioxidant, antihypertensive, anti-inflammatory, and antibacterial characteristics, millet has been linked to improved human health in research. Including millets in one's diet has several health benefits, one of which is improved nutrition due to the minerals and vitamins it supplements. By primarily acting as a scavenger, the presence of bioactive chemicals lessens and delays the progression of lifestyle illnesses and maladies. If you're deficient in nutrients like zinc and iron, millets can help you get back on track. Recent findings in the field point to millets as a potential solution to many modern problems, including diabetes, obesity, and hunger. As a nutritional supplement, millets have great potential as a nutraceutical in the medical and pharmaceutical fields.

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Mr. C. P. Bhagat is an accomplished academician in the Department of Botany at Karmaveer Hire College, Gargoti, Dist. Kolhapur, Maharashtra. With 12 years of teaching experience and four years of research experience, he has significantly contributed to botanical education and research. He has published 10 research articles and authored four book chapters, reflecting his scholarly engagement in the field. Additionally, he has served as an editor for two books, showcasing his expertise and commitment to academic publishing. Mr. Bhagat has also played an active role in organizing conferences and workshops, fostering academic growth and collaborative learning among students and faculty. His dedication to teaching, research, and knowledge dissemination continues to inspire students and peers in the field of Botany and Life Sciences.

Dr. Averineni Ravi Kumar earned his B.Pharm (1992) and M.Pharm in Pharmacognosy (1994) from AU College of Pharmaceutical Sciences, Visakhapatnam. He completed his Ph.D. in Biotechnology from Bharathidasan University in 2009, focusing on ethnopharmacological studies of Caesalpiniaceae plants. With over 31 years of teaching and research experience, he has held various academic positions and is currently the Postgraduate Head of Department at Nimra College of Pharmacy since 2021. Dr. Kumar has guided over 55 UG and PG students, published more than 145 research papers, authored 30+ textbooks and chapters, and holds seven patents. A distinguished speaker, he has participated in numerous conferences, workshops, and FDPs. He is a life member of APTI, IPA, ABAP, OPF, and LMAPPC, and serves as Evaluation Chief for several reputed universities.

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