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Integrative Approaches in Modern Life Science

Volume II

Editors:
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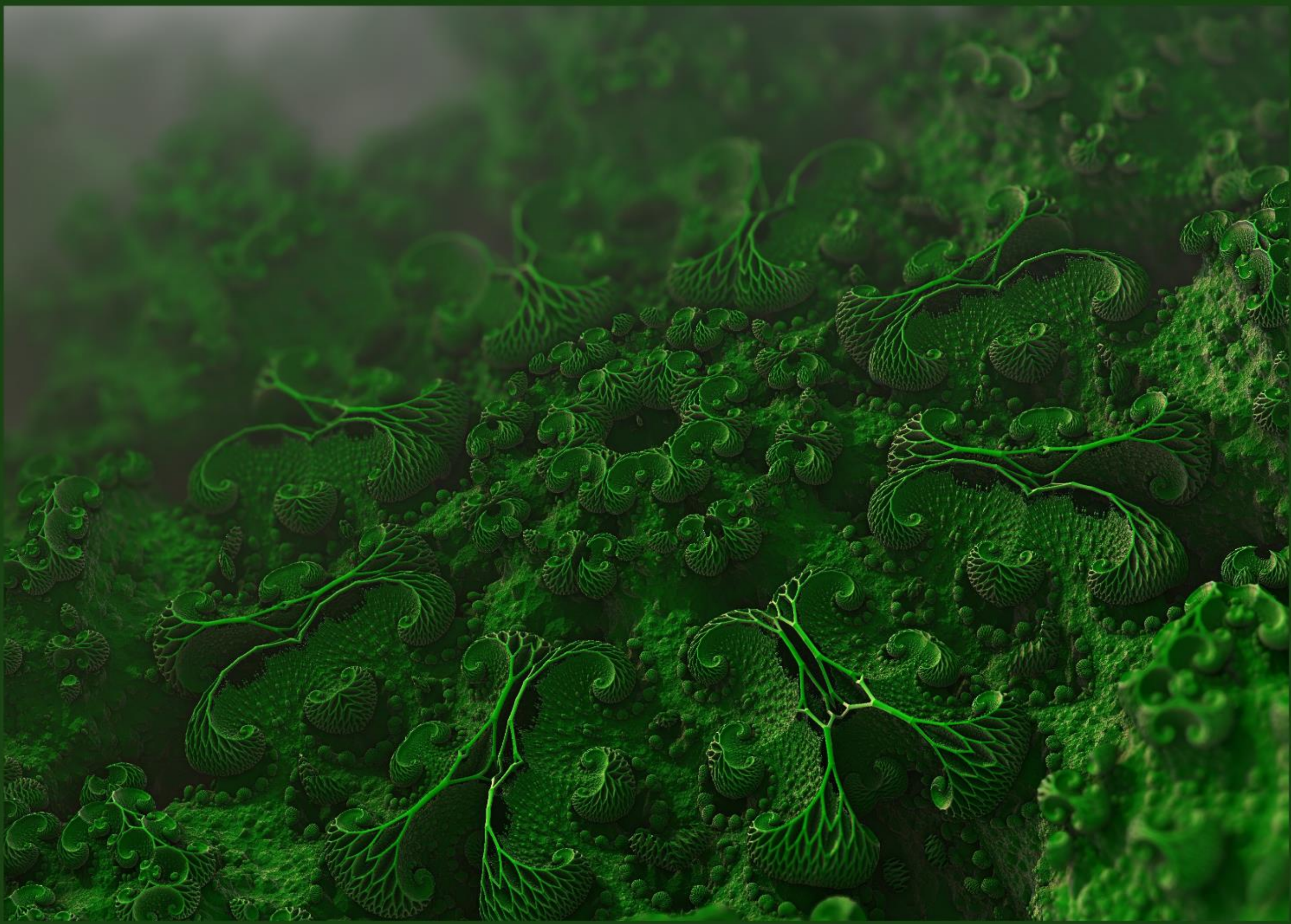
Dr. Prasad M. Deshmukh
Dr. Pravin V. Gadakh
Dr. Tekchand C. Gaupale



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PREFACE

The life sciences have entered a new era marked by convergence—where once-disparate disciplines now collaborate to unlock deeper insights into the complexities of living systems. The book Integrative Approaches in Modern Life Science is a testament to this evolving landscape, where traditional boundaries between biology, chemistry, physics, mathematics, and computational science are increasingly blurred to foster innovation, discovery, and real-world applications.

This volume brings together a collection of scholarly contributions that reflect the spirit of integration across multiple domains of life science. Whether it is the amalgamation of molecular biology and bioinformatics to decode the genome, the fusion of pharmacology and nanotechnology in therapeutic design, or the interplay of systems biology and ecological modeling to address environmental challenges, each chapter underscores the value of interdisciplinary thinking.

Modern scientific challenges—ranging from understanding the molecular basis of disease to tackling global sustainability—demand holistic approaches. As such, this book not only highlights theoretical and methodological advancements but also focuses on applied research that has the potential to revolutionize health care, agriculture, environmental science, and biotechnology.

The contributors to this volume include established researchers and emerging scholars whose work exemplifies the cutting-edge of integrative life science. The book is designed to serve a broad audience—students, academicians, industry professionals, and policy makers—who are committed to advancing knowledge through collaborative inquiry and innovation.

We hope this book inspires readers to explore new intersections within their own work, encourages cross-disciplinary collaborations, and contributes to a more unified and impactful scientific endeavor. The integration of diverse perspectives and techniques is not only the hallmark of modern life sciences but also the pathway to addressing the complex biological questions of our time.

- Editors

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INTEGRATING ARTIFICIAL INTELLIGENCE IN PHARMACY PRACTICE: OPPORTUNITIES AND CHALLENGES

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Abstract:

The incorporation of Artificial Intelligence (AI) within the realm of pharmacy practice is revolutionizing the delivery of pharmaceutical care, introducing innovative prospects for augmenting efficiency, precision, and patient outcomes. AI technologies, encompassing machine learning, natural language processing, and predictive analytics, are currently being deployed across diverse facets of pharmacy operations, such as medication management, monitoring drug interactions, providing clinical decision support, and advancing personalized medicine. The increasing prominence of AI in the healthcare domain is particularly conspicuous in its capacity to analyze extensive datasets, recognize patterns, and facilitate real-time evidence-based decision-making. Within the sphere of pharmacy practice, this translates into the enhancement of drug therapy efficacy, mitigation of medication errors, and promotion of adherence through the utilization of digital health tools and intelligent dispensing systems. Moreover, AI empowers pharmacists to dedicate more time to direct patient care by automating routine tasks like inventory management and prescription validation. Nevertheless, the integration of AI also brings forth notable obstacles, including ethical considerations, data confidentiality concerns, the necessity for regulatory structures, and the potential displacement of human personnel. The successful assimilation of AI necessitates not solely technological preparedness but also educational restructuring and interdisciplinary cooperation to guarantee that pharmacists are suitably equipped to collaborate with AI technologies. This section delves into the emerging prospects and urgent challenges linked to the integration of AI in pharmacy, underscoring the significance of an equitable, ethical, and patient-centric approach. Embracing AI as a complementary tool rather than a substitute for clinical acumen is indispensable for fostering a sustainable and efficient evolution of pharmacy practice.

Keywords: Artificial Intelligence, Pharmacy Practice, Clinical Decision Support, Medication Management, Predictive Analytics, Digital Health, Personalized **Medicine**, Healthcare Innovation, AI Ethics, Pharmacist Roles.

Introduction to AI in Pharmacy

The Growing Role of AI in Healthcare

The healthcare industry is currently experiencing a notable shift, primarily driven by the incorporation of artificial intelligence (AI). AI's transformative capacity is altering multiple facets of healthcare such as pharmaceutical exploration, drug administration, and patient treatment, heralding a novel phase characterized by enhanced effectiveness and accuracy [1]. Artificial Intelligence (AI) represents a transformative advancement in the delivery and administration of healthcare services, rather than a simple incremental progression. This transformative change is propelled by the growing acknowledgment of AI's capacity to manage intricate data, automate mundane responsibilities, and offer insights that were previously inaccessible. AI introduces novel efficiencies, treatments, and diagnostic tools that possess the capability to revolutionize healthcare systems facing challenges [2]. Conventional healthcare systems frequently face difficulties related to increased expenses, workforce deficits, and inefficiencies in providing services. Artificial intelligence (AI) offers novel approaches to tackle these challenges by simplifying procedures, enhancing precision, and elevating the general standard of healthcare. Through AI-fueled diagnostic instruments capable of early and precise disease detection and customized treatment strategies adjusted to individual patient requirements, AI is set to transform all aspects of healthcare. AI-driven progressions are reshaping healthcare administration and pharmaceutical practice by delivering inventive resolutions to boost medication control, enhance healthcare provisions, expand availability, and optimize patient results [3]. The progress in healthcare technology is not confined to clinical domains but encompasses administrative and operational facets of healthcare, including supply chain management, patient scheduling, and billing procedures. The incorporation of artificial intelligence (AI) seeks to establish a healthcare environment that is smoother, more effective, and centered around patient needs. The increasing utilization of AI in healthcare represents not merely a passing phenomenon but a foundational transformation with the potential to redefine the trajectory of medical practice and enhance the well-being of numerous individuals.

Defining AI and its Applications in Pharmacy

Artificial Intelligence (AI) is focused on the development of intelligent models to assist in knowledge acquisition, problem-solving, and decision-making [2]. AI transcends mere automation by constructing systems capable of reasoning, learning, and adapting to novel information, simulating human cognitive functions. This capacity is achieved through a variety of methods, including machine learning, deep learning, and natural language processing, empowering AI systems to analyze intricate data and render well-informed decisions. The emphasis on intelligent modeling enables AI to surpass rudimentary data processing, offering insights and forecasts that can enhance outcomes across diverse domains. AI encompasses methodologies such as machine learning, natural language processing (NLP), computer vision, and predictive analytics [1], each playing a distinct role in enabling AI applications within pharmacy and healthcare. Machine learning algorithms empower AI systems to glean patterns and make predictions from extensive datasets without explicit programming. Natural language processing enables AI systems to comprehend and process human language, facilitating communication between healthcare providers and patients. Computer vision allows AI systems to interpret and scrutinize images, assisting in tasks like diagnostic imaging and medication validation. Predictive analytics employs statistical methodologies to predict future outcomes, aiding healthcare providers in making proactive decisions and optimizing resource allocation. AI applications span various domains, including drug discovery, personalized medicine, clinical decision-making, and pharmacy operations [2]. In drug discovery, AI is utilized to scrutinize extensive genomic and proteomic data to pinpoint potential drug targets and expedite the development of novel medications. Personalized medicine employs AI to customize treatment regimens to individual patient attributes, enhancing therapeutic outcomes and minimizing adverse effects. AI enhances clinical decision-making by offering real-time decision support tools that aid healthcare providers in making well-informed choices grounded on the latest evidence. AI optimizes pharmacy operations by automating tasks such as prescription validation, inventory management, and medication dispensing.

Scope of AI Integration in Pharmacy Practice

Artificial intelligence (AI) is increasingly being integrated into various sectors within the pharmaceutical industry, including community pharmacies, hospital pharmacies, and pharmaceutical manufacturing, highlighting its wide-ranging applicability throughout the pharmaceutical domain [4]. In community pharmacy settings, AI plays a crucial role in improving medication adherence by offering personalized reminders and counseling services, alongside enhancing inventory control measures and mitigating dispensing errors. Hospital pharmacies harness AI technologies for automated dispensing processes, real-time alerts for drug interactions, and enhanced patient monitoring capabilities. Within the pharmaceutical industry, AI is leveraged to expedite drug discovery, optimize clinical trial procedures, and refine manufacturing operations. This pervasive integration underscores the transformative capacity of AI to enhance operational efficiency, precision, and patient safety across the entire pharmaceutical supply chain. The incorporation of AI is geared towards optimizing medication management, enhancing healthcare provision, bolstering accessibility, and refining patient outcomes [3]. Medication management is advanced through AI-powered systems capable of identifying potential drug interactions, optimizing dosing schedules, and tailoring medication regimens based on individual patient attributes. Healthcare services are enriched by AI through the automation of routine duties, heightened diagnostic precision, and improved communication channels between healthcare professionals and patients. AI-supported telehealth platforms and remote monitoring devices expand healthcare accessibility by enabling patients to receive medical attention from their residences. The primary objective of AI integration is to refine patient outcomes by delivering more efficient, effective, and personalized care. AI aids pharmacists in optimizing medication choices, forecasting adverse drug occurrences, streamlining inventory control, and automating prescription validation procedures, thereby enhancing patient care and alleviating workloads [5]. By scrutinizing patient data and medical literature, AI aids pharmacists in selecting the most suitable medications for individual patients, considering aspects like age, weight, medical background, and concurrent medications. AI algorithms can forecast the probability of adverse drug events based on patient characteristics and medication profiles, empowering pharmacists to take preemptive actions to avert harm. Inventory management is optimized through AI-driven mechanisms that can predict demand, refine stock levels, and diminish wastage. The automation of prescription validation liberates pharmacists' time, enabling them to concentrate on more intricate responsibilities like patient counseling and medication therapy oversight.

AI-Driven Medication Management

Enhancing Prescription Accuracy and Safety

Artificial intelligence (AI) systems play a crucial role in reducing medication errors and enhancing patient safety by optimizing treatment regimens [1]. Medication errors pose a substantial risk in healthcare settings, resulting in adverse events, higher expenses, and decreased patient satisfaction. AI-driven systems mitigate these errors through task automation, real-time decision support, and proactive risk identification. By tailoring treatment plans to individual patient characteristics and current evidence, AI contributes to better therapeutic outcomes and minimizes adverse effects. AI streamlines prescription validation processes, decreasing distribution errors in hospital settings [6, 4]. Prescription validation is a pivotal stage in medication management, ensuring accurate dispensing of medications in terms of type, dosage, and timing. AI automates this validation by verifying prescription accuracy, detecting potential drug interactions, and highlighting discrepancies or errors. This automation not only reduces medication error risks but also enables pharmacists to focus on more complex responsibilities like patient counseling and medication therapy management. Machine learning algorithms can identify inappropriate hospital medication orders, enhancing pharmacy practices [7]. Inappropriate orders can lead to adverse events, increased costs, and decreased patient satisfaction. Machine learning algorithms analyze extensive patient and medication data to recognize patterns and forecast the likelihood of inappropriate orders. By notifying pharmacists of these orders for review, machine learning algorithms help prevent medication errors and elevate care quality. The incorporation of machine learning in pharmacy practice marks a significant advancement in improving prescription precision and safety.

Personalizing Medication Therapy

Artificial intelligence (AI) plays a crucial role in enabling personalized medicine, which customizes treatment decisions according to patient-specific data and medical background [1], [2]. Personalized medicine involves considering unique patient attributes like genetics, lifestyle, and environmental factors to tailor treatment strategies to their individual requirements. AI contributes to personalized medicine by examining extensive patient data to recognize patterns and forecast the probability of treatment efficacy. Through individualizing treatment choices based on specific patient characteristics, AI has the potential to enhance treatment outcomes and reduce the occurrence of adverse reactions. AI-based systems offer personalized guidance and lifestyle management, fostering treatment compliance and enhancing health results [5]. Adherence to treatment is a prominent issue in healthcare, as many patients do not adhere to their prescribed medication regimens. AI-powered systems can enhance adherence rates by supplying personalized guidance and lifestyle management, while considering factors such as patient preferences, beliefs, and cultural influences. By tailoring interventions to the unique needs of each patient, AI can foster treatment adherence and enhance health results. AI algorithms analyze patient data to detect patterns, anticipate health results, and optimize medication plans [8]. These algorithms are capable of analyzing vast datasets, encompassing medical histories, laboratory findings, and medication histories, to recognize trends that may elude human healthcare providers. By forecasting health results and refining medication plans based on individual patient characteristics, AI can enhance treatment effectiveness and diminish adverse reactions. The integration of AI algorithms in medication therapy signifies a substantial advancement in customizing healthcare and enhancing patient outcomes.

Improving Medication Adherence

Artificial intelligence (AI) enhances medication adherence by employing personalized strategies, reminders, and digital tools [9]. Adherence to medication is a crucial element in achieving favorable health results, yet numerous patients encounter difficulties in following their prescribed medication regimens. AI presents novel approaches to tackle this issue by offering tailored strategies, reminders, and digital tools that cater to the unique needs of individual patients. These tools aid patients in adhering to their medication schedules, resulting in enhanced health outcomes and decreased healthcare expenses. AI-driven telepharmacy services facilitate adherence and access to pharmacy services in regions with geographical obstacles [10]. These services utilize digital technologies to extend pharmacy services beyond physical establishments, enabling patients in distant or underserved areas to access essential care. AI can enrich telepharmacy services by delivering personalized medication guidance, monitoring adherence, and recognizing potential drug interactions. By surmounting geographical barriers, AI-powered telepharmacy services can enhance care accessibility and encourage medication adherence in patients who might otherwise face challenges in obtaining it. AI-fueled predictive analytics allow for preemptive intervention for patients prone to non-adherence [11]. Non-adherence to medication regimens is a prevalent issue that can result in unfavourable health outcomes and escalated healthcare expenditures. AI-based predictive analytics can pinpoint patients at elevated risk of non-adherence by considering factors such as medical background, socioeconomic status, and complexity of medication regimens. By early identification of these patients, healthcare providers can proactively intervene to address the underlying reasons for non-adherence and boost medication adherence rates. These interventions may comprise medication counseling, simplification of medication regimens, and provision of reminders and assistance.

Optimizing Pharmacy Workflow with AI

Automating Dispensing and Inventory Management

Artificial intelligence (AI) is utilized in pharmacy operations for tasks such as inventory management and adherence monitoring, aiming to boost operational efficiency and precision [2]. Conventional manual procedures in pharmacy operations are often time-intensive and error-prone. AI presents solutions to automate these functions, thereby diminishing the burden on pharmacists and enhancing the overall efficiency of pharmacy operations. Through the automation of inventory management and adherence monitoring, AI aids pharmacies in resource optimization and enhancing patient care. AI-driven inventory management and supply chain forecasting enhance pharmaceutical logistics, reducing medication wastage and ensuring optimal drug availability [1]. Effective inventory management is crucial for pharmacies to uphold sufficient stock levels, minimize waste, and guarantee patient access to necessary medications. AI-powered inventory management systems can assess historical sales data, predict future demand, and optimize stock levels accordingly. Supply chain forecasting assists pharmacies in anticipating potential disruptions in the supply chain, enabling proactive measures to safeguard patient care. By enhancing pharmaceutical logistics, AI can assist pharmacies in cost reduction, efficiency improvement, and ensuring optimal drug availability. AI-powered systems simplify intricate processes like inventory management and automated prescription validation [6]. The intricacies associated with managing inventory and validating prescriptions can be daunting for pharmacies, particularly those serving high patient volumes. AI-driven systems can automate these processes, lessening the workload on pharmacists and refining the accuracy and efficiency of pharmacy operations. Through the simplification of complex processes, AI enables pharmacies to concentrate on delivering top-tier patient care and enhancing health outcomes.

Streamlining Prescription Verification

Artificial intelligence (AI) has the capability to streamline the process of prescription verification in pharmacies, thereby enhancing operational efficiency [5]. The conventional prescription verification procedure is often labor-intensive, necessitating pharmacists to manually inspect each prescription for precision and completeness. AI can automate this process through the utilization of machine learning algorithms to authenticate prescriptions, identify potential drug interactions, and highlight any inconsistencies or inaccuracies. By automating prescription verification, AI enables pharmacists to allocate their time towards more intricate responsibilities such as patient counseling and medication therapy management. AI-driven systems alleviate the human workload, leading to enhanced accuracy and reduced timelines in pharmaceutical activities [12]. The pharmaceutical sector is under mounting pressure to curtail expenses, boost efficiency, and hasten the progress of novel medications. AI-powered systems can aid in accomplishing these objectives by automating routine duties, offering real-time decision-making support, and optimizing resource distribution. By alleviating the human workload, AI can enhance precision and expedite timelines in pharmaceutical operations, resulting in accelerated drug development and more effective healthcare provision. AI contributes to diminishing administrative burdens, allowing healthcare providers to concentrate on patient-centric care [3]. Administrative responsibilities can pose a substantial challenge for healthcare providers, consuming valuable time that could be devoted to patient care. AI has the capacity to automate numerous administrative tasks, including appointment scheduling, insurance claims processing, and patient records management. By reducing the administrative load on healthcare providers, AI enables them to concentrate on delivering superior patient-centered care. This transition towards patient-centered care has the potential to enhance patient contentment, improve health outcomes, and reduce healthcare expenditures.

Enhancing Communication and Collaboration

AI-powered systems play a crucial role in enhancing communication between healthcare providers, thus facilitating seamless coordination of care and ultimately leading to improved patient outcomes [8]. Effective communication and collaboration among healthcare professionals are fundamental in delivering top-notch patient care. AI systems play a pivotal role in streamlining communication processes by offering a centralized platform for exchanging patient data, coordinating care strategies, and interacting with patients and their families. Through enhancing communication and collaboration, AI technology contributes to ensuring that patients receive timely and appropriate care, consequently resulting in enhanced health outcomes. AI aids in fostering interprofessional communication by simulating dialogues among various healthcare professionals, such as pharmacists and physicians [13]. Proficient communication among healthcare professionals is paramount for ensuring patient safety and optimizing treatment results. AI technologies can simulate discussions among healthcare professionals, offering a secure environment for honing communication skills. These simulated interactions assist healthcare professionals in refining their communication abilities, gaining insights into diverse viewpoints, and establishing robust interprofessional relationships. AI-based platforms deliver real-time market intelligence, enabling swift adaptation to evolving market dynamics and patient demands [14]. The pharmaceutical market undergoes continual transformations due to the introduction of new medications, evolving regulations, and shifting patient demographics. AI-driven platforms furnish instantaneous market insights, empowering pharmacies to promptly adjust to market fluctuations and patient requirements. By scrutinizing market data and patient specifics, AI aids pharmacies in refining their product portfolios, enhancing marketing strategies, and boosting overall competitiveness. These platforms equip pharmacies with the necessary information to make well-informed decisions and proactively respond to market trends.

AI in Pharmacovigilance and Drug Safety

Detecting Adverse Drug Reactions

AI-powered predictive analytics plays a vital role in identifying adverse drug reactions (ADRs), stratifying patient risks, and optimizing treatments [1]. The timely detection of ADRs is critical for patient well-being, enabling prompt interventions to prevent severe complications. By scrutinizing patient data encompassing medical backgrounds, medication histories, and laboratory findings, AI-driven predictive analytics can pinpoint individuals prone to ADRs. This proactive strategy empowers healthcare professionals to undertake preventative actions like adjusting dosages, recommending alternative drugs, or instituting closer monitoring. Additionally, AI can refine treatment regimens by considering potential ADR risks and selecting medications that are both efficacious and safe for specific patients. AI significantly advances the detection of adverse medication reactions, thereby enhancing drug safety [4], [9]. Conventional ADR detection methods typically hinge on spontaneous reports, which may be incomplete and biased. AI has the capacity to boost ADR identification by sifting through extensive datasets from diverse origins, such as electronic health records, social platforms, and scientific literature, to unearth potential ADR indicators. This comprehensive approach enables the recognition of ADRs that might have eluded traditional techniques, culminating in improved drug safety and superior patient outcomes. Machine learning and natural language processing bolster pharmacovigilance endeavors, facilitating more precise and efficient ADR identification [15]. Pharmacovigilance encompasses the science and practices concerning the detection, evaluation, comprehension, and prevention of adverse effects or any other drug-related issues. Machine learning algorithms can analyze copious data to detect patterns and forecast the probability of ADRs, while natural language processing can extract valuable insights from unstructured content like patient narratives and social media entries. The integration of these technologies enhances the effectiveness and accuracy of pharmacovigilance activities, ultimately leading to enhanced drug safety and improved patient outcomes.

Predicting Drug Interactions

Artificial intelligence (AI) algorithms have the capability to forecast potential drug interactions, thereby enhancing medication safety [3]. Drug interactions pose a significant concern in the realm of healthcare due to their potential to result in adverse events, diminished medication efficacy, and escalated healthcare expenditures. AI algorithms can scrutinize extensive datasets on drug interactions to pinpoint potential hazards for individual patients. By preemptively predicting these interactions, healthcare providers can undertake precautionary measures such as adjusting medication dosages, recommending alternative medications, or instituting closer supervision. This proactive strategy augments medication safety and betters patient outcomes. AI-powered systems scrutinize potential drug reactions and recognize possible drug interactions [16]. These systems have the capacity to retrieve and evaluate comprehensive repositories of drug data encompassing pharmacological attributes, contraindications, and established interactions. Through juxtaposing a patient's medication profile with these repositories, AI-driven systems can discern potential risks and prompt healthcare providers to take suitable action. This functionality proves particularly beneficial for patients on multiple medications, as the likelihood of drug interactions rises with the number of medications ingested. AI has the capability to analyze copious amounts of medical data to detect drug targets and refine drug formulation [2]. Aside from predicting drug interactions, AI can be leveraged to scrutinize extensive medical data to pinpoint potential drug targets and fine-tune drug formulation. By identifying novel drug targets and formulating more potent medications, AI can contribute to the creation of safer and more efficacious therapies for a myriad of ailments. This utilization of AI harbors the potential to transform the pharmaceutical sector and ameliorate the well-being of numerous individuals.

Improving Patient Monitoring

Utilization of AI-driven patient engagement tools has been shown to enhance counseling and patient monitoring [9]. Patient engagement plays a crucial role in attaining optimal health results; nonetheless, many patients encounter difficulties in actively engaging in their own care. These AI-powered tools offer tailored education, reminders, and assistance to aid patients in remaining well-informed and engaged in their treatment strategies. Additionally, they can oversee patient progress and notify healthcare professionals of any potential issues, enabling timely interventions and prevention of severe complications. AI-facilitated systems support immediate tracking of medication adherence, delivering valuable insights for pharmacists and healthcare providers [6]. Non-adherence to prescribed medications presents a significant challenge in healthcare, with numerous patients failing to adhere to their medication regimens. AI-driven systems are capable of monitoring medication adherence promptly through diverse methods like electronic pill dispensers, wearable sensors, and mobile applications. This timely monitoring equips pharmacists and healthcare providers with actionable information on patient behavior, enabling the identification of individuals struggling with adherence and offering targeted interventions to enhance their medication adherence practices. Telehealth platforms, backed by AI algorithms, enable instantaneous consultations and remote monitoring [3]. These platforms are revolutionizing healthcare by granting patients the opportunity to receive care from their residences. AI algorithms can enrich telehealth platforms by furnishing real-time decision-making support, monitoring patient advancement, and customizing treatment plans. Through the provision of real-time consultations and remote monitoring, telehealth platforms can boost care accessibility, decrease healthcare expenses, and enhance patient outcomes. The assimilation of AI into telehealth platforms signifies a notable progression in reshaping healthcare delivery and enhancing patient results.

AI in Drug Discovery and Development

Accelerating Drug Identification

Artificial intelligence (AI) plays a crucial role in expediting the discovery of therapeutic candidates and repurposing existing drugs [1]. Traditional drug development processes are known for being protracted, expensive, and ineffective, requiring substantial time and financial resources to introduce a novel medication to the market. AI has the capability to notably hasten this procedure by scrutinizing extensive datasets, pinpointing potential drug targets, and forecasting the success probability of new drug prospects. Through diminishing the duration and expenses associated with drug exploration, AI can facilitate the swift and efficient delivery of new drugs to patients. AI algorithms possess the capacity to scrutinize copious medical information for the purpose of recognizing drug targets and refining drug formulation [2]. The identification of an appropriate drug target is a pivotal phase in the drug discovery process, as it dictates the likelihood of new drug success. AI algorithms can evaluate extensive medical datasets, encompassing genetic, proteomic, and clinical data, to pinpoint potential drug targets and anticipate the success likelihood of novel medications. By enhancing drug formulation grounded on these findings, AI can foster the creation of more potent and safer drugs. AI empowers the pharmaceutical sector to efficiently accomplish ambitious goals by alleviating human workload, enhancing accuracy, and condensing project timelines [12]. The pharmaceutical industry is increasingly under pressure to expedite the production of new drugs, while simultaneously curbing expenses and bolstering safety. AI serves as a valuable tool in attaining these objectives by automating routine duties, furnishing instantaneous decision-making support, and optimizing resource distribution. By lessening human workload, enhancing precision, and shortening project durations, AI enables the pharmaceutical sector to realize its ambitious aims and expedite the delivery of new drugs to patients.

Optimizing Clinical Trials

Artificial intelligence (AI) optimizes clinical trial procedures through predictive modeling, target identification, and personalized treatment approaches [17]. Clinical trials constitute a crucial phase in drug development, characterized by time-consuming, expensive, and inefficient processes. AI enhances the efficiency of clinical trials by employing predictive modeling to pinpoint promising drug candidates, target identification to select suitable trial participants, and individualized treatment strategies to enhance trial structuring. The integration of AI in clinical trials expedites the introduction of new drugs to patients. AI facilitates sample size determination [18], a pivotal aspect in ensuring the statistical power of a clinical trial. By leveraging historical data analysis and outcome measure variability prediction, AI aids in accurately estimating the required sample size, consequently diminishing clinical trial costs and durations. AI-driven algorithms enhance the retrieval of pertinent and current studies, refining the efficiency of literature reviews [12]. Literature reviews play a fundamental role in drug development, yet navigating vast data sets can be arduous and time-consuming. AI-driven algorithms streamline the identification of relevant and current studies, improving the efficiency of literature reviews and granting researchers access to the most recent information. This advancement accelerates drug development processes and elevates research quality.

Enhancing Drug Repurposing

Artificial intelligence (AI) plays a crucial role in drug repurposing, which involves discovering novel applications for existing drugs [1], [12]. This strategy offers a quicker and more cost-efficient pathway for developing new therapeutic solutions for various diseases. AI contributes to drug repurposing by scrutinizing extensive datasets, pinpointing potential drug targets, and assessing the probability of success for alternative therapeutic uses. By uncovering fresh applications for established medications, AI expedites the delivery of innovative treatments to patients with heightened efficiency. AI algorithms possess the capacity to sift through copious medical information for the identification of drug targets and the enhancement of drug formulation [2]. Apart from assisting in drug repurposing, AI algorithms can analyze substantial medical datasets to pinpoint drug targets and refine drug development. By unveiling novel drug targets and formulating more potent medications, AI aids in the creation of safer and more efficacious treatment options for a myriad of conditions. This utilization of AI holds the promise of transforming the pharmaceutical sector and elevating the well-being of numerous individuals. AI streamlines the detection of potential drug interactions, thereby bolstering medication safety [3]. Drug interactions pose a considerable challenge in healthcare, precipitating adverse events, diminished drug efficacy, and escalated healthcare expenses. AI can streamline the recognition of potential drug interactions by scrutinizing extensive data on such interactions and forecasting the likelihood of interactions in individual patients. By preemptively identifying these interactions, healthcare providers can adopt precautionary measures like adjusting medication dosages, prescribing alternative drugs, or increasing monitoring frequency. This proactive stance strengthens medication safety protocols and enhances patient health outcomes.

Ethical Considerations in AI Implementation

Data Privacy and Security

Data privacy represents a significant multifaceted challenge, encompassing ethical, regulatory, and financial dimensions, linked to the integration of artificial intelligence (AI) in the domain of pharmacy [1], [19]. The utilization of AI within pharmacy settings entails the acquisition, retention, and examination of extensive volumes of patient data, thereby eliciting notable apprehensions regarding data confidentiality and protection. Patients frequently exhibit reluctance in divulging their personal details, encompassing medical background, pharmaceutical records, and genetic information, unless assured of stringent data safeguarding protocols. The susceptibility to data breaches, unauthorized infiltration, and misappropriation of patient data constitutes a substantial hazard to patient confidence and could potentially erode the advantages offered by AI within pharmacy contexts. Consequently, the resolution of data privacy issues emerges as pivotal for the ethical and efficient application of digital health technologies in pharmacy practice [8]. To counteract these concerns, the implementation of robust data privacy and security mechanisms is imperative, incorporating encryption methodologies, access restrictions, and data depersonalization strategies. Patients necessitate comprehensive enlightenment concerning the utilization and protection of their data, alongside the entitlement to data accessibility, rectification, and erasure. Adherence to data protection statutes, such as the Health Insurance Portability and Accountability Act (HIPAA) and the General Data Protection Regulation (GDPR), assumes paramount importance in ensuring data confidentiality and protection. Substantial cybersecurity protocols are indispensable to shield patient data within AI frameworks [19]. In conjunction with data privacy safeguards, formidable cybersecurity measures are indispensable to fortify patient data against cyber incursions and unauthorized entry. These measures should encompass firewalls, intrusion detection systems, and recurrent security evaluations to pinpoint and rectify potential vulnerabilities. Healthcare establishments should institute training initiatives for employees to heighten awareness regarding cybersecurity risks and optimal strategies for safeguarding patient data. Through the integration of these measures, healthcare entities can alleviate the risk of data breaches and assure the confidentiality, integrity, and accessibility of patient data within AI infrastructures.

Algorithmic Bias and Fairness

Algorithmic bias in artificial intelligence (AI) is a significant concern in clinical settings due to its implications for transparency and interpretability [1]. This bias manifest when AI systems exhibit systematic unfairness or discrimination towards specific demographic groups, stemming from factors such as biased training data, flawed algorithms, or biased human input. In clinical practice, algorithmic bias can result in inaccurate diagnoses, inappropriate treatment choices, and disparities in healthcare outcomes. Mitigating algorithmic bias is crucial to establish the fairness, equity, and reliability of AI systems. Ethical considerations emphasize the importance of equitable access and justice in AI utilization [19]. Equitable access to AI-based healthcare services is vital to ensure that patients from diverse backgrounds have equal opportunities to benefit from these technologies. Justice in AI implementation necessitates fair, unbiased, and non-discriminatory use of AI systems, preventing the reinforcement or exacerbation of existing health inequalities. Healthcare institutions must prioritize equitable access and justice in AI integration to promote inclusive benefits for all patients. Algorithmic transparency plays a key role in fostering responsible AI deployment [12]. Transparency in AI entails comprehending the decision-making processes and rationale behind AI-generated conclusions. This transparency is critical for detecting and addressing algorithmic bias, ensuring accountability, and fostering trust in AI systems. Healthcare organizations should prioritize algorithmic transparency to promote the responsible and ethical use of AI technologies.

Professional and Social Responsibility

Ethical concerns arise regarding the potential replacement of non-specialized pharmacists by artificial intelligence (AI) [19]. The automation of traditional pharmacist tasks through AI raises apprehensions regarding possible job displacement, particularly among non-specialized pharmacists. While AI has the capacity to enhance efficiency and accuracy, it is crucial to contemplate the societal and economic repercussions of its integration and prevent unjust displacement of pharmacists. Healthcare institutions should allocate resources to training and educational schemes aimed at assisting pharmacists in adapting to the evolving pharmacy landscape, acquiring new skills that complement AI technologies. It is imperative to implement comprehensive educational campaigns advocating for informed and responsible utilization of AI [20]. Ensuring effective and ethical use of AI necessitates educating healthcare professionals, patients, and the general public on the advantages and risks associated with AI in healthcare. These educational programs should address aspects such as data confidentiality, algorithmic partiality, and the constraints of AI systems. By advancing informed and responsible AI implementation, healthcare establishments can endorse the beneficial use of these technologies for all stakeholders. Collaboration, education, and ethical frameworks are fundamental for the ethical deployment of AI in pharmacy practice [19]. Collaborative efforts among healthcare professionals, AI developers, and policymakers are indispensable for ensuring the responsible and ethical use of AI. Education and training initiatives are imperative to empower healthcare professionals with the competencies and insights essential for proficient AI utilization. Ethical frameworks are crucial to steer the development and execution of AI systems, guaranteeing their fair, just, and professional value-aligned application. Through fostering collaboration, advocating for education, and formulating ethical frameworks, healthcare institutions can ensure that AI is wielded in a manner that benefits patients and society at large.

Regulatory and Legal Frameworks

Evolving Guidelines and Standards

The regulatory landscape concerning the ethical and safety implications of artificial intelligence (AI) in pharmaceutical applications, exemplified by guidelines like GDPR and FDA regulations, is continuously developing [1]. Due to the swift progress of AI technology, ongoing adaptations of regulatory frameworks are imperative to adequately address ethical and safety issues. Regulatory authorities, such as the Food and Drug Administration (FDA) in the US and the European Medicines Agency (EMA) in Europe, are actively engaged in formulating guidelines and standards for the utilization of AI in pharmaceutical applications. These guidelines are aimed at fostering innovation while safeguarding patient safety and ensuring data confidentiality. Adherence to the evolving regulatory frameworks is crucial for healthcare entities and pharmaceutical firms incorporating AI technologies. The regulatory environment governing AI in healthcare necessitates precise guidelines and standards to ensure the secure and efficient deployment [9]. The absence of explicit guidelines and standards for AI utilization in healthcare introduces uncertainty and may impede the adoption of such technologies. Collaborative efforts involving healthcare professionals, AI developers, and policymakers are essential for the development of practical, effective, and ethically aligned guidelines. Regulatory conformity poses a significant obstacle in the assimilation of AI technologies [4]. The intricate and dynamic regulatory framework for AI in healthcare poses a notable challenge for healthcare organizations and pharmaceutical companies. Ensuring compliance with regulations such as HIPAA, GDPR, and other data protection statutes requires substantial investments in data security and privacy measures. Moreover, the validation and demonstration of the safety and efficacy of AI systems can be intricate and time-intensive. Healthcare entities should prioritize regulatory adherence in the integration of AI technologies to avert potential legal and financial repercussions.

Legal Liabilities and Accountability

Regulatory oversight is crucial for the integration of artificial intelligence (AI) in pharmaceutical settings [19]. The escalating utilization of AI in pharmacies prompts inquiries into legal responsibilities and liabilities related to adverse occurrences or mistakes. It is imperative to establish unambiguous legal frameworks delineating the duties of healthcare practitioners, AI developers, and healthcare establishments in instances of harm stemming from AI systems. These frameworks need to encompass aspects like negligence, product accountability, and data security breaches. Well-defined regulatory structures are indispensable to ensure the secure, efficient, and fair integration of AI [9]. Safeguarding the secure, effective, and fair integration of AI in healthcare necessitates well-defined regulatory structures that tackle matters such as data confidentiality, algorithmic partiality, and the authentication of AI systems. These structures should be collaboratively devised with healthcare practitioners, AI developers, and policymakers to guarantee their feasibility, efficacy, and adherence to ethical standards. Moreover, these frameworks should be periodically revised to mirror the swift progressions in AI technology and the evolving requisites of the healthcare sector. Addressing legal responsibilities and liabilities is pivotal for the conscientious deployment of AI in healthcare [12]. The conscientious deployment of AI in healthcare demands a clear comprehension of legal responsibilities and liabilities in instances of adversities or errors. Healthcare establishments should craft guidelines and protocols to handle these concerns, encompassing incident notification, examination, and resolution. Additionally, healthcare establishments should secure suitable insurance coverage to shield themselves against plausible legal litigations. By tackling legal responsibilities and liabilities, healthcare establishments can advocate for the secure and ethical utilization of AI in healthcare.

Data Governance and Compliance

Data governance policies are crucial for addressing privacy, security, and ethical considerations during the implementation of artificial intelligence (AI) systems [1]. Data governance encompasses the regulations, procedures, and criteria governing the acquisition, retention, utilization, and dissemination of data. In the context of AI deployment, data governance policies are essential to address privacy, security, and ethical concerns to safeguard patient data and ensure its responsible utilization. These policies should encompass directives on data de-identification, access management, and data exchange agreements. Moreover, it is imperative that data governance policies undergo periodic assessments and revisions to align with the dynamic regulatory environment and the most current data privacy and security protocols. Adherence to data protection statutes such as the Health Insurance Portability and Accountability Act (HIPAA) and the General Data Protection Regulation (GDPR) is indispensable [21]. Healthcare institutions integrating AI technologies must comply with data protection statutes like HIPAA, which establishes nationwide safeguards for safeguarding protected health information (PHI) in the United States, and GDPR, which imposes stringent stipulations on personal data processing within the European Union. Healthcare entities should establish protocols and practices to ensure compliance with these regulations, encompassing securing patient authorization for data gathering and utilization, instituting data security mechanisms, and facilitating patient access to their data. Active compliance monitoring is critical to ensure equitable and ethical Pharmacy Benefit Managers (PBM) operations [22]. PBMs are pivotal in administering prescription drug benefits for health schemes and employers. The integration of AI in PBM activities, such as drug pricing and formulary management, generates apprehensions regarding equity and ethical conduct. It is imperative to monitor PBMs' adherence to regulations and ethical standards to guarantee that AI applications are advantageous to patients and facilitate cost-effective medication accessibility. This monitoring process should involve transparent pricing strategies, impartial formulary determinations, and safeguarding patient data confidentiality.

Challenges in AI Adoption

Technological Barriers

The integration of artificial intelligence (AI) into clinical pharmacy practice is impeded by multiple technological challenges [9]. These obstacles include the absence of interoperability among diverse AI platforms, the intricate nature of AI algorithms, and the necessity for specialized proficiency in developing and managing AI systems. Such impediments can constrain the extensive implementation of AI in clinical pharmacy and restrict its potential advantages. Resolving these technological hindrances necessitates cooperation among healthcare professionals, AI experts, and policymakers to establish compatible systems, streamline AI algorithms, and offer training and education to healthcare practitioners. Technical integration difficulties present notable obstacles to the deployment of AI within pharmacy decision frameworks [11]. The assimilation of AI into prevailing pharmacy decision frameworks can be technically demanding, requiring substantial investments in infrastructure, software, and expertise. Challenges related to technical integration may emerge from the absence of standardized data formats, the intricacy of merging AI algorithms into existing processes, and the imperative for real-time data analysis. Overcoming such technical integration challenges demands meticulous planning, collaboration between healthcare practitioners and AI specialists, and a dedication to interoperability and standardization. The intricacy of AI decision-making, particularly the issue known as the "black box" problem, elicits concerns [1]. The term "black box" conveys the challenge of comprehending the decision-making process of AI systems, especially with the utilization of complex algorithms like deep learning. This opacity can raise doubts regarding the reliability and liability of AI systems, notably in clinical contexts where decisions may significantly impact patient well-being. Resolving the "black box" problem requires the advancement of explainable AI (XAI) methodologies that offer insights into the rationale behind AI-generated conclusions.

Financial Constraints

Financial barriers, such as substantial implementation expenses, impede the broad adoption of AI technologies [4]. The integration of AI technologies into pharmacy practice necessitates a significant financial commitment towards hardware, software, and specialized knowledge. These costs can pose a challenge for numerous healthcare institutions, particularly those with limited financial means. Moreover, the continual expenses associated with the upkeep and enhancement of AI systems can also pose a financial strain. Overcoming these financial obstacles necessitates the exploration of innovative funding mechanisms, such as governmental subsidies, collaborations between public and private sectors, and cost-sharing agreements, to enhance the accessibility of AI technologies for healthcare institutions. Adequate financial backing is crucial to address issues like elevated operational costs [23]. Besides implementation expenses, the ongoing operational costs related to AI systems can also financially strain healthcare institutions. These expenses encompass data storage, data processing, and continual maintenance and assistance costs. Sufficient financial support is imperative to aid healthcare institutions in surmounting these obstacles and ensuring the sustainability of AI systems over the long term. Various funding sources, including governmental allocations, charitable contributions, and revenues derived from AI-powered services, can provide this support. The expenses associated with implementation present a challenge in integrating AI technologies within community pharmacy settings [10]. Community pharmacies frequently operate within narrow profit margins and may lack the financial means to invest in AI technologies. Implementation costs may encompass expenses related to hardware, software, training, and ongoing maintenance.

The Future of AI in Pharmacy

Novel Technologies and Advancements: Novel technologies such as federated learning and quantum computing hold promise in enhancing the prediction of interactions between proteins and drugs, thereby expediting the process of drug discovery and development [4]. The incorporation of supervised and unsupervised artificial intelligence (AI) models in conjunction with Internet of Things (IoT) based monitoring systems is anticipated to propel the pharmaceutical sector towards a more data-centric approach, enabling refined and personalized healthcare interventions [1]. Subsequent investigations should concentrate on formulating and executing customized training initiatives and protocols to ensure healthcare practitioners are proficient in the effective and ethical utilization of AI in their clinical settings [20]. Augmenting Patient Involvement: The involvement of AI in pharmacy is anticipated to broaden, resulting in heightened medication safety, cost savings, and improved patient engagement, reflecting the increasing acknowledgment of the significance of patient-centered care [1]. AI-driven tools for patient engagement enhance counseling and patient surveillance, empowering patients to play a more active role in managing their well-being and medications [9]. AI has the capacity to tailor drug cost estimations and project out-of-pocket expenditures, nurturing enhanced reliance and proactive decision-making in medication management, thereby assisting patients in making well-informed decisions concerning their healthcare [22]. Prognostic and Tailored Healthcare: The pharmaceutical sector is on the verge of transitioning towards a data-driven, predictive, and patient-centric healthcare approach, facilitated by the advancing sophistication and availability of AI technologies [1]. AI-powered systems support personalized medicine, clinical decision aids, automated drug dispensing, and pharmacovigilance, thereby amplifying the efficiency and efficacy of healthcare provision [1]. Predictive models evaluate patient-specific variables to propose optimal treatments, diminishing errors and enhancing clinical decision-making, ultimately resulting in improved patient outcomes [6].

Artificial Intelligence's (AI) Potential in Pharmacy: AI exhibits significant promise in transforming healthcare delivery and enhancing patient outcomes within pharmacy practice, offering innovative solutions to enduring obstacles. AI has the capacity to enhance outcomes through facilitating precise, individualized, and efficient medication management, ultimately improving patient safety and optimizing therapeutic interventions. Through the provision of pioneering solutions, AI is reshaping healthcare administration and the practice of pharmacy, leading the way towards a more streamlined, efficient, and patient-centric healthcare system. Addressing Challenges for Successful Integration: The mitigation of ethical considerations and critical impediments is imperative for advancing research and the successful integration of AI, ensuring responsible and ethical utilization of AI technologies. Overcoming obstacles associated with privacy, ethical implications, and regulatory adherence is vital for realizing the complete potential of AI in pharmacy. Ethical governance of AI and continuous research efforts are essential for fully leveraging AI's capabilities, fostering transparency, equity, and responsibility in the deployment of AI technologies.

Conclusion:

Artificial Intelligence's (AI) Potential in Pharmacy: AI exhibits significant promise in transforming healthcare delivery and enhancing patient outcomes within pharmacy practice, offering innovative solutions to enduring obstacles. AI has the capacity to enhance outcomes through facilitating precise, individualized, and efficient medication management, ultimately improving patient safety and optimizing therapeutic interventions. Through the provision of pioneering solutions, AI is reshaping healthcare administration and the practice of pharmacy, leading the way towards a more streamlined, efficient, and patient-centric healthcare system. Addressing Challenges for Successful Integration: The mitigation of ethical considerations and critical impediments is imperative for advancing research and the successful integration of AI, ensuring responsible and ethical utilization of AI technologies. Overcoming obstacles associated with privacy, ethical implications, and regulatory adherence is vital for realizing the complete potential of AI in pharmacy. Ethical governance of AI and continuous research efforts are essential for fully leveraging AI's capabilities, fostering transparency, equity, and responsibility in the deployment of AI technologies.

Recommendations for Future Research and Practice

The results underscore the significance of ethical principles, educational initiatives, and patient self-governance in the integration of artificial intelligence (AI), promoting a climate of conscientious advancement and safeguarding the primacy of patient welfare. Collaborative efforts across disciplines are essential to fully exploit the capabilities of AI, uniting specialists from various domains to confront the intricate challenges and possibilities introduced by AI. Well-defined regulatory structures, ethical standards, and technological progress are crucial to guaranteeing the safe, efficient, and fair deployment of AI, establishing a robust basis for cultivating trust and assurance in AI technologies and unlocking their complete capacity to enhance healthcare outcomes.

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CARDIOPROTECTIVE EFFECTS OF MILLET-BASED DIETS

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Abstract:

Cardiovascular diseases (CVDs) remain the leading cause of mortality globally, largely influenced by dietary patterns and lifestyle factors. In recent years, millets—nutrient-dense, drought-resistant ancient grains—have garnered renewed attention for their potential role in promoting cardiovascular health. This chapter explores the cardioprotective effects of millet-based diets by examining their unique nutritional composition, including high fiber content, essential micronutrients (such as magnesium and potassium), low glycemic index, and abundance of antioxidants and phytochemicals. The chapter reviews existing scientific evidence from epidemiological studies, clinical trials, and experimental research, highlighting the impact of millets on lipid profiles, blood pressure, blood glucose regulation, and inflammation—key risk factors for CVDs. It also discusses the physiological mechanisms by which millets exert these protective effects, such as improving endothelial function, reducing oxidative stress, and enhancing insulin sensitivity. Furthermore, traditional dietary practices involving millets across different cultures are analyzed to draw insights into their long-standing association with lower incidences of heart disease. The chapter concludes with practical recommendations for integrating millets into modern diets and emphasizes the need for further research to strengthen clinical evidence and support public health policy.

Keywords: Cardiovascular Diseases, Millet Based Diet, Unique Nutritional Composition, Improved Dietary Patterns

Introduction:

Cardiovascular diseases (CVDs) encompass a group of disorders affecting the heart and blood vessels, including coronary artery disease, hypertension, heart failure, stroke, and arrhythmias. They are the leading cause of death globally, responsible for approximately 17.9 million deaths each year, with risk factors such as poor diet, physical inactivity, tobacco use, obesity, diabetes, and high blood pressure playing a major role in their development. The underlying pathology often involves atherosclerosis—a condition characterized by the buildup of fatty deposits in the arteries—which impairs blood flow and increases the risk of heart attacks and strokes. Early prevention through lifestyle changes, including dietary interventions, remains a cornerstone strategy in reducing the burden of CVDs worldwide[1,2].

Millets, a diverse group of small-seeded cereal grains such as pearl millet, finger millet, foxtail millet, and sorghum, are gaining recognition as valuable dietary interventions for promoting health and preventing chronic diseases. Traditionally consumed in Asia and Africa, millets are rich in dietary fiber, essential minerals (like magnesium and potassium), antioxidants, and have a low glycemic index, making them particularly beneficial for managing lifestyle-related conditions such as cardiovascular disease, diabetes, and obesity. Unlike refined grains, millets provide sustained energy release, improve lipid profiles, and support metabolic health. Their resilience to harsh growing conditions and minimal processing needs also position them as sustainable, nutrient-dense alternatives in modern diets aimed at disease prevention and overall well-being[3,4].

Nutritional Composition of Millets

Millets are a diverse group of ancient cereal grains that offer a rich and balanced nutritional profile, making them a valuable component of a health-promoting diet. Unlike many refined cereals, millets retain their outer layers and germ during processing, preserving their nutrient density. Here's a detailed breakdown of the nutritional composition of millets[5-7]:

1. Macronutrients

a. Carbohydrates

- Millets are high in complex carbohydrates, typically ranging from **60% to 70%** of their dry weight.
- They have a **low glycemic index (GI)**, particularly foxtail and finger millet, which helps regulate blood sugar and insulin levels—important for cardiovascular and metabolic health.

b. Proteins

- Millets contain **7–13% protein**, depending on the type.
- Rich in essential amino acids, especially **methionine and cysteine**, which are often lacking in staple grains like rice and wheat.
- Though not a complete protein source, when combined with legumes, millets contribute to a well-balanced amino acid profile.

c. Fats

- Contain **3–5% fat**, primarily unsaturated fatty acids including omega-6 fatty acids.
- The lipid content in millets, particularly in pearl millet and finger millet, includes **phytosterols**, which can aid in lowering LDL cholesterol.

d. Dietary Fiber

- Millets are an excellent source of **dietary fiber**, especially **insoluble fiber**, ranging from **8–12%**.

- Fiber aids digestion, helps control blood lipid levels, and promotes satiety—beneficial for weight and cholesterol management.

2. Micronutrients

a. Minerals

Millets are particularly rich in several heart-healthy minerals:

- **Magnesium**: Crucial for vascular tone and heart rhythm regulation. Finger millet contains up to 137 mg/100g.
- **Potassium**: Helps regulate blood pressure and fluid balance.
- **Iron**: Important for oxygen transport and energy metabolism. Pearl millet contains ~8–9 mg/100g.
- **Calcium**: Finger millet is especially high, containing **~344 mg/100g**, beneficial for bone and cardiovascular health.
- **Zinc and Phosphorus**: Contribute to enzyme function and metabolic activity.

b. Vitamins

- Millets contain **B-complex vitamins** such as niacin (B3), thiamine (B1), riboflavin (B2), and folic acid, essential for energy metabolism and cardiovascular function.
- Small amounts of **vitamin E and vitamin K** are also present, contributing to antioxidant and blood clotting functions, respectively.

3. Bioactive Compounds and Antioxidants

- Millets are rich in **polyphenols**, **flavonoids**, **phytosterols**, and **tannins**, especially in the outer seed coat.
- These compounds exhibit **antioxidant, anti-inflammatory, and anti-hyperlipidemic** properties.
- Finger millet and foxtail millet are among the richest in antioxidant activity.

4. Antinutritional Factors (and Their Management)

- Millets contain **phytates, tannins, and oxalates**, which can reduce the bioavailability of certain minerals like iron and calcium.
- However, **traditional processing methods** such as soaking, fermenting, sprouting, and cooking can significantly reduce these compounds while enhancing nutrient absorption.

Comparison with Refined Grains

Comprehensive comparison of millets with refined grains is mentioned below, focusing on their nutritional value, health impact, and overall dietary benefits—especially in the context of cardiovascular health[8].

Parameter	Millets (e.g., Finger, Foxtail, Pearl)	Refined Grains (e.g., White Rice, Refined Wheat Flour)
Carbohydrate Quality	Complex carbs, slow-digesting, low glycemic index	Simple carbs, quickly digested, high glycemic index
Dietary Fiber	High (8–12%) – promotes satiety, lowers cholesterol	Very low – most fiber lost during refining
Protein Content	Moderate (7–13%), with better amino acid profile	Lower (5–9%), lacks key amino acids
Fats and Fatty Acids	Contains healthy unsaturated fats and phytosterols	Minimal fat content, negligible health-promoting fats
Micronutrients	Rich in iron, calcium, magnesium, phosphorus, zinc	Low in micronutrients due to removal of bran and germ
B Vitamins	Good source of B1, B2, B3, and folate	Significantly reduced during refining
Antioxidants & Polyphenols	High in antioxidants (especially finger and foxtail)	Very low – lost in milling process
Glycemic Index (GI)	Low to moderate GI (especially foxtail, barnyard)	High GI – spikes blood glucose levels
Impact on Heart Health	Supports lower blood pressure, cholesterol, and weight	Increases risk of insulin resistance, obesity, and heart disease
Satiety & Weight Control	High satiety; helps in weight management	Low satiety; leads to overeating
Processing Level	Minimally processed; retains bran, germ, and endosperm	Highly processed; mostly endosperm retained
Shelf Life & Storage	Shorter shelf life; can go rancid without refrigeration	Longer shelf life; less nutritious but more convenient
Sustainability	Grows in arid regions, climate-resilient	Requires more water and chemical inputs

Mechanisms of Cardioprotection

Millets contribute to cardiovascular health through multiple physiological and biochemical pathways. Their cardioprotective effects are largely attributed to their unique combination of dietary fiber, essential micronutrients, antioxidants, and low glycemic index. Below are the key mechanisms[9,10]:

1. Regulation of Lipid Metabolism

- Millets help lower LDL (bad) cholesterol and triglyceride levels while maintaining or increasing HDL (good) cholesterol.
- This is due to their high dietary fiber and phytosterols, which reduce cholesterol absorption in the intestine and enhance excretion of bile acids.
- The soluble fiber binds to bile acids, requiring the liver to use more cholesterol to produce new bile acids, thereby lowering blood cholesterol.

2. Blood Pressure Reduction

- Rich in potassium and magnesium, millets help regulate vascular tone and control blood pressure by promoting vasodilation and reducing arterial stiffness.
- Magnesium plays a crucial role in the relaxation of blood vessels and preventing vascular calcification.
- Regular consumption of millets may contribute to the prevention and management of hypertension, a major risk factor for heart disease.

3. Improvement in Blood Glucose Control

- Millets have a low glycemic index, leading to a slower release of glucose into the bloodstream.
- This helps prevent insulin resistance and hyperinsulinemia, which are closely linked to atherosclerosis and endothelial dysfunction.
- Better glycemic control also reduces the risk of diabetic cardiomyopathy.

4. Antioxidant and Anti-inflammatory Effects

- Millets contain polyphenols, flavonoids, and tannins, which exhibit potent antioxidant properties.
- These compounds neutralize free radicals and reduce oxidative stress, a key contributor to endothelial damage and plaque formation in arteries.
- Anti-inflammatory effects help reduce chronic low-grade inflammation that promotes heart disease progression.

5. Endothelial Function and Vascular Health

- Millets improve endothelial function, which is critical for healthy arteries and proper blood flow.
- Bioactive compounds like ferulic acid and catechins in millets help maintain nitric oxide (NO) balance, enhancing vasodilation and blood vessel elasticity.

6. Weight Management and Metabolic Syndrome Prevention

- The high fiber content and slow digestibility of millets increase satiety, reduce overall calorie intake, and support weight loss.

- Healthy body weight reduces the burden on the heart and lowers the risk of metabolic syndrome, a cluster of conditions that increase cardiovascular risk.

7. Gut Microbiota Modulation

- The prebiotic fibers in millets promote the growth of beneficial gut bacteria, which are associated with lower inflammation, improved lipid metabolism, and better immune responses—all factors that contribute to heart health.

Millet-based diets exert cardioprotective effects through a synergistic action of nutritional and functional components. By improving lipid profiles, regulating blood pressure, reducing oxidative stress, and supporting metabolic balance, millets serve as a natural dietary approach to preventing and managing cardiovascular diseases.

Scientific and Clinical Evidence

Scientific and clinical studies have increasingly supported the role of millets in promoting cardiovascular health. The body of evidence includes in vitro studies, animal models, human clinical trials, and epidemiological research, all pointing to the beneficial effects of millets on lipid metabolism, blood pressure, glycemic control, inflammation, and overall cardiovascular function[11-14].

1. In Vitro and Animal Studies

- **Antioxidant Properties**: Laboratory analyses have shown that millets like finger millet and foxtail millet have high polyphenol and flavonoid content, which exhibit strong antioxidant activity, scavenging free radicals that contribute to atherosclerosis.
- **Animal Models**:
  - Studies in rats fed millet-based diets have demonstrated significant reductions in total cholesterol, LDL cholesterol, and triglyceride levels.
  - Millets improved endothelial function and reduced inflammatory markers such as C-reactive protein and TNF-α in rodents.
  - Millet-fed rats exhibited lower systolic blood pressure, indicating a hypotensive effect attributed to magnesium and potassium content.

2. Human Clinical Trials

A. Lipid Profile Improvement

- A randomized controlled trial (RCT) in India found that participants with hyperlipidemia who consumed foxtail millet for 30 days showed:
  - ↓ 13% in total cholesterol
  - ↓ 10% in LDL cholesterol
  - ↑ 8% in HDL cholesterol

B. Blood Pressure Regulation

- In hypertensive adults, barnyard millet and little millet diets over 6 weeks resulted in:

  - ↓ Systolic and diastolic blood pressure by an average of 5–7 mmHg

C. Glycemic and Metabolic Benefits

- In patients with type 2 diabetes, finger millet consumption led to:
  - ↓ Postprandial blood glucose
  - ↓ HbA1c levels after 3 months
  - Improved insulin sensitivity
  - These outcomes indirectly reduce cardiovascular risk.

D. Weight and BMI Reduction

- A study involving overweight adults found that a millet-based diet:
  - ↓ Body Mass Index (BMI)
  - Improved satiety levels
  - Reduced visceral fat – a key factor in reducing cardiovascular disease risk.

3. Meta-analyses and Systematic Reviews

- A 2021 meta-analysis by the International Crops Research Institute for the Semi-Arid Tropics (ICRISAT) concluded that:
  - Regular millet consumption leads to a 7–9% decrease in total cholesterol and a 12% reduction in systolic blood pressure.
  - Millets significantly improved cardiovascular risk factors compared to control diets based on refined grains.
- Another review published in *Frontiers in Nutrition* (2022) noted that millets consistently reduce CVD markers when replacing rice or wheat, especially in populations with metabolic syndrome.

4. Epidemiological Evidence

- Populations in rural India and Africa, where millet is a staple, have historically reported lower incidences of coronary artery disease and hypertension, compared to urban populations consuming high amounts of refined grains.
- Studies correlating traditional millet diets with long-term heart health outcomes reinforce the protective role of these grains.

5. Limitations and Research Gaps

- Small sample sizes and short study durations in some trials.
- Variability in millet types and preparation methods may affect outcomes.
- Need for longitudinal studies and diverse population samples to validate benefits across demographics.

There is strong and growing scientific evidence supporting the cardioprotective benefits of millet-based diets. Both experimental and clinical studies confirm that regular millet consumption can positively impact lipid profiles, blood pressure, glycemic control, and overall cardiovascular function. While more large-scale and long-term trials are needed, the current data establish millets as a valuable dietary tool in the prevention and management of cardiovascular diseases.

Millets and Specific Cardiovascular Risk Factors

Millets contribute significantly to cardiovascular health by positively modulating several well-known risk factors. Their unique nutritional and phytochemical profile allows them to address the metabolic imbalances that lead to cardiovascular diseases (CVDs). Below is an analysis of how millets affect key cardiovascular risk factors[15-16]:

1. **Dyslipidemia (Abnormal Lipid Levels)**

Effect of Millets:

- Millets are rich in dietary fiber, especially soluble fiber, which binds to bile acids and promotes cholesterol excretion.
- Presence of phytosterols competes with cholesterol for absorption in the intestines.
- Studies show significant reductions in total cholesterol, LDL (bad) cholesterol, and triglycerides, with a mild increase in HDL (good) cholesterol.

Evidence:

- Clinical trials with foxtail millet and pearl millet showed reductions of up to 13% in LDL and 10% in total cholesterol within 4–8 weeks of daily consumption.

2. **Hypertension (High Blood Pressure)**

Effect of Millets:

- Millets are naturally high in magnesium and potassium, which support blood vessel relaxation (vasodilation) and counteract sodium's hypertensive effects.
- They also contain arginine, an amino acid that enhances nitric oxide production for improved endothelial function.

Evidence:

- Regular millet intake (especially barnyard millet) was shown to reduce systolic and diastolic blood pressure by 5–7 mmHg in hypertensive individuals.

3. **Hyperglycemia and Insulin Resistance**

Effect of Millets:

- Millets have a low glycemic index (GI) and are digested slowly, preventing blood sugar spikes.
- This stabilizes insulin levels and improves glucose utilization.
- Reduces risk of developing diabetic cardiomyopathy—a heart condition caused by poor blood sugar control.

Evidence:

- Finger millet and kodo millet consumption led to lower postprandial blood glucose and improved HbA1c in diabetic patients over a 3-month period.

4. Obesity and Central Adiposity

Effect of Millets:

- High in fiber and protein, millets promote satiety and reduce total caloric intake.
- Their slow digestibility helps maintain energy balance and prevent overeating.
- Millets improve leptin sensitivity and reduce visceral fat, both linked to lower cardiovascular risk.

Evidence:

- Studies showed reductions in BMI and waist circumference after replacing refined grains with millet in weight-loss interventions.

5. Oxidative Stress and Inflammation

Effect of Millets:

- Millets are rich in polyphenols, flavonoids, and tannins, which have anti-inflammatory and antioxidant properties.
- These compounds protect the vascular endothelium and reduce the progression of atherosclerosis.
- They also lower C-reactive protein (CRP) and other inflammatory markers.

Evidence:

- Antioxidant assays and human trials showed reductions in oxidative markers like malondialdehyde (MDA) after millet consumption.

6. Endothelial Dysfunction

Effect of Millets:

- The bioactive compounds in millets support nitric oxide (NO) synthesis, improving endothelial function and preventing arterial stiffness.
- Reduced oxidative stress also enhances vascular tone and reactivity.

Evidence:

- Improvements in flow-mediated dilation (FMD) have been reported in early-phase clinical studies involving millet-enriched diets.

Millets exert multifaceted benefits by targeting several cardiovascular risk factors simultaneously—making them a strategic dietary choice for both prevention and management of heart disease. Incorporating millets into regular diets can lead to measurable improvements in blood lipids, blood pressure, glucose regulation, weight control, oxidative stress, and endothelial health.

Integration into Modern Diets

As the health benefits of millets gain global recognition, integrating them into modern diets has become both a nutritional and strategic imperative. This transition requires innovation in food processing, consumer education, and culinary adaptation to replace or complement commonly consumed refined grains. Below are key strategies and considerations for successful incorporation of millets into contemporary eating patterns[17-21]:

1. Substitution for Refined Grains

- Replace white rice or refined wheat with millets in daily meals—e.g., use foxtail millet or little millet instead of rice, or sorghum flour in place of wheat flour.
- Millets can be used to make common staples like idli, dosa, rotis, porridges, and pilafs, without major alterations to taste or texture.

2. Ready-to-Cook and Packaged Foods

- Demand for convenience has led to the rise of millet-based noodles, pasta, breakfast cereals, energy bars, and instant mixes.
- These products preserve nutritional quality while offering palatable, modern food formats appealing to urban populations.

3. Bakery and Snack Products

- Millets can be used in baked goods such as breads, cookies, muffins, and crackers, either alone or blended with other flours.
- They are ideal for gluten-free baking, making them suitable for individuals with celiac disease or gluten sensitivity.
- Roasted millet puffs, chips, and granola bars are healthy snack alternatives to refined and fried options.

4. Restaurant and Culinary Innovations

- Chefs and restaurants are increasingly introducing millet-based dishes into fine dining and casual menus to promote health-conscious choices.
- Millet risottos, grain bowls, salads, and millet-based sushi are examples of fusion dishes that bridge tradition and trend.

5. Institutional and School Meals

- Integrating millets into government nutrition programs, school lunches, and hospital diets supports broader health and sustainability goals.
- India's POSHAN Abhiyan and inclusion of millets in midday meal schemes are notable examples of large-scale interventions.

6. Cultural and Regional Dishes

- Reviving traditional millet recipes—like bajra khichdi, ragi mudde, jowar roti, kodo millet upma—resonates with local food habits and enhances acceptability.

- Millets align with ancestral diets and sustainable agriculture, making them culturally significant.

7. Public Awareness and Education

- Promoting the health benefits and cooking versatility of millets through campaigns, social media, and workshops is crucial.
- Celebrations like International Year of Millets (2023) by the UN have helped rebrand millets as "smart foods."

8. Nutritional and Culinary Guidelines

- Dietitians and nutritionists can include millet-based meal plans in dietary interventions for conditions like diabetes, obesity, and CVD.
- Cooking workshops and nutrition education can improve culinary skills and confidence in using millets.

Integrating millets into modern diets is both feasible and beneficial. With culinary creativity, technological innovation, and public engagement, millets can become a mainstream dietary component. This shift supports not only personal health but also sustainable agriculture, food security, and the prevention of non-communicable diseases such as cardiovascular disease.

Conclusion:

Millet-based diets offer a promising, evidence-backed approach to promoting cardiovascular health. Through their rich nutritional profile—characterized by high dietary fiber, essential micronutrients like magnesium and potassium, low glycemic index, and abundant antioxidants—millets address several key cardiovascular risk factors, including dyslipidemia, hypertension, obesity, insulin resistance, and chronic inflammation. Scientific and clinical studies have consistently demonstrated the ability of various millets to improve lipid profiles, regulate blood pressure, support glycemic control, and enhance endothelial function.

Integrating millets into modern diets is not only feasible but also sustainable. Their adaptability to diverse culinary traditions, availability in innovative food formats, and compatibility with modern health trends make them a valuable dietary intervention in the prevention and management of cardiovascular diseases. As global health systems continue to grapple with the burden of non-communicable diseases, reintroducing millets into daily consumption can play a transformative role in creating healthier, more resilient food systems and populations. Thus, promoting millet consumption is not merely a return to traditional grains but a forward-looking strategy for cardiovascular wellness and public health nutrition.

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STEM CELLS IN PHARMACOLOGICAL RESEARCH AND REGENERATIVE MEDICINE

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Abstract:
Stem cells have emerged as transformative tools in pharmacological research and regenerative medicine due to their unique ability to self-renew and differentiate into diverse specialized cell types. Their applications span drug discovery, toxicological testing, disease modeling, and therapeutic regeneration. Embryonic stem cells (ESCs), adult stem cells, and induced pluripotent stem cells (iPSCs) each offer specific advantages in terms of plasticity, safety, and ethical considerations. ESCs are primarily used for developmental studies and high-throughput drug screening, while adult stem cells such as hematopoietic and mesenchymal stem cells play a critical role in cell therapy and immune modulation. iPSCs, derived from reprogrammed somatic cells, enable patient-specific modeling and personalized drug testing without the ethical controversies associated with ESCs. Stem cell-derived tissues such as cardiomyocytes, hepatocytes, and neurons offer human-relevant platforms that outperform traditional animal models in drug screening and toxicity assessments. Moreover, stem cells are pivotal in regenerative medicine, facilitating tissue repair, immune regulation, and even gene correction when combined with CRISPR-Cas9 technology. Despite their potential, challenges such as teratoma formation, immunological rejection, ethical disputes (especially with ESCs), high costs, and regulatory complexities continue to limit widespread clinical translation. Nevertheless, with advancements in biotechnology and increasing global interest in personalized medicine, stem cells are likely to become foundational components in the future of drug development and disease therapy.

Keywords: Stem Cells, Pharmacology, Regenerative Medicine, Drug Screening, Personalized Therapy

Introduction:

In recent decades, stem cells have significantly impacted the landscape of pharmacological science and regenerative medicine. Defined by their dual capacity for self-renewal and differentiation, stem cells have become vital research tools and therapeutic agents. Their ability to model human physiology, replicate disease pathology, and respond to pharmacological agents in a tissue-specific manner presents a substantial leap forward from traditional approaches relying on animal models or immortalized cell lines.

Pharmacology increasingly requires platforms that reflect individual genetic variability and complex biological interactions. In this regard, stem cells particularly induced pluripotent stem cells (iPSCs) allow for the development of patient-specific models, facilitating a shift toward precision medicine. Researchers can now generate human cardiomyocytes, hepatocytes, or neurons in vitro, permitting detailed analysis of drug efficacy and toxicity at a cellular level. This minimizes the translational gap between preclinical studies and human clinical trials [1].

Regenerative medicine also benefits enormously from stem cell technologies. Adult stem cells like mesenchymal stem cells (MSCs) have already been used clinically to treat degenerative and autoimmune disorders. Embryonic stem cells (ESCs) and iPSCs hold further potential for repairing cardiac, neural, and ocular tissues. The integration of stem cell biology with gene-editing platforms, such as CRISPR-Cas9, promises to revolutionize the treatment of genetic disorders, enabling permanent correction at the genomic level.

However, despite these advances, challenges such as tumorigenicity, ethical controversy (especially with ESCs), immunogenicity, and regulatory hurdles remain. Balancing therapeutic potential with safety and societal acceptance is critical to the future integration of stem cell technologies in pharmacology [2].

Types of Stem Cells Used in Pharmacology

Stem cells have revolutionized pharmacological research by offering more accurate models for drug testing, disease modeling, and regenerative therapies. Their unique ability to differentiate into various specialized cells makes them essential in developing safer, more effective treatments. Three major types of stem cells are widely used in pharmacology: embryonic stem cells (ESCs), adult (somatic) stem cells, and induced pluripotent stem cells (iPSCs). Each type offers specific advantages and limitations based on their origin, plasticity, and clinical utility [3].

1. Embryonic Stem Cells (ESCs)

Embryonic stem cells are derived from the inner cell mass of a blastocyst, an early-stage embryo formed within five to seven days post-fertilization. These cells are pluripotent, meaning they have the potential to differentiate into any cell type derived from the three germ layers: ectoderm, mesoderm, and endoderm. This broad differentiation ability makes ESCs a valuable tool in pharmacological studies, particularly for modeling early human development, studying congenital disorders, and screening the effects of drugs on various tissues during embryogenesis.

In drug discovery, ESCs are used in high-throughput screening platforms, where thousands of drug compounds can be tested on ESC-derived tissues, such as cardiac or hepatic cells. This allows researchers to detect early signs of toxicity, efficacy, or teratogenic potential. Despite their scientific value, the use of ESCs is controversial due to ethical concerns related to the destruction of embryos during cell extraction, which has spurred the development of alternative stem cell models [4].

2. Adult (Somatic) Stem Cells

Adult stem cells, also known as somatic stem cells, are multipotent they can give rise to a limited range of cell types related to their tissue of origin. These cells are present in various body tissues, including bone marrow, adipose tissue, skin, and dental pulp. Unlike embryonic stem cells, adult stem cells are involved in natural tissue repair and regeneration throughout life.

Two commonly studied types of adult stem cells in pharmacology are:

- Hematopoietic stem cells (HSCs): Found in bone marrow, these cells generate all types of blood cells and are widely used in bone marrow transplants to treat leukemia and other hematologic disorders.
- Mesenchymal stem cells (MSCs): Found in bone marrow, fat, and umbilical cord tissue, MSCs can differentiate into bone, cartilage, and fat cells. They have shown promise in treating inflammatory conditions, autoimmune disorders, and degenerative diseases such as osteoarthritis.

Adult stem cells are often used in cell-based therapy research, drug efficacy testing, and regenerative medicine due to their relatively low ethical concerns and established clinical applications. However, their limited differentiation capacity and reduced proliferation potential compared to pluripotent cells can be a disadvantage in certain research contexts [5].

3. Induced Pluripotent Stem Cells (iPSCs)

Induced pluripotent stem cells represent a breakthrough in stem cell science. These are somatic (adult) cells like skin fibroblasts that have been genetically reprogrammed to revert to a pluripotent state. iPSCs behave similarly to ESCs in that they can differentiate into cells of all three germ layers. However, iPSCs are generated without using embryos, resolving ethical issues surrounding embryonic stem cells.

iPSCs have opened up new avenues for personalized medicine. Since they can be created from a patient's own cells, iPSCs can be used to develop patient-specific disease models, enabling researchers to study genetic diseases in vitro and test tailored therapeutic agents. For example, iPSCs derived from patients with Parkinson's disease or inherited cardiac disorders can be used to generate neural or cardiac cells for drug screening and toxicity testing.

Moreover, iPSCs offer a platform to test how individual genetic backgrounds affect drug response, paving the way for pharmacogenomic applications. This level of personalization enhances drug safety and efficacy predictions in preclinical stages. iPSC technology also faces challenges, including variability in reprogramming efficiency, risk of genetic mutations during reprogramming, and the potential for tumorigenicity if cells are not properly differentiated before use.

Each stem cell type ESCs, adult stem cells, and iPSCs contributes uniquely to pharmacological research. ESCs provide a model for developmental drug screening, adult stem cells are vital for regenerative applications, and iPSCs offer customizable, ethically sound platforms for disease modeling and personalized testing. Collectively, these stem cell technologies are reshaping the future of drug discovery, safety evaluation, and regenerative therapies [6].

Applications of Stem Cells in Pharmacological Research

Stem cells have revolutionized the field of pharmacology by offering physiologically relevant, renewable, and ethically viable models for understanding disease mechanisms and evaluating drug responses. Traditional pharmacological testing has relied heavily on animal models, which often fail to predict human responses accurately due to interspecies differences. Stem cell-based models particularly those derived from human tissues provide more accurate and customizable platforms for testing drug efficacy, toxicity, and mechanism of action. Among the most impactful applications are drug screening and development, disease modeling, and toxicology testing [7].

1. Drug Screening and Development

One of the most transformative roles of stem cells in pharmacology is their use in high-throughput drug screening (HTS) and lead compound evaluation. Stem cell-derived human tissues, such as cardiomyocytes (heart cells), hepatocytes (liver cells), and neurons, are now being used to simulate real human organ responses to new drug candidates. These in vitro platforms allow researchers to observe drug behavior under human-like physiological conditions without involving human subjects or relying solely on animal testing.

For instance, cardiac toxicity, a common cause of drug failure in later development stages, can now be detected early using stem cell-derived cardiomyocytes. These cells demonstrate actual human cardiac electrophysiological activity, enabling researchers to observe how new drugs influence heart rhythm, ion channels, and contractility. Similarly, hepatocyte-like cells derived from stem cells can mimic liver metabolism, assisting in predicting drug-drug interactions, bioactivation, and metabolite formation [8].

This approach has several advantages:

- Reduces development time and cost
- Enhances prediction of human-specific responses
- Allows for patient-specific drug screening using induced pluripotent stem cells (iPSCs)

By integrating automated systems with stem cell-based assays, pharmaceutical companies are now able to screen thousands of compounds efficiently, selecting those with favorable pharmacokinetic and pharmacodynamic profiles early in the development pipeline.

2. Disease Modeling

Stem cells particularly induced pluripotent stem cells (iPSCs) have become indispensable in creating in vitro models of human diseases. By reprogramming somatic cells from patients into iPSCs, researchers can generate cell types that carry the patient's genetic mutations. This capability allows for the recreation of disease-specific cell phenotypes in the laboratory, providing an ideal environment for studying disease progression and identifying therapeutic targets.

For example:

- iPSCs derived from individuals with Parkinson's disease can be differentiated into dopaminergic neurons, enabling the study of neuronal degeneration and testing neuroprotective drugs.
- In amyotrophic lateral sclerosis (ALS), iPSC-derived motor neurons help scientists observe disease-related cellular changes such as axonal transport defects and protein aggregation.
- In Type 1 diabetes, iPSC-derived pancreatic beta-like cells allow for the study of autoimmune destruction and insulin secretion dynamics.

These patient-specific disease models are invaluable for identifying biomarkers, evaluating targeted therapies, and implementing personalized medicine approaches. They also provide an ethical and practical alternative to studying rare or genetically inherited diseases in humans, which would otherwise be difficult due to the limited availability of clinical samples or subjects [9].

3. Toxicology Testing

Another significant contribution of stem cells to pharmacological science is in the realm of predictive toxicology. Many promising drugs are withdrawn during clinical trials or even after-market release due to unanticipated toxic effects. Traditional animal models often fail to predict such adverse effects because of species differences in metabolism, receptor distribution, and immune response [10].

Stem cell-derived human cells, particularly from liver, heart, and nervous tissue, offer a more accurate and sensitive tool for toxicity assessment. These models are used to evaluate:

- Cytotoxicity: Determining whether a compound is harmful to living cells
- Cardiotoxicity: Assessing whether drugs affect heart rhythm, contractility, or cause arrhythmias
- Hepatotoxicity: Predicting liver injury or metabolic dysfunction caused by bioactive compounds
- Neurotoxicity: Evaluating effects on synaptic function, neurotransmitter release, or nerve cell viability

For instance, stem cell-derived hepatocytes express drug-metabolizing enzymes such as cytochrome P450, making them suitable for detecting reactive metabolites that could cause liver injury. Likewise, electrophysiological recordings from stem cell-derived cardiomyocytes help detect potential QT interval prolongation, a key marker of proarrhythmic risk [11].

Incorporating these assays early in the drug development process can significantly reduce the risk of late-stage failure and ensure that only the safest compounds proceed to clinical testing.

Stem cell technologies have dramatically enhanced pharmacological research by providing human-relevant platforms for drug discovery, disease modeling, and toxicity testing. By bridging the gap between traditional animal studies and human clinical trials, stem cells help improve the reliability, safety, and personalization of drug development. Their applications not only accelerate the pace of innovation but also bring us closer to the goals of precision medicine and safer therapeutics.

As these tools become more refined, scalable, and standardized, they are poised to become integral components of mainstream pharmacological workflows and regulatory evaluation processes [12].

Regenerative Medicine Applications of Stem Cells

Regenerative medicine is an innovative field aimed at restoring the structure and function of damaged tissues and organs. Stem cells, with their unique ability to self-renew and differentiate into various specialized cell types, have become central to this approach. Through tissue repair, stem cell-based therapy, and advanced gene editing technologies, stem cells offer promising solutions for treating chronic, degenerative, and previously incurable diseases [13].

Tissue Repair and Replacement

One of the most promising applications of stem cells in regenerative medicine is tissue regeneration. Unlike conventional treatments that often manage symptoms, stem cell-based strategies aim to restore damaged tissues at the cellular level. Researchers are actively investigating the use of mesenchymal stem cells (MSCs), embryonic stem cells (ESCs), and induced pluripotent stem cells (iPSCs) to regenerate tissue in organs affected by trauma or disease.

In heart failure, stem cell-derived cardiomyocytes have shown potential in regenerating damaged myocardium, improving heart function after myocardial infarction. In spinal cord injuries, transplanted neural stem cells or glial progenitor cells may help re-establish nerve connections, offering hope for partial motor recovery. Conditions like retinal degeneration, including age-related macular degeneration, are also being targeted, with retinal pigment epithelium derived from iPSCs being tested in clinical settings. Similarly, in osteoarthritis, stem cells are being explored to regenerate cartilage and reduce inflammation, improving joint mobility and reducing pain [14].

Stem Cell Therapy

Stem cell therapy involves the transplantation or injection of stem cells into patients to treat or prevent disease. Numerous clinical trials are underway worldwide to assess the efficacy of such therapies for a broad spectrum of conditions.

Mesenchymal stem cells (MSCs), due to their anti-inflammatory and immunomodulatory properties, are being evaluated for stroke recovery, autoimmune diseases, and chronic obstructive pulmonary disease (COPD). In Type 1 diabetes, scientists are working to differentiate stem cells into insulin-producing beta cells to restore endogenous insulin secretion. iPSC-derived cells, owing to their compatibility with patient-specific genomes, are also being tested in myocardial infarction and neurodegenerative disorders like Parkinson's disease.

What makes stem cell therapy particularly appealing is the potential for personalized treatment using cells derived from the patient, reducing the risk of immune rejection. However, this therapy still faces challenges related to cell survival, integration, and long-term safety [15].

Gene Editing and Correction

A cutting-edge development in regenerative medicine involves combining stem cells with gene-editing tools such as CRISPR-Cas9. This powerful technology allows researchers to precisely modify defective genes within a patient's own cells before they are reintroduced into the body.

For example, in genetic blood disorders like sickle cell anemia or beta-thalassemia, hematopoietic stem cells can be harvested, genetically corrected in the lab, and then transplanted back into the patient to restore healthy blood cell production. Similarly, in inherited retinal disorders, gene-edited iPSCs are being explored to regenerate functional retinal cells.

This strategy offers a potential cure rather than lifelong management of genetic diseases, and clinical trials in this area are rapidly expanding.

Stem cells have unlocked new dimensions in regenerative medicine through their roles in tissue regeneration, therapeutic transplantation, and gene correction. These applications represent a paradigm shift from symptom management to disease modification and potential cures. Although challenges remain such as immune response, scalability, and regulatory approvalthe integration of stem cell science with modern biotechnology continues to reshape the future of medicine, offering renewed hope for millions suffering from degenerative and genetic conditions [16].

Advantages and Challenges of Stem Cell Applications

The advent of stem cell technologies has marked a significant breakthrough in both pharmacological research and regenerative medicine. From modeling disease processes to creating personalized therapeutic options, stem cells offer unprecedented advantages that are reshaping the future of healthcare. However, their implementation is not without serious scientific, ethical, and logistical challenges. Understanding both the benefits and limitations of stem cell applications is essential for advancing research and ensuring safe clinical use [17].

Advantages

One of the most impactful benefits of using stem cells is their ability to accurately model human-specific biological responses. Unlike animal models, which often fail to replicate human physiology and disease progression, stem cells particularly those derived from human tissues can be differentiated into relevant cell types such as neurons, cardiomyocytes, or hepatocytes. These models enhance our understanding of disease mechanisms and improve the prediction of drug safety and efficacy.

A second major advantage is the reduction in animal testing. Traditional drug development relies heavily on animal models for preclinical testing, but ethical concerns and species differences in drug metabolism often limit their utility. By using human stem cell-derived tissues in in vitro systems, researchers can minimize animal use while obtaining data that are more relevant to human health [18].

Additionally, stem cells, especially induced pluripotent stem cells (iPSCs), open doors to personalized medicine. Since iPSCs can be derived from a patient's own cells, they allow for the creation of patient-specific disease models and therapies. This means drugs can be tested on cells that mirror an individual's genetic profile, helping tailor treatment plans and reduce adverse reactions.

Another critical advantage lies in the potential for long-term correction of chronic or genetic diseases. For instance, stem cells used in conjunction with gene-editing tools like CRISPR-Cas9 offer prospects for curing conditions such as sickle cell anemia, diabetes, or muscular dystrophy rather than merely managing symptoms.

Challenges

Despite their remarkable potential, stem cell applications also come with substantial risks and obstacles. A key biological concern is the risk of teratoma formation, particularly when using embryonic stem cells (ESCs) or iPSCs. If these cells are not fully differentiated before transplantation, they may form tumors or unintended tissues, posing a serious safety threat.

Another significant challenge is immunological rejection. In cases where stem cells are not derived from the patient (e.g., allogeneic transplants), the immune system may recognize them as foreign and attack, requiring immunosuppressive therapy that carries its own risks.

Ethical concerns, especially regarding the use of ESCs, remain a controversial aspect. Harvesting ESCs involves the destruction of human embryos, leading to debate over the moral status of embryonic life. This has prompted stringent regulations and public scrutiny in many countries, influencing research funding and development.

Lastly, the high cost and complex regulatory landscape hinder the widespread clinical translation of stem cell-based therapies. Manufacturing, quality control, long-term safety testing, and meeting regulatory standards demand significant investment, slowing down the transition from laboratory to clinical use. Stem cells hold immense promise for advancing medical science, from drug testing and disease modeling to personalized and regenerative therapies. Their ability to reflect human biology, reduce animal testing, and offer curative solutions is unmatched. However, realizing their full potential requires careful navigation of safety risks, ethical concerns, and regulatory hurdles. A balanced approach combining scientific innovation with responsible oversight will be key to integrating stem cell applications into mainstream medicine [19].

Conclusion:

Stem cell technology has emerged as a cornerstone in modern pharmacology and regenerative medicine, offering unprecedented tools for drug development, disease modeling, and therapeutic intervention. Their versatility enables researchers to simulate human physiology, evaluate drug responses more accurately, and explore innovative treatments for a wide array of diseases. The use of ESCs, adult stem cells, and iPSCs has expanded the possibilities for personalized and precision medicine. From screening new drugs on human-derived cell types to regenerating damaged tissues or correcting faulty genes, stem cells offer approaches that were once considered science fiction. Clinical trials have already shown promise in treating heart failure, diabetes, neurodegenerative disorders, and various genetic conditions. However, to fully harness their potential, it is essential to address ongoing challenges, including the risks of teratoma formation, ethical debates, immune rejection, and the complexity of regulatory pathways. The cost and infrastructure required for clinical-grade stem cell production also remain barriers to widespread application. Moving forward, interdisciplinary collaboration among stem cell biologists, pharmacologists, bioethicists, and policymakers will be essential. With continued innovation and responsible oversight, stem cells are likely to redefine therapeutic standards and bridge critical gaps between laboratory research and clinical care.

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WILDLIFE: DIVERSITY, THREATS AND CONSERVATION IN INDIA

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Abstract:

This review highlights the major issues about wildlife extinction, endangerment and conservation. It is necessary to know current scenario about wildlife protection and conservation at national level. Habitat conservation is the key solution to conserve wildlife. The term 'Wild Life' was coined by William Hornady in 1913 in his book "Our vanishing Wild Life". Wild Life implies to the biotic elements on the Earth including all species of plants, animals, birds and microbes of the world excluding man, domestic animals and cultivated plants. Therefore the wild life means the total natural biodiversity ranging from tiny microbes to mighty mammals. Wild life consider as a renewable resources. 2.2% of world's land area India harbors 13% of its bird species and 7% of the mammals as well as significant diversity of other animal and plant taxa. The term, 'Wildlife' is a part of the larger term- Biodiversity. Wildlife occupies a crucial place in our cultural and spiritual tradition. Our care for animal including many species leaves a lot to be desired. It's understood that preservation of wildlife is sort of essential not for animals but also for survival of human races.

Keywords: Wildlife, Biodiversity, Conservation, Habitat, Threats

Introduction:

India's wildlife is a priceless natural treasure, with a wide range of flora and animals. India is home to one of the world's most diverse biodiversity hotspots. This country fauna includes a diverse range of plant and animal species. Tigers, lions, wolves, bears, rhinoceros, camels, monkeys and a variety of reptiles, crocodiles, deer, bison and the Asian elephant are all indigenous to this nation. Peafowl, pelicans, parakeets, woodpeckers and flamingos are among the many bird species found there. Among the world's 34 biodiversity hotspots, India contain four biodiversity hotspots which are the Western Ghats, the Eastern Himalayas, The Indo-Burma region and Sundaland. The Indian cheetah is no longer found in its native habitat, although lions and leopards still roam the plains. India still has 65% of Asia's tiger population, 85% of the Asian rhino population. 80% of the Asian elephant population and 100% of the Asiatic lion population. These are all highly endangered and poached animals.

It occupies 2.4% of the world's area i.e. 329 million ha. and is host to 7% of the global biodiversity, accounting for 8% of the word's mammals i.e. 456 species, 13% birds i.e. 1,232 species, 6% reptiles i.e. 460, 4% amphibians i.e. 219 species, 12% fish i.e. 2,546 species and 6%

flowering plants i.e.16,500 species. Besides these, 68,000 species of insects, 17,000 species of fungi, and bacteria, 6500 species of algae, 2,850 species of bryophytes and 1100 species of pteridophytes, 5000 species of mollusks and 86,413 species of invertebrates. It is one of the 12 mega biodiversity hotspots. 1,00,000 species of animals and 49,000 species of plants have been documented in the country. Approximately 33% of plant species are unique to India, making it one of the world's biodiversity hotspots with around 70% endemic and varied plant and animal species. But due to lack of awareness for the value of biodiversity and inadequate forest protection planning, this rich biodiversity is in continuous decline (Soni, 2020). As per the International Union for Conservation of Nature (IUCN) Red List version 2010.4, 94 species of mammals, 78 species of bird, 66 species of amphibian, 30 species of reptiles, 122 species of fish, 113 species of invertebrates and 255 species of plants are listed as 'Critically Endangered', 'Endangered' or 'Vulnerable'.

Wildlife Conservation and its Threats

Wildlife conservation is referred to as the process by which the animal and plant species are protected in their natural habitat. The main aim of wildlife conservation is to ensure protection of the wildlife and preservation of the nature and natural habitats for humans as well as wildlife. The human activities for their own living and benefits have affected the wildlife considerably across the world. It has been observed that a considerable number of species of animals and birds have become extinct in the past 2000 years. Some reasons were because of climatic change and some have been because of human activities for their own benefits such as food, clothing, shelter, medicine etc. It is also expected that many more species of wildlife will become extinct very soon if they are not protected by proper means of conservation and by enacting effective legislations. The necessity for effective strategies and solutions for protection of wildlife in India and conservation of wildlife is the need of the hour (Soni, 2020). There is great demand of the conservation of the biodiversity databases of the species which are either rare or about to go the extinct. In India for the conservation of the biodiversity by eco-development project was launched with the help of GEF (Global Environment Facility) and World Bank (Chaurasia and Vineeta, 2015).

There are a number of conservation projects taken up in India. Many of these projects are adopted by the central government

1887- The wild Birds Protection Act was passed which enabled the British government to frame rules prohibiting possession or sale of any kind of specified wild birds only during breeding season.

1912- The Wild Birds and Animals Protection Amendment Act was passed. For the first time, a codified law was enacted prohibiting the killing or capturing of wild animals and disobedience of which entailed a penal offence. The Act also comprised scheduled animals, which listed birds and animals which could not be killed, captured or sold.

1935- The Wild Birds and Animals Protection Amendment Act, 1935 was enacted. This was a land mark year in the history of wildlife as it was for the first time that the provincial government, could, by notification, set aside an area to be a sanctuary for protection and growth of wild animals and birds.

1935- This year also witnessed the passing of the Government of India's Acts, 1935 in which the legislative powers were distributed between federal and provincial legislatures. The Protection of Wild Birds and Animals was entrusted to the provincial legislature vide Entry 25 of the state List.

1952- The first Wildlife Authority called as Central Board for Wildlife renamed as Indian Board of Wildlife was set up.

1972- The Wildlife Protection Act, 1972 was passed. It was the first comprehensive Act passed for the protection of wild animals.

1973- The 'Project Tiger' was launched. Subsequently, several other schemes were initiated for protection of specific habitats and to save threatened species such as the Asiatic Lion in Gujrat, Barasingha in Madhya Pradesh, Hungul in Kashmir and many more.

1976- The Constitution (Forty – second Amendment) Act, 1976 was passed in which Article 48A was inserted in the Directive Principals of State Policy, A separate Chapter IV A was also incorporated where Article 51A(g) constituted of Fundamental Duties.

1980- The Forest Conservation Act, 1980 was passed, which is interalia, also aimed to preserve the natural habitat of India's wildlife.

1982- The Wildlife Institute of India was established whose prime objective was to provide a professional and scientific support to the management and development of wildlife in India.

1992- The Central Zoo Authority was constituted on February 3, 1992.

2002- The Wildlife Protection Amendment Act was passed.

2006- The Wildlife Protection Amendment Act was passed and new chapter IV B titled as "National Tiger Conservation Authority and Chapter IV C titled as Tiger and other Endangered Species Crime Control Bureau' were added.

The wildlife is facing many threats due to the human encroachment and their activities as well as few natural factors which can be enumerated below:

Habitat loss by destruction, fragmentation and degradation:

Habitat destruction and fragmentation can take place by human activities such as felling of trees, dredging rivers, constructing dams, filling wetlands and mowing fields, use of lands for agriculture, constructions of houses and roads etc.

Illegal trading, hunting and poaching of endangered species: Illegal hunting and poaching has posed a major threat to wildlife which is further fuelled by the lack of proper management and use of resource by the forest officials to curb the menace and save the wildlife.

Climate change: Global warming and climate change has also played a major role in posing threat to the wildlife. It is estimated that global warming may cause the extinction of 15-37% of species by 2050 (Hundal, 2004). This is also again due to human induce activities which is done by the burning of fossil fuel etc. which resulted in the changing of the climate globally.

Over exploitation of resources: Exploitation and Over exploitation for food and other purposes has resulted in posing a threat to the wildlife, especially to the endangered species. The over use of the wild animals and plants for food, medicines, clothing etc has badly affected the wildlife population and thus has become a threat to their existence.

Pollution: The ever-increasing pollution level due to human activities and industrial operations has resulted in the release of harmful and toxic pollutants in the air, water and land. Hence, it has affected the wildlife in an adverse manner and ultimately posed a threat to become extinct.

Introduction of invasive species: An invasive or Allian species introduced in a new environment by accidently or manually. It will compete for survival with endemic species of that area which lead to death and decline.

As a result, the threat to wildlife and endangered plant and animal species necessitates their protection in order to preserve the ecosystem's balance and rescue the planet. The Indian government has created national parks, animal sanctuaries, biosphere reserve, and protected regions in response to the dangers.

National Park: Under sec. 35 of the wildlife Protection Act (1972), the first National Park was created in 1936 and was originally known as the Hailey National Park before being renamed the Jim Corbett National Park. The number of national parks steadily increased after then, and as of the country has 106 national parks. All kinds of destruction, exploitation and removal of wild life and damage to the habitat of any animal are strictly prohibit inside a National park. Grazing of domestic animals is also prohibited.

Wildlife Sanctuary: Under section 26-A (b) of the Wild life Protection Act of 1972, the state government may declare any area comprised within any reserve forest or any part territorial water which is considered to be of adequate ecological, faunal, floral, geo-morphological, natural or zoological significance for the purpose of protecting, propagating or developing wildlife or its environment to be included in a sanctuary. There are now 573 wildlife sanctuaries, 54 of which have been designated as Tiger reserve under Project Tiger. In addition, the Indian government has passed a number of laws and acts relating to the preservation and conservation of wildlife in the nation.

Biosphere Reserves – Biosphere Reserves are areas of terrestrial and coastal ecosystems which are internationally recognized within the framework of UNESCO's Man and Biosphere (MAB) Program launched in 1971. The first biosphere reserves in the country came into being on 1st August 1986 in Nilgiri. Today,18 biosphere reserves were established through the nation.

Challenges for successful operations of wildlife protection laws in india

The laws enacted with the objective of protecting and conserving wildlife has strict provisions but despite these laws, the exploitation of wildlife resources and their illegal trade continues. The wildlife Protection Act, Customs Act, Import-Export policies in India though have provision in regulating the conservational measures and trade of wildlife species, especially the endangered species, the illegal hunting and poaching activities and trade is still flourishing and these endangered species are still exploited. It is noticed that the punishment and penalties for offences made under the Act is not enough to stop and control exploitation of wildlife.

There is another problem identified that the Forest department and the Forest officers are not able to work effectively in implementing the laws and facilitate the conservation activities because they are not adequately trained or have adequate resources. On the other hand, the forest department itself plays a role in the exploitation activities for their selfish reasons and corruption. It has been noticed that the forest officials have never involved the local people residing in the surrounding places to stop the exploitation of wildlife despite the fact that these people can actually help in preventing the exploitation and protecting the wildlife resources (Singh, 2000). Recently, a new problem has come into the notice that many bird killed, listed in the Schedule I of the Wildlife Protection Act, 1972, due to human recreation of flying kites. Many birds are killed by the threads, called as 'manja' locally, which is especially the Chinese thread. In spite of the imposed ban on the use of Chinese thread for Kite flying under Section 5 of the Environment (Protection) Act, 1986, it is still in use among the people. This has killed quite a number of birds which are endemic to this country while some of these birds belong to migrating species (Suvidha, 2022). The need for effective methods and solutions for the preservation and conservation of wildlife in India is urgent (Mishra, 2022)

Conclusion:

Animals are still hunted and sold for human gain, and nature is still abused. Illegal wildlife hunting and trading continue to take place in India, notwithstanding the law's provisions. As a result, there is a significant need for public Knowledge of wildlife preservation and conservation, as well as efficient and rigorous enforcement of these laws by each state. The state governments are required to keep vigilance on the effective implementation of wildlife protection laws and conservation at the district and municipal level. The government must work in accordance to the present needs and demands in a situation when these wildlife species are threatened and many of which have come to the verge of extinction. If we take into consideration the conventional reason why wildlife is disappearing, India is doing far better than other countries. India has launched an extensive protected area network of research institutions in which legislation, socio-economic factors and wildlife research are playing a great role.

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MULTIFUNCTIONAL ROLE OF FENUGREEK: A HIGHLIGHT ON PHARMACOLOGICAL ASPECTS

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Abstract:
Medicinal plants have been integral to the evolution of human culture, serving as a cornerstone of traditional medicine across virtually all civilizations. These plants are esteemed as abundant sources of natural remedies, forming the basis for numerous modern pharmaceuticals. For centuries, medicinal plants have been employed to address health issues, enhance the flavour and preservation of food, and prevent disease outbreaks. The seeds and green leaves of fenugreek (*Trigonella foenum graecum*) have been utilized in both culinary and medicinal applications, a tradition rooted in ancient human history. In recent years, numerous animal studies and human trials have highlighted the health-promoting physiological properties of fenugreek seeds such as antiarthritic, antidiabetic, anticancer, anti-inflammatory, antioxidant, memory enhancing, antiulcer. This study emphasizes the traditional applications and pharmacological properties of TFG, as demonstrated by numerous research findings.

Keywords: Fenugreek, *Trigonella foenum-graecum*, Anti-inflammatory, Anti-cancer, Antidiabetic, Antioxidant, Antiulcer, Anti-Alzheimer.

Introduction:

The significance of plants in traditional medicine is undeniable. In non-industrialized societies, spices are frequently employed to treat illnesses. However, by the late twentieth century, various traditions began hindering the practice of natural medicine. Despite this, the use of therapeutic plants is growing globally, driven by the widespread adoption of traditional remedies and an increasing interest in herbal treatments. Plants play a vital role in maintaining and enhancing physical and mental health, as well as serving as essential raw materials in pharmaceutical manufacturing, highlighting their indispensable value. Nature consistently stands as a brilliant symbol, demonstrating the profound phenomenon of coexistence. Nature serves as a shining example, illustrating the remarkable harmony of coexistence. Natural substances derived from plants, animals, and minerals form the foundation for treating human illnesses. The demand for medicinal plants is growing, and their acceptance continues to rise steadily. Plants undeniably play a vital role by offering essential services to ecosystems. Without them, humans and other living organisms could not sustain life as it is meant to be. Medicinal herbs, in particular, have consistently served as a reliable indicator of ecosystem health. Since ancient times, medicinal plants have undoubtedly held significant importance for humanity. It can be stated that even before recorded history, early humans discovered and utilized the plants surrounding them for petroleum, clothing, housing, and diet, gradually becoming aware of their various properties. [1]

Herbal medicines are naturally derived, plant-based substances used in traditional healing practices across various cultures to address a wide range of illnesses. These remedies consist of complex mixtures of organic compounds obtained from raw or processed plant parts. The knowledge of medicinal uses for plant-based natural products has largely developed over centuries through human experimentation, often relying on trial and error, including taste testing and accidental poisonings, as people searched for food and treatments for various ailments. Herbal medicine is an integral part of cultures worldwide. Although traditional medicine systems vary in philosophies and practices depending on their geographic origins, they share a common focus on a holistic approach to health. The use of medicinal herbs supports overall well-being by addressing the whole person rather than isolating a specific illness, often aiming to restore balance between the mind, body, and environment.[2]

The practice of using medicinal plants to treat diseases dates back to the earliest days of human existence. From the moment humans began seeking remedies in their surroundings to recover from illnesses, plants became their primary and only means of treatment. The global distribution of medicinal plants is uneven, with most medicinal herbs being sourced primarily from wild populations. In recent decades, the demand for wildlife resources has grown by 8 to 15 percent annually in Asia & North America as well as Europe. The term "medicinal plant" encompasses a wide range of plants with therapeutic properties. These plants serve as valuable sources of compounds essential for drug development and synthesis. The active compounds found in various parts of medicinal plants possess direct or indirect healing properties and are utilized as therapeutic agents. Within these plants, specific substances known as active compounds are produced and stored, which have physiological effects on living organisms. [3,4]

Among ancient civilizations, India is recognized as a rich source of medicinal plants. The forests in India serve as the main reservoir for a vast variety of medicinal and aromatic plants, which are primarily harvested as raw materials for producing medicines and perfumes. Humans primarily rely on raw plant materials to fulfil medical needs for maintaining health and treating diseases. Medicinal plants are utilized for treatment due to their specific properties, including synergistic effects. The plant's components may interact in ways that can be either beneficial to both, harmful to one or both, or even neutralize each other's negative effects. Additionally, some plants are regarded as valuable sources of nutrition and are recommended for their therapeutic benefits. It is estimated that around thirteen thousand plant species have been used as traditional medicines by different cultures worldwide for at least a hundred years. Nowadays, the term

"Alternative Medicine" has become widely recognized in Western culture, emphasizing the use of plants for healing purposes. Among ancient civilizations, India is recognized as a rich source of medicinal plants. The forests in India serve as the main reservoir for a vast variety of medicinal and aromatic plants, which are primarily harvested as raw materials for producing medicines and perfumes. Developing drugs from medicinal plants is generally more affordable than creating synthetic drugs, with reserpine serving as a notable example. India's diverse agro-climatic conditions provide an ideal environment for the abundant growth of various plants. Additionally, medicinal plants often generate higher income compared to many traditional field crops. India is home to 25 percent of the world's biodiversity. There has been a significant increase in demand from Western countries for phytopharmaceutical raw medicinal herbs and vegetable drugs sourced from India. Our nation proudly holds a rich medical heritage that includes several traditional systems of medicine, such as Ayurveda, Siddha as well as Unani. [4-6]

A large number of people in developing regions, particularly in Africa and Asia, continue to rely on herbal extracts to treat various human and animal illnesses. Numerous compounds derived from medicinal plants have been shown to positively influence many physiological and chemical processes. or thousands of years, indigenous cultures worldwide have relied on traditional herbal medicine to address numerous health conditions. Throughout history, plants have served as an invaluable source of cost-effective natural compounds, particularly secondary metabolites. Since that time, humans have created numerous medicines using natural products extracted from medicinal plants. Ayurveda, a specialized form of therapeutic practice that originated in India, remains widely practiced in many developing countries. Its popularity is due to easy accessibility, low production costs, effective results, and minimal side effects.[7]

Despite remarkable progress in medicine development, medicines of herbal nature endure to be broadly utilized for the treatment as well as prevention of numerous ailments, owing to their healing and nutraceutical assets. TFG is a plant of medicinal property, historically utilized both as a food seasoning and for its diverse therapeutic properties. While fenugreek is best known for its seeds, its leaves and stems have also been recognized for their medicinal applications. Fitting to the family i.e. Fabaceae, it is pollinating by itself as well as herbaceous aromatic annual plant, commonly raised to as bird’s foot, methi. & Greek hayseed, halba. Fenugreek is predominantly cultivated in India, contributing to 80% of the global production. Its seeds as well as leaves are extensively cast-off as a flavoring spice and a key element in cookery dishes crossways numerous nations. It is applied as both a purposeful and traditional food, as well as in supplement of nutrients and biological claims. Fenugreek is familiar as one of the primogenital therapeutic herbs worldwide, with its seeds as well as leaves conventionally castoff for treatment of numerous illnesses. The leaves and seeds of *TFG* are widely used to prepare extracts and powders for therapeutic purposes in various studies. Fenugreek seeds have been discovered to contain numerous chemical compounds, collectively referred to as phytochemicals. These include various alkaloids, flavonoids as well as saponins, among them saponins being the most abundant at a concentration of more than 4.60 gram in each ten gram of seeds. [8]

TFG has been used as a remedial shrub in the region of Central Asia later about 4000 BC. has been extensively used in Ayurvedic and Chinese medicine for its medicinal properties, serving as a demulcent, lactation enhancer & laxative. In ancient Rome, TFG was utilized to ease labour, relieve cramps of menstrual cycle, and act as a tonic for better metabolism. It has also been utilized in folk medication to treat conditions such as tuberculosis. During the nineteen centuries, fenugreek was a main element in patent medications used to relieve symptoms of disturbed mensuration and menopause. Traditionally the Chinese medicine similarly employs seeds of fenugreek for issues of kidney, including stones inside kidney, as it aids diminish calcium oxalate, the crystal responsible for formation of stone in kidney. Traditionally TFG is too employed for skin problems like eczema. [9,10, 11]

The biological classification of TFG is presented in figure 1. The active constituents which are isolated from TFG are numerous. Also, these active bioactive constituents are proved for effectiveness for various disorders such as microbial infections, cancer, inflammatory disorders, immunomodulation, diabetes, cardiovascular problems, arthritis and many more. In the figure 2 isolated bioactive phytochemicals are presented. [10]

Classification of *Trigonella foenum-graecum* linn.

Kingdom:	Plantae
Division:	Magnoliophyta
Class:	Magnoliopsida
Order:	Fabales
Family:	Fabaceae
Subfamily:	Papilionoideae
Genus:	*Trigonella*
Species:	*Trigonella foenum-graecum Linn*

Figure 1: Classification of TFG.[10]

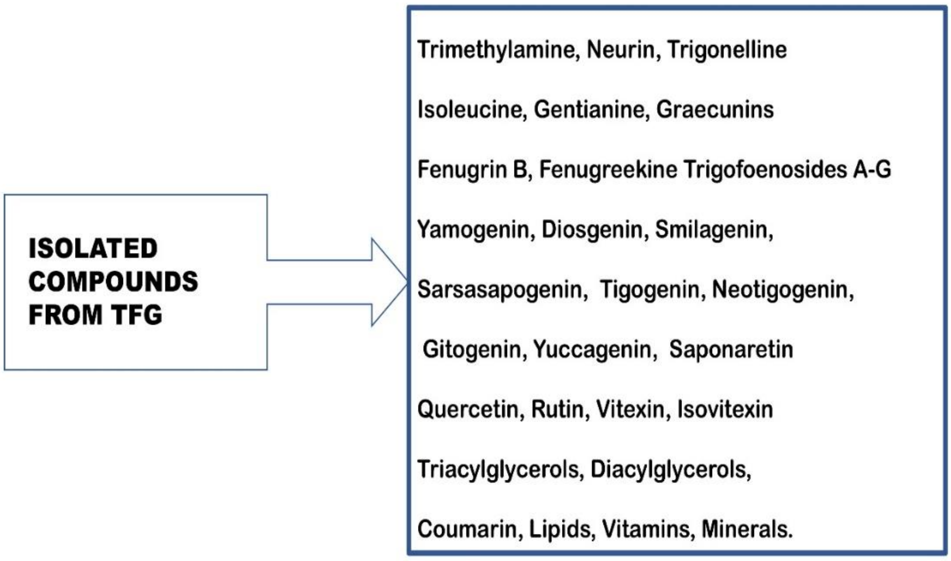

Figure 2: Isolated phytocompounds of TFG. [10,11]

Pharmacological activities of TFG

1. **Antioxidant:** Stress specially of oxidative nature get up after a disproportion between the construction of reactive oxygen species (ROS) and the capacity of antioxidant defences to counteract them. Oxidative stress arises when there is an imbalance between the production of free radicals and the cells' ability to eliminate them. It can contribute to chronic conditions, including cancer & aging as well as disorders associated with neurodegenerative & cardiovascular function, by causing damage to lipids & nucleic acids chiefly DNA as well as proteins. Oxidative stress primarily outcomes from disparity in the action of endogenous pro-oxidation enzymes. Reactive intermediates, such as photoexcited states of tissue chromophores & ROS as well as reactive carbonyl species (RCS), have been linked to the onset and progression of various human diseases, including cancer, atherosclerosis, diabetes, and neurodegenerative disorders. Free radicals are highly reactive molecules or chemical entities that can exist independently. The production of ROS is a fundamental aspect of normal cellular processes, such as the respiratory chain of mitochondria, phagocytosis, metabolism of arachidonic acid, ovulation, as well as fertilization. TFG's ability to prevent oxidation is credited to its abundant bioactive compounds that possess strong antioxidant effects. Previous researchers reported that TFG has potential against scavenging of free radicals, increased production of enzymes responsible for antioxidant effects, suppressing oxidation of lipids, reduces oxidative damage to nucleic acids and proteins, potent anti-inflammatory effect. These factors contribute to the antioxidant effect of TFG. [13]
2. **Anti-arthritic:** Rheumatoid Arthritis (RA) is identified as a chronic autoimmune disorder with an unclear origin. Chronic synovitis is a hallmark of the condition, frequently associated with multi-organ involvement and the generation of autoantibodies such as rheumatoid factor

and anti-citrullinated peptide protein antibodies. Joint impairment, especially in the hands and wrists, as well as the knees, is a common symptom of RA. As the disease progresses, it affects not only the joints but also other parts of the body, resulting in premature mortality and multiple complications such as disability and reduced quality of life, particularly in developing nations. Chronic inflammation causes bodily imbalance and joint deterioration, a frequent issue experienced by almost all patients. Epidemiological studies show that RA impacts about one percent of the adult population. The condition is especially common in women and older individuals, with about 40 new RA cases diagnosed annually per lakh people. In the reported previous literature TFG has a very good potential for the treatment of RA. The utilization of TFG in RA is chiefly due to reduction of IL-1β- chiefly of nitric oxide (NO) as well as prostaglandins chiefly E2 (PGE2), suppress the release of inflammatory mediators such as of TNF-α & interleukin-6 (IL-6), inhibit the production of enzymes such as cyclo-oxygenase. All of the mentioned factors play a crucial role in causing arthritic disorders. [14-15]

3. **Anti-Alzheimer:** Dementia is a cognitive condition marked by a significant decline in intellectual abilities that disrupts an individual's professional or social functioning. Dementia exists in various forms and consistently includes memory impairment as a key feature. Alzheimer's disease, a progressive neurodegenerative condition characterized by the loss of neurons in specific regions of the brain, is the leading cause of dementia. The central cholinergic pathways are crucial for facilitating learning and memory functions. Centrally acting antimuscarinic medications disrupt learning and memory in both animals as well as humans. Epidemiological research on the Indian population indicates that dementia is predominantly an underrecognized issue, with its prevalence rising sharply as age progresses. Given the absence of a definitive cure in the allopathic system of medicine, exploring alternative approaches to reduce memory loss in elderly patients is a valuable endeavour. In traditional medicine, the leaves and seeds of TFG have been utilized clinically for eras. The literature has shown that TFG has very good potential to diminish oxidative stress and neuroprotective role to enhance learning and memory. The active constituent of TFG like quercetin has also proved beneficial in dementia due to their action against oxidative stress and inflammation. It also protects neurons from damage induced by excitotoxicity or other neurodegenerative mechanisms, preserving the pathways involved in learning and memory. Quercetin has the potential to affect neurotransmitter levels, especially acetylcholine, a key player in cognitive functions. Lastly the TFG and its constituents has potential to modulate hypothalamus and pituitary axis which reduces long term stress and responsible for impairment of memory. [16, 17]

4. **Anti-diabetic activity:** Diabetes mellitus (DM) is a long-term metabolic disorder characterized by persistently elevated blood glucose levels, known as hyperglycaemia, which over time leads to serious and irreversible damage to multiple organs. The number of people worldwide with DM is expected to exceed 635million by 2030 and reach more than 778 million by the year 2045. Diabetes mellitus causes the body to either produce insufficient insulin or respond poorly to it, leading to an inability to regulate proper blood sugar levels. This imbalance results in various negative effects and complications associated with the disease. Diabetes mellitus causes hyperglycaemia, which is a key factor in the development of oxidative stress. It plays an active role in hindering insulin action, impairing insulin function, and reducing its secretion. There is substantial evidence indicating that oxidative stress plays a significant role in the connection between stress and complications related to diabetes mellitus. Additionally, antioxidants play an important role in managing complications in diabetic patients. Oxidative stress occurs in the body due to the production of free radicals, which causes cellular damage and the destruction of pancreatic beta cells. TFG contain various chemical compounds, primarily flavonoids & phenols as well as quercetin. TFG demonstrate significant antidiabetic effects through various mechanisms. They enhance insulin sensitivity and promote glucose uptake by cells, supporting improved blood sugar control. TFG also decrease oxidative stress and inflammation, factors associated with diabetes complications. Furthermore, they may block enzymes responsible for carbohydrate digestion, resulting in a slower release of glucose into the blood. [18,19]
5. **Anti-obesity activity:** Obesity is a component of metabolic syndrome, along with hypertension, resistance of insulin, and dyslipidaemia. Its rising prevalence heightens the risk of cardiovascular diseases and various cancers, resulting in significant public health expenses. Obesity is a long-term condition defined by excessive fat accumulation that can negatively impact health. The rate of obesity is growing speedily. The rising prevalence of overweight and obese individuals has become a significant global concern, contributing to an estimated more than 3.3 million deaths. Obesity arises from multiple factors, including genes, hormonal imbalances, and environmental influences. Obesity is linked to a heightened risk of various comorbidities, including diabetes mellitus, cardiovascular & respiratory disorders, few types of cancers, as well as psychological and social disorders. Previous studies on TFG and its constituents reported that they supress the inflammatory reactions, inhibits the generation of adipocytes, promotes expenditure of body's energy, modulation of microbiota of gut and also augment the resistance of insulin. Therefore, TFG is a potential herb for anti-obesity effect due to its appetite suppression, regulation of lipid as well as glucose metabolism, inhibiting absorption of fat and lastly thermogenic effect.[20]

6. **Anticancer:** Cancer has impacted multicellular organisms for more than 200 million years, with the ancestors of present-day species having encountered it hundreds of thousands of years ago. Cancer is a leading cause of death and illness globally. Currently, it stands as the world's second most significant cause of mortality, accounting for more than 9 million deaths. The number of cancer cases is expected to increase significantly in the coming decades, driven by lifestyle changes and behavioural factors such as obesity, smoking, lack of physical activity, and alterations in reproductive habits. The widespread use of chemotherapy and the rapid emergence of drug resistance have led to tumours becoming unresponsive. Consequently, natural products are gaining popularity as anticancer agents for treating drug-resistant malignancies due to their minimal side effects, potent antitumor properties, low toxicity, and targeted multi-action capabilities. In the previous studies it is reported that TFG has potential effects on cancer. The mechanism by which TFG has showed anticancer effects are inhibition of cell cycle, modifiable effect on pathway associated with Mitogen-Activated Protein Kinase (MAPK), Nuclear factor-Kappa B suppression, stimulation of mitochondrial pathway associated with apoptosis. The extract of TFG also having potential of cytotoxic effects against numerous cell lines. Previous studies reported that the extract of TFG possess anti-metastatic effect, stimulates inhibition of migration of cells, and activating apoptosis process. [21, 22]
7. **Antiulcer:** Gastric as well as duodenal peptic ulcers impact thousands of individuals and are among the most frequently encountered gastrointestinal disorders in clinical practice. Peptic ulcer is a prevalent gastrointestinal condition characterized by sores in the mucous membrane of the stomach and duodenum. Because of the drawbacks of traditional treatments, herbal remedies have become increasingly popular for managing digestive disorders. Peptic ulcer disease (PUD) is a widespread gastrointestinal condition characterized by lesions and damage to the mucous lining of the stomach and duodenum. The primary causes of peptic ulcers include *H. pylori* infection and the use of nonsteroidal anti-inflammatory drugs (NSAIDs), which lead to ulcer development by promoting increased secretion of acid, causing harm to mucosa, and compromising the defence barrier of mucosa. Furthermore, complications of peptic ulcers, including mucosal tear, bleeding, impediment, and infiltration, are linked to increased mortality and morbidity rates. PUD is estimated to occur in one out of every thousand individuals annually and impacts millions worldwide. It has a prevalence rate of 5 to 10 percent in the general populace, significantly influencing quality of life and contributing to substantial health care costs. As reported in various literature TFG has antiulcer potential due to its chemical components which helps in protection of mucosal damage, suppress the secretion of acid, increases the production of prostaglandins in mucosal lining as well as dipping the level of circulating nitric oxide. also possess cytoprotective effect. [23]

8. **Anti-inflammatory**: Inflammation is a protective response that defends organs against external injury and infection. Inflammation can be categorized as either acute or chronic, with both types involving a similar fundamental mechanism. When a trigger is detected, the inflammatory cascade begins at the cell surface receptors, leading to the production of inflammatory markers and the activation of inflammatory cells. Initially, the process ends once the trigger is removed or resolved; however, in the other case, the body is unable to repair the damage or eliminate the cause. In response to changes causing tissue damage, the immune system elevates the activity of immune cells and various inflammatory mediators. When the inflammatory response is triggered by excessive stimulation, it can become chronic, which contributes to the development and advancement of diseases in different tissues. Acute inflammation is triggered by an immediate reaction to a microbial or viral infection, whereas chronic inflammation arises from a slow and prolonged response. These inflammatory responses spread throughout the body via the blood and lymphatic vessels, worsening the onset and symptoms of various diseases. An elevated chronic and systemic inflammatory response is recognized as a key characteristic of diseases including diabetes, cancer cardiotoxicity as well as respiratory & metabolic disorders. The TFG and its bioactive constituents function by blocking important inflammatory pathways and decreasing the production of pro-inflammatory substances like cytokines and enzymes. By regulating the immune response, catechins help reduce inflammation at the cellular level, protecting tissues from damage and aiding in the prevention and treatment of several long-lasting inflammatory ailments. [24]

Conclusion:

Herbs are widely used for medicinal purposes in many countries, driven by the common belief that natural products are free of side effects and easily accessible. Nature has long been a valuable reservoir of therapeutic compounds, offering a wide array of medicinal plants that produce vital phytochemicals. TFG is a commonly utilized herb in Ayurvedic medicine, widely distributed throughout Asia and certain regions of Europe as well as Africa & Australia. TFG is one of the world's most economically important plants, known for its wide range of applications. This overview highlights the traditional uses and pharmacological effects of TFG as revealed through various studies. Fenugreek is demonstrated to be more than just a dietary supplement, serving as a source of potential therapeutic compounds for treating various health conditions. However, further research into its mechanisms of action and the disease-specific signalling pathways is essential to fully unlock its potential. Understanding this information will allow researchers to identify compounds and their targets, which can ultimately be utilized in drug development.

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A REVIEW ON MICROBALLOONS: A BETTER APPROACH FOR GASTRO-RETENTIVE DRUG DELIVERY SYSTEM

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Abstract:
Oral route is generally best and broadly utilized route for the organization of drug in microballoons. Microballoons vows to be a probable approach for gastric retention. Microballoons drug delivery system is depended on non-effervescent system containing empty particles of spherical shape without center preferably having a size less than 200 micrometer. Microballoons become new technology in pharmaceutical field in the floating drug delivery for accomplishing the gastric retention. Microballoons are also known as hollow microspheres. Microballoons are permeable smooth in nature with good floating properties in gastric fluid. Microballoons are gastro retentive drug delivery system. It gives controlled release properties. Microballoons are spherical empty vehicles without core. That can remain buoyant in gastric region for prolong period of time without aggravation in gastrointestinal tract. The factor affecting physical properties in microballoons, GRDDS, advantages, disadvantages, methods of preparation of microballoons, application and various evaluation techniques are covered in detail.

Keywords: Microballoons, Gastric Retention, Hollow Microspheres, Gastro Retention Drug Delivery Systems

Introduction:

Microballoons are gastro retentive drug delivery system with non-effervescent system. Microballoons or hollow microspheres are in empty particles of spherical shape without core. These microballoons are include some characteristics like free-flowing powders containing proteins or synthetic polymers and having ideal size less than 200 micrometer (1). Microballoons are reflected as one of the appropriate buoyant systems with the unique advantages of floating properties because hollow space is central inside the microsphere. The various techniques involved in their preparation like simple solvent evaporation method, emulsion solvent diffusion method, solvent diffusion evaporation method, spray drying method, single emulsion technique, double emulsion technique, coacervation phase separation method etc.

Gastro Retentive Drug Delivery System (GRDDS)

Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper Gastro Intestinal Tract (GIT) for local or systemic effect. It is obtained by retaining dosage form into stomach and by releasing in the controlled manner. To overcome physiological adversities such as short Gastric Residence Times (GRT) and unpredictable Gastric Emptying Times (GET). This dosage forms will be very much useful to deliver narrow absorption window drugs. Oral route is most acceptable route for drug administration. Apart from conventional dosage forms several other forms were developed in order to enhance the drug delivery for prolonged time period and for delivering drug to a particular target site.

Factors affecting physicochemical properties of microballoons

- Temperature of preparation
- Plasticizer
- Volume of aqueous phase
- Effect of solvent
- Amount of polymer and viscosity
- Solvent ratio
- Emulsifier concentration
- Stirring rate

Application

- For reduction of adverse effect of gastric irritation, gastro retentive floating microspheres are very effective.
- This system is stable in stomach for long period of time.
- Microballoons are effective method in delivery of drug with poor bioavailability.
- Dye to increase in gastric retention time the higher dose of drug is reduced because of low dose frequency.

Advantages

- Dosing frequency decreases because of improvement in patient compliance.
- Maintain concentration of plasma drug.
- Increases gastric retention time.
- Controlled manner of prolonged period is releasing the drug.
- Dose dumping having no risk.
- For decreasing of material density microballoons are mostly used.
- Gastric retention time is increased cause of buoyancy by microballoons.

Disadvantages

- This kind of dosage forms should not be chewed or crushed.

- The release rate of controlled release dosage form may differ from the rate of transit though gut.
- The formulations are release modified.
- Higher drug load includes in the controlledrelease release formulations.
- In from one dose to another dose the release rate is different.

Methods of preparation

Solvent evaporation method improvement of the polymers, such systems include Eudragit, HPMC KM4 and ethyl cellulose etc. These polymers are mixed with the drug, then after the mixture is dissolved in solution of acetone and ethanol. The final solution is poured into 100 ml of liquid paraffin and then rotating at 1500 rpm. Finally, emulsion is prepared and heated at 35^0C temperature for 3hrs. After the emulsion is stable, acetone is completely evaporated and prepared microspheres are filtered using whattman filter paper.

Emulsion solvent diffusion method

Prepared solution of ethanol: dichloromethane and dissolved the drug polymer mixture in the above solution. This mixture is adding drop by drop in polyvinyl alcohol solution and rotating at 1500 rpm for 1 hr. and at different temperature (4). In this method, the affinity between the organic solvent and drug is stronger than the organic solvent and aqueous solvent. This drug is dissolved in organic solvent. Then the solution is distributed in the aqueous solvent developing the emulsion droplets though the organic solvent. This organic solvent is diffuse out of emulsion droplets in the aqueous phase. The drug crystallizer is diffuse the aqueous phase into the droplets (3,5).

Solvent diffusion evaporation technique

This technique is mixture of both emulsion solvent evaporation method and emulsion solvent diffusion method. These two drug polymers and 0.1% of surfactant like PEG are mixed with the solution of ethanol: dichloromethane (1:1) at normal temperature. This prepared solution is slowly dissolved into 80 ml of 0.46% w/w of polyvinyl alcohol as emulsifier. The propeller organic solvent. The resulting solution is filtered.6 The optimizer result of various processes like polymer ratio, stirring speed, concentration of emulsifier and drug:polymer ratio based on the selection of best formulation (6).

Spray drying

This method is most active industrial process for drying and formation of particle. It is a best process where the required bulk density, particle size distribution and particle shape can be obtained (7). The polymer is dissolved in organic solvent like dichloromethane and acetone etc. to production of slurry. Then the slurry is sprayed into the drying chamber and concentration gradient of solvent form. This process is used because the time of the solute diffusion is longer than the solvent during the drying process in the droplet evaporation (8).

Evaluation of microballoons

Percentage yield

The actual yield is amount of product that is actually formed when the reaction is carried out in the laboratory. Percentage yield of microballoons is resulted for drug & it is calculated using the following equation (10,11,12).

Percentage yield = M/Mo x 100

Where M = weight of beads

Mo = total expected weight of polymer & drug

Micromeritic properties

The microballoons are evaluated by following micromeritics properties:

1. Particle shape & size

The most widely used procedure to visualize microparticle is conventional light microscopy and SEM.

2. Bulk density

Bulk density is calculated by following equation:Bulk density = mass of microspheres / bulk volume.

3. Tapped density

It is calculated by following equation: Tapped density = mass of microspheres / tapped volume.

4. Hausner's ratio

Hausner's ratio is calculated by following equation:Hausner's ratio = tapped density /bulk density.

5. Carr's index

It is calculated by following equation: Carr's index = (bulk density – tapped density / tapped density) x 100.

6. Angle of repose

The powder mass is allowed to flow through the funnel orifice kept to a plane paper kept on the horizontal surface, giving a heap angle of paper The angle of repose is calculated by following equation:tan ϴ = h/r.

In vitro buoyancy

Suitable quantity of microballoons is placed in 900 ml of 0.1N HCl. This mixture is rotating at 100 rpm for 8-10 hrs. in dissolution apparatus. After this rotation the layer of buoyant microballoons are separated by filtration. Particles which is including in the layer of sinking particulate are separated. Particles of both types (buoyant microspheres and settled microspheres) are dried until constant weight is reached. The fractions of microballoons are weighed (13).

Buoyancy is calculated by following equation:

Buoyancy (%) = [Wf / (Wf + Ws)] x 100

Where, Wf = weight of floating microsphere

Ws = weight of settled microsphere

Scanning electron microscopy

Dry microballoons are placed on electron microscope brass stub a coated. The spectrorandom canning of the stub is taking pictures of microballoons. The microballoons are viewed at a voltage of 20KV of microscope (14).

In vitro drug release studies

The release rate is determined by microballoons in United States Pharmacopoeia XXIII basket type dissolution apparatus. Weighed microballoons are equivalent to dose of drug and place in the basket of apparatus. The maintained temperature and rotation speed by dissolution fluid. Addition of 5 ml of dissolution fluid maintained initial volume of the dissolution fluid (15).

Data analysis of release studies

This type of study includes five kinetic models like Zero order, first order, Higuchi matrix, Peppas-Korsmeyer and Hixon-Crowell release equations are used to process the in vitro release data (16,17).

Swelling studies

These types of studies are used for calculation of molecular parameters of polymers. Determination of swelling studies takes place using optical microscopy, dissolution apparatus and other techniques. These techniques are including CLSM, Cryo-SEM, and LSI etc. For the swelling studies, dissolution apparatus is used and it is calculated as following equation (18):

Swelling ratio = weight of wet formulation / weight

In vivo studies

To performed the in vivo studies, use the suitable animal models examples like rat and beagle dogs etc. the radio graphical studies investigate the floating behavior using sulphate microballoons (19,20).

Conclusion:

Microballoons are gastro retentive drug delivery system which has low-density, sufficient buoyancy to float over gastric contents and stay in stomach for prolonged period in gastro intestinal tract. From the review we proved as the most promising drug delivery than conventional drug delivery system. Microballoons find the central place in particularly in diseased cell sorting, diagnostics, novel drug delivery and effective in vivo delivery. In microballoons all methods of preparations are depend on the emulsification.

Future Scope

Various new products expected that the new technologies may increase this possibility using gastro retentive drug delivery. In future, further market research may concentration on microballoons models:

- The design of gastro retentive drug delivery system having narrow GRT for clinical need, example: dosage & state of disease.
- Development of gastro retentive drug delivery system is beneficial for the treatment of Parkinson's disease, gastric and cancers.

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EMERGING TRENDS AND INNOVATIONS BASED ON ORGANIC PRACTICES ARE ADVANCING THE SECTOR OF SERICULTURE

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Abstract:

Sericulture, the cultivation of silkworms for silk production, is evolving with significant advancements in sustainability technology and organic farming. It accommodates a whole lot of on-farm and stale-farm activities producing employment and earnings to rural population of India. Improvements are technical answers to the problems faced in each sector of sericulture. The improvement of innovative techniques and organic farming in mulberry cultivation can help farmers to plant mulberry on huge place of mulberry leaf development. The need of convenient, strategic and price-powerful approaches might also make certain mass scale rearing of silkworms and provide mulberry leaves for feeding of silk larvae. Conduct of packages/trainings/workshop by using familiar useful resource staff can persuade the farmers to undertake the novel strategies that may assist in transfer of technologies and adoption of innovations organic farming culture. The large number of rearing of silkworms can generate large quantity of silk output gives chance for incensement of financial reputation of silk rearer's rural population as used the wastage and by product of cattles grow mulberry. There are numerous policies associated with sericulture development and assist consists of government initiatives in research and improvement, subsidies and economic resource for silk farmers. The prison structure controlling the protection and first-rate necessities in the silk enterprise is some other important aspect. Standards for processing silk, satisfactory manage processes, and legal guidelines governing using chemicals and pesticides in mulberry farming are all included on this. The global alternate rules affecting the silk industry include alternate agreements, non-tariffs, and tariff boundaries that have an effect on the worldwide silk market. These policies have main effect on silk exports and imports, as well as on domestic silk industries. The regulatory framework related to labor and ethical practices in sericulture which incorporates laws and guidelines concerning exertions rights, working conditions, and honest alternate practices within the silk enterprise. Sericulture's policy and regulatory frameworks face a number of difficulties, which includes coordinating regulations on the countrywide and worldwide tiers and aligning them with social and environmental dreams, organic farming as well as technological enhancements.

Keywords: Organic Farming, Moriculture, Innovation of Silkworm Rearing and Innovation in Post Cocoon Sector.

1. Introduction about Mulberry Cultivation:

Mulberry foliage is the only meals for the silkworm (*Bombyx mori*) and is grown under numerous climatic situations starting from temperate to tropical. Mulberry leaf is a primary monetary detail in sericulture because of the fact the number one beauty and amount of leaf produced in line with unit region have a right away relating cocoon harvest. In India, most states have taken up sericulture as an essential agro-business enterprise with tremendous effects. The complete location of mulberry within the United States is around 2 to three lakhs ha. The data is of the region below mulberry cultivation in certainly one of a kind kingdom in India. In India, there are numerous species of Morus, of which Morus alba, M. indica, M. indica, M. serrata and M. laevigata increase wild inside the Himalayas. Several varieties had been introduced belonging to M. multicaulis, M. nigra, M. sinensis and M. philippinensis. Maximum of the Indian varieties of mulberry belong to M. indica. In China there are 15 species, of which 4 species (Sarkar, A. 1996), Morus alba, M. multicaulis, M. atropurpurea and M. mizuho are cultivated for sericulture rearers even though mulberry cultivation is practiced in numerous climates, the principal place is in the tropical area covering Karnataka, Andhra Pradesh, and Uttar Pradesh and Tamil Nadu states, with about ninety percent. Within the sub-tropical sector and the northern states have primary regions under mulberry cultivation. The data is of the mulberry sorts under cultivation in exclusive states of India. Mulberry is a brief developing deciduous woody perennial plant. It has a deep root system. The leaves are simple, alternate, stipulate, petiolate, entire or lobed. The type of lobes varies from 1 to 5. Vegetations are generally dioecious. Inflorescence is catkin with pendent or drooping peduncle bearing unisexual vegetation. Inflorescence is catkin with pendent or drooping peduncle bearing unisexual flowers. Inflorescence is always auxiliary. Male catkins are generally longer than the woman catkins. Male vegetation is loosely organized and after losing the pollen, the inflorescence dries and falls off. These are four chronic parianth lobes and four stamens impelled in bud. Female inflorescence is generally short and the plant life is very compactly prepared. There are 4 continual parianth lobes. The ovary is one-celled and the stigma is bifid. The leader pollinating agent in mulberry is wind. Mulberry fruit is a sorosis, especially violet black in shade. Most of the species of the genus Morus and cultivated sorts are diploid, with 28 chromosomes. But, triploids (2n= (3x) = 42) are also substantially cultivated for their adaptability, active boom of leaves. Mulberry prospers below numerous climatic situations beginning from temperate to tropical placed north of the equator among 28° N and 55°N latitude. The correct variety of temperature is from 26±1°C. Mulberry grows well in places with an annual rainfall ranging from 600 to 2500 mm. In regions with low rainfall, boom is limited via moisture strain, ensuing in low yields. On common, mulberry requires 340m3/ha of water each ten days in case of loamy soils and 15 days in clayey soils (Watt, G. 1981). Atmospheric humidity within the style of 70-85% is right for mulberry boom. Sunshine is one of the important elements controlling increase and leaf best. In the tropics, mulberry grows with a sunshine variety of nine to 14 hours an afternoon. Mulberry can be cultivated from sea diploma as an awful lot as an elevation of 600 to 1000m.

Establishment of Mulberry:

Soil Situation of Plantation Mulberry: Mulberry prospers nicely in soils which can be flat, deep, fertile, nicely drained, loamy to clayey, and porous with real moisture retaining ability. The best sort of soil pH is 6.2 to 6.8, the most fantastic being pH price is 6.5 to 6.8. Soil amendments may be used to accurate the soil to reap the desired pH. The quantity of gypsum or lime is to be performed in one in every of type instances to supply the pH to 6.8. Approach of software program is the powdered gypsum/lime combined well with lawn of soil and irrigated to stagnation for 48-72 hours. Later the water is leached out through drainage and dried (suitable for ploughing and inter cultivation operations). Appropriate mulberry kinds are the Kanva-2, S-13 and S-34 kinds are recommended for rain fed (rainfall: 500-800 mm) regions of South India (Uttar Pradesh, Karnataka, Andhra Pradesh and Tamil Nadu). Kanva-2 Belongs to Morus indica is Diploid and extensively cultivated in Southern India. Choice is the website of herbal populace of Mysore nearby variety (Jolly, M.S. 1987). Inflorescence and soros is lady of mulberry plant, profuse flowering, and plenty of soroses. Production tendencies medium leaf adulthood yields about 30 to 35 tones/ha/year is below irrigated conditions. Leaf moisture content material is 70%, protein content material cloth 21% and sugar content 11.5%. Excessive rooting capability is (eighty percent) and full-size adaptability. Resistant verities are to leaf spot. Pretty tested towards leaf rust are powdery mildew. S-thirteen belongs to M. indica. Choice is the open pollinated hybrids of Kanva-2. Encouraged for rain fed is an area of South India at some stage in 1990. Inflorescence: male, profuse flowering. Manufacturing trends yields 8-12 tones/ha/year underneath rain fed conditions, relying on rainfall. Moisture content material cloth 70.6% protein content material 24.3% and sugar content material 13.8%. Resistant kinds are to leaf spot and powdery mildew, moderately evidence towards leaf rust and tukra infestation. S-34 belongs to M. indica diploid. Choice is from progeny of S30 x Berc 776. Endorsed at some point of the 12 months 1990 is for rain fed regions with black cotton soils of South India. Inflorescence and soros is male, profuse flowering, now and again few soroses. Production trends: under rain fed situations, yields about 15 tones/ha/year. Moisture content 70%, crude protein content material 23.7%. Soluble sugar content material is 32.2%. Resistant is to powdery mould and leaf rust (Ravindran, S., 1988). Reasonably resistant sorts are to leaf spot and vulnerable to tukra infestation.

Land Preparation: Land for mulberry cultivation is ploughed deep with a heavy mold board ploughs as much as a intensity of 30-35 cm. Thereafter the land is repeatedly ploughed or three times with a rustic plough to convey the soil to a best tilth. The land should be properly leveled.

A basal dose of nicely decomposed farmyard manure (FYM) or compost is implemented on the fee of 10 tones/ha and thoroughly included into the soil.

Spacing: The spacing typically observed for a rain fed lawn is 90 x 90 cm Pits of 35 x 35 cm are organized. Approximately 1 kg FYM/pit must be added.

Stakes and Planting: Branches of eight-10 months old and about 50 mm in diameter ought to be used for the guidance of stakes of 22-25 cm duration with 5 to six wholesome buds. 3 stakes are planted per pit in a triangular shape with spacing of 15 cm, leaving best one bud exposed above soil surface. If planting is completed with saplings, then one sapling is enough perpit. Planting are need to be completed at some point of June/July after the onset of the monsoon.

Inter-cultivation: for the duration of the first year, inter-cultivation must be achieved manually. once mulberry plants are established, bullock ploughing is performed.

Fertilization: 50N:25P:25K (kg/ha/year) in doses. First dose: suphala (15:15:15) 167 kg, after 2 months of planting. Second dose: urea fifty-five kg or cam (one hundred kg) or ammonium sulfonate (one hundred twenty-five kg), at quit of September or early October before cessation of monsoon rains.

Pruning and Leaf Harvest. The primary crop must be harvested six months after plantation when the mulberry is properly mounted. Two extra crops are harvested during the primary 12 months by means of the leaf selecting method. Mulberry must be pruned after three hundred and sixty five days on the onset of the next monsoon. Pruning is finished by way of sharp sickle or pruning noticed at a top of 25-30 cm from the floor. In experienced manuring and mulching: inexperienced manure vegetation can be grown as an intercrop with mulberry for the duration of the monsoon simplest. Green manure plants (cowpea, horse gram, dhaincha) ought to be included into soil with the aid of ploughing before the flowering starts and nicely earlier than the rains stop. in the end, plots can be mulched with any dry fabric or vegetation so that it will now not reason wishes.

Protection underneath rain fed conditions (2nd 12 months onwards):

Endorsed inputs (in step with ha according to yr) for gardens maintained below rain fed conditions at spacing of 90 cm x ninety cm:

- FYM or compost, 10 tones in a unmarried dose on the onset of monsoon
- Azotobacter biofertilizer, four kg/crop, two times a year (for the duration of wet season)
- VAM inoculum, 1 000 kg, once in mulberry lifespan (inoculation via maize rootlets)
- Suphala, 167 kg, first crop
- Single splendid phosphate, 156 kg, first crop
- Muriate of potash, 42 kg, first crop
- Urea (fifty-five kg) or cam (one hundred kg), 1/3 crop
- In experienced manuring, 15 kg

Plants inclusive of horse gram, cowpea, sun hemp and dhaincha ought to be incorporated into the soil by ploughing before flowering and cessation of the monsoon. Leaf harvest person leaf harvesting has to be completed. The expected yield (tones/ha/12 months) for different sorts are: Kanva-2, 10-12; S-13, 14-15; S-34, 14-15.

Suitable Mulberry Varieties: Kanva-2, S-36, S-54, DD, MR-2:

Victoria-1: Types are endorsed for irrigated conditions.

Kanva-2: Belongs to M. indica. Diploid widely cultivated in southern India after it becomes advocated for cultivation in 1969 by means of CSRTI (Mysore). Choice is herbal populace of Mysore nearby range. Inflorescence and soros is: female, profuse flowering, many soroses. Manufacturing traits and Medium of leaf is adulthood, yields 30-35 tones/ha/yr underneath irrigated situations. Leaf moisture content is 70%, protein content 21% and sugar content material 11.5%. Resistant to leaf spot is fairly immune to leaf rust and powdery mildew. High rooting is capability (80%) and extensive adaptability.

S-36: Belongs to M. indica. Evolved at CSRTI and endorsed at some point of 1984. Evolved from Berhampore neighborhood is by way of chemical mutagenesis. The S-36 variety is mostly cultivated in Southern India. Slight rooting is ability. Manufacturing traits: yields 38-45 tones/ha/year underneath assured irrigated conditions of South India. Moisture content material 76%, CP 22% and carbohydrate content 28%. Tolerant to leaf spot are and powdery mold. Fairly vulnerable to leaf rust are to tukra infestation. Most appropriate to younger age silkworm rearing. Sapling plantation advocated due to slight rooting ability.

S-54: Belongs to M. indica. Advanced at CSRTI and encouraged all through 1984. Selected from Berhampore neighborhood is by way of chemical mutagenesis (EMS). Recommended for confident irrigated conditions is of South India. Manufacturing characteristics: yields approximately forty-five tones/ha/year under assured irrigated conditions. Enormously aware of agronomical enter. Moisture content material of leaf 70.5 percent, CP 23.nine percentage and sugar content thirteen.8 percent. Moderately immune to powdery mildew and leaf rust and proof against leaf spot. Loses moisture is in no time appropriate rooting capability.

DD: selected from herbal population of Dehra Dun variety and endorsed via Karnataka country Sericultural research and improvement Institute, Thalaghattapura and Endorsed for southern India Morphology: erect, skinny branches, coarse leaves, greenish gray bark. Lower branches spreading, leaves unlobed, large length, ovate shape. Yields are 35-40 tones/ha/year under assured irrigation conditions.

MR-2: Belongs to M. sinens is Diploid choice is from open pollinated hybrid population. Evolved at CSRTI and advocated for propagation in Tamil Nadu. Mainly cultivated area is in Tamil Nadu underneath each irrigated situations inside the plains and rainfed situations in hilly areas. Manufacturing characteristics: yields 30-35 tones/ha/yr below irrigated situations of Tamil

Nadu. Moisture content 68 percentage, protein content 23.2 percent, sugar content thirteen.2 percentage. Immune responses are powdery mould disease. Suitable for mulberry growth is at hilly regions (Kerenhap, W., *et al.,* 2007). Victoria-1 (V-1): Belongs to M. indica. Lately evolved is from a move of S-30 and Berc 776 at CSRTI. Encouraged is all through 1996 for assured irrigated conditions. Flower: male, profuse flowering, from time to time few so roses. Manufacturing traits: yields approximately 70 tones/ha/year below confident irrigated situations. Very high sprouting moisture is content 78.9% and 72%. Five percentages in younger and matured leaves are respectively, protein content material 24.6 percent and overall sugar content 16.98 percent. Reasonably proof is against leaf rust and tukra infestation and resistant to leaf spot. Quick sprouting capability and really high rooting ability (> 94 percentage) high photosynthetic rate and higher water use performance are extra blessings. Moreover, leaves are suitable for each young and grown bivoltine silkworm rearing.

Figure 1: Mulberry Garden and mulberry fruits.

2. Innovation in Silkworm Rearing:

Silkworm rearing is the mass scale rearing of silkworms for manufacturing of silk (Vijayakumar *et al.,* 2007). Each on-farm and stale-farm sports imparts more employment potential viable for lady's fork of the agricultural society as nicely. But, want of technological tendencies asserts better silk manufacturing with higher profits to farming people. The modern sericulture has been superior by way of the implementation of novel technological innovations at farm and enterprise stage to beautify the silk productiveness (Andadari *et al.,* 2022). The boom and development of silkworm is stimulated by environmental factors. Therefore, the upkeep of environmental parameters as according to requirements of silkworm fitness is a bit difficult procedure (Rahmathulla, 2012). but, the capacity overall performance of novel improvements viz., Arduino aided net of things (IoT), photograph processing technique and clever sensors of technological innovation is appraised as a master stroke key to the problem. It is simple, convenient and fee powerful approach to attain successful cocoon crop production (Rokhade *et al.,* 2021). One greater innovation, is the improvement of internet of factors (IoT) empowered wireless private location community (WPAN) gadget using sensors for monitoring of environmental factors in step with diagnosed specific life cycle stages and taking pictures pix simultaneously to achieve the development in collection of life cycle levels in silkworm (Nivashini *et al.,* 2018; Singh *et al.,* 2021). Many fashions have been proposed time to time based on net of factors (IoT) for the improvement of smart sericulture technology to promote sericulture (Srinivas *et al.,* 2019; Sreedhar *et al.,* 2020; Eethamakula *et al.,* 2020; Jeegadeesan *et al.,* 2021). Within the UT of Jammu and Kashmir, there are 3 different agro-climatic zones viz., temperate, intermediate (lies among temperate and sub-tropical) and sub-tropical sector. Therefore, there may be want of different mulberry cultivars, cultivation practices and silkworm breeds which are particular to exceptional agro-climatic regions. The development of location precise silkworm is of earlier importance to revive sericulture industry in Jammu and Kashmir. Fortification of mulberry leaves with proteins and different supplements is a today's method to enhance the cocoon manufacturing. It employs use of different plant or animal based totally products rich in proteins more specifically to feed the silkworm larvae (Islam *et al.,* 2023). A chawki leaf chopper for cutting the mulberry leaf in thin slices for intake of young age larvae have been advanced. A synthetic silkworm food plan referred to as "Nutrid" have been developed for healthful and full of life increase of silkworms (Gahukar, 2014). CSRTI Mysore, have advanced a device which acts as each heater and humidifier as in line with requirement of rearing room (Chanotra and Bali., 2019). A device which selections and separates matured silkworms from mulberry twigs in shoot system of rearing and from trays in tray device of rearing were developed with nearly negligible harm chance to silkworms. Disinfection is the foremost operation to be carried before commencement of silkworm rearing to preserve the pathogen-loose environment for silkworm. An ecofriendly and fee-effective device which employs the use of fireplace-flames and LPG as fuel known as flame-gun, were advanced to disinfect the incubation, rearing, leaf, cocoon storage room and rearing equipments (Verma and Dandin., 2006). Many mattress-disinfectants were evolved which includes, to guard the sickness inflicting pathogens in silkworm rearing mattress (Surapwar *et al.,* 2019). Guide dusting of mattress-disinfectants is risky for prices and time in silkworm rearing (Chanotra and Bali 2019) applier. CSRTI Mysore have evolved power/battery operated duster which calmly spreads the disinfectants over the silkworm body on trays in less time (Dandin and Verma., 2002). Pest manipulate can be executed via application of uzitrap, uzicide and so on. to manipulate the important pest, Exorista bombycis in silkworm rearing (Singh and Saratchandra., 2003). Plastic tray washing device possesses performance of washing one hundred twenty trays/hr are with entire disinfection are advanced to keep the labour costs and time in silkworm rearing (Chanotra and Bali., 2019).

3. Innovation in Post Cocoon Sector:

The gathering and separation of cocoons from cocoon frames is arduous and time ingesting technique. CSRTI Mysore has evolved deal with/ pedal operated cocoon harvesting device used for harvesting from 25-50 frames/hr and 50-60 frames/hr from hand operated and pedal operated harvester respectively. Deflossing is the procedure of casting off floss layer of the cocoon. Guide deflossing is time ingesting system and calls for labour (Angel, et. al., 2018). Cocoon removing silk fibers machines viz., hand operated, hand operated cum motorized and absolutely motorized which can remove silk 25-30 kg/hr, 50-60 kg/hr and seventy-five-eighty kg/hr respectively had been evolved. In grainages, an adequate amount of cocoon desires to be cut for sex dedication of pupae and estimation of amount parameters such cocoon weight, shell weight and shell ratio (Subramanian *et al.,* 2012). Cocoon cutting their silken cage device were advanced with performance of cutting 5000 cocoons/hr were developed (Bindroo and Verma., 2014). Cocoon boiling or cooking is the process of boiling the cocoons to melt the sericin layer for easy unwinding of silk fiber from cocoon. Its miles in the main carried by using simple cooking either in single pan device or in 3 pan gadgets at one-of-a-kind temperatures. These techniques render the cocoons either over-boiled or under-boiled those are unsuitable for reeling manner (Naik and Somashekar., 2007). A brand-new technique "Vacuum boiling machine" has been developed wherein the uniform softening of all of the layers is attained with higher reelability. Steel buttons are non-circular chrome steel tool used as thread guide with required specification as that of yarn size, were developed to keep away from slubs in yarn and may be used for comparatively longer time (Lee, 2011).

4. Why Organic Farming in Mulberry?

India, a major donor to worldwide nourishment generation, customarily utilized cultivating strategies like edit revolution, compost, excrements, and polyculture. Within the past, agriculturists utilized conventional strategies, but presently they frequently utilize modern ways with chemicals to urge more crops. Be that as it may, these chemical strategies can hurt the environment and the nourishment we eat. That's why in India, there's been a alter towards organic agriculture in later a long time. The natural cultivating strategy could be a superior way to utilize characteristic assets and techniques to keep the soil sound and help the environment and ranchers at the same time. The essential thought of natural agribusiness isn't around developing crops; it's approximately keeping everything in nature sound just like the soil, the plants, and all the living things around. The most objective of natural developed cultivating is to develop nourishment that's great for you without utilizing destructive stuff. To do this, ranchers utilize distinctive cultivating hones, like uncommon ways of planting and taking care of the soil (Gangopadhyay and Debnirmalya., 2009). This approach emphasizes maintainable hones, counting animal's integration; weed administration, chemical free development, and vermiculture. By spurning engineered fertilizers and pesticides, agriculturist's points to develop crops that are not as it were solid for shoppers but too eco-friendly. Natural cultivating in India implies a move from conventional agricultural farming practices by maintaining a strategic distance from the utilize of chemical pesticides and engineered fertilizers. Instep, it depends on common bug control strategies inferred from natural sources such as fertilizer, plant buildups, and creature squander. This move towards natural agriculture could be a reaction to the natural repercussions related with the far reaching utilize of chemical inputs. It speaks to a cutting edge natural farming framework outlined not as it were to amend the biological lopsided characteristics caused by routine cultivating but too to preserve and improve the by and large wellbeing of the biological system. The natural strategy of cultivating handle is considered to be a small more troublesome than ordinary cultivating. A fundamentally portion of strategies for natural cultivating strategy includes the utilize of natural inputs like green excrements and bovine waste. Green fertilizers and developed cover crops play a vital part in moving forward soil richness, whereas dairy animal's fertilizer serves as a important natural farming, contributing to soil improvement and cultivating a economical approach to trim development. In substance, natural cultivating in India epitomizes a agreeable and naturally cognizant approach to horticulture, advancing the well-being of both the arrive and its inhabitants. Once planted, mulberry is being kept up for a few a long time with persistent agronomical hones in bimonthly interims (Ramakrishna Naika., 2011). Chemical based inputs are much favored by the agriculturists since of brief term comes about and economy. Buildups of the chemicals (fertilizers / weedicides / bug sprays / fungicides) utilized within the mulberry plant posture a potential chance of natural contamination other than antagonistic impacts on the clients, silkworms, common adversary complex, useful micro-organisms etc. In spite of the fact that chemical cultivating at first yields great comes about, the sericulture ranchers certainly involvement its negative impacts on leaf surrender as well as quality and cocoon productivity, few a long time after mulberry development. Subsequently, advancement of natural cultivating is require of the hour in sericulture to maintain a strategic distance from unpredictable utilize of chemicals in mulberry plant. In this setting, this bulletin lists conceivable natural inputs and their utility in mulberry cultivating as well as later headways in eco-friendly agronomical package of practices created for feasible sericulture.

Integrated Organic Nutrient Management Practices:

Natural fertilizers play crucial part on soil wellbeing by progressing its physical, chemical and organic properties. It upgrades water holding capacity in sandy soils, encourages air circulation and penetration in overwhelming soils, increments supplement supply control of antacid soil by decreasing its pH, advances the exercises of advantageous microorganisms to form the soil more prolific other than it claim supplement values. The buffering nature of the natural matter is considered to be profitable to overcome the issue of buildups of pesticides, fungicides, herbicide and other overwhelming metals in agro-ecosystem. The critical natural excrements and their utility for mulberry leaf generation are outlined below:

(i) Farmyard Manure (FYM):

Farmyard excrement (FYM) could be a sort of natural fertilizer made from deteriorated creature squander (compost and pee) and remaining materials from creature nourish. It's a profitable instrument in farming, making strides soil structure, ripeness, and water maintenance. FYM is bulky natural excrement arranged essentially by storing bovine / buffalo waste, droppings of sheep, goat, poultry etc., beside extra grains (accessible from claim source of animal's culture of agriculturists) in pits for few months for decay. The well decayed FYM contains around 0.5 % N, 0.2 % P O and.0.5 % K O. 252 Be that as it may to realize the complete supplement potential of animal's squanders, they must be legitimately decayed, through appropriate strategy of composting. Cultivate yard excrement (FYM) and compost is age ancient hones of returning plant supplements to the soil. These are arranged by breaking down compost and pee of cultivate creatures and other natural buildups such as kitchen squanders, trim buildups, creature squanders, butcher house squanders etc. In natural cultivating framework, arrangement of on-farm compost is suggested. We need to take after the NPOP (National Program for Natural Generation) standards whereas planning the compost. The NPOP benchmarks permit and confine certain fixings for composting and utilize as supplement beneath natural cultivating. The conventional methods of planning natural excrements and composts are defective in which misfortunes of the nutrients are higher. These methods are moderate. The method of composting and supplement substance of the compost can be improved on the off chance that the compost is ready utilizing the night crawlers. Such compost is called vermi compost. Fluid fertilizer called vermi wash is additionally arranged utilizing worms. The fluid excrements are arranged to utilize them specifically on the edit plants. We know that through foliar application, plants can retain supplements 20 times speedier as compared to the soil application. Fluid excrements are use for moment plant reaction and when there are supplement insufficiencies in standing trim. Application of liquid fertilizers is additionally valuable for overcoming unfavorable soil conditions. As demonstrated within the procedure, we mix a few takes off of leguminous plants beside the FYM. This blend gets decayed steadily and the weakened material oozed out from the cloth and blended with the water. Five to seven kg of dairy animals' compost beside comparable number of green clears out of leguminous plants are blended and filled in a gunny pack. At that point the substance is inundated in a dun containing fish water. The water of the drum is to be mixed for five minutes each day. After 20 to 25 days, your fluid fertilizer will be prepared for utilize. Evacuate gunny pack from the drum, crush it and include 200 to Planning of Cultivate Yard 250 g molasses. The molasses increments are the staying quality of the manure (Mahesh, D. S., 2014). Before Fertilizer (FYM) and Compost utilize, weaken this with break even with sum of water. The natural matter in the gunny pack breaks down and gradually the excreta comes out within the drum. The water is wealthy in supplement substance. The substance will be dim brown in colour. Being bulky and cheap source of natural excrement, FYM is an integral portion of soil wellbeing and coordinates supplement administration (INM) techniques in India. In sericulture, soil test based FYM application is profoundly calculable.

(ii) Compost:

Compost is a critical frame of natural fertilizer. In natural cultivating, composts are arranged at the cultivate utilizing trim buildups, waste, bedding and pee of creatures and other cultivate squanders. Compost may be a item of biodegradation of natural squanders accessible from diverse sources like trim buildups, weeds, green and dry clears out, bovine fertilizer, poultry squanders, urban squanders, squanders from agro based businesses (pressmud, sericulture squanders etc.,) which is carried out by differing bunch of heterotrophic microorganisms such as microbes, organisms, actinomycetes and protozoa. The standards behind composting are narrowing down of C: N proportion, the overall annihilation of destructive pathogens and weed seeds by high temperature advanced amid decomposition and stabilization. When the natural materials broken down within the nearness of oxygen the method is called high-impact deterioration and conclusion item shaped are carbon dioxide, humic substances and discharge of accessible plant supplements. The quality of compost is depending upon the accessibility of natural squanders and their composition other than the wise blending and planning. In any case it holds wealthy supplement esteem than FYM. The supplement esteem of compost can advance be expanded by application of superphosphate or shake phosphate @ 10 to 15 kg / MT of crude fabric at the starting organize of filling the compost pit. Let us look at the guideline and necessities of this explore. a) Rule The guideline of composting has been depicted within the over alluded units. If it's not too much trouble go through it. Be that as it may, fair to remind you, the composts are arranged with the assistance of organisms (ordinary compost) and night crawlers (vermi compost). These organisms bring down the C: N proportion to the level of 20:l of the natural matter. They change over the complex materials into straightforward and effectively accessible shapes. For illustration: the protein is broken down within the frame of amino acids and encourage into nitrogen. b) Necessities Creature fertilizer, trim residues, green leguminous takes off, gunny pack, stones, pits, open space, buckets, drum and spade. Here we should depict the pit strategy of compost planning. The steps for preparation are: 1- Burrow a pit with the assistance of spade in an open shaded put. The pit ought to have a measurement of 6 m long, 2 m wide and 1 m profound. (The total trench may be separated into 1 m areas). 2- Chop up all the accessible natural buildups (green and dried) into helpful measure and mix the green buildups with dried. 3- Whereas filling the pits, to begin with put the sand and little rock at the foot of the pit. 4- Put 30-45cm thickness agro squander as moment layer and splash waste slurry. This hone ought to be rehashed till the pit is filled up to a stature of 0.5 m over ground surface. 5- Then the top of the pile is adjusted off to the shape of a arch and put with the blend of soil and dairy animals waste slurry. The putting preserves nitrogen and dampness additionally avoids fly nuisance. 6- You will fill as it were one area at a time and fill the following segment whereas turning. This handle is repeated till the fabric is out from 4th pit. This strategy is called parallel pit method. 7- Keep up adequate dampness 55-60% within the pits by splashing water at normal interim compost is considered prepared when it is free streaming and having dim brown colour. The free stream characteristic is gotten when the dampness level is between 15 to 25 %. You should degree the dampness substance of compost utilizing Gravimetric strategy, after you accept that the compost is prepared. The development by and large comes after 3-4 months. Gravimetric strategy of dampness assurance the strategy is taken over dried dampness boxes and weigh. Fill the boxes with compost (take the compost test from diverse bearings and weigh. Keep filled boxes within the hot discuss stove 105Â°C for overnight 24hrs. Take out the boxes from stove, cool and weigh. Rehashed steps till you get a steady weight for the arrangement of compost.

Figure 2: Compost farming for grows fertile soil for plantation of mulberry plant.

(iii) Vermi Compost:

Earthworms as companions of cultivating community, renders offer assistance in soil enhancement, natural matter deterioration and in improving the quality of rural deliver. Vermi composting may be a bio-oxidation handle of natural squanders including a joint activity of night crawlers and micro-organisms. In this handle night crawlers act as flexible bioreactors changing over natural materials into fine granules called vermi cast (excreta of night crawlers). Vermi compost may be a useful soil revision for developed mulberry in India, advertising preferences like made strides soil wellbeing and improved leaf abdicate and quality. A prescribed application rate is 7.5 metric tons per hectare per year, which can be supplemented with other natural matter like barnyard fertilizer. Vermi compost is wealthy in plant nutrients, chemicals, anti-microbial, plant development hormones and huge useful microbial populaces which offer assistance to extend the quality and surrender of mulberry leaves appropriate for higher efficiency of silk. Application of 10 MT of vermi compost with 50% decrease within the application of prescribed measurements of chemical fertilizers (NPK) / ha/ year might deliver leaf surrender at standard with application of 20 MT of FYM /ha/year with full prescribed dosage of chemical fertilizers. Benefits of Vermi compost for Mulberry: Moved forward Soil Wellbeing: Vermi compost upgrades soil structure, increments water maintenance, and advances advantageous microbial action, driving to more advantageous soil for mulberry development. Supplement Accessibility: It gives a slow-release source of fundamental supplements like nitrogen, phosphorus, and potassium, which are significant for mulberry leaf generation. Expanded Leaf Abdicate: Considers have appeared that vermi compost application can essentially increment mulberry leaf abdicate compared to conventional fertilization strategies. Upgraded Leaf Quality: Vermi compost can make strides the supplement substance of mulberry clears out, counting nitrogen, zinc, press, copper, and manganese, which is imperative for silkworm rising. Diminished Fertilizer Needs: By supplementing or supplanting chemical fertilizers, vermi compost can lower the taken a toll of mulberry development. Eco-friendly: Vermi compost is a natural and feasible soil amendment, promoting eco-friendly sericulture hones.

Figure 3: Vermi-composting units grow the mulberry plants and fruiting of mulberry fruits

Vermi compost is the end-product of breakdown of natural matter by a few species of night crawler, coming about within the arrangement of supplements wealthy natural fertilizer with soil conditioning properties. On the other hand, sericulture being agro-based industry includes era of huge number of natural squanders and by-products at each and each steps extending from mulberry cultivation to silkworm raising and reeling etc. In this way, the squander created from mulberry development and raising squanders counting silkworm litter, bed buildups and other materials may be utilized for arrangement of supplements wealthy vermi compost for quickening the development and quality of mulberry leaf. The current vermi compost are utilizing for developing mulberry plant opens modern roads for advancing by-product utilization seri-waste in sericulture. The resultant item may be utilized for agrarian and green as well.

(iv) Poultry Manure:

Poultry manure is a good source of organic nutrients and is used after decomposition. Buy Poultry (4.55-5.46%), Phosphorus (2.46-2.82%), Potassium (2.02-2.32%), Calcium (4.52-8.15%), Magnesium (0.52-0.73%), and a notable amount of Micron Laccarter (20%). Hermicellulose (1.89-2.77%) and lignin (1.07-2.16%). This can be degraded in appropriate organic alteration applications such as hacked rice straws and koia piths by adding Pleurotus sajor-caju (1.25 kg or 0.5 kg) of fungal column. It consists of a combination of feces, urine, springs, bed linen and spilled food. Poultry junk is a valuable resource for agriculture because it is high in nutrients. Fertilizer/waste is collected, sought to prevent the growth of unwanted pathogens and prevent excessive chemical reactions. Chicken fertilizer can be applied 500 grams to 500 grams depending on the size of the plant before planting or as a top dressing for existing plants. You can also mix with water and then pour the mixture at the bottom of the plant. Poultry crap can be mixed with other organic materials such as harvest residues, straws, or wood chips to create a balanced, nutrient-rich compost and fertilizer mixture.

Figure 4: Poultry manure for mulberry garden

Sericultural activities mainly depended on the quality and quantity of mulberry leaves and were given silk crushes for breeding. Continuous production of mulberry leaves has long been a practice of commercially available breeding silk laupien, requiring proper care of the soil, which leads to sustainable leaf production and quality. Based on research and development in the celic culture, best practices for silk cubic breeding with advanced mulberry varieties such as G4 can produce 60-70 mt/ha/year of Foliage. To produce large quantities of mulberry leaves, this is the highest ratio of chemical fertilizers and mulberry plantations, using several years. H. 360:180:180 (n: p: k) (Shinde, K. S., 2012). Mulberry leaf production in India mainly relies on the use of chemical fertilizers that help plants to produce continuously without compromising without affecting quantity and quality (Shankar, M.A., 2012). However, continuing use of chemical fertilizers is not recommended as it may change soil type, as it reduces acidity or alkalinity, reduces soil fertility, and means further damage such as microorganisms available in the soil, eutrophication, and ratios of chemical fertilizers applied to mulberry plants. This practice not only affects the environment, but also produces coco around farmers. Therefore, it takes an hour to find your manager with supplementation and color organic fertilizers to reduce the use of chemical fertilizers for sustainable celic cultures. Searching for fertilizers that can supplement chemical fertilizer replenishment leads to junk in poultry. This contains the highest amount of carbon and nitrogen in the fertilizers that are normally available to farmers (Ren, T., 2014). The use of poultry junk in mulberry cultivation is an unexplored area commonly considered farm gardens. India is the fifth largest producer of poultry meat in the world. Therefore, poultry junk production will also accumulate, and UN environmental pollution will accumulate. The use of poultry fertilizers in other edible plants has been proven, testing and testing improved carbon nitrogen content in the soil and increasing production of rice, wheat, corn, and more. Effective use of chicken fertilizer is not only from the use of fertilizers, but also from the use of other organic lints and green spouts. The use of bio fertilizers such as Azosprillum SPP, rhoscocci, and potash mobilization is more effective than sustainable plant production using green manure (Meelu, O.P., 2007). Therefore, the combination of poultry junk and biofertilizer and green manure can complement the use of chemical fertilizers. The goal of supplementing chemical fertilizers by examining the effects of the combination of chicken junk and biofertilizer and green chicken, and the analysis of the (N, P, K, and K) content of mulberry leaves. Investigation of the effects of poultry junk on the growth and development of mulberry vars G4 showed significant improvements in various growth parameters, particularly using poultry junk, in combination with chemical fertilizers. The number of drives per plant increased, especially with T7 (75% chemical fertilizer + 10 mt poultry fertilizer). In combination with 75% of the particularly recommended chemical fertilizers, the use of poultry junk highly effectively promotes the growth and development of mulberry. G4. This approach not only supports sustainable agricultural practices by reducing the use of chemical fertilizers, but also ensures optimal plant growth for symptoms purposes.

(v) Sheep and Goat Manure:

The sheep and goat droppings have more nutrients than farmyard manure and compost. This manure consists of 3 % N, 1% P O and 2% K O. There are two methods of 252 applications of droppings of sheep or goat. In first method, the decomposed droppings of sheep or goat in pits applied later to the field where in the nutrients present in the urine are wasted. In the second method, sheep and goats are kept overnight in the field by which urine and faecal matter incorporated to the soil in shallow depth by using working blade harrow or cultivator (Sakthivelet et. al., 2014). Sheep and Goat Droppings are generally used as fertilizers for plants as they contain higher nutrients than farmyard manure and compost manure. The manure has an average N content of 3%, a P2O5 content of 1%, and a K2O content of 2%. The sweeping of sheep or goat shelters is disposed of in pits for subsequent application to the field. It is also known to loosen up heavy and tight soils. This article will explain to you about Sheep and Goat Droppings which will be helpful in preparing the Agriculture soil. Fertilizer is one of the most popular uses for goat manure. Farmers can increase crop yields and plant health by using fertilizer made from goat and sheep droppings.

Figure 5: Sheep and Goat dropping and manure used for mulberry cultivation.

Sheep and Goat Droppings are naturally in the form of pellets and are cleaner. Sheep and goat droppings in general don't often burn plants or attract insects like those of cows or horses. Both are practically odorless and good for the soil. Sheep and goat droppings can be used in the following ways: Sweeping of sheep or goat sheds is placed in pits for decomposition before being applied to the field. In this method, the nutrients in the urine are wasted. The second method is sheep penning, which involves keeping sheep and goats overnight in the field and incorporating urine and fecal matter into the soil to a shallow depth with a working blade harrow or cultivator. The application of the Sheep and Goat Droppings are One of the best ways to improve the soil is to use goat and sheep droppings in garden areas. Its pelleted form allows for direct application to vegetable and flower gardens without having to worry about burning the plants. The pellets are additionally simple to toss and till into the garden. Another method is to mix equal amounts of goat manure, sand, and straw into the spring beds, adding more or less manure as the plants mature. One can nourish the garden with goat dung and then let it seep into the soil during the winter. The sheep and Goat Droppings are benefited as for growing herbs, vegetables, and other crops, goat and sheep manure is a great fertilizer. It is renowned for enhancing the soil's ability to store water. Sheep and goat droppings are generally drier than the droppings of cows and horses. It is easier to spread, easier to work with, and has a milder odor. Additionally, it composts faster. With 22 pounds of nitrogen per ton, it has higher nitrogen content than typical horse and cow manures. The pelletized droppings allow for increased airflow into compost piles, which reduces the amount of time it takes for compost to mature and is another advantage of utilizing this as fertilizer. For both new and old gardens, goat and sheep droppings are a great soil conditioner. By enhancing the soil's texture, more oxygen can reach the roots and water may be used more effectively. It provides an inexpensive, organic supply of nitrogen and other nutrients. It may be concluded that the Sheep and goat droppings are excellent fertilizers. However, since goats consume hay and grass, weed seeds may be found in their dropping. Most grazing animals, including sheep and horses, also pose the same danger. To lessen this issue, it is always advised to use well-composted goat manure. To prevent weeds, spreading mulch over the soil and then removing any weeds that emerge immediately before they go to seed is mandatory.

(vi) Green Manure:

Green manure is a farming practice where specific crops, typically legumes, are grown and then incorporated into the soil while still green to improve soil fertility and structure. These crops, known as green manure crops, are not harvested for consumption but are tilled into the soil, where they decompose and release nutrients. This process enhances soil health by adding organic matter, improving nitrogen levels, and reducing the need for synthetic fertilizers. Green manuring can be defined as a practice of embodying the soil with the unrecompensed green plant tissues for improving its physical structure as well as fertility. It is a best alternative to FYM in the prevailing situation of its scarcity and high cost due to decline in livestock farming in recent past. Green manure crop is grown in inter rows of mulberry plants and incorporated in soil at pre flowering stage because they are grown only for their biomass which is high in organic matter and nutrients. The green-manure crop also supplies additional nitrogen due to its ability to fix nitrogen from the air with the help of its root nodule bacteria. Further in-situ composting of green manure promotes the build-up of beneficial rhizosphere micro-flora in the garden which enhance the availability and mobilization of soil nutrients to the plants. Green manures will break down in to the soil gradually and add some nutrients to the soil for the next crop too. Green manuring in mulberry with dhaincha (Sesbania aculeata) and sunn hemp (Crotalaria juncea) @ 15 kg seeds / acre is recommended for alkaline and neutral soil conditions respectively. The seeds are treated with Rhizobium (200g) with sufficient quantity (300 ml) of rice gruel in room temperature and shade dried for 30 minutes (Ram Rao, D.M., 2007). After sowing, it is better to give splash irrigation for 2-3 times followed by flood irrigation. The green manure crop is embodied in the soil before flowering (approximately 40-45 days after sowing) either by trampling method or by power tiller. About 15-17 tonnes of green biomass per hectare per year can be incorporated to soil by green manuring with dhaincha or sun hemp in mulberry garden annually for soil fertility improvement. The additional benefit of green manuring is that it prevents weed growth and saves the weeding cost.

Green manure refers to crops grown to be incorporated into the soil, enhancing its organic matter. These crops are usually fast-growing and include species such as legumes. Leguminous plants are popular as they add nitrogen to the soil through nitrogen fixation. Other plants used as green manure can include grasses and clove rs. These crops are grown for a specific period and then plowed under, rather than being harvested for sale or consumption. This method enriches the soil with nutrients and organic matter, which helps improve its quality and structure. The primary goal of green manuring is to improve soil health. When green manure crops are turned into the soil, they add nutrients that are essential for plant growth. This method can increase soil organic matter, improve soil structure, and enhance moisture retention. Another goal is to manage weeds by suppressing their growth during the green manure crop's growing season.

Green manuring can also reduce soil erosion by providing ground cover. Additionally, it can help break disease cycles by rotating crops that are not hosts to particular pests or diseases, making it a valuable tool in sustainable agriculture practices. Green manure is used to enhance soil fertility by plowing living plants into the soil. This practice releases nutrients slowly, which supports microbial activity and benefits plant growth. For example, incorporating green manure crops like legumes can add nitrogen to the soil, improving crop yields. Farmers often use green manures to break pest and disease cycles. For instance, planting a green manure crop between regular crop cycles can reduce weed growth and suppress soil-borne diseases.

Figure 6: Green manuring in mulberry with sunnhemp and a view of root nodules.

(vii) Bio-Fertilizers:

A bio-fertilizer is a substance which consists of residing microorganisms which, when applied to seed, plant surfaces or soil, colonizes the rhizosphere or the interior of the plant and promotes boom by way of growing the supply or availability of primary nutrients to the plant. In gift scenario, bio-fertilizers are the one of the inevitable alternatives to chemical fertilizers. positive commonplace micro organism like Azotobacter chroococcum, Azospirillum spp. (A. brasilense, A. lipoferum, A. amazonense, A. halopraeferens and A. irakense) are capable of fixing atmospheric nitrogen (biological nitrogen fixation). however, the Azospirillum plays additional function that it secretes increase selling substance (Indole Acetic Acid) in the soil, induces disease resistance and drought tolerance in the vegetation. in addition, every other bacterium, Bacillus megaterium known as phosphorus solubilizing bacteria (PSB) which is successful of solubilizing insoluble phosphorus and making available to the plants.

So proper amount of mulberry leaves production approach suitable meals for silkworms and in turn silk yield will be better. by way of chemical fertilization soil fitness has been declining daily as a way to fight this hassle of soil fitness bio fertilizer application is one suitable technique to revitalize soil health. The bio fertilizer, which is fabricated from biological wastes, is used to growth the soil's fertility. they're freed from insecticides and help to enhance the soil by way of containing micro-organisms, which produce natural nutrients and stop the unfold of ailment

(Sakthivel, N., et. al., 2014). Azotobacterial Biofertilizer: it is a bacterial practise crafted from live Azotobacter cells and the proper carrier substance, like powdered lignite. With the aid of organic nitrogen fixation, it may offer nitrogen to the plant life. Developing plants is progressed. It will increase the profitability of sericulture and serves as an efficient supplement to chemical fertilizer. Vesicular-Arbuscular Mycorrhiza: it is a symbiotic association among plant root and fungus. Inoculation of mulberry with positive mycorrhizal fungi is highly useful. Glomus mosseae and Glomus fasciculatum are such for instance. benefits conferred via this VAM are root pathogens can be minimized. It complements the absorptive surface region of root systems significantly and nourishes the vegetation via different micro-nutrients and phosphorus. It colonizes the root of higher plants, in particular below phosphorus poor conditions. Certain useful fungus paperwork vesicles and arbuscules in host root cells. Phosphate Solubilizing Bio fertilizers: Phosphorous is the second most crucial plant nutrient next to nitrogen. The provision of implemented phosphates is only 15-20% due to its fixation in non to be had bureaucracy. Its availability may be improved through the usage of phosphate solubilizing microorganisms

Figure 7: Figure represent as the bio fertilizers used in mulberry garden.

Seriphos: Phosphate solubilizing micro-organisms developed specifically for mulberry cultivation. Blessings are phosphorus availability to flowers, phosphorus use efficiency. Enhances root improvement. Increases leaf yield by 10-15%. Induces plant growth promoting materials for improve soil, fertility and productiveness.

(viii) Neem Oil Cake (NOC):

Neem oil cake (NOC), a byproduct of neem oil extraction, is a precious organic fertilizer and pest repellent for mulberry plantations. It improves soil fertility, presents vital vitamins, and enables manage nematodes and different soil-borne pests and diseases. Some of the specific organic sources are the non-safe to eat oilcakes in standard and NOC in particular incorporate high amount of plant vitamins and alkaloids which induces immunity in opposition to pests and sicknesses in mulberry except its better nutrient content material than other oil desserts. The alkaloid contents (nimbin and nimbicidine) which inhibit the nitrification manner of N transformation in soil at the same time as applying nitrogenous fertilizers and makes N to be had slowly. The NOC @ 60 kg/ac/crop blended with N fertilizer notably increased the mulberry leaf yield. however, the software of 800 kg /ac in 4 cut up doses at an c programming language of 3 months at some stage in inter-cultural operations is suggested to govern root-knot sickness.

Figure 8: Neem cake fertilizer and pellets for mulberry garden

Benefits of Neem Oil Cake (NOC) are representing as the Nutrient source is NOC is a good supply of nitrogen, phosphorus, and potassium (NPK), in conjunction with different micronutrients which are critical for plant growth. Soil development is it complements soil shape, increases water retention, and improves ordinary soil fitness. The Pest manage are NOC acts as a herbal nematicide, insecticide, and fungicide, assisting to govern diverse soil-borne pests and illnesses that have an effect on mulberry. decreased Chemical input are the use of NOC reduces the want for artificial fertilizers and insecticides, promoting sustainable and organic mulberry cultivation. Stepped forward Yield of mulberry leaves are via providing vital vitamins and controlling pests, NOC can make a contribution to healthier mulberry plant life and probably better leaf yields. Cost-powerful is several sources country that neem products, consisting of NOC, may be an inexpensive and sustainable alternative for farmers. The Use Neem Oil Cake (NOC) in Mulberry Plantations are software technique is NOC can be applied at once to the soil around the mulberry plant life or blended with water to create a drench. The Dosage is a not unusual application charge is 5-10 kg in step with a hundred rectangular meters, but it is always fine to alter the dosage primarily based at the specific wishes of your mulberry vegetation and soil conditions. Timing is applying NOC throughout land education or at the beginning of the developing season. Frequency is applying NOC every 2-3 months, or as wished based on plant fitness and pest stress. Guidance of NOC may be blended with water (100g in step with liter) and soaked overnight before utility. For direct software, mix it with soil across the plant, avoiding contact with the roots. The precaution is as store NOC in groovy, dry vicinity, far from direct daylight. Over-software is heading off excessive use of NOC, as it may negatively impact soil pH and nutrient stability. The first-rate is making sure that the NOC is sourced from a good supplier to assure its best and effectiveness. mixture with different organic practices are Neem oil cake can be used together with different organic farming practices, such as green manure and composting, to in addition decorate soil fitness and fertility (Sangeetha, R., et. al., 2012) via incorporating Neem Oil Cake (NOC) into your mulberry cultivation practices, you could enhance soil health, beautify plant growth, and probably reduce the reliance on artificial inputs, main to extra sustainable and efficient mulberry farming.

(ix) Press Mud:

Press dust, a byproduct of sugar manufacturing, is a valuable natural modification for mulberry cultivation. It improves soil structure, enhances nutrient availability, and may be used as a soil conditioner, especially in alkaline soils. Decomposition of press dust earlier than utility is usually recommended to avoid warmness era at some stage in decomposition in the soil. Press mud plays essential position in alkaline soil amelioration. The clean fabric as such is no longer beneficial due to generation of heat at thermophilic stage of decomposition in the soil. as a result, decomposition of the press mud is inevitable before its application in the soil. The composting is executed by using spreading clean press mud to 1meter width and 3meter length (relying upon the amount) to about 15 cm thicknesses. Then microbial subculture of Pleurotus or Trichoderma viride (1kg/ MT of press mud), urea (5kg/MT) and cow dung as a starter (50kg/MT) are sprinkled over this layer by way of blending them in water. Then some other layer of press mud to a thickness of 30 cm is delivered and again the microbial way of life, urea and cow dung are sprinkled. This process is repeated until attain a peak approximately one metre. The top layer is blanketed with soil. Water is sprinkled to moisten it to 50% water maintaining ability. This moisture level is to be maintained all through. Decomposition may be over inside 6 to eight weeks. Rock phosphate, ferrous sulphate, zinc sulphate and many others., can additionally be brought to improve the nutrient contents. The press mud thus composted is dark in coloration with narrow C:N ratio (about 12:1). It carries about 2.08% N, 30.63% P O, 1.40% ok and 22.38% natural carbon (Samuthiravelu, P., et. al., 2012). Inside the context of mulberry cultivation is press mud can be a precious tool for improving soil health and promoting healthy mulberry growth, which is important for silkworm rearing.

(x) Foliar Fertigation:

Foliar fertigation in mulberry flowers includes making use of liquid fertilizers without delay to the leaves, bearing in mind green nutrient uptake. This technique is especially beneficial in addressing nutrient deficiencies in the soil and improving leaf first-class for silkworm rearing. The foliar spray of nano-fertilizers showed higher consequences for cocoon and silk developments of hybrid silkworms. Mineral supplementation for improvement of leaf great and next feeding to silkworms plays a critical function in silkworm improvement, cocoon characters and yield. Cocoon weight, cocoon shell weight, pupal weight, cocoon shell ratio, cocoon filament period, denier and silk protein various substantially some of the treatments with higher values for nano NPK (19:19:19) at 6 g/l which might be due to better nutrition as it substances N, P and okay which play a crucial position in improving silkworm boom and improvement which in the end have an effect on silk production resulting in proper nice cocoons. Feeding silkworms on nano fertilizers viz., nano NPK (19:19:19) at 6 g/l, nano NPK (19:19:19) at 4 g/l and nano urea at 6 ml/l sprayed mulberry leaves led to stepped forward larval boom and development, along with improvements in cocoon and silk trends of FC1 X FC2 hybrid silkworm. Therefore those nano-fertilizers keep promise as valuable guidelines for farmers. Reading the underlying mechanisms by using which nano-fertilizers impact silkworm physiology and development can provide valuable insights. this could contain analyzing gene expression, metabolic pathways, and cellular responses and additionally exploring the capability lengthy-term results of repeated publicity to nano-fertilizers on silkworms' fitness, duplicate, and next generations can provide a comprehensive expertise in their sustainability and protection.

(xi) Vermi-wash:

Vermi-wash is a collection of excretory merchandise and mucus secretion of earthworms along with micronutrients from the soil natural molecules and used as foliar spray. It contains plant increase hormones like auxins and cytokinins aside from nitrogen, phosphorus, potash and different micro-vitamins. grownup worms measuring 100g of identical species are collected, launched into a box having 50ml of lukewarm water (37 - 40 C) and agitated for two minutes. Then earthworms are taken out and washed in another 50ml of water at room temperature for two mins and released lower back into tanks. Dilute 1 litre of vermi-wash with four-five liters of water and spray as foliar spray at some stage in the overdue night hours. A aggregate of vermi-wash (1 liter) with cow urine (1 liter) in 10 liters of water acts as bio-pesticide cum liquid manure.

(xii) Panchgavya:

Panchagavya, a natural guidance, may be used to decorate mulberry increase and yield. research have proven that foliar sprays of Panchagavya can appreciably increase the wide variety of leaves and branches in mulberry plants. Additionally, it can assist manage pests and enhance overall plant fitness. Panchagavya is a well recognized organic product which plays primary role in selling boom and immunity in plant gadget. Panchagavya is prepared the use of five cow merchandise viz., cow dung (7kg), cow urine (10 liters), milk (three liters), curd (2 liters), ghee (1kg) and different ingredients viz., jaggery (3kg), properly ripened poovan banana (1 dozen), tender coconut water (three liters) and undeniable water (10 liters). to begin with, cow dung and ghee are mixed very well in a plastic box and stirred once at morning and night hours for 3 days. Then it is brought with cow urine & water and allowed for 15 days with regular stirring as above (Venkataramana, P., et. al., 2009). After 15 days, milk, curd, tender coconut water, jaggery and banana are combined. Panchagavya may be geared up after 30 days. The field should be stored below color and blanketed with a wire mesh or mosquito internet to save you development of housefly maggots within the solution Panchagavya has all macro and micro nutrients aside from the increase hormones (IAA and GA) essential for manufacturing of quality mulberry leaves.

Figure 9: Panchagavya Preparation for spraying on the mulberry leaf

It holds low pH fee due to the production of natural acids by using the fermentative microbes. Lactobacillus gift in the panchagavya produces numerous useful metabolites such as natural acids, hydrogen peroxide and antibiotics, which might be powerful towards pathogenic microorganisms. Impact of leaf extracts and panchagavya foliar spray on mulberry plant characters, yield and resultant seed, leaf and end result nice of morus concludes that the foliar spray of panchagavya three% increases the plant characters, yield attributes and resultant seed, leaf and fruits traits. This boom changed into due to the presence of mulberry plant growth substance, growth enzymes, cow dung in panchagavya acts as a medium for the increase of useful microbes, vitamins found in panchagavya and presence of numerous amino acids, nutrients and increase regulators. hence foliar spray of panchagavya three% which suits for growing the mulberry plant characters, yield and resultant seed, leaf and fruits qualities of Morus.

(xiii) Recycling and Utility of Sericulture Wastes:

About 12-15 MT of sericulture waste comprising silkworm litter, leftover mulberry leaves, tender twigs, farm weeds and so forth., are being obtained from one hectare of mulberry lawn annually which have top notch manorial fee of nitrogen (280-300kg), phosphorus (ninety-100 kg) and potash (150-two hundred kg) as well as micronutrients like iron, zinc, copper and so forth., while properly composted and it's far determined to be tons superior in comparison to farmyard manure.

(xiv) Composting:

Composting is a microbial conversion of biodegradable natural wastes into a solid product called humus with the aid of indigenous micro-plants found in nature the use of a easy approach. All sericulture wastes may be converted into compost wealthy in nutrient cost in addition to the load of beneficial micro-organisms. pits, size of 3x1x1m are ok to get hold of sericulture wastes from

01acre of mulberry plantation. Sericulture wastes like silkworm muddle, left over mulberry leaves weeds etc., are amassed in the pit and fresh cow dung or biogas slurry mixed in a bucket of water is sprinkled over the layer after each series. at the give up of rearing, all left over leaves from the lawn along with the pruned mulberry twigs are brought to the pit and compacted with mud. A consortium of lignocelluloses decomposing fungi like Aspergillus sp., T richoderma sp., and Belaromyces sp., be brought @ 1kg / MT of sericulture waste to speed up the decomposing procedure terrific phosphate will also be mixed to complement the compost (Vivek Uppar and Rayar, S. G., 2014). when the pit is filled to a peak of 30-40 cm above the floor level, it is plastered with 2.five cm layer of a combination of dust and cow dung and allowed for composting. Thatch the shed to protect the compost pit from rain and direct sunlight.

(xv) Vermi Composting:

A thatched shed of approximately 7.5 x 6.0 meters size on a slightly elevated floor is enough for making use of sericultural waste from one hectare mulberry area. All round the shed stone bund is to be organized to save you infestation of predators. In the shed, eight trenches measuring 2.4 x 0.6 x zero.45 meters in two rows of 4 trenches every side are made and coated with polythene sheet. For each tone of waste blend five kg cow dung / biogas slurry in a hundred liters of water in an open pit and permit for about 7-10 days for partial decomposition. Later, fill each trench with 200-300 kg of semi-decomposed sericultural waste having 30-forty% moisture. Introduce a blended tradition of earthworms into the feed @ 1.five kg/MT of waste and go away for 6-7 weeks. Sprinkle water often to hold moisture around 30-40%. After 6-7 weeks, the casts seem as loose granules. Harvest the vermi-compost and sieve via cord mesh to split earthworms.

5. Future Trends and Research:

The grassroots improvements are technical or preferred solutions to simple issues faced by way of silkworm rearers, reelers, mulberry growers, which are related to the sericulture enterprise. innovations at grassroots degree can be beneficial in analyzing the genetics of silkworm which plays substantial position in enhancing the traits of silkworm by means of biotechnological techniques. It presents an facet for greater advanced innovations with sizable balance between innovation and lifestyle by using making use of the accuracy and efficiency of advanced equipment. it may serve as bedrock in retaining the cultural legacy related with conventional methods employed in unique sectors of sericulture. the present want of sustainable silk manufacturing approaches can be achieved by way of ecofriendly techniques evolved as grassroots innovation (Seyfang and Smith 2007). usage of biodegradable and recyclable substances in equipment, discount in electricity consumption and waste technology at some stage in silk reeling can make contributions to extra sustainable silk enterprise (Moriwaki, 2018). The advancement of rearing strategies and modernizing of silk production processes and mechanization can boom silk output at minimum labour work and charges (Mwasiagi *et al.,* 2012). Consequently, may also contribute to increased silk manufacturing and development in excellent of silk.

Destiny trends in organic mulberry farming emphasize sustainable practices and increasing leaf high-quality for more desirable silkworm rearing. research is that specialize in optimizing organic nutrient management, growing disorder-resistant mulberry varieties, and exploring progressive strategies like precision agriculture to improve both mulberry and silk manufacturing whilst minimizing environmental effect. This consists of selling organic silk production and adopting round economic system concepts in the sericulture industry. Sericulture is an industry with deep economic, cultural, and social significance in lots of areas during the arena. The legal guidelines and regulations that control the sericulture commercial enterprise has a significant effect on how the arena is fashioned, affecting the entirety from international exchange to production strategies. Sericulture is vital in worldwide and local economies and the want for a strong policy and regulatory surroundings. This lays the basis for comprehending the function of global organizations and the government in sericulture, as well as how regulations can assist or harm the growth of the silk enterprise. There are many regulations related to sericulture improvement and help includes authority's projects in research and improvement, subsidies and monetary resource for silk farmers. The legal shape controlling the safety and satisfactory necessities within the silk enterprise is any other essential element. Standards for processing silk, exceptional manipulate techniques, and legal guidelines governing using chemicals and pesticides in mulberry farming are all covered in this. The international change policies affecting the silk enterprise encompass alternate agreements, non-price lists, and tariff obstacles that affect the worldwide silk marketplace. These policies have predominant effect on silk exports and imports, as well as on domestic silk industries. The regulatory framework related to exertions and moral practices in sericulture which incorporates laws and guidelines concerning labor rights, working situations, and honest alternate practices inside the silk enterprise. Sericulture's policy and regulatory frameworks face a number of problems, together with coordinating rules at the country wide and global levels and aligning them with social and environmental goals in addition to technological improvements.

Conclusion:

Silk is understood for its ethnicity and luxurious and has been a valued fabric within the textile industry for hundreds of years. In latest years, the market trends and possibilities of consumers in silk merchandise have passed through extensive adjustments. These changes are tormented by factors which includes technological advancements, sustainability worries, new fashion tendencies, and changing socio-economic situations. The ancient significance of silk and its evolution are in the global marketplace units the degree for know-how the modern-day function of marketplace of silk products and the factors that have an effect on purchaser selections.

Sustainability has a main impact on consumer possibilities in silk products. As environmental awareness and ethical issues are getting greater critical, customers are increasingly more wanting sustainable and ethically produced silk. A vital factor of this research is how silk items are laid low with technological changes. The possibilities for silk products have accelerated thanks to advancements in digital printing, fabric technology, and fabric manufacturing. Patron preferences also are modified by way of cultural and new fashion traits. There are some demanding situations and opportunities inside the silk industry in response to these converting market developments and patron options which encompass the want for product layout innovation and advertising strategies, the ability of online retail and direct-to-consumer fashions, and the demanding situations of opposition from artificial options. The field of sericulture has proven a dynamic transformation inside the last little a long time. This has been stimulated considerably by innovative studies, technological innovations, and evolving new marketplace demands among clients globally. The rising new trends together with genetic engineering for advanced silk best, sustainable and silk manufacturing, journal of Survey in Fisheries Sciences and diversification into non-textile programs, and so forth. Verify capability for increase of this quarter. Moreover, there are big future possibilities for improving silk pleasant and characteristics, developing more effective sericulture strategies, and investigating novel packages in the biomedical, beauty, and electrical industries. Specific technology like artificial intelligence (AI) and the net of factors (IoT) can enhance fine of silk through sustainable and green techniques. Similarly, authority's regulations that desire innovation and lengthy-term boom in sericulture have to be applied, in addition to collaboration a few of the intellectual, medical, and commercial communities shall be stimulated. It isn't always simplest contributing to the textile enterprise but also useful appreciably for different industries like Biotechnology, prescribed drugs, and the biomedical industries. The sericulture zone is likewise relevant new numerous developments globally and is believed to have a bright destiny in advance of it. With the aid of the powerful utilization of organic sources great mulberry leaf may be received, which might be wealthy in nutrient contents and unfastened from pest and ailment incidence. Development within the biochemical materials of mulberry by the software of natural vitamins increases the rearing parameters, cocoon parameters and submit cocoon parameters of the silkworm. Consequently we can enhance the sericulture and silk productivity to more quantity. Natural nutrients in sericulture are in neonate degree and calls for complete and multidimensional approach to maximize the sericulture productivity. The statistics on possible utilization of biogas spent slurry, coir pith compost, press mud and urban stable compost is scanty and desires further observe in this path huge scale trails can be essential to layout the proportion of natural source to be carried out to mulberry gardens of various soils of various agro climatic zones.

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CULTIVATING THE FUTURE: ADVANCES, APPLICATIONS, AND CHALLENGES IN CELLULAR AGRICULTURE

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Abstract:

The rising global demand for sustainable food, materials, and bio-based products has positioned cellular agriculture as a viable alternative to conventional farming. This field focuses on producing agricultural goods by cultivating cells and tissues, instead of entire plants or animals. Cellular agriculture includes cellular approaches, such as cultured meat developed using scaffolds and growth media, and acellular methods, which employ engineered microbes to produce compounds like casein, collagen, and bioactives through precision fermentation. These innovations address ethical, environmental, and resource-related concerns linked to traditional agriculture. Additionally, cellular agriculture supports the creation of biofabricated materials and plant-based compounds for nutraceutical and pharmaceutical applications. Despite notable progress, challenges remain in cost, scalability, regulation, and consumer acceptance. This chapter explores key technologies, cellular and acellular products, scaffold materials, and product applications, while highlighting the major challenges and future prospects of this evolving and impactful field.

Introduction:

The growing worldwide need for food, materials, and bio-based products is being driven by rapid population growth, urban expansion, and evolving dietary preferences. Traditional agricultural systems are facing growing pressure not just to increase production, but also to address escalating concerns related to environmental impact, ethics, and long-term sustainability. In this context, cellular agriculture has emerged as a transformative approach that aims to produce agricultural products such as meat, milk, eggs, leather, and bioactive compounds through the cultivation of cells and tissues, rather than whole plants or animals (Post, 2012; Chriki & Hocquette, 2020).

Cellular agriculture involves two main approaches: acellular production, using engineered microbes to produce compounds like casein and collagen, and cellular production, which grows animal or plant cells into tissues like cultured meat (Stephens *et al.,* 2018). Enabled by synthetic biology and bioprocessing, the field is advancing rapidly, with precision fermentation already producing animal-free dairy proteins and functional ingredients (Tubb & Seba, 2019).

Moreover, companies are producing bio fabricated materials such as leather, spider silk, and cosmetics using similar principles. At the same time, cultured meat also known as lab-grown or in vitro meat is progressing from proof-of-concept prototypes to regulatory approval and limited commercialization (Bhat *et al.,* 2010). Plant cell and tissue cultures also offer immense promise, providing bioactive molecules for nutraceutical, cosmetic, and pharmaceutical use (Smetanska *et al*., 2008)

As the world looks to reduce its environmental footprint and develop alternative protein and material sources, cellular agriculture offers a compelling solution. However, despite its potential, the sector faces significant technical, economic, regulatory, and social challenges. This chapter explores recent advancements in cellular agriculture, with a focus on the production technologies, scaffold development, culture media, and product applications of both plant- and animal-based cell and tissue cultures, while also addressing the limitations and future outlook of this emerging field.

Acellular and Cellular Products in Cellular Agriculture

Acellular products represent a significant advancement in cellular agriculture, focusing on the production of specific biomolecules rather than whole cells or tissues. These products are synthesized using genetically engineered microorganisms such as bacteria, yeast, or fungi that are programmed to produce target compounds like casein, whey, collagen, egg white proteins, gelatin, and even fats. This process, known as precision fermentation, enables the production of animal-free alternatives with identical molecular structures to their animal-derived counterparts. Acellular production offers numerous advantages, including scalability, reduced resource usage, and elimination of animal cruelty. These products are already being used in food (e.g., dairy-free cheese, egg substitutes), cosmetics, textiles, and pharmaceuticals (*Ruggera et al., 2023; Nielsen & Meyer, 2024)*. This technology offers environmental and ethical benefits by avoiding animal husbandry while maintaining

Acellular products derived through cellular agriculture represent a transformative approach to producing animal-free functional ingredients, particularly in the dairy sector. Unlike cultured meat, these products are synthesized without growing entire cells or tissues, often using microbial hosts engineered via synthetic biology or precision fermentation techniques. One of the most promising applications lies in the production of bioactive components of human milk, such as human milk oligosaccharides (HMOs) and lactoferrin, which are critical for infant nutrition and immune development. These components are being produced using microbial fermentation systems and mammary gland organoid models, offering a sustainable and ethical alternative for infants who cannot be breastfed. Cellular agriculture not only addresses issues of ingredient safety and supply security but also enables the customization of functional ingredients to meet specific nutritional needs (Yart *et al*., 2023)

Cellular products in cellular agriculture involve culturing whole animal or plant cells to create structured food products—such as cultured meat, fish, and plant cell–based ingredients—unlike acellular products, which are isolated molecules (Stephens *et al.,* 2018). This process typically uses stem cells or muscle satellite cells harvested from donor animals. These cells are then proliferated and differentiated in controlled bioreactors with scaffolding materials designed to mimic the texture and structure of muscle tissue (Frontiers *et al.,* 2023;

Cellular products in cellular agriculture encompass the cultivation of whole animal or plant cells to produce structured foods such as cultured meat, seafood, and plant tissue–based ingredients. This approach starts with stem cells or satellite cells harvested from donor animals or plants, which are then expanded and differentiated within bioreactors to build tissue-like structures (Chang Ge *et al.,* 2023). To replicate the complex texture and alignment of muscle, these cells are often seeded onto biocompatible scaffolds or grown on microcarriers that mimic the extracellular matrix, supporting cell adhesion, proliferation, and maturation (Kulus *et al.,* 2023). Advances in scaffold engineering including edible materials, decellularized plant tissues, and 3D-bioprinted frameworks enable the formation of fibrous structures that closely resemble conventional meat in texture and mouthfeel (Wang *et al.,* 2023). Despite these promising innovations, significant challenges remain particularly in scaling production, reducing costs, and perfecting sensory attributes to rival traditional meat cuts (Chang Ge *et al.,* 2023) As research progresses, cellular products are poised to become viable alternatives to animal farming, offering ethical and environmental benefits through precision-engineered bioprocessing

Cultured Meat as a Cellular Product

Cultured meat, the leading product of animal cell and tissue culture based cellular agriculture, includes various forms such as lab-grown beef, poultry, and fish (Rubio *et al.,* 2019). This meat is primarily derived from skeletal muscle cells, but also incorporates other essential cell types like adipocytes, red blood cells, fibroblasts, endothelial cells, and leukocytes that contribute to the texture, flavor, and nutritional profile of conventional meat (Datar & Betti, 2010). These cell types are cultivated in vitro and assembled into three-dimensional tissue structures to closely mimic the sensory experience of traditionally produced meat. By replicating the biological complexity of real meat including connective tissue and vascular networks cell-based meat technologies strive to match both the taste and nutrient content of animal-derived products. Commonly referred to as cultured, clean, or in vitro meat, these innovations offer a promising alternative to conventional meat production, aiming to reduce environmental impacts and improve food safety while preserving the sensory qualities consumers expect

Despite promising advancements, commercially available animal cell and tissue culture-based meat products have not yet reached widespread market shelves. Early prototypes such as Mosa Meat's cultured beef burger, JUST's chicken nuggets, Avant Meats cultivated fish maw, and

Vow's kangaroo dumplings have been introduced only recently at public and media events. As of 2019, a global overview by Crosser *et al*. (2020), published by the Good Food Institute, reported that over 40 companies across 19 countries were actively developing cultured meat and seafood. About one-third of these companies are based in the United States. Current strategies for production primarily fall into three technological categories: **(a)** bioprinting or organ printing; **(b)** self-organizing tissue engineering; and **(c)** cell culture methods utilizing scaffolding systems. These diverse approaches aim to optimize texture, scalability, and cost-efficiency in replicating the structure of conventional meat products.

Bioprinting technologies also known as organ printing enable the fabrication of biological tissue structures that replicate the anatomical and functional characteristics of native tissues (Gillispie *et al.,* 2019). This approach holds particular promise for cultured meat production, as it can reproduce meat-like features such as texture, vascular networks, and fat marbling, thereby enhancing both visual appeal and sensory experience (Bhat *et al.,* 2017; Boland *et al.,* 2003).

Similar to bioprinting, the self-organizing tissue culture approach allows for the development of complex 3D meat structures, including steak-like products. This technique involves the spontaneous aggregation and alignment of muscle cells into tissue-like forms without the need for scaffolding. A landmark study by Benjaminson *et al*. (2002) demonstrated the feasibility of this method by culturing skeletal muscle explants from goldfish. By optimizing the culture media, they were able to increase the tissue surface area by 13% to 79% within one week. Remarkably, the resulting tissue resembled a fish fillet and received positive sensory feedback from a taste-testing panel. However, a major limitation of meat produced using the self-organizing method is the lack of vascularization and intramuscular fat marbling, which are critical to replicating the taste and texture of conventional meat. A similar limitation applies to meat produced via cell culture with scaffolding, although this latter method is more amenable to scale-up for commercial production

Scaffold Materials Used in Cellular Agriculture

Scaffold materials are foundational in cellular agriculture, providing the structural framework required for cultivating tissue-like products. Natural polymers such as chitosan, alginate, collagen, and gelatin are favored for their excellent biocompatibility, edibility, and capacity to replicate extracellular matrix (ECM) environments. Li *et al*. (2022) reported a 3D-printed edible scaffold composed of chitosan sodium alginate collagen/gelatin that supported porcine muscle satellite cell adhesion, proliferation, and differentiation, ultimately producing a meat-like construct with realistic texture and appearance.Furthermore, Wang *et al*. (2024) fabricated a gelatin/alginate/ε-poly-L-lysine (GAL) hydrogel with a Young's modulus of approximately 11 kPa, closely matching muscle tissue stiffness, and demonstrated its suitability for 3D printing with high cell viability and early-stage myogenesis in both mouse C2C12 and porcine muscle stem cells.Synthetic polymers, including PLGA and PEG, enable precise tuning of mechanical strength and degradation rates. While specific studies in cellular agriculture are pending, tissue engineering research highlights PLGA's customizable non-toxic degradation profiles and PEG's FDA-approved biocompatibility, albeit requiring functionalization to support cell adhesion. Advances in 3D bioprinting and biomimetic design technologies allow meticulous control over scaffold geometry, porosity, and anisotropic properties, closely emulating native tissue structures. Alginate-gelatin blends supplemented with nanocellulose have especially proven effective in recapitulating muscle tissue architecture with structural integrity and favourable cell viability (Chawla *et al*.,2020). These scaffolds are both edible and biodegradable, eliminating the need for removal post-harvest and conforming to food safety protocols. Despite significant progress, the industry faces ongoing challenges in optimizing the balance between mechanical integrity, biodegradability, cell compatibility, and economic scalability to realize industrial-scale applications in cellular agriculture.

Benefits of Cellular Agriculture

Reduction of greenhouse gas emission: One of the most significant environmental advantages of cellular agriculture is its potential to dramatically reduce greenhouse gas emissions compared to conventional livestock farming. Traditional animal agriculture is a major contributor to methane, nitrous oxide, and carbon dioxide emissions due to factors such as enteric fermentation, manure management, feed cultivation, and transportation. In contrast, cultured meat and acellular products require far fewer inputs no grazing land, fewer animals, and less water and feed resulting in a significantly smaller carbon footprint. According to life cycle assessments, cultured meat production may generate up to 78–96% fewer greenhouse gas emissions depending on the production method and energy sources used (Tuomisto & de Mattos, 2011). As the global demand for protein continues to grow, adopting cellular agriculture could play a crucial role in mitigating agriculture-related climate change impacts.

Another key benefit of cellular agriculture is its potential to promote long-term environmental sustainability by offering a resource efficient alternative to traditional animal farming. Producing animal products through cell culture or precision fermentation requires significantly less land**,** water, and feed, reducing pressure on natural ecosystems. This approach helps mitigate major environmental concerns such as deforestation; biodiversity loss, water scarcity, and land use conflicts often associated with industrial livestock operations. For example, estimates suggest that cultured meat could reduce land use by up to 99% and water use by up to 96% compared to conventional beef production (Tuomisto & Teixeira de Mattos, 2011). As the global population grows and demand for animal protein increases, cellular agriculture presents a scalable, sustainable solution to meet food security needs without overburdening planetary resources. (Tuomisto & de Mattos, 2011). cellular agriculture offers a promising alternative to traditional livestock farming by addressing several ethical, environmental, and public health concerns. One of its most notable advantages is the potential to improve animal welfare**,** as it eliminates the need for confining or slaughtering animals' practices often associated with pain, stress, and disease in conventional farming systems. Instead, animal cells are cultured in controlled environments that provide ideal conditions for growth and differentiation. This controlled setting also contributes to a significant reduction in antibiotic use, as the sterile conditions eliminate the need for growth-promoting or disease-preventing drugs, which are heavily used in animal farming and linked to rising antibiotic resistance. Furthermore, because cellular agriculture is free from fecal contamination and zoonotic exposure, it greatly reduces the risk of foodborne illnesses such as *E. coli* and *Salmonella*. In terms of environmental impact, lab-based cultivation of cells demands less water and land than conventional meat production, which traditionally requires large-scale grazing, irrigation, and feed cultivation. Lastly, because cultured meat can be engineered under tightly regulated conditions, it may offer improved nutritional profiles without the need for antibiotics, hormones, or environmental contaminants often present in animal-derived meat (Post *et al.,* 2020).

Challenges of Cellular Agriculture

Cellular agriculture, despite its potential, faces several critical challenges that hinder its widespread adoption. High production costs remain a major barrier, driven by expensive bioreactors, growth media, and ongoing research and development efforts. Optimizing cell growth and differentiation is another complex issue, requiring precise control over environmental conditions to mimic natural tissue formation. Additionally, the field must navigate regulatory uncertainties related to food safety, labeling, and approval processes, as current frameworks are not fully equipped to govern lab-grown products. Scalability is also a concern, as production must expand dramatically to meet global demand. Consumer acceptance remains a significant challenge, as doubts persist regarding the taste, texture, and nutritional benefits of these products. Despite being promoted as environmentally friendly, the industry continues to face issues related to high energy and water usage, as well as sourcing truly sustainable raw materials. Furthermore, disputes over intellectual property rights surrounding key technologies have sparked concerns about equitable market access, collaboration in innovation, and maintaining fair competition within this developing field.

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INTERDISCIPLINARITY

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Interdisciplinarity is a fundamental concept in modern life sciences, representing a shift from siloed disciplinary approaches to a more integrated and holistic understanding of complex biological systems and problems.

What is Interdisciplinarity?

At its core, Interdisciplinarity involves the combination of methods, insights, and perspectives from two or more distinct academic disciplines to pursue a common task, such as a research project, problem-solving, or education. It essentially means "working between different academic disciplines."

Rather than staying within the confines of a single field (e.g., pure biology, pure chemistry), interdisciplinary work seeks to bridge traditional boundaries to address issues that cannot be adequately understood or solved by one discipline alone.

Key Aspects of Interdisciplinarity:

- **Integration of Knowledge**: It's not just about juxtaposing different fields, but actively synthesizing knowledge, concepts, theories, and methodologies from various disciplines to create a more comprehensive framework.
- **Addressing Complex Problems**: Many of the world's most pressing challenges – from climate change and global pandemics to neurodegenerative diseases and sustainable development – are inherently complex and transcend disciplinary borders. Interdisciplinarity provides the necessary tools to tackle these "grand challenges."
- **New Perspectives and Insights**: By bringing together experts with different backgrounds, interdisciplinary collaboration can lead to novel questions, innovative experimental designs, and breakthrough discoveries that might not emerge from a single-discipline approach.
- **Holistic Understanding**: It fosters a more complete and nuanced understanding of phenomena, as it considers multiple facets and levels of analysis. For example, understanding a disease might require biological, genetic, environmental, social, and even economic perspectives.

Examples of Interdisciplinarity in Modern Life Sciences:

The life sciences are a prime example of a field where Interdisciplinarity is not just beneficial, but often essential. Here are some key areas:

- **Systems Biology**: This field explicitly integrates biology with mathematics, computer science, engineering, and physics to model and understand biological systems as a whole, rather than focusing on individual components in isolation. It uses computational tools to analyze vast amounts of "omics" data (genomics, proteomics, metabolomics, etc.).
- **Bioinformatics and Computational Biology**: These disciplines merge biology with computer science, statistics, and information technology. They are crucial for managing, analyzing, and interpreting the massive datasets generated by modern biological research (e.g., DNA sequencing, protein structures, gene expression profiles).
- **Biophysics:** This field applies principles and methods of physics to study biological phenomena. Examples include using X-ray crystallography to determine protein structures, developing advanced microscopy techniques, or understanding the mechanics of cells and tissues.
- **Biomedical Engineering**: This involves applying engineering principles and design concepts to medicine and biology for healthcare purposes. This includes developing medical devices, diagnostic tools, biomaterials, and regenerative medicine strategies.
- **Synthetic Biology**: This combines biology with engineering to design and construct new biological parts, devices, and systems, or to re-design existing natural biological systems for useful purposes (e.g., creating microbes that produce biofuels or drugs).
- **Neuroscience**: Understanding the brain requires insights from biology, psychology, computer science, physics, chemistry, and medicine. Researchers study everything from molecular mechanisms of neurons to complex cognitive functions.
- **Environmental Science/Ecology**: Addressing environmental issues often requires integrating biology, chemistry, geology, social sciences, economics, and policy studies.

Benefits of Interdisciplinary Research:

- **Solves Complex Problems**: Enables a more comprehensive approach to tackling intricate real-world issues.
- **Fosters Innovation and Creativity**: Different perspectives spark new ideas, methodologies, and solutions.
- **Bridges Knowledge Gaps**: Connects disparate areas of knowledge, leading to a more complete picture.
- **Enhances Critical Thinking**: Researchers learn to evaluate conflicting viewpoints and synthesize diverse data.
- **Greater Societal Impact**: Leads to more robust, applicable, and effective solutions for societal challenges.
- **New Research Avenues**: Opens up entirely new fields of study and research questions.

Challenges of Interdisciplinary Collaboration:

Despite its benefits, Interdisciplinarity comes with its own set of challenges:

- **Communication Barriers**: Different disciplines often have their own jargon, terminology, and ways of thinking, which can lead to misunderstandings.
- **Cultural Differences**: Academic cultures can vary significantly between fields, affecting collaboration styles, publication norms, and funding priorities.
- **Methodological Differences**: Integrating diverse methodologies (e.g., qualitative vs. quantitative, experimental vs. theoretical) can be complex.
- **Funding Structures**: Traditional funding bodies are often structured along disciplinary lines, making it challenging to secure funding for truly interdisciplinary projects. * **Publication and Peer Review**: Finding appropriate journals and reviewers who understand and can assess research from multiple disciplines can be difficult.
- **Evaluation and Promotion**: Academic promotion and tenure systems may not always adequately recognize or reward interdisciplinary contributions, which might not fit neatly into a single department's metrics.
- **Time and Resource Constraints**: Building effective interdisciplinary teams and projects often requires significant time investment in understanding each other's fields and establishing common ground.

In conclusion, Interdisciplinarity is a driving force in modern life sciences, essential for addressing the intricate challenges and unlocking the vast potential of biological discovery and application. While it presents challenges, the benefits of combining diverse expertise far outweigh the difficulties, leading to more profound insights and impactful solutions.

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DRUG-INDUCED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Abstract:

Drug-induced hemophagocytic lymphohistiocytosis (DI-HLH) is an uncommon yet life-threatening hyperinflammatory condition that arises secondary to exposure to pharmacologic agents. It is classified under secondary HLH and is marked by an uncontrolled and dysregulated immune response involving cytotoxic T lymphocytes (CTLs), natural killer (NK) cells, and activated macrophages. These immune cells, under normal physiological circumstances, maintain immune homeostasis through cytolytic granule-mediated apoptosis. However, in DI-HLH, either due to genetic predisposition, immune hypersensitivity, or direct pharmacologic stimulation, this regulatory balance is lost, resulting in sustained immune activation and excessive cytokine release—a phenomenon often referred to as a cytokine storm.

Several drug classes have been implicated in triggering DI-HLH, with antiepileptics (such as lamotrigine and phenytoin), antibiotics (especially sulfonamides and beta-lactams), immune checkpoint inhibitors (like nivolumab and pembrolizumab), and biologics (e.g., infliximab, etanercept) being the most frequently reported. These medications may act as haptens, stimulate toll-like receptors, or disrupt immune checkpoints, all of which can lead to excessive T-cell and macrophage activation. The clinical presentation of DI-HLH is variable and can closely resemble other systemic conditions such as sepsis, malignancy, or autoimmune disease flares, thereby posing a diagnostic challenge. Key clinical features include persistent high-grade fever, hepatosplenomegaly, pancytopenia, coagulopathy, liver dysfunction, neurological involvement, and marked hyperferritinemia, often exceeding 10,000 ng/mL.

Timely diagnosis is critical and typically relies on the HLH-2004 criteria and/or the more recently developed HScore, which includes clinical, laboratory, and histopathological parameters. Early recognition and immediate cessation of the suspected causative drug are essential first steps in management. Immunosuppressive therapy—most commonly with high-dose corticosteroids—forms the cornerstone of treatment. In severe or refractory cases, etoposide and cyclosporine A may be required to suppress activated immune cells. Novel targeted therapies, such as IL-1 receptor antagonists (anakinra) and IL-6 inhibitors (tocilizumab), are increasingly being explored for their ability to modulate the inflammatory response with fewer systemic side effects.

Supportive care remains vital, including transfusions for cytopenias, organ support in intensive care settings, and management of metabolic derangements. In this complex therapeutic landscape, clinical pharmacists play a critical role—not only in adverse drug reaction (ADR) reporting and causality assessment—but also in monitoring drug interactions, identifying hypersensitivity patterns, and guiding safe re-exposure decisions where necessary. This chapter aims to provide a comprehensive overview of DI-HLH, including its pathophysiology, epidemiology, clinical presentation, diagnostic challenges, implicated drugs, therapeutic interventions, prognosis, and future directions. Real-world case insights further illustrate the urgency of early detection and multidisciplinary management in improving patient outcomes.

Introduction:

Hemophagocytic lymphohistiocytosis (HLH) is a rare, hyperinflammatory syndrome characterized by excessive and dysregulated immune activation that results in uncontrolled proliferation and activation of cytotoxic T lymphocytes (CTLs), natural killer (NK) cells, and macrophages. This hyperactivation leads to an overproduction of proinflammatory cytokines such as interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and soluble interleukin-2 receptor (sCD25), culminating in a cytokine storm and rapid progression to multiorgan dysfunction and failure if not promptly treated [1,2].

HLH can be broadly classified into two main categories: primary (familial) and secondary (acquired). Primary HLH is typically diagnosed in infancy or early childhood and is associated with inherited genetic mutations that impair the cytotoxic function of immune cells, including mutations in genes such as PRF1, UNC13D, STX11, and STXBP2 [3]. In contrast, secondary HLH, which is more commonly observed in adolescents and adults, arises in the context of an external trigger, such as infections (especially Epstein–Barr virus, cytomegalovirus, and tuberculosis), autoimmune diseases (systemic lupus erythematosus, adult-onset Still's disease), malignancies (especially lymphomas), or pharmacologic agents [4,5].

Among the secondary causes, Drug-Induced HLH (DI-HLH) is increasingly recognized as a critical but underdiagnosed etiology, particularly in adult patients. In DI-HLH, the inciting factor is a drug or class of drugs that either directly stimulates aberrant immune responses or alters immune regulation in genetically or immunologically predisposed individuals. The mechanism may involve drug hypersensitivity reactions, formation of reactive metabolites, or immune checkpoint modulation leading to uncontrolled T-cell activation and macrophage recruitment [6,7]. Antiepileptic agents such as lamotrigine and carbamazepine, antibiotics like sulfonamides and vancomycin, immune checkpoint inhibitors (e.g., nivolumab, pembrolizumab), and biologics (e.g., infliximab, etanercept) have all been implicated in published case reports and pharmacovigilance databases [8–10].

The clinical challenge with DI-HLH lies in its nonspecific presentation—often mimicking sepsis, drug hypersensitivity syndromes, or exacerbations of underlying inflammatory diseases. Symptoms such as prolonged high-grade fever, hepatosplenomegaly, cytopenias, hyperferritinemia, and liver dysfunction may overlap with other common clinical conditions, delaying diagnosis and appropriate intervention. Without timely recognition and treatment, DI-HLH carries a high risk of mortality due to rapid progression to systemic inflammation, coagulopathy, and multiorgan failure [11].

Thus, awareness of DI-HLH as a distinct and potentially fatal adverse drug reaction is essential in clinical practice. Early identification, prompt withdrawal of the offending agent, and initiation of immunosuppressive therapy are critical steps in management. Clinical pharmacists play a vital role in monitoring high-risk medications, facilitating early adverse drug reaction (ADR) reporting, and assisting in the multidisciplinary care of patients with suspected HLH.

Pathophysiology

Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome marked by the dysregulated activation of cytotoxic T lymphocytes (CTLs), natural killer (NK) cells, and macrophages. Normally, CTLs and NK cells eliminate infected or abnormal cells via perforin- and granzyme-mediated apoptosis, maintaining immune balance. However, in HLH, this cytotoxic function is impaired, either due to inherited mutations (e.g., *PRF1*, *UNC13D*, *STX11*, *STXBP2*) in primary HLH or due to secondary triggers such as infections, malignancies, or drugs. This results in sustained immune activation, leading to excessive release of proinflammatory cytokines like interferon-gamma (IFN-γ), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and soluble interleukin-2 receptor alpha (sCD25) [12–14]. These cytokines initiate a cascade that activates macrophages, which then begin engulfing hematopoietic cells in the bone marrow and organs, a process known as hemophagocytosis. The resultant cytokine storm leads to systemic inflammation, cytopenias, hepatosplenomegaly, coagulopathy, and potentially multiorgan failure [15–17].

In drug-induced HLH (DI-HLH), the pathophysiologic process is similar but initiated by pharmacologic agents. Offending drugs may act as haptens, binding to host proteins and forming immunogenic complexes that activate T-cells and macrophages. Others stimulate immune responses through Toll-like receptors (TLRs) or interfere with regulatory immune pathways. Notably, immune checkpoint inhibitors such as nivolumab and pembrolizumab can disrupt T-cell inhibition, provoking unchecked immune activation resembling HLH [18–20]. Additionally, common drugs like lamotrigine, carbamazepine, and sulfonamides have been implicated in triggering HLH through hypersensitivity reactions or by unmasking subclinical cytotoxic dysfunction. The end result in DI-HLH is an inability of the immune system to self-regulate after activation, causing persistent cytokine release and immune-mediated tissue damage if not promptly treated [21]

Epidemiology Hemophagocytic lymphohistiocytosis (HLH) is a rare but life-threatening disorder, with familial or primary HLH estimated to occur in approximately 1 in 800,000 individuals annually. This form typically manifests in infants and young children and is linked to mutations in genes critical to cytolytic function. In contrast, secondary HLH, including drug-induced HLH (DI-HLH), occurs predominantly in adolescents and adults. The actual incidence of DI-HLH remains elusive, as it is often underdiagnosed due to its overlapping clinical presentation with conditions such as sepsis, drug hypersensitivity reactions, autoimmune disease flares, and malignancy-related complications [22,23]. Although many DI-HLH cases present without identifiable genetic mutations, underlying immune dysregulation or subclinical cytolytic pathway defects may predispose susceptible individuals to this immune hyperactivation following drug exposure [24].

Most of the available epidemiological evidence for DI-HLH is based on individual case reports, case series, and pharmacovigilance data. A systematic review of 25 reported cases between 2003 and 2022 by Kim et al. revealed that antiepileptic drugs (e.g., lamotrigine, carbamazepine) and antibiotics (e.g., sulfonamides, beta-lactams) were the most frequently implicated agents. Immune checkpoint inhibitors, biologics, and chemotherapeutics also constituted notable but less frequent triggers [25]. The latency between drug administration and HLH onset varied from a few days to several weeks, complicating causality determination. Increasing awareness, along with the use of diagnostic aids such as the HLH-2004 criteria and HScore, has led to a rising number of reports submitted to FAERS and WHO's VigiBase [26,27]. However, the true prevalence remains underestimated due to misdiagnoses, the non-specific nature of early symptoms, and lack of routine hemophagocytosis identification in initial marrow biopsies [28]. DI-HLH affects both sexes and a broad age range, though middle-aged adults (30–60 years) are disproportionately represented in current literature. As immune-modulating therapies expand across specialties, particularly oncology, rheumatology, and dermatology, clinicians and clinical pharmacists must remain vigilant to ensure early detection, drug withdrawal, and initiation of life-saving therapy [29].

Drugs Implicated in Drug-Induced Hemophagocytic Lymphohistiocytosis (DI-HLH)

A wide range of pharmacological agents has been implicated in the development of DI-HLH. These agents span across multiple drug classes and typically share an ability to modulate or dysregulate immune pathways. The association between specific drugs and HLH is often identified through case reports, post-marketing surveillance, and adverse drug reaction databases. Notably, drug-induced HLH may occur even in previously healthy individuals without known immunodeficiency or genetic predisposition.

Antiepileptic Drugs

Antiepileptic medications are among the most frequently reported triggers of DI-HLH. Lamotrigine is particularly well-documented and has been associated not only with HLH but also with severe cutaneous adverse reactions (SCARs) such as Stevens–Johnson syndrome and drug reaction with eosinophilia and systemic symptoms (DRESS), suggesting a hypersensitivity-mediated mechanism. The latency period from drug initiation to symptom onset typically ranges from one to six weeks [30]. Carbamazepine and phenytoin have also been implicated in rare cases of DI-HLH. These agents are hypothesized to cause immune dysregulation through altered T-cell activation and inflammatory cytokine release [31].

Antibiotics

Antibiotics, particularly those associated with hypersensitivity reactions, are recognized as potential triggers of HLH. Among them, sulfamethoxazole-trimethoprim (SMX-TMP) has been most frequently implicated. It is thought to act via haptenization and subsequent T-cell sensitization, which leads to systemic immune activation [32]. Other antibiotics such as vancomycin and ceftriaxone have been reported in isolated cases, though the mechanism remains unclear. These may represent idiosyncratic reactions or secondary immunologic responses in predisposed individuals [33].

Immune Checkpoint Inhibitors

The introduction of immune checkpoint inhibitors (ICIs) has revolutionized cancer therapy but has also been associated with a range of immune-related adverse events (irAEs), including HLH. Drugs such as nivolumab and pembrolizumab, which inhibit the PD-1 receptor, effectively enhance T-cell activity against tumor cells. However, in certain patients, this can result in uncontrolled immune activation resembling HLH. These drugs remove the inhibitory "brakes" on the immune system, potentially triggering cytokine storms and macrophage hyperactivation [34].

Biologic Agents

Biologic therapies, particularly tumor necrosis factor-alpha (TNF-α) inhibitors, have been implicated in HLH, especially in patients with autoimmune or inflammatory disorders. Infliximab and etanercept, used to treat conditions such as rheumatoid arthritis and inflammatory bowel disease, have been associated with HLH in several reports. The mechanism may involve paradoxical immune activation or infection reactivation leading to secondary HLH [35].

Other Agents

Other drugs implicated in rare cases of DI-HLH include all-trans retinoic acid (ATRA), which is used in the management of acute promyelocytic leukemia. ATRA-related HLH may result from differentiation syndrome, which features cytokine overproduction and capillary leak. Additionally, drugs such as minocycline, azathioprine, and dapsone have been associated with HLH in isolated case reports. These agents likely trigger HLH through immunoallergic mechanisms or direct cytotoxic effects on immune cells, though more evidence is needed to clarify their role [36,37].

Clinical Manifestation

Drug-induced hemophagocytic lymphohistiocytosis (DI-HLH) typically manifests with an abrupt onset of systemic symptoms following exposure to a triggering medication. One of the earliest and most consistent features is a persistent high-grade fever exceeding 38.5°C, which may not respond to standard antipyretic or antimicrobial therapy. Patients often exhibit hepatosplenomegaly due to infiltration by activated macrophages, alongside pancytopenia—anemia, thrombocytopenia, and neutropenia—caused by both bone marrow suppression and peripheral destruction of blood cells. Liver dysfunction, reflected in elevated liver enzymes and bilirubin, may be an early sign of systemic involvement and can progress to hepatic failure in severe presentations [38,39]. Among laboratory markers, hyperferritinemia is especially significant, often with levels far exceeding 10,000 ng/mL, and serves as a surrogate for the underlying cytokine storm and macrophage activation. Additional findings may include elevated triglycerides, low fibrinogen, and increased D-dimer, indicating a coagulopathy that can evolve into disseminated intravascular coagulation (DIC) [40].

Cutaneous manifestations such as generalized rash—commonly morbilliform or maculopapular—are frequently observed in cases associated with antiepileptic drugs like lamotrigine or phenytoin and may overlap with drug hypersensitivity syndromes such as DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) [41]. Neurological symptoms, including altered sensorium, seizures, irritability, or even coma, are seen in some patients and often point toward central nervous system involvement. This may be confirmed by cerebrospinal fluid abnormalities or neuroimaging findings consistent with inflammation or demyelination. Importantly, these clinical features are nonspecific and can mimic severe infections, autoimmune flares, or sepsis, often leading to diagnostic delays. Therefore, early suspicion and investigation are critical in patients with recent drug exposure and progressive systemic illness, especially when traditional therapies fail to elicit improvement [42].

Management Strategies

The management of drug-induced hemophagocytic lymphohistiocytosis (DI-HLH) hinges on the urgent recognition and immediate cessation of the offending drug. Early discontinuation of the suspected agent is critical to halting the progression of immune hyperactivation and improving prognosis. Delay in drug withdrawal may result in irreversible organ damage and poor outcomes. Following drug discontinuation, immunosuppressive therapy forms the cornerstone of treatment. High-dose corticosteroids, such as dexamethasone, are considered first-line agents due to their broad anti-inflammatory effects and ability to suppress cytokine production. In cases where steroid monotherapy is insufficient—especially in patients with multiorgan involvement—

etoposide, a chemotherapeutic agent that targets activated lymphocytes and histiocytes, is employed. Cyclosporine A, a calcineurin inhibitor, may be added for further T-cell suppression and is typically used in combination regimens modeled on HLH-94 and HLH-2004 protocols [43,44].

Emerging therapies are gaining attention in refractory or cytokine-driven cases of HLH. Anakinra, an interleukin-1 (IL-1) receptor antagonist, and tocilizumab, an interleukin-6 (IL-6) receptor inhibitor, are increasingly used off-label in patients with HLH, particularly when a cytokine storm is suspected, and may offer targeted suppression with a better safety profile than traditional cytotoxic agents [45]. Supportive care is essential and includes transfusion of red cells or platelets to manage cytopenias, close monitoring and treatment of liver dysfunction, and intensive care unit (ICU) support in cases of hemodynamic instability or respiratory failure. Clinical pharmacists play an integral role in the multidisciplinary approach to DI-HLH by facilitating adverse drug reaction (ADR) reporting, evaluating potential drug–drug interactions, reviewing hypersensitivity histories, and counseling patients and clinicians on the risks of rechallenge or cross-reactivity with related agents [46]. The integration of pharmacovigilance data, clinical expertise, and early immunosuppressive intervention is essential to improving survival in DI-HLH.

Case Reports and Literature

Insights Individual case reports in recent literature provide valuable clinical insight into the spectrum and severity of drug-induced hemophagocytic lymphohistiocytosis (DI-HLH), particularly emphasizing the importance of early recognition and timely drug withdrawal. One well-documented case involved a 25-year-old female who developed high-grade fever, pancytopenia, and a generalized rash approximately three weeks after starting lamotrigine for mood stabilization. Bone marrow biopsy confirmed hemophagocytosis, and her symptoms resolved promptly following drug cessation and initiation of high-dose corticosteroids, underscoring the potential reversibility of DI-HLH when managed early [47]. Another noteworthy report described a patient with metastatic melanoma who developed HLH following treatment with nivolumab, a PD-1 immune checkpoint inhibitor. The case highlighted the expanding use of immunotherapies in oncology and their capacity to trigger severe immune dysregulation. The patient's condition improved after administration of high-dose steroids and supportive care, reinforcing the role of immune suppression in treating checkpoint inhibitor-induced HLH [48]. These reports illustrate that while DI-HLH is rare, heightened vigilance is crucial when initiating high-risk medications, especially those with known immunomodulatory properties.

Prognosis

The prognosis of drug-induced hemophagocytic lymphohistiocytosis (DI-HLH) largely depends on the timeliness of diagnosis and initiation of appropriate therapy. In the absence of treatment, HLH—whether primary or secondary—has a historically poor outcome, with reported mortality rates ranging from 50% to 70%, often due to rapid progression to multiorgan failure and overwhelming cytokine storm [49]. However, early recognition of the syndrome, prompt discontinuation of the causative agent, and the initiation of immunosuppressive therapy can significantly improve clinical outcomes.

Several prognostic indicators have been identified in the literature. Poor outcomes are more frequently observed in patients presenting with central nervous system involvement, prolonged diagnostic delays, or fulminant multiorgan dysfunction. Additionally, elevated levels of ferritin, persistent cytopenias, and refractory shock at presentation have been associated with increased mortality risk [50]. Although recent advances, including the use of cytokine-directed therapies and revised diagnostic criteria, have improved survival in some subsets, DI-HLH remains a medical emergency with a guarded prognosis. Long-term follow-up is often necessary to monitor for relapse, especially in patients with underlying immune dysregulation or recurrent exposure to high-risk drugs [51].

Future Directions

Advancing our understanding of drug-induced hemophagocytic lymphohistiocytosis (DI-HLH) will rely heavily on the integration of emerging diagnostics, precision medicine, and novel therapeutics. One promising area of development lies in the identification of more specific biomarkers. Traditional markers like ferritin and sCD25 lack disease specificity, whereas newer candidates such as CXCL9—a chemokine induced by interferon-gamma—and interleukin-18 (IL-18) have shown potential in enhancing diagnostic precision by directly reflecting macrophage and T-cell activation characteristic of HLH [52].

In parallel, the field of pharmacogenomics offers significant promise in uncovering individual susceptibility to DI-HLH. Genetic screening for polymorphisms or subclinical variants in genes involved in cytolytic granule function (e.g., PRF1, UNC13D) may help identify patients at higher risk when exposed to known trigger drugs. This personalized approach could enable preemptive risk mitigation strategies before initiating immunomodulatory or high-risk medications [53].

From a therapeutic standpoint, targeted immunomodulators are being actively investigated. Agents such as IL-18 binding protein (tadekinig alfa) aim to neutralize IL-18-mediated inflammation, while JAK inhibitors like ruxolitinib are showing promise in dampening downstream cytokine signaling, particularly in refractory or relapsing HLH cases [54]. As research evolves, integrating these targeted therapies with current treatment protocols may offer improved safety and efficacy, reducing the morbidity and mortality associated with DI-HLH.

Conclusion:

Drug-induced hemophagocytic lymphohistiocytosis is a life-threatening immunologic emergency that requires swift diagnosis and aggressive management. Although its rarity and clinical overlap with sepsis or autoimmune disorders make it a diagnostic challenge, awareness is increasing due to a growing body of case reports and expanded use of immunomodulatory therapies. Early withdrawal of the offending agent remains the cornerstone of treatment, followed by immunosuppressive and supportive therapies tailored to disease severity. Novel targeted treatments like anakinra and tocilizumab offer hope for improved outcomes, especially in refractory cases. Clinical vigilance, interdisciplinary collaboration, and real-time pharmacovigilance are critical in mitigating the morbidity and mortality associated with DI-HLH. As more potent drugs enter clinical practice, particularly in oncology and immunology, healthcare professionals must maintain a high index of suspicion for this rare but serious condition and ensure prompt therapeutic intervention.

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CONNECTING WITH AQUATIC LIFE: THE ROLE OF BIO-SENSING TECHNOLOGIES IN AQUACULTURE

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Abstract:

Aquaculture, the farming of aquatic organisms in controlled environments, faces numerous challenges due to biotic and abiotic stresses, poor water quality, and improper management. These issues adversely affect sustainability and productivity. Traditional monitoring techniques are resource-intensive and require skilled personnel, highlighting the need for more efficient solutions. Biosensors offer a promising alternative by enhancing detection capabilities, streamlining the monitoring process, and addressing the limitations of conventional methods. This approach could significantly improve the management and health of aquaculture systems, ultimately contributing to their success and resilience.

Keywords: Aquaculture, Health, Sustainability, Feeding strategies, Animal-Environment interaction

Introduction:

This massive advancement in aquaculture production surpassing capture fisheries is predominantly due to efficient management practices incorporated with advanced science and technology (United Nations). In 2022, the global production of aquatic animals reached a new world high of 185 million tonnes, an increase of 4 percent from 2020. Farming of aquatic animals produced an estimated 94 million tonnes, representing 51 percent of the total, surpassing for the first time capture fisheries, which produced 91 million tonnes (49 percent). Production from marine areas was 115 million tonnes. Inland waters contributed 70 million tonnes of which 84 percent was from aquaculture (FAO, 2024).

Efficient management practices include direct visual observations to assess the health and welfare of farmed animals. However, this is challenging in aquaculture, as the farmed animals live underwater. This challenge is further exacerbated by the ongoing intensification of the aquaculture industry, as many twenty-first-century farming operations contain populations of up to millions of individuals (FAO, 2024).

This problem has, to an extent, been over come in aquaculture through the use of optical (e.g. underwater cameras) and/or acoustic technologies (e.g. sonars and echo sounders). These technologies allow farmers to observe the behavioral responses of groups of farmed animals to environmental and/or anthropogenic perturbations within their enclosures (Føre M *et al*. 2018; Oppedal, 2011). However, such methods cannot track individuals over extended periods or provide additional insights into variables pertaining to the inner workings of the animal. These factors are crucial not only for assessing the health and welfare of farmed animals but also for evaluating the potential trade-offs that they fade in captivity (Andrewartha *et al.,* 2015).

The rapid development and miniaturization of bio-sensing systems present innovative and exciting tools for scientists seeking to address pertinent issues in aquaculture. Bio-sensing in the aquatic environment is based on equipping animals with electronic devices containing sensors capable of measuring environmental, behavioural and physiological variables such as temperature, dissolved gases, depth, acceleration, ventilation, heart rate and blood flow, as well as levels of glucose and L-lactic acid (Endo and Wu, 2019).

Biosensor

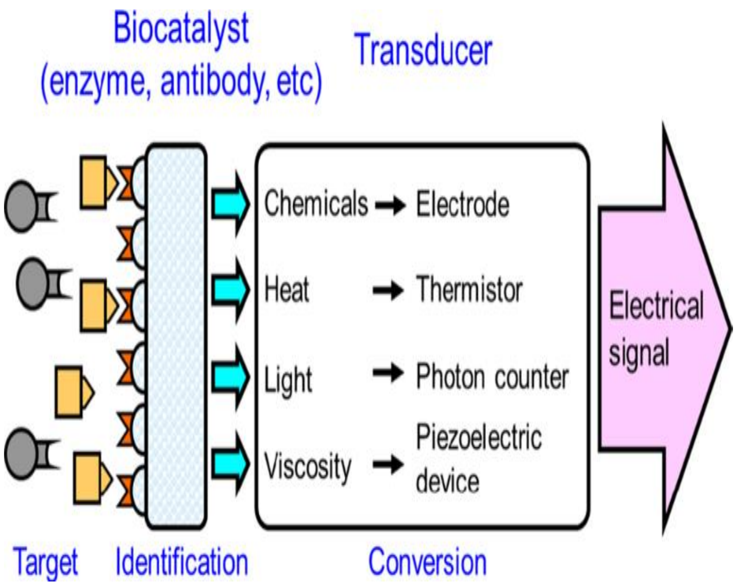
A biosensor is a chemical sensing device in which a biologically derived recognition entity is coupled to a transducer to allow the quantitative development of complex biochemical parameters. A biosensor is an analytical device incorporating a deliberate and intimate combination of a specific biological element (that creates a recognition event) and a physical element (that transduces the recognition event) (Mohanty and Kougianos, 2006).

The name "biosensor" signifies that the device is a combination of two parts:

1. **A Bio-Element:** A specific biological element (eg., antibody, living cells, enzyme) recognizes a specific analyte.
2. **A Sensor-Element:** The "sensor" element (electric current, electric potential) transduces the change in the biomolecule into an electrical signal.

Types

Source: Endo, H. and Wu, H., 2019. Biosensors for the assessment of fish health: a review. *Fisheries science*, *85*,



Sensor type	Sensor implementation	Animal variables	Information level	Sensing range
Sonar	Single beam sonar	Biomass depth distribution within beam	Group	1 - 200 m
	Split-beam sonar	Biomass depth distribution Movement dynamics (position, speed) within beam	Individual based group	1 - 200 m
	Multibeam sonar	Biomass depth distribution Movement dynamics (position, speed) within entire cage volume Feed pellet detection	Group	1 -200 m
Hydroacoustic Telemetry	Individual fish tags	E.g. depth, position, acceleration and spatial orientation	Individual history	0 - 1000 m
Passive hydroacoustic sensing	Hydrophone	Sound emitted from fish population, general soundscape	Group	0 - 50 m
Camera	Surface camera	Surface activity (jumping/splashing)	Group	0.5-30 m
	Feeding camera (submerged)	Sea-lice count Skin characteristics (scratches, wounds) Behavioural characteristics (e.g. systematic vs. chaotic swimming patterns, normal vs. unexpected behaviour) Species identification	Individual based group	0.5-25 m
	Stereo camera (submerged)	Sea-lice count Skin characteristics (scratches, wounds) Behavioural characteristics (e.g. systematic vs. chaotic swimming patterns, normal vs. unexpected behaviour) Species identification	Individual based group	0.5-25 m

	Hyperspectral imager	Skin spectral characteristics Sea-lice detection and -count	Individual based group	0.5-25 m
	Multispectral imager	Detection of spectral signatures Sea-lice count	Individual based group	0.5-25 m

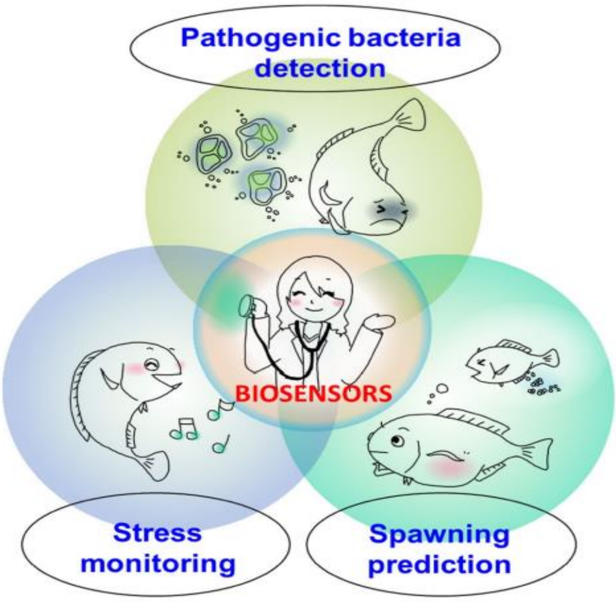
Sensor systems and monitoring methods commonly used to observe Animal variables in aquaculture industry and research, and some properties of these systems.

SOURCE: Føre, M., Frank, K., Norton, T., Svendsen, E., Alfredsen, J.A., Dempster, T., Eguiraun, H., Watson, W., Stahl, A., Sunde, L.M. and Schellewald, C., 2018. Precision fish farming: A new framework to improve production in aquaculture. *biosystems engineering*, *173*, pp.176-193.

Types of fish health checks that can be achieved with biosensors

Leveraging bio-sensors to tackle challenges in aquaculture

1. Revolutionizing Feeding Strategies



Feeding practices in commercial fish farming play a key role in production efficiency by affecting fish behaviour and competition for food (Thorpe and Huntingford1992; Juell, 1995). Proper feeding strategies helps farmers determine the right amount of feed (Ang and Petrell, 1998). Overfeeding wastes feed that pollutes the environment and increases the feed: weight gain ratio (kg feed/kg biomass gain). On the other hand, underfeeding reduces growth, increases inter-fish competition, and also elevates the feed: gain ratio (Cho1992; Talbot and Hole, 1994; Einen *et al.,* 1995). These inefficiencies necessitate improved feeding strategies for commercial fish farming.

The amount of feed needed for fishes varies from meal to meal (Juell *et al.,* 1994; Ang and Petrell, 1997), and it is hard to determine the exact amount, leading to inefficient production. Current methods for assessing feed requirements such as using growth rates or energy requirements (Cho 1992), depend on body weight and water temperature. However, factors such as environmental conditions affect fish appetite, making these methods inconsistent (Brett, 1979; Jobling, 1994) often resulting in overfeeding on some days and underfeeding on other days (Johansen and Jobling, 1998). Monitoring surface feeding activity is also unreliable, as it fails to account for the behavior of fish swimming at depth (Juell, 1995; Ang and Petrell, 1997, 1998).

Feeding efficiency can be optimized by fine-tuning the temporal and spatial delivery of feed, taking into account species-specific physiological responses before and after a meal (i.e., pre- and postprandial responses) and environmental conditions (Alfredsen, 2007). Bio-sensors capable of identifying and quantifying these physiological responses provide valuable insights for optimizing feeding efficiency, as feeding is an individual-level process.

Ingestion and digestion cause long-lasting physiological disturbances such as the alkaline tide and specific dynamic action (SDA), which animals must compensate to maintain homeostasis (Secor, 2009). The disturbances can constrain the animal's physiological capacity to cope up with stressors during digestion (Seth *et al.,* 2011; Thorarensen and Farrell, 2006). Thus, feeding strategies may need to be adjusted during stressful conditions, or stressful practices must be avoided during peak postprandial responses.

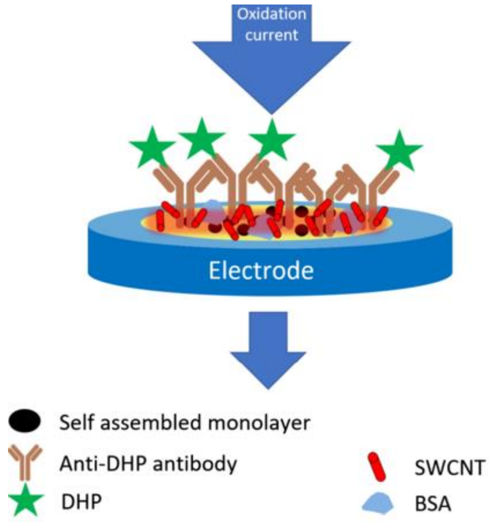
Bio-sensors that monitor animal physiology can monitor and track feeding behaviour in aquaculture. For instance, it is possible to predict the feeding status of rainbow trout (Oncorhynchus mykiss) by continuously monitoring swimming activity with devices that record electromyograms (bio-electrical voltage generated by skeletal muscle cells during activation) from axial swimming muscles. Hungry individuals display significantly different activity levels compared to satiated ones (McFarlane,2004).

The integration of bio-sensors in aquaculture represents a significant advancement in feeding strategies, allowing for the optimization of feeding practices and enhancement of production efficiency.

2. Estimation of Spawning Time

In aquaculture, ensuring the systematic production of stable and high-quality fish eggs immediately after ovulation is critical for successful fish culture (Matsuyama *et al.,* 1991). Establishing a quick and easy method for predicting the timing of ovulation is essential to reduce labor in fish farms and enable efficient eggs collection. Various environmental and physiological factors significantly influence the maturation and ovulation of fish, making it challenging to accurately predict ovulation timing. Under these circumstances, DHP(17α,20β-dihydroxy-4-pregnen-3-one), a hormone that rapidly increases in the blood during the egg maturation stage, has been identified as a potential indicator for predicting ovulation (Young *et al.,* 1983; Lou *et al.,* 1984).

A DHP biosensor can be utilized to quantify DHP levels by analyzing the current change on the electrode surface during the reaction between DHP and anti-DHP antibody. This process employs cyclic voltammetry, providing a reliable and precise method to predict ovulation timing effectively.



Source: Endo, H. and Wu, H., 2019. Biosensors for the assessment of fish health: a review. *Fisheries science*, *85*, pp.641-654.

Methodological basis of the 17,20β-dihydroxy-4-pregnen-3 one (DHP) biosensor.

3. Monitoring and improving Animal Welfare

The welfare of farmed animals is a key concern in aquaculture, involving issues like animal ethics, public perception, social license, marketing, and the improvement of production efficiency, quality, and quantity (Ashley, 2007). One major focus is monitoring stress, which is any condition or state that affects an animal's homeostasis (Segner *et al.,* 2012).

Precision Livestock Farming (PLF) priciples have become central aspect to improving animal welfare and productivity in farming (Berckmans, 2004). PLF-based methods, uses continuous monitoring of animal states to make better decisions, which improves animal health, welfare, productivity and sustainability (Berckmans, 2014). This approach can also be applied to aquaculture, especially in managing crowding in salmon farming, but it requires knowing which animal states to track (Føre *et al.,* 2018).

Monitoring the spatial behaviour of salmon can provide insights into how they respond before, during and after delousing. While these behaviors are not yet scientifically quantified, they offer potential advancing welfare monitoring techniques (Føre *et al.,* 2018). Bio-sensors are also vital in detectingstress from both within and between species in the farming environment. For example, placing rainbow trout in a new social group caused a significant stress response, with their heart rate increasing by about 36%, likely due to territorial behavior (Brijs *et al.,* 2019; Pottinger and Pickering, 1992).

4. Assess Animal Environment Interactions

Aquaculture operations are highly influenced by environmental factors such as temperature, oxygen, salinity, and pH, which can affect the growth, health, and welfare of farmed animals (Reid *et al.,* 2019; Sarà *et al.,* 2018). Bio-sensors can enhance our understanding of these impacts by providing high-resolution data on animal physiology and environment conditions. These devices have shown that factors like oxygen levels, temperature, light intensity, and competition affect salmon's vertical habitat use, highlighting the complex trade-offs animals make between environmental, nutritional, and social factors (Oppedal, 2011; Johansson *et al.,* 2009; Stehfest *et al.,* 2017).

Bio-sensors that measure heart rate, ventilation rate, and activity (e.g., tail beat) are useful for estimating energetic expenditure. Heart rate and ventilation rates are linked to metabolic rate (Green, 2011), while accelerometers provide insights into swimming activity and energy use (Robson, 2016). Estimating energetic expenditure throughout the production cycle and in response to environmental changes helps assess metabolic costs and determine the energy available for growth, locomotion, feeding, and reproduction (Andrewartha, 2015).

Bio-sensors play a key role in detecting sub-optimal environmental conditions that affect the growth, welfare, and survival of animals. For example, many bivalve species respond to unfavorable environmental conditions, such as pollution or harmful algal blooms, by closing their shells (Comeau *et al.,* 2018). Monitoring shell movements using devices like Hall effect sensors or electromagnetic induction systems allows farmers to use bivalves as sentinels within the production environment (Kramer, Botterweg, 1991). Similarly, bio-sensing devices designed for freely swimming fish could enable early detection of environmental issues, allowing timely remedial actions. This would enhance the sustainability and profitability of aquaculture operations.

5. Monitoring Stress Response

Physiological stress in fish triggers a primary response involving changes in hormone levels, such as cortisol and catecholamines, followed by a secondary response where stress hormones increase blood glucose levels through metabolic activation (Mazeaud *et al.,* 1977).

Bio-sensors implanted in the interstitial sclera fluid behind the fish's eyeball can detect these stress indicators. This fluid closely reflects blood hormone levels but lacks coagulation factors, which improves sensor performance (Endo, Wu., 2019).

These sensors have been used to monitor stress levels in Nile tilapia *(Oreochromis niloticus)* under high ammonia conditions and during territorial confrontations with other fish (Wu *et al.,* 2015). Their electrochemical design allows integration into portable devices, enabling real-time monitoring of stress in freely swimming fish, offering a valuable tool for advancing fish welfare research (Endo, Wu., 2019).

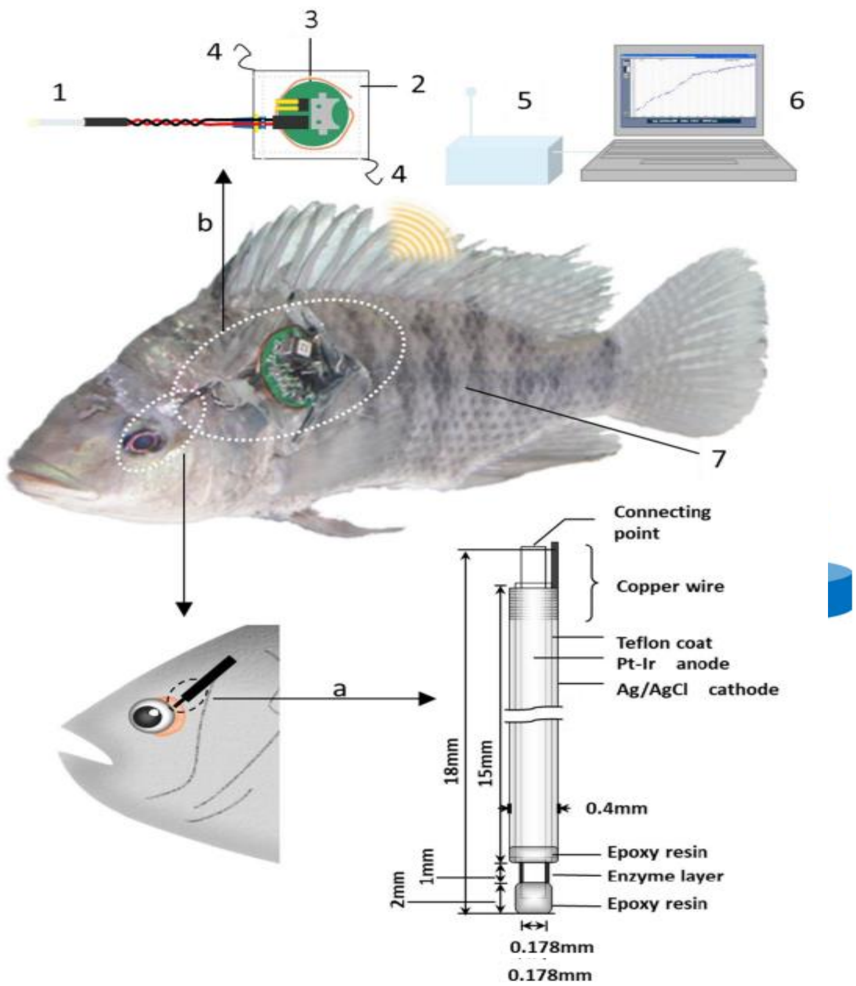
I. Cortisol Level Determination

Cortisol is a widely studied biomarker of stress in fish, as it plays a key role in stimulating glucose production through gluconeogenesis, which increases plasma glucose levels (Pickering and Pottinger, 1989). Pottinger and Carrick (2001) further detailed cortisol profiles and physiological effects in response to various stressors in fish.

A recent advancement in cortisol detection involves the use of glucose oxidase (Gox) as a signal amplifier to measure plasma cortisol levels more reliably (Wu *et al.,* 2017). This method uses a one-step immunoreaction, where cortisol in the sample binds to immobilized anti-cortisol antibodies, forming an antigen-antibody complex. This complex creates a barrier to electrical transmission between the immobilized Gox and the electrode surface, reducing the output current. The decrease in current, measured through amperometry, is proportional to the cortisol concentration, allowing for easy calculation of stress levels in fish.

II. Glucose Level Determination

Schematic diagram of the wireless biosensor system for fish.



1 Needle-type enzyme sensor, 2 waterproof sheet, 3 wireless potentiostat, 4 nylon threads, 5 receiver, 6 personal computer, 7 test fish (Nile tilapia *Oreochromis niloticus*)

In contrast to cortisol, the level of glucose varies in response to stress but returns totheir typical values within 24 hours (Silbergeld, 1974). These substances are measured using chemical methods, which are inexpensive and easy to perform. For rapid determination of glucose concentrations in fish blood, A needle type biosensor system was developed (Endo *et al.,* 2006). The sensor is inserted into the caudal vein of the fish, which measures changes in the concentration of dissolved oxygen inside the hollow container due to oxidization by Gox according to the following formula:

D-glucose + O2 Gox → D-gluconolactone + H2O2

Conclusion:

The integration of biosensors in aquaculture holds significant promise for the advancement of the industry. By transforming traditional practices into knowledge-based approaches, these innovative tools offer deep insights into the conditions that farmed aquatic animals face, which is essential for enhancing their growth, health, and welfare. Although there may be challenges in encouraging traditional fish farmers to adopt such technology, the potential benefits are substantial. Embracing biosensors could not only optimize production but also contribute to food security, making fish a vital and sustainable resource for the future. As we move forward, fostering awareness and facilitating the adoption of these technologies will be crucial for the evolution of aquaculture and the sustainable management of aquatic resources.

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INTERCONNECTED ECOSYSTEMS: THE ROLE OF BIOTA IN AQUATIC–TERRESTRIAL INTERFACES

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Abstract:

Aquatic - terrestrial interactions represent fundamental ecological processes that shape the structure and function of both water and land ecosystems. This chapter synthesizes the critical roles of flora and fauna in these dynamic interconnections. Riparian and aquatic vegetation exert significant influence on bank stability, water quality and habitat provision within. aquatic environments, while surrounding. terrestrial flora regulates hydrological cycles-and minimizes erosion impacting aquatic Systems. Conversely aquatic fauna drive nutrient cycling and predator-prey dynamics-within their ecosystems, and terrestrial animals facilitate cross-ecosystem energy. and nutrient transfer through predation, migration and decomposition. Amphibians, uniquely-positioned across both realms, serve as vital trophic links. The interplay between these ecosystems is further manifested through nutrient exchange via runoff and animal movement, energy flow across food webs, and the creation of shared habitats. Understanding these intricate relationships is paramount for ecological research, informing conservation strategies and the mitigation of anthropogenic impacts on ecosystem integrity and biodiversity. This synthesis underscores the necessity of considering aquatic and terrestrial ecosystems not as discrete entities, but Components of a as inter connected larger ecological continuum. The distinction between the deliberate behaviours of soil organisms- such as annelids innate behaviour of burrowing, and indirectly increase the water holding capacity of soil. Some of burrow for shelter and the incidental outcomes they produce, including the redistribution of organic material, Rainfall nutrient cycling, migration are crucial for comprehending the intricate network of belowground ecological interactions.

Keywords: Flora, Fauna, Ecological Role, Annelids - Amphibians, Linking Ecosystems, Biodiversity.

Introduction:

A healthy stream can be described as a resilient and sustainable ecosystem that preserves its ecological integrity and functionality over time, while also fulfilling societal demands and expectations (Meyer, 1997). Traditionally, aquatic and terrestrial ecosystems have been studied as distinct systems, each characterized by unique biological communities, environmental conditions, and ecological functions. However. these aquatic and terrestrial ecosystems deeply interconnected through a variety physical, chemical and biological processes. Aquatic terrestrial Interactions encompass. The flow of energy, the exchange of nutrients. the movement of organisms, transfer of materials between land and water environments

fundamentally shaping the systems. Such interactions. ecology of both are critical for Sustaining ecosystem health and biodiversity. Terrestrial landscapes, for instance, contribute organic inputs like leaf litter and woody debris to aquatic habitats, providing essential energy sources. for aquatic food webs. In turn, many aquatic species-such as emerging insects like dragonflies and other flies become key food resources for terrestrial predators, linking aquatic production to land-based ecological networks.

Human activities including deforestation, agricultural intensification, urban development have disrupted many natural connections. between land and water, leading to ecosystem degradation and the loss of vital ecological services, therefore necessary to more effective conservation efforts and sustainable management practices this show the real-world case studies. It further examines the impacts of human-induced changes and discusses strategies for conserving and restoring these vital ecological connections. Our objective is to advance a more holistic and resilient framework for the stewardship of interconnected ecosystems.

Aquatic and terrestrial ecosystem interactions is important to understand the concepts of nutrient exchange and energy flow which help for ecosystem management and climate change understanding. Nutrients from land enrich water bodies, while aquatic life and sediments Impact land ecosystems. These ecosystems constantly exchanging nutrients and energy. Organisms like salmon and insects. act as bridges, transferring energy and matter between the two. These systems also shape each other's habitats- wetlands support land animals, while trees influence aquatic environments. Understanding these dynamic interactions is vital for conserving biodiversity and ensuring ecosystem health amid environmental pressures. eg. leaf litter falling into streams. From an ecosystem standpoint, the riparian zone constitutes a vital Component of and stream land the interconnected forest ecosystem continuum. Integrating Terrestrial and Aquatic systems to enhance understanding of organic. matter Dynamics across landscapes: emphasizing the role of Humans in sustaining ecological balance. These Interactions investigates Energy and nutrient Boundaries. transfers across ecosystem boundaries.

The Dynamic Interplay:

Nutrient runoff from terrestrial landscapes, carrying elements like nitrogen and phosphorus, can enrich aquatic ecosystems, fuelling primary productivity. As per above example the animal migrations, such as the upstream spawning of salmon, represent a significant transfer of marine derived nutrients into freshwater Systems, enriching terrestrial food webs along their migratory routes. Wetlands provide critical breeding grounds and foraging as areas for numerous bird species well as refuge for mammals and reptiles. Insects lay their eggs on emergent plants.

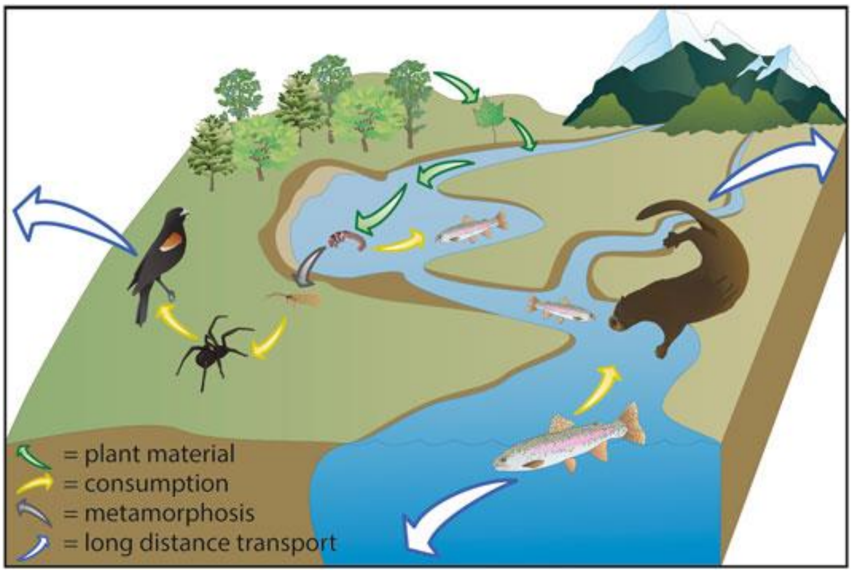
Challenges:

- Contaminants can and terrestrial move between aquatic areas.
- Ecosystems may be damaged or broken apart
- Climate impacts differ between land and water systems.
- Non-native species may spread both environments. across

Opportunities:

- Movement of nutrients and energy boosts biodiversity.
- Joint management improves protection efforts.
- Helps maintain sustainable farming and fishing practices.
- Natural buffer zones like wetlands help ecosystems stay stable.

Ecological role of Flora and fauna in aquatic-terrestrial interactions: -



1. Salt Marsh Grasses (Spartina spp).

Habitat: estuarine environments. Ecological role -These grasses trap sediments reduce coastal erosion, and provide critical habitat for wildlife, supporting nutrient-rich detritus in aquatic food webs.

2.Seagrasses (Zostera spp.)

Habitat: Shallow coastal waters

Ecological Role: Seagrasses Stabilize Sediments, improve water clarity and provide habitat for marine life, playing a role in carbon sequestration and nutrient cycling.

3.Water Clover (Marsilea spp.)

Habitat: Shallow freshwater bodies and wet soils.

Ecological Role: Water clover helps control. algae growth, provides shelter for aquatic life and contributes to the ecological diversity of aquatic- terrestrial interfaces.

4.Bladderworts (Utricularia spp)

Habitat: Freshwater environments

Ecological role - These carnivorous plants control populations of small aquatic organisms influencing aquatic food webs and nutrient dynamics.

5.Sedges (Carex spp.)

Habitat: Wet meadows and stream banks.

Ecological Role: Sedges stabilize soil, filter runoff, and offer food and habitat for wildlife, maintaining the integrity of riparian zones.

6.Water Lilies (Nymphaea spp.)

Habitat: slow-moving freshwater bodies. Ecological Role: Regulate water temperature, and provide shelter for aquatic organisms, contributing to oxygenation and habitat complexity.

The best overall plant is, Cattails Typha latifolia Habitat Wetlands and marshes.

Ecological Role: Cattails filter pollutants reduce erosion and provide habitat for various species, Supporting Cycling nutrient between terrestrial and aquatic environments Provides habitat for birds. insects, and amphibians.

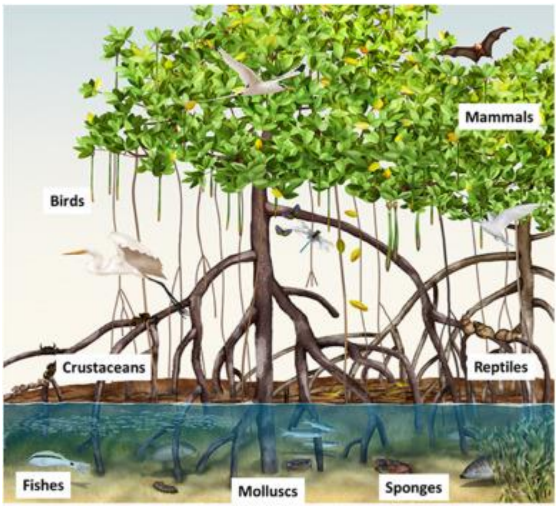
Ecological Role of Earthworms in Aquatic Terrestrial Ecosystem:

Earthworms link terrestrial and aquatic ecosystems by decomposing organic material and promoting nutrient flow. Their actions in soil and riparian boost areas vegetation and deliver nutrients and organic Water systems. matter to adjacent bodies, benefiting both systems.

Earthworm species such as Lumbriculus variegatus and Tubifex adapted to live in are freshwater habitats and contribute significantly to ecosystem. functions like Sediment mixing their burrowing improves oxygen flow and supports beneficial microbial activity. In nutrient Recycling they help decompose organic materials, promoting the circulation of essential nutrients like nitrogen and phosphorus. They also known as water quality Indicators, large number. of Tubifex may signal polluted water. These worms. Serve as a food source for fish (bait) Sustaining the aquatic food chain. They play a crucial role in Pollution. control by their natural activities assist in breaking down harmful substances in Contaminated sediments. So, they preserve the health and balance of freshwater ecosystems. Although earthworms are terrestrial fauna play significant roles in aquatic ecosystems.

Like Earthworms the Amphibians play important ecological role in aqua-terrestrial Ecosystems. They include frogs, toad's and salamanders, connect ecosystem through their dual life cycle. In water, their larvae help control algae and recycle nutrients, while serving as food for aquatic predators. On land adult amphibians feed on insects and pests, Supporting ecological balance. They also move between water and land and act as sensitive bioindicators due to their Vulnerability to pollution and habitat changes. By supporting food webs and nutrient flow, amphibians play a vital role in ecosystem health and their decline often signals environmental problems.

Ecological Role of Aquatic terrestrial Mangroves and their Relationship: -



Mangroves form a crucial bridge between land and sea. Their roots prevent erosion, trap sediments, and filter pollutants, improving coastal water quality. They offer shelter for fish, birds, crabs and insects, supporting both aquatic and terrestrial life. Mangroves also store carbon and protect shorelines from storms, playing a key role in maintaining ecosystem balance. So, Energy exchanges by one ecosystem to another (land to waters) serving as prey and predator. Coastal intertidal zones cover the Mangroves (Rhizophora spp.)

Ecological role: - Stabilize shorelines. 8 mitigate storm impacts, serve as nurseries for marine life. Their leaf litter enriches both land and aquatic food webs, enhancing ecosystem connectivity.

Biotic and abiotic connectors like organisms live in both beavers, dragon-flies, turtles etc and abiotic factors like tides, floods, rainfall connect physically aquatic and terrestrial ecosystem by rivers, coastal zones, estuaries etc.

Human being gets lot of benefits like Integrated fishery Science the connector between aquatic and terrestrial ecosystem Another the Mudskippers are excellent example of fish that connects both ecosystem Unique trait of this fish can survive both in water and on land by absorbing gen through their skin and the moist Surfaces inside their mouth and throat (A process called cutaneous respiration). Behaviour: They crawl use their front fins to on land and dig into the mud to stay moist and protected.

Ecological role of Turtles: -

They play an important role in both land and aquatic habitats by managing populations of plants, insects, and jellyfish. They aid in seed dispersal and nutrient recycling through their diet and waste, helping sustain biodiversity and the connector factor between aqua-terrestrial ecosystem Keep balanced.

Ecological role of Crayfish:

Link between ecosystems: Crayfish play a key role in connecting water and land ecosystems through their natural activities. Burrowers and soil modifiers: By digging burrows, they alter sediment structure and help improve soil aeration. Support nutrient cycling: Their feeding and burrowing contribute to the recycling of nutrients in both water and soil. Control aquatic populations: As omnivores, they help manage the levels of algae, decaying matter, and small aquatic animals. Enhance terrestrial soil: In areas like riverbanks and floodplains, they enrich the soil with organic material through their movement and waste. Key prey species: Crayfish are a food source for many animals such as fish, birds, and mammals, thus maintaining ecological balance.

Climate Change and Aquatic-Terrestrial Interactions:

Climate change modifies key environmental temperature, precipitation patterns, and sea levels, significantly impacting the connectivity aquatic and terrestrial between ecosystems.

These changes influence species distribution, disrupt migration and reproduction cycles, and elevate the frequency of extreme events like droughts. and floods, ultimately reducing ecosystem Stability and resilience.

Conservation and Restoration Strategies:

1.Plant vegetation along waterways for filtration and habitat

2.Wetland restoration Rebuild wetlands to improve water quality and reduce floods. Remove barriers to support fish migration and nutrient flow.

4.Nutrient management: - Limit land-based pollution entering water bodies.

5.Invasive species control: - Manage non-native species to protect ecosystems.

6.Integrated land use (Plan development)

7.Ecotone Protection: - Preserve transition. zones between land and water.

8.Community involvement: - Engage locals in conservation activities.

Future Directions and Research Gaps:

Future Directions:

1.Sustainable Practice Promotion:

Encouraging environmentally responsible methods in agriculture, forestry and fisheries to minimize ecological harm.

2.Climate Resilience Planning:

Advancing adaptive measures, including habitat restoration, to better prepare ecosystems for climate- related impacts.

3.Holistic Ecosystem system Management:Emphasis is shifting toward integrated approaches that address both land and water systems collectively for effective conservation.

4.Advanced Technological Applications:Leveraging tools such as remote sensing, artificial intelligence, and ecosystem modelling to enhance monitoring and forecasting capabilities.

Research Gaps:

- Insufficient Long-Term Data:
  There is a notable lack of extended monitoring needed to fully understand dynamic ecosystem interactions over time.
- Limited Knowledge of Species Dynamics:
  More research is required on how climate variations influence species behaviour, relationships. movement and food web relationships.

Unclear Pollution Linkages

Current studies. are inadequate in tracing how contaminants travel and affect both terrestrial and aquatic ecosystems.

Understudied Human Influences:

Further investigations is necessary into the ecological consequences of urban expansion and land-use changes on habitat connectivity.

Conclusion:

Aquatic and terrestrial ecosystems are of closely connected through the exchange energy, nutrients and Interactions like insect organisms. emergence and lent litter input are vital for ecosystem health, making their understanding crucial for effective conservation and management.

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AN OVERVIEW OF TANKYRASE THERAPEUTIC ROLE IN CANCER

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Abstract:

Tankyrases are responsible for regulating mitosis, telomere maintenance, and Wnt signaling, among other cellular functions. They are multifunctional poly (ADP-ribose) polymerases. By interacting with target proteins and poly (ADP-ribosyl) ating them, tankyrases control the stability and interactions of these proteins. In addition to controlling mitosis and telomere maintenance, tankyrase proteins also regulate tumor suppressors such as AXIN, phosphatase and tensin homolog, and angiomotin. For this reason, tankyrases have the potential to be useful cancer therapeutic targets. Possible cancer-promoting pathways that tankyrase inhibitors could influence include Wnt, AKT, yes-associated protein, telomere maintenance, and mitotic regulation. Novel features of tankyrase activity and mechanism, as well as several inhibitors of this enzyme, have recently come to light. Synergistic anticancer effects may be achieved by combining standard chemotherapy drugs with tankyrase inhibitors. More potent tankyrase inhibitors are likely in the horizon, which bodes well for the development of new approaches to treating cancer and other disorders linked to tankyrase.

Keywords: Tankyrases, Epidermal Growth Factor Receptor, Cancer, Inhibitor

1. Introduction:

Several cellular and molecular activities rely on the vast protein family known as poly (ADP-ribose) polymerases, or PARPs. Post-translational modifications, such as poly(ADP-ribosyl)ation (PARsylation), allow PARPs to transport transfer of ADP-ribose units from NAD+ donor molecules to protein targets[1]. PARsylation controls a wide variety of biological activities, such as DNA repair, stress signaling inside cells, gene transcription, and the aging process. The human body contains seventeen different PARPs. As members of the PARP family, the two proteins known as tankyrase 1 (TNKS1) and tankyrase 2 (TANK2) are also called PARP5A and ARTD5, respectively. An amino-terminal region called the HPS domain contains homopolymeric stretches of His, Pro, and Ser residues. Then, there is an ankyrin domain with 24 ankyrin repeats. Lastly, there is a sterile α module (SAM) domain and a carboxy-terminal PARP catalytic domain that make up TNKS1. Although it is linked to TNKS1, TANK2 does not have an HPS domain at its N-terminus. While 83% of the TANK2 ANK domain is identical to TNKS1, 74% of the TANK2 SAM domain is identical to TNKS1. With 94% identity, the C-terminal PARP domain is a highly conserved PARP polymerase. Both the SAM domain and the ankyrin domain are involved in protein-protein interactions and self-oligomerization, respectively[2]. At this time, the function of the HPS domain is a mystery. Through telomere repeat binding factor 1 (TRF1), tankyrases regulate cellular processes such as telomere maintenance by interacting with many target proteins. An interaction between TNKS1 and tankyrase-binding partners is facilitated by a 6-amino acid motif. Tankyrases play an important role in maintaining telomeres, Wnt signaling, cell division, glucose uptake, and cherubism, a hereditary disease, other cellular processes. Earlier research identified novel tankyrase binding partners like PTEN, PrxII, APC2, AMOTs, ABRO1, CD2AP, PEX14, and ATG9A[3].

2. Tankyrases: A Structure Analysis

The human TNKS1 and TNKS2 tankyrases are multidomain proteins with 1327 and 1166 residues, respectively. Although full-length Tankyrase structures are not yet known, Isolated protein domain crystallography has yielded several valuable insights. At its very end lies a catalytic ARTD domain of both Tankyrases. Protein crystallography has provided a wealth of information on the ARTD domain, and structural insights into this domain have helped in the development of TNKS inhibitors[4]. With a total sequence similarity of 89%, TNKS1 and TNKS2 have a well preserved ARTD domain. Below, we will go over the structural characteristics of the ARTD domain and how it is similar to and different from other ARTD enzymes. Upstream of the ARTD domain is a conserved SAM domain[5]. The extent to which the SAM domain affects the neighboring ARTD domain's structure and activity remains unknown. But the tankyrase SAM domain, like other proteins' SAM domains, is involved in homo- or heterooligomer formation.

The majority of Tankyrases are composed of five clusters of ankyrin repeats, which play a role in the interactions between proteins. Two regions of Tankyrase ankyrin repeats and their peptides have been studied using yeast two hybrid systems, pull-down experiments, and protein crystallography. The two Tankyrases have three conserved domains and TNKS1's N-terminus has a His, Pro, Ser rich (HPS) region. Specifically, it has been reported that an alternate promoter was used to produce an absence of the HPS region in the TNKS1a protein. So far, little is known about the structure or function of the HPS motif[6].

3. Domain Catalyzing Tankyrase Activity

Function: The ADP ribosyltransferase activity of ARTDs is carried out by the catalytic domain. This domain acts as a catalyst in the hydrolysis reaction that converts NAD+ to ADPr and nicotinamide. Initiation reactions involve the release of nicotinamide from the binding site and the transfer of ADPr to the amino acid side-chain of an acceptor protein[7]. As far as we know, the human ARTD catalyzed change can take place on Glu, Asp, and Lys. Other ADP-ribosyltransferases can modify phospho-serine, diphthamide, Cys, Arg, and Asn as well. None of the acceptor proteins have the amino acids that tankyrase like to modify.

In order to create a poly ADP-ribose (PAR) chain, the reaction is extended by adding the next ADPr unit to the current modification. A conserved Glu at the active site is required for this activity, similar to ARTD1, to maintain in accordance with the ARTD1 protocol, use the oxocarbenium intermediate to activate the ribose hydroxyl of the ADPr attached to the acceptor site in order to launch a nucleophilic attack. Currently, two-dimensional thin-layer chromatography has only demonstrated a branching reaction of the PAR chain for ARTD1, and not for tankyrase-mediated PARsylation. The concentration of NAD+ determines the PAR chain length in vitro. Although 20 ADPr units is the typical length of the PAR chain for Tankyrases, it has been observed that the chain length can rise with increasing concentrations of enhanced NAD+, reaching 100 units at 100 M NAD+ in vitro. At low quantities of NAD+ (100 nM), mono-ADPribosylation may predominate, though[8].

4. Cancer-Related Tankyrase.

Tankyrase plays an important role in several cancer-related biological processes, such as mitosis, DNA repair, telomere maintenance, oncogenic pathways (including Wnt, YAP, and AKT), and cell death. One protein that interacts with TRF1 is TNKS1, which is involved in telomere maintenance. TRF1 prevents telomerase from reaching telomeres. The ubiquitin-proteasome pathway degrades the liberated TRF1 once it is PARsylated by TNKS1, which releases it from telomeres[9]. As telomere maintenance Since telomerase keeps cancer cells replicating, it is considered a promising target for cancer treatments. One possible target for telomere-directed anticancer therapy is TNKS1, which regulates telomerase inhibition in human cancer cells. Proposed for use in conjunction with tankyrase inhibitors, telomere-directed inhibitors cause telomeres to gradually shrink without causing acute cytotoxicity. Lung and stomach cancer cell lines showed a synergistic impact when TNKS1 and telomerase were both inhibited at the same time. Also, human lung adenocarcinoma cells are more likely to undergo cell death and less likely to proliferate when both tankyrase and telomerase are inhibited. These findings suggest that human lung cancer therapeutic strategies including co-inhibition of telomerase and tankyrase could be fruitful. The processes that cause cancer. Tankyrases may play a role in pathways that promote cancer. Signaling through Wnt pathways[10]. In cancer and other disorders, the Wnt signal transduction pathway controls many biological activities. AXIN has been discovered to be a tumor suppressor and is a critical effector in the Wnt pathway. While inhibitors of tankyrases tend to stabilize AXIN, the enzyme itself is a target for destruction. The degradation of downstream effector β-catenin is controlled by the This sentence describes the Wnt pathway and the β-catenin destruction complex, which includes APC, AXIN, and GSK3β. The process of AXIN PARsylation induced by TNKS1 leads to its degradation through the ubiquitin-proteasome pathway.

The subsequent breakdown of AXIN causes the β-catenin destruction complex to be disrupted[11]. The activation of Wnt-dependent transcription is triggered when released β-catenin moves into the nucleus. The β-catenin destruction complex is supported by the tumor suppressor APC. More than 80% of colorectal cancer cases will have a mutant APC. Therefore, inhibitors of tankyrases may provide a potential therapeutic target for colorectal cancer (CRC) because of their role in controlling Wnt signaling. Reducing TNKS1 expression enhances chemosensitivity in colon cancer cell lines and inhibits Wnt signaling and tumor formation in APC-mutant colorectal cancers. Tankyrases have the potential to be antineoplastic targets in lung cancer, and its role in the Wnt pathway implies that blocking this route might be beneficial in the battle against this malignancy. Tankyrases regulate destruction complex activity, and there is mounting evidence that the fly APC homolog APC2 may serve as a substrate for tankyrases. These findings strengthen the case for targeting tankyrases as a potential Wnt pathway-based cancer treatment. Transmitting signals by means of YAP gene expression[12].

The Hippo pathway controls the growth of organs and the balance of tissues. An oncoprotein called YAP is the principal effector in the Hippo pathway. Additionally, YAP signaling is associated with a number of human malignancies. According to a new study, YAP oncogenic activity can be reduced by stabilizing AMOTs and restricting their degradation through the tankyrase RNF146 axis. This occurs because AMOTs inhibit YAP expression[13].

These results suggest a new avenue for cancer therapy to explore. The study's authors demonstrated that YAP signaling adds to pharmaceutical resistance in cancer treatments that aim to inhibit RAF and MAPK. The growth inhibition of the epidermal growth factor receptor (EGFR) is enhanced in non-small cell lung cancer (NSCLC) by inhibiting tankyrase[14].

According to these findings, inhibiting tankyrase could be a viable strategy for combinatorial cancer treatment to circumvent drug resistance. signaling through AKT molecules. Mutations in the tumor suppressor protein pTEN have been linked to an assortment of cancers including the Cowden syndrome. It was determined that PTEN is a protein that binds to tankyrase. By inhibiting tankyrase, PTEN can be stabilized, which in turn reduces cell proliferation and tumor formation by downregulating AKT phosphorylation. Results like this lend support to the theory that tankyrase inhibitors that work by blocking the AKT oncogenic pathway can be useful in therapy. Controlling the mitotic process. This process of mitosis must resolve sister telomeres, TNKS1 must be present. During replication in the S phase until they separate during mitosis, sister chromatids remain attached to each other due to sister chromatid cohesion. Maintaining chromatid cohesion is a difficult process that calls for several proteins, including Smc1, Smc3, and Scc1. Cohesion is lost from centromeres and arms when TNKS1 isn't present, but sister telomeres stay connected, suggesting persistent cohesion; inhibitory TNKS1 during mitosis causes telomere cohesion to persist, which delays anaphase progression. Sister telomere resolution timing is impacted by the cell cycle-regulated K63-ubiquitination of tankyrase mechanism, as demonstrated.

TNKS1 is involved in the proper production of the mitotic spindle because it colocalizes with NuMA and PARsylates NuMA during mitosis[15]. Additionally, cells lacking TNKS1 show abnormalities in the assembly and structure of the mitotic spindle. Centrosome localization, maturation promotion, interaction with CPAP, PARsylation of CPAP, and regulation of centrosome CPAP protein stability and function throughout the cell cycle are all responsibilities of TNKS1. Due to TNKS1's ability to promote centrosome maturation via Miki PARsylation, CPAP and Miki are postulated to have a broad function in centrosome activity. Aneuploidy and chromosome missegregation, two hallmarks of cancer, are accelerated by aberrant centrosomes. Centrosomes were highlighted as a possible therapeutic target for cancer. DNA restoration. A crucial component of DNA repair mechanisms that include non-homologous end joining is the DNA-dependent protein kinase, more often known as DNA-PK. The DNA-PK catalytic subunit, DNA-PKcs, is present in both in vitro and in vivo in a PARsylated. Through the stability of DNA-PK through PARsylation and the regulation of telomere-associated sister chromatid exchange, TNKS1 regulates DNA repair[16]. DNA damage checkpoint protein 1 mediator, tankyrases promote homologous recombination and trigger the checkpoint in response to DBS. Therefore, tankyrases are particularly useful for DSB repair. Possible cancer therapeutic targets include DNA-PK due to its involvement in tumor-associated processes including genomic stability, hypoxia, metabolism, inflammatory response, and transcription[17].

The Functions of Tankyrases in Cells

Multiple cellular sites are designated for tankyrases. Multiple locations in human cells have been identified as TNKS sites, including telomeres, nuclear pores, the Golgi complex, cytoplasm, cell membrane, and spindle poles. Tankyrases' posttranslational protein modifications and their changing subcellular localizations both impact protein-protein interactions[18].

Signaling Between Wnt and -catenin and Tankyrase and Axin

A key regulator of -catenin turnover, the DC mediates the Wnt/-catenin signaling pathway. Within the DC, Axin functions as the rate-limiting structural protein, forming a multiprotein complex with APC, CK1, and GSK3. Phosphorylation of -catenin by the DC triggers its destruction by the 26S proteasome. On the other hand, when Wnt signaling is active, Axin can join the Wnt signalosome, connect to structural protein disheveled, bring in the kinases CK1 and GSK3, and finally, form a complex with the transmembrane proteins LRP5/6 and frizzled. Binding of the insufficiently abundant protein Axin to the Wnt signalosome hinders the possibility of functional DC production. Even more intriguing is the idea that Axin can transport -catenin from the nucleus to the cytoplasm, as outlined by other researchers. Problems with Axin export from the nucleus are suggested by the enrichment of Axin in the nuclei of cells from various cancer cell lines and tissues[19].

Colorectal cancer cells may become resistant to TNKS suppression of Wnt/-catenin signaling via the DC following persistent Wnt activation, according to recent research. Chronic Wnt signaling can cause LEF1 and B9L to accumulate in the nucleus, protecting -catenin from TNKS control by preventing it from binding to cytoplasmic Axin. In addition, there is evidence that nuclear Axin can no longer block Wnt/-catenin signaling but may instead function as a positive regulator, and that this effect is attenuated when Axin accumulates in the nucleus. In colon cancer cell lines with increased Wnt/-catenin signaling downstream of the DC, Axin and USP34 were found to affect -catenin-dependent transcription. The nuclear accumulation of Axin was facilitated by USP34. New evidence suggests that TNKS and Axin play a crucial role in context-dependent master regulation of Wnt/-catenin signaling[20].

The biological effects of this may be substantial. We expected a decrease in Wnt/-catenin signaling in most tissues when we mutated Axin2 in mice to make it more stable (Axin2canp). The mutation causes a phenotype that is linked to an ectopic second tail and enhanced Wnt/-catenin signaling at the late primitive streak stage, though. It was possible to replicate a comparable phenotype using the TNKS inhibitor IWR-1. As shown by Lau and colleagues in a variety of colorectal cancer (CRC) cells with APC or -catenin mutations, Axin plays diverse functions, which could explain why tumors react differently to the TNKS inhibitor G007-LK. The APC mutant colorectal cancer cell lines SW420, SW403, HCT-15, DLD1, and SW320 showed a decrease in nucleus active -catenin and a notable stabilization of Axin2 in the cytoplasm upon TNKS inhibition[21]. Cytoplasmic Axin stabilization was observed in the colon cancer cell lines HT-29 and Colo205, but no discernible impact on nuclear -catenin was noted. While nuclear -catenin levels were elevated in the LS174T -catenin mutant cell line, Axin stabilization was seen.

Since APC inactivating truncations, Axin loss-of-function mutations, and -catenin activating mutations constitute functionally relevant components of the Wnt/-catenin signaling pathway, it is crucial to comprehend the involvement of TNKS in CRC cells. Roughly 80% of colon cancers exhibit these mutations. A number of additional tumor types have shown a link between TNKS and -catenin; this includes colon carcinomas, which are considered classic Wnt dependent malignancies. The pathological grade, positive -catenin immunostaining, and TNKS1 up-regulation were said to be significantly associated in 51 patient astrocytomas. Additionally, immunohistochemistry revealed an over-expression of -catenin in some lineages of prostate cancer cells that have developed resistance to castration, as well as the androgen-independent LNCaP-AI cell line showed a growth reduction in response to the TNKS inhibitor XAV939.

In addition, a comparison of Twelve different cell lines that have been created from human lung cancer and cyclin E-expressing transgenic NSCLC models in mice revealed a connection between TNKS and substances involved in the Wnt/-catenin signaling cascade[22]. Treatment with TNKS1 and TNKS2 siRNA, XAV939, and IWR-1 all contributed to elevated in cells Axin1 and TNKS concentrations in some of the NSCLC models, but not all. Cell lines A549, Hop62, and H522 from humans with lung cancer showed a decrease in proliferation when treated with XAV939 and IWR-1, however higher dosages were required for this effect. In their study, Bao and colleagues demonstrated that Numerous breast cancer cell lines showed elevated Axin1 and Axin2 protein levels and decreased Wnt-induced transcriptional responses after TNKS suppression by XAV939 or siRNA-mediated abrogation of TNKS expression. The serum-deprived basal-like triple-negative breast cancer cell line was the only one in which they saw a slowing of growth, though. Human Cancer Cell Line MDA-MB-231A[23].

Vesicles containing Tankyrase and GLUT4

The interaction between TNKS and Axin extends beyond the realm of Wnt/-catenin signaling. An Axin/KIF1a/TNKS complex has been suggested to play a role in the insulin-dependent surface-to-Golgi apparatus trafficking of GLUT4 vesicles in 3T3-L1 adipocytes. The GLUT4 protein helps transport glucose into cells at the surface of the cell. TNKS inhibits PARsylation through insulin-induced Akt signaling, which is necessary for GLUT4 exocytosis. Without insulin-Akt signaling, GLUT4 cannot be delivered to the cell surface because Once Axin is PARsylated, the ternary complex breaks down. TNKS and Axin engage in interactions outside of the realm of Wnt/-catenin signaling as well.

Vesicles containing GLUT4 are transported to the cell surface from the Golgi apparatus by an insulin-dependent process in 3T3-L1 adipocytes has been associated with an Axin/KIF1a/TNKS complex. One such protein that aids in glucose uptake by cells is GLUT4 from the outside[24]. TNKs suppress PARsylation via insulin-induced Akt signaling, which is necessary for GLUT4 exocytosis. When insulin-Akt signaling is not present, Axin undergoes PARsylation and the tertiary complex disintegrates, blocking the transport of GLUT4 to the cell surface. In addition to interacting with GLUT4, TNKS also interacts with IRAP, which is found in exocytotic vesicles. It is not known whether TNKS might impact MHC-I cross presentation, however IRAP is known to be the primary part in the presentation of MHC-I ligands and to trim aminopeptidase in endosomes and phagosomes. Insulin controls the IRAP/TNKS complex through stoichiometric phosphorylation of TNKS by MAPK during insulin stimulation[24].

5. Potential cancer TNKS1/2 inhibitors

The wide variety of substrates for tankyrases has led to their association with a number of disorders, issues include obesity, diabetes, fibrosis, infections with the Epstein-Barr and Herpes simplex viruses, cherubism, multiple sclerosis, cancer, and enzyme variants that are either downregulated or mutated. By analyzing the public cancer portal cBioportal, we were able to compile a list of the most common cancers caused by TNKS/2 gene mutations. The mutations in TNKS and TNKS2 were most common in endometrial cancer, bladder, esophagogastric, colorectal, and prostate cancers, respectively.

Mutations in TNKS expression in esophagogastric cancer are mostly produced by TNKS gene amplification, in contrast to colorectal, bladder, hepatocellular, and ovarian carcinomas where deep deletion is the underlying reason[25]. Most malignancies, with the exception of prostate adenocarcinoma and B-cell neoplasms, had TNKS2 changes due to point mutations. Research on the causes of the distinct mutation pathways impacting TNKS and TNKS2 is still in its early stages. In terms of gene sequences, missense mutations were dispersed throughout the genes, with truncating, fusion, and in-frame mutations following closely after. We cannot draw any conclusions about overall survival rates for patients with TNKS or TNKS2 expression abnormalities because the studies that are publicly available for these cancer types show conflicting results. Although TNKS1 and TNKS2 expression levels are often highest in colon and lung cancers, they have also been found in brain, breast, ovarian, and liver cancers. In 2009, Huang and colleagues found the first TNKS inhibitor, XAV939, while investigating inhibitors of the Wnt/β-catenin pathway. Although various malignancies have shown changes in Wnt/β-catenin signaling, no direct inhibitors of this system are currently being used in clinical practice. This is why effective inhibitors targeting the Wnt/β-catenin pathway have been developed[26]. Research on the effects of blocking the secretion of Wnt ligands and blocking the ligand's binding to the receptor, respectively, has been conducted in clinical studies utilizing porcupine inhibitors and anti-Frizzled antibodies. Another alternative to traditional cancer treatments is the development of tankyrase inhibitors.

These inhibitors can be classified as either nicotinamide subsite (NS) or adenosine subsite (AS) binders, or as dual binders (DB) if they can recognize both nicotinamide and adenosine subsites of the donor NAD+ site. They all recognize the catalytic domain. Among PARPs, the nicotinamide subsite is very conserved, whereas the adenosine subsite is unique to tankyrases. Because of this, TNKS can be selectively inhibited by inhibitors that target the adenosine subsite. Following this, we will revise the previous data about tankyrases' function in cancer and present the most current methods for targeting tumors with TNKS inhibitors, both singly and in combination. The present literature suggests that TNKS1/2 inhibitors have primarily been tested on colon and lung cancer models, possibly because of the high frequency of mutations in the Wnt/β-catenin signaling components. So, we'll look at the inhibitor data through the lens of the cancer model that tested them, showcasing the successes and failures of each model[27].

Conclusion:

The importance of tankyrases in enhancing the Wnt/β-catenin pathway, which plays a crucial role in the progression of colorectal cancer and has consequences for many other forms of cancer, is evident. Hence, to enhance our present understanding of TNKS1/2's function in the genesis of tumor-initiating mutations and the utilization of novel therapeutic drugs based on tankyrase inhibition, it is imperative to integrate clinical trials with global data analysis. Further research on the TNKS interactoma in both normal and malignant cells is required for the purpose of defining and identifying novel TNKS substrates. To design pharmacological inhibitors affecting the TBM-ARC connection independently of the poly (ADP-ribosylation) activity, future research into the novel roles of tankyrases is required. Despite tankyrases' significance as therapeutic targets and their involvement in numerous cellular processes, little is known about their molecular mechanisms and specific roles. To further understand the roles and mechanisms of tankyrase, new protein binding partners have been identified, including as PTEN, AMOTs, CD2AP, APC2, ABRO1, PrxII, PEX14, and ATG9A. Tankyrase substrates such as AXIN, PTEN, and AMOTs all play a role in tumor suppression. The fact that inhibitors of tankyrases target many carcinogenic pathways suggests that tankyrases could be useful therapeutic targets in the fight against cancer.

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