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Emerging Insights in Pharma and Health Science Volume III

Editors:
Dr. A. K. Seth
Dr. S. A. Vhanalakar

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Editors

Dr. A. K. Seth

Department of Pharmacy,

Sumandeep Vidyapeeth Deemed to be

University, Piparia, Vadodara, Gujarat

Dr. S. A. Vhanalakar

Department of Zoology,

Karmaver Hire College, Gargoti,

Dist. Kolhapur, Maharashtra

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E-mail: bhumipublishing@gmail.com

PREFACE

The pharmaceutical and health sciences sectors are undergoing a transformative evolution, driven by technological advancements, innovative research methodologies, and a deeper understanding of disease mechanisms. This dynamic landscape demands a continuous exploration of emerging trends, groundbreaking discoveries, and interdisciplinary collaborations to address global health challenges and improve patient outcomes.

"Emerging Insights in Pharma and Health Science" is a scholarly endeavor that brings together a collection of contemporary research findings, critical reviews, and case studies across a broad spectrum of pharmaceutical and health-related disciplines. This volume aims to bridge the gap between fundamental science and clinical application by showcasing the latest developments in drug discovery, pharmacology, biotechnology, nanomedicine, diagnostics, personalized therapies, and regulatory practices.

The chapters in this book are authored by academicians, researchers, and professionals who are at the forefront of innovation in their respective fields. Each contribution reflects a rigorous academic approach while highlighting practical implications and future directions. By presenting multidisciplinary perspectives, the book serves as a valuable resource for students, educators, industry professionals, and policy makers who seek to stay informed about the rapidly evolving paradigms in healthcare and pharmaceutical sciences.

We extend our heartfelt gratitude to all the contributors for their valuable insights and scholarly efforts. We also thank the editorial and review team for their meticulous work in ensuring the quality and coherence of this compilation. It is our sincere hope that this book will inspire further research, foster knowledge exchange, and contribute meaningfully to the advancement of health science and pharmaceutical innovation.

- Editors

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RECENT ADVANCES IN ACUTE LYMPHOBLASTIC LEUKEMIA

Varunsingh Saggu

Department of Pharmacy,

Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara, Gujarat, India

Corresonding author E-mail: varunsvdu@gmail.com

Abstract:

Acute Lymphoblastic Leukemia (ALL) is a complex and heterogeneous disease that affects both children and adults. Despite significant advances in treatment outcomes, relapse remains a major challenge. Recent breakthroughs in molecular genetics, epigenetics, and immunology have deepened our understanding of ALL pathogenesis, enabling the development of targeted therapies and innovative treatment strategies. In the recent years, we have come to know the mechanism of leukemia in BCR-ABL1, NOTCH1 and PI3K/AKT pathways. Diagnostic innovations such as Genetic testing, Next-Generation Sequencing (NGS), minimal residual disease (MRD) detection and Lethal-7 family of microRNA found its base on monitoring the response of cytotoxic and chemotherapy. as new variants of ALL. Targeted therapies (tyrosine-kinase inhibitors), antibody immunotherapies, Chimeric Antigen Receptor T-Cells (CAR T-cell), RNAi mediated therapies and Hematopoietic Stem Cell Transplantation have been developed in the previous years to treat the different variants of ALL and increase the event-free survival in such patients. Additionally, there have been advances in the age-specific treatment in ALL patients. These developments hold promise for improving treatment outcomes, reducing relapse rates, and enhancing the quality of life for ALL patients.

Keywords: Leukemia, CAR-T Cell Therapy, Next-Generation Sequencing, Minimal Residual Disease, B-ALL, T-ALL

I. Introduction:

A blood malignancy known as leukemia impacts the bone marrow's ability to replicate White blood cells (WBCs). Acute and chronic leukemia are the two primary classifications. Leukemia that is acute progresses rapidly to its worst stage, while leukemia that is chronic takes comparatively longer to worsen. Acute Lymphoblastic Leukemia (ALL) and Acute Myeloid Leukemia (AML) are subtypes of acute leukemia. ALL is a rapidly expanding blood malignancy that primarily affects lymphoid progenitor cells in the bone marrow, blood, and extramedullary locations [1]. It is classified by WHO on the basis of maturation of cells into B-cells or T-cells as B-cell lymphoblastic leukemia (B-ALL) and T-

cell lymphoblastic leukemia (T-ALL) respectively. Both adults and children can develop ALL, with a peak incidence occurring between the ages of one and four years, mostly in children (1–14 years), but also in adolescents and young adults (15–39 years) [2]. Males are diagnosed with the disease at a 3:1 ratio, which is a large majority [3]. Lethargic or fatigued moods, fevers, sweats at night, weight loss, dizziness, dyspnea, infections, and easily bruised or bleeding are some of the symptoms that commonly accompany these conditions [4]. 90% of the patients are curable if the illness is identified early on using widespread screening methods combined with a sophisticated computerized diagnosis system. A range of techniques, including blood chemistry analysis, imaging, and biopsy, are used to diagnose ALL [5]. Throughout the previous few decades, there has been a significant improvement in the survival rates and cure rates for pediatric ALL patients. The current therapeutic options for ALL include chemotherapy, radiotherapy and cytotoxic therapy. The understanding of molecular genetics and etiology of the disease, the use of allogeneic hematopoietic stem cell transplantation (HSCT), and the development of new targeted drugs are all major contributors to the improvements in ALL. This review presents improvements in pediatric to adult ALL treatment, ranging from conventional therapy to immunotherapeutic drugs, in light of the field's rapid advancements.

II. Molecular and Genetic Insights:

A. Genetic Mutations and Alterations:

ALL is linked to unique genetic abnormalities that have been discovered recently thanks to breakthroughs in genetic studies. For example, key genetic events that identify and prognosticate B-ALL include the discovery of particular copy number changes (CNA) such as PAX5, PAR1 Region, BTG1, and RB1 gene deletion [6]. Research using Next Generation Sequencing (NGS) has revealed new genetic mutations in ALL, with a particular focus on mutations in the RAS signalling pathway and tyrosine kinase-2 (TYK2) gene. RAS pathway mutations are common in relapsed B-ALL and often appear early as small subclones, contributing to relapse and poorer outcomes. These mutations are more frequent in B-ALL than T-ALL and serve as important markers for relapse risk. TYK2 mutations also show promise as potential targets for precision treatment, though further research is needed to fully understand their role in leukemia and how to effectively target them for therapy [7,8]. Such breakthroughs underline the importance of continuous genomic profiling in refining ALL classification and therapeutic strategies. MicroRNAs (miRNAs), proteins involved in relapse are crucial for improving survival rates. Key miRNAs, such as miR-24, miR-27a, miR-99/100, and miR-335-3p are valuable for prognosis

and treatment response. This review also aims to analyse these miRNAs in pediatric ALL relapse and explore their potential as therapeutic targets [9].

B. Molecular Pathways & Implications for Targeted Therapy

Acute lymphoblastic leukemia's molecular pathways highlight the disease's complexity and provide important new information about possible treatment approaches.

BCR-ABL1 Pathway: Ph-positive ALL is characterized by the BCR-ABL1 fusion protein, a product of the Philadelphia chromosome translocation. This protein promotes cell survival and proliferation through constitutive tyrosine kinase activity. BCR-ABL1 stimulates downstream signaling pathways like JAK/STAT, PI3K/AKT, and RAS/MAPK, promoting cell proliferation and inhibiting apoptosis, leading to a poor prognosis. Tyrosine kinase inhibitors (TKIs) were developed to target the BCR-ABL1 pathway in Ph-positive ALL [10].

NOTCH1 Pathway: T-ALL is primarily influenced by the NOTCH1 signalling pathway, affected by genetic abnormalities. Mutations in this gene promote T-cell survival and proliferation, while those in this pathway decrease pro-apoptotic signals and increase anti-apoptotic proteins, leading to aggressive T-ALL with worse prognosis. Clinical trials are underway for gamma-secretase inhibitors, which target the NOTCH1 pathway, a potential treatment approach for T-ALL. These inhibitors may slow leukemia cell proliferation, reduce survival, and improve treatment responses [11].

PI3K/AKT Pathway: The PI3K/AKT signalling pathway is a key biological mechanism in ALL, often dysregulated in various leukemias. Dysregulation can lead to leukemogenesis and resistance to conventional therapy, particularly in Ph+ and T-ALL. Mutations in this pathway can cause increased AKT phosphorylation, making leukemic cells less responsive to therapy. Targeting this pathway for therapeutic intervention is crucial, with PI3K inhibitors, mTOR inhibitors, and dual inhibitors showing potential to improve clinical outcomes, especially for patients with ALL resistance [12].

III. Diagnostic Advances in Acute Lymphoblastic Leukemia:

The molecular subtype classification of ALL has significantly led to increased event free-survival rates (EFSR). However, 20% of children and more than 50% of adults experience relapsing ALL events along with resistance to chemotherapy leading to therapeutic failure and eventually death. This emphasizes the importance of diagnostic advancements for appropriate treatment. Understanding the various genetic variants of ALL have been simplified via different diagnostic methods such as NGS and Polymerase chain reaction (PCR).

Genetic testing: It is the strongest tool for identifying genomic variation for prompt diagnosis and management in ALL. It contains a *discovery phase* wherein new molecular targets are discovered and *Clinical practice phase* which detects the alterations. It is performed via low throughput techniques for investigation of frequent alteration in ALL subtypes (Eg: BCR-ABL1-fusion). Before introducing NGS, effective genomic testing was performed. It revealed lack of large genomic instability in ALL patients. Transcriptome microarrays discovered BCR-ABL1 subset of B-ALL (Ph+ ALL) which led to the discovery of the patients who respond to Tyrosine kinase inhibitors (TKI) more than conventional chemotherapy. However, genomic testing is difficult to detect point mutation and Focal aberrations [13].

Next-generation sequencing (NGS): A method of DNA/RNA sequencing to study the genetic abnormalities is called NGS. It is of four types namely, Whole genome sequencing (WGS) (detects Structural variants), Whole exome sequencing (WES) (detects point mutation), Transcriptome sequencing (RNA-seq)(mRNA or non-coding RNA expression detection) and Targeted gene sequencing (TGS). It is performed in three stages—firstly short-reads are aligned and matched with the reference human genome (Alignment stage). The mismatched positions are identified and a list is produced in variant call format file (VCF) (Variant calling stage). Produced variants are minimized to small set (Filtering) and known information of each variant is questioned in order to explain the biological effect (Annotation). In ALL, many cohort studies are being performed to update information of ALL on pathogenic level [14] (Table 1).

Table 1: Applications of NGS in B-ALL and T-ALL

Sr. No.	Author	Disease (NGS Type)	NGS Finding
1.	Hu *et al.,* 2017 [5]	T-ALL (WGS, RNA-Seq)	In 30 patients, identified 6.4 coding mutation or point mutation. Frequent alteration in NOTCH gene.
2.	Chen *et al.,* 2018 [6]	T-ALL (RNA-Seq)	61 adult and 61 pediatrics, SET-NUP214 was highly found in adults.
3.	Feng *et al.,* 2017 [7]	B-ALL, T-ALL (TGS)	JAK-STAT and epigenetic regulators found in early T-ALL patients.
4.	Liu *et al.,* 2016 [8]	B-ALL (WGS, RNA-Seq and TGS)	29 new in-frame gene fusions and eight gene expression subgroups with genetic abnormalities were identified: (RUNX1–like, BCR–ABL1/Ph–like).

Minimal residual disease (MRD) detection: Low amount of carcinogenic malignant cells which remain in the body after therapeutic management is called MRD detection. MRD can be performed by conventional cytogenetics, cell-culture system, southern blotting, PCR, immunophenotyping and fluorescent in-situ hybridization. It works by identifying clonal immunoglobulin molecules. In ALL, MRD detection is useful to detect early response to cytotoxic therapy, chemotherapy and subsequent treatment titration. Studies show that level of MRD at the start of treatment is the strongest prognostic factor. Decreasing MRD is associated with better prognosis and increasing MRD detects disease relapse.

Recently, MRD was quantified by PCR in which isolated DNA/RNA are serially diluted to estimate the tumor load. This serial dilution decreases the difficulty in follow up samples. At present however, Real-time quantification PCR (RTqPCR) is done which promotes appropriate quantification in PCR amplification in a dynamic definitive range. RTqPCR is quick and there is no need of serial dilution of follow up samples [15].

Lethal-7 family of microRNA (Let-7): It includes Let-7b, Let-7e and Let-7i. Let-7 is currently associated with the presence of tumors and marker of poor prognosis of leukemia patients. Let-7b is used as miRNA biomarker in ALL and AML patients. Let-7e and Let-7i test the therapy level in pediatric ALL. In a study with ALL patients, Let-7b was detected in RT-PCR in 70 patients. Let-7e and Let-7i levels initially decreased followed by increase after therapy thus, inhibiting tumor cells and decreasing MRD, indicating complicated role of Let-7 in ALL [16].

IV. Therapeutic Advances in Acute Lymphoblastic Leukemia:

The standard treatment of ALL involves multidrug involved chemotherapy with HSCT in severe patients. Recently, a translocation in BCR-ABL1 was seen, which emphasized the need for treatment of this specific sub-group. At first, the prognostic factor of Ph+ ALL patients were quite unfavorable, however with the invention of TKIs, prognosis has become little favourable.

A. Targeted Therapies:

TKIs: TKIs work by inhibiting the tyrosine-kinase enzyme, which helps in cell signalling and growth. These include Imatinib, Dasatinib, Erlotinib, etc. Imatimib mesylate has shown to increase the EFS rate from 35% to 80% in pediatric Ph+ALL. On combination with corticosteroids, Imatinib can give complete response but the downside of this drug is that it causes resistant clones due to point mutations in BCR-ABL gene. Dasatinib has shown potency in treating Imatinib-resistant clones. With respect to chemotherapy, adding ponatinib to chemotherapy has shown increased EFS rates in adult Ph+ALL [17]. In ABL-

class fusion subtype, Imatinib has induced remissions on combining with chemotherapy. Currently, trials (NCT03263572) are conducting on the efficacy of Ponatinib in ABL-class mutated Ph+ALL patients.

Poly (ADP-ribose) polymerase (PARP) inhibitors: Olaparib, niraparib, Veliparib work by inhibiting PARP, inhibiting cell proliferation by initiating apoptosis. Two trials are ongoing (NCT01139970, NCT00588991) to assess the efficacy of Veliparib with Temozolomide and Topotecan with or without Carboplatin respectively in refractory ALL patients [18].

BTK inhibitors: Ibrutinib has the ability to permanently inhibit BTK, a component of the BCR signalling pathway that is crucial in B cell development. Ibrutinib has been shown to dramatically lower BCR-positive human ALL cell lines of cell proliferation. The effectiveness of ibrutinib combined with blinatumomab in treating adults with relapsed B-ALL is being evaluated in a Phase II trial (NCT02997761).

Proteasome inhibitors: Proteasome inhibitors work by deregulating NF-κB activity in ALL, which is necessary for preventing cell death. Preclinical research has demonstrated the efficacy of 26S proteasome inhibitor Bortezomib, in conjunction with chemotherapeutics such as dexamethasone and asparaginase. Clinical trials showing good response rates in relapsed ALL patients treated with bortezomib include the TACL Phase I/II study and the COG Phase II investigations (NCT06034561). In ongoing trials for patients with ALL, carfilzomib—a more effective and specific proteasome inhibitor—and ixazomib are also being studied in combination with chemotherapy.

Epigenetic modifying inhibitors: Epigenetic abnormalities in ALL are targeted by inhibitors of epigenetic alterations, such as DNA methyltransferase inhibitors (DNMTs) and histone deacetylase inhibitors (HDACs). HDAC inhibitors can cause apoptosis and stop cell division. Examples of these inhibitors are vorinostat, panobinostat, and belinostat. Nevertheless, these drugs cause excessive toxicity, resulting in the cancellation of several studies (NCT01312818, NCT01483690). Study involving different immunotherapies to clear persistent leukemia (NCT05848687) is also ongoing.

JAK/STAT inhibitors: For Ph-like ALL patients with changes in the JAK/STAT system, such as JAK2 fusions, and EPOR rearrangements, JAK/STAT inhibitors offer promising treatment approaches. For this reason, givinostat, a HDAC, USP9X inhibitors, and the selective JAK inhibitor rufolitinib are being investigated. NCT02723994 (a subgroup of SJCRH Total XVII, and COG AALL1521 Phase II) trials are assessing the addition of ruxolitinib to multi-agent chemotherapy in patients with JAK pathway lesions that are Ph-like.

PI3K/mTOR inhibitors (mTORi): mTORi such as Temsirolimus, everolimus target PI3K/Akt/mTOR pathway, causing minimized signalling and B-ALL apoptosis. Temsirolimus is under study in combination with other therapies for ALL. Current studies (NCT01756118) assessed the safety of mTORi in adult refractory ALL patients. A study (NCT03740334) is evaluating ribociclib (LEE011) in combination with everolimus and standard chemotherapy for treating ALL.

FMS-like tyrosine kinase 3 (FLT3) inhibitors: FLT3 mutations are rare in ALL but are frequently found in MLL rearrangement and childhood hyperdiploid ALL. Midostaurin, quizartinib, and lestaurtinib, are being explored as potential treatments. A Phase III trial (NCT00557193) studied the effectiveness of combination chemotherapy with or without lestaurtinib in treating younger adult ALL, aiming to determine increased chemotherapy efficacy by lestaurtinib.

Apoptosis inhibitors: YM155, an inhibitor of survivin (an apoptosis inhibitor protein), has demonstrated effectiveness when combined with dasatinib, causing survivin downregulation and DNA damage pathways to cause enhanced sensitivity and death in ALL cells. Navitoclax had potential in preclinical animals but caused thrombocytopenia. In MLL-rearranged ALL, Venetoclax showed promise in lowering BCL-2 levels and improving chemosensitivity.

MEK inhibitors: The MAPK/ERK pathway, dysregulated in many hematologic malignancies, is the target of MEK inhibitors. Forty percent of children with relapsed ALL and six percent of those with Ph-like ALL have mutations in KRAS and NRAS. A MEK inhibitor called selumetinib has demonstrated efficacy in ALL cell models with a mutant RAS gene. Furthermore, combining BCL-2 and MEK inhibitors, such as trametinib and ABT-199/ABT-263, showed a synergistic effect that markedly reduced B-ALL cell growth and induced apoptosis [19].

B. Antibody Immunotherapy:

Anti-CD19 monoclonal Antibodies (mAbs): A bispecific T-cell engager called blinatumomab binds to CD19 on B lymphoblasts and CD3 on T cells, causing T-cell activation and CD19+ cell lysis. It was FDA-approved in 2016 for adult relapsed Ph-ALL and has demonstrated a 40–60% CR rate in relapsed/refractory paediatric B-ALL. Its better overall survival and CR rate when compared to conventional chemotherapy were validated by the Phase III TOWER trial (NCT02013167). Although it can result in neurologic toxicities and cytokine release syndrome, blinatumomab is also being considered for frontline and maintenance therapy. **Figure 1** illustrates the various immune-based therapeutic

approaches targeting B-ALL, showcasing the diversity of cellular interactions and molecular targets that can be leveraged to overcome resistance mechanisms.

Anti-CD22 mAbs: Anti-CD22 mAbs target the CD22 antigen, expressed in 90% of B-ALL lymphoblasts, making it a promising therapeutic target. Inotuzumab ozogamicin, an antibody-drug conjugate (ADC) combining a humanized anti-CD22 antibody with calicheamicin, has shown efficacy in treating relapsed/refractory CD22+ ALL. The Phase III INO-VATE trial (NCT01564784) demonstrated that inotuzumab ozogamicin significantly improved complete remission (CR) rates (81% vs. 29.4%) and overall survival (7.7 months vs. 6.7 months) compared to standard chemotherapy with an increased risk of veno-occlusive disease (VOD), in patients undergoing transplantation. Other anti-CD22 agents, such as moxetumomab pasudotox, coltuximab ravtansine, and epratuzumab, are being explored in various clinical trials. Coltuximab ravtansine, another ADC, demonstrated modest efficacy in a Phase II trial for recurrent ALL. Epratuzumab, a humanized anti-CD22 mAb, has been explored in combination with chemotherapy, though results have been variable, with some studies showing an overall response rate of 40-52% in people with recurrent ALL [20].

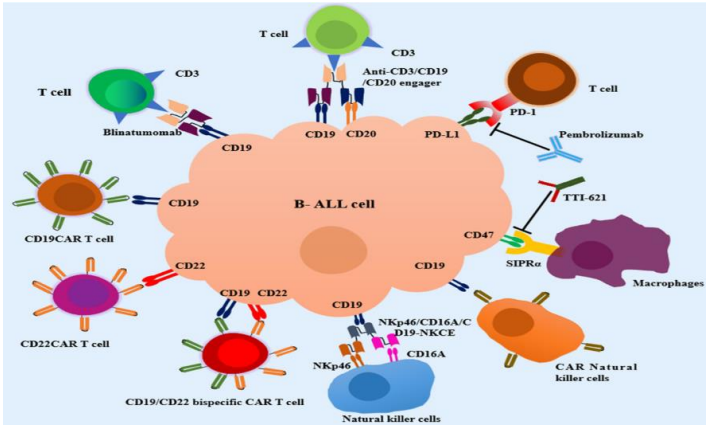

Fig. 1: Immune-Based Therapeutic Strategies Targeting B-ALL

C. Chimeric Antigen Receptor T-Cells (CAR T-cell) therapies:

B-ALL treatment has been greatly progressed by cellular therapies, especially CAR-T cell therapies. Chimeric antigen receptors (CARs), which target tumour antigens (CD19) on B-cell malignancies, are expressed by CAR-T cells through engineering. Clinical investigations have demonstrated the amazing success of this treatment, with remission rates reaching up to 90%. Tisagenlecleucel is one of the CAR-T therapies that the FDA has approved for use in patients up to the age of 25. This approval is based on encouraging findings from trials like ELIANA, which showed an 83% full remission rate. But there are common side effects which include neurotoxicity and cytokine release syndrome (CRS),

which need to be managed proactively with tocilizumab. New approaches seek to overcome the limitations of CAR-T, including inadequate persistence and target antigen loss (such as CD19-negative relapses). Targeting several antigens, such as CD19 and CD22, and employing "universal" or allogeneic T-cells are two examples of innovations. T-cell acute lymphoblastic leukemia and lymphoma are being treated in new trials by CD7 CAR-T therapy (NCT06316427) and Senl-T7 CAR-T cells (NCT05626400). These developments demonstrate the promise of CAR-T therapy but also draw attention to the continuing obstructions in enhancing and extending its efficacy [21].

D. RNAi mediated therapy:

Drug resistance and off-target side effects are two of the drawbacks of traditional treatments that can be addressed by RNA interference (RNAi) therapy. RNA interference (RNAi) selectively silences abnormal proteins implicated in cancer by destroying or preventing the translation of particular mRNAs. Using tiny interfering RNA (siRNA), antisense oligonucleotides (ASO), or short hairpin RNA (shRNA) are some of the methods. RNA molecules have trouble passing through cellular membranes, which can be solved by cationic hydrophobic carriers and non-viral delivery methods.

Histone deacetylases (HDAC), MXD3, CD22ΔE12, and other molecules implicated with B-ALL have all been the focus of RNAi treatments in preclinical research. Targeting TCF3-PBX1 using lipid nanoparticle (NP) encapsulated siRNA is another recent advancement that has increased survival in mice models. Because of their involvement in gene regulation and carcinogenesis, miRNAs and long non-coding RNAs (lncRNAs) are becoming more and more interesting as therapeutic targets. In B-ALL cells, for example, suppressing the lncRNA RP11-137H2.4 triggered apoptosis and increased glucocorticoid sensitivity. Preclinical studies have demonstrated the potential of RNAi prodrugs, such as modified siRNAs that are activated within cells, to target polo-like kinase 1 (Plk1) and induce apoptosis and mitotic arrest in T-ALL cells while posing low harm to normal cells. These advancements demonstrate how RNA interference (RNAi) may be used to precisely and successfully treat B-ALL and other cancers [22].

V. Advances in Stem Cell Transplantation:

A. Hematopoietic Stem Cell Transplantation (HSCT)

HSCT is vital for treating blood disorders, including sickle cell disease and leukemia. It replaces damaged bone marrow with healthy stem cells from various sources, classified as (derived from the patient), allogenic (from a donor) or syngeneic (from an identical twin) **(Figure2).**

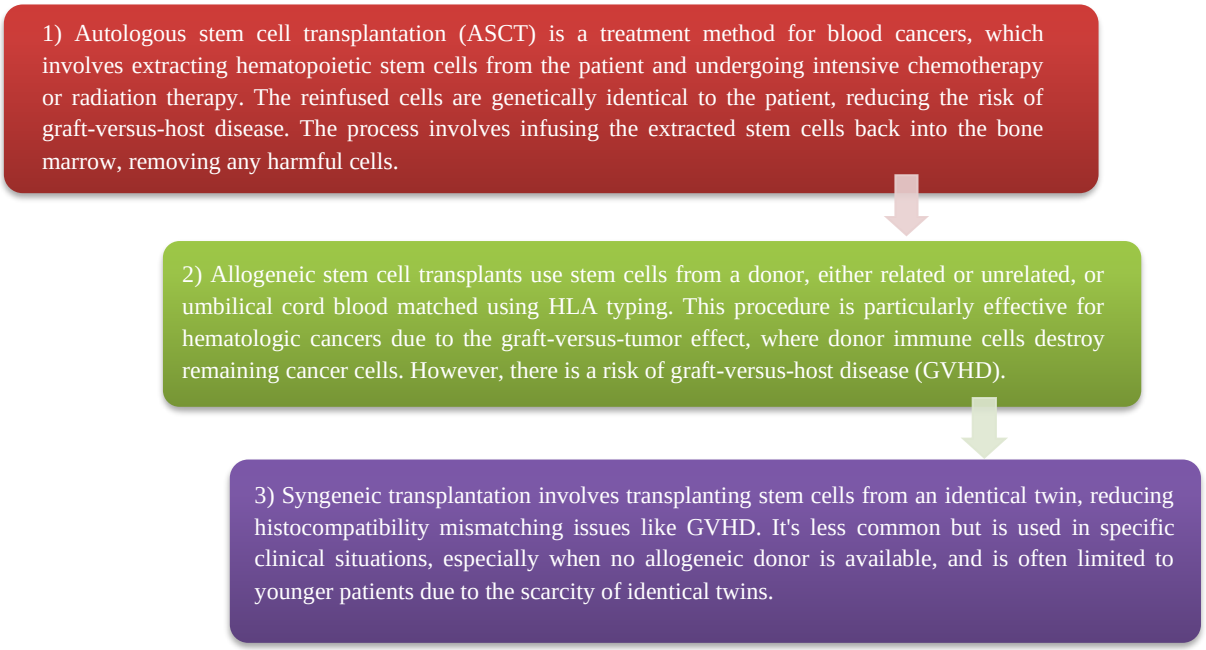

Fig. 2: Types of Hematopoietic Stem Cell Transplantation

B. Innovations in Donor Selection and Post-transplantation care:

The expansion of the donor pool for HSCT has revolutionized the treatment of ALL. Patients now have access to umbilical cord blood units, unrelated donors, and haploidentical donors, improving treatment availability and survival rates. Donor selection is based on factors like HLA matching, recipient age, and disease characteristics, with advanced HLA typing techniques making it easier to identify suitable donors. Modified conditioning protocols and innovative strategies like treosulfan-based regimens are enhancing outcomes and reducing relapse rates. Post-transplantation care plays a crucial role in improving patient outcomes, focusing on long-term surveillance, infection prevention, and psychosocial support. Post-transplant cyclophosphamide (PTCY) is commonly used to reduce graft-versus-host disease (GvHD) and improve transplant success. Overall, these advancements are expanding treatment options and improving the quality of life for ALL patients undergoing HSCT [23].

C. Innovations in Donor Selection and Post-transplantation care:

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D. Cord Blood and Haploidentical Transplantation:

Cord blood transplantation (CBT) and haploidentical transplantation are two effective options for treating ALL patients who lack suitable matched donors. CBT has shown a five-year overall survival rate of approximately 66% in some cohorts, comparable to other donor transplants but with a lower risk of acute GvHD. However, caution is needed due to risks of delayed engraftment and higher infection rates. Haploidentical transplantation is gaining popularity as a safe and effective alternative, especially with partially matched family donors, showing similar outcomes to matched donors when using post-transplant cyclophosphamide to reduce GvHD. Both procedures require careful management of post-transplant issues like infections and GvHD.

Recent research highlights the potential of CBT in reducing severe GvHD in ALL patients, while advancements in techniques like TPO and SCF can enhance outcomes through expanded stem cell availability. CRISPR/Cas9 technology plays a key role in targeting genetic regions associated with ALL, enabling personalized treatment options based on individual genetic profiles. Additionally, haploidentical transplants are becoming safer and more effective thanks to T-cell depletion techniques and novel immunosuppressive medications. Combining CAR-T cell therapy with haploidentical transplantation shows promising results in improving anti-leukemic benefits and reducing relapse risk. Overall, personalized medicine strategies are revolutionizing ALL treatment by tailoring interventions to patients' genetic and molecular profiles, ultimately improving transplant effectiveness and patient outcomes [24].

VI. Age Specific Advances for ALL:

Adolescent and young adult (AYA) survival rates have significantly improved because of the use of pediatric protocols in their care. Relapsed or resistant disease is being treated differently according to new treatments such CAR T-cell therapy, monoclonal antibodies, and TKIs.

Pediatric ALL: The most common cancer in children, accounts for 30% of all childhood cancers and 75% of all childhood leukemia cases. Despite adult ALL survival rates being around 40%, pediatric ALL has achieved an overall survival rate of 90%. The development of safer medicines and targeted therapy and immunological techniques like CAR-T cells and bispecific T-cell engager (BiTE) are crucial for achieving 100% OS in pediatric ALL. Treatment typically lasts two to three years and involves induction, consolidation, intensification, and maintenance. Steroids like prednisone and dexamethasone are often used in combination with cytostatic drugs. A Phase I CTA101 trial tests CRISPR-edited CAR T-cell therapy for pediatric ALL patients targeting CD19/CD22 (NCT04227015) [25].

Adolescent and Young Adult (AYA): In adolescents and young adults with ALL, risk stratification is essential to determine the appropriate treatment course. Patients are categorized into high-risk and standard-risk groups based on factors like resistance to induction chemotherapy and risk indicators for relapse. Age, white blood cell count, disease genetics, and MRD status are key considerations in this process. Different protocols may impact treatment choices such as allogeneic hematopoietic cell transplantation (HCT). Allogeneic HCT is crucial for managing ALL in young adults, especially for high-risk individuals. TKIs have improved outcomes for Ph-positive ALL patients, while HCT remains the recommended treatment. Trials are exploring new treatment approaches, such as combining blinatumomab with chemotherapy for B-cell ALL (NCT02003222) [26].

Elder ALL: Elder ALL patients face unique clinical and molecular challenges, including B-lineage ALL, complex cytogenetic abnormalities, and Ph+ ALL, which are poor prognostic characteristics. TP53 mutations are more common in elderly patients, and secondary ALL is more common and has a worse prognosis. Comorbidities, such as diabetes, cardiovascular problems, and chronic lung disease, can affect treatment approaches. Prognostic factors in older ALL patients include age, performance status, and MRD persistence. Treatment with targeted chemotherapy (TKIs) for Ph+ ALL in elderly patients is encouraging, with studies showing high complete remission rates when used in conjunction with reduced-intensity chemotherapy. However, relapses are still frequent, necessitating further study into long-term consequences and novel therapeutic approaches. Stem cell transplantation (SCT) is rarely advised in older ALL patients due to high transplant-related mortality. However, reduced-intensity conditioning (RIC) has a promising survival rate in patients aged 38 to 56 years [27].

Future Prospectives:

Future leukaemia treatment options are promising due to advancements in molecular, genetic, and epigenetic analysis. Combining transcriptome, proteome, and genetic profiling will enable highly customized, less harmful, and more successful therapies. New libraries of TKIs, monoclonal antibodies, and CAR-T cells will enable targeted treatment for diverse subsets. These developments will lead to a new age of tailored leukaemia care with improved results and reduced adverse effects.

Conclusion:

ALL is a type of leukemia which affects the replication of WBCs. It occurs mostly in the pediatric population with males being affected than females by 3-fold. However, new altercations of ALL arise with time, which gave rise to diagnostic techniques like NGS and MRD detection. Therapies like Temzolomide, Imatinib, Blinatumomab, CAR-T cell therapies and RNAi mediated drugs are used to control relapse, increase EFS rates and observe response to chemo and cytotoxic therapy. Addition of CAR-T with stem cell transplantation are done to prevent relapse. There have been advances in treatment according to age as well. Advancing epigenetic and genomic profiling leads to an open door of future ALL management options.

References:

1. Das PK, Diya VA, Meher S, Panda R, Abraham A. A systematic review on recent advancements in deep and machine learning based detection and classification of acute lymphoblastic leukemia. IEEE access. 2022 Aug 3;10:81741-63.
2. Malard F, Mohty M. Acute lymphoblastic leukaemia. The Lancet. 2020 Apr 4;395(10230):1146-62.
3. Malczewska M, Kośmider K, Bednarz K, Ostapińska K, Lejman M, Zawitkowska J. Recent advances in treatment options for childhood acute lymphoblastic leukemia. Cancers. 2022 Apr 16;14(8):2021.
4. Brown P, Inaba H, Annesley C, Beck J, Colace S, Dallas M, DeSantes K, Kelly K, Kitko C, Lacayo N, Larrier N. Pediatric acute lymphoblastic leukemia, version 2.2020, NCCN clinical practice guidelines in oncology. Journal of the National Comprehensive Cancer Network. 2020 Jan 1;18(1):81-112.
5. Khandekar R, Shastry P, Jaishankar S, Faust O, Sampathila N. Automated blast cell detection for Acute Lymphoblastic Leukemia diagnosis. Biomedical Signal Processing and Control. 2021 Jul 1;68:102690.

6. Aisyi M, Andriastuti M, Kosasih A, Utomo A, Saputra F, Tjitra Sari T, *et al.* Unraveling copy number alterations in pediatric B-cell acute lymphoblastic leukemia: Correlation with induction phase remission using MLPA. Asian Pac J Cancer Prev [Internet]. 2024;25(7):2421–6.
7. Li X, Lin S, Liao N, Mai H, Long X, Liu L, *et al.* The RAS-signaling-pathway-mutation-related prognosis in B-cell acute lymphoblastic leukemia: A report from South China Children's Leukemia Group. *Hematol Oncol* [Internet]. 2024;42(3)..
8. Tavakoli Shirazi P, N Eadie L, L Heatley S, L White D. TYK2 activating alterations in acute lymphoblastic leukemia: Novel driver oncogenes with potential avenues for precision medicine? J Cancer Sci Clin Ther [Internet]. 2021;05(02).
9. Barrios-Palacios D, Organista-Nava J, Balandrán JC, Alarcón-Romero L del C, Zubillaga-Guerrero MI, Illades-Aguiar B, *et al.* The role of miRNAs in childhood acute lymphoblastic leukemia relapse and the associated molecular mechanisms. Int J Mol Sci [Internet]. 2023;25(1):119.
10. Amarante-Mendes GP, Rana A, Datoguia TS, Hamerschlak N, Brumatti G. BCR-ABL1 tyrosine kinase complex signaling transduction: Challenges to overcome resistance in chronic myeloid leukemia. Pharmaceutics [Internet]. 2022;14(1):215.
11. Palomero T, Lim WK, Odom DT, Sulis ML, Real PJ, Margolin A, *et al.* NOTCH1 directly regulates *c-MYC* and activates a feed-forward-loop transcriptional network promoting leukemic cell growth. Proc Natl Acad Sci U S A [Internet]. 2006;103(48):18261–6.
12. Grüninger PK, Uhl F, Herzog H, Gentile G, Andrade-Martinez M, Schmidt T, *et al.* Functional characterization of the PI3K/AKT/MTOR signaling pathway for targeted therapy in B-precursor acute lymphoblastic leukemia. Cancer Gene Ther [Internet]. 2022;29(11):1751–60.
13. Coccaro N, Anelli L, Zagaria A, Specchia G, Albano F. Next-generation sequencing in acute lymphoblastic leukemia. International journal of molecular sciences. 2019 Jun 15;20(12):2929.
14. Qin D. Next-generation sequencing and its clinical application. Cancer biology & medicine. 2019 Feb;16(1):4.
15. Szczepariski T, Orfão A, van der Valden VH, San Miguel JF, van Dongen JJ. Minimal residual disease in leukaemia patients. The lancet oncology. 2001 Jul 1;2(7):409-17.

16. Chen H, Wang J, Wang H, Liang J, Dong J, Bai H, Jiang G. Advances in the application of Let-7 microRNAs in the diagnosis, treatment and prognosis of leukemia. Oncology Letters. 2022 Jan 1;23(1):1-8.
17. Jabbour E, Kantarjian H, Ravandi F, Thomas D, Huang X, O'Brien S. Combination of hyperCVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: a singlecentre, phase 2 study. Lancet Oncol 2015; 16: 1547-55.
18. Bai XT, Moles R, Chaib-Mezrag H. Small PARP inhibitor PJ-34 induces cell cycle arrest and apoptosis of adult T-cell leukemia cells. J Hematol Oncol 2015; 8: 1-12.
19. Mohseni M, Uludag H, Brandwein JM. Advances in biology of acute lymphoblastic leukemia (ALL) and therapeutic implications. American journal of blood research. 2018;8(4):29.
20. Jabbour E, Kantarjian H. Immunotherapy in adult acute lymphoblastic leukemia: the role of monoclonal antibodies. Blood Adv 2016; 1: 260-4.
21. Maude SL, Teachey DT, Porter DL, Grupp SA. CD19-targeted chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. Blood 2015; 125: 4017-23.
22. Uckun FM, Qazi S, Ma H, Yin L, Cheng J. A rationally designed nanoparticle for RNA interference therapy in B-lineage lymphoid malignancies. EBioMedicine 2014; 1: 141-55.
23. Zhao, X., Wang, L., Na, I., Porrata, L.F., Junghanss, C., & Sano, H. (2017). Advances in Hematopoietic Stem Cell Transplantation.
24. Vittayawacharin P, Kongtim P, Ciurea SO. Future directions in haploidentical hematopoietic stem cell transplantation. Hematology [Internet]. 2024;29(1).
25. Inaba H, Mullighan CG. Pediatric acute lymphoblastic leukemia. Haematological [Internet]. 2020 [cited 2024 Aug 16];105(11):2524–39.
26. Stock W, Luger SM, Advani AS, Yin J, Harvey RC, Mullighan CG, *et al.* A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403. Blood [Internet]. 2019 [cited 2024 Aug 16];133(14):1548–59.
27. Fathi AT, DeAngelo DJ, Stevenson KE, Kolitz JE, Asch JD, Amrein PC, *et al.* Phase 2 study of intensified chemotherapy and allogeneic hematopoietic stem cell transplantation for older patients with acute lymphoblastic leukemia: Intensified Therapy for Older Adults With ALL. Cancer [Internet]. 2016;122(15):2379.

ANTIMICROBIAL HERBAL NANOFORMULATIONS: A SOLUTION TO ANTIBIOTIC RESISTANCE

Sapana Patil*, Sweta B. Besh, Maitri Mahant and Divya Kanojiya

Department of Pharmacy,

Sumandeep Vidypeeth Deemed to be University, Piparia, Vadodara, Gujarat, India, 391760

*Corresonding author E-mail: sapanapatel1112@gmail.com

Abstract:

The need to investigate new therapeutic approaches outside of traditional antibiotics has arisen due to the global increase in antimicrobial resistance (AMR). In this chapter various antibiotic resistance mechanisms are also discussed briefly. With their synergistic effects between phytochemicals and nanocarriers to improve antibacterial activity, herbal nanoformulations have become a viable substitute. The use of herbal nanoformulations in the treatment of infections, including wounds, skin conditions, and mouth ailments, is thoroughly reviewed in this chapter. The enhanced solubility, stability, and targeted administration of nano-encapsulated herbal medicines have been shown to be more effective than their traditional counterparts in a number of in vitro and in vivo investigations. Certain formulations, like silver nanoparticles from Solanum virginianum, gold nanoparticles generated from Eclipta alba, and nanocomposites based on clove oil, have demonstrated strong antibacterial and wound-healing capabilities. All things considered, this chapter promotes the use of nanotechnology and phytomedicine together as a feasible route to biocompatible, sustainable, and efficient antimicrobial treatments.

Keywords: Antimicrobial Herbal Nanoformulations, Antibiotic Resistance, Conventional Antibiotics *vs.* Nano Herbal Medicines, Nanocarriers.

1. Introduction:

The effectiveness of traditional antimicrobial treatments is in danger due to antibiotic resistance, which has become a serious worldwide health concern. Antibiotic abuse and overuse have sped up the development of multidrug-resistant (MDR) bacteria, making many conventional therapies useless. Without immediate action, antibiotic resistance may lead to ten million fatalities a year by 2050, surpassing cancer mortality rates, according to the World Health Organization. [1] Alternative antimicrobial approaches are gaining popularity as a solution to this challenge. It has long been known that herbal remedies, which are abundant in bioactive substances such terpenoids, alkaloids,

flavonoids, and essential oils, have antibacterial qualities. But issues with stability, bioavailability, and low solubility have restricted their practical use.[2]

One fascinating way to overcome these restrictions is through nanotechnology. It is feasible to improve the solubility, prevent degradation, and enable targeted delivery of herbal components to infection sites by encapsulating them in nanoparticles. Curcumin, for example, a substance that comes from Curcuma longa, has strong antibacterial properties but a low bioavailability. Curcumin nanoformulations have shown increased stability and effectiveness against a range of infections.[3]

"Herbal nanoformulations"—the combination of herbal medicine with nanotechnology—represent a synergistic strategy to counteract antibiotic resistance. These formulations provide a sustainable and environmentally responsible substitute for synthetic antibiotics while also enhancing the medicinal potential of herbal components. [4]

2. Limitations of Conventional Antibiotics vs. Nano Herbal Medicines

Traditional antibiotics have been crucial in the fight against bacterial infections, but their effectiveness is waning because of several intrinsic drawbacks. Antibiotic abuse and overuse have sped up the creation of multidrug-resistant (MDR) bacteria, making many conventional therapies useless. Furthermore, antibiotics frequently have poor specificity, indiscriminately attacking both beneficial and pathogenic bacteria, which results in dysbiosis and related health problems. Their therapeutic potential is further limited by their pharmacokinetic characteristics, which include poor solubility and stability.[5]

On the other hand, by improving the delivery and effectiveness of antimicrobial chemicals originating from plants, nano-herbal medicines present a possible substitute. Improved phytochemical stability, bioavailability and solubility are made possible by nanotechnology, allowing for targeted and prolonged release at infection sites. In addition to improving treatment results, this strategy reduces the risk of resistance development and systemic side effects. [6,7] Plant-derived substances with antibacterial qualities are used in herbal medicine, which has its roots in ancient methods. Terpenoids, alkaloids, polyphenols, and flavonoids are examples of phytochemicals that have a variety of modes of action, such as interfering with quorum sensing, disrupting microbial cell walls, and inhibiting the production of nucleic acids.[8]

The effectiveness of herbal extracts against MDR infections has been demonstrated by recent investigations. For example, thymol and carvacrol, which are present in oregano and thyme, have shown strong antibacterial properties. Furthermore, the combination of

herbal medicine with nanotechnology has increased the therapeutic potential of both, providing a workable solution to the growing problem of antibiotic resistance. [9]

3. Antibiotic Resistance: An Overview

Resistance Mechanisms:

To avoid the effects of antibiotics, bacteria have evolved a number of mechanisms:

- Efflux Pumps: By removing antibiotics from bacterial cells, these transport proteins lower intracellular drug concentrations and reduce their effectiveness. For example, *Pseudomonas aeruginosa's* MexJK efflux pump contributes to multidrug resistance by requiring the OprM protein for antibiotic efflux. [10]
- Formation of biofilms: Forming biofilms, which form structured communities coated in a protective matrix, is a capability of bacteria that can impede the entry of antibiotics and promote persistent infections. Biofilm production has been demonstrated to be prevented by inhibiting multidrug efflux, suggesting a connection among the efflux mechanism and biofilm development [11]
- Genetic Mutations: Antibiotic targets may change as a result of spontaneous mutations, which could decrease drug binding and efficacy. Many bacterial species share this type of mutation as a means of developing resistance.[12]

4. Need for alternative therapeutic strategies:

Beyond using traditional antibiotics, alternative therapeutic approaches must be investigated due to the growing problem of antimicrobial resistance (AMR). Novel strategies are being researched to address this worldwide health emergency as conventional antibiotics lose their effectiveness against organisms that have developed resistance.

The alternative strategies like antimicrobial Peptides (AMPs), bacteriophage therapy, CRISPR-Cas systems, and nanoparticle-based therapies, are being used to combat the antibiotic resistance of bacteria.

Natural substances with broad-spectrum antibacterial activity are known as antimicrobial peptides, or AMPs. They work by altering immunological responses and rupturing bacteria membranes. Compared to conventional antibiotics, AMPs are less prone to cause resistance because of their distinct mechanisms of action. For clinical application, however, issues including stability and possible toxicity must be resolved.[13]

Bacteriophage therapy involves the use of viruses called bacteriophages, which only infect and lyse bacteria. Phage therapy is a focused method for getting rid of harmful

bacteria, particularly types that are resistant to drugs. Although encouraging, factors like regulatory frameworks and phage-host specificity must be taken into account before broad adoption can occur. [14]

CRISPR-Cas Systems: Antibiotic resistance genes in bacterial genomes can be targeted and disrupted using the CRISPR-Cas gene-editing technology. Reversing resistance mechanisms and restoring antibiotic efficacy are possible with this precision technique. [15]

Therapies Based on Nanoparticles: Silver and gold nanoparticles, for example, have inherent antibacterial qualities and can improve the effectiveness of antimicrobial medicines. Their capacity to damage bacterial membranes and alter metabolic processes renders them effective instruments in combating resistant infections. Some NPs, like zinc oxide and silver nanoparticles, have antibacterial qualities by nature. Bacterial cell death can result from their ability to damage bacterial cell membranes, produce reactive oxygen species (ROS), and obstruct vital cellular functions.[16]

5.Herbal Nanoformulations: A Synergistic Approach

Herbal nanoformulations are a synergistic strategy that combines the superior delivery capabilities of nanotechnology with the medicinal qualities of substances obtained from plants. Particularly in light of the growing prevalence of antibiotic resistance, this integration improves the antibacterial efficiency of herbal remedies and presents viable substitutes for traditional antibiotics.

Mechanisms of nanoformulations for Enhancing Antimicrobial Efficacy:

- Enhanced Bioavailability: Curcumin and other phytochemicals are more soluble and stable when encapsulated in nanoparticles, which improves absorption and prolongs release. For example, in diabetic rats, gold nanoparticles coated with curcumin have shown improved wound healing and antimicrobial activity. [17]
- Targeted Delivery: Herbal components can be delivered to infection areas directly using nanocarriers, which will increase local medicine concentration and lessen systemic negative effects.
- Enhanced Penetration: Nanoparticles can get past obstacles that frequently stand in the way of traditional treatments by more efficiently penetrating cellular membranes and biofilms than free chemicals.[18]

Synergistic Effects Between Nanocarriers and Herbal Compounds

Green Synthesis of Nanoparticles:

Plant extracts can contribute extra antibacterial qualities to the green synthesis of nanoparticles by serving as stabilizing and reducing agents. For instance, silver nanoparticles made from flower extract from Curcuma longa have demonstrated strong antibacterial activity against a range of diseases. [19]

Enhanced antibacterial Activity:

When compared to the crude extracts alone, the antibacterial efficiency of silver nanoparticles made from Waltheria americana root extracts was higher, suggesting a synergistic enhancement. [20] A frequent pathogen in endodontic infections, Enterococcus faecalis, was significantly inhibited by curcumin encapsulated in solid lipid nanoparticles. In comparison to free curcumin, the nanoformulation reduced bacterial viability by more than 90% after 72 hours. Studies that contrasted curcumin-loaded nanoparticles with free curcumin found that the nanoformulations continuously demonstrated improved antibacterial activity and reduced minimum inhibitory concentrations (MICs). [21] When compared to the extracts alone, silver nanoparticles made with plant extracts frequently exhibit better potency and broader-spectrum antibacterial action, demonstrating the advantages of incorporating nanoparticles. Strong antibacterial action against Ralstonia solanacearum, the cause of tomato vascular wilt, was demonstrated by silver nanoparticles made with Salvia nubicola extract, underscoring their potential for use in agricultural settings. [22]

6.Applications of Herbal Nanoformulations in Wound Healing, Skin, and Oral Infections

Wound Healing

Nanoformulations have proven to be effective in avoiding infections and accelerating wound healing. For example, gentamicin-containing chitosan nano-biocomposite films have improved wound healing and demonstrated encouraging outcomes in both in vitro and in vivo tests. Similarly, the ability of magnesium oxide nanoparticle-containing nanofiber antimicrobial bandages to hasten wound healing has been investigated. [23,24] For example, a study showed that in both in vitro and in vivo scenarios, a cellulosic textile/clove nanocomposite enhanced wound healing and had antibacterial characteristics. In animal models, phyto-engineered gold nanoparticles made with Eclipta alba also shown to improve wound healing and antibacterial activity. [25]

Skin infection:

Herbal extract-based nanoformulations have shown promise in treating skin infections. Nanoparticles of silver, gold, and their alloys produced by actinobacteria have demonstrated strong antibacterial qualities and have been useful in wound healing applications. Furthermore, the multifunctional properties of electrospun nanodiamond-silk fibroin membranes in biosensing and wound healing have been investigated, demonstrating antibacterial activity and biocompatibility.[26] An essential oil-based nano-emulgel, for instance, showed improved skin penetration and antibacterial activity, making it appropriate for treating skin infections. Furthermore, silver nanoparticles made using Solanum virginianum show antioxidant and antibacterial qualities, suggesting that they may be used to treat skin infections. [27]

Oral Infections:

The antibacterial activity of herbal nanoformulations has been investigated in the field of oral health. According to a study, a poly-herbal extract showed strong antibacterial action when used against dental microorganisms. Additionally, recent herbal remedies have been examined as substitute dental therapies, and their efficacy has been demonstrated by in vitro, in vivo, and clinical research. [28,29]

Conclusion:

Combining herbal medicine and nanotechnology is a novel and promising strategy to counter the growing threat of antibiotic resistance. Herbal nanoformulations have overcame many of the drawbacks of traditional antibiotics and unrefined herbal extracts by exhibiting greater antibacterial qualities, increased bioavailability, and targeted delivery. Numerous in vitro and in vivo investigations have demonstrated the efficacy of these nanoformulations in the treatment of oral infection, skin conditions, and wound infections. Their medicinal potential is demonstrated by research examples such clove oil-based nanocomposites, gold nanoparticles generated from Eclipta alba, and curcumin-loaded nanoparticles. Furthermore, the increased interest and viability of these technologies are highlighted by the translation of this research and clinical applications, which are demonstrated by patents, product development, and commercialization. Herbal nanoformulations are still being developed and incorporated into common pharmaceutical and medical applications, owing to the ongoing trajectory of research and validation. Herbal nanoformulations stand out as a multidimensional option as the health community

looks for sustainable and efficient antibiotic substitutes. They combine the accuracy and efficiency of nanotechnology with the rich pharmacological legacy of plant-based therapy.

References:

1. Sharma D, Gautam S, Singh S, Srivastava N, Khan AM, Bisht D. Unveiling the nanoworld of antimicrobial resistance: integrating nature and nanotechnology. Frontiers in Microbiology. 2025 Jan 9;15:1391345.
2. Moradi N, Taghizadeh SM, Hadi N, Ghanbariasad A, Berenjian A, Khoo KS, Varjani S, Show PL, Ebrahiminezhad A. Synthesis of mesoporous antimicrobial herbal nanomaterial-carrier for silver nanoparticles and antimicrobial sensing. Food and Chemical Toxicology. 2022 Jul 1;165:113077.
3. Chaturvedi A, Shukla R. Nanoantibiotics-driven approaches as an advanced therapy for bacterial infections and chemotherapeutic resistance. In Nanostructured Drug Delivery Systems in Infectious Disease Treatment 2024 Jan 1 (pp. 183-217). Academic Press.
4.
5. Alaoui Mdarhri H, Benmessaoud R, Yacoubi H, Seffar L, Guennouni Assimi H, Hamam M, Boussettine R, Filali-Ansari N, Lahlou FA, Diawara I, Ennaji MM. Alternatives therapeutic approaches to conventional antibiotics: advantages, limitations and potential applications in medicine. Antibiotics. 2022 Dec 16;11(12):1826.
6. Ashraf MV, Pant S, Khan MH, Shah AA, Siddiqui S, Jeridi M, Alhamdi HW, Ahmad S. Phytochemicals as antimicrobials: prospecting Himalayan medicinal plants as source of alternate medicine to combat antimicrobial resistance. Pharmaceuticals. 2023 Jun 15;16(6):881.
7. Nausch B, Bittner CB, Höller M, Abramov-Sommariva D, Hiergeist A, Gessner A. Contribution of symptomatic, herbal treatment options to antibiotic stewardship and microbiotic health. Antibiotics. 2022 Sep 29;11(10):1331.
8. Enioutina EY, Teng L, Fateeva TV, Brown JC, Job KM, Bortnikova VV, Krepkova LV, Gubarev MI, Sherwin CM. Phytotherapy as an alternative to conventional antimicrobials: combating microbial resistance. Expert review of clinical pharmacology. 2017 Nov 2;10(11):1203-14.
9. Abdallah EM, Alhatlani BY, de Paula Menezes R, Martins CH. Back to nature: Medicinal plants as promising sources for antibacterial drugs in the post-antibiotic era. Plants. 2023 Aug 28;12(17):3077.

10. Kumar A, Schweizer HP. Bacterial resistance to antibiotics: active efflux and reduced uptake. Advanced drug delivery reviews. 2005 Jul 29;57(10):1486-513.
11. Darby EM, Trampari E, Siasat P, Gaya MS, Alav I, Webber MA, Blair JM. Molecular mechanisms of antibiotic resistance revisited. Nature Reviews Microbiology. 2023 May;21(5):280-95.
12. Wang GE, Wilson TJ, Jiang Q, Taylor DE. Spontaneous mutations that confer antibiotic resistance in Helicobacter pylori. Antimicrobial agents and chemotherapy. 2001 Mar 1;45(3):727-33.
13. Ribeiro SM, De La Fuente-Núñez C, Baquir B, Faria-Junior C, Franco OL, Hancock RE. Antibiofilm peptides increase the susceptibility of carbapenemase-producing Klebsiella pneumoniae clinical isolates to β-lactam antibiotics. Antimicrobial agents and chemotherapy. 2015 Jul;59(7):3906-12.
14. Singha B, Singh V, Soni V. Alternative therapeutics to control antimicrobial resistance: a general perspective. Frontiers in Drug Discovery. 2024 Jul 17;4:1385460.
15. Tao S, Chen H, Li N, Liang W. The application of the CRISPR-Cas system in antibiotic resistance. Infection and drug resistance. 2022 Jan 1:4155-68.
16. Parvin N, Joo SW, Mandal TK. Nanomaterial-based strategies to combat antibiotic resistance: Mechanisms and applications. Antibiotics. 2025 Feb 18;14(2):207.
17. Salama A, Elsherbiny N, Hetta HF, Safwat MA, Atif HM, Fathalla D, Almanzalawi WS, Almowallad S, Soliman GM. Curcumin-loaded gold nanoparticles with enhanced antibacterial efficacy and wound healing properties in diabetic rats. International journal of pharmaceutics. 2024 Dec 5;666:124761.
18. Bodnár K, Fehér P, Ujhelyi Z, Bácskay I, Józsa L. Recent approaches for the topical treatment of psoriasis using nanoparticles. Pharmaceutics. 2024 Mar 25;16(4):449.
19. Karthik K, Tuteja G, Das P, Mishra R. Exploring the Antibacterial, Mechanical and Thermal Properties of Calabash Fiber Reinforced Epoxy Composite with Natural Fillers. Results in Engineering. 2025 Jan 21:104113.
20. Shahzadi S, Fatima S, Shafiq Z, Janjua MR. A review on green synthesis of silver nanoparticles (SNPs) using plant extracts: a multifaceted approach in photocatalysis, environmental remediation, and biomedicine. RSC advances. 2025;15(5):3858-903.
21. Ferreira S, Grenho L, Fernandes MH, Lima SA. Curcumin-Loaded Lipid Nanoparticles: A Promising Antimicrobial Strategy Against Enterococcus faecalis in Endodontic Infections. Pharmaceutics. 2025 Jan;17(1):108.

22. Pradhan U, Prajapati JP, Majhi P, Sahu D, Singh RK, Mallick S, Shukla AK. Green synthesis and characterization of Blumea sinuata silver nanoparticles: antibacterial, antifungal, and antioxidant properties. Nanoscale Advances. 2025.
23. Asgarirad H, Ebrahimnejad P, Mahjoub MA, Jalalian M, Morad H, Ataee R, Hosseini SS, Farmoudeh A. A promising technology for wound healing; in-vitro and in-vivo evaluation of chitosan nano-biocomposite films containing gentamicin. Journal of microencapsulation. 2021 Feb 17;38(2):100-7.
24. Nikfarjam S, Aldubaisi Y, Swami V, Swami V, Xu G, Vaughan MB, Wolf RF, Khandaker M. Polycaprolactone electrospun nanofiber membrane with skin graft containing collagen and bandage containing MgO nanoparticles for wound healing applications. Polymers. 2023 Apr 24;15(9):2014.
25. Parham S, Kharazi AZ. Cellulosic textile/clove nanocomposite as an antimicrobial wound dressing: In vitro and in vivo study. Colloids and Surfaces B: Biointerfaces. 2022 Sep 1;217:112659.
26. Shanmugasundaram T, Radhakrishnan M, Gopikrishnan V, Kadirvelu K, Balagurunathan R. In vitro antimicrobial and in vivo wound healing effect of actinobacterially synthesised nanoparticles of silver, gold and their alloy. RSC advances. 2017;7(81):51729-43.
27. Anand K, Ray S, Rahman M, Shaharyar A, Bhowmik R, Bera R, Karmakar S. Nano-emulgel: emerging as a smarter topical lipidic emulsion-based nanocarrier for skin healthcare applications. Recent patents on anti-infective drug discovery. 2019 May 1;14(1):16-35.
28. Moghadam ET, Yazdanian M, Tahmasebi E, Tebyanian H, Ranjbar R, Yazdanian A, Seifalian A, Tafazoli A. Current herbal medicine as an alternative treatment in dentistry: In vitro, in vivo and clinical studies. European journal of pharmacology. 2020 Dec 15;889:173665.
29. Rauf A, Ahmad T, Khan A, Maryam, Uddin G, Ahmad B, Mabkhot YN, Bawazeer S, Riaz N, Malikovna BK, Almarhoon ZM. Green synthesis and biomedicinal applications of silver and gold nanoparticles functionalized with methanolic extract of Mentha longifolia. Artificial Cells, Nanomedicine, and Biotechnology. 2021 Jan 1;49(1):194-203.

REFLUX CONDENSATION: PRINCIPLES, APPLICATIONS, AND ADVANTAGES IN CHEMICAL PROCESSES

Shivkant Patel*[1], Dillip Kumar Dash[1], Surabhi Jain[2] and Anubha Jain[3]

[1]Department of Pharmacy,

Sumandeep Vidyapeeth Deemed to be University, Piparia, 391760, Vadodara, Gujarat

[2]Monark Goswami College of Pharmacy, Gandhinagar, Gujarat, India

[3]Sri Aurobindo College of Pharmacy, Indore (M.P.)

*Corresponding author E-mail: shivapatel2609@gmail.com

Abstract:

Reflux condensation is a critical technique in chemical synthesis, widely used in laboratories and industries to enable efficient, controlled, and prolonged heating of reaction mixtures. It involves the boiling of a solvent with the concurrent condensation of vapors, which are returned to the system to maintain solvent volume and thermal consistency. This method allows reactions to be conducted at a constant temperature (the boiling point of the solvent) without loss of volatile components, thus facilitating improved yields, reproducibility, and safety. This chapter explores the fundamental principles, thermodynamic considerations, apparatus design, and diverse applications of reflux condensation. Special attention is given to its role in organic synthesis, solvent recovery, extraction, purification, and polymerization. The advantages of reflux—including minimization of solvent loss, enhanced reaction efficiency, and eco-friendliness—are elaborated in detail. The chapter also highlights how reflux aligns with green chemistry goals and provides a foundation for scalable and reproducible chemical operations.

Keywords: Reflux Condensation, Organic Synthesis, Solvent Recovery, Chemical Reactions, Laboratory Techniques, Thermal Control, Soxhlet Extraction, Distillation, Reaction Kinetics, Green Chemistry.

1. Introduction:

Reflux condensation is a foundational technique in both chemistry and chemical engineering, playing a pivotal role in numerous laboratory and industrial operations. It is particularly indispensable in organic synthesis, distillation, extraction, and various large-scale manufacturing processes where precise temperature control and solvent retention are crucial. The essence of reflux lies in its ability to facilitate reactions that require sustained heating by allowing the vapor generated during boiling to condense and return

to the reaction vessel. This cyclic process ensures that volatile solvents or reagents are not lost to the environment, thereby maintaining a constant reaction volume and concentration throughout the procedure. In a typical reflux system, the reaction mixture is heated to the boiling point of the chosen solvent. As the solvent vaporizes, it rises into a reflux condenser—a specialized glass apparatus cooled by a circulating coolant (usually water or antifreeze solution). Upon reaching the cool surfaces of the condenser, the vapor loses energy, condenses back into liquid, and drips back into the reaction flask. This continuous condensation and return cycle enable prolonged heating at the solvent's boiling point, thereby driving reactions to completion without the need for additional solvent replenishment or pressurization of the system [1]. The advantages of this technique are manifold. By providing a stable thermal environment, reflux enhances reaction kinetics, promotes complete conversion of reactants, and reduces the risk of side reactions that may occur at higher or fluctuating temperatures. Furthermore, because the solvent is recycled within the system, it minimizes environmental impact and operational costs, aligning well with the principles of green chemistry. This chapter delves into the comprehensive understanding of reflux condensation by exploring its underlying principles, a wide range of applications, the design and function of associated apparatus, safety protocols, and critical operational parameters. Mastery of reflux techniques is not only essential for successful laboratory synthesis and experimentation, but also for scaling up processes in pharmaceutical, petrochemical, and fine chemical industries. A detailed exploration of these elements will empower the reader to design efficient, safe, and reproducible reflux-based processes that adhere to both academic and industrial standards [2].

2. Definition and Basic Concept

Reflux is a core technique in chemistry that involves the boiling of a liquid with simultaneous condensation of the generated vapor, followed by its return to the original container. This process creates a closed-loop system where the solvent continuously evaporates, condenses, and re-enters the reaction mixture without any net loss of volume. It is especially useful for conducting chemical reactions that require extended heating over a period of time at a constant temperature. In the laboratory setting, reflux is typically carried out using a reflux condenser, a piece of specialized glassware that is attached vertically to the neck of a round-bottom flask containing the reaction mixture. The flask is usually heated with a heating mantle, water bath, or oil bath, which brings the solvent to its boiling point. As the solvent boils, it forms vapours that rise into the cooler inner chamber

of the condenser. Cold water or another coolant is circulated through the outer jacket of the condenser, which rapidly removes heat from the vapours, causing them to condense back into liquid form. The condensed droplets then trickle back into the reaction flask under gravity. This system enables the reaction to occur at the boiling point of the solvent, which is ideal for many organic reactions, because it provides sufficient thermal energy to overcome activation energy barriers without causing thermal decomposition of heat-sensitive reactants or products. Unlike an open boiling system, reflux prevents the loss of volatile components and maintains the concentration and integrity of the reaction mixture. The fundamental concept behind reflux is the conservation of mass and energy within a controlled environment. The solvent acts as both a medium for the reaction and a temperature regulator, ensuring that the reaction proceeds uniformly. Refluxing also enhances reaction efficiency and reproducibility, making it a widely adopted technique in both academic and industrial chemical laboratories. In essence, reflux allows chemists to harness the benefits of sustained thermal energy without the drawbacks of solvent evaporation or system pressurization. It is a cornerstone technique in organic synthesis, chemical kinetics, and process chemistry, where time, temperature, and concentration must be precisely regulated for successful outcomes [3].

2.1 Principle of Reflux

The principle of reflux is grounded in the concept of achieving and maintaining a thermal equilibrium within a chemical reaction system, specifically at the boiling point of the solvent being used. In many chemical reactions—particularly those involving organic compounds—elevated temperatures are needed to increase the rate of reaction and drive the process to completion. However, simply heating a reaction mixture in an open system can lead to evaporation and loss of volatile solvents and reagents, which compromises the reaction's efficiency, safety, and reproducibility. Reflux addresses this problem by creating a closed, self-regulating system where the solvent is allowed to boil, but the generated vapours are not lost. Instead, they are directed into a condenser, where they are cooled usually by the circulation of cold water or another cooling fluid in a surrounding jacket. Upon contact with the cool inner surface of the condenser, the vapor loses its latent heat of vaporization, transitions back into the liquid phase, and returns under gravity to the reaction flask. This cycle continues throughout the duration of the reaction. The key advantage of reflux is that it permits prolonged heating at a stable temperature, specifically the boiling point of the solvent. Since the temperature of a boiling solvent remains constant

under atmospheric pressure, the system effectively becomes thermally buffered, meaning it resists sudden fluctuations in temperature. This is particularly important for reactions that are thermally sensitive or require consistent kinetic energy over time. Additionally, reflux helps in maintaining the concentration of reactants and solvents in the system, which is critical for reactions that are dependent on stoichiometry or reaction equilibrium. In equilibrium-controlled reactions, the continuous return of condensed solvent ensures that the reaction can proceed in both forward and reverse directions until a dynamic balance is achieved. This results in better reaction control, higher yields, and reduced waste [4].

2.2 Thermodynamic Considerations

The process of reflux condensation is not merely a mechanical operation—it is deeply rooted in fundamental thermodynamic principles. Understanding the energy transformations involved provides insight into why reflux is so effective in maintaining controlled reaction conditions. At its core, reflux involves phase transitions governed by enthalpy changes and energy balance. When a liquid solvent is heated, it absorbs energy in the form of heat (q) supplied by an external source such as a heating mantle or oil bath. This energy increases the kinetic energy of the molecules within the liquid until they reach a threshold energy level that allows them to overcome intermolecular forces and transition from the liquid phase to the vapor phase. This change of phase vaporization occurs at the solvent's boiling point, a temperature where the vapor pressure of the liquid equals the atmospheric pressure. This phase transition requires a specific quantity of energy known as the latent heat of vaporization (ΔH vap). During this process, the temperature of the solvent remains constant even as energy is continuously added. The energy input at this stage does not increase the temperature but is used to change the phase of the solvent from liquid to gas. Once vaporized, the solvent molecules rise upward into the reflux condenser, where they encounter a surface maintained at a significantly lower temperature due to the circulation of a coolant, typically water. At this cooler surface, the vapor molecules lose their energy—primarily through conduction and convection—and as a result, their kinetic energy decreases. This loss of energy causes the vapor to condense back into the liquid state. This phase transition from vapor to liquid is exothermic, meaning energy is released in the form of heat. The condensed liquid then flows back into the reaction vessel due to gravity. The system operates in a closed-loop manner, where energy is continuously supplied to keep the solvent at its boiling point, and condensed vapours are recycled. This dynamic equilibrium between vaporization and condensation is crucial for thermally

controlled reactions. Since the boiling point of the solvent acts as a thermal ceiling, the reaction temperature is naturally regulated, preventing overheating and thermal degradation of reactants or products [5].

3. Apparatus for Reflux

A standard reflux setup includes:

- **Round-bottom flask:** Contains the reaction mixture.
- **Heating mantle or water/oil bath:** Provides heat to the system.
- **Reflux condenser:** Usually a Liebig, Allihn, or Dimroth condenser.
- **Clamps and stands:** Secure the apparatus.
- **Rubber tubing:** Circulates coolant (typically water).
- **Thermometer adapter (optional):** Monitors temperature at the vapor-liquid interface.

3.1 Types of Condensers

1. **Liebig Condenser:** A straight inner tube surrounded by a water jacket.
2. **Allihn Condenser:** Contains multiple bulbs for increased surface area.
3. **Dimroth Condenser:** Has a coiled internal tube for improved heat exchange [6].

3.2 Cooling Media

Typically, tap water or antifreeze mixtures are circulated through the outer jacket of the condenser. Chilled water is used when the boiling point of the solvent is very low or for highly volatile solvents [7].

4. Applications of Reflux Condensation

Reflux condensation is an essential technique that finds widespread application in both academic research and industrial processes. Its ability to provide a stable thermal environment, prevent solvent loss, and promote reaction completeness makes it highly valuable in multiple branches of chemistry, especially in organic synthesis, purification, and large-scale manufacturing [8]. Below are the key areas where reflux plays a central role:

4.1 Organic Synthesis

In organic chemistry, many reactions require sustained heating over long periods to proceed efficiently or to reach completion. These reactions often involve high activation energy barriers or slow kinetics, necessitating the continuous input of heat. Some common examples include:

- Esterification reactions: Involving carboxylic acids and alcohols, catalyzed by acid, requiring prolonged heating.

- Hydrolysis reactions: Where esters, amides, or other compounds are broken down using water under acidic or basic conditions.
- Cyclization and condensation reactions: Especially in the synthesis of heterocycles, polyaromatic compounds, or complex intermediates in drug development.

The use of reflux in such reactions ensures that the solvent is kept at its boiling point, providing uniform heat distribution throughout the mixture. Simultaneously, it prevents the evaporation of volatile solvents or low-boiling reactants. This leads to:

- Improved reaction rates
- Minimized solvent loss
- Reduced risk of decomposition
- Reproducibility and scalability [9]

4.2 Extraction Techniques

Reflux plays a key role in Soxhlet extraction, a method commonly used in natural product isolation, environmental analysis, and food chemistry. In this technique, a solid sample (such as powdered plant material) is placed in a porous thimble inside the extraction chamber. A solvent is heated to reflux, and its vapours rise, condense, and drip into the chamber, extracting soluble compounds from the sample. Once the solvent reaches a certain level, it siphons back into the boiling flask, carrying the extracted compounds with it.

This cycle continues for hours, resulting in:

- Thorough and efficient extraction
- Reduced solvent consumption compared to maceration
- Automation and consistency
- Minimized degradation of thermally sensitive compounds

Soxhlet extraction is widely used for isolating essential oils, alkaloids, pesticide residues, and other analytes from complex matrices [10].

4.3 Purification

Reflux is integral to certain purification techniques, particularly recrystallization, which is employed to purify solid compounds. In recrystallization, the crude solid is dissolved in a suitable solvent at elevated temperatures, often near or at the boiling point. Refluxing ensures complete dissolution of the compound and associated impurities. Upon slow cooling, the desired compound crystallizes out, while the impurities remain in the solution.

Reflux enhances this process by:

- Ensuring maximum solubilization of the solute
- Allowing extended time for the solvent to interact with impurities
- Minimizing solvent evaporation, preserving consistent concentration

It is also used in chemical digestion processes, such as removing inorganic salts from organics before analysis [11].

4.4 Distillation and Solvent Recovery

In distillation, reflux is used to improve the efficiency and resolution of component separation, particularly in fractional distillation. Here, a fractionating column is used above the boiling flask, and reflux is partially condensed and returned down the column.

This serves two purposes:

1. Increased number of theoretical plates – Each condensation-vaporization cycle simulates a mini-distillation, improving separation between compounds with similar boiling points.
2. Controlled reflux ratio – Adjusting how much condensate is returned versus collected enhances purity and yield.

In solvent recovery systems, reflux enables energy-efficient condensation of solvent vapors, which can then be collected, filtered, and reused—an approach aligned with green chemistry principles [12].

4.5 Polymerization Reactions

Certain polymerization reactions, especially step-growth polymerizations (e.g., polyesters, polyamides), require prolonged heating at consistent temperatures to allow monomer coupling and chain extension.

Reflux serves an important role by:

- Ensuring homogeneous reaction conditions, which is crucial for obtaining uniform polymers
- Maintaining optimal viscosity and molecular mobility within the system
- Allowing removal of small-molecule byproducts (e.g., water, methanol) via azeotropic distillation, while returning unreacted monomers

Examples include:

- Polycondensation reactions involving diols and dicarboxylic acids
- Ring-opening polymerization (ROP) of lactones or epoxides under reflux

These conditions are critical in both laboratory-scale research and industrial polymer production to obtain desired molecular weight distributions and material properties [13].

5. Operational Procedure

A typical reflux process involves the following steps:

1. **Preparation of the Reaction Mixture:** Reactants are measured and added to the round-bottom flask.
2. **Assembly of Apparatus:** The condenser is attached to the flask, secured, and coolant is connected.
3. **Heating:** The heating device is turned on. The solvent begins to boil, and vapor rises into the condenser.
4. **Condensation:** Vapours condense and drip back into the flask.
5. **Reaction Monitoring:** The process is monitored periodically, either by TLC, GC, or HPLC.
6. **Completion and Work-Up:** After completion, the heating is stopped, and the mixture is cooled for downstream processing [14].

6. Factors Affecting Reflux Efficiency

Several parameters influence the effectiveness of reflux condensation:

6.1 Solvent Choice

The boiling point of the solvent determines the temperature of the reaction. Polar solvents like ethanol or acetonitrile and nonpolar solvents like toluene are commonly used depending on the nature of reactants.

6.2 Heating Rate

A controlled heating rate prevents bumping and ensures that only solvent vapors reach the condenser.

6.3 Cooling Efficiency

Efficient cooling ensures complete condensation. Poor cooling can lead to vapor escape and solvent loss.

6.4 Condenser Design

A longer or more complex condenser provides greater surface area and improved condensation for more volatile solvents [15].

7. Safety Considerations

Reflux setups must be assembled with care to avoid accidents:

- **Avoid Closed Systems:** Ensure there's an open path for pressure release.
- **Use Proper Clamps:** Prevents tipping or breaking of glassware.
- **Monitor Temperature and Pressure:** Prevents overheating and ensures safe operation.
- **Ventilation:** Work under a fume hood to avoid exposure to toxic vapors.
- **Coolant Flow Check:** Ensure consistent flow to avoid overheating or condenser failure [16].

8. Advantages of Reflux Condensation

Reflux condensation is a foundational technique in chemical laboratories and industrial settings, prized for its efficiency, simplicity, and reliability. By allowing reactions to proceed at a solvent's boiling point while continuously condensing and returning the vapor to the system, reflux creates a stable, closed-loop system that supports a wide array of chemical transformations [17]. The advantages of using reflux are numerous and offer both scientific and practical benefits, which are detailed below:

8.1. Minimizes Solvent Loss

One of the most significant benefits of reflux is its ability to prevent solvent evaporation. During heating, the solvent is vaporized, but rather than escaping into the environment:

- The vapours rise into a condenser.
- They are cooled and condense into liquid form.
- The liquid returns to the reaction flask by gravity.

This continuous recycling of the solvent not only reduces material costs but also:

- Preserves reaction concentration.
- Improves safety by minimizing flammable vapor release.
- Supports environmental sustainability by reducing solvent waste and emissions.

8.2. Maintains a Consistent and Sustained Temperature

Reflux provides an isothermal environment where the reaction occurs at the boiling point of the solvent, ensuring:

- Uniform heat distribution across the reaction mixture.
- Prevention of thermal degradation of sensitive compounds.
- Stable energy input to overcome activation energy barriers.

This temperature control is essential for reactions requiring prolonged heating, as it avoids the risks of overheating or fluctuating temperatures that could lead to side reactions or incomplete reactions.

8.3. Enhances Reaction Rates

Reflux allows for efficient molecular interactions by supplying continuous heat, which increases the kinetic energy of the reactants. As a result:

- Reactant molecules collide more frequently and with greater energy.
- The system overcomes activation energy barriers more effectively.
- Reaction kinetics are improved, especially for slow or equilibrium-limited processes.

Examples include nucleophilic substitution, esterification, and condensation reactions that benefit from elevated temperatures and extended reaction times.

8.4. Improves Product Yield

With constant solvent volume and sustained heating:

- Reactions can proceed to completion, minimizing unreacted starting materials.
- Side reactions due to thermal degradation or solvent loss are reduced.
- By-product formation is minimized, especially in reversible reactions.

In systems where product yield is equilibrium-dependent (like esterification), maintaining a stable thermal environment and concentration profile helps shift the reaction towards maximum product formation.

8.5. Ensures Reproducibility and Standardization

Reflux setups are simple to replicate and yield highly reproducible results, making them ideal for:

- Routine laboratory synthesis.
- Industrial batch production.
- Educational demonstrations.

Key parameters such as temperature, solvent volume, reaction time, and concentration can be easily controlled and repeated, ensuring consistent results across multiple experimental runs.

This reproducibility is particularly important in:

- Pharmaceutical synthesis (GMP compliance),
- Analytical chemistry (standard methods),
- Academic research (peer-reviewed studies).

8.6. Enhances Safety in Heating Volatile Compounds

Direct open heating of volatile or flammable solvents (e.g., ether, acetone, methanol) can be hazardous. Reflux enhances safety by:

- Containing vapours within a closed apparatus.
- Preventing build-up of pressure due to the open system design.
- Avoiding solvent depletion, which could lead to dry heating and fire risk.

Additionally, water-cooled condensers or more advanced cooling systems (e.g., reflux chillers) make the system more stable and controllable, further reducing operational risks.

8.7. Environmentally Friendly and Cost-Effective

By eliminating solvent loss, reflux contributes to:

- Reduced chemical waste.
- Lower operational costs due to minimized solvent consumption.
- Sustainable laboratory practices, aligning with green chemistry principles.

In large-scale chemical manufacturing, reflux-based solvent recovery systems significantly cut down on chemical waste and operational expenditure.

8.8. Facilitates Long-Duration Reactions Without Intervention

Some reactions require many hours to reach completion, especially:

- Polymerizations,
- Multistep syntheses,
- Natural product extractions,
- Metal-ligand complexations.

Reflux allows these reactions to proceed unattended for long durations without worrying about solvent evaporation or temperature instability, making it an ideal technique for both routine and complex procedures [18].

9. Limitations and Challenges

Despite its advantages, reflux has certain limitations:

- **Not Suitable for Heat-Sensitive Compounds:** Extended heating may degrade thermolabile substances.
- **Requires Continuous Monitoring:** Although semi-automated systems exist, manual setups need vigilance.
- **Potential for Solvent Bumping:** Sudden boiling can cause dangerous splashing [19].

10. Reflux in Industrial Applications

In industrial chemical engineering, reflux is critical for operations such as:

10.1 Fractional Distillation

Large-scale distillation columns use reflux to enhance separation efficiency. The **reflux ratio**, which is the ratio of condensed liquid returned to the column to that collected as distillate, is a key operational parameter.

10.2 Continuous Reactors

Continuous stirred-tank reactors (CSTRs) often use reflux to maintain reactant levels and conserve solvents while allowing prolonged heating.

10.3 Pharmaceutical Manufacturing

Reflux is widely used in drug synthesis, including the preparation of heterocyclic compounds, amide formation, and protection/deprotection steps [20].

11. Innovations and Automation in Reflux Systems

Recent advancements have led to the development of automated and digitized reflux systems:

- **Reflux Controllers:** Devices that regulate temperature, time, and coolant flow.
- **Microwave-Assisted Reflux:** Speeds up reaction rates and improves yields.
- **Green Chemistry Reflux Systems:** Minimize solvent use and employ biodegradable materials [21].

12. Case Studies and Examples

12.1 Esterification of Acetic Acid and Ethanol

In the presence of sulfuric acid, acetic acid reacts with ethanol under reflux to form ethyl acetate. The reflux allows the reaction to proceed at ~78°C (boiling point of ethanol), ensuring effective conversion.

12.2 Synthesis of Benzothiazole Derivatives

Many benzothiazole-based reactions require refluxing in acetic acid, DMF, or DMSO to facilitate ring closure and increase yield.

12.3 Hydrolysis of Esters

Alkaline hydrolysis (saponification) of esters like ethyl acetate uses aqueous NaOH under reflux to yield carboxylates and alcohols [22].

Conclusion:

Reflux condensation stands as one of the most fundamental and versatile techniques in the chemist's toolbox. By allowing chemical reactions to be carried out under controlled,

isothermal conditions, reflux ensures enhanced safety, reproducibility, and efficiency. Its ability to recycle solvents within a closed-loop system minimizes environmental impact and operational costs, making it particularly valuable in both academic research and industrial applications. The technique plays a pivotal role in a wide range of chemical processes, including organic synthesis, purification, solvent extraction, and polymerization. With the growing emphasis on sustainable and green chemistry practices, the relevance of reflux condensation is more prominent than ever. Understanding its principles, appropriate applications, and operational advantages is essential for chemists and engineers striving for optimal reaction performance, environmental stewardship, and process reliability.

References:

1. Souidi N, Bontemps A. Reflux condensation in narrow rectangular channels with perforated fins. Appl Therm Eng. 2003;23(7):871-91.
2. Obinelo IF, Round GF, Chang JS. Condensation enhancement by steam pulsation in a reflux condenser. Int J Heat Fluid Flow. 1994;15(1):20-9.
3. Gross U. Reflux condensation heat transfer inside a closed thermosyphon. Int J Heat Mass Transfer. 1992;35(2):279-94.
4. Livzan MA, Mozgovoi SI, Gaus OV, Bordin DS, Kononov AV. Diagnostic principles for chronic gastritis associated with duodenogastric reflux. Diagnostics. 2023;13(2):186.
5. Carey MC, Small DM. Micelle formation by bile salts: physical-chemical and thermodynamic considerations. Arch Intern Med. 1972;130(4):506-27.
6. Nesaraj AS, Nesaraj AS. Reflux condensation synthesis and characterization of Co3O4 nanoparticles for photocatalytic applications. Iran J Catal. 2014;4(4).
7. Lam K, Armstrong B, Margelefsky EL. Gravimetric and Thermal-Imaging Characterization of Water-Free Reflux Condensers for Laboratory Applications. ACS omega. 2024;9(14):16563-71.
8. Elango M, Deepa M, Subramanian R, Mohamed Musthafa A. Synthesis, characterization, and antibacterial activity of polyindole/Ag–Cuo nanocomposites by reflux condensation method. Polym-Plast Technol Eng. 2018;57(14):1440-51.
9. Tanemura K. Silica gel-mediated self-aldol reactions of highly volatile aldehydes under organic solvent-free conditions without reflux condenser. Tetrahedron Lett. 2019;60(29):1924-8.

10. Cameron AE. Large-capacity soxhlet extractor and reflux condenser. Ind Eng Chem, Anal Ed. 1932;4(4):394-5.
11. Elango M, Deepa M, Subramanian R, Saraswathy G. Synthesis, structural characterization and antimicrobial activities of polyindole stabilized Ag-Co3O4 nanocomposite by reflux condensation method. Mater Chem Phys. 2018;216:305-15.
12. Rundquist EM, Pink CJ, Livingston AG. Organic solvent nanofiltration: a potential alternative to distillation for solvent recovery from crystallisation mother liquors. Green Chem. 2012;14(8):2197-205.
13. Carothers WH. Studies on polymerization and ring formation. I. An introduction to the general theory of condensation polymers. J Am Chem Soc. 1929;51(8):2548-59.
14. Deng H, Liu J, Yang T, Wu S. Numerical study and visualization on flow characteristics of reflux condensation in air-cooled condenser. Appl Therm Eng. 2019;148:1310-23.
15. Manyele SV. The effect of reflux ratio and feed thermal conditions on ethanol-water distillation process performance. Int J Eng Res Sci Technol. 2024;16(4):66-90.
16. Yamada M, Kinoshita I, Torige T, Murase M, Yoshida Y, Nakamura H. Application of the Statistical Safety Evaluation Method to Reflux Cooling in the Loss-of-RHR Event During Mid-Loop Operation. Nucl Technol. 2017;200(2):125-43.
17. Meng N, Zhou Y, Nie W, Chen P. Synthesis of CdS-decorated RGO nanocomposites by reflux condensation method and its improved photocatalytic activity. J Nanopart Res. 2016;18:1-3.
18. Shrivastav G, Prava Jyoti T, Chandel S, Singh R. Eco-friendly extraction: innovations, principles, and comparison with traditional methods. Sep Purif Rev. 2024:1-7.
19. Liao Y, Guentay S, Suckow D, Dehbi A. Reflux condensation of flowing vapor and non-condensable gases counter-current to laminar liquid film in a vertical tube. Nucl Eng Des. 2009;239(11):2409-16.
20. Sharma MM, Mahajani SM. Industrial applications of reactive distillation. Reactive distillation: Status Future Dir. 2002:1-29.
21. Edwards TC, LaSalle S, Luong S, Andresen F, Quarles J, Wilson D, *et al.* Automated real-time hit picking, retesting, and reflux testing. J Lab Autom. 2004;9(3):135-9.
22. McElvain SM. Some observations on the acetoacetic ester condensation J Am Chem Soc. 1929;51(10):3124-30.

SARPAGANDHA'S PHARMACOLOGICAL SPECTRUM: TRADITIONAL ROOTS TO MODERN APPLICATIONS

Sonal Singh Kushwaha
Department Of Dravyaguna Vigyana,
Shri Dhanwantry Ayurvedic College and Hospital, Chandigarh
Corresponding author E-mail: sonal27091999@gmail.com

Abstract

Sarpagandha (*Rauwolfia serpentina*), a prominent medicinal shrub native to the Indian subcontinent, has been extensively used in traditional systems such as Āyurveda, Unani, and Chinese medicine. Its roots are renowned for containing pharmacologically active alkaloids, notably reserpine, which has established use in modern medicine for treating hypertension and mental disorders. This review provides a comprehensive overview of the ethnobotanical significance, chemical constituents, pharmacological activities, and contemporary scientific applications of *R. serpentina*. Notably, the plant shows potential in novel domains such as antiviral activity, enzymatic biosynthesis, and immune modulation. Recent studies highlight the antiviral potential of *R. tetraphylla* compounds against SARS-CoV-2, the role of *R. serpentina* UDP-glycosyltransferase (RsUGT) in gastrodin production, and the ability of endophytic Bacillus spp. to synthesize host-derived reserpine. Furthermore, supplementation with *R. serpentina* root powder in poultry improved immune gene expression and growth performance, showcasing its promise in ethnoveterinary medicine. Several Ayurvedic formulations incorporate *R. serpentina*, reinforcing its therapeutic legacy. Together, these insights underline the multifaceted value of *R. serpentina*, urging further research and conservation.

Keywords: *Rauwolfia serpentina, Sarpagandha,* Modern Therapeutics

Introduction:

Sarpagandha (*Rauwolfia serpentina)* is a medicinal shrub native to India, Bangladesh, and Southeast Asia [1]. It holds a prominent place in traditional systems like Āyurveda, Unani, and Chinese medicine, with references in classical texts such as the *Caraka Samhita [2]*, *Suśruta [3].*, Ashtanga Sangraha [4] Ashtanga Hrudaya [5] and various *Nighantus [6, 7].*. It is used for treating Hyperlipidemia [8] Hypertension [9] Diabetes [10] Dyslipidemia [11], Diarrhoea [12] Hepatic disorders [13] bacterial infestations [14] acts as Anti-oxidant [15] its roots are valued for their potent alkaloids.

The plant's key bioactive compound, reserpine, has been widely studied for its antihypertensive and antipsychotic properties. Other alkaloids like ajmaline, serpentine, and yohimbine contribute to its pharmacological relevance.

Modern medicine continues to utilize Sarpagandha, particularly for cardiovascular and neurological disorders. However, overharvesting has endangered its wild populations, highlighting the need for sustainable cultivation and conservation.

Sarpagandha exemplifies the integration of traditional wisdom with modern therapeutics, warranting continued research and protection.

Scientific/taxonomical classification	**Vernacular names**
Kingdom: Plantae	Hindi: Dhavalbarua, Chandramarva, Chota chanda, Nakulakanda, Nakulikanda
Phylum: Streptophyta	English: Serpentina root, Rauwolfia root, Serpentina root, Snake dog-bane
Class: Equisetopsida	Bengali: Chandra, Chandar, Chandar, Chota Chanda, Nakuli, Gandharasna
Order: Gentianales	Gujarati : Nolbela, Amelpoḍi
Family: Apocynaceae	Marathi : Adkai, Chandra, Sayasan, Amelpoḍi, Mungusabela, Nai, Sapaṇda
Genus: Rauwolfia	Marvadi: Harkaya, Harki
Species: *Rauwolfia serpentina*	Tulu: Patala-garuḍada-beru

Chemical constituents [16]

Alkaloids	Ajmalicidine, Ajmalicine, Ajmaline, Alstonine, Chandrine, Coryanthine, Corynanthine, Deserpidine, Indobinine, Ophioxylin, Papaverine, Raunatine, Rescinnamine, Reserpiline, Reserpine, Rauvolfinine, Sandwicolidine, Serpaajmaline, Serpentine, Serpentinine, Serpoterpine, Sarpagine, and Yohimbine.
Amino acids	Alanine, Aminobutyric acid, Arginine, Asparagine, Aspartic acid, Cystine, Glutamic acid, Glutamine, Glycine, Histidine, Isoleucine, Lysine, Oleic acid, Phenylalanine, Proline, Serine, Threonine, Tryptophan, Tyrosine, Valine.

Pharmacological Activity

Sarpagandha, commonly known as Indian snakeroot, is prized in traditional medicine for its diverse therapeutic benefits. One of its most prominent uses is in managing hypertension, or high blood pressure. It achieves this by reducing the activity of the sympathetic nervous system, which helps to calm the body's stress responses and lower blood pressure levels. Beyond its role in cardiovascular health, *Sarpagandha* is valued for its sedative and anxiolytic properties, making it effective in treating anxiety and insomnia by promoting relaxation and aiding sleep. Additionally, it has been traditionally employed in the management of certain psychiatric disorders due to its tranquilizing effects.

Anti- Viral Studies

This study explores the antiviral potential of *Rauvolfia tetraphylla* L., traditionally used in medicine and known for its antimicrobial properties. Focusing on in silico analysis, the research investigates the plant's activity against SARS-CoV-2 using molecular docking and pharmacokinetic screening. Of 20 phytochemicals identified via GC-MS, 8 met ADMET criteria and passed TOPKAT Ames mutagenicity tests. Docking these compounds against the SARS-CoV-2 main protease (3CLpro, PDB ID: 7DPV) revealed three promising candidates: (E, E, E, E, E, E)-2,6,10,15,19,23-hexamethyltetracosa-1,6,10,14,18,22-hexaen-3-ol, α-Tocospiro A, and α-Tocopherol. The findings suggest the plant's potential as a source for future antiviral drug development **[17]**

Efficient Biosynthesis of Gastrodin

This study focused on producing gastrodin, a key compound from *Gastrodia elata*, using a specific enzyme (RsUGT) from *Rauvolfia serpentina*. The enzyme was successfully expressed, purified, and characterized. It worked best at 40°C and pH 10, with 2% DMSO enhancing its activity. Under optimized conditions, RsUGT converted nearly all the substrate into gastrodin, achieving high yields (up to 285.35 mg/l). A recombinant bacterial strain (BL-RsUGT) also produced gastrodin efficiently. These results highlight RsUGT's strong potential for industrial-scale gastrodin production. [18]

Antibacterial and Antioxidant Properties

This study explored the endophytic bacteria found in the leaves of *Rauvolfia serpentina* to assess their ability to produce bioactive compounds, including the host-derived compound reserpine. Nine bacterial isolates were identified, with two (RSLB3 and RSLB18, both *Bacillus* species) showing strong antibacterial and antioxidant activity. RSLB3 showed higher flavonoid content and DPPH scavenging activity. Reverse Phase

HPLC confirmed the presence of reserpine in bacterial extracts, while UHPLC-HRMS/MS revealed a wide range of known and unknown bioactive compounds. This is the first detailed profiling of such endophytes in *R. serpentina*, suggesting their significant potential in natural product research. [19]

Ethnoveterinary Supplementation

This study explored the use of *Rauwolfia serpentina* powder (RSP) as an ethnoveterinary supplement to counter *Salmonella Gallinarum* infection in broiler chickens. Birds fed diets with 1.5% or 3% RSP showed reduced expression of inflammatory genes (SOCS3, P20K), increased MHC class IIβ expression, improved gut health, weight gain, and feed conversion ratio compared to infected controls. The findings suggest RSP effectively modulates immune response and supports growth performance in infected poultry, offering a natural alternative to antibiotics. Zhang Y, Rehman H, Khattak F, Tariq M, Khan BN, Chaman S, Riaz A, Ovais Omer M, Ali A, Un Nisa Q, Muddassir Ali M, Saleem G. Immunomodulatory and growth-promoting effects of *Rauwolfia serpentina* root powder in broiler chicks challenged with *Salmonella* Gallinarum. [20]

Formulation containing *Rauwolfia serpentina*

Sarpagandha ghana vati, Chandravalehya, Bṛhatyadi taila, Kṣhara agada, Mahapaiachika Ghrita, Palaṇkashadi taila, Sarpagandha ghana vati, Sarpagandhadi churna, Sarpagandhadi yoga, Shampakadi guṭika, Vachadi yoga, Yogaraja avalehya, Agaruvadya Taila, Trivṛtadya yoga, Charaṭyadi Ghṛta, Hṛveradi yoga, Dhavarkadi kwatha, Ashwagandhadi Kalka, Bṛhatyadi taila.

Conclusion:

Sarpagandha (*Rauwolfia serpentina*) exemplifies the confluence of ancient wisdom and modern scientific innovation. Its diverse pharmacological properties—ranging from antihypertensive and antipsychotic effects to antimicrobial, antioxidant, antiviral, and immunomodulatory activities—make it a valuable resource in both human and veterinary medicine. Emerging research into its enzymes, endophytic microbiota, and applications in poultry health broadens its therapeutic potential. With several classical and proprietary Ayurvedic formulations incorporating its root, *R. serpentina* remains integral to traditional and modern healthcare systems. However, due to overexploitation and habitat degradation, sustainable cultivation and biotechnological approaches for metabolite production are imperative. Conservation strategies, coupled with continued

interdisciplinary research, are essential to harness the full therapeutic promise of this endangered medicinal plant.

References:

1. Nadkarni KM. *Indian Materia Medica with Ayurvedic, Unani & Home Remedies*. Vol. 1. 1st ed. Mumbai: Popular Prakashan Pvt. Ltd.; 2007. p. 1050–1053.
2. Kushwaha HS. *Charak Samhita. Chikitsa Sthana*. Varanasi: Chowkhamba Orientalia; 2022. Ch. 3/267.
3. Shastri AD. *Susruta Samhita. Kalpa Sthana*. Varanasi: Chowkhamba Sanskrit Samsthan; 2019. Ch. 5/84–86.
4. Sharma S. *Ashtanga Sangraha. Sutra Sthana*. Varanasi: Chowkhamba Sanskrit Series Office; 2022. Ch. 8/94.
5. Kushwaha HS. *Ashtanga Hrudaya. Chikitsa Sthana*. Varanasi: Chowkhamba Orientalia; 2018. Ch. 17/27.
6. Chunekar KC. *Bhavaprakash Nighantu. Haritakyadi Varga*. Varanasi: Chowkhamba Bharati Academy; 2004. p. 79.
7. Ojha J. *Dhanvantari Nighantu. Karveeradi Varga*. Varanasi: Chowkhamba Surbharti Prakashan; 1996. p. 184.
8. Qureshi SA, Udani SK. Hypolipidaemic activity of *Rauwolfia serpentina* Benth. *Pak J Nutr*. 2009;8(7):1103–6.
9. Wilkins RW, Judson WE. The use of *Rauwolfia serpentina* in hypertensive patients. *N Engl J Med*. 1953;248(2):48–53.
10. Azmi MB, Qureshi SA, Rais S, Sultana S. Methanolic root extract of *Rauwolfia serpentina* lowers atherogenic dyslipidemia, arteriosclerosis and glycosylation indices in type 1 diabetic mice. *J Appl Pharm Sci*. 2015;5(8):61–7.
11. Azmi MB, Qureshi SA, Rais S, Sultana S. Methanolic root extract of *Rauwolfia serpentina* lowers atherogenic dyslipidemia, arteriosclerosis and glycosylation indices in type 1 diabetic mice. *J Appl Pharm Sci*. 2015;5(8):61–7.
12. Ezeigbo II, Ezeja MI, Madubuike KG, Ifenkwe DC, Ukweni IA, Udeh NE, et al. Antidiarrhoeal activity of leaf methanolic extract of *Rauwolfia serpentina*. *Asian Pac J Trop Biomed*. 2012;2(6):430–2.
13. Gupta AK, Chitme HC, Dass SK, Misra NM. Hepatoprotective activity of *Rauwolfia serpentina* rhizome in paracetamol intoxicated rats. *J Appl Biol Pharm Technol*. 2006;1(2):82–8.

14. Shrinivasa Murthy KM, Narayanappa M. In vitro study of antibacterial activity of leaf and root extract of *Rauwolfia serpentina* against Gram positive and negative bacteria strains. *Int J Recent Res Interdiscip Sci*. 2015;2(3):33–7.
15. Rathi P, Kumari R, Rajput CS, Sawhney SS. Therapeutic characteristics of *Rauvolfia serpentina*. *Int J Pharm Pharm Sci*. 2013;2(2):1038–42.
16. Rastogi RM. *Compendium of Indian Medicinal Plants*. Vol. 1. Lucknow: Central Drug Research Institute; 1990. p. 388–9.
17. Ramakrishnan G, Gujjula KR, Mekala JR, Thanay ASS, Praveen T, Priyanka H, et al. Exploring bioactive compounds of *Rauvolfia tetraphylla* L. (RT) for 3CLprotease of SARS-CoV2: GC-MS analysis and in-silico studies. *Cell Biochem Biophys*. 2024;82(4):3383–93.
18. Ge L, Xia Y, Xu W, Jia R, Zhang T. Efficient biosynthesis of gastrodin by UDP-glycosyltransferase from *Rauvolfia serpentina*. *J Microbiol Biotechnol*. 2025;35:e2501002.
19. Lata R, Gond SK. Antibacterial and antioxidant potentials, detection of host origin compounds, and metabolic profiling of endophytic *Bacillus* spp. isolated from *Rauvolfia serpentina* (L.) Benth. ex Kurz. *Sci Rep*. 2025;15(1):2094.
20. Zhang Y, Rehman H, Khattak F, Tariq M, Khan BN, Chaman S, et al. Immunomodulatory and growth-promoting effects of *Rauwolfia serpentina* root powder in broiler chicks challenged with *Salmonella Gallinarum*. *Front Vet Sci*. 2025;12:1534347.

IMPACT OF JUNK FOOD ON CHILDREN HEALTH

D. P. Swapna

Telangana Social Welfare Residential Degree College (TGSWRDC),

Warangal, Telangana

Corresponding author E-mail: swapnapadigela85@gmail.com

Abstract:

The increasing prevalence of fast food and processed, oily food has become a common feature of Indian diets, leading to various health problems such as obesity, heart disease, diabetes, etc. It is important to note that the shift in food habits in recent years has played a significant role in the surge of major health problems. Fast food outlets have become increasingly prevalent in cities and towns, offering affordable, convenient, and flavorful options often high in calories, saturated fats, sugars, and sodium. Burgers, fries, pizza, fried chicken, and sugary beverages have become major in many diets across the world, contributing to weight gain and a myriad of health problems. In addition to junk food, consuming large amounts of fatty food has become a common and unhealthy eating habit. Many restaurants and homes frequently provide fried food, processed snacks, and oil-filled meals. These meals might taste good, but they are frequently loaded with harmful oils, trans fats, and saturated fats that are bad for our health. Regular eating of high-fat meals can raise blood pressure, cause clogged arteries, cause weight gain, and raise the risk of heart disease. Research published by the Indian Heart Association states that the leading cause of death is cardiovascular diseases (CVDs). Heart disease is a result of unhealthful diets heavy in salt, trans fats, and saturated fats. Trans fats, which are frequently included in processed and fried meals, are especially dangerous because they increase the risk of cardiovascular issues by lowering good cholesterol and raising bad cholesterol. In the variety of food landscapes, there are plenty of delicious options for individuals who want healthy food choices to enhance their overall health.

Keywords: Nutrients, Hormones, Junk Food, Obesity, CVDs, Cholesterol.

Introduction:

Junk food consumption can negatively impact several organs, increasing the risk of chronic diseases and impairing overall health. Specifically, it can harm the liver, kidneys, heart, and digestive system, as well as contribute to obesity and related health issues.

Organ-Specific Impacts:

- **Liver:**
  High-sugar junk food can lead to non-alcoholic fatty liver disease (NAFLD), where excessive fat accumulates, impairing liver function.
- **Kidneys:**
  The high sodium content in junk food can strain the kidneys, potentially leading to high blood pressure and chronic kidney disease.
- **Heart:**
  Junk food's saturated fats, cholesterol, and sodium can increase the risk of heart disease, high blood pressure, and stroke.
- **Digestive System:**
  Junk food's high fat, sugar, and artificial additives can disrupt the balance of gut bacteria, leading to digestive problems like bloating, constipation, and nutrient deficiencies.
- **Brain:**
  Junk food can trigger inflammation in the brain, potentially affecting brain cells and function.
- **Pancreas:**
  Frequent consumption of high-sugar junk food can increase the risk of type 2 diabetes.

Other Health Impacts:

- **Obesity:**
  Junk food's high calorie and fat content contribute to weight gain and obesity, a major risk factor for numerous health problems.
- **Nutrient Deficiencies:**
  Junk food often lacks essential nutrients like vitamins, minerals, and fiber, leading to deficiencies that can weaken the immune system.
- **Mental Health:**
  Nutrient deficiencies and blood sugar fluctuations from junk food can negatively impact mood and mental well-being.

Junk food can negatively impact cells by causing inflammation, oxidative stress, and disrupting normal cellular functions, leading to various health problems. It can also impair the immune system, contributing to increased susceptibility to infections and diseases.

Here's a more detailed breakdown of the effects:

1. Inflammation and Oxidative Stress:

1. **Inflammation:**

   Junk food, especially high in sugar and unhealthy fats, can trigger inflammation in the body, including in the brain. This inflammation can damage cells and contribute to chronic diseases.

2. **Oxidative Stress:**

   Junk food can increase the production of free radicals, which can damage cells and contribute to oxidative stress. This can lead to a loss of collagen and elastin in skin cells, affecting their firmness.

2. Immune System Dysfunction:

- **Weakened Immunity:**

  High sugar content in junk food can suppress the activity of immune cells, making the body more vulnerable to infections.

- **Altered Immune Response:**

  Junk food can trigger a strong immune response, potentially leading to a hyperactive immune system and contributing to chronic inflammation.

3. Cellular Damage and Dysfunction:

- **DNA Damage:**

  The changes in the genome of immune cells caused by a junk food diet can have long-term consequences, potentially leading to epigenetic changes and further health complications.

- **NADH+ Depletion:**

  Poor diet, including excessive junk food consumption, can lead to lower levels of NADH+, a vital coenzyme for cellular processes like energy production and repair.

4. Other Effects:

- **Digestive Issues:**

  Junk food can disrupt the gut microbiome, affecting digestion and potentially leading to inflammation in the gut.

- **Skin Problems:**

  Junk food can contribute to skin problems like acne due to the presence of bad carbs and fats that stimulate oil production.

- **Increased Risk of Chronic Diseases:**

  Long-term consumption of junk food is linked to an increased risk of various chronic diseases, including heart disease, diabetes, and certain cancers.

Lack of iodine:

One needs to understand that iodine is essential for the production of thyroid hormones. An iodine deficiency can lead to various health issues including underactive thyroid. It can cause symptoms of fatigue, weight gain, and slowed growth. Ensure that your child gets enough iodine through their diet to maintain thyroid hormone levels.

Nutrient deficiencies:

If your little ones are picky about their diet then they are more likely to suffer from nutrient deficiencies. A deficiency of essential nutrients like selenium, zinc, or iron can negatively weaken your thyroid gland's ability to produce and regulate hormones. This can further lead to mood swings, unable to concentrate on one particular thing, or delayed development.

Inflammation:

Unhealthy food obsession is quite common in children. They are more attracted to foods that are usually processed or packaged. These fruits are high in fats, sodium, and preservatives that can easily cause inflammation. This can negatively affect the functioning of the thyroid gland. Chronic inflammation can also interfere with hormone production which can easily make them tired and irritated. Avoid giving them unhealthy or processed foods. Encourage them to eat healthy and nutritious foods. Fluctuating blood sugar levels: Irregular food habits when combined with excessively eating foods that are high in sugar can cause sudden blood sugar spikes. This sugar spike can put additional pressure on your thyroid gland while disrupting hormonal levels. Healthy habits like eating their meals on time can help maintain consistency and also support their thyroid health. Create strict restrictions when it comes to eating sugary foods or drinks like chocolates, pastries, cupcakes, cakes, donuts, juices or candies.

Junk foods taste good that’s why it is mostly liked by everyone of any age group especially kids and school going children. They generally ask for the junk food daily because they have been trending so by their parents from the childhood. They never have been discussed by their parents about the harmful effects of junk foods over health. According to the research by scientists, it has been found that junk foods have negative effects on the health in many ways. They are generally fried food found in the market in the

packets. They become high in calories, high in cholesterol, low in healthy nutrients, high in sodium mineral, high in sugar, starch, unhealthy fat, lack of protein and lack of dietary fibers. Processed and junk foods are the means of rapid and unhealthy weight gain and negatively impact the whole body throughout the life. It makes able a person to gain excessive weight which is called as obesity. Junk foods taste good and looks good however do not fulfil the healthy calorie requirement of the body. Some of the foods like french fries, fried foods, pizza, burgers, candy, soft drinks, baked goods, ice cream, cookies, etc are the example of high-sugar and high-fat containing foods. Eating junk food daily led us to the nutritional deficiencies in the body because it is lack of essential nutrients, vitamins, iron, minerals and dietary fibers. It increases risk of cardiovascular diseases because it is rich in saturated fat, sodium and bad cholesterol. High sodium and bad cholesterol diet increases blood pressure and overloads the heart functioning.

One who like junk food develop more risk to put on extra weight and become fatter and unhealthier. Junk foods contain high level carbohydrate which spike blood sugar level and make person more lethargic, sleepy and less active and alert. Reflexes and senses of the people eating this food become dull day by day thus they live more sedentary life. Junk foods are the source of constipation and other disease like diabetes, heart ailments, clogged arteries, heart attack, strokes, etc because of being poor in nutrition.

Why Junk Food is Harmful

Obesity and Weight Gain

One of the most direct consequences of consuming junk food is weight gain. Junk food is high in calories but low in nutritional value, meaning that it contributes to an excessive caloric intake. When these calories are not burned off through physical activity, they are stored as fat in the body, leading to weight gain and eventually obesity.

Obesity is a major risk factor for many chronic diseases, including heart disease, stroke, and diabetes. It is especially dangerous for children and adolescents, as it sets the foundation for a lifetime of health problems.

Mental Health Effects

The effects of junk food are not limited to physical health; they can also affect mental well-being. Diets high in sugar and fat have been linked to mood swings, irritability, and poor mental health. Studies suggest that excessive consumption of junk food can contribute to the development of conditions like depression and anxiety.

Additionally, there is evidence to suggest that poor diet can impair cognitive function, making it harder to focus, learn, and retain information. This is particularly concerning for students who are still in their developmental years.

Chronic Diseases

Consuming junk food regularly increases the risk of developing several chronic diseases. Some of the most common include:

- **Type 2 diabetes**: High sugar consumption can lead to insulin resistance, a precursor to type 2 diabetes.
- **Heart disease**: The high fat content, particularly trans fats, in junk food can contribute to the buildup of plaque in the arteries, increasing the risk of heart attacks and strokes.
- **Hypertension (high blood pressure)**: High salt intake from junk food can raise blood pressure, putting additional strain on the heart and kidneys.

The Popularity of Junk Food

Junk food has become a staple in modern diets due to its convenience, affordability, and taste. Fast food chains, packaged snacks, and sugary drinks are widely available and marketed aggressively. Advertisements, especially those targeted at children, promote these foods as fun, exciting, and desirable.

The popularity of junk food is also linked to the fast-paced lifestyles of today's society. Many people, especially students, opt for quick, easy meals that require little preparation. This preference for convenience leads to a higher consumption of junk food, despite its negative health consequences

How Junk Food Affects Students

Lack of Nutrients

Students are particularly vulnerable to the effects of junk food consumption due to their growing bodies and minds. While junk food may fill up the stomach, it provides little in the way of essential nutrients like vitamins, minerals, and fiber. As a result, students may experience nutrient deficiencies, which can impair their overall health and development.

For example, a lack of essential nutrients like calcium and iron can affect bone health and cognitive function. Students who frequently consume junk food may also be at a higher risk of developing conditions such as anemia or weakened immune systems.

Impact on Learning and Concentration

Junk food can also have a direct impact on a student's ability to learn and concentrate. Diets high in sugar and unhealthy fats have been linked to reduced attention spans and poor cognitive performance. The fluctuations in blood sugar caused by sugary foods can lead to energy crashes, making it harder for students to focus on their studies.

In the classroom, students who consume junk food regularly may struggle with memory retention, problem-solving, and overall academic performance. This can lead to poor grades and a lack of motivation. In the classroom, students who consume junk food regularly may struggle with memory retention, problem-solving, and overall academic performance. This can lead to poor grades and a lack of motivation. Fast food or junk food is a generic term for all kinds of foods which are rich in energy, because they contain a lot of fat and sugar, as well as salt, but are relatively low in other important nutrients such as protein, fiber, vitamins, and minerals. However, fast food is extremely attractive to most children because of the taste, comparatively lower price, and convenience (doesn't require any cooking or preparation). Since children typically do not understand how this kind of food negatively impacts their health, it can be quite addictive.

Negative Aspects of Junk Food

Regular junk food intake leads to long-term health problems such as obesity, accompanying emotional and self-esteem problems, and chronic illnesses in later life. A single fast food meal could add 160 and 310 extra kilocalories to the daily caloric intake for teenagers and younger children, respectively. Lack of vitamins such as A and C, and minerals such as magnesium and calcium, encourage the development of deficiency diseases and osteoporosis, as well as dental caries due to higher sugar intake. The presence of hazardous food coloring agents and/or unhealthy trans fats in many fast food items, and issues with food preparation safety, often complicate the issue further.

Atopy

Fast food intake more than three times a week is associated with greater odds of atopic disorders such as asthma, eczema or rhinitis, while asthma severity is almost 40% higher in teenagers and more than 25% in younger children. Eating junk food 4-6 times a week leads to lower math and reading skills compared with the children who did not eat so much junk food.

Constipation

An overdose of calories, fats, sugars, and other carbohydrates in repeated meals changes the food desires of the child, and makes it less likely that the child will eat fibers, fruits, milk, and vegetables. This can result in greater chances of constipation.

Addiction

Eating a lot of fast food in childhood makes it hard to eat healthy in later life, even if related medical problems are already evident, because childhood food habits solidify by adulthood. The addictive taste of fast food makes it quite unlikely that the palate will later savor the less complicated and less spicy flavors of ordinary food.

Poor Academics

Fast food can lead to impaired academic performance because high sugar levels followed by sugar crashes and poor concentration levels make it difficult to accomplish tasks which need extended periods of focused attention. Blood sugar fluctuations can also result in mood swings and lack of alertness, lowering classroom participation.

Less Energy

Fast food can inhibit participation in extracurricular activities because it doesn't provide adequate nutrients for physical activity. Lack of physical activity not only keeps children out of peer groups but also impairs physical and mental health.

Depression

Obesity can result in lowered self-esteem, and perhaps depression. Some children who eat junk food are at risk of developing depression even without obesity. Depression in turn affects growth and development parameters, academic performance, and social relationships. It also results in a higher risk of suicide.

Sleep Disturbances

Pop and cola drinks often contain caffeine which can make bedtime an ordeal by postponing normal sleep-wake cycles.

Hyperactivity

Essential fatty acids are typically missing or lacking in fast foods. These include omega-3 and omega-6 polyunsaturated fatty acids which cannot be produced within the body, but are essential for the manufacture of cell membranes, and are also required in high concentrations within the brain and retina. The lack of such nutrients is thought to be associated with increased antisocial behavior.

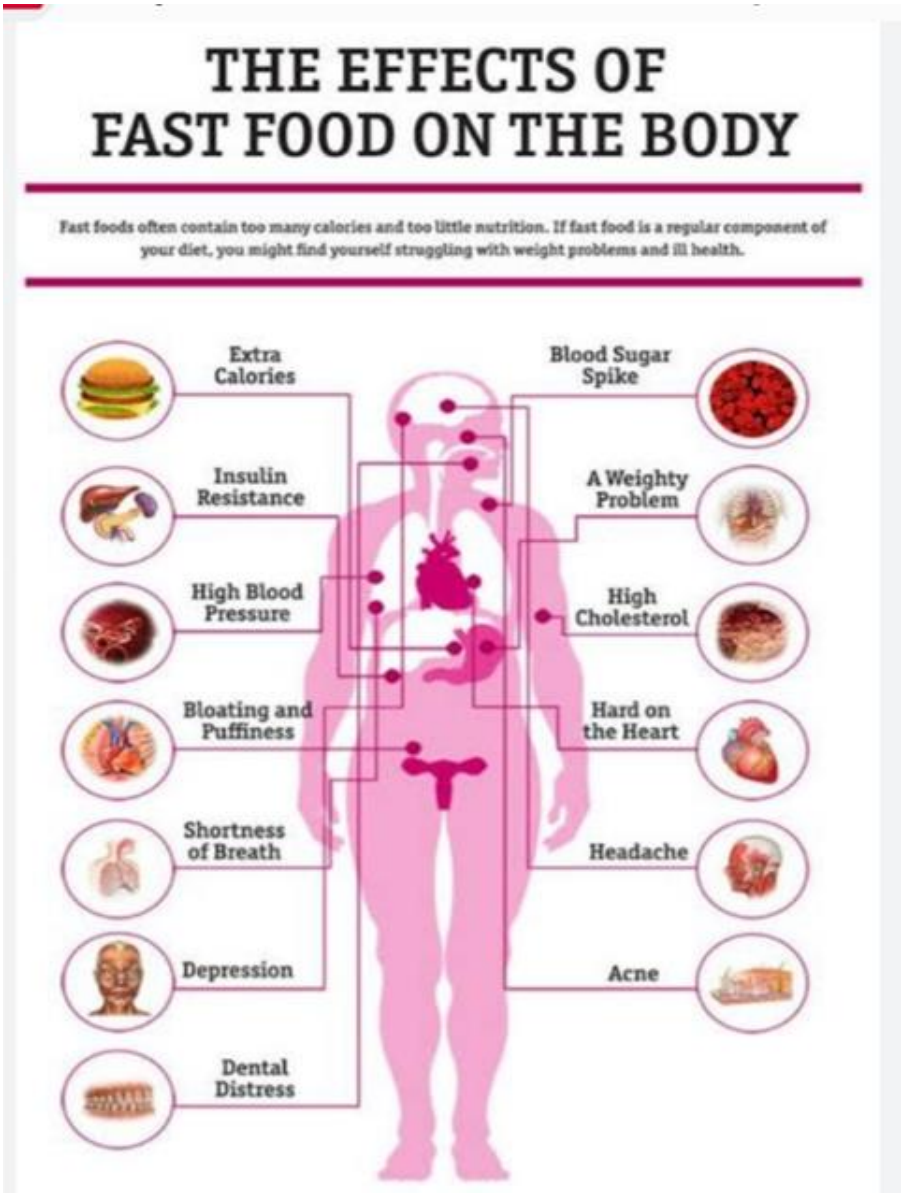

Fig. 1: Effect of fast food on the body

How to Avoid Junk Food

Healthy Alternatives

One of the best ways to avoid junk food is by incorporating healthier alternatives into the diet. Here are some nutritious substitutes for common junk foods:

- **Instead of soda**: Drink water, fresh fruit juices, or smoothies.
- **Instead of chips**: Try air-popped popcorn, roasted nuts, or vegetable sticks.
- **Instead of candy**: Choose fruits like apples, bananas, or berries, which provide natural sweetness and essential nutrient

Junk food refers to food that is high in calories but low in nutritional value. It is often packed with fats, sugars, and salts but lacks essential nutrients such as vitamins, minerals, and fiber. Common examples of junk food include fast food, processed snacks, sugary

beverages, and sweets. Despite its popularity due to convenience and taste, junk food poses significant health risks, especially when consumed frequently. Over time, it can contribute to various health issues such as obesity, heart disease, diabetes, and other chronic conditions. This essay aims to explore the concept of junk food, its effects on health, and how to reduce consumption, especially among children and students.

What is Junk Food?

Junk food is a term commonly used to describe foods that provide little to no nutritional value. These foods are typically high in unhealthy fats, sugars, and salts but are low in vitamins, minerals, and other essential nutrients. Junk food can be tempting due to its taste, convenience, and low cost. However, regular consumption of junk food can have serious consequences for both physical and mental health.

Examples of junk food include:

- Fast food (burgers, fries, pizzas)
- Processed snacks (chips, cookies, candy)
- Sugary drinks (sodas, energy drinks)
- Sweetened cereals and pastries

These foods are often advertised aggressively, particularly to children, leading to an increase in their consumption despite their negative health effects. Junk food is an informal term for food that is of little nutritional value and is often high in calories, fat, sugar, and salt. It can include fast food, processed snacks, and sugary drinks. Junk food is often convenient and easy to eat, but it is not always healthy. It is generally considered to be unhealthy food that is high in calories but low in nutrients. Junk food has been linked to a number of health problems, including obesity, heart disease, and diabetes. Some experts believe that the high levels of sugar, fat, and salt in junk food can lead to cravings and overeating. Good health is the necessity of living a healthy life for every one of us which needs to maintain a healthy diet and healthy habits throughout the life. However, the custom of eating junk food in many is increasing day by day and making our future sad and diseased especially our future generations. Parents should be very conscious towards the eating habits of their kids and children because in the childhood they never know and decide their good or bad so it is parents who are fully responsible for the good or bad eating habits among their kids. They should train their kids about eating habits from childhood and make them clear about the differences between healthy and junk foods.

Generally, junk foods look so attractive and yummy for the people of every age group. However, it is very true that they are so coarse from inside. What they look from outside never become from inside. Junk foods are never considered healthy to the health; they have been proved unhealthy in all ways. Junk foods are unfit to the health and one who practice to eat junk foods calls so many disorders to his/her health. It may cause heart diseases, cancer, early ageing, high blood pressure, bone problems, diabetes, mental disorders, liver disorders, digestive system problems, constipation, diarrhoea, heart attack, prostate and breast cancer, osteoporosis, and so many health disorders. According to the research, it is found that puberty is the most sensitive age during which one should practice healthy eating habits because during this age there are many changes occur in the body to prepare one to enter to the adult age group. The term junk food means a food do not good to the body health in anyway. It is less nutritional and harmful to the body systems. Most of junk foods contain high level of saturated fats, sugar, salt and bad cholesterol which are toxin to the health. They become lack of dietary fibers so easily get involve in causing constipation and other digestive disorders.

Unhealthy food refers to heavily processed and refined food products. It's typically less nutritious than natural, whole foods. Unhealthy food is often linked to weight gain and can lead to significant health problems, especially in kids, including the risk of developing conditions like diabetes. Junk foods have gained so much popularity because of the nice taste and easy to cook. There are many readymade junk foods available in the market packed in the polybags. Most of the people are depend on such readymade foods because of their busy schedule or they do not know to cook food at home. The consumption of junk food all over the world is increasing day by day which is not good for the future. People of all age groups like to eat junk food and they generally chose to eat whenever they enjoy special time with family like birthday party, marriage anniversary, etc. They easily become used to of taking soft drinks, wafers, chips, noodles, burgers, pizza, french fries, Chinese dishes, and other varieties of fast food available in the market. As we all know the truth about junk foods and it needs no introduction. However, it is a most interesting question that why everyone likes to eat junk foods even after knowing its truth. Nowadays every one of us is enjoying well the taste of junk food because it is delicious, affordable and readily available. Junk foods have no nutritional value and essential ingredients required for the health. I t is very harmful to the health if consumed on regular basis. It causes a spike in body energy level and creates sleeping disorders. It reduces level of concentration and calls

to chronic diseases such as obesity, hormonal imbalances, heart diseases, high blood pressure, diabetes, etc.

Junk foods become very oily and lack of dietary fibers thus they are hard to digest and require more energy to perform the process from body and make a person lack of oxygen level in the body which lead towards improper brain functioning. Junk foods are high in bad cholesterol and cause heart and liver damage. Because of lack of dietary fibers, they cause strain to the stomach and other digestive organs and result in constipation. Junk foods are always harmful to the heath and deteriorate the health condition if taken on regular basis without providing any health benefits. We should avoid eating junk foods in order to enjoy the good health and happy life all through the life.

The word junk food speaks itself a lot and indicates its harmful nature to the health. Junk foods are trash food to the health because they are high in calorie, fat, cholesterol, sugar and salt components. Nowadays kids and teenagers are more prone to eat junk foods daily in bulk amount. They are leading their lives towards danger through their unhealthy lifestyle. They generally eat chips, french fries, cracks, snack, chawmin, burger, pizza, pasta, and other junk foods whenever they feel hungry. No junk foods are beneficial and provide no nutritional value. It affects the health in all ways of the people of any age group, weight and health condition. Junk foods are considered as high in calories however one who eat end up easily getting exhausted and need more food frequently. Junk food does not provide appropriate level of energy thus the eater develops tendencies of craving more food frequently. What we generally acquire from the junk foods are unhealthy fats and not healthy ingredients thus we feel lack of oxygen which causes poor brain functioning. We absorb much cholesterol from such type of foods which causes plaque formation in the arteries and creates problems for the heart to pump normal amount of blood. That's why we feel high level fatigue. High level of bad cholesterol destroys our liver and put more weight at the same time.

According to the research, kids and children eating more junk food on daily basis are overweight and obese and highly prone to the heart and liver disorders. Such kids are more prone to become diabetic and lethargic because of high sugar collection in their body in the early ages. They get high blood pressure because of high amount of sodium mineral in the junk foods. Kids and children should be trained by their parents to follow healthy eating habits from the childhood. It is found according to the Centres for Disease Control and Prevention that Kids and children eating junk food are more prone to the type-2 diabetes. In type-2 diabetes our body become unable to regulate blood sugar level. Risk of

getting this disease is increasing as one become more obese or overweight. It increases the risk of kidney failure. One who like junk food develop more risk to put on extra weight and become fatter and unhealthier. Junk foods contain high level carbohydrate which spike blood sugar level and make person more lethargic, sleepy and less active and alert. Reflexes and senses of the people eating this food become dull day by day thus they live more sedentary life. Junk foods are the source of constipation and other disease like diabetes, heart ailments, clogged arteries, heart attack, strokes, etc because of being poor in nutrition.

Why Junk Food is Harmful

Obesity and Weight Gain

One of the most direct consequences of consuming junk food is weight gain. Junk food is high in calories but low in nutritional value, meaning that it contributes to an excessive caloric intake. When these calories are not burned off through physical activity, they are stored as fat in the body, leading to weight gain and eventually obesity. Obesity is a major risk factor for many chronic diseases, including heart disease, stroke, and diabetes. It is especially dangerous for children and adolescents, as it sets the foundation for a lifetime of health problems.

Mental Health Effects

The effects of junk food are not limited to physical health; they can also affect mental well-being. Diets high in sugar and fat have been linked to mood swings, irritability, and poor mental health. Studies suggest that excessive consumption of junk food can contribute to the development of conditions like depression and anxiety. Additionally, there is evidence to suggest that poor diet can impair cognitive function, making it harder to focus, learn, and retain information. This is particularly concerning for students who are still in their developmental years.

Chronic Diseases

Consuming junk food regularly increases the risk of developing several chronic diseases. Some of the most common include:

- **Type 2 diabetes**: High sugar consumption can lead to insulin resistance, a precursor to type 2 diabetes.
- **Heart disease**: The high fat content, particularly trans fats, in junk food can contribute to the buildup of plaque in the arteries, increasing the risk of heart attacks and strokes.

- **Hypertension (high blood pressure)**: High salt intake from junk food can raise blood pressure, putting additional strain on the heart and kidneys.

The Popularity of Junk Food

Junk food has become a staple in modern diets due to its convenience, affordability, and taste. Fast food chains, packaged snacks, and sugary drinks are widely available and marketed aggressively. Advertisements, especially those targeted at children, promote these foods as fun, exciting, and desirable.

The popularity of junk food is also linked to the fast-paced lifestyles of today's society. Many people, especially students, opt for quick, easy meals that require little preparation. This preference for convenience leads to a higher consumption of junk food, despite its negative health consequences.

Fig. 2: Junk food *vs* Healthy food

How Junk Food Affects Students

Lack of Nutrients

Students are particularly vulnerable to the effects of junk food consumption due to their growing bodies and minds. While junk food may fill up the stomach, it provides little in the way of essential nutrients like vitamins, minerals, and fiber. As a result, students may experience nutrient deficiencies, which can impair their overall health and development. For example, a lack of essential nutrients like calcium and iron can affect bone health and cognitive function. Students who frequently consume junk food may also be at a higher risk of developing conditions such as anemia or weakened immune systems.

Impact on Learning and Concentration

Junk food can also have a direct impact on a student's ability to learn and concentrate. Diets high in sugar and unhealthy fats have been linked to reduced attention spans and poor cognitive performance. The fluctuations in blood sugar caused by sugary foods can lead to energy crashes, making it harder for students to focus on their studies. In the classroom, students who consume junk food regularly may struggle with memory retention, problem-solving, and overall academic performance. This can lead to poor grades and a lack of motivation.

How to Avoid Junk Food

Healthy Alternatives

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- **Instead of chips**: Try air-popped popcorn, roasted nuts, or vegetable sticks.
- **Instead of candy**: Choose fruits like apples, bananas, or berries, which provide natural sweetness and essential nutrients.

By making these simple swaps, students can significantly improve their health while still enjoying delicious snacks and meals.

Better Eating Habits

Adopting better eating habits can help reduce the consumption of junk food. Some helpful tips include:

- **Meal planning**: Preparing meals in advance can reduce the temptation to grab fast food or processed snacks.
- **Eat balanced meals**: Aim for meals that contain a mix of protein, healthy fats, fiber, and complex carbohydrates to keep energy levels stable.
- **Portion control**: Even healthy foods can contribute to weight gain if eaten in excess. Learning to control portion sizes can help prevent overeating.

Conclusion:

In conclusion, junk food can have a significant negative impact on cells, leading to inflammation, oxidative stress, immune system dysfunction, and potentially contributing to various health problems over time. Junk food may be convenient and tasty, but its negative impact on health is undeniable. From weight gain and obesity to chronic diseases and mental health issues, the long-term effects of junk food consumption can be severe. It is

important to make healthier choices and reduce the intake of junk food, particularly among children and students who are still developing. By adopting healthier eating habits and choosing nutritious alternatives, we can improve our overall well-being and prevent the harmful effects of junk food. Fast food intake definitely needs to be strictly controlled in children as it does no good and may do much harm. The antidote Surprisingly, a simple increase in fruit intake can improve the mood and reduce the severity of atopic diseases. Stopping the marketing of junk foods directed at children with attractive characters and gifts may be one way to help children eat better. Another method is to make healthy food more easily available at affordable prices and in a more appealing format.

Reference:

1. Grant MJ, Booth A. A typology of reviews: an analysis of 14 review types and associated methodologies. Health Inf Libr J. 2009;26(2):91–108. doi:10.1111/j.1471-1842.2009.00848.x
2. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid. 2016;26(10):1343–421.
3. Unnikrishnan AG, Menon UV. Thyroid disorders in India: an epidemiological perspective. Indian J Endocrinol Metab. 2011;15(Suppl 2):S78–81.
4. Das S, Bhansali A, Dutta P, Aggarwal A, Bansal MP, Garg D, et al. Persistence of goitre in the post-iodization phase: micronutrient deficiency or thyroid autoimmunity? Indian J Med Res. 2011;133:103–9.
5. Taylor PN, Albrecht D, Scholz A, Gutierrez-Buey G, Lazarus JH, Dayan CM, et al. Global epidemiology of hyperthyroidism and hypothyroidism. Nat Rev Endocrinol. 2018;14(5):301–16.
6. IQVIA Institute for Human Data Science. Medicines use and spending in the U.S.: a review of 2016 and outlook to 2021. 2017 May 4 [cited 2019 Sep 24]. Available from: https://www.iqvia.com/
7. Singh SA, Dhanasekaran D, Ganamurali N, Preethi L, Sabarathinam S. Junk food-induced obesity—a growing threat to youngsters during the pandemic. Obes Med. 2021;26:100364. doi:10.1016/j.obmed.2021.100364
8. Cena H, Calder PC. Defining a healthy diet: evidence for the role of contemporary dietary patterns in health and disease. Nutrients. 2020;12(2):334.

DISABILITY REHABILITATION:
A MULTIDISCIPLINARY APPROACH TO HOLISTIC RECOVERY

Rajesh Kumar Mohanty[1] and Pratibha Mohanty[2]

[1]Department of Prosthetics and Orthotics,

Swami Vivekanand National Institute of Rehabilitation Training and Research,

Cuttack, Odisha - 754010

[2]Department of Rheumatology & Immunology,

Institute of Medical Sciences & SUM Hospital (SOA University),

Shampur, Bhubaneswar, Odisha – 751003

Corresponding author E-mail: rajeshmpo48@gmail.com, pratibha.bpo@gmail.com

Abstract:

Disability rehabilitation is a dynamic and integral part of healthcare aimed at enabling individuals with physical, mental, sensory, or intellectual impairments to achieve and maintain optimal functioning in interaction with their environments. This manuscript explores the key principles, strategies, and emerging trends in disability rehabilitation, emphasizing a multidisciplinary and patient-centered approach. Through case studies and evidence-based practices, this paper outlines the roles of various healthcare professionals, the importance of individualized care plans, and the integration of technology in modern rehabilitation practices.

Keywords: Disability, Practice, Principles, Rehabilitation, Service

Introduction:

Disability affects over a billion people globally, and rehabilitation plays a crucial role in improving their quality of life. Rehabilitation services help reduce the impact of a broad range of health conditions, including injury, chronic disease, or aging, on functioning. The goal is not only to restore lost skills but also to foster independence and participation in all areas of life. Disability rehabilitation is a vital aspect of healthcare that aims to enable individuals with physical, sensory, intellectual, or mental health impairments to achieve and maintain optimal physical, emotional, social, and vocational functioning [1]. It is a broad and multidisciplinary field that includes medical, psychological, educational, and social interventions. It refers to a set of interventions designed to optimize functioning and reduce disability in individuals with health conditions in interaction with their environment. It is a process designed to help individuals recover and regain skills, abilities,

and independence after illness, injury, surgery, or chronic conditions. The goal is to improve quality of life by restoring function and minimizing disability. It is not limited to medical treatment but also includes therapies and support systems to help individuals regain independence and improve quality of life.

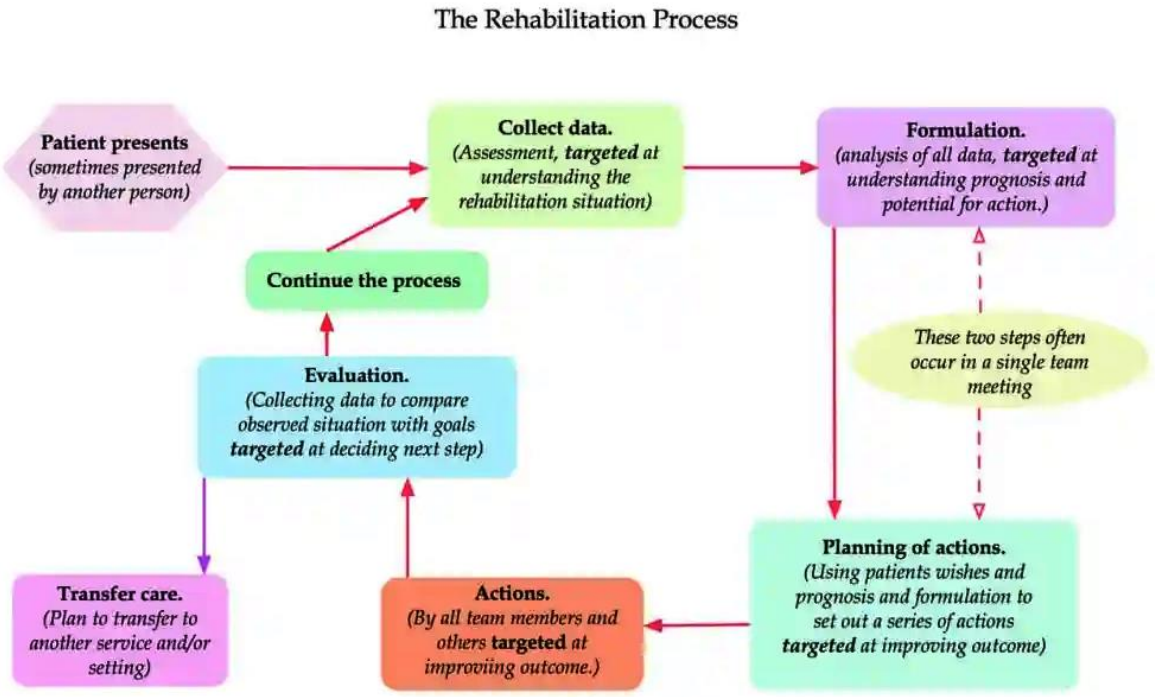

Fig. 1: The Rehabilitation Process [2]

The main objectives of rehabilitation are [3]:

- *Restore Functionality:* Help individuals regain physical, mental, or social abilities lost or impaired due to injury, illness, or disability.
- *Promote Independence:* Enable patients to perform daily activities on their own as much as possible, improving their quality of life.
- *Enhance Quality of Life:* Improve overall well-being by addressing physical, emotional, and social needs.
- *Prevent Complications:* Reduce risks of secondary health problems, such as muscle atrophy, contractures, or depression.
- *Facilitate Social Reintegration:* Assist individuals in returning to work, school, and community life, fostering social participation.
- *Provide Psychological Support:* Help patients cope with the emotional impact of disability or chronic illness.
- *Educate Patients and Families:* Teach self-care skills, use of assistive devices, and promote understanding of condition management.

- *Maximize Potential:* Help individuals achieve their highest possible functional level and life satisfaction.

Principles of Rehabilitation

The process of rehabilitation is grounded in several core principles [4]:

- **Patient-Centered Care**: Patient-centered care in disability rehabilitation is a holistic, respectful, and individualized approach that prioritizes the preferences, values, and needs of individuals living with disabilities. The goal is to empower patients to actively participate in their care, enhancing outcomes and improving their quality of life. It transforms the traditional model of care by focusing on collaboration, respect, and personalized support. It requires a system-wide commitment to adapting practices and mindsets, ensuring that individuals with disabilities are not just recipients of care but active participants in shaping their path to recovery and independence [5].
- **Multidisciplinary Collaboration**: Multidisciplinary collaboration in disability rehabilitation refers to the coordinated effort of professionals from various disciplines working together to provide comprehensive care for individuals with disabilities. This approach ensures that the complex and diverse needs of patients are met through a holistic and person-centered rehabilitation process. Multidisciplinary collaboration is a cornerstone of effective disability rehabilitation. It brings together diverse expertise to address the physical, emotional, cognitive, and social dimensions of disability, ultimately supporting individuals to achieve the highest possible level of independence and participation in society [6].
- **Continuity of Care**: Rehabilitation is an ongoing process that may continue in various settings from hospitals to community centers and homes. This refers to the consistent and coordinated delivery of health and social services over time and across different settings to individuals with disabilities. It is a critical concept in ensuring long-term recovery, functional improvement, and overall well-being for people undergoing rehabilitation due to physical, intellectual, or sensory disabilities. It is essential for maximizing recovery and participation in society. It requires a coordinated, patient-centered approach that spans across time, services, and settings. Health systems should strive to build structures that support seamless care transitions, holistic rehabilitation plans, and lifelong support for individuals with disabilities [7].

- **Empowerment and Participation**: Empowerment and participation are fundamental principles in disability rehabilitation aimed at improving the quality of life, independence, and social inclusion of people with disabilities. It provides emphasis on involving patients in decision-making and encouraging active participation. They create a patient-centered approach where individuals are seen as active agents, not passive recipients. Rehabilitation programs are tailored to individual needs, preferences, and cultural contexts. This encourages the peer support groups and community integration activities [8].

Rehabilitation Settings and Services

The rehabilitation services are provided across a continuum of care in following settings.

- **Acute Care Hospitals**: It is the early intervention post-injury or diagnosis. Acute care hospitals primarily focus on short-term treatment of severe or urgent medical conditions, such as surgeries, trauma, or serious illness. However, they also play an important role in the continuum of care for patients with disabilities, especially during the early stages of rehabilitation following an acute event (like stroke, spinal cord injury, traumatic brain injury, or major surgery) [9].
- **Inpatient Rehabilitation Facilities**: It is the intensive therapy for patients who need coordinated care. Inpatient Rehabilitation Facilities are specialized healthcare centers that provide intensive rehabilitation services to patients recovering from serious injuries, illnesses, or surgeries. They focus on helping patients regain functional independence and improve quality of life [10].
- **Outpatient Clinics**: It is for individuals who require ongoing therapy but not hospitalization. Outpatient clinics in disability rehabilitation are specialized healthcare settings where patients with disabilities receive assessment, treatment, and ongoing management without being admitted to a hospital overnight. These clinics focus on helping individuals improve their functional abilities, independence, and quality of life through multidisciplinary approaches [11].
- **Community-Based Programs**: These are the services that support integration and participation in everyday life. Community-Based Rehabilitation programs are initiatives aimed at helping people with disabilities or those recovering from injury or illness to reintegrate into society. These programs focus on empowering

individuals within their own communities by providing accessible rehabilitation services, social support, and opportunities for education and employment [12].

The Rehabilitation Team

A rehabilitation team is a group of healthcare professionals with distinct training and backgrounds who collaborate with each other to help the patient and their families achieve attainable short and long-term goals of maximal restoration of physical and cognitive function while receiving necessary medical care [13].

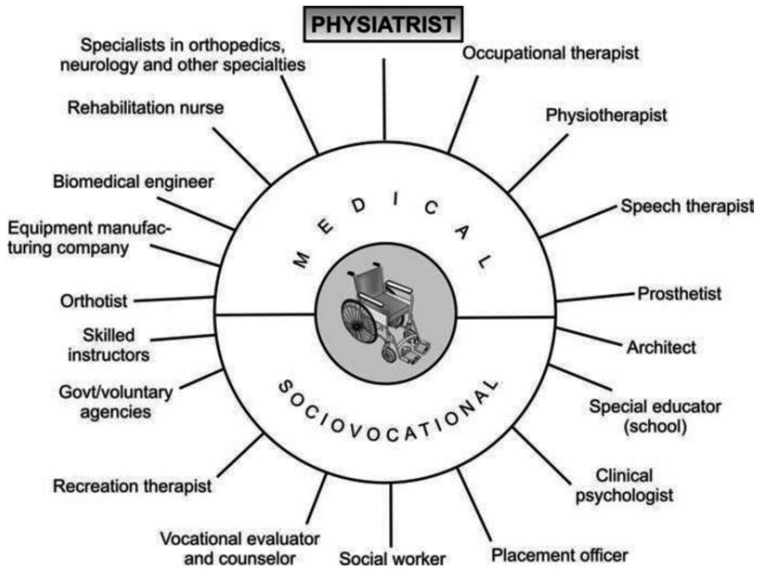

Fig. 2: The Rehabilitation Team [14]

The effectiveness of rehabilitation relies on the coordinated efforts of various professionals:

- **Physiatrists**: A physiatrist is a medical doctor specializing in Physical Medicine and Rehabilitation (PM&R). Their focus is on restoring function and improving quality of life for people with physical impairments or disabilities caused by injury, illness, or chronic conditions. Physiatrists play a crucial role in helping patients regain movement and improve quality of life after injuries or illnesses. They focus on comprehensive rehabilitation strategies that support recovery, pain management, and functional independence without surgery.
- **Physical Therapists**: A Physical therapist is a healthcare professional who help individuals recover, improve, or maintain their physical abilities after injury, surgery, illness, or disability. In rehabilitation, PTs focus on restoring movement, reducing pain, and improving function to help patients return to their daily activities or improve their quality of life.

- **Occupational Therapists**: An Occupational therapist helps individuals regain or improve the skills needed for daily living and working after an injury, illness, or disability. In rehabilitation, the Occupational Therapist focuses on enabling patients to perform meaningful activities (occupations) despite physical, cognitive, or emotional impairments.
- **Prosthetist and Orthotist**: Prosthetists and Orthotists play a crucial role in rehabilitation by designing, fitting, and maintaining devices that help individuals regain or improve mobility and function. Prosthetist is a healthcare professional who designs and fits prosthetic limbs (artificial limbs) for individuals who have lost a limb. Orthotist is a specialist who designs and fits orthotic devices (braces, splints, supports) to correct or support musculoskeletal deformities or weaknesses. They focus on the enhanced mobility through advanced design and materials.
- **Speech and Language Therapists**: Speech and Language Therapists are healthcare professionals specializing in the assessment, diagnosis, and treatment of communication disorders, swallowing difficulties, and cognitive-communication impairments.
- **Psychologists and Psychiatrists**: Psychologists often provide ongoing therapy and behavioral interventions, while psychiatrists handle medication and complex psychiatric care. Their joint efforts help optimize mental health, emotional adjustment, and overall rehabilitation outcomes for patients recovering from injuries, surgeries, strokes, neurological disorders, or chronic illnesses.
- **Social Workers**: Social workers in rehabilitation play a crucial role in helping individuals recover and adjust after illness, injury, or disability. Their work is centered on supporting clients' emotional, social, and practical needs to promote independence and quality of life. They help bridge the gap between medical treatment and real-life adaptation, addressing psychological and social barriers that affect recovery. By focusing on holistic well-being, social workers enable clients to achieve greater independence and improved quality of life. They connect patients with community resources and support systems.

Technological Advancements in Rehabilitation

Technological advancements are revolutionizing rehabilitation, offering innovative solutions for improved patient outcomes and accessibility. These tools enhance patient

engagement, provide personalized treatment plans, and improve remote care. In simple words, technology is revolutionizing rehabilitation [15]:

- **Robotics and Exoskeletons**: Robotics and exoskeletons are transforming the field of rehabilitation by offering new methods to assist patients with mobility impairments, neurological disorders, or musculoskeletal injuries. These technologies can enhance recovery outcomes, improve therapy efficiency, and promote patient independence. Robotics and exoskeletons are ushering in a new era of rehabilitation by enhancing recovery potential, personalizing therapy, and empowering patients. While challenges remain in accessibility and integration, continued innovation and clinical validation are likely to make these technologies increasingly standard in rehabilitative care [16].
- **Tele-rehabilitation**: Tele-rehabilitation refers to the delivery of rehabilitation services over telecommunication networks and the internet. It is a subset of telemedicine and involves the remote assessment, monitoring, education, and therapy for patients who require rehabilitative care, such as physical therapy, occupational therapy, speech-language pathology, and more [17].
- **Virtual Reality**: Virtual Reality is transforming the field of rehabilitation by offering immersive, interactive environments that enhance physical, cognitive, and psychological therapy outcomes. Virtual Reality in rehabilitation refers to the use of computer-generated, interactive environments to aid in the recovery of patients with physical injuries, neurological conditions, or cognitive impairments. Using VR headsets, motion sensors, and sometimes haptic devices, patients can perform therapeutic exercises in simulated real-life scenarios [18].

Challenges in Rehabilitation

The objective of this section is to determine the challenges faced during rehabilitation process or centers in the management of persons with disabilities. Despite advances, several challenges still persist in the rehabilitation [1]:

- **Access and Affordability**: Access and affordability are significant challenges in rehabilitation services, particularly for individuals recovering from illness, injury, or managing chronic conditions. These challenges can hinder recovery, reduce quality of life, and exacerbate health disparities. The main issues are mostly related to geographic barriers, financial constraints, infrastructure and resource limitations, awareness and educational gaps, and cultural and social factors [19].

- **Workforce Shortages**: There is a global shortage of rehabilitation professionals and most professionals are based in cities, creating disparities in service availability [20].
- **Stigma and Discrimination**: Stigma and discrimination can significantly impair recovery by reducing help-seeking behavior due to fear of judgment, increasing stress, anxiety, and feelings of isolation, hindering reintegration into society, including work, family, and community life and undermining the effectiveness of rehabilitation programs [21].
- **Policy and Funding Gaps**: It refers to the systemic shortcomings that hinder the effective delivery, accessibility, and quality of rehabilitation services. This is a major concern in both high- and low-income countries and affects various populations, including those with disabilities, chronic illnesses, injuries, or the elderly. The primary effects may include worsened health outcomes, prolonged disability, and reduced quality of life, increased long-term health and social care costs and lost productivity and economic exclusion of individuals with impairments [22].

Future Directions

The ultimate purpose of future trends in rehabilitation is to improve clinical and community-based practice and service delivery to maximize the function and quality of life of individuals with disabilities. Throughout the current trends in rehabilitation, knowledge translation needs to be implemented so that decisions informing practice and future research can be made on a solid evidence base. Improving disability rehabilitation requires the following future directions [23]:

- **Policy Development**: It basically describes the comprehensive national strategies and funding. Policy Development in Rehabilitation involves creating, implementing, and evaluating guidelines, regulations, and laws that promote the rights, inclusion, and well-being of individuals with disabilities. It encompasses healthcare, education, employment, and social participation, with the goal of improving access to and quality of rehabilitation services.
- **Integration into Primary Healthcare**: Integration of rehabilitation into primary healthcare is a critical strategy to ensure timely, equitable, and effective access to rehabilitation services. Integrating rehabilitation into Primary Health Care (PHC) ensures accessibility, continuity, and comprehensiveness of care for all, particularly in underserved communities. Integrating rehabilitation into primary healthcare is

vital for inclusive, person-centered care. It bridges service gaps and empowers communities to manage health conditions more effectively, fostering a more resilient and equitable healthcare system.

- **Community Engagement**: Community Engagement in Rehabilitation refers to the active involvement of local communities in the planning, implementation, and evaluation of rehabilitation services and programs. This approach emphasizes partnership, shared responsibility, and local empowerment to ensure that rehabilitation efforts are inclusive, effective, and sustainable. Community-Based Rehabilitation (CBR) is a well-known approach that incorporates community engagement and is endorsed by the World Health Organization. It operates on five key components: health, education, livelihood, social inclusion, and empowerment.
- **Ongoing Research**: Rehabilitation research is a dynamic field focused on improving outcomes for individuals recovering from injury, illness, or disability. It often involves multidisciplinary approaches spanning medicine, physical therapy, occupational therapy, psychology, engineering, and technology. Ongoing research in rehabilitation is vital for continuous improvement in patient care, development of innovative treatments, and informed healthcare policies. It ensures that rehabilitation practices evolve with scientific advances, leading to better recovery and enhanced quality of life for patients. The importance of ongoing research in rehabilitation is critical for improving patient outcomes, advancing therapeutic techniques, and enhancing quality of life for individuals recovering from injury, illness, or disability through innovating studies and clinical trials.

Conclusion:

Disability rehabilitation is a transformative process that restores dignity and functionality to millions of individuals worldwide. By adopting a holistic and inclusive approach, societies can ensure that everyone, regardless of their abilities, has the opportunity to live a fulfilling life. The continued evolution of rehabilitation services promises greater independence and quality of life for persons with disabilities.

References:

1. Kumar SG, Roy G, Kar SS. Disability and rehabilitation services in India: issues and challenges. J Family Med Prim Care. 2012;1(1):69–73. https://doi.org/10.4103/2249-4863.94458

2. What is rehabilitation? [Internet]. Rehabilitation Matters. [cited 2024 May 30]. Available from: https://rehabilitationmatters.com/what-is-rehabilitation-2/process-of-rehabilitation/
3. Rehabilitation [Internet]. World Health Organization. [cited 2024 May 30]. Available from: https://www.who.int/news-room/fact-sheets/detail/rehabilitation
4. Futrell M, Rozzi SL. Principles of Rehabilitation. Prim Care. 2020;47(1):87–103. https://doi.org/10.1016/j.pop.2019.10.004
5. Ahmed A, van den Muijsenbergh METC, Vrijhoef HJM. Person-centred care in primary care: What works for whom, how and in what circumstances? Health Soc Care Community. 2022;30(6):e3328–41. https://doi.org/10.1111/hsc.13913
6. Taberna M, Gil Moncayo F, Jané-Salas E, Antonio M, Arribas L, Vilajosana E, et al. The Multidisciplinary Team (MDT) Approach and Quality of Care. Front Oncol. 2020;10:85. https://doi.org/10.3389/fonc.2020.00085
7. Interdisciplinary Rehabilitation [Internet]. NCBI Bookshelf. [cited 2024 May 30]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK525298/
8. Saran A, Hunt X, White H, Kuper H. Effectiveness of interventions for improving social inclusion outcomes for people with disabilities in low- and middle-income countries: A systematic review. Campbell Syst Rev. 2023;19(1):e1316. https://doi.org/10.1002/cl2.1316
9. Hirshon JM, Risko N, Calvello EJ, Stewart de Ramirez S, Narayan M, Theodosis C, et al. Health systems and services: the role of acute care. Bull World Health Organ. 2013;91(5):386–8. https://doi.org/10.2471/BLT.12.112664
10. Cary MP Jr, Merwin EI, Oliver MN, Williams IC. Inpatient Rehabilitation Outcomes in a National Sample of Medicare Beneficiaries With Hip Fracture. J Appl Gerontol. 2016;35(1):62–83. https://doi.org/10.1177/0733464814541325
11. Chen P, Zanca J, Esposito E, Barrett AM. Barriers and Facilitators to Rehabilitation Care of Individuals With Spatial Neglect: A Qualitative Study of Professional Views. Arch Rehabil Res Clin Transl. 2021;3(2):100122. https://doi.org/10.1016/j.arrct.2021.100122
12. Introduction to Rehabilitation [Internet]. NCBI Bookshelf. [cited 2024 May 30]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK310933/
13. Physical Medicine and Rehabilitation Overview [Internet]. NCBI Bookshelf. [cited 2024 May 30]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK13112/

14. Srignanalokesh E. Rehabilitation Engineering. Kindle Direct Publisher; 2022. p.13.
15. Chua KSG, Kuah CWK. Innovating With Rehabilitation Technology in the Real World: Promises, Potentials, and Perspectives. Am J Phys Med Rehabil. 2017;96(10 Suppl 1):S150–6. https://doi.org/10.1097/PHM.0000000000000799
16. Salgado-Gomes-Sagaz F, Zorrilla-Muñoz V, Garcia-Aracil N. Rehabilitation Technologies by Integrating Exoskeletons, Aquatic Therapy, and Quantum Computing for Enhanced Patient Outcomes. Sensors. 2024;24(23):7765. https://doi.org/10.3390/s24237765
17. Muñoz-Tomás MT, Burillo-Lafuente M, Vicente-Parra A, Sanz-Rubio MC, Suarez-Serrano C, Marcén-Román Y, et al. Telerehabilitation as a Therapeutic Exercise Tool versus Face-to-Face Physiotherapy: A Systematic Review. Int J Environ Res Public Health. 2023;20(5):4358. https://doi.org/10.3390/ijerph20054358
18. Bateni H, Carruthers J, Mohan R, Pishva S. Use of Virtual Reality in Physical Therapy as an Intervention and Diagnostic Tool. Rehabil Res Pract. 2024;2024:1122286. https://doi.org/10.1155/2024/1122286
19. Rehabilitation after Critical Illness [Internet]. NCBI Bookshelf. [cited 2024 May 30]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK500097/
20. Charumbira MY, Kaseke F, Conradie T, Berner K, Louw QA. A qualitative study on rehabilitation services at primary health care: insights from primary health care stakeholders in low-resource contexts. BMC Health Serv Res. 2024;24(1):1272. https://doi.org/10.1186/s12913-024-11748-9
21. Brandt L, Liu S, Heim C, Heinz A. The effects of social isolation stress and discrimination on mental health. Transl Psychiatry. 2022;12(1):398. https://doi.org/10.1038/s41398-022-02178-4
22. Abdi K, Arab M, Rashidian A, Kamali M, Khankeh HR, Farahani FK. Exploring Barriers of the Health System to Rehabilitation Services for People with Disabilities in Iran: A Qualitative Study. Electron Physician. 2015;7(7):1476–85. https://doi.org/10.19082/1476
23. Garg A, Skempes D, Bickenbach J. Legal and Regulatory Approaches to Rehabilitation Planning: A Concise Overview of Current Laws and Policies Addressing Access to Rehabilitation in Five European Countries. Int J Environ Res Public Health. 2020;17(12):4363. https://doi.org/10.3390/ijerph17124363

ANTIMUTAGENIC EFFECTS OF THE SPECIFIED HERBAL PLANTS, DELVING INTO SCIENTIFIC EVIDENCE, PHYTOCHEMICAL CONSTITUENTS, AND PROPOSED MECHANISMS

Sunil Kardani*, Dipti Gohil, Sunil Baile and Ujjval Vaghela

Department of Pharmacy,

Sumandeep Vidyapeeth Deemed to be University, Vadodara-391760, Gujarat, India.

*Corresponding author E-mail: sunilkardani@yahoo.co.in

Abstract:

Mutations in DNA are central contributors to the development of cancer and other chronic diseases. This chapter explores the antimutagenic potential of selected herbal plants based on their phytochemical profiles, scientific studies, and underlying mechanisms of action. Eight botanicals-*Carum carvi*, *Withania somnifera*, *Panax ginseng*, *Mentha spicata*, *Curcuma longa*, *Glycyrrhiza glabra*, *Capsicum annuum*, and *Asparagus racemosus*-are evaluated for their capacity to mitigate mutagenic effects through antioxidant activity, modulation of metabolic enzymes, and DNA repair enhancement. Special emphasis is given to curcumin from turmeric (*Curcuma longa*) due to their multifaceted mechanisms, including Nrf2 activation, ROS scavenging, and suppression of inflammatory signaling pathways such as NF-κB. Each plant's phytoconstituents, including flavonoids, saponins, phenolics, and terpenes, contribute uniquely to antimutagenesis via desmutagenic and bio-antimutagenic pathways. Both in vitro and in vivo studies support these findings, showing protection against DNA damage, chromosomal aberrations, and micronuclei formation. This review underscores the promise of plant-based antimutagens as nutraceuticals or chemo preventive agents and encourages further investigation into their potential role in maintaining genomic stability.

Keywords: Antimutagenic Activity, Phytochemicals, DNA Protection, Medicinal Plants

Introduction:

Mutagenesis and the Protective Role of Herbal Plants

Life's genetic blueprint, deoxyribonucleic acid (DNA), is constantly under threat from endogenous and exogenous agents that can alter its structure and sequence. These alterations, known as mutations, can arise spontaneously during DNA replication or repair, or be induced by exposure to mutagens-physical agents like ultraviolet (UV) and ionizing

radiation, chemical compounds found in pollution, food contaminants, industrial chemicals, and certain drugs, or biological agents like viruses and bacterial toxins[1,2]. DNA damage, if not accurately repaired, can lead to stable mutations that disrupt gene function. Accumulation of such mutations is a critical factor in the etiology of various diseases, most notably cancer, but also contributes to aging and certain hereditary disorders[3].

Cells possess intricate defense systems, including DNA repair pathways and detoxification enzymes, to counteract mutagenic threats. However, these systems can be overwhelmed or become less efficient with age or due to genetic factors. Consequently, there is significant interest in identifying external agents that can bolster the body's defenses against mutagenesis. Antimutagens are substances that reduce the frequency of mutations[2,4]. They can operate through diverse mechanisms, broadly categorized as:

1. **Desmutagenesis:** Acting outside the cell or before the mutagen reaches the DNA target. This includes inhibiting the formation of mutagens, inactivating mutagens directly (e.g., through chemical reaction), or inhibiting the metabolic activation of pro-mutagens into their ultimate mutagenic forms (often involving cytochrome P450 enzymes)[4,5].
2. **Bio-antimutagenesis:** Acting after mutagen exposure, often at the cellular level. This includes enhancing the fidelity of DNA replication, improving the efficiency or capacity of DNA repair pathways (e.g., base excision repair, nucleotide excision repair), scavenging reactive oxygen species (ROS) that cause oxidative DNA damage (antioxidant effect), or inducing apoptosis (programmed cell death) in cells with irreparable DNA damage[4,6].

Phytochemicals, the vast array of secondary metabolites produced by plants, represent a rich source of potential antimutagens. Compounds like polyphenols (flavonoids, phenolic acids), carotenoids, alkaloids, terpenoids, and organosulfur compounds often exhibit potent antioxidant, anti-inflammatory, and enzyme-modulating activities that underpin their protective effects against DNA damage and mutation[1,7]. Traditional medicine systems worldwide have long utilized plants for health maintenance and disease treatment, and modern scientific investigation is increasingly validating the protective roles of these botanicals at the molecular level.

This chapter delves into the scientific evidence supporting the antimutagenic and antigenotoxic (preventing DNA damage) effects of a diverse selection of herbal plants: *Carum carvi*, *Withania somnifera*, *Panax ginseng*, *Mentha spicata*, *Curcuma longa*,

Glycyrrhiza glabra, *Capsicum annuum*, *Asparagus racemosus*. For each plant, we will explore key phytochemicals, findings from *in vitro* and *in vivo* studies, and proposed mechanisms underlying their protective effects against genetic damage. Special attention will be given to curcumin from *Curcuma longa* and avicins from *Acacia victoriae*, as requested.

Plant-Specific Antimutagenic Profiles

***1. Carum carvi* (Caraway)**

- **Phytochemistry:** Caraway seeds are rich in essential oil, primarily composed of monoterpenes like (+)-carvone (responsible for the characteristic aroma) and limonene. They also contain flavonoids (quercetin, kaempferol glycosides), phenolic acids, fatty oils, and proteins[8,9].
- **Antimutagenic Evidence**: Studies on caraway's antimutagenic potential often focus on its essential oil and key terpenes. Limonene, a major component, has shown chemo preventive activity against various cancers in preclinical models, partly attributed to its ability to induce phase II detoxification enzymes like glutathione S-transferase (GST), which helps neutralize carcinogens[10]. Carvone also possesses antioxidant properties. *In vitro*, caraway extracts and essential oil have demonstrated antioxidant activity by scavenging free radicals like DPPH (2,2-diphenyl-1-picrylhydrazyl) and inhibiting lipid peroxidation[9]. While direct studies using standardized mutagenicity assays (like the Ames test) specifically on *Carum carvi* extracts are less abundant compared to some other herbs, its strong antioxidant profile suggests a capacity to mitigate oxidative DNA damage, a major source of spontaneous mutations. A study evaluating several Lamiaceae and Apiaceae species found that caraway extracts exhibited moderate protective effects against hydrogen peroxide (H_2O_2)-induced DNA damage in human lymphocytes using the comet assay[11].
- **Mechanisms**: The likely antimutagenic mechanisms for caraway primarily involve antioxidant action (ROS scavenging by carvone, limonene, and phenolic compounds) and potential modulation of carcinogen metabolism (induction of phase II enzymes by limonene) [9, 10].

***2. Withania somnifera* (Ashwagandha)**

- **Phytochemistry:** Known as Indian ginseng or Winter cherry, Ashwagandha's roots are the primary part used medicinally. They contain a group of steroidal lactones called withanolides (e.g., withaferin A, withanolide D, withanone) and various alkaloids (e.g., tropine, cuscohygrine) and sitoindosides[12,13].

- **Antimutagenic Evidence:** Ashwagandha is renowned as an adaptogen, helping the body cope with stress. Its antimutagenic properties have been investigated against chemically induced genotoxicity. *In vivo* studies in mice demonstrated that pre-treatment with *W. somnifera* root extract significantly reduced the frequency of micronuclei (a marker of chromosomal damage) induced by the anticancer drug cyclophosphamide in bone marrow erythrocytes[14,15]. Another study showed that Ashwagandha extract protected against chromosomal aberrations induced by lead nitrate in mouse bone marrow cells[16]. The protective effects were associated with increased levels of antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) in the liver and blood, suggesting mitigation of oxidative stress induced by the mutagens[14,16]. Withaferin A, while having anticancer properties at higher doses, has also been shown to protect normal cells from certain types of damage at lower concentrations, potentially through Nrf2 activation, a key regulator of antioxidant responses[13].
- **Mechanisms**: The primary antimutagenic mechanisms appear to be potent antioxidant activity (boosting endogenous antioxidant enzymes, scavenging ROS) and potentially modulating detoxification pathways. Its adaptogenic effects might also contribute by reducing systemic stress responses that can indirectly lead to increased oxidative damage[12,14].

***3. Panax ginseng* (Ginseng)**

- **Phytochemistry:** Ginseng root contains a complex mixture of bioactive compounds, most notably triterpenoid saponins known as ginsenosides (e.g., Rb1, Rg1, Rg3, Rh2). Other constituents include polysaccharides, polyacetylenes, phenolic compounds, and peptides[17,18].
- **Antimutagenic Evidence:** Ginseng has been extensively studied for its diverse pharmacological effects, including antimutagenicity and cancer chemoprevention. *In vitro*, ginsenosides and ginseng extracts have shown protective effects against DNA damage induced by various mutagens, including H_2O_2, UV radiation, benzo[a]pyrene (B[a]P), and aflatoxin B1 (AFB1), as assessed by the Ames test, comet assay, and DNA adduct formation[18,19]. For instance, ginsenoside Rb1 was found to inhibit the mutagenicity of B[a]P and AFB1 in the Ames test, partly by inhibiting the cytochrome P450 enzymes (like CYP1A1) responsible for activating these pro-carcinogens[19]. *In vivo*, administration of ginseng extracts or purified ginsenosides reduced the

frequency of micronuclei induced by mitomycin C and cyclophosphamide in mice[20]. Studies also suggest ginseng can enhance DNA repair mechanisms. For example, certain ginsenosides were shown to promote the repair of oxidative DNA damage (e.g., 8-oxo-guanine) by potentially upregulating DNA glycosylases involved in base excision repair[18,21]. Furthermore, the antioxidant properties of ginsenosides and phenolic components contribute significantly by neutralizing ROS[17].

- **Mechanisms**: Ginseng exerts antimutagenic effects through multiple pathways: potent antioxidant activity (ROS scavenging), modulation of carcinogen metabolism (inhibiting Phase I activation enzymes like CYP1A1, inducing Phase II detoxification enzymes like GST), enhancement of DNA repair capacity, and immunomodulatory effects that might contribute to eliminating damaged cells[18,19,21].

***4. Mentha spicata* (Spearmint)**

- **Phytochemistry**: Spearmint leaves are rich in essential oil, characterized by (-)-carvone (distinct from the (+)-carvone in caraway). Other components include limonene, dihydrocarvone, menthone, pulegone (in some varieties), flavonoids (e.g., luteolin, apigenin glycosides), and phenolic acids (especially rosmarinic acid)[22,23].
- **Antimutagenic Evidence:** Spearmint extracts and essential oil exhibit significant antioxidant properties. Studies using DPPH, ABTS (2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid)), and ORAC (Oxygen Radical Absorbance Capacity) assays confirm its free radical scavenging ability (23). Rosmarinic acid, a major phenolic compound, is a well-known potent antioxidant and anti-inflammatory agent[24]. *In vitro* studies have demonstrated the antigenotoxic potential of spearmint. For example, aqueous extracts of *M. spicata* protected human peripheral blood lymphocytes against H_2O_2-induced DNA damage, as measured by the comet assay[25]. Another study found that spearmint essential oil reduced the mutagenicity induced by sodium azide in the *Salmonella*/microsome (Ames) assay, suggesting desmutagenic activity[26]. The protective effects are largely attributed to the antioxidant capacity of its phenolic compounds and potentially some components of the essential oil.
- **Mechanisms**: The primary mechanism appears to be antioxidant activity, neutralizing ROS and RNS (reactive nitrogen species) that can damage DNA. Phenolic compounds like rosmarinic acid and flavonoids are key contributors. Potential modulation of metabolic enzymes or direct interaction with mutagens by essential oil components might also play a role[23,25,26].

5. Curcuma longa (Turmeric) and Curcumin

- **Phytochemistry:** Turmeric rhizome's vibrant yellow color and potent bioactivity are primarily due to a group of phenolic compounds called curcuminoids, the most abundant and studied of which is curcumin (diferuloylmethane). Turmeric also contains essential oils (turmerones, atlantones, zingiberene), polysaccharides, and other phenolic compounds[27,28].
- **Antimutagenic Evidence:** Curcumin is one of the most extensively investigated natural compounds for its antimutagenic and chemopreventive properties. Its effects have been demonstrated against a wide range of mutagens in numerous *in vitro* and *in vivo* systems[2, 28,29].
  - ***In vitro*:** Curcumin effectively inhibits the mutagenicity of various chemical carcinogens (e.g., B[a]P, dimethylbenz[a]anthracene (DMBA), AFB1) and oxidative agents (e.g., H_2O_2) in the Ames test using different *Salmonella typhimurium* strains (TA98, TA100) with and without metabolic activation (S9 mix)[29,30]. It protects various cell types (lymphocytes, fibroblasts, hepatocytes) from DNA strand breaks, oxidative base damage (like 8-oxo-dG), and DNA adduct formation induced by mutagens, as shown by comet assay, HPLC-ECD, and ^{32}P-postlabeling techniques[28,31].
  - ***In vivo*:** Animal studies have consistently shown curcumin's protective effects. Oral administration of curcumin reduced carcinogen-induced DNA adducts in liver and other tissues, decreased the frequency of micronuclei in bone marrow cells exposed to clastogens (chromosome-breaking agents), and inhibited tumor development in various cancer models (colon, skin, stomach) initiated by chemical carcinogens[28,32]. Human studies, although more limited, have shown promising results, such as reduced levels of smoking-related DNA adducts in lymphocytes of smokers supplemented with curcumin[33].
- **Mechanisms**: Curcumin's antimutagenicity stems from its multifaceted actions:
  - Potent Antioxidant: It directly scavenges ROS (superoxide anion, hydroxyl radical) and RNS (nitric oxide, peroxynitrite) and induces endogenous antioxidant enzymes (SOD, CAT, GPx, heme oxygenase-1) via Nrf2 activation[27,28].
  - Modulation of Metabolic Enzymes: Curcumin can inhibit Phase I enzymes (e.g., CYP1A1, 1A2, 2B1) that activate pro-carcinogens and induce Phase II detoxification enzymes (e.g., GST, UDP-glucuronosyltransferase) that conjugate

and eliminate mutagens[29,30].

- **Anti-inflammatory Effects**: It inhibits key inflammatory mediators (NF-κB, AP-1, COX-2, LOX, TNF-α, interleukins) that contribute to chronic inflammation, a state associated with increased oxidative stress and mutagenesis[27].
- **DNA Interaction/Repair**: Some evidence suggests curcumin might interact with DNA or influence DNA repair pathways, although these mechanisms are less established than its antioxidant and enzyme-modulating roles[28].

***6. Glycyrrhiza glabra* (Licorice)**

- **Phytochemistry:** The main bioactive component of licorice root is the triterpenoid saponin glycyrrhizin (or glycyrrhizic acid), which is metabolized to glycyrrhetinic acid. It also contains numerous flavonoids (e.g., liquiritin, isoliquiritigenin, glabridin), chalcones, coumarins, and polysaccharides[34,35].
- **Antimutagenic Evidence:** Licorice extracts and its constituents have demonstrated antimutagenic properties in various assays. *In vitro*, licorice phenolics, particularly glabridin and isoliquiritigenin, exhibit strong antioxidant activity[35]. Studies using the Ames test showed that licorice extracts could inhibit the mutagenicity of Trp-P-1 (a heterocyclic amine found in cooked food) and AFB1[4,36]. Isoliquiritigenin was shown to protect against oxidative DNA damage in cell cultures[37]. Glycyrrhizin has also been reported to reduce the mutagenicity of certain chemicals *in vitro* and *in vivo*, possibly by influencing metabolic enzymes or through antioxidant effects[34]. *In vivo* studies indicated that licorice components could reduce chemically induced skin and liver tumorigenesis in animal models, suggesting chemopreventive activity potentially linked to antimutagenic effects[34,38].
- **Mechanisms**: Antimutagenic actions are attributed to the antioxidant properties of flavonoids and chalcones (scavenging ROS, inhibiting lipid peroxidation), modulation of carcinogen metabolism (some flavonoids can induce Phase II enzymes), and anti-inflammatory effects (inhibiting pathways like NF-κB)[34,35,37]. Glycyrrhizin's contribution might also involve interferon induction or other immunomodulatory effects[34].

***7. Capsicum annuum* (Bell Pepper/Chili Pepper)**

- **Phytochemistry:** *Capsicum annuum* encompasses a wide range of varieties from sweet bell peppers to hot chili peppers. Key compounds include:
  - Capsaicinoids: Primarily capsaicin and dihydrocapsaicin in hot varieties,

responsible for pungency. Paradoxically, capsaicin can act as a co-carcinogen or promoter at high doses but shows antioxidant and chemopreventive effects at lower doses or in specific contexts[39].

- **Carotenoids**: Beta-carotene (pro-vitamin A), capsanthin, capsorubin (responsible for red color), lutein, zeaxanthin. These are potent antioxidants.
- Flavonoids: Quercetin, luteolin, and their glycosides.
- Vitamin C (Ascorbic Acid): A major water-soluble antioxidant[40].

- **Antimutagenic Evidence**: The antimutagenic potential of *Capsicum* extracts often relates to their high antioxidant content, especially from carotenoids, flavonoids, and Vitamin C. Studies focusing on non-pungent varieties (bell peppers) show strong antioxidant capacity[40]. Extracts have demonstrated protection against oxidative DNA damage *in vitro*. For instance, bell pepper extracts reduced H_2O_2-induced DNA damage in human lymphocytes (comet assay)[41]. Carotenoids like beta-carotene and lutein are known quenchers of singlet oxygen and peroxyl radicals, protecting lipids and DNA from oxidation[42]. Vitamin C directly scavenges various ROS and can regenerate other antioxidants like Vitamin E. Regarding capsaicin (from hot peppers), the data is complex. While some studies report antimutagenic effects against certain chemical mutagens *in vitro* (e.g., reducing AFB1 mutagenicity in Ame's test possibly via CYP inhibition), others show it can induce DNA damage or act as a promoter under specific conditions[39,43]. However, epidemiological studies often link consumption of *Capsicum* fruits with reduced risk of certain cancers, suggesting an overall protective effect likely dominated by the antioxidant constituents in a typical diet.
- **Mechanisms**: Predominantly antioxidant mechanisms involving carotenoids, Vitamin C, and flavonoids scavenging ROS/RNS. Capsaicin's role is dose-dependent and context-specific, potentially involving modulation of metabolic enzymes (CYPs, GST) and cellular signaling pathways (e.g., TRPV1 activation, effects on apoptosis)[39,40,42].

***8. Asparagus racemosus* (Shatavari)**

- **Phytochemistry:** Shatavari root is rich in steroidal saponins known as shatavarins (e.g., shatavarin I-IV). It also contains alkaloids, flavonoids (quercetin, rutin, kaempferol), polysaccharides, and mucilage[44,45].
- **Antimutagenic Evidence:** Traditionally used in Ayurveda for female reproductive health and as a general tonic, Shatavari has shown promise as an antigenotoxic agent. *In vivo* studies in mice demonstrated that treatment with *A. racemosus* root extract

provided significant protection against chromosomal aberrations and micronuclei formation induced by cyclophosphamide in bone marrow cells[14,46]. It also offered protection against gamma-radiation-induced DNA damage and lethality in mice, suggesting radioprotective effects[47]. These protective effects were often correlated with an enhancement of antioxidant status (increased SOD, CAT, GSH levels) and a reduction in lipid peroxidation[14,47]. *In vitro* studies using root extracts confirmed antioxidant activity through scavenging of various free radicals[45].

- **Mechanisms**: The antimutagenic and radioprotective effects are strongly linked to its antioxidant properties, attributed to saponins and flavonoids, which scavenge ROS and bolster endogenous antioxidant defenses. Immunomodulatory effects might also contribute to its overall protective capacity[44,45,47].

Conclusion:

The diverse array of herbal plants chaptered here showcases the vast potential residing in nature for mitigating the risks associated with DNA damage and mutation. From the well-established, multifaceted actions of curcumin (*Curcuma longa*) and the potent Nrf2-activating and NF-κB-inhibiting effects of avicins (*Acacia victoriae*), to the antioxidant prowess of constituents from Ginseng (*Panax ginseng*), Ashwagandha (*Withania somnifera*), Hawthorn (*Crataegus sanguinea*), and Curry Leaves (*Murraya koenigii*), a common thread emerges: phytochemical complexity often translates into multiple mechanisms of protection. These include direct scavenging of ROS/RNS, modulation of metabolic enzymes governing mutagen activation and detoxification, enhancement of DNA repair fidelity, and suppression of inflammation-driven genotoxicity.

The scientific exploration of traditional herbal remedies continues to unveil potent natural agents capable of protecting our genetic material. These plants and their bioactive constituents offer promising avenues for developing functional foods, nutraceuticals, and potentially chemopreventive drugs to combat the mutagenic challenges inherent in our environment and biology.

References:

1. Ferguson LR. Natural products as sources of new antimutagens. *Human & Experimental Toxicology*. 2000;19(11):637-40.
2. De Flora S, Izzotti A, D'Agostini F, Balansky RM, Noonan D, Albini A. Multiple points of strength of the natural antioxidant benzo[a]pyrene from the plant kingdom for the prevention of cancer and other degenerative diseases. *Mutation Research/Chapters in*

Mutation Research. 2001;480–481:9-22.

3. Hoeijmakers JHJ. DNA damage, aging, and cancer. *New England Journal of Medicine*. 2009;361(15):1475-85.
4. Kada T, Inoue T, Namiki M. Environmental desmutagens and antimutagens. In: Stich HF, editor. *Carcinogens and Mutagens in the Environment*. Boca Raton (FL): CRC Press; 1983. p. 133-151.
5. Gutterman JI, Lai HT, Vasquez KM. Avicins: Triterpenoid saponins from Acacia victoriae Bentham. In: Bagchi D, Preuss HG, editors. *Phytopharmaceuticals in Cancer Chemoprevention*. Boca Raton (FL): CRC Press; 2005. Chapter 27.
6. Ramel C, Alekperov UK, Ames BN, Kada T, Wattenberg LW. Inhibitors of mutagenesis and their relevance to carcinogenesis. Report by ICPEMC expert group on antimutagens and desmutagens. *Mutation Research/Chapters in Genetic Toxicology*. 1986;168(1):47-65.
7. Edenharder R, Grünhage D. Free radical scavenging and antigenotoxic effects of flavonoids. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis*. 2003;543(1):1-18.
8. Johri AK. Cuminum cyminum and Carum carvi: An update. *Pharmacognosy Chapters*. 2011;5(9):63-72.
9. Deepak D, An M, Bhargavi GR, Rani KU. A chapter on phytochemical and pharmacological potential of Carum carvi. *Asian Journal of Pharmaceutical and Clinical Research*. 2013;6(Suppl 4):22-5.
10. Crowell PL. Prevention and therapy of cancer by dietary monoterpenes. *Journal of Nutrition*. 1999;129(3):775S-778S.
11. Konyalioglu S, Saglam H, Ozgen U, Karamenderes C. Evaluation of antioxidant and antimutagenic activities of some Turkish medicinal plants. *Pharmaceutical Biology*. 2005;43(1):55-61.
12. Singh N, Bhalla M, de Jager P, Gilca M. An overview on ashwagandha: a Rasayana (rejuvenator) of Ayurveda. *African Journal of Traditional, Complementary and Alternative Medicines*. 2011;8(5 Suppl):208-13.
13. Dar NJ, Hamid A, Ahmad M. Pharmacologic overview of Withania somnifera, the Indian Ginseng. *Cellular and Molecular Life Sciences*. 2015;72(23):4445-60.
14. Sharma P, Sharma S, Sharma M, Singh T, Singh S. Protective efficacy of Asparagus racemosus and Withania somnifera against cyclophosphamide induced mutagenicity.

Food and Chemical Toxicology. 2014; 74:27-32.

15. Davis L, Kuttan G. Suppressive effect of cyclophosphamide-induced toxicity by Withania somnifera extract in mice. *Journal of Ethnopharmacology*. 1998;62(3):209-14.
16. Verma S, Sharma S, Kumar A. Protective effect of Withania somnifera root extract against lead induced oxidative stress in mice. *Acta Poloniae Pharmaceutica-Drug Research*. 2011;68(6):887-93.
17. Attele AS, Wu JA, Yuan CS. Ginseng pharmacology: multiple constituents and multiple actions. *Biochemical Pharmacology*. 1999;58(11):1685-93.
18. Kim HG, Yoo SR, Park HJ, Lee NH, Shin JW, Sathyanath R, *et al.* Antioxidant effects of Panax ginseng C.A. Meyer in healthy subjects: a randomized, placebo-controlled clinical trial. *Food and Chemical Toxicology*. 2011;49(9):2229-35.
19. Lee BM, Lee SK, Kim HS. Inhibition of nitrosation and mutagenicity by components of ginseng. *Planta Medica*. 1997;63(5):431-4.
20. Panwar M, Samarth R, Kumar M, Yoon WJ, Kumar A. Inhibition of benzo(a)pyrene induced lung adenoma by Panax ginseng extract, K-frin, in Swiss albino mice. *Biological & Pharmaceutical Bulletin*. 2005;28(11):2063-7.
21. Kwok HH, Yue PY, Mak NK, Wong RN. Ginsenoside Rg1 stimulates the repair of H_2O_2-induced DNA damage in human umbilical vein endothelial cells. *Journal of Ginseng Research*. 2011;35(1):49-57.
22. Hussain AI, Anwar F, Sherazi STH, Przybylski R. Chemical composition, antioxidant and antimicrobial activities of basil (Ocimum basilicum) essential oils depends on seasonal variations. *Food Chemistry*. 2008;108(3):986-95.
23. Brahmi F, Khodir M, Mohamed C, Pierre D. Chemical composition and biological activities of Mentha species. *Medicinal and Aromatic Plant Science and Biotechnology*. 2011;5(Special Issue 1):1-11.
24. Petersen M, Simmonds MSJ. Rosmarinic acid. *Phytochemistry*. 2003;62(2):121-5.
25. Stoilova I, Krastanov A, Stoyanova A, Denev P, Gargova S. Antioxidant activity of a spearmint (Mentha spicata L.) extract. *Journal of Food Quality*. 2007;30(3):362-75.
26. Zeinab RA, Mossa ATH, El-Behairy AM, Bin Helal EED. Antimutagenicity and antioxidant activities of Mentha spicata L. essential oil. *Journal of Applied Pharmaceutical Science*. 2017;7(08):150-156.
27. Aggarwal BB, Sundaram C, Malani N, Ichikawa H. Curcumin: The Indian solid gold.

Advances in Experimental Medicine and Biology. 2007; 595:1-75.

28. Goel A, Kunnumakkara AB, Aggarwal BB. Curcumin as "Curecumin": from kitchen to clinic. *Biochemical Pharmacology*. 2008;75(4):787-809.
29. Nagabhushan M, Bhide SV. Antimutagenicity of curcumin against environmental mutagens. *Food and Chemical Toxicology*. 1992;30(7):557-60.
30. Anto RJ, George J, Dinesh Babu KV, Rajasekharan KN, Kuttan R. Antimutagenic and anticarcinogenic activity of natural and synthetic curcuminoids. *Mutation Research/Genetic Toxicology*. 1996;370(2):127-31.
31. Singh M, Singh N. Curcumin counteracts the proliferative effect of estradiol and induces apoptosis in human breast cancer MCF-7 cells. *Molecular and Cellular Biochemistry*. 2011;347(1-2):1-11.
32. Thangapazham RL, Sharma A, Maheshwari RK. Multiple molecular targets in cancer chemoprevention by curcumin. *AAPS Journal*. 2006;8(3): E443-9.
33. Polasa K, Raghuram TC, Krishna TP, Krishnaswamy K. Effect of turmeric on urinary mutagens in smokers. *Mutagenesis*. 1992;7(2):107-9.
34. Wang ZY, Nixon DW. Licorice and cancer. *Nutrition and Cancer*. 2001;39(1):1-11.
35. Asl MN, Hosseinzadeh H. Chapter of pharmacological effects of Glycyrrhiza sp. and its bioactive compounds. *Phytotherapy Research*. 2008;22(6):709-24.
36. Lee BK, Kim JH, Oh SM, Lee SG, Pyo HB, Zhang YH, *et al.* Inhibitory effects of 18β-glycyrrhetinic acid on intracellular reactive oxygen species production by ligands of the receptor for advanced glycation end products. *Biological & Pharmaceutical Bulletin*. 2003;26(5):661-5.
37. Haraguchi H, Tanimoto K, Tamura Y, Mizutani K, Kinoshita T. Mode of antibacterial action of retrochalcones from Glycyrrhiza inflata. *Phytochemistry*. 1998;48(1):125-9.
38. Shibata S. A drug over the millennia: pharmacognosy, chemistry, and pharmacology of licorice. *Yakugaku Zasshi: Journal of the Pharmaceutical Society of Japan*. 2000;120(10):849-62.
39. Surh YJ, Lee SS. Capsaicin in hot chili peppers: carcinogen, co-carcinogen or anticarcinogen? *Food and Chemical Toxicology*. 1996;34(3):313-6.
40. Zimmer AR, Leonardi B, Miron D, Schapoval E, Oliveira JR, Gosmann G. Antioxidant and anti-inflammatory properties of Capsicum baccatum: From traditional use to scientific approach. *Journal of Ethnopharmacology*. 2012;139(1):228-33.
41. Kaur C, Kapoor HC. Antioxidant activity and total phenolic content of some Asian

vegetables. *International Journal of Food Science & Technology*. 2002;37(2):153-61.

42. Edge R, McGarvey DJ, Truscott TG. The carotenoids as anti-oxidants-a chapter. *Journal of Photochemistry and Photobiology B: Biology*.1997;41(3):189-200.
43. Agrawal RC, Wiessler M, Hecker E, Bhide SV. Tumor-promoting effect of chilli extract in BALB/c mice. *International Journal of Cancer*. 1986;38(5):689-95.
44. Goyal RK, Singh J, Lal H. Asparagus racemosus-an update. *Indian Journal of Medical Sciences*. 2003;57(9):408-14.
45. Sharma U, Sharma P, Singh S. Phytochemical constituents and pharmacological profile of Asparagus racemosus: An overview. *International Research Journal of Pharmacy*. 2012;3(6):75-9.
46. Adhav MS, Shrikhande BK. Evaluation of antigenotoxic potential of Asparagus racemosus Willd root extract in mice using micronucleus test. *Toxicology International*. 2014;21(2):170-3.
47. Gautam M, Diwan V, Saha S, Dube SN, Jeengar MK, Yedla P, *et al.* Radioprotective effects of Asparagus racemosus (Willd) root extract in mice against whole body gamma irradiation. *Journal of Ayurveda and Integrative Medicine*. 2010;1(2):119-26.

NOVEL POLYMERS USED IN GASTRO RETENTIVE DRUG DELIVERY SYSTEM

Nirmal Shah

Department of Pharmacy,

Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara, Gujarat

Corresponding author E-mail: nimspharma@gmail.com

Abstract:

The chapter titled *"Novel Polymers Used in Gastroretentive Drug Delivery Systems"* delves into the critical role of advanced polymeric materials in enhancing gastric retention and controlled drug release. Gastroretentive drug delivery systems (GRDDS) are designed to prolong the residence time of dosage forms in the stomach, thereby improving the bioavailability of drugs with narrow absorption windows or those degraded in the intestinal environment. This chapter explores a wide range of novel polymers—including natural derivatives, synthetic agents, and hybrid materials—that exhibit unique properties such as swelling, mucoadhesion, floating capacity, and responsiveness to physiological stimuli. Emphasis is placed on polymers like thiolated chitosan, graft copolymers, Eudragit variants, and smart hydrogels, which have shown significant potential in overcoming challenges associated with traditional GRDDS. The chapter also addresses the physicochemical and biological considerations in polymer selection, recent advancements in formulation technologies, and future directions in the development of polymer-based gastroretentive systems. Gastroretentive Drug Delivery Systems (GRDDS) represent a specialized approach to prolong gastric residence time, thereby enhancing the bioavailability of drugs with narrow absorption windows, pH-dependent solubility, or local action in the stomach. Central to the effectiveness of these systems is the use of novel polymers that provide desirable properties such as buoyancy, mucoadhesion, swelling, and controlled drug release. This chapter focuses on recent advancements in polymer science that have led to the development of innovative materials for GRDDS applications. These include thiolated polymers, smart polymers responsive to pH or temperature, graft copolymers, and nanostructured hydrogels. Such materials offer improved mechanical strength, bioadhesiveness, and responsiveness to the gastric environment, making them ideal candidates for advanced drug delivery. The chapter also highlights the formulation strategies, mechanisms of action, and evaluation techniques associated with these novel

polymer-based systems, aiming to provide a comprehensive understanding of their role in modern pharmaceutical design.

Keywords: Novel Polymers, Gastroretentive Drug Delivery System (GRDDS), Gastric Retention, Site-Specific Drug Delivery, Polymer-Based Drug Carriers.

Introduction:

Oral drug delivery remains the most preferred and convenient route for drug administration due to its non-invasive nature, ease of administration, and high patient compliance. However, conventional oral formulations often suffer from limited bioavailability, especially for drugs that are primarily absorbed in the upper Gastrointestinal Tract (GIT), exhibit pH-dependent solubility, or degrade in the intestinal or colonic environment. To address these limitations, Gastroretentive Drug Delivery Systems (GRDDS) have been developed to prolong the gastric residence time of dosage forms, thereby enhancing drug absorption and therapeutic efficacy.

GRDDS are designed to retain the drug formulation in the stomach for extended periods, allowing for a sustained release of the active pharmaceutical ingredient at the desired site of absorption. This is particularly advantageous for drugs with a narrow absorption window in the proximal small intestine, those that are locally active in the stomach, or are unstable at higher pH levels encountered beyond the stomach[1-4].

Various approaches have been utilized to achieve gastroretention, including:

- Floating systems, which remain buoyant on gastric fluid due to low density;
- Swelling and expandable systems, which increase in size and resist gastric emptying;
- Mucoadhesive systems, which adhere to the gastric mucosa;
- High-density systems, which settle in the lower part of the stomach;
- Raft-forming systems, which form a viscous cohesive gel layer that floats.

The success of GRDDS relies heavily on the selection of appropriate polymeric materials that can modulate the mechanical and release characteristics of the dosage form. Innovations in polymer science have played a crucial role in the development of more effective GRDDS, incorporating features such as controlled drug release, environmental responsiveness, and improved stability.

In conclusion, GRDDS offer significant potential in improving the pharmacokinetic and therapeutic profiles of drugs with specific gastric requirements. The ongoing exploration of advanced polymers further enhances the applicability and effectiveness of this drug delivery strategy.

Limitations Of Conventional Polymers in GRDDS

Polymers play a fundamental role in the design and functionality of Gastroretentive Drug Delivery Systems (GRDDS). Conventional polymers such as hydroxypropyl methylcellulose (HPMC), carbopol, sodium alginate, pectin, and ethyl cellulose have been widely employed due to their established safety profiles, ease of formulation, and functionality in swelling, gelling, or floating mechanisms. Despite their widespread use, these traditional polymers present several limitations that hinder the optimization and performance of GRDDS, especially in the context of next-generation pharmaceutical requirements[5,6].

One major limitation is the inadequate control over drug release profiles. Conventional polymers often lack precision in responding to dynamic gastrointestinal conditions, such as fluctuating pH, enzymatic activity, and gastric motility. As a result, they may lead to premature drug release or incomplete gastric retention, reducing therapeutic efficacy.

Additionally, mechanical strength and integrity of some conventional polymers are insufficient to withstand gastric contractions for prolonged periods. This can result in fragmentation or early disintegration of the dosage form, which compromises the intended gastroretentive effect.

Another challenge is the limited mucoadhesive capability of many conventional polymers. Weak adhesion to the gastric mucosa may reduce the residence time of dosage forms intended to stay anchored at specific sites in the stomach.

Moreover, conventional polymers often show inconsistent performance in variable physiological environments. Factors such as food intake, gastric emptying time, and inter-patient variability can significantly affect the behavior of these polymers, making it difficult to achieve reproducible and predictable drug delivery outcomes.

In summary, while conventional polymers have laid the foundation for GRDDS development, their functional limitations, lack of environmental responsiveness, and restricted physicochemical tunability have driven the need for novel, advanced polymers. These new materials aim to overcome existing challenges and enable more efficient, stable, and patient-specific gastroretentive drug delivery systems.

Need For Novel Polymers in Advanced GRDDS

The advancement of gastroretentive drug delivery systems (GRDDS) has significantly improved the therapeutic performance of drugs requiring prolonged gastric retention. However, the evolving demands of modern pharmacotherapy, including the need for enhanced drug stability, precise release control, and personalized treatment,

have highlighted the limitations of traditional polymeric materials used in GRDDS. This growing complexity necessitates the exploration and integration of novel polymers with improved physicochemical, mechanical, and biological properties.

Conventional polymers often fall short in adapting to variable gastrointestinal conditions such as pH fluctuations, enzymatic degradation, and gastric motility. Furthermore, they may lack stimuli-responsive behavior, target-specific adhesion, and mechanical robustness, all of which are critical for the reliable performance of advanced GRDDS. In contrast, novel polymers—including smart polymers, bioadhesive derivatives, biodegradable copolymers, and engineered hydrogels—can be tailored to overcome these challenges.

These innovative materials offer site-specific functionality, such as pH-sensitive swelling, temperature-responsive gelation, or enzymatically triggered drug release. They also enable longer gastric retention, controlled release kinetics, and improved compatibility with a broader range of drug molecules, including peptides, proteins, and poorly water-soluble compounds.

Moreover, novel polymers can be engineered to form multifunctional GRDDS platforms, combining floating, expanding, and mucoadhesive properties in a single system. This versatility enhances formulation flexibility and ensures better adaptability to individual patient needs[6].

In conclusion, the integration of novel polymers is essential for the development of next-generation GRDDS that are more efficient, stable, and responsive to the dynamic environment of the gastrointestinal tract. These materials represent the future of smart drug delivery and hold great promise for improving therapeutic outcomes in various clinical scenarios.

Categories of Novel Polymers

Natural Modified Polymers

1. Thiolated Chitosan as a Novel Polymer in GRDDS

Thiolated chitosan (also known as thiomers) is a chemically modified derivative of chitosan, designed to enhance its mucoadhesive, permeation-enhancing, and gastroretentive properties. It is a prominent example of novel natural polymers developed for advanced GRDDS applications[7-9].

Structural Characteristics

Thiolated chitosan is synthesized by covalently attaching thiol (-SH) groups to the chitosan backbone. The thiol groups enable disulfide bond formation with cysteine-rich domains in gastric mucin, greatly enhancing mucoadhesiveness.

Advantages in GRDDS

- Superior Mucoadhesion: Forms strong covalent disulfide bonds with gastric mucus, leading to prolonged gastric residence.
- Enzyme Inhibition: Can inhibit peptidases and proteases, thus protecting peptide drugs from degradation.
- Controlled Drug Release: Its gel-forming ability contributes to sustained and site-specific release.
- Enhanced Permeability: Temporarily opens tight junctions in epithelial cells, improving the absorption of poorly permeable drugs.
- Biodegradability: Maintains the biocompatibility and biodegradability of natural chitosan.

Applications in GRDDS

- Mucoadhesive tablets and gels: Prolong drug retention in the stomach.
- Floating drug delivery systems: Can be combined with gas-generating agents.
- Nanoparticles and microparticles: For enhanced mucosal delivery of peptides, proteins, and poorly soluble drugs.

2. Modified Guar and Xanthan Gum as Novel Polymers in GRDDS

Guar gum and xanthan gum are natural polysaccharides widely recognized for their biocompatibility, swelling capacity, and viscosity-enhancing properties. However, their native forms have certain limitations such as rapid hydration, poor mechanical strength, and susceptibility to enzymatic degradation. To overcome these, modified forms of guar and xanthan gum have been developed, enhancing their suitability as novel polymers for gastroretentive drug delivery applications[10,11].

Structural Modifications

Chemical and physical modifications of guar and xanthan gum aim to:

- Improve mechanical stability and control hydration/swelling rates.
- Enhance resistance to acidic pH and gastric enzymes.
- Introduce mucoadhesive or crosslinkable functional groups.

Common modifications include:

- Carboxymethylation
- Graft copolymerization with acrylic acid, methacrylic acid, or vinyl monomers
- Crosslinking with agents such as glutaraldehyde, citric acid, or borax

Advantages in GRDDS

- Swelling Ability: Modified gums swell upon hydration, forming a gel-like matrix that can trap the drug and control release.

- Mucoadhesion: Functional group modification can enhance bioadhesion to gastric mucosa, increasing retention time.
- Biocompatibility: Being naturally derived, they retain non-toxic and biodegradable profiles post-modification.
- Floating Ability: When formulated with gas-generating agents, they assist in developing low-density, floating matrices.

Applications in GRDDS

- Matrix tablets: Provide controlled and sustained drug release in the gastric region.
- Floating beads and films: With entrapped air or gas-forming agents, enhance buoyancy in gastric fluids.
- Mucoadhesive gels or microparticles: Improve contact time with the gastric lining for local or systemic delivery.

3. Carboxymethyl Tamarind Kernel Powder (CMTKP) as a Novel Polymer in GRDDS

Carboxymethyl tamarind kernel powder (CMTKP) is a chemically modified form of tamarind seed polysaccharide (TSP)—a natural, non-toxic, biodegradable polymer obtained from the seeds of *Tamarindus indica*. By introducing carboxymethyl groups, the native polymer is significantly improved in terms of hydrophilicity, mucoadhesion, and drug release control, making CMTKP a promising novel polymer for gastroretentive drug delivery systems (GRDDS)[12,13].

Structure and Modification

Tamarind kernel powder (TKP) is primarily composed of polysaccharides with a high content of galactoxyloglucan.

Carboxymethylation introduces carboxymethyl (-CH_2COOH) groups to the hydroxyl groups of TKP, enhancing:

- Solubility in aqueous and acidic media
- Anionic character, facilitating mucoadhesive interactions
- Swelling capacity in the gastric environment

Desirable Properties in GRDDS

- Excellent Mucoadhesiveness: Carboxymethyl groups promote electrostatic interaction with the gastric mucosa, prolonging residence time.
- Swellability: CMTKP swells in gastric fluids to form a gel-like matrix, contributing to sustained drug release.
- pH Stability: Maintains integrity and function in acidic gastric pH (1.0–3.5).
- Biodegradability and Biocompatibility: Non-toxic and suitable for oral drug delivery, with minimal risk of irritation or immunogenicity.

Applications in GRDDS

- Mucoadhesive tablets and films: Improve drug bioavailability by localizing release in the stomach.
- Floating drug delivery systems: Due to its lightweight gel-forming nature, it supports buoyancy in gastric fluids.
- Hydrophilic matrix systems: Sustains drug release over extended periods.
- Beads and microspheres: Serve as carriers for site-specific delivery of anti-ulcer, antibiotic, or anti-diabetic drugs.

4. Alginate Derivatives (e.g., Alginate-PEG Conjugates) as Novel Polymers in GRDDS

Alginate, a naturally occurring, linear anionic polysaccharide derived from brown seaweed, has been extensively used in pharmaceutical applications due to its biocompatibility, gel-forming ability, and low toxicity. However, its native form has limitations such as instability in acidic conditions and insufficient mechanical strength. To overcome these, alginate derivatives, especially alginate–polyethylene glycol (PEG) conjugates, have been developed as novel polymers for advanced gastroretentive drug delivery systems (GRDDS)[14-15].

Structural Characteristics

- Alginate consists of β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues arranged in homopolymeric and heteropolymeric blocks.
- Alginate-PEG conjugation involves covalent bonding of alginate with PEG chains through esterification or amide linkages.
- The PEGylation of alginate improves hydrophilicity, flexibility, and resistance to acidic degradation.

Advantages in GRDDS

- Enhanced Mucoadhesion: PEG chains promote interfacial adhesion to gastric mucosa by increasing polymer flexibility and hydration.
- Improved Stability in Gastric pH: Conjugation reduces alginate's tendency to precipitate in acidic environments, maintaining gel integrity.
- Controlled Drug Release: Alginate-PEG hydrogels form viscous matrices that regulate drug diffusion and prolong gastric residence.
- Biocompatibility and Biodegradability: Safe for oral administration with minimal immunogenicity or toxicity.
- Reduced Burst Release: PEG conjugation minimizes initial drug leakage, providing a more sustained release profile.

Applications in GRDDS

- Floating beads and gels: Crosslinked alginate-PEG hydrogels exhibit low density and buoyancy in gastric fluids.
- Mucoadhesive microspheres: Enhance gastric retention for drugs targeting Helicobacter pylori or peptic ulcers.
- Nanoparticles and *in situ* gelling systems: For site-specific delivery of antibiotics, antiemetics, or anti-diabetic drugs.

Synthetic and Smart Polymers

Synthetic and smart polymers represent a new frontier in gastroretentive drug delivery, offering customizable, stimuli-responsive solutions for overcoming limitations associated with natural polymers. These polymers can be engineered at the molecular level to respond to physiological triggers such as pH, temperature, enzymes, or mechanical forces, enabling controlled release, targeted delivery, and enhanced gastric retention.

Synthetic Polymers in GRDDS

Synthetic polymers are man-made macromolecules with defined, reproducible structures that can be customized for specific drug delivery objectives.

Common Examples:

- Eudragit® polymers (e.g., Eudragit RS, RL): pH-independent swelling and sustained-release characteristics; widely used in floating and matrix systems.
- Polyvinyl alcohol (PVA): Good film-forming and swelling properties; used in gastroretentive films and hydrogels.
- Polyvinylpyrrolidone (PVP): Enhances drug solubility and forms matrices for controlled release.
- Polyethylene oxide (PEO): High molecular weight, swellable polymer that contributes to floating ability and matrix integrity.

Advantages:

- High reproducibility and purity
- Controlled degradation rates
- Customizable swelling, adhesion, and release properties
- Good mechanical strength

Smart Polymers in GRDDS

Smart polymers (also known as stimuli-responsive polymers) undergo reversible changes in response to specific triggers in the gastric environment. These changes can lead to gel formation, swelling, mucoadhesion, or drug release, enhancing the effectiveness of gastroretentive systems.

1. pH-Responsive Polymers in GRDDS

pH-responsive polymers are a class of smart materials that exhibit solubility, swelling, or structural changes in response to the pH of the surrounding environment. In the context of GRDDS, these polymers are specifically designed to function in the acidic environment of the stomach (pH 1.0–3.5), where they can aid in drug retention, protection, and controlled release[16-18].

Mechanism of Action

pH-responsive polymers contain ionizable functional groups such as carboxylic acids or amines. These groups undergo protonation or deprotonation based on environmental pH, resulting in changes in: Swelling behavior, Solubility, Ionic interactions, Polymer chain conformation. In GRDDS, polymers are typically designed to remain intact and swell in the stomach (acidic pH), protect acid-sensitive drugs and sustain drug release within the gastric environment

Common pH-Responsive Polymers

Polymer	Functional Group	Behavior in Acidic pH	Application
Eudragit® RS/RL	Quaternary ammonium	Swell, pH-independent	Sustained-release matrix
Carbopol	Carboxylic acid	Swells in acidic pH	Mucoadhesive gels and tablets
Polyacrylic acid (PAA)	Carboxyl	Swelling and drug retention	Bioadhesive systems
HPMC phthalate (HPMCP)	Esterified cellulose	Remains intact in gastric pH	Enteric coatings; used in dual-release systems
Chitosan (cationic)	Amino	Soluble in low pH	Mucoadhesive and film-forming systems

2. Temperature-Sensitive Polymers (e.g., PNIPAM) in GRDDS

Temperature-sensitive polymers (also known as thermoresponsive polymers) are smart materials that exhibit phase transitions—such as sol-gel conversion—in response to temperature changes. These polymers are especially attractive for gastroretentive drug delivery systems (GRDDS), where they can be administered as a liquid at room temperature and form a gel in situ at body temperature, thus enabling prolonged gastric retention and controlled drug release[19,20].

Mechanism of Action

Temperature-sensitive polymers undergo a sharp change in solubility or physical state at a specific temperature known as the Lower Critical Solution Temperature (LCST). Below the LCST, the polymer is hydrophilic and soluble in water. Above the LCST, the polymer becomes hydrophobic, resulting in chain aggregation and gelation. In GRDDS, this behavior is exploited to form a gastric-retentive gel upon exposure to body temperature (~37°C) after oral administration.

Key Example: PNIPAM

- Poly(N-isopropylacrylamide) (PNIPAM) is the most widely studied thermoresponsive polymer. LCST ≈ 32°C — forms a gel at body temperature. PNIPAM-based hydrogels can be tailored with co-polymers or additives to modify gel strength, degradation rate, and drug loading capacity.

Other Examples

- Poloxamers (e.g., Pluronic F127): Block copolymers that form micelles and gels above their LCST.
- Chitosan–β-glycerophosphate systems: Biocompatible in situ gelling formulations for GRDDS.

3. Floating Nanocomposite Polymers in GRDDS

Floating nanocomposite polymers are an emerging class of materials designed to enhance the performance of gastroretentive drug delivery systems (GRDDS) by improving buoyancy, mechanical stability, and controlled drug release. These systems integrate nanomaterials into a polymeric matrix to develop a low-density, floating structure that remains buoyant in the gastric environment for prolonged periods[21].

Mechanism of Action

The buoyancy of nanocomposite systems is achieved by entrapping gas, reducing density, or generating CO_2 in situ. Embedded nanoparticles (NPs) reinforce the polymer matrix, reducing degradation, and enabling sustained drug release.

Common strategies include:

- Gas-forming agents within a swellable matrix
- Nanofillers that lower density or modify rheological properties
- Use of porous or foamed polymer structures

Stimuli-Responsive / Smart Polymers in GRDDS

Stimuli-responsive or smart polymers are an advanced class of materials that undergo reversible physical or chemical transformations in response to specific environmental triggers. These stimuli can be internal (e.g., pH, temperature, enzymes) or external (e.g., magnetic fields, light, or pressure). In the context of Gastroretentive Drug Delivery Systems (GRDDS), smart polymers offer precision-controlled drug release, improved gastric retention, and adaptive behavior that enhances therapeutic efficacy and patient compliance[22,23].

1. Enzyme-Responsive Polymers in GRDDS

Enzyme-responsive polymers are smart materials designed to undergo chemical or physical changes in the presence of specific enzymes. These polymers exploit the local enzymatic activity present in the gastrointestinal (GI) tract to achieve targeted, site-specific, and controlled drug release. In Gastroretentive Drug Delivery Systems (GRDDS), enzyme-responsive materials are particularly promising for local delivery in gastric infections, ulcers, or inflammation, where enzyme overexpression provides a natural trigger for drug activation or matrix degradation.

Mechanism of Action

The polymer matrix is engineered with cleavable bonds or side chains that are substrates for specific enzymes. When exposed to the gastric or microbial enzymes, these bonds are cleaved, resulting in: Polymer degradation or swelling, controlled drug release and targeted release at pathological sites.

Target Enzymes in the Gastric Environment

Enzyme	**Source**	**Targeted Polymer/Linkage**
Pepsin	Stomach lining	Protein-based polymers (e.g., gelatin)
β-Glucuronidase	Pathogenic bacteria	Glucuronide linkages
Matrix metalloproteinases	Inflamed or ulcerated tissues	MMP-sensitive peptide sequences
Urease (from *H. pylori*)	Gastric pathogens	Urea-containing copolymers

2. Dual- or Multi-Stimuli Responsive Systems in GRDDS

Dual- or multi-stimuli responsive systems are an advanced class of smart polymeric materials engineered to respond to two or more environmental cues—such as pH,

temperature, enzymes, redox conditions, or external fields—to achieve precise spatial and temporal control over drug release. In the context of Gastroretentive Drug Delivery Systems (GRDDS), these systems enhance the specificity, adaptability, and robustness of oral drug delivery, especially under complex or variable gastric conditions.

Types of Dual/Multi-Stimuli Responsive Systems in GRDDS

Stimuli Combination	**Responsive Behavior**	**Example Materials**
pH + Temperature	Swelling, gelation, and drug diffusion changes	PNIPAM-grafted Eudragit® or chitosan
pH + Enzyme	Targeted degradation and release in disease sites	MMP-cleavable hydrogels with pH-sensitive backbones
Redox + pH	Disulfide bond cleavage + solubility modulation	PEG–SS–PAA (polyacrylic acid) complexes
pH + Magnetic Field	Site-specific release + externally controlled motion	Chitosan–Fe_3O_4 nanoparticles embedded in Eudragit® matrix
Temperature + Gas-forming (buoyancy)	Floatation + controlled gelation	Thermo-responsive HPMC systems with sodium bicarbonate
Enzyme + Redox	Synergistic targeting in ulcerative/infected tissue	Hybrid dextran–thioketal polymer conjugates

References:

1. Murphy CS, Pillay V, Choonara YE, du Toit LC. Gastroretentive drug delivery systems: current developments in novel system design and evaluation. Current drug delivery. 2009;6(5):451-60.
2. Dhiman S, Philip N, Gurjeet Singh T, Babbar R, Garg N, Diwan V, Singh P. An insight on novel approaches & perspectives for gastro-retentive drug delivery systems. Current Drug Delivery. 2023;20(6):708-29.
3. Shah S, Pandya S. A novel approach in gastro retentive drug delivery system: floating drug delivery system. International Journal of Pharmaceutical Sciences and Research. 2010;1(6):7-18.

4. Mandal UK, Chatterjee B, Senjoti FG. Gastro-retentive drug delivery systems and their in vivo success: A recent update. asian journal of pharmaceutical sciences. 2016;11(5):575-84.
5. Tripathi J, Thapa P, Maharjan R, Jeong SH. Current state and future perspectives on gastroretentive drug delivery systems. Pharmaceutics. 2019;11(4):193.
6. Singh M, Das MK. A Comprehensive Review on Role of Natural Polymers in Gastro Retentive Drug Delivery System (GRDDS). Drug Delivery Letters. 2024.
7. Sreenivas SA, Pai KV. Thiolated chitosans: novel polymers for mucoadhesive drug delivery–a review. Tropical Journal of Pharmaceutical Research. 2008;7(3):1077-88.
8. Federer C, Kurpiers M, Bernkop-Schnürch A. Thiolated chitosans: A multi-talented class of polymers for various applications. Biomacromolecules. 2020;22(1):24-56.
9. Grosso R, de-Paz MV. Thiolated-polymer-based nanoparticles as an avant-garde approach for anticancer therapies—reviewing thiomers from chitosan and hyaluronic acid. Pharmaceutics. 2021;13(6):854.
10. Waqar MA, Mubarak N, Khan AM, Khan R, Shaheen F, Shabbir A. Advanced polymers and recent advancements on gastroretentive drug delivery system; a comprehensive review. Journal of Drug Targeting. 2024;32(6):655-71.
11. Ananthakumar R, Chitra K, Satheshkumar S. A review on applications of natural polymers in gastroretentive drug delivery system. Drug Invention Today. 2018;10(3).
12. Kaur G, Jain S, Tiwary AK. Chitosan-carboxymethyl tamarind kernel powder interpolymer complexation: investigations for colon drug delivery. Scientia pharmaceutica. 2009;78(1):57.
13. Khushbu SG. Carboxymethyl tamarind kernel gum based controlled drug delivery excipients: a review. Journal of Engg. Research ICAPIE Special Issue pp. 2022;27:40.
14. Sen O, Manna S, Nandi G, Jana S, Jana S. Recent advances in alginate based gastroretentive technologies for drug delivery applications. Medicine in Novel Technology and Devices. 2023;18:100236.
15. Dhiman S, Philip N, Gurjeet Singh T, Babbar R, Garg N, Diwan V, Singh P. An insight on novel approaches & perspectives for gastro-retentive drug delivery systems. Current Drug Delivery. 2023;20(6):708-29.
16. Yang J, Wang Y, Wei A, Peng K, Huang R, Wang Z, Ma X, Tian Q, Chen Y. Polyelectrolyte composite hydrogels based on a derivative of functional dietary fiber

for long-term gastric retention and drug delivery. Composites Part B: Engineering. 2024;272:111194.

17. Zanke AA, Gangurde HH, Ghonge AB, Chavan PS. Recent Advance in Gastroretantive Drug Delivery System (GRDDS). Asian Journal of Pharmaceutical Research. 2022;12(2):143-9.
18. Malik R, Garg T, Goyal AK, Rath G. Polymeric nanofibers: targeted gastro-retentive drug delivery systems. Journal of Drug Targeting. 2015;23(2):109-24.
19. Shaibie NA, Ramli NA, Mohammad Faizal ND, Srichana T, Mohd Amin MC. Poly (N-isopropylacrylamide)-based polymers: recent overview for the development of temperature-responsive drug delivery and biomedical applications. Macromolecular Chemistry and Physics. 2023;224(20):2300157.
20. Li L, He Y, Zheng X, Yi L, Nian W. Progress on preparation of pH/temperature-sensitive intelligent hydrogels and applications in target transport and controlled release of drugs. International Journal of Polymer Science. 2021;2021(1):1340538.
21. Dubey A, Ovais M, Bisen AC, Rajendiran A. Advancements and Challenges in Gastroretentive Drug Delivery Systems: A Comprehensive Review of Research Innovation, Technologies, and Clinical Applications. Recent Advances in Drug Delivery and Formulation. 2025.
22. Gupta S, Rajak AK, Yadav K, Pradhan M, Mongia P, Raj R, Minz S. Nanocarriers for Gastro-Retentive Drug Delivery. InSmart Nanocarrier for Effective Drug Delivery 2024 (pp. 169-198). CRC Press.
23. Singh B, Kaur A, Dhiman S, Garg B, Khurana RK, Beg S. QbD-enabled development of novel stimuli-responsive gastroretentive systems of acyclovir for improved patient compliance and biopharmaceutical performance. Aaps Pharmscitech. 2016;17:454-65.

ANCIENT REMEDIES AND FOLK USES OF PASSION FRUIT

Dhanya B. Sen*, Rajesh A. Maheshwari, Kinjal Patel and Ashim Kumar Sen

Department of Pharmacy,

Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara - 391760, Gujarat

*Corresponding author E-mail: dhanyab1983@gmail.com

Abstract:

This chapter summarizes the diverse biological activities of *Passiflora edulis* and related passion fruit species, emphasizing their inflammation-reducing, cancer-fighting, blood sugar lowering, antidepressant, and heart-protective properties. Various bioactive compounds such as saponins, flavonoids, stilbenes (notably piceatannol), and unsaturated fatty acids were extracted and identified from different parts of the plant—including leaves, peel, pulp, seeds, and bagasse—using advanced extraction and analysis methods. Flavonoid-rich leaf extracts and saponins demonstrated strong anti-inflammatory effects by inhibiting nitric oxide synthase and reducing inflammatory cytokines, while yellow passion fruit bagasse extract suppressed NF-κB signaling and enhanced wound healing in periodontal cells. Passion fruit seed oil, abundant in unsaturated fatty acids and antioxidants, showed lipid-lowering activity by inhibiting key digestive enzymes and improving lipid metabolism in cellular models. Anticancer effects were observed via apoptosis induction and cell cycle disruption in various cancer cell lines, with stilbene-rich seed extracts targeting metabolic enzymes crucial to tumor growth. Extracts from seed and pulp also exhibited blood glucose-lowering activity through enzyme inhibition and antioxidant effects. Antidepressant-like effects were linked to flavonoids and cycloartane triterpenoids, acting through serotonin and dopamine pathways. Cardiovascular benefits were evidenced by lowered blood pressure and oxidative stress in hypertensive animal models following passion fruit extract treatment. Overall, these findings highlight the promising therapeutic potential of passion fruit-derived compounds for managing inflammation, cancer, metabolic disorders, mood conditions, and cardiovascular health, supporting further clinical research.

Keywords: *Passiflora edulis*, Anti-Inflammatory, Anticancer, Antidiabetic, Hypolipidemic, Antidepressant, Cardioprotective, Flavonoids

Introduction:

Passion fruit, which refers to various species within the *Passiflora* genus, has been an integral component of traditional healing systems across numerous cultures globally. Native to South America—particularly regions such as Brazil, Paraguay, and northern Argentina—this tropical and subtropical plant is celebrated not just for its distinctive, fragrant fruit but also for its extensive medicinal applications rooted in ethnobotanical practices.[1] Among the diverse species, *P. edulis* is the most extensively cultivated and researched, while others like *P. incarnata*, *P. alata*, and *P. quadrangularis* are also well known for their therapeutic potential. Indigenous populations have historically used these plants to address a variety of health concerns, ranging from digestive issues to neurological conditions.[2,3] For generations, traditional medical practices have taken advantage of the therapeutic properties found in various parts of the passion fruit plant, including its leaves, flowers, roots, and fruits.[4] In South American herbal traditions, infusions made from the leaves are often administered as gentle sedatives and treatments for anxiety—a practice now supported by scientific inquiry.[5] These soothing effects are largely due to the presence of bioactive compounds such as flavonoids, alkaloids, and glycosides, which influence neurotransmitter function, particularly within the GABA system. Consequently, passion flower has become a staple in natural remedies aimed at managing conditions like anxiety, insomnia, and epilepsy across various cultural traditions.[6]

Aside from its neurological applications, passion fruit is also known for its pain-relieving, inflammation lowering, spasm-relieving, and gastrointestinal benefits.[7,8] In Brazilian folk healing, teas brewed from different *Passiflora* species are employed to manage respiratory ailments like asthma, bronchitis, and persistent coughs. Additionally, indigenous groups utilize leaf and root-based poultices to aid in wound care and to combat infections and fevers. In regions of Africa and Asia where passion fruit has been introduced and adapted, similar ethnomedicinal uses have emerged, with traditional healers incorporating it into treatments for chronic conditions such as hypertension, diabetes, and even parasitic diseases.[9-11]

The traditional use of passion fruit has also sparked scientific interest, prompting detailed investigation into its chemical constituents and medicinal value. Research has identified numerous bioactive elements within the plant, including key flavonoids (such as chrysin and vitexin), alkaloids (like harman and harmine), cyanogenic glycosides, saponins, and essential oils. These compounds demonstrate a wide range of biological effects, such as

free radical scavenging, germ-fighting, calming, hypotensive, and blood sugar-regulating properties. In particular, its free radical scavenging activity has positioned passion fruit as a promising natural agent in addressing oxidative stress-related conditions, such as cardiovascular diseases and neurodegenerative disorders.[10-12] In traditional healing systems, the plant is not only used internally but also applied externally. Folk remedies frequently involve the use of crushed leaves or fruit pulp for the treatment of skin conditions like burns, rashes, and boils, capitalizing on the plant's antibacterial and inflammation supressing actions. Recent scientific evidence supports these traditional uses, suggesting that extracts from passion flower may aid skin regeneration and reduce infection risks.[12-14]

Despite its prominence in folk medicine and growing recognition in scientific circles, much of passion fruit's therapeutic potential remains unexplored. Many traditional uses remain undocumented, especially those preserved by isolated or indigenous communities. The gradual loss of ethnobotanical knowledge, driven by cultural change and environmental degradation, highlights the urgency of conserving and studying traditional uses of *Passiflora* species. Bridging this traditional wisdom with contemporary biomedical research can lead to the development of new medicinal products while promoting sustainable and respectful use of natural resources. Beyond its medicinal applications, passion fruit also carries symbolic and spiritual importance in various cultures. In Christian iconography, the passion flower is believed to represent the Passion of Christ, with its floral components symbolizing aspects of the crucifixion—a symbolic layer that may have enhanced its perceived healing properties in traditional beliefs. This chapter highlights how the use of passion fruit in traditional medicine reflects a deep-rooted heritage of botanical healing, developed over many generations of indigenous and cultural wisdom. As modern science increasingly supports and broadens our understanding of these traditional applications, passion fruit serves as a prime example of how ethnobotanical knowledge can be combined with contemporary pharmacological research. The careful documentation and preservation of this cultural heritage, alongside thorough scientific investigation, are crucial for promoting sustainable and effective natural health solutions.[1-3]

Inflammation Lowering Effect

The research successfully extracted and identified key bioactive compounds from the leaves of *P. edulis f. edulis*, including a variety of saponins and flavonoids. Notably, this study represents the first definitive identification of three particular saponins—

cyclopassiflosides IX, XI, and III—as well as three minor flavonoids within this species. When tested in a mouse model of chronic skin inflammation, the flavonoid-rich fraction exhibited the most potent anti-inflammatory activity, highlighting its potential as a natural treatment for inflammation. Additionally, all evaluated fractions and isolated compounds showed significant inhibition of nitric oxide synthase, an enzyme integral to the inflammatory process. This inhibition likely underlies their anti-inflammatory effects. Overall, these findings enhance the knowledge of the phytochemical profile of *P. edulis* leaves and support their therapeutic promise in inflammation management, paving the way for further pharmacological studies and the development of plant-based anti-inflammatory agents.[15] The research found that exposing periodontal ligament cells to *Fusobacterium nucleatum* led to an increase in inflammatory markers and activated the NF-κB signaling pathway, which drives inflammation. Treatment with yellow passion fruit bagasse extract (PFBE), rich in piceatannol, significantly diminished these inflammatory responses and blocked NF-κB activation. PFBE was non-toxic to the cells and also promoted wound healing in vitro. These results suggest that PFBE possesses valuable inflammation lowering, anti-proteolytic, and tissue-repair properties, highlighting its potential as a therapeutic option for the prevention and treatment of periodontal disease.[16]

The research showed that the aqueous extract of *P. edulis* forma *flavicarpa* leaves, along with its butanolic and aqueous fractions, possessed notable inflammation lowering properties in mouse models of inflammation caused by carrageenan, histamine, and substance P. These extracts significantly reduced the migration of leukocytes and neutrophils and decreased levels of inflammatory markers including myeloperoxidase, nitric oxide, IL-1β, and MIP-2. Unlike dexamethasone, the extract and its fractions specifically lowered MIP-2 concentrations, whereas dexamethasone alone was able to reduce mononuclear cell infiltration in certain instances. In summary, the extract and its fractions exhibited powerful anti-inflammatory effects by inhibiting immune cell migration and reducing essential proinflammatory factors.[17] The study investigated the polyphenol composition of three Colombian passion fruit varieties—*P. edulis* var. *Flavicarpa* (Maracuyá), *P. edulis* var. *Sims* (Gulupa), and *P. ligularis* var. *Juss* (Granadilla)—and assessed their ability to protect the intestinal barrier in Caco-2 cells exposed to inflammation. Various polyphenols, xanthenes, and a terpene were identified, with cyanidin 3-rutinoside, (+)-catechin, and ferulic acid being the main compounds in each variety. All extracts successfully prevented the decline in transepithelial electrical

resistance, an indicator of barrier integrity, with *P. ligularis* var. *Juss* showing the strongest protective effect. These findings suggest that passion fruit polyphenols may help support intestinal barrier function during inflammatory stress.[18]

The study explored the protective effects of soluble dietary fiber (SDF) obtained from yellow passion fruit peel in a mouse model of ulcerative colitis (UC) induced by dextran sulfate sodium (DSS). Treatment with varying doses of SDF significantly improved clinical symptoms by reducing weight loss, preserving colon length, and lowering the disease activity index. SDF also alleviated oxidative stress by regulating glutathione (GSH) levels and enhancing superoxide dismutase activity. Additionally, it influenced the inflammatory response by reducing levels of MPO, TNF-α, and IL-1β, while increasing anti-inflammatory cytokines IL-10 and IL-6. Histological analysis confirmed that SDF contributed to maintaining colon structure, protecting the mucus barrier, and decreasing inflammatory cell infiltration. These findings suggest that SDF could be a beneficial adjunct in UC management, though further research is necessary to fully understand its protective effects.[19]

Cancer-Inhibiting Effect

This research evaluated the antitumor activity of yellow passion fruit (YPF) juice on T47D (breast cancer) and HeLa (cervical cancer) cell lines. When applied at different concentrations, YPF juice exhibited cytotoxic effects by inhibiting cell growth and inducing apoptosis. Treated cells showed extended doubling times and significantly higher rates of apoptosis than untreated controls. At the IC_{50} concentration, YPF juice disrupted the cell cycle—HeLa cells experienced a 13% reduction in the G0–G1 phase, while T47D cells mainly accumulated in the sub-G0 phase, indicating widespread cell cycle arrest. These results suggest that YPF juice may exert anticancer effects by triggering apoptosis and disrupting cell cycle progression in both cancer types.[20] The study demonstrated that passion fruit seed extract (PFSE), rich in bioactive stilbenes like piceatannol and scirpusin B, effectively inhibits glyoxalase I (GLO I), an enzyme essential for detoxifying harmful metabolic byproducts such as methylglyoxal. This inhibition significantly suppressed the proliferation of cancer cells, particularly those with elevated GLO I expression, like the NCI–H522 cell line, compared to cells with lower GLO I levels such as HCT116. These results indicate that PFSE has potential as a targeted anticancer treatment by interfering with cancer cell metabolism through GLO I inhibition. The findings support further research into

PFSE and its stilbene compounds as promising candidates for developing novel cancer prevention and therapy options that target metabolic vulnerabilities in tumor cells.[21]

This study explored the anticancer effects of piceatannol (PIC), a polyphenol present in yellow passion fruit extract (PFE), on prostate cancer cell lines and a prostate cancer mouse model (TRAMP). PIC treatment decreased the viability of several prostate cancer cell types in a dose- and time-dependent way. In androgen-dependent cell lines (22Rv1 and LNCaP), PIC caused cell cycle arrest at the G0/G1 phase and induced apoptosis, without notably affecting lactate levels or glucose metabolism. The treatment also influenced key regulators of the cell cycle, including p53, p21, cyclin D1, and cdk4. In TRAMP mice, both short- and long-term PFE administration modified these proteins and delayed cancer progression by reducing the number of preneoplastic lesions. Overall, the anticancer effects of PIC seem largely driven by inducing cell cycle arrest and modulating p53, rather than altering glucose metabolism, particularly in androgen-dependent prostate cancer cells.[22] The research investigated the anticancer effects of passion fruit seed extract on different cell lines. The extract exhibited cytotoxicity and induced apoptosis in oral cancer (HSC-3) and breast cancer (MCF-7) cells, with IC_{50} values of 572.79 µg/mL and 439.54 µg/mL, respectively. It showed no toxic effects on HSC-2 oral cancer cells and, at the highest concentration, stimulated the growth of normal human keratinocytes (HaCaT). Apoptosis was confirmed by DNA fragmentation and characteristic morphological changes. These findings indicate that the seed extract selectively targets cancer cells while remaining non-toxic to normal cells, highlighting its potential as an adjunct in cancer therapy.[23]

Blood Sugar Lowering Effect

The research investigated the antidiabetic, antiglycation, and antioxidant properties of the ethanolic extract from *P. edulis* seeds (PESE) and its key compound, piceatannol (PIC). Both PESE and PIC were found to inhibit crucial diabetes-associated enzymes such as alpha-amylase, alpha-glucosidase, and DPP-4. They also effectively prevented the formation of advanced glycation end-products and β-amyloid fibrils. Furthermore, PESE and PIC demonstrated strong antioxidant effects by neutralizing harmful radicals and safeguarding human cells from carcinogen-induced oxidative damage. Although PESE was non-toxic to some normal human and mouse cells at certain doses, it showed toxicity towards non-cancerous breast epithelial cells at lower concentrations. These results indicate PESE and PIC have promising potential for further exploration as treatments for diabetes.[24] The research evaluated the free radical scavenging, blood sugar lowering, and

germ fighting effects of different solvent extracts from *P. ligularis* fruits. Among these, the acetone extract had the highest concentrations of phenolics, tannins, and flavonoids, showing strong antioxidant activity through free radical scavenging and metal chelation. It also effectively inhibited key diabetes-related enzymes, α-amylase and α-glucosidase. Moreover, the extract displayed antibacterial activity against both Gram-positive and Gram-negative bacteria, as well as antifungal effects against Candida albicans and Aspergillus niger. Key polyphenols identified included ellagic acid, gallic acid, and rutin. These results indicate that *P. ligularis* fruit pulp possesses valuable antioxidant and antimicrobial properties, supporting its potential use in food and pharmaceutical industries.[25]

The study found that yellow passion fruit pulp juice significantly lowered blood glucose levels in diabetic rats, especially at higher doses (2 mL and 2.5 mL). The juice showed no toxic effects and demonstrated potential as a safe and natural anti-hyperglycemic treatment. These results support its possible use as an alternative therapy for managing diabetes mellitus.[26] The study found that methanolic extracts of *P. incarnata* leaves significantly reduced blood glucose and improved lipid profiles in diabetic mice. Treated mice also showed better glucose tolerance, weight gain, and pancreatic cell regeneration compared to untreated diabetic controls. These results suggest that *P. incarnata* has notable anti-hyperglycemic and hypolipidemic effects, supporting its traditional use in diabetes management.[27]

Antidepressant Effect

This research explored the antidepressant-like effects of *P. edulis* fo. *edulis* and its various extract fractions in mice using the forced swimming test. The aqueous extract (AE), ethyl acetate (AcOEt), and butanol (BuOH) fractions significantly reduced immobility time, indicating potential antidepressant activity, whereas the residual aqueous fraction showed no such effect. HPLC analysis revealed that AE, AcOEt, and BuOH shared comparable flavonoid-rich compositions. Further pharmacological studies showed that the antidepressant effects of AcOEt and BuOH were dependent on functional serotonin (5-HT) and dopamine systems, as these effects were blocked by inhibitors of 5-HT and catecholamine synthesis, along with a dopamine D2 receptor antagonist. Overall, the results suggest that the flavonoid-rich fractions of *P. edulis* exert antidepressant effects through serotonergic and dopaminergic pathways.[28] The research assessed the antidepressant-like effects of alcoholic extracts derived from the stems and leaves of *P.*

edulis Sims in mice through behavioral experiments. Phytochemical investigation revealed the presence of multiple cycloartane triterpenoids and their saponins, including two newly discovered compounds, cyclopassifloside XII and XIII, as well as six previously known triterpenoids. Both the ethanol extracts and the isolated compounds cyclopassiflosides IX and XI demonstrated promising antidepressant-like properties. In summary, the results indicate that cycloartane triterpenoids are major constituents of *P. edulis* Sims and play a significant role in its antidepressant activity.[29]

This research explored the free radical scavenging and mood-enhancing effects of a flavonoid-rich extract from the leaves of *P. edulis* f. *flavicarpa*. Through optimized extraction methods, the total flavonoid content was quantified, and isoorientin was identified as a principal active compound. Both the extract and isolated isoorientin significantly reduced immobility time in mice during the forced swimming test, indicating antidepressant-like activity. These findings suggest that isoorientin is a key contributor to the extract's antidepressant effectiveness, underscoring a strong link between this flavonoid and its bioactive properties.[30]

Cardio Protective Effect

The research investigated the chemical composition of yellow passion fruit pulp and its ability to reduce blood pressure in spontaneously hypertensive rats. Using HPLC-PDA-MS/MS, the study identified phenolic compounds, ascorbic acid, carotenoids, and flavonoids within the pulp. Administered at doses of 5, 6, or 8 g/kg for five days, the highest dose notably lowered systolic blood pressure, improved antioxidant defenses by increasing glutathione levels, and reduced oxidative stress indicators. Importantly, no harmful effects on kidney function or genetic material were observed. These results suggest that the antihypertensive effects of yellow passion fruit pulp may be linked to its antioxidant properties, though further investigation is needed to clarify the exact mechanisms involved.[31] This research employed radiotelemetry to directly evaluate the effects of *P. edulis* peel extract (PFPE) on blood pressure and associated hemodynamic parameters in spontaneously hypertensive rats. It was found that a dose of 50 mg/kg was the lowest amount needed to significantly decrease blood pressure and other hemodynamic indicators. When tested at comparable doses, edulilic acid (EA) and the anthocyanin fraction (AF) effectively reduced these parameters, while γ-aminobutyric acid (GABA) had no blood pressure-lowering effect and actually increased heart rate. These findings suggest that the antihypertensive effects of PFPE in hypertensive rats are primarily driven by EA

and AF. Further investigation is required to clarify the mechanisms at play and to assess the potential use of PFPE in managing blood pressure in humans.[32]

This research applied a novel low-temperature continuous phase transition extraction technique to obtain passion fruit seed oil, resulting in a 20.37% yield—almost twice that of conventional solvent extraction. The oil was rich in unsaturated fatty acids (84%), vitamin E, and β-carotene, and exhibited excellent quality, reflected by low acid and peroxide values. It demonstrated significant hypolipidemic effects by inhibiting pancreatic lipase and cholesterol esterase. Additionally, cell-based studies revealed that the oil decreased lipid synthesis and reduced levels of triglycerides, total cholesterol, and LDL cholesterol, while boosting HDL cholesterol. These results highlight the potential of passion fruit seed oil as a beneficial functional lipid with health-promoting properties.[33]

Conclusion:

P. edulis shows a wide range of therapeutic benefits, including potent inflammation lowering effects by inhibiting nitric oxide synthase and NF-κB pathways, as well as aiding in wound repair. Its extracts and active compounds demonstrate significant cancer fighting properties by triggering apoptosis and interfering with cancer cell cycles. The plant also helps lower blood sugar through enzyme inhibition and antioxidant mechanisms. Its mood enhancing effects are associated with flavonoids and triterpenoids that influence serotonin and dopamine systems. Moreover, passion fruit-based products offer cardiovascular protection by lowering blood pressure and enhancing lipid profiles. Overall, these results highlight *P. edulis* as a valuable natural remedy for inflammation, cancer, diabetes, mental health, and heart conditions.

References:

1. Lim TK. *Passiflora edulis*. In: Edible medicinal and non-medicinal plants: volume 4, fruits. 2012:147-65.
2. He X, Luan F, Yang Y, Wang Z, Zhao Z, Fang J, *et al. Passiflora edulis*: an insight into current researches on phytochemistry and pharmacology. Front Pharmacol. 2020;11:617.
3. Fonseca LR, Rodrigues RD, Ramos AD, da Cruz JD, Ferreira JL, Silva JR, *et al.* Herbal medicinal products from Passiflora for anxiety: an unexploited potential. Sci World J. 2020;2020:6598434.
4. Dhawan K, Dhawan S, Sharma A. Passiflora: a review update. J Ethnopharmacol. 2004;94(1):1-23.

5. Holanda DK, Wurlitzer NJ, Dionisio AP, Campos AR, Moreira RA, de Sousa PH, *et al.* Garlic passion fruit (*Passiflora tenuifila* Killip): assessment of eventual acute toxicity, anxiolytic, sedative, and anticonvulsant effects using in vivo assays. Food Res Int. 2020;128:108813.
6. Araújo PC, Ramos CC, de Oliveira DB. Investigation into the sleep-promoting effects of the traditional use of passionflower (Passiflora spp.), chamomile (*Matricaria chamomilla* L.) and mulungu (Erythrina spp.) in Brazil. Drugs Drug Candidates. 2025;4(1):11.
7. Narain N, Shanmugam S, de Souza Araújo AA. Antioxidant, antimicrobial, analgesic, anti-inflammatory and antipyretic effects of bioactive compounds from Passiflora species. In: Medicinal plants: from farm to pharmacy. 2019:243-74.
8. Kumar VA, Ramkumar M, Kanthlal SK. The benefit of passion fruit as an anti-ulcerogenic diet: scientific evidence by in vitro and in silico H+/K+ ATPase inhibitory activity assessment. Curr Comput Aided Drug Des. 2020;16(5):555-63.
9. Watson RR, Zibadi S, Rafatpanah H, Jabbari F, Ghasemi R, Ghafari J, *et al.* Oral administration of the purple passion fruit peel extract reduces wheeze and cough and improves shortness of breath in adults with asthma. Nutr Res. 2008;28(3):166-71.
10. Koriem KM, Saleh HN. Evaluation of the anti-diabetic, anti-obesity, anti-inflammatory, analgesic and antipyretic activities of *Herba passiflora*. Proc Natl Acad Sci India B Biol Sci. 2025:1-8.
11. Konta EM, Almeida MR, Amaral CL, Darin JD, de Rosso VV, Mercadante AZ, *et al.* Evaluation of the antihypertensive properties of yellow passion fruit pulp (*Passiflora edulis* Sims f. flavicarpa Deg.) in spontaneously hypertensive rats. Phytother Res. 2014;28(1):28-32.
12. Lima DS, Duarte NB, Barreto DL, Oliveira GP, Takahashi JA, Fabrini SP, *et al.* Passion fruit and apple: from residues to antioxidant, antimicrobial and anti-Alzheimer's potential. Ciência Rural. 2018;48:e20180076.
13. Zahra F, Rahman AM. Medicinal us Bangladesh. Sci Technol. 2018;4:52-70.
14. Kawakami S, Morinaga M, Tsukamoto-Sen S, Mori S, Matsui Y, Kawama T. Constituent characteristics and functional properties of passion fruit seed extract. Life. 2021;12(1):38.

15. Urrego N, Sepúlveda P, Aragón M, Ramos FA, Costa GM, Ospina LF, *et al.* Flavonoids and saponins from *Passiflora edulis* f. edulis leaves (purple passion fruit) and its potential anti-inflammatory activity. J Pharm Pharmacol. 2021;73(11):1530-8.
16. Nogueira AV, Faria LV, Lopes ME, Viganó J, Martínez J, Eick S, *et al.* Anti-inflammatory properties of yellow passion fruit bagasse extract and its potential role in periodontal wound healing in vitro. Biomedicines. 2025;13(5):1134.
17. Benincá JP, Montanher AB, Zucolotto SM, Schenkel EP, Fröde TS. Evaluation of the anti-inflammatory efficacy of *Passiflora edulis*. Food Chem. 2007;104(3):1097-105.
18. Carmona-Hernandez JC, Taborda-Ocampo G, Valdez JC, Bolling BW, González-Correa CH. Polyphenol extracts from three Colombian passifloras (passion fruits) prevent inflammation-induced barrier dysfunction of Caco-2 cells. Molecules. 2019;24(24):4614.
19. Bueno LR, da Silva Soley B, Abboud KY, França IW, da Silva KS, de Oliveira NM, *et al.* Protective effect of dietary polysaccharides from yellow passion fruit peel on DSS-induced colitis in mice. Oxid Med Cell Longev. 2022;2022:6298662.
20. Hussaana A, Daminggo CH, Kusuma MD, Pantiarti RE, Fitri ZA, Maulidinawati Q, *et al.* Cytotoxic and antiproliferative effects of yellow passion fruit (*Passiflora edulis* f. flavicarpa) juice against T47D breast cancer and HeLa cervical cancer cell lines. Trop J Nat Prod Res. 2024;8(5).
21. Yamamoto T, Sato A, Takai Y, Yoshimori A, Umehara M, Ogino Y, *et al.* Effect of piceatannol-rich passion fruit seed extract on human glyoxalase I–mediated cancer cell growth. Biochem Biophys Rep. 2019;20:100684.
22. Kido LA, Hahm ER, Kim SH, Baseggio AM, Cagnon VH, Singh SV, *et al.* Prevention of prostate cancer in transgenic adenocarcinoma of the mouse prostate mice by yellow passion fruit extract and antiproliferative effects of its bioactive compound piceatannol. J Cancer Prev. 2020;25(2):87.
23. Sari LM, Sari DK, Bustami A, Gazali AD, Auerkari EI. Cytotoxicity and apoptosis activities of passion fruit seed extract. J Pharm Pharmacogn. 2024;12(4):659-72.
24. Dos Santos FA, Xavier JA, da Silva FC, Merlin JP, Goulart MO, Rupasinghe HP. Antidiabetic, antiglycation, and antioxidant activities of ethanolic seed extract of *Passiflora edulis* and piceatannol in vitro. Molecules. 2022;27(13):4064.

25. Saravanan S, Parimelazhagan T. In vitro antioxidant, antimicrobial and anti-diabetic properties of polyphenols of *Passiflora ligularis* Juss. fruit pulp. Food Sci Hum Wellness. 2014;3(2):56-64.
26. Medallon MC, Quinto L, Nipolo AM, Pujante EM, Sebolino JM, Toreja JS. Evaluation of anti-hyperglycemic effect of *Passiflora edulis* sims (yellow passion fruit) juice on alloxan monohydrate induced diabetes mellitus in male Sprague Dawley rats. Eur J Mol Clin Med. 2020;7(2):4107-13.
27. Gupta RK, Kumar D, Chaudhary AK, Maithani M, Singh R. Antidiabetic activity of *Passiflora incarnata* Linn. in streptozotocin-induced diabetes in mice. J Ethnopharmacol. 2012;139(3):801-6.
28. Ayres AS, Santos WB, Junqueira-Ayres DD, Costa GM, Ramos FA, Castellanos L, *et al.* Monoaminergic neurotransmission is mediating the antidepressant-like effects of *Passiflora edulis* Sims fo. edulis. Neurosci Lett. 2017;660:79-85.
29. Wang C, Xu FQ, Shang JH, Xiao H, Fan WW, Dong FW, *et al.* Cycloartane triterpenoid saponins from water soluble of *Passiflora edulis* Sims and their antidepressant-like effects. J Ethnopharmacol. 2013;148(3):812-7.
30. Alves JS, Marques JI, Demarque DP, Costa LR, Amaral JG, Lopes NP, *et al.* Involvement of isoorientin in the antidepressant bioactivity of a flavonoid-rich extract from *Passiflora edulis* f. flavicarpa leaves. Rev Bras Farmacogn. 2020;30(2):240-50.
31. Konta EM, Almeida MR, Amaral CL, Darin JD, de Rosso VV, Mercadante AZ, *et al.* Evaluation of the antihypertensive properties of yellow passion fruit pulp (*Passiflora edulis* Sims f. flavicarpa Deg.) in spontaneously hypertensive rats. Phytother Res. 2014;28(1):28-32.
32. Lewis BJ, Herrlinger KA, Craig TA, Mehring-Franklin CE, DeFreitas Z, Hinojosa-Laborde C. Antihypertensive effect of passion fruit peel extract and its major bioactive components following acute supplementation in spontaneously hypertensive rats. J Nutr Biochem. 2013;24(7):1359-66.
33. Chen P, Zhang X, Yang Q, Li L, Cao Y, Zhong R, *et al.* Extraction and characterization of passion fruit seed oil and investigation of its hypolipidemic activity. J Agric Food Res. 2025;101672.

FOLK WISDOM AND MEDICINAL USES OF AJWAIN

Rajesh A. Maheshwari*, Dhanya B. Sen, Ujjval P. Vaghela and Ashim Kumar Sen
Department of Pharmacy,
Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara - 391760, Gujarat
Corresponding author E-mail: rajpharma2007@gmail.com

Abstract:

Trachyspermum ammi (Ajwain) is a widely used medicinal plant recognized for its broad range of pharmacological effects. This review and experimental study explore Ajwain's various therapeutic properties, including protection against gastric ulcers, antifilarial action, anti-inflammatory benefits, antimicrobial activity, effects on reproductive health, and antidiabetic potential. The aqueous extract showed significant protection against ethanol-induced gastric ulcers in rats, with effects comparable to the drug ranitidine. Its methanolic extract demonstrated strong antifilarial activity both in laboratory settings against *Setaria digitata* and in living models against *Brugia malayi*, impairing parasite energy metabolism and displaying anthelmintic effects in both animals and humans. Ajwain also exhibited anti-inflammatory benefits; an herbal vaginal tablet containing Ajwain essential oil effectively treated mixed vaginitis as well as metronidazole, and Ajwain oil reduced symptoms of allergic rhinitis in mice by lowering markers such as IgE, histamine, oxidative stress, and inflammatory cytokines. Studies on antimicrobial properties showed that Ajwain oil moderately inhibited oral pathogens and effectively acted against foodborne bacteria and antibiotic-resistant urinary pathogens, with synergistic effects observed when combined with antibiotics like ampicillin. The extraction temperature influenced the essential oil's yield and composition, with thymol as the main bioactive component, which enhanced antioxidant and antimicrobial properties, supporting its use as a natural preservative. In terms of reproductive health, a clinical trial on Iranian female students found that Ajwain capsules significantly reduced pain from primary dysmenorrhea more effectively than mefenamic acid, without side effects. Additionally, Ajwain oil showed promising antidiabetic activity by inhibiting α-amylase and α-glucosidase enzymes and promoting glucose uptake in muscle cells. Nanosuspensions made from Ajwain extracts exhibited moderate antioxidant, antibacterial, cytotoxic, and antidiabetic effects, highlighting their potential as herbal nanomedicines. Overall, these results emphasize *Trachyspermum ammi* as a safe, natural, and cost-effective option with diverse therapeutic applications, encouraging further exploration in pharmaceutical and nutraceutical fields.

Keywords: *Trachyspermum ammi*, Gastric Ulcers, Antifilarial Action, Anti-Inflammatory Benefits, Antimicrobial Activity

Introduction:

For countless generations, traditional medicine has been a cornerstone of community health, especially in areas where access to modern healthcare remains limited or unreliable. Among the diverse range of herbs and seeds relied upon in folk healing, Ajwain (*Trachyspermum ammi*)—also known as carom seeds or bishop's weed—has secured a significant role in both culinary and medicinal practices, particularly throughout South Asia and the Middle East. Despite their tiny size, ajwain seeds are loaded with powerful natural compounds that contribute to their enduring status in herbal medicine. Ajwain has long been relied upon for managing everyday health concerns. Its medicinal value has been preserved through oral traditions, passed down through families and local healers. Recognized for its sharp aroma and strong, slightly bitter flavor, ajwain is a familiar presence in Indian, Persian, and Middle Eastern households. While modern research is still unfolding its full medicinal scope, traditional knowledge has long praised ajwain for its benefits in treating digestive ailments, respiratory issues, and infections caused by harmful microbes.[1-3]

In Indian homes, ajwain often serves as the first line of defense against common digestive issues such as bloating, indigestion, and gas. A widely used home remedy—mixing the seeds with rock salt and warm water—is still practiced today to soothe stomach discomfort. In rural and underserved communities, where conventional medicines may be out of reach, this simple and cost-effective approach remains highly favored. Ajwain is also commonly chewed in its raw form or steeped into herbal teas, frequently combined with other digestive-friendly ingredients like fennel, cumin, or ginger. Folk medicine also highlights ajwain's usefulness in alleviating respiratory conditions. Steam inhalation with ajwain or the use of ajwain oil is a common household remedy for colds, congestion, and mild asthma. This practice is especially prevalent in Indian and Pakistani cultures, where the high thymol content in ajwain—a compound known for its antimicrobial and decongestant effects—is thought to clear mucus and relieve nasal blockages. In addition, ajwain is often placed in warm cloth compresses to ease gas and chest pain, even in babies and young children.[1-3]

In the Unani system of medicine**,** which blends Greco-Arabic traditions with South Asian healing wisdom, ajwain is esteemed for its resolving (muhallil) and mucus-expelling (munaffis) properties. It is commonly prescribed for conditions such as liver disorders, kidney stones, menstrual issues, and inflammation of the joints.[1,4] Herbalists often prepare ajwain in the form of teas, powders, or decoctions, frequently blending it with complementary herbs such as black seed (kalonji), fenugreek, or ashwagandha to enhance

its healing effects. Ajwain's medicinal use extends beyond the Indian subcontinent and the Middle East. In Ethiopian traditional medicine, where it is referred to as "nanawee," ajwain is included in both cooking and healing preparations. It is commonly added to hot beverages or meals to alleviate labor pain and support postpartum recovery, further demonstrating its wide-ranging applications across cultures.[1-5]

One of the most unique aspects of ajwain's use in folk traditions is how seamlessly it straddles the worlds of food and medicine. Often included in heavy or oily dishes, ajwain not only improves flavor but also reduces the likelihood of digestive discomfort, embodying the principle of "food as medicine" that is central to many ancient healing systems. As global interest in natural remedies and plant-based wellness grows, modern scientific studies are beginning to affirm many of ajwain's traditional uses—particularly its antibacterial, antioxidant, and anti-inflammatory properties. However, long before these findings reached laboratories and academic journals, ajwain was already deeply embedded in the healing knowledge of traditional cultures. Exploring these ancient practices provides not only a deeper appreciation of cultural heritage but also practical insights into incorporating time-tested natural remedies into modern health routines.[1-6] In the chapters to come, we will take a closer look at the various dimensions of ajwain's healing potential—covering its roots in folk medicine, its cultural and scientific relevance, and how it can be used effectively in everyday life.

Gastroprotective Effect

The research revealed that the aqueous extract of *Trachyspermum ammi* (Ajwain) is rich in various bioactive constituents such as alkaloids, volatile oils, flavonoids, tannins, steroids, and triterpenoids. In an experimental model using rats with ethanol-persuaded gastric ulcers, oral administration of the extract at 250 mg/kg and 500 mg/kg doses led to a notable decrease in ulcer severity. The protective effect observed was similar to that of the standard anti-ulcer medication Ranitidine, indicating that Ajwain may serve as an effective natural remedy for ulcer treatment.[7] Ajwain's methanolic extract was evaluated *in vitro* for its antifilarial properties against adult *Setaria digitata*, a filarial parasite found in cattle. The study utilized a bioassay-guided fractionation approach, where the crude extract was initially separated using thin-layer chromatography. Both the crude and the active fractions underwent analysis via high-performance liquid chromatography. Significant antifilarial activity was observed in both fractions, as demonstrated by the MTT assay and a noticeable decrease in worm motility. Structural analysis using H-NMR, infrared spectroscopy, and mass spectrometry identified the active constituent as a phenolic monoterpene. This compound was subsequently tested *in vivo* against *Brugia*

malayi, a human filarial parasite, where it showed notable macrofilaricidal effects and induced sterility in female worms. Further studies confirmed Ajwain's anthelmintic potential in treating *Haemonchus contortus* infections in sheep and *Ascaris lumbricoides* in humans. The extract's efficacy is attributed to its ability to disrupt the parasites' energy metabolism by stimulating ATPase activity, ultimately depleting their energy stores. Additionally, Ajwain exhibits cholinergic activity, enhancing gut peristalsis and facilitating the expulsion of intestinal parasites.[8,9]

Inflammation Lowering Effect

Vaginitis is a widespread condition among women, often caused by bacterial infections or parasites like *Trichomonas vaginalis*. Traditional Persian medicine has long employed natural treatments such as oak gall and ajwain to address these infections. This pilot randomized, double-blind clinical trial was designed to compare the effectiveness of a new herbal vaginal tablet containing dried oak gall extract and ajwain essential oil with that of the conventional metronidazole vaginal tablet. The study involved 24 women diagnosed with mixed vaginitis, who were split into two groups receiving either the herbal or metronidazole tablets for seven days. Clinical symptoms and laboratory indicators—including sexual function and characteristics of vaginal discharge such as volume, pH, odor, leukocyte count, and parasite presence—were evaluated before treatment and at follow-up intervals on day 10, 4 weeks, and 12 weeks after treatment. Both groups exhibited statistically significant improvements across all measured outcomes ($p<0.05$), indicating effective relief of symptoms. Notably, the herbal tablet group showed a significant reduction in vaginal discharge at day 10 and the 4-week follow-up, suggesting sustained effectiveness. These findings demonstrate that the herbal formulation performs comparably to metronidazole in treating mixed vaginitis. Given the growing concerns regarding antibiotic resistance and adverse effects linked to standard medications, this study supports further exploration of herbal therapies as safe, effective, and culturally appropriate options for vaginitis treatment.[10]

This research investigated the impact of Ajwain oil on allergic rhinitis (AR), an inflammatory disorder of the nasal lining caused by immune reactions and oxidative stress. While Ajwain oil is recognized for its antioxidant, anti-inflammatory, and other health benefits, its effectiveness against allergies had not been examined before. Using a mouse model of ovalbumin-induced AR, the study administered Ajwain oil orally for 13 days and compared the outcomes with Montelukast, a commonly used anti-allergic drug. The treatment notably decreased AR symptoms such as sneezing, nasal discharge, and nasal irritation. Additionally, Ajwain oil improved body, spleen, and lung weights, suggesting

overall health improvements. Biochemical tests revealed reductions in allergy-associated markers like IgE, histamine, and oxidative stress indicators including malondialdehyde, Nrf2, and HO-1, alongside an increase in antioxidant enzyme activity (superoxide dismutase). The oil also diminished the presence of inflammatory cells, such as eosinophils and neutrophils. On a molecular level, Ajwain oil inhibited key inflammatory signaling pathways, NF-κBp65 and STAT3, which decreased pro-allergic Th2 and Th17 cytokine production and boosted anti-inflammatory cytokines. These combined effects helped reduce allergic inflammation. In summary, Ajwain oil showed potent anti-allergic, antioxidant, and anti-inflammatory properties in this AR model, indicating its promise as a natural therapy for allergic rhinitis.[11]

Antimicrobial Effect

This in vitro study investigated the antibacterial effects of Ajwain oil on five bacteria linked to oral plaque formation: *Streptococcus mutans*, *Streptococcus oralis*, *Lactobacillus acidophilus*, *Lactobacillus fermentum*, and *Candida albicans*. The antimicrobial activity of Ajwain oil was compared to that of chlorhexidine, a widely used chemical antimicrobial agent. The results demonstrated that Ajwain oil moderately inhibited bacterial growth, with minimum inhibitory concentrations ranging from 125 to 250 µg/ml and minimum bactericidal concentrations between roughly 11.5 and 18.6 mm. Although these values were higher than those for chlorhexidine, reflecting somewhat lower potency, the differences were statistically significant. Overall, the study indicates that Ajwain oil may serve as a natural, safe, and affordable alternative for managing dental plaque and supporting oral health.[12] This study evaluated the antioxidant and antimicrobial activities of an ethanolic extract from Ajwain seeds. Extracted using supercritical fluid extraction, the extract was mainly composed of thymol (71.06%) along with other compounds like o-Cymene and γ-Terpinene. It showed strong antioxidant capacity, with DPPH radical scavenging increasing from 50% to 83% as concentrations rose from 50 to 250 µg/mL. Antimicrobial testing revealed the extract effectively inhibited both Gram-positive and Gram-negative foodborne bacteria, producing inhibition zones between 15 and 19 mm, compared to chloramphenicol's 33 to 37 mm. These findings suggest that Ajwain seeds, rich in phenolic compounds such as thymol, possess significant antioxidant and antimicrobial properties, indicating their promise as natural biopreservatives and medicinal agents to help extend the shelf life of perishable and lipid-rich foods.[13]

This research evaluated the antibacterial efficacy of ethanolic Ajwain extracts against antibiotic-resistant uropathogens, including 7 Metallo β-lactamase (MBL) and 50 Extended Spectrum β-lactamase (ESBL) producing strains. Prepared via Soxhlet ethanol

extraction, the extract showed significant antibacterial activity, with inhibition zones ranging from 14 to 21 mm against these resistant bacteria. The minimum bactericidal concentrations (MBC) were between 0.5 and 10 mg/mL. Importantly, the extract exhibited a synergistic effect when combined with ampicillin, lowering ampicillin's MBC from 10 mg/mL to 200-400 μg/mL. Time-kill studies demonstrated that the extract fully eradicated bacterial viability within 2 hours at MBC concentrations and significantly reduced it after 4 hours. These results indicate that ethanolic Ajwain extracts have potent antibacterial effects against resistant uropathogens and can boost the efficacy of traditional antibiotics like ampicillin.[14] This study examined how different extraction temperatures influence the yield, antioxidant potential, and antimicrobial effectiveness of essential oil from ajwain seeds, aiming to find a natural alternative to synthetic preservatives in the food and pharmaceutical sectors. The oil was extracted at temperatures ranging from 60°C to 90°C, with the highest yield achieved at 70°C. GC-MS analysis identified 25 chemical compounds, with thymol as the main constituent at 31.40%. Antioxidant activity, measured by hydrogen peroxide scavenging, increased with temperature, peaking at 90°C alongside the highest thymol concentration (67.66%). Antimicrobial tests showed that oils extracted at all temperatures effectively inhibited bacteria such as *Staphylococcus aureus* and *Escherichia coli*, with inhibition zones slightly larger at higher extraction temperatures. The minimum inhibitory concentrations were 10 μL/mL for Gram-positive and 25 μL/mL for Gram-negative bacteria. Although oil yield decreased at elevated temperatures, the antioxidant and antimicrobial effects were enhanced. In summary, the findings suggest that *Trachyspermum ammi* essential oil is a powerful natural preservative and a viable eco-friendly substitute for synthetic preservatives in food and pharmaceutical applications, regardless of extraction temperature.[15]

Impact on Reproductive Health Conditions

This clinical trial assessed the pain-relieving effects of ajwain in comparison to the commonly prescribed drug mefenamic acid (MFA) among Iranian female college students suffering from primary dysmenorrhea. Seventy participants were randomly allocated to receive either ajwain capsules (500 mg, three times daily) or MFA over three menstrual cycles. Both treatments significantly reduced peak pain intensity, average pain levels, and the duration of pain as measured by the visual analog scale. Notably, the ajwain group showed a significantly greater reduction in pain severity than the MFA group. Additionally, participants using ajwain reported fewer instances of passing blood clots. No side effects were observed in either group throughout the study. These findings suggest that ajwain may offer a safe, effective, and natural alternative to conventional pharmaceuticals for

relieving symptoms of primary dysmenorrhea, helping to reduce menstrual pain and improve women's quality of life.[16]

Antidiabetic Activity

Ajwain oil, which is high in thymol, exhibited notable anti-hyperglycaemic activity in several in vitro assays. It effectively inhibited the enzymes α-amylase and α-glucosidase, with inhibition rates similar to those of the standard medication acarbose. The IC50 values confirmed its strong enzyme inhibitory capacity. Moreover, ajwain oil increased glucose uptake in muscle cells (L6 myotubes) in a dose-dependent way. These findings highlight ajwain oil's potential as a natural and effective blood sugar-lowering agent, indicating its promise for further exploration as a treatment for diabetes.[17] This study investigated the in vitro biological activities of nanosuspensions derived from *Trachyspermum ammi* extracts, highlighting their potential as affordable natural agents with antioxidant, antibacterial, cytotoxic, and antidiabetic properties. Chemical analyses identified important compounds such as kaempferol and sinapic acid. The nanosuspensions exhibited moderate antioxidant effects, with free radical scavenging up to 14.9%, and significant biofilm inhibition against *Escherichia coli* at approximately 29.5%. Their antidiabetic capabilities were confirmed through antiglycation and α-amylase inhibition tests, showing maximum inhibition rates of around 25.35% and 34.6%, respectively. Hemolytic activity assessment showed 22.73% hemolysis. Collectively, these findings suggest that plant-based nanosuspensions from *Trachyspermum ammi* could serve as effective herbal nanomedicines, enhancing bioavailability and providing a natural alternative to synthetic drugs in pharmaceutical applications.[18]

Conclusion:

Trachyspermum ammi (Ajwain) demonstrates diverse therapeutic activities, including gastroprotective effects by reducing gastric ulcer severity comparable to ranitidine. Its antifilarial properties disrupt parasite energy metabolism and promote parasite expulsion. Ajwain's anti-inflammatory effects effectively alleviate vaginitis and allergic rhinitis by reducing inflammatory markers and oxidative stress. It exhibits antimicrobial activity against oral pathogens, resistant uropathogens, and foodborne bacteria, supporting its use as a natural preservative. Clinically, Ajwain relieves dysmenorrhea pain better than standard drugs without side effects. Additionally, it shows antidiabetic potential through enzyme inhibition and enhanced glucose uptake. Overall, Ajwain offers a safe, natural, and multifaceted alternative for various health conditions.

References:

1. Das S. Bishop's Weed or Ajwain (*Trachyspermum ammi* Linn.): A Traditional Medicinal Plant with Pharmacological Importance, Ethno-Botanical Uses, and Nutritional Benefits for Quality Life Improvement. In: Advances in Medicinal and Aromatic Plants 2025. vol. 2. Apple Academic Press; 2025. p. 355.
2. Goyal S, Chaturvedi V, Dhingra G, Tanwar S, Sharma K, Singh S. *Trachyspermum ammi*: a review on traditional and modern pharmacological aspects. Biol Sci. 2022;2(4):324–37.
3. Saraswat N, Sachan N, Chandra P. A review on ethnobotanical, phytochemical, pharmacological and traditional aspects of indigenous Indian herb *Trachyspermum ammi* (L). Curr Tradit Med. 2020;6(3):172–87.
4. Zali F, Dadmehr M, Bahrami M, Ghobadi A, Kashanian M, Akhtari E. A comparison of the effect of Ajwain (*Trachyspermum ammi* (L.) Sprague) and mefenamic acid for alleviating the symptoms of primary dysmenorrhea: an open-label randomized controlled trial. Tradit Integr Med. 2023;8(2):130–6.
5. Jaiswal D, Roy A. Dietary practices in various regions of India in post-partum women. Int J Res Innov Soc Sci. 2024;8(9):3544–59.
6. Singh H, Meghwal M. Ajwain: a potential source of phytochemical for better health. Pharma Innov. 2019;8:599–603.
7. Pandey P, Jain P, Raja W. A study on antioxidant and gastro-protective effects of *Trachyspermum ammi* Linn extract using different in-vitro techniques. World J Pharm Res. 2023;12(18):566–74.
8. Tamura T, Iwamoto H. Thymol: a classical small-molecule compound that has a dual effect (potentiating and inhibitory) on myosin. Biochem Biophys Res Commun. 2004;318(3):786–91.

   Jabbar A, Khan M, Iqbal Z. In vitro anthelmintic activity of *Trachyspermum ammi* seeds. Phcog Mag. 2006;2(6):126–9.
9. Heidari EF, et al. Genetic structure and diversity of ajowan (*Trachyspermum ammi*) populations based on molecular, morphological markers, and volatile oil content. Ind Crops Prod. 2016;92:186–96.
10. Mehri Ardestani M, Mirahi A, Bahman M, Rahimi R, Toliyat T. Effectiveness of a herbal vaginal tablet containing oak gall and ajwain on vaginitis: a randomized, double-blind pilot study. Res J Pharmacogn. 2022;9(4):49–58.

11. Li J, Raghav P, Hu C. Ajwain oil attenuates allergic response of ovalbumin-induced allergic rhinitis via alteration of inflammatory, oxidative stress, and Th1/Th2 responses. J Food Biochem. 2021;45(12):e13963.
12. Dadpe MV, Dhore SV, Dahake PT, Kale YJ, Kendre SB, Siddiqui AG. Evaluation of antimicrobial efficacy of *Trachyspermum ammi* (Ajwain) oil and chlorhexidine against oral bacteria: an in vitro study. J Indian Soc Pedod Prev Dent. 2018;36(4):357–63.
13. Bhatt V, Kumar MM, Selvam SP. Antimicrobial effect of ajwain seed ethanolic extract against food borne pathogenic bacteria. Int Food Res J. 2018;25(3):908–12.
14. Tariq MO, Gore M, Aruna K. Antibacterial and synergistic activity of ethanolic Ajwain (*Trachyspermum ammi*) extract on ESBL and MBL producing uropathogens. Int J Pharm Pharm Sci. 2014;6(6):278–84.
15. Zare MR, Khorram M, Barzegar S, Asadian F, Zareshahrabadi Z, Saharkhiz MJ, et al. Antimicrobial core–shell electrospun nanofibers containing Ajwain essential oil for accelerating infected wound healing. Int J Pharm. 2021;603:120698.
16. Zali F, Dadmehr M, Bahrami M, Ghobadi A, Kashanian M, Akhtari E. A comparison of the effect of Ajwain (*Trachyspermum ammi* (L.) Sprague) and mefenamic acid for alleviating the symptoms of primary dysmenorrhea: an open-label randomized controlled trial. Tradit Integr Med. 2023;8(2):130–6.
17. Aneesa NN, Anitha R, Varghese S. Antidiabetic activity of ajwain oil in different in vitro models. J Pharm Bioall Sci. 2019;11(2):142–7.
18. Jabeen R, Ali T, Naeem M, Hussain F, Danish S, Alahmadi TA, et al. An insight into biochemical characterization and explorations of antioxidant, antibacterial, cytotoxic, and antidiabetic activities by *Trachyspermum ammi* Nanosuspensions. Front Biosci. 2023;28(12):340.

NATURE'S SHIELD:
EXPLORING ANTIMUTAGENIC EFFECTS OF HERBAL MEDICINES

Ashim Kumar Sen*, Sunil Kardani, Dipti Gohil and Sunil Baile

Department of Pharmacy,

Sumandeep Vidyapeeth Deemed to be University, Vadodara - 391760, Gujarat, India.

*Corresponding author E-mail: ashim01@gmail.com

Abstract:

Genetic mutations, defined as irreversible alterations in the DNA sequence, are pivotal contributors to the development of various diseases, including cancer, neurodegenerative disorders, and inherited conditions. While environmental mutagens and endogenous reactive species are significant drivers of genomic instability, the limitations and side effects of synthetic chemopreventive agents have catalyzed interest in plant-based alternatives. Herbal medicines, widely used in traditional systems like Ayurveda, Traditional Chinese Medicine, and Unani, have garnered scientific attention due to their rich phytochemical profiles and multifaceted antimutagenic properties. These include desmutagenic actions that prevent DNA interaction with mutagens and true antimutagenic effects that interfere with mutation fixation or promote DNA repair. This chapter explores the antimutagenic potential of selected medicinal plants, such as *Pteris multifida*, *Smilax china*, *Prunella vulgaris*, *Viola odorata*, *Coptis teeta*, *Coriandrum sativum*, *Murraya koenigii*, *Crataegus sanguinea*, *Maytenus ilicifolia*, *Peltastes peltatus*, and *Acacia victoriae*. These plants contain bioactive compounds like flavonoids, alkaloids, saponins, terpenoids, and phenolic acids, which exhibit antioxidant, anti-inflammatory, enzyme-modulatory, and apoptosis-inducing effects. Their protective mechanisms often involve scavenging reactive oxygen species (ROS), enhancing phase II detoxification enzymes, and modulating pro-inflammatory and DNA repair pathways. Using assays such as the Ames test, comet assay, and micronucleus assay, these herbs have demonstrated varying degrees of antimutagenic efficacy. While the evidence for some plants remains preliminary, others like *Coptis teeta* and *Murraya koenigii* show strong promise. Continued multidisciplinary research is essential to standardize, validate, and integrate these natural protectants into preventive healthcare strategies.

Keywords: Antimutagenic Activity**,** Herbal Medicine**,** Oxidative DNA Damage**,** Phytochemicals

Introduction:

Genetic mutations, defined as permanent alterations in the DNA sequence, play a central role in the onset of various pathological conditions, particularly cancer, neurodegenerative diseases, and hereditary disorders. Mutagenic agents-whether chemical, physical, or biological-interact with cellular DNA, often leading to mutations that compromise genomic stability. While synthetic chemopreventive agents have been employed to mitigate these risks, concerns regarding their toxicity and side effects have stimulated a growing interest in natural alternatives. In this context, herbal medicines have emerged as promising antimutagenic agents due to their bioactive phytochemicals, multifaceted mechanisms, and lower toxicity profiles. Antimutagenic compounds function by inhibiting the mutagenic process at different stages-before the interaction with DNA (desmutagens) or by interfering with the repair or fixation of mutations (true antimutagens). Numerous medicinal plants, long used in traditional systems such as Ayurveda, Traditional Chinese Medicine (TCM), and Unani, are now being scientifically validated for their antimutagenic properties. Their mechanisms of action include scavenging reactive oxygen species (ROS), enhancing DNA repair pathways, modulating phase I and II detoxification enzymes, and interacting directly with mutagenic metabolites to neutralize their effects. Phytochemicals such as flavonoids, alkaloids, tannins, saponins, and terpenoids have demonstrated notable antimutagenic activity in various in vitro and in vivo models. For instance, curcumin from *Curcuma longa*, epigallocatechin gallate (EGCG) from green tea, and quercetin found in many fruits and vegetables have all shown the capacity to inhibit mutagenicity induced by known carcinogens such as benzo[a]pyrene and nitrosamines. Such evidence underscores the potential of plant-derived substances in the development of preventive strategies against mutation-associated diseases. Modern molecular biology techniques, including Ames test, micronucleus assay, and comet assay, have significantly facilitated the evaluation of antimutagenic potential of plant extracts. These tools not only provide insights into the efficacy of herbal compounds but also help elucidate their underlying mechanisms at the cellular and molecular levels. Additionally, advancements in chromatographic and spectrometric techniques have enabled the isolation and structural characterization of key bioactive constituents, paving the way for the development of phytopharmaceuticals with defined safety and efficacy profiles. Despite growing scientific validation, the integration of antimutagenic herbal agents into mainstream medical practice faces challenges. These include variability in phytochemical content due to environmental and genetic factors, lack of standardized dosages, and limited clinical trials. Therefore, a multidisciplinary approach combining ethnobotanical

knowledge, pharmacological research, and molecular studies is essential to fully harness the therapeutic potential of these natural agents.[1-5]

This chapter aims to explore the antimutagenic effects of selected herbal medicines, with an emphasis on their phytochemical profiles, scientific evidence from experimental models, and proposed mechanisms of action. By bridging traditional wisdom with contemporary science, this chapter underscores the role of nature's shield-herbal medicines-in safeguarding genomic integrity and preventing mutation-induced diseases.

***1. Pteris multifida* (Spider Brake Fern)**

- **Phytochemistry:** Ferns, including *Pteris* species, are known to contain flavonoids, terpenoids, phenolic acids, and sometimes alkaloids or cyanogenic glycosides. Specific phytochemical analysis of *P. multifida* has identified various flavonoids (like kaempferol, quercetin glycosides), pterosin derivatives (sesquiterpenes), and phenolic compounds. This species is particularly noted for its ability to hyperaccumulate arsenic, but its other bioactivities are less explored than common medicinal herbs.[6-8]
- **Antimutagenic Evidence:** Direct studies specifically investigating the antimutagenic or antigenotoxic effects of *Pteris multifida* extracts using standard assays (Ames, micronucleus, comet) are scarce in mainstream literature. However, the presence of significant amounts of flavonoids and phenolic compounds implies considerable antioxidant potential. Antioxidant activity is a major mechanism for preventing oxidative DNA damage, a key source of mutations. Extracts have shown free radical scavenging activity *in vitro*. Therefore, while direct experimental proof of antimutagenicity might be limited, a potential protective effect against ROS-induced genotoxicity can be inferred based on its phytochemical profile. More research is needed to directly assess its antimutagenic capabilities.[6,7]
- **Mechanisms:** Potential antimutagenic mechanisms would likely rely on the antioxidant activity of its flavonoid and phenolic constituents, scavenging free radicals and protecting cellular components from oxidative damage.[6,7]

***2. Smilax china* (China Root)**

- **Phytochemistry:** Rhizomes of *Smilax china* is rich in steroidal saponins (e.g., dioscin, gracillin), flavonoids (e.g., astilbin, engeletin), phenolic acids, stilbenoids (resveratrol), and polysaccharides.[8,9]
- **Antimutagenic Evidence:** Extracts of *Smilax china* have demonstrated significant antioxidant and anti-inflammatory activities *in vitro* and *in viv*[1]. Studies evaluating its protective effects against genotoxicity have shown positive results. For instance, an ethanol extract of *S. china* rhizome was found to protect against CCl_4 (carbon tetrachloride)-induced oxidative stress and DNA damage in rat liver. Another study

using the Ames test indicated that extracts could inhibit the mutagenicity induced by known mutagens, suggesting desmutagenic potential. Flavonoids like astilbin and saponins are likely major contributors to these effects through their ability to scavenge free radicals and modulate inflammatory pathways.[9-12]

- **Mechanisms:** The antimutagenic activity is primarily linked to potent antioxidant effects (ROS scavenging by flavonoids and phenolics) and anti-inflammatory action (reducing ROS production associated with inflammation). Modulation of metabolic enzymes or direct interaction with mutagens by saponins might also contribute.[9,11,12]

***3. Prunella vulgaris* (Self-heal)**

- **Phytochemistry:** This herb contains a wealth of bioactive compounds, including phenolic acids (especially rosmarinic acid, caffeic acid), flavonoids (rutin, quercetin, luteolin), triterpenes (ursolic acid, oleanolic acid), polysaccharides (prunellin), and tannins.[13,14]
- **Antimutagenic Evidence:** *Prunella vulgaris* extracts exhibit strong antioxidant, anti-inflammatory, antiviral, and anticancer activities. Its high content of rosmarinic acid contributes significantly to its antioxidant capacity. Studies have investigated its potential to protect against DNA damage. An aqueous extract of *P. vulgaris* demonstrated protective effects against H_2O_2-induced DNA damage in human lymphocytes using the comet assay.[15] Research has also shown that compounds like ursolic acid possess chemopreventive properties and can inhibit tumor promotion, potentially involving protection against DNA damage or induction of apoptosis in damaged cells. Polysaccharides from *P. vulgaris* have also shown immunomodulatory and antioxidant effects.
- **Mechanisms:** Key mechanisms include potent antioxidant activity (ROS scavenging by phenolic acids and flavonoids), anti-inflammatory effects (inhibiting pro-inflammatory enzymes and cytokines), and potential modulation of cell signaling pathways involved in cell survival and apoptosis by triterpenes.

***4. Viola odorata* (Sweet Violet / Banafshah)**

- **Phytochemistry:** Sweet violet contains flavonoids (rutin, violanthin), saponins, alkaloids (odoratine), phenolic glycosides (salicylic acid methyl ester - giving its scent), mucilage, and Vitamin C.[16]
- **Antimutagenic Evidence:** Traditionally used for respiratory ailments and as an anti-inflammatory agent, *Viola odorata*'s potential antimutagenic effects are primarily inferred from its antioxidant and anti-inflammatory properties. Studies have confirmed the antioxidant activity of its extracts *in vitro*, demonstrating scavenging of DPPH radicals and reducing power[18]. Flavonoids like rutin are known antioxidants and

can protect against oxidative DNA damage. Saponins may also contribute to protective effects. While direct studies using standardized mutagenicity assays appear limited, its established antioxidant capacity suggests a potential role in mitigating oxidative stress-induced genotoxicity. Further specific research is needed.

- **Mechanisms:** Primarily based on the antioxidant activity of flavonoids and Vitamin C, and potential anti-inflammatory effects mediated by various constituents.[17,18]

***5. Coptis teeta* (Mameeran / Mishmi Teeta / Goldthread)**

- **Phytochemistry:** The rhizomes of *Coptis* species, including *C. teeta*, are exceptionally rich in protoberberine alkaloids, with berberine being the most prominent. Other related alkaloids like coptisine, palmatine, and jatrorrhizine are also present.[19]
- **Antimutagenic Evidence:** Berberine, the principal alkaloid, is extensively studied for its diverse pharmacological activities, including antimicrobial, anti-inflammatory, antidiabetic, and anticancer effects. It's antimutagenic and antigenotoxic properties are also documented. *In vitro*, berberine has shown inhibitory effects against the mutagenicity of various chemicals (e.g., B[a]P, Trp-P-1, AFB1) in the Ames test, often attributed to inhibition of CYP enzymes involved in their activation.[20] It can protect against DNA damage induced by oxidative stress (H_2O_2, radiation) and certain chemicals in cell cultures, assessed by comet assay and markers of oxidative DNA damage. Some studies suggest berberine can intercalate into DNA, which might influence DNA replication and repair, although this interaction could also potentially lead to toxicity at high concentrations. *In vivo*, berberine has demonstrated protective effects against chemically induced carcinogenesis in animal models, partly via its anti-inflammatory and antioxidant actions.
- **Mechanisms:** Antimutagenic mechanisms of berberine (and thus *Coptis teeta*) include: potent antioxidant activity, inhibition of Phase I enzymes (CYPs) activating pro-mutagens, anti-inflammatory effects (inhibiting NF-κB, COX-2), potential modulation of DNA repair pathways, and DNA intercalation (which may have complex effects).[21,22]

***6. Coriandrum sativum* (Coriander)**

- **Phytochemistry:** Coriander seeds and leaves (cilantro) contain different profiles. Seeds are rich in essential oil (linalool being major), fatty acids (petroselinic acid), and some phenolics. Leaves are rich in flavonoids (quercetin, kaempferol), phenolic acids, carotenoids (beta-carotene, lutein), and Vitamin K.[23]
- **Antimutagenic Evidence:** Both seeds and leaves exhibit significant antioxidant activity due to their phenolic and carotenoid content. Studies have explored their protective effects against genotoxicity. Aqueous extracts of coriander leaves showed

protective effects against H_2O_2-induced DNA damage in human lymphocytes (comet assay). Linalool, the main component of seed essential oil, possesses antioxidant and anti-inflammatory properties. Studies using coriander seed extracts have shown protection against oxidative stress and lipid peroxidation *in vivo*. While direct Ames test or micronucleus test data might be less extensive than for some herbs, the strong antioxidant profile, particularly of the leaves, strongly suggests antimutagenic potential against oxidative damage.[24]

- **Mechanisms:** Primarily antioxidant activity via scavenging of ROS/RNS by phenolic compounds (flavonoids, phenolic acids) and carotenoids. Linalool may contribute through antioxidant and anti-inflammatory actions.[25]

***7. Murraya koenigii* (Curry Leaves)**

- **Phytochemistry:** Curry leaves are notably rich in carbazole alkaloids (e.g., mahanimbine, girinimbine, koenigine, mahanine). They also contain flavonoids (quercetin, myricetin), phenolic acids, vitamins (A, C, E), and minerals.[26]
- **Antimutagenic Evidence:** Curry leaves are recognized for their potent antioxidant properties, largely attributed to their carbazole alkaloids and phenolic constituents. Several studies have directly assessed their antimutagenic potential. Aqueous and ethanol extracts of *M. koenigii* significantly inhibited the mutagenicity of benzo[a]pyrene and aflatoxin B1 in the Ames test (both with and without S9 activation), indicating both desmutagenic and bio-antimutagenic effects. Carbazole alkaloids like mahanimbine have shown potent antioxidant activity and protective effects against oxidative stress *in vitro*. *In vivo*, curry leaf supplementation reduced oxidative damage markers and enhanced antioxidant enzyme levels in diabetic rats, suggesting systemic protective effects[27].
- **Mechanisms:** Strong antioxidant activity (ROS scavenging by carbazole alkaloids and phenolics), potential modulation of carcinogen metabolizing enzymes (Phase I inhibition/Phase II induction suggested by Ames test results), and anti-inflammatory effects contribute to its antimutagenicity.[28,29]

***8. Crataegus sanguinea* (Siberian Hawthorn)**

- **Phytochemistry:** Like other hawthorns (*Crataegus* genus), *C. sanguinea* fruits, leaves, and flowers are rich in flavonoids (hyperoside, rutin, quercetin, vitexin, vitexin-2"-O-rhamnoside) and oligomeric proanthocyanidins (OPCs). Other components include triterpenes (ursolic acid, oleanolic acid) and phenolic acids (chlorogenic acid).[30]
- **Antimutagenic Evidence:** Hawthorn species are best known for their cardioprotective effects, primarily linked to their potent antioxidant and vasodilatory properties. While specific studies on the antimutagenicity of *C. sanguinea* might be

limited, extensive research on *Crataegus* genus extracts (often *C. monogyna* or *C. laevigata*) confirms their strong antioxidant capacity, effectively scavenging free radicals and inhibiting lipid peroxidation.[31] This antioxidant power directly implies protection against oxidative DNA damage. Flavonoids like quercetin and OPCs are well-documented DNA protectors. Studies on other *Crataegus* species have shown protective effects against ischemia-reperfusion injury, partly by mitigating oxidative stress, which is relevant to preventing DNA damage in such conditions. Therefore, *C. sanguinea*, sharing a similar phytochemical profile, is highly likely to possess antimutagenic potential primarily via antioxidant mechanisms.

- **Mechanisms:** Potent antioxidant activity due to high concentrations of flavonoids and OPCs, scavenging ROS/RNS and protecting cellular structures, including DNA, from oxidative damage.[32]

***9. Maytenus ilicifolia* (Espinheira Santa)**

- **Phytochemistry:** Primarily known for its use in treating gastric ulcers, the leaves of *M. ilicifolia* contain pentacyclic triterpenes (friedelin, friedelanol), maitenin, phenolic compounds (tannins, flavonoids like quercetin and kaempferol glycosides), and proanthocyanidins.[33]
- **Antimutagenic Evidence:** Research has focused on its antiulcer, anti-inflammatory, and antioxidant activities. Studies have demonstrated the antioxidant potential of *M. ilicifolia* extracts *in vitro*, showing scavenging of free radicals. Direct investigations into its genotoxicity and antigenotoxicity have yielded somewhat mixed but generally protective results. Some early studies suggested potential clastogenicity at very high doses *in vivo*, but more recent and comprehensive studies indicate protective effects. For example, an aqueous extract of *M. ilicifolia* showed antigenotoxic effects against damage induced by cyclophosphamide in mice (micronucleus test) and protected against DNA damage induced by doxorubicin *in vitro* (comet assay). Another study found it lacked mutagenicity in the Ames test and wing spot test in *Drosophila* and showed protective effects against H_2O_2-induced damage.[34-36]
- **Mechanisms**: Antioxidant effects of flavonoids and tannins likely play a significant role. Anti-inflammatory actions and potential modulation of DNA repair or detoxification pathways may also contribute to the observed antigenotoxic effects. The triterpenes might also be involved.

10. Peltastes peltatus

- **Phytochemistry:** Information on *Peltastes peltatus* (sometimes considered a synonym or closely related to *Mandevilla* species) is relatively sparse compared to commonly used medicinal plants. Plants in the Apocynaceae family (to which

Mandevilla/Peltastes belong) often contain alkaloids (indole alkaloids), iridoids, cardenolides, or terpenoids. Specific, detailed phytochemical analyses focusing on compounds relevant to antimutagenicity in *P. peltatus* are limited in readily available literature. Some related *Mandevilla* species are known to contain pregnane glycosides with cytotoxic activities.[37]

- **Antimutagenic Evidence:** Direct scientific studies investigating the antimutagenic or antigenotoxic effects of *Peltastes peltatus* extracts using standard assays are currently lacking or not widely published. Without detailed phytochemical analysis and specific bioactivity testing for DNA protection, assessing its antimutagenic potential is speculative. If it contains phenolic compounds or certain types of terpenoids with antioxidant properties, it might offer some protection against oxidative damage. However, the potential presence of cytotoxic compounds (like cardenolides or certain alkaloids common in Apocynaceae) would require careful evaluation for safety and net effect. Further research is essential to characterize its phytochemistry and bioactivities, including any potential antimutagenic effects.
- **Mechanisms:** Hypothetical, based on general knowledge of related plant families; could involve antioxidant activity if phenolic compounds are present. Requires investigation.

***11. Acacia victoriae* (Elegant Wattle / Gundabluie) and Avicins**

- **Phytochemistry:** This Australian Acacia species is notable for producing a unique class of triterpenoid saponins called avicins (e.g., avicin D, G). These are complex molecules derived from acyl-CoA:triterpene acyltransferases.[38,39]
- **Antimutagenic Evidence:** Avicins, isolated from *A. victoriae*, have attracted significant research interest as potent chemopreventive and potentially therapeutic agents. They exhibit remarkable biological activities relevant to antimutagenesis and cancer prevention.
  - **Antioxidant/Electrophilic Response:** Avicins are potent inducers of the antioxidant/electrophile response element (ARE/EpRE) pathway, leading to the upregulation of numerous cytoprotective genes, including Phase II detoxification enzymes (GST, NQO1) and antioxidant proteins (heme oxygenase-1) via Nrf2 activation. This enhances the cell's ability to neutralize mutagens and ROS.[40]
  - **Anti-inflammatory:** Avicins are powerful inhibitors of the pro-inflammatory transcription factor NF-κB, suppressing the expression of downstream inflammatory mediators (TNF-α, COX-2, iNOS). Chronic inflammation generates ROS/RNS, contributing to DNA damage, so this anti-inflammatory action is inherently antimutagenic.

- **Apoptosis Induction:** Avicins can selectively induce apoptosis (programmed cell death) in precancerous or cancerous cells, potentially by inhibiting mitochondrial respiration and triggering stress pathways, thus eliminating cells with accumulated DNA damage.[41]
- *In vitro* and *in vivo* studies have confirmed these activities. Avicins protect cells from oxidative stress-induced damage and have shown efficacy in preclinical models of skin and lung cancer prevention. While direct testing in standard mutagenicity assays like the Ames test might be less common (as their primary action is bio-antimutagenic/chemopreventive rather than simple desmutagenic), their known mechanisms strongly support a profound protective effect against processes leading to mutation and carcinogenesis.

- **Mechanisms:** Multifaceted and potent: strong induction of Phase II/antioxidant enzymes via Nrf2/ARE pathway, potent inhibition of NF-κB-mediated inflammation, induction of apoptosis in damaged/transformed cells, and direct antioxidant effects.[40,41]

Conclusion:

The reviewed herbal plants highlight nature's potential in protecting against DNA damage and mutations. Phytochemicals from herbs like *Pteris multifida* and other above herbal drug act through diverse mechanisms, including antioxidant activity, modulation of detoxifying enzymes, DNA repair enhancement, and inflammation reduction. Other plants contribute via terpenes, alkaloids, saponins, and phenolic acids. While some herbs have limited direct evidence, their bioactive compounds show promise. However, challenges remain, including extract standardization, bioavailability, dose optimization, and the need for human studies. Overall, these herbs hold potential for use in functional foods, nutraceuticals, and chemopreventive therapies. In summary, the scientific exploration of traditional herbal remedies continues to unveil potent natural agents capable of protecting our genetic material. These plants and their bioactive constituents offer promising avenues for developing functional foods, nutraceuticals, and potentially chemopreventive drugs to combat the mutagenic challenges inherent in our environment and biology.

References

1. Aggarwal BB, Kumar A, Bharti AC. Anticancer potential of curcumin: preclinical and clinical studies. Anticancer Res. 2003;23(1A):363–98.
2. Yang CS, Wang H, Li GX, Yang Z, Guan F, Jin H. Cancer prevention by tea: evidence from laboratory studies. Pharmacol Res. 2011;64(2):113–22.
3. Boots AW, Haenen GRMM, Bast A. Health effects of quercetin: from antioxidant to nutraceutical. Eur J Pharmacol. 2008;585(2–3):325–37.

4. Kada T, Morita K, Inoue T. Antimutagenic action of vitamins and their analogs. Mutat Res. 1978;53(3):351–3.
5. Ames BN, McCann J, Yamasaki E. Methods for detecting carcinogens and mutagens with the Salmonella/mammalian-microsome mutagenicity test. Mutat Res. 1975;31(6):347–64.
6. Chen CC, Namba T. Pharmacognostical studies on the crude drugs of Laminariae plants origin (II): On "GUAN ZHONG" derived from ferns of Pteris genus. Shoyakugaku Zasshi. 1989;43(4):325–32.
7. Fang J, Chen Q, Wang M, Zhong J, Li F, Li H, et al. Antioxidant activities of fractions and constituents from *Pteris multifida* Poir. Nat Prod Res. 2011;25(17):1625–34.
8. Ma LQ, Komar KM, Tu C, Zhang W, Cai Y, Kennelley ED. A fern that hyperaccumulates arsenic. Nature. 2001;409(6820):579.
9. Shao B, Guo H, Cui Y, Ye M, Han J, Guo D. Steroidal saponins from *Smilax china* and their cytotoxic activities. Phytochemistry. 2007;68(5):623–30.
10. Xu LJ, Choi JY, Kim YK, Ryu JH. Astilbin inhibits the adjuvant-induced arthritis in rats via suppression of the activation of T cells and inflammatory mediators. Biol Pharm Bull. 2008;31(8):1502–7.
11. Shu XS, Gao ZH, Yang XL. Anti-inflammatory and anti-nociceptive activities of Smilax china L. J Ethnopharmacol. 2006;103(3):327–32.
12. Zhang QF, Zhang Z, Yue XQ, Ling CQ. An overview on the clinical application, ethnopharmacology, phytochemistry, pharmacology of *Smilax glabra* Roxb. and Smilax china L. Chin Med. 2021;16(1):1–27.
13. Fang X, Chang RC, Yuen WH, Zee SY. Immune modulatory effects of *Prunella vulgaris* L. Int J Mol Med. 2005;15(3):491–6.
14. Psotová J, Kolář M, Šoušková J, Švagera Z, Vičar J, Ulrichová J. Biological activities of *Prunella vulgaris* extract. Phytother Res. 2003;17(9):1082–7.
15. Lamaison JL, Petitjean-Freytet C, Carnat A. Medicinal Lamiaceae with antioxidant properties, a potential source of rosmarinic acid. Pharm Acta Helv. 1991;66(7):185–8.
16. Vishal A, Parveen K, Pooja S, Kannappan N, Kumar S. Viola odorata: A review. Int J Adv Res. 2014;2(12):498–503.
17. Ebrahimzadeh MA, Nabavi SM, Nabavi SF, Pourmorad F, Bekhradnia AR. Antioxidant and free radical scavenging activities of genus Viola. Pharmacologia. 2013;4(4):281–5.
18. Koochek M, Mozafari SA, Abdolhoseinzadeh M. Evaluation of chemical composition, antioxidant and antibacterial activities of the essential oil and methanolic extract of *Viola odorata* flowers. J Essent Oil Bear Plants. 2018;21(3):773–85.

19. Wang J, Wang L, Lou GH, Zeng HW, Hu J, Huang QW, Peng W. Coptidis Rhizoma: a comprehensive review of its traditional uses, botany, phytochemistry, pharmacology and toxicology. Pharm Biol. 2019;57(1):193–225.
20. Singh A, Singh AK. Berberine: A plant alkaloid with therapeutic potential for cardiovascular diseases. Int J Mol Sci. 2010;11(4):1892–909.
21. Lee IS, Lee KG, Kim YS, Namkung W, Shin DS. Inhibitory effect of berberine on cytochrome P450 1A1 and 1B1 activities in human liver microsomes. Food Chem. 2013;138(2–3):1126–31.
22. Patil JB, Kim J, Jayaprakasha GK. Berberine induces apoptosis in ovarian cancer cells (SKOV-3) through generation of reactive oxygen species and mitogen-activated protein kinase activation. PLoS One. 2010;5(12):e15560.
23. Laribi B, Kouki K, M'Hamdi M, Bettaieb T. Coriander (*Coriandrum sativum* L.) and its bioactive constituents. Fitoterapia. 2015;103:9–26.
24. Wangensteen H, Samuelsen AB, Malterud KE. Antioxidant activity in extracts from coriander. Food Chem. 2004;88(2):293–7.
25. Cortés-Eslava J, Gómez-Arroyo S, Villalobos-Pietrini R, Espinosa-Aguirre JJ. Antimutagenicity of coriander (*Coriandrum sativum*) juice on the mutagenesis produced by plant metabolites of aromatic amines. Toxicol Lett. 2004;153(2):283–92.
26. Tachibana Y, Kikuzaki H, Lajis NH, Nakatani N. Antioxidative activity of carbazoles from *Murraya koenigii* leaves. J Agric Food Chem. 2001;49(11):5589–94.
27. Khan BA, Abraham A, Leelamma S. Murraya koenigii and Brassica juncea - alterations on lipid profile in 1-2 dimethyl hydrazine induced colon carcinogenesis. Investig New Drugs. 1996;14(4):365–9.
28. Ningappa MB, Dinesha R, Srinivas L. Antioxidant and free radical scavenging activities of polyphenol-enriched curry leaf (*Murraya koenigii* L.) extract. Food Chem. 2008;106(2):720–8.
29. Baliga MS, Jagetia GC, Rao SK, Babu K. Evaluation of the antioxidant and radioprotective effect of *Murraya koenigii* (L) spreng. in cultured human peripheral blood lymphocytes exposed to gamma-radiation. J Zhejiang Univ Sci B. 2011;12(3):177–87.
30. Tadić VM, Dobrić S, Marković GM, Đorđević SM, Arsić IA, Menković NR, et al. Anti-inflammatory, gastroprotective, free-radical-scavenging, and antimicrobial activities of hawthorn berries ethanol extract. J Agric Food Chem. 2008;56(17):7700–9.
31. Chang WT, Dao J, Shao ZH. Hawthorn: potential roles in cardiovascular disease. Am J Chin Med. 2005;33(1):1–10.

32. Gülçin İ, Topal F, Ozturk Sarikaya SB, Bursal E, Bilsel G, Gören AC. Polyphenol contents and antioxidant properties of Medlar (*Mespilus germanica* L.). Rec Nat Prod. 2011;5(3):158–75.
33. Niero R, Andrade SF, Cechinel Filho V. A review of the ethnopharmacology, phytochemistry and pharmacology of the Maytenus species. Curr Pharm Des. 2011;17(7):636–56.
34. Leite JP, Fassin M, Cechinel Filho V, Niero R, de Andrade SF, Pizzolatti MG, et al. Antioxidant potential of *Maietenus ilicifolia*. Fitoterapia. 2002;73(6):533–5.
35. Carvalho JCT, Ferreira LP, Santos JS, Correa MJC, Campos LM, Marques LC, et al. Preliminary studies of analgesic and anti-inflammatory properties of *Maytenus ilicifolia* Mart. ex Reissek aqueous extract. J Ethnopharmacol. 2004;90(1):85–9.
36. Ferreira-Machado SC, Rodrigues MP, Nunes APM, Dantas FJS, De Mattos JCP, Silva CR, et al. Genotoxic and antigenotoxic evaluation of *Maytenus* ilicifolia Mart ex Reissek, Celastraceae (*espinheira* santa) extracts in prokaryotic and eukaryotic assays. Genet Mol Biol. 2004;27(4):575–80.
37. Aquino R, De Simone F, Pizza C, Conti C, Stein ML. Plant metabolites. Structure and in vitro antiviral activity of quinovic acid glycosides from *Uncaria tomentosa* and *Guettarda platypoda*. J Nat Prod. 1991;54(2):453–9.
38. Haralampidis K, Bryan G, Qi X, Papadopoulou K, Bakht S, Melton R, Osbourn A. A new class of plant glycosyltransferases required for saponin biosynthesis. Plant Cell. 2001;13(7):1513–24.
39. Jayatilake GS, Jayasuriya H, Lee ES, Koonchanok NM, Geahlen RL, Ashendel CL, et al. Kinase inhibitors from *Polygonum cuspidatum*. J Nat Prod. 1993;56(10):1805–10.
40. Xu Z, Chen J, Li X, Gutterman JU. Avicins, a family of triterpenoid saponins derived from *Acacia victoriae* Bentham, induce apoptosis in human breast cancer cells. Breast Cancer Res Treat. 2002;76(1):31–41.
41. Haridas V, Hanausek M, Nishimura G, Soehnge H, Gaikwad A, Narog M, et al. *Triterpenoid electrophiles* (avicins) suppress inflammatory responses by activating antioxidant pathways. J Clin Invest. 2004;113(1):65–73.

PSYCHOTROPICS AND NUTRIENT METABOLISM: A CLINICAL PERSPECTIVE WITH EMPHASIS ON NURSING RESPONSIBILITIES

Suresh Velumani

Sumandeep Nursing College,

Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara – 391760

Corresponding author E-mail: vss_ssh@yahoo.in

Abstract:

Based on a well-documented assessment of benefits and risks, antipsychotic and psychoactive medications continue to be prescribed despite the emergence of commonly known side effects. This review examines the consequences of certain psychoactive drugs, concentrating particularly on drug–food interactions as well as other clinically important issues. The chapter discusses Clozapine, drawing attention to the crucial interaction of MAOIs and tyramine. Furthermore, this review focuses on the effect of glucose concerning thiamine metabolism in Alcohol Dependence Syndrome. Given the complexity of these pharmacological effects, nurses play a vital role in understanding the mechanisms of action, potential side effects, and interactions of these medications. Such knowledge is essential for preventing complications and promoting optimal patient outcomes in mental health care.

Keywords: Role of Nurse, psychotropic medications, Tyramine, Thiamine and Clozapine.

Introduction:

Monoamine oxidase inhibitors

Monoamine oxidase inhibitors (MAOIs), initially developed for depression, have found utility in managing affective and neurological disorders, as well as stroke and aging-related neurocognitive changes. These drugs, ranging from irreversible to reversible and selective to non-selective, act on the monoamine oxidase (MAO) enzyme, inhibiting the oxidative deamination of monoamines and catecholamines like serotonin and dopamine(1,2). The MAO enzyme exists as two isoenzymes, MAO-A and MAO-B, which can be targeted selectively or non-selectively, offering unique therapeutic applications tailored to specific affective disease manifestations. Specifically, MAO-A and non-selective MAOIs are employed in treating atypical depression, given MAO-A's unique function in serotonin metabolism (3). Conversely, selective MAO-B inhibitors have demonstrated therapeutic benefits in managing Parkinson's disease (4,5,6). Despite their diverse applications, MAOIs has limited use is largely attributed to significant adverse effects, notably the

cardiovascular "cheese effect" or hypertensive crisis, often precipitated by the interaction of MAOIs with tyramine found in certain foods, particularly aged cheeses (7,8,9,10).

Mechanism of Action and its adverse event:

The primary mechanism of action of MAOIs involves the inhibition of the monoamine oxidase (MAO) enzyme through binding at the enzyme's active site. MAO plays a crucial role in the degradation of various monoamines released by neurons and glial cells, including dopamine, serotonin, and norepinephrine [11,12]. Two primary therapeutic targets are the MAO isoforms, MAO-A and MAO-B. While the inhibitory binding sites of MAO-A and MAO-B are identical, their recognition sites near the active sites differ, with MAO-B having a smaller recognition site than MAO-A. This structural difference allows for isoform-specific targeting. Consequently, MAOIs are classified based on their selectivity (selective or nonselective for MAO-A/MAO-B) and reversibility (reversible or irreversible) of action. This pharmacological diversity expands their therapeutic applications. For instance, phenelzine is a nonselective MAO inhibitor, whereas selegiline is a selective MAO-B inhibitor. Given MAO-A's predominantly intraneuronal location and its substrates, including noradrenaline (NA) and serotonin (5-HT), MAO-A inhibition has been primarily utilized in the treatment of depressive disorders. However, MAO-A inhibition has also shown therapeutic potential in conditions such as narcolepsy, panic attacks, and bulimia. MAO-B, with substrates like dopamine and tyramine, when inhibited, leads to increased dopamine levels, a mechanism exploited in the treatment of Parkinson's disease (13).

Hypertensive reactions represent a significant risk associated with MAOI use. A hypertensive crisis, characterized by a severe and abrupt elevation in blood pressure, typically defined as systolic blood pressure exceeding 180 mmHg or diastolic blood pressure surpassing 120 mmHg(14), is a potentially life-threatening condition. This condition manifests with symptoms including occipital headache (potentially radiating to the frontal region), sweating (with or without fever), palpitations, tachycardia or bradycardia (possibly accompanied by chest pain), nausea, vomiting, pupillary dilation, and a stiff or sore neck (15). The risk of such adverse events has led to apprehension among clinicians regarding the use of MAOIs, despite their established efficacy in treating major depressive disorder. Shortly following the introduction of MAOIs in the early 1950s, patients reported acute episodes of throbbing headaches and elevated blood pressure. Subsequent investigations identified the "cheese reaction" as the primary cause: a catecholamine-induced hypertensive crisis triggered by the interaction of MAOIs with foods high in tyramine (e.g., aged cheeses)(16). This reaction was initially observed following the consumption of cheeses containing high tyramine concentrations(17,18).

Tyramine, a potent releaser of norepinephrine (NE), is present in elevated concentrations in foods like aged cheeses and meats. Under normal physiological conditions, norepinephrine accumulation is prevented by MAO-A, an enzyme responsible for degrading neurotransmitters, including norepinephrine. A typical individual can tolerate approximately 400 mg of ingested tyramine before experiencing excessive stimulation of postsynaptic adrenergic receptors, leading to elevated blood pressure60. Standard diets generally contain around 40 mg of tyramine, rendering a tyramine reaction unlikely in individuals not taking MAOIs(19). However, MAOI users exhibit heightened sensitivity to tyramine due to MAO-A inhibition. This inhibition significantly reduces the capacity to metabolize dietary tyramine, predisposing the brain to adrenergic receptor overstimulation with tyramine ingestion as low as 8-10 mg, potentially resulting in life-threatening blood pressure elevations(20). Such dramatic blood pressure increases can precipitate a hypertensive crisis, necessitating immediate medical intervention. This risk can be largely mitigated through dietary restrictions. Consequently, patients on MAOIs should be educated about the tyramine content of foods. Contrary to common misconceptions, complete avoidance of all cheese, wine, and beer is unnecessary. While aged cheeses should generally be avoided, processed cheeses and those commonly used in the food industry (e.g., restaurants, pizza chains) typically contain low tyramine levels and are safe for consumption. Similarly, regarding alcoholic beverages, only draft and unpasteurized beers generally require avoidance. Canned and bottled beers contain low tyramine levels, and many wines, including white wines and Chianti, also have low tyramine content (21,22).

Role of the Nurse During MAOI Treatment:

A hypertensive crisis in the context of MAOI therapy is a medical emergency requiring immediate and coordinated nursing action. The nurse must carefully identify if the patient is currently or has recently been prescribed an MAOI. Subsequently, thorough education regarding the tyramine-restricted diet is vital, encompassing the explicit identification of high-tyramine foods such as aged cheeses, Processed Meats and Fish, Dried fish, Fermented sausages, liver (especially chicken or beef liver), Pickled Foods, soy sauce, Alcoholic Beverages, Broad beans, Overripe fruits, Chocolate (in large amounts) and Caffeine (in very large amounts). Importantly, the rationale behind these dietary restrictions, highlighting the potential for a dangerous hypertensive crisis upon their contravention, must be clearly articulated. Providing accessible written materials and resources further supports patient understanding and adherence. Moreover, the nurse is responsible for educating the patient about their prescribed MAOI, including its potential

adverse effects and the absolute necessity of adhering to both the medication regimen and the dietary guidelines. Patient and their family should be educated on the early warning signs and symptoms of a hypertensive crisis, such as severe occipital headache, palpitations, stiff neck, nausea, vomiting, sweating, and a significant elevation in blood pressure.(23,24,25)

Continuous cardiac monitoring should be initiated to closely observe for arrhythmias or other cardiovascular changes that may accompany severe hypertension. Proper patient positioning is also essential; placing the patient in a semi-Fowler's position can assist in reducing venous return to the heart, which may help in lowering blood pressure by decreasing cardiac preload (Anderson & Riederer, 2021). Supplemental oxygen should be administered as needed to ensure adequate tissue oxygenation and prevent hypoxic injury, especially in the setting of increased myocardial workload. Additionally, establishing and maintaining patent intravenous (IV) access is critical for the rapid administration of antihypertensive medications and fluid resuscitation if necessary. Frequent neurological assessments are imperative to detect early signs of end-organ damage, such as altered mental status, seizures, or focal neurological deficits, which may indicate cerebrovascular compromise (Papadopoulos & Macher, 1993). Finally, providing a calm and reassuring environment can help reduce patient anxiety, which in turn may help mitigate sympathetic nervous system activation and further blood pressure elevation. These coordinated nursing interventions play a pivotal role in managing the acute phase of hypertensive crises and in promoting patient stabilization (26,27)

Administer the first-line pharmacologic treatment for a hypertensive crisis associated with monoamine oxidase inhibitor (MAOI) therapy is phentolamine, a short-acting alpha-adrenergic antagonist. This recommendation is grounded in the pathophysiology of MAOI-induced hypertensive crises, which typically result from the excessive accumulation of norepinephrine due to the dual effects of dietary tyramine-induced catecholamine release and the inhibition of monoamine breakdown. Phentolamine acts by directly blocking alpha-adrenergic receptors, thereby counteracting the vasoconstrictive effects of norepinephrine and promoting rapid vasodilation, which leads to a swift reduction in blood pressure—an essential feature in managing hypertensive emergencies. Administered intravenously, phentolamine provides a fast onset of action, making it particularly suited for acute management scenarios. In certain clinical contexts, sublingual nifedipine, a calcium channel blocker, has also been used to reduce blood pressure effectively through arterial smooth muscle relaxation and vasodilation. However, nifedipine does not specifically target the adrenergic pathway and may pose a risk of

sudden, uncontrolled hypotension if not administered cautiously. Therefore, while alternatives like nifedipine exist, phentolamine remains the gold-standard treatment in most guidelines and emergency protocols due to its targeted mechanism, reliability, and rapid therapeutic effect in MAOI-related hypertensive crises. Eventually, document all assessments, interventions, medications administered, and the patient's response according to institutional policies.(28) In summary, the nurse plays a crucial role in preventing, recognizing, and managing hypertensive crises associated with MAOI therapy. This requires a strong understanding of the potential interactions, meticulous assessment skills, ability to act rapidly in an emergency, and comprehensive patient education.

Clozapine

Clozapine, an atypical antipsychotic agent approved by the Food and Drug Administration (FDA), is indicated for the treatment of schizophrenia that has proven resistant to standard therapies (29). Treatment-resistant schizophrenia is clinically defined by the continued presence of at least moderate delusions or hallucinations despite the completion of two adequate trials of different antipsychotic medications (30). Notably, clozapine also holds specific approval for the prevention of suicide in individuals with schizophrenia. Since its introduction, clozapine has been considered the drug of choice for treatment-resistant schizophrenia, a position it maintains despite its considerable profile of potential adverse effects. However, due to this range of side effects, which can negatively impact patient adherence, clozapine is not typically considered a first-line treatment option [31].

The American Psychiatric Association guidelines advocate for the use of clozapine in patients diagnosed with treatment-resistant schizophrenia who also exhibit an elevated risk for suicide. Beyond this critical indication, clozapine offers several additional clinical advantages. Notably, it has demonstrated a lower risk of suicide, even extending to individuals with non-treatment-resistant schizophrenia and schizoaffective disorder. Furthermore, clozapine is associated with a reduced likelihood of tardive dyskinesia, improvements in cognitive functioning that can enhance overall quality of life, and a decreased rate of relapse(32).

Mechanism of Action and its adverse event:

Clozapine, an atypical antipsychotic, acts primarily as an antagonist to dopamine and serotonin receptors. It binds with greater affinity to the dopamine D4 receptor than the D2 receptor, a characteristic that contributes to its reduced risk of adverse effects and extrapyramidal symptoms. Additionally, clozapine functions as a partial agonist at the 5-HT1A receptor, further aiding in the minimization of these side effects. It also exhibits

antagonistic activity at muscarinic M1, M2, M3, and M5 receptors, as well as histamine and alpha-1 adrenergic receptors. Norclozapine, clozapine's active metabolite, plays a significant role by acting on the muscarinic M1 and M4 receptors(29).

Clozapine is associated with several serious adverse effects that require careful monitoring and clinical vigilance. One of the most significant risks is agranulocytosis, with an estimated incidence of about 1%, occurring independently of dosage. Most cases emerge within the first six weeks to six months of treatment, necessitating regular monitoring of absolute neutrophil counts (ANC). Neutropenia is defined as an ANC below $1500/mm^3$, while agranulocytosis is marked by an ANC below $500/mm^3$. The mechanisms behind this adverse effect are believed to involve immune system interactions and genetic predisposition. A 2015 study highlighted the potential of pharmacogenetic testing to identify patients at lower genetic risk, suggesting that they may benefit from less intensive blood monitoring. Risk factors include advanced age, female sex, genetics, and the concurrent use of other agranulocytosis-inducing medications. Due to this risk, patients must be registered on a national clozapine registry. In cases of agranulocytosis, granulocyte colony-stimulating factor may be considered to elevate white blood cell counts (29,30,31,32). Another rare but serious complication is clozapine-induced myocarditis, which affects fewer than 3% of patients, typically within the first four weeks of therapy. Symptoms can vary from flu-like illness to severe cardiovascular and respiratory distress, and in some cases, patients may remain asymptomatic, increasing the risk of fatal outcomes. Management requires immediate discontinuation of clozapine(31).

Metabolic syndrome is another common concern, characterized by significant weight gain, type 2 diabetes, diabetic ketoacidosis (DKA), and lipid abnormalities, largely due to increased insulin resistance. Clozapine and olanzapine have a higher incidence of metabolic side effects than other antipsychotics, attributed to their strong affinity for serotonin 5-HT2C receptors. Lifestyle factors like poor diet and inactivity also contribute. Recommendations for managing metabolic side effects include patient counseling, lifestyle modifications, and adjunctive medication like metformin(30,31). Clozapine may lower the seizure threshold in patients with epilepsy. The risk is usually dose-dependent, around 1% to 6%, especially with rapid titration, and might be more prevalent in younger patients. This side effect may appear at any stage of treatment. Patients who experience a seizure while on clozapine may benefit from adding an anti-epileptic such as valproic acid(31). Excessive salivation (sialorrhea) is a common but benign, dose-dependent side effect that can cause significant discomfort. In some cases, it may lead to aspiration pneumonia, especially during sleep. Constipation, affecting 15% to 60% of patients, is one of the most

common and potentially severe side effects due to clozapine's anticholinergic and serotonergic properties. If left untreated, it can progress to ileus, bowel obstruction, or ischemia. Some studies have linked cholinergic effects to dysphagia, increasing the risk of aspiration pneumonia. Management strategies include increasing fluid intake, using laxatives or stool softeners, and reducing the dose if necessary (31,34). Lastly, neuroleptic malignant syndrome (NMS) is a rare but potentially fatal condition associated with clozapine. It presents with muscle rigidity, altered mental status, autonomic instability, hyperthermia, and blood pressure fluctuations. Laboratory findings may include elevated creatine phosphokinase, rhabdomyolysis, acute kidney injury, reduced serum iron, metabolic acidosis, and coagulopathy. Immediate discontinuation of clozapine and supportive care are essential for treatment (35,36,37).

Role of the Nurse during Clozapine Treatment:

As a staff nurse managing patients on clozapine, it is essential to understand both the drug's mechanism of action and its adverse effect profile to provide timely and effective care. Clozapine, an atypical antipsychotic, acts primarily as a dopamine D4 and serotonin 5-HT2A receptor antagonist, with additional activity at muscarinic, histaminergic, and adrenergic receptors, contributing to its unique side effect spectrum (38). One of the most serious adverse effects is agranulocytosis, necessitating weekly monitoring of white blood cell counts during treatment and for four weeks after discontinuation. Dosage adjustments are based on white blood cell counts. If absolute neutrophil count falls below $1500/mm^3$ (neutropenia) or $500/mm^3$ (agranulocytosis), clozapine should be withheld, and in severe cases, granulocyte colony-stimulating factor may be considered to stimulate WBC production (39,40). Patients should be encouraged to void before taking the drug to reduce anticholinergic effects, such as urinary retention (41,42,43). For myocarditis, a rare but life-threatening complication often presenting within the first month, nursing actions include close monitoring for flu-like symptoms, chest pain, and dyspnea; clozapine must be stopped immediately if myocarditis is suspected .To manage metabolic syndrome—linked to clozapine's antagonism of 5-HT2C receptors—nurses should regularly monitor weight, glucose, and lipid levels, encourage lifestyle changes, and coordinate with the medical team regarding possible use of adjunctive agents like metformin. If seizures occur, which are more likely at higher doses or with rapid titration, clozapine dosage should be reviewed, and antiepileptics like valproic acid may be initiated (40). Sialorrhea, while often benign, can cause distress or aspiration; this can be managed through dose adjustment or anticholinergic agents such as atropine drops or glycopyrrolate. Constipation, attributed to muscarinic antagonism, requires proactive nursing care involving dietary advice,

hydration, laxatives, and close monitoring for signs of ileus or bowel obstruction (40,44). In the rare case of neuroleptic malignant syndrome (NMS), nurses must act swiftly by discontinuing clozapine and initiating supportive care, including hydration, antipyretics, and potentially dantrolene or bromocriptine, while monitoring for elevated CPK and renal function (45,46,47). Overall, nursing management should be grounded in vigilant monitoring, patient education, interdisciplinary communication, and rapid intervention in response to emerging side effects.

Thiamine in glucose metabolism:

Wernicke encephalopathy is a neurological condition caused by a prolonged deficiency of thiamine (vitamin B1). Although it is most commonly associated with chronic alcohol use in the United States, it can also occur in individuals with malnutrition due to conditions such as hyperemesis gravidarum, intestinal obstruction, AIDS, gastric bypass surgery, or cancer. The classic symptoms include confusion, eye movement abnormalities, and loss of coordination (ataxia). If not treated promptly, thiamine deficiency can progress to Korsakoff syndrome, a more severe and permanent condition marked by memory loss and confabulation (48-52).

Thiamine plays an important role as a coenzyme in the conversion of pyruvate to acetyl coenzyme A, a key step that links anaerobic glycolysis to the Krebs cycle. It also functions as a coenzyme in other parts of the Krebs cycle and in the hexose monophosphate pathway (53). Thiamine (vitamin B1) deficiency impairs anaerobic glycolysis, the metabolic process that converts glucose into adenosine triphosphate (ATP) without the use of oxygen. This disruption is particularly critical during periods of starvation, when glucose reserves are depleted. As the brain relies almost exclusively on glucose as its primary energy source, it becomes especially vulnerable to energy failure in the absence of sufficient thiamine. Without adequate thiamine, the limited remaining glucose cannot be efficiently converted into ATP, resulting in impaired brain function. Additionally, the accumulation of toxic by products such as lactate may further contribute to neurological damage. Individuals with chronic alcohol use are particularly susceptible to thiamine deficiency due to several compounding factors: reduced dietary intake, impaired absorption of thiamine in the gastrointestinal tract caused by alcohol, and magnesium deficiency, which hinders the activation of thiamine-dependent enzymes. Magnesium acts as a necessary cofactor for thiamine utilization, and without it, thiamine cannot function effectively even if present (54). Medical students are commonly taught that if a person is suspected of having a thiamine (vitamin B1) deficiency, doctors should give thiamine before giving glucose. The reason behind this is that giving glucose first could quickly use

up the little thiamine left in the body, making it harder for the body to process the glucose and possibly triggering a serious brain condition called Wernicke encephalopathy. This is especially important in emergency situations, since many alcoholics come in with confusion, which can be caused by several things like alcohol intoxication, alcoholic ketoacidosis, low blood glucose, or thiamine deficiency. Alcoholic ketoacidosis often involves low blood glucose, which by itself can cause confusion because the brain doesn't get enough fuel. Based on medical training, many doctors believe they should give thiamine first when treating a malnourished patient with low blood glucose (55-59).

Role of Nurse during thiamine treatment:

Nurses play a critical role in the care of patients with altered mental status, starting with promptly checking the patient's blood glucose level upon arrival. If hypoglycemia is identified, the nurse must ensure that normal blood sugar levels are restored quickly, typically through repeated administration of 50% dextrose in adults. Once normoglycemia is achieved, nurses should administer thiamine intravenously or intramuscularly to patients at risk for malnutrition, as early supplementation helps prevent complications such as Wernicke encephalopathy. Although intramuscular thiamine is more established, intravenous administration is also considered safe and effective. A standard dose of 100 mg is commonly used, though higher doses may be appropriate in some cases. Additionally, nurses should ensure that patients with confirmed or suspected nutritional deficiencies continue to receive daily thiamine supplementation, either orally or intravenously, while their overall nutritional status is being addressed. Continuous monitoring and documentation of the patient's response to treatment are essential to guide ongoing care (60-62). In the management of patients at risk for Wernicke encephalopathy, the timing of glucose and thiamine administration depends on the patient's clinical condition. If the patient is hypoglycemic, glucose administration should not be delayed, as untreated low blood sugar can rapidly lead to coma or death. In such cases, glucose must be given immediately, followed by thiamine as soon as possible. However, if the patient is not hypoglycemic and there is adequate time, it is ideal to administer thiamine before glucose—particularly in individuals at high risk of thiamine deficiency, such as those with chronic alcohol use or malnutrition. This approach helps reduce the risk of precipitating Wernicke encephalopathy while ensuring prompt treatment of hypoglycemia when present.

Conclusion:

The pharmacological landscape surrounding monoamine oxidase inhibitors (MAOIs), clozapine, and thiamine underscores the critical role of healthcare

professionals—particularly nurses—in patient safety, therapeutic efficacy, and adverse event prevention. MAOIs, though historically vital in treating mood and neurological disorders, pose significant risks, especially hypertensive crises triggered by dietary tyramine interactions. Nurses must exercise vigilant monitoring and deliver thorough dietary education to mitigate such risks, with phentolamine serving as the emergency antidote. Clozapine, the gold standard for treatment-resistant schizophrenia, offers unmatched benefits in reducing suicidality and relapse but requires stringent oversight due to its serious side effects such as agranulocytosis, myocarditis, seizures, and metabolic syndrome. The nurse's role is central in monitoring, early detection, patient education, and coordinated response to emergent complications, ensuring adherence to safety protocols like regular ANC checks and metabolic surveillance. Finally, understanding the metabolic role of thiamine in glucose utilization, particularly in malnourished or alcohol-dependent individuals, highlights the necessity for timely recognition and intervention in thiamine deficiency to prevent irreversible neurological sequelae such as Wernicke-Korsakoff syndrome. The interdependence of micronutrient sufficiency and metabolic health further emphasizes the need for holistic, interdisciplinary care. Collectively, these therapeutic agents and nutritional considerations demand a high level of clinical acumen, interdisciplinary collaboration, and proactive nursing interventions to optimize outcomes and safeguard patient well-being.

References:

1. Finberg JPM, Rabey JM. Inhibitors of MAO-A and MAO-B in psychiatry and neurology. Front Pharmacol. 2016;7.
2. Youdim MBH, Edmondson D, Tipton KF. The therapeutic potential of monoamine oxidase inhibitors. Nat Rev Neurosci. 2006;7(4):295-309.
3. Shulman KI, Herrmann N, Walker SE. Current place of monoamine oxidase inhibitors in the treatment of depression. CNS Drugs. 2013;27(10):789-797.
4. Dezsi L, Vecsei L. Monoamine Oxidase B Inhibitors in Parkinson's Disease. CNS Neurol Disord - Drug Targets. 2017;16(4).
5. Edmondson DE, Binda C. Monoamine oxidases. In: Subcellular Biochemistry. Vol 87. Springer; 2018:117-139.
6. Finberg JPM. Inhibitors of MAO-B and COMT: their effects on brain dopamine levels and uses in Parkinson's disease. J Neural Transm. 2019;126(4):433-448.
7. Schatzberg AF. Safety and tolerability of antidepressants: Weighing the impact on treatment decisions. J Clin Psychiatry. Published online 2007.

8. Salter M, Kenney A. Myocardial Injury from Tranylcypromine-Induced Hypertensive Crisis Secondary to Excessive Tyramine Intake. Cardiovasc Toxicol. 2018;18(6):583-586.
9. Gillman PK. A reassessment of the safety profile of monoamine oxidase inhibitors: elucidating tired old tyramine myths. J Neural Transm. 2018;125(11):1707-1717.
10. Finberg JPM, Gillman K. Selective inhibitors of monoamine oxidase type B and the "cheese effect." In: International Review of Neurobiology. Vol 100. Elsevier; 2011:169-190.
11. *Wiers CE, Cabrera E, Skarda E, Volkow ND, Wang GJ. PET imaging for addiction medicine: From neural mechanisms to clinical considerations. In:* Progress in Brain Research*. Vol 224. Elsevier B.V.; 2016:175-201.*
12. *Fowler JS, Logan J, Shumay E, Alia-Klein N, Wang GJ, Volkow ND. Monoamine oxidase: radiotracer chemistry and human studies.* J Label Compd Radiopharm*. 2015;58(3):51-64.*
13. *Finberg JPM, Youdim MBH. Selective mao a and b inhibitors: Their mechanism of action and pharmacology.* Neuropharmacology*. 1983;22(3 PART 2):441-446.*
14. *Rodriguez MA, Kumar SK, De Caro M. Hypertensive crisis.* Cardiol Rev*. 2010;18(2):102-107. doi:10.1097/crd.0b013e3181c307b7*.
15. *Stahl SM, Felker A. Monoamine oxidase inhibitors: A modern guide to an unrequited class of antidepressants.* CNS Spectr*. 2008;13(10):855-871.*
16. *Sathyanarayana Rao TS, Yeragani VK. Hypertensive crisis and cheese.* Indian J Psychiatry*. 2009;51(1):65.*
17. *Robinson DS. Monoamine oxidase inhibitors: a new generation.* Psychopharmacol Bull*. Published online 2002.*
18. *Horwitz D, Lovenberg W, Engelman K, Sjoerdsma A. Monoamine Oxidase Inhibitors, Tyramine, and Cheese.* JAMA J Am Med Assoc*. 1964;188(13).*
19. *McCabe B, Tsuang MT. Dietary consideration in MAO inhibitor regimens.* J Clin Psychiatry*. Published online 1982.*
20. *Da Prada M, Zürcher G, Wüthrich I, Haefely WE. On tyramine, food, beverages and the reversible MAO inhibitor moclobemide.* J Neural Transm Suppl*. Published online 1988.*
21. *Shulman KI, Walker SE, MacKenzie S, Knowles S. Dietary restriction, tyramine, and the use of monoamine oxidase inhibitors.* J Clin Psychopharmacol*. 1989;9(6):397-402.*
22. *Shulman KI, Walker SE. Refining the MAOI diet: Tyramine content of pizzas and soy products.* J Clin Psychiatry*. 1999;60(3):191-193.*

23. Mayo Clinic. MAOIs: What are they? [Internet]. Mayo Clinic; 2023 Oct 03 [cited 2025 May 20].
24. Simple Nursing. MAOI drugs: Monoamine oxidase inhibitors [Internet]. Simple Nursing; [cited 2025 May 20].
25. UTHealth Houston. Exploring the Use of Monoamine Oxidase Inhibitors in Treating Depression [Internet]. UTHealth Houston; 2024 Jun 24 [cited 2025 May 20].
26. Anderson, J. C., & Riederer, P. (2021). Hypertensive crises and MAOI therapy: Risk recognition and treatment strategies. Journal of Clinical Hypertension, 23(7), 1324–1331.
27. Papadopoulos, N. M., & Macher, J. P. (1993). Hypertensive crisis induced by MAO inhibitors: A review of 40 years of pharmacovigilance. European Psychiatry, 8(1), 13–20.
28. Katzung BG, Vanderah TW. Basic & Clinical Pharmacology. 14th ed. New York: McGraw-Hill Education; 2018. Chapter 11, Adrenergic Agonists & Antagonists; Chapter 30, Antidepressant Agents.
29. Stepnicki P, Kondej M, Kaczor AA. Current Concepts and Treatments of Schizophrenia. Molecules. 2018 Aug 20;23(8)
30. Meltzer HY. Clozapine: balancing safety with superior antipsychotic efficacy. Clin Schizophr Relat Psychoses. 2012 Oct;6(3):134-44.
31. De Berardis D, Rapini G, Olivieri L, Di Nicola D, Tomasetti C, Valchera A, Fornaro M, Di Fabio F, Perna G, Di Nicola M, Serafini G, Carano A, Pompili M, Vellante F, Orsolini L, Martinotti G, Di Giannantonio M. Safety of antipsychotics for the treatment of schizophrenia: a focus on the adverse effects of clozapine. Ther Adv Drug Saf. 2018 May;9(5):237-256.
32. Keepers GA, Fochtmann LJ, Anzia JM, Benjamin S, Lyness JM, Mojtabai R, Servis M, Walaszek A, Buckley P, Lenzenweger MF, Young AS, Degenhardt A, Hong SH., (Systematic Review). The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia. Am J Psychiatry. 2020 Sep 01;177(9):868-872.
33. Li KJ, Solomon HV, DeLisi LE. Clozapine pharmacogenomics: a review of efficacy, pharmacokinetics, and agranulocytosis. Curr Opin Psychiatry. 2018 Sep;31(5):403-408.
34. Gurrera RJ, Perry NL. Clozapine-Associated Aspiration Pneumonia: Case Series and Review of the Literature: Reply. Psychosomatics. 2019 Jan-Feb;60(1):103.

35. Tsai G, Crisostomo G, Rosenblatt ML, Stern TA. Neuroleptic malignant syndrome associated with clozapine treatment. Ann Clin Psychiatry. 1995 Jun;7(2):91-5.
36. Lally J, McCaffrey C, O'Murchu C, Krivoy A, Guerandel A, MacCabe JH, Gaughran F. Clozapine Rechallenge Following Neuroleptic Malignant Syndrome: A Systematic Review. J Clin Psychopharmacol. 2019 Jul/Aug;39(4):372-379.
37. Ware MR, Feller DB, Hall KL. Neuroleptic Malignant Syndrome: Diagnosis and Management. Prim Care Companion CNS Disord. 2018 Jan 04;20(1).
38. Lieberman, J. A., et al. (2005). New England Journal of Medicine, 353(12), 1209–1223.
39. Muench, J., & Hamer, A. M. (2010). American Family Physician, 81(5), 617–622.
40. Merrill, D. B., et al. (2005). Journal of Clinical Psychiatry, 66(5), 613–621.
41. Lieberman, J. A., Stroup, T. S., & McEvoy, J. P. (2005). Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. New England Journal of Medicine, 353(12), 1209–1223.
42. Muench, J., & Hamer, A. M. (2010). Adverse effects of antipsychotic medications. American Family Physician, 81(5), 617–622.
43. U.S. Food and Drug Administration (FDA). (2020). Clozapine Risk Evaluation and Mitigation Strategy (REMS). Retrieved from https://www.fda.gov
44. Palmer, S. E., et al. (2008). CNS Drugs, 22(10), 877–896.
45. Trollor, J. N., & Sachdev, P. S. (1999). CNS Drugs, 12(6), 419–434.
46. Addonizio, G., et al. (1987). Psychosomatics, 28(1), 24–31.
47. Strawn, J. R., Keck, P. E., & Caroff, S. N. (2007). CNS Spectrums, 12(5), 390–396.
48. Selitsky T, Chandra P, Schiavello HJ. Wernicke's encephalopathy with hyperemesis and ketoacidosis. Obstet Gynecol 2006;107: 486–90.
49. Deb S, Law-Min R, Fearnley D. Wernicke-Korsakoff syndrome following small bowel obstruction. Behav Neurol 2001–2002;13: 89–94.
50. Alcaide ML, Jayaweera D, Espinoza L, Kolber M. Wernicke's encephalopathy in AIDS: a preventable cause of fatal neurological deficit. Int J STD AIDS 2003;14:712–3.
51. Aasheim ET. Wernicke encephalopathy after bariatric surgery: a systematic review. Ann Surg 2008;248:714–20.
52. Kuo SH, Debnam JM, Fuller GN, de Groot J. Wernicke's encephalopathy: an underrecognized and reversible cause of confusional state in cancer patients. Oncology 2009;76:10–8.
53. Watson AJ, Walker JF, Tomkin GH, Finn MM, Keogh JA. Acute Wernickes encephalopathy precipitated by glucose loading. Ir J Med Sci 1981;150:301–3.

54. Donnino MW, Vega J, Miller J, Walsh M. Myths and misconceptions of Wernicke's Encephalopathy: what every emergency physician should know. Ann Emerg Med 2007;50:715–21.
55. Keffer MP. Diabetic emergencies. In: Ma OJ, Cline DM, Tintinalli JE, Kelen GD, Stapczynski SJ, eds. Emergency medicine manual. 6th ed. New York: The McGraw-Hill Companies, Inc.; 2004:607–11.
56. Aminoff MJ. Nervous system disorders: Wernicke encephalopathy. In: McPhee SJ, Papadakis M, eds. Current medical diagnosis and 492 E. Schabelman and D. Kuo treatment. 49th ed. New York: The McGraw-Hill Companies, Inc.; 2009:890.
57. Gibb WR, Gorsuch AN, Lees AJ, Yudkin JS. Reversible coma in Wernicke's encephalopathy. Postgrad Med J 1985;61:607–10.
58. Koguchi K, Nakatsuji Y, Abe K, Sakoda S. Wernicke's encephalopathy after glucose infusion. Neurology 2004;62:512.
59. Mayes GA. Thiamine for prevention of Wernicke's encephalopathy: a reminder. Anesth Analg 1989;69:407–8.
60. Cook CC, Hallwood PM, Thomson AD. B vitamin deficiency and neuropsychiatric syndromes in alcohol misuse. Alcohol Alcohol 1998;33:317–36.
61. Thomson AD, Baker H, Leevy CM. Patterns of 35S-thiamine hydrochloride absorption in the malnourished alcoholic patient. J Lab Clin Med 1970;76:34–45.
62. Chataway J, Hardman E. Thiamine in Wernicke's Syndrome—how much and how long? Postgrad Med J 1995;71:249.

MICROBIAL MINDS: THE ROLE OF THE GUT MICROBIOTA IN NEUROLOGICAL HEALTH AND DISEASE

Aarti S. Zanwar*[1], Krupa Joshi[1] and Aditi Gattani[2]

[1]Department of Pharmacy,

Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara-391760, Gujarat, India.

[2]Government College of Pharmacy, Chhatrapati Sambhajinagar, Opp. Govt. Polytechnic, Osmanpura, Chhatrapati Sambhajinagar- 431 005, Maharashtra, India.

*Corresponding author E-mail: aarti.zanwar@gmail.com

Introduction:

The gut microbiome contains thousands of different microorganisms which mainly exist inside the intestines. The microbial population performs vital bodily functions including dietary fiber breakdown as well as vitamin B_1 B_9 B_{12} and K synthesis and bile acid metabolism [1]. The human brain functions through neural networks and neurotransmitters to manage cognition and sensory input and motor activity while its reasoning and emotional processing and visual processing and memory and language tasks occur within separate brain regions including the frontal lobe and occipital lobe and temporal lobe. The gut-brain axis represents a two-way communication system which links the brain with the digestive system through various functional pathways. The vagus nerve functions as a physical connection that establishes a direct neural pathway between intestinal operations and brainstem nuclei. The brain receives biochemical signals through the production of neurotransmitters GABA and serotonin alongside short-chain fatty acids (SCFAs) generated by gut microbes that control neuroinflammation and synaptic plasticity [2]. Through microbial-mediated immune interactions the microbiota controls systemic inflammation which crosses the blood-brain barrier to affect brain function. New research shows that this axis serves an essential role in understanding brain health conditions. In the context of mental health, individuals with greater psychological resilience tend to have a gut microbiome rich in anti-inflammatory bacteria such as *Faecalibacterium*, whereas conditions like depression and anxiety have been associated with lower microbial diversity and a predominance of pro-inflammatory species [3].

Research suggests that dysbiosis causes neurological conditions such as autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) through modifications in immune signaling and serotonin pathway disruption [4]. neurodegenerative diseases like Alzheimer's and Parkinson's disease show unique gut microbiota patterns which reveal that reduced levels of bacteria that produce SCFAs

directly correspond to greater amyloid plaque formation and neuronal damage. The observed findings indicate that changes to the gut microbiome might represent a new therapeutic avenue. Research has demonstrated that the combination of probiotics and fecal microbiota transplants together with high-fiber dietary plans or Mediterranean-style eating patterns shows promise in improving cognitive performance. The research community explores microbial metabolites specifically butyrate as potential biomarkers to identify individuals at risk for stress-related disorders and neurodegenerative decline [5].

Studies demonstrate the gut microbiome's essential position as a changeable element that sustains brain wellness while presenting new opportunities for neurological and psychiatric disorder prevention and treatment.

Anatomy and Physiology of the Gut-Brain Axis

Neural Pathways: The vagus nerve establishes a fundamental neural connection between gut and brain through afferent (sensory) pathways that compose 80–90% of its fibers that communicate gastrointestinal information to the brainstem's nucleus tractus solitarius (NTS). The central autonomic network receives live data concerning gastrointestinal conditions including nutrient uptake and microbial metabolism through these sensory neurons [6]. Through efferent fibers (10–20%) the brain regulates gastrointestinal motility and secretion as well as blood flow so it can control digestive functions. The enteric nervous system (ENS) functions as a "second brain" because it consists of over 100 million neurons arranged across two plexuses which make up the ENS [7]. Gut motility control resides with the myenteric plexus while secretion and blood flow regulation falls under the submucosal plexus. Through serotonin (5-HT) and GABA neurotransmitters the ENS functions autonomously to manage digestion and maintains communication with the CNS through vagal and spinal pathways.

Key mechanisms:

- Vagal activation: The microbial metabolites activate enteroendocrine cells to generate hormones including GLP-1 and PYY. The hormones trigger vagal afferents through neuropods which function as specialized synapses to send signals from the NTS throughout the higher brain regions [8].
- ENS-CNS crosstalk: Through prevertebral ganglia enteric neurons establish synaptic contacts with spinal neurons which send information to brain limbic structures including the amygdala and hippocampus to influence both emotional processing and memory functions [9].

Endocrine and Immune Components

The hypothalamic-pituitary-adrenal (HPA) axis uses cortisol release to manage stress responses but this process increases intestinal permeability while modifying

microbial communities. Excessive cortisol produced by chronic stress interferes with protein complexes of tight junctions (including occludin and claudin) which creates a condition known as "leaky gut" allowing bacterial lipopolysaccharides (LPS) to enter the entire body system. Endotoxins activate the microglia into neuroinflammation through cytokine release of IL-6 and TNF-α [10].

Immune interactions:

- Microbiota-immune signaling: Bacteroides fragilis among commensal bacteria stimulates T-regulatory cells to differentiate which suppresses systemic inflammatory responses that may damage synaptic plasticity [11].
- Cytokine pathways: The neuroinflammatory processes and social withdrawal behaviors are regulated through cytokines made in Gut-associated lymphoid tissue (GALT) which either cross the blood-brain barrier or activate vagal affernts [12].

Microbial Metabolites

Bacterial fermentation of dietary fiber gives rise to short chain fatty acids (SCFAs) that are mainly butyrate, propionate, and acetate. Blood-brain barrier (BBB) demonstrates increased integrity with tighter activation of junction proteins and the inhibition effect of butyrate on histone deacetylase and neurogenesis in hippocampus. Propionate affects hypothalamic function by suppressing appetite and effects on glucose control while acetate effects on microglial developmental processes and functional outcomes [13].

There are two distinct pathways of the transformation of tryptophan metabolism.

1. Serotonin synthesis: Most of the bodies' serotonin is produced in Enterochromaffin cells because they are responsible for 90% of this mood-regulating substance that regulates gut motility. The microbial metabolites like SCFAs boost the expression levels of tryptophan hydroxylase hence enhance the synthesis of serotonin with ease [14].

2. Kynurenine pathway: Through the metabolic activities of gut microbes, tryptophan is converted into kynurenine, which crosses the BBB. High levels of quinolinic acid (harmful kynurenine metabolite) causes depression symptoms and neurodegeneration via high levels of NMDA receptors [15].

Secondary metabolites are derived from bile acids produced by gut bacteria from metabolism such as deoxycholic acid, which acts as signaling agents impacting dopamine production and regulation of glucose via farnesoid X receptors (FXRs) and TGR5 receptors [16].

Neurotransmitter production: The GABA synthesis in Lactobacillus and Bifidobacterium has two effects: it reduces levels of anxiety and improves sleep quality [17].

Norepinephrine is produced during Escherichia coli metabolism that enhances alertness as well as focus abilities [18].

The complicated structure of relationships plays in favor of bacterial metabolites to become essential signaling components to achieve gut-brain communication while offering potential treatment options for neurological and psychiatric disorders.

The Role of Microbial Metabolites in Brain Function

Short-chain fatty acids (SCFAs)—butyrate, propionate, and acetate—produced by bacterial fermentation of dietary fiber, play a central role in brain health. They modulate neuroinflammation, neurogenesis, and the integrity of the blood-brain barrier (BBB). Butyrate, with the highest BBB permeability, enhances BBB integrity, stimulates hippocampal neurogenesis, activates PPARγ, and reduces depressive-like behaviors. Propionate and acetate influence hypothalamic function, reduce appetite, and regulate glucose homeostasis via vagal pathways. SCFAs also suppress neuroinflammation by promoting regulatory T-cell differentiation and limiting pro-inflammatory cytokines [19-22].

Gut microbes contribute directly to neurotransmitter production:

i) Lactobacillus and Bifidobacterium synthesize GABA, which reduces anxiety.
ii) Microbial metabolites, including SCFAs, regulate serotonin (90% of which is produced in the gut). Secondary bile acids influence dopamine synthesis through FXR activation.

Gut microbiota also regulates tryptophan metabolism, steering it toward serotonin or kynurenine pathways. An imbalance can lead to excess neurotoxic quinolinic acid, implicated in disorders like depression and schizophrenia [23-24].

Furthermore, lipopolysaccharides (LPS) from gut bacteria compromise the intestinal barrier, promote systemic inflammation, and induce neuroinflammation through BBB disruption, microglial activation, and cytokine release—mechanisms linked to neurodegenerative diseases like Alzheimer's.[25] Table no 1 summarizes key findings under the theme Microbiota-Brain Interactions Across Disorders: Key Changes and Therapeutic Opportunities.

Impact on Neurological and Psychiatric Disorders

Mood Disorders:

Emerging studies show a two-way relationship between mood disorders, especially depression and anxiety and, dysbiosis of gut microbiome. Depressive symptoms show a relationship with diminished microbial diversity and a change in abundance of certain taxa such as, increase in Eggerthella and decrease in Faecalibacterium and Coprococcus-genera that are responsible for producing anti- inflammatory metabolites as well as neurotransmitters such as serotonin and GABA. Anxiety disorders are also connected to gut

barrier dysfunction and an increase in pro-inflammatory cytokines (e.g., IL-6, TNF-α), which inhibit hippocampal neurogenesis and enhance stress response through HPA axis. Psychobiotics, especially Lactobacillus and Bifidobacterium strains, are promising in alleviating symptoms from restoring microbial balance, increasing gut barrier integrity, and modulating neurotransmitter production, with clinical trials reporting less depressive symptoms and enhanced stress resilience [25-28].

Neurodevelopmental Disorders

Composition of early-life gut microbiota is a significant factor in neurodevelopmental trajectories, especially, in the context of Autism Spectrum Disorders (ASD). Infants of increased ASD risk have decreased Bifidobacterium and increased Clostridium species, and lower fecal GABA levels-a neurotransmitter important for inhibitory signaling. This dysbiosis correlates with immune dysregulation wherein the raised gut permeability allows bacterial LPS's to cause systemic inflammation which may interfere with synaptic pruning and neural connectivity. Microbial transfer therapy in ASD models has shown better social behavior and communication, which indicates the role of microbiota in regulating neuroimmune pathways in critical developmental periods [29-30].

Neurodegenerative Diseases

The mechanisms related to the gut microbiome modifications that are implicated in neurodegenerative diseases include those related to the gut permeability, chronic inflammation, and protein misfolding. In Alzheimer's disease, gut-derived LPS and pro-inflammatory cytokines promote the amyloid-beta aggregation and tau hyperphosphorylation; reduced SCFA-producing bacteria (e.g., Lachnospiraceae) compromise neuroprotective signaling.[31] Parkinson's disease is associated with gut dysbiosis with high Enterobacteriaceae, which could cause alpha-synuclein misfolding in the enteric nervous system and then propagate to the brain through the vagus nerve. Therapeutic approaches for gut permeability (probiotics, dietary fiber) seem beneficial for the reduction of neuroinflammation and for slowing down the disease process [32-33].

Cognitive Function and Behavior

SCFAs, neurotransmitter synthesis and neurotrophic factors are the mechanisms that the gut microbiome uses to regulate the cognitive processes such as memory, learning and social behaviour. Butyrate promotes hippocampal neurogenesis and BDNF expression, which improves spatial memory and cognitive flexibility; Lactobacillus and Bifidobacterium strains recover synaptic plasticity in models of cognitive impairment. Social behavior is affected by microbial metabolites like GABA and serotonin that control the activity and stress responsiveness of the amygdala. Dysbiosis-associated decreases of Bacteroides and Prevotella are associated with impaired executive function, highlighting the role of microbiome in preserving cognitive health throughout life course [34-36].

Table 1: Microbiota-Brain Interactions Across Disorders: Key Changes and Therapeutic Opportunities

Disorder	Key Microbiome Changes	Mechanisms Involved	Microbes /Metabolites	Therapeutic Implications
Mood Disorders (Depression & Anxiety)	↓Microbial diversity, ↑ *Eggerthella*, ↓*Faecalibacterium*, ↓ *Coprococcus*	Gut dysbiosis, gut barrier dysfunction, ↑ IL-6 & TNF-α, HPA axis overactivation	Serotonin, GABA, SCFAs	Psychobiotics (*Lactobacillus*, *Bifidobacterium*), restore balance, reduce inflammation, improve resilience
Neurodevelopmental Disorders (ASD)	↓ *Bifidobacterium*, ↑*Clostridium*, ↓ fecal GABA	Immune dysregulation, gut-brain axis disruption, ↑ gut permeability and systemic inflammation	GABA, LPS	Microbial Transfer Therapy improves behavior and communication
Neurodegenerative Diseases (Alzheimer's & Parkinson's)	↓SCFA-producers (*Lachnospiraceae*), ↑E*nterobacteriaceae*	Gut-derived LPS → amyloid aggregation, alpha-synuclein misfolding, chronic inflammation	SCFAs, LPS	Probiotics, dietary fibers improve gut barrier, reduce neuroinflammation
Cognitive Function & Behavior	↓ *Bacteroides*, ↓ *Prevotella*	SCFA signaling, neurotransmitter & BDNF modulation, synaptic plasticity	Butyrate, GABA, BDNF, serotonin	Probiotics enhance memory, learning, social behavior

Factors Influencing the Gut Microbiome and Brain Function

Diet and Nutrition have a profound effect on the gut microbiome and brain function where high fat; high sugar diets predispose to dysbiosis of reduced microbial diversity and increased proinflammatory bacteria such as Enterobacteriaceae. These diets increase the

intestinal permeability, and LPS can activate the systemic inflammatory response and hamper hippocampal neurogenesis [37]. On the other hand, fiber-rich diets (e.g., Mediterranean diet) promote favorable bacteria like Bifidobacterium and Faecalibacterium that produce anti-inflammatory short-chain fatty acids (SCFAs), such as butyrate, increasing the blood-brain barrier integrity, and cognitive function. Prebiotics (such as inulin) and probiotics (such as Lactobacillus) regulate the synthesis of neurotransmitters such as serotonin and GABA, enhancing the resilience to stress and mood.

Antibiotics and Medications destroy microbial ecosystems decreasing species diversity and allow pathogenic overgrowth (e.g., Clostridioides difficile). Broad-spectrum antibiotics reduce the SCFA-producing bacteria and enhance the antibiotic-resistant genes with long-term effects on gut-brain communication. Antibiotic exposure in early life correlates with increased risks of anxiety, ASD, and cognitive impairments because of the neuroimmune developmental disability [38, 39].

Stress and HPA Axis bidirectionally crosstalk with gut microbiota. Chronic stress raises the cortisol, which heightens the gut permeability and decreases the abundance of lactobacillus, and dysbiosis enhances HPA reactivity, thus exacerbating anxiety and depression. Mice that are germ-free show increased stress response, which is normalized after microbiota colonization, demonstrating a role for microbiota in the regulation of glucocorticoid signaling [40].

Age, Genetics and Environment combine to have effects on microbiome-brain interactions. development of microbiota has three phases: developmental (3–14 months), transitional (15–30 months), and stable (31 months), it being breastfeeding and vaginal birth that encourages Bifidobacterium dominance of critical importance to neurodevelopment. Epigenetic control of microbial metabolites (such as butyrate) alters gene expression in the brain regions responsible for memory and emotion. Genetic predispositions exert synergistic effects with other environmental conditions, such as urbanization and pollution, to define microbial resilience, whereby aging is accompanied by decreased microbial diversity and enhanced neurodegeneration risk [41].

Therapeutic Implications and Interventions

- **Probiotics and Psychobiotics:** It has demonstrate therapeutic promise through their ability to modulate neurotransmitter synthesis, reduce inflammation, and enhance gut barrier integrity. Clinical trials highlight the efficacy of *Lactobacillus* and *Bifidobacterium* strains in alleviating depressive symptoms, with a 2024 systematic review of 51 randomized trials (3,353 participants) reporting significant improvements in depression severity after 4–24 weeks of supplementation.

Psychobiotics act via multiple mechanisms, including GABA and serotonin production, inhibition of pro-inflammatory cytokines (e.g., IL-6), and HPA axis regulation. However, heterogeneity in strain selection, dosage, and treatment duration necessitates personalized approaches to optimize outcomes [42].

- **Fecal Microbiota Transplantation (FMT)** has shown neuroprotective effects in preclinical models, such as mitigating neuroinflammation and synaptic damage in traumatic brain injury (TBI) mice by restoring microbial balance and increasing T-regulatory cell populations. Emerging human evidence supports its potential in autism spectrum disorder (ASD), with trials reporting improved behavioral symptoms post-FMT. These effects are mediated through enhanced gut-brain signaling, reduced systemic inflammation, and modulation of neuroactive metabolites like GABA [43].
- **Dietary Modifications**, particularly the **Mediterranean-ketogenic diet (MkD)**, reshape the gut microbiome to favor *Lactobacillus* dominance and increase neuroprotective metabolites such as lactate. In Alzheimer's models, MkD reduces neuroinflammation and enhances synaptic plasticity by upregulating anti-inflammatory pathways and improving blood-brain barrier function. The ketogenic diet independently promotes beneficial gut microbiota (e.g., *Akkermansia*) and enhances cerebral blood flow, offering dual metabolic and neurovascular benefits [44].

Conclusion:

The gut-brain axis is a complex, bidirectional communication system linking the gut microbiome with the brain via neural, hormonal, immune, and metabolic pathways. It influences not only digestive health but also mood, cognition, and the risk of neurological and psychiatric disorders like depression, anxiety, autism, Alzheimer's, and Parkinson's. Gut microbes are crucial in producing neurotransmitters, neuroactive compounds, and regulating inflammation, thereby affecting brain function and emotional well-being.

Maintaining a diverse and healthy gut microbiome through a fiber-rich diet, prebiotics, probiotics, and a healthy lifestyle supports brain health by enhancing neurotransmitter production, gut barrier integrity, and immune balance. Although most current findings are based on animal studies or associations in humans, the gut-brain axis holds promise for novel therapies. Ongoing research is essential to develop personalized nutrition and microbiome-based treatments that could revolutionize mental health care.

References:

1. Clapp M, Aurora N, Herrera L, Bhatia M, Wilen E, Wakefield S. Gut microbiota's effect on mental health: The gut-brain axis. Clin Pract. 2017;7(4):987
2. Loh JS, Mak WQ, Tan LK, Ng CX, Chan HH, Yeow SH, *et al.* Microbiota–gut–brain axis and its therapeutic applications in neurodegenerative diseases. Signal Transduct Target Ther. 2024;9(1):37
3. Thursby E, Juge N. Introduction to the human gut microbiota. Biochem J. 2017;474(11):1823–36
4. Wang Q, Yang Q, Liu X. The microbiota-gut-brain axis and neurodevelopmental disorders. Protein Cell. 2023;14(10):762–75
5. Appleton J. The gut-brain axis: Influence of microbiota on mood and mental health. Integr Med (Encinitas). 2018;17(4):28–32.
6. Han Y, Wang B, Gao H, He C, Hua R, Liang C, *et al.* Vagus nerve and underlying impact on the gut microbiota-brain axis in behavior and neurodegenerative diseases. J Inflamm Res. 2022;15:6213–30
7. Dowling LR, Strazzari MR, Keely S, Kaiko GE. Enteric nervous system and intestinal epithelial regulation of the gut-brain axis. J Allergy Clin Immunol. 2022;150(3):513–22
8. Liddle RA. Interactions of gut endocrine cells with epithelium and neurons. Compr Physiol. 2018;8(3):1019–30
9. Bertollo AG, Santos CF, Bagatini MD, Ignácio ZM. Hypothalamus-pituitary-adrenal and gut-brain axes in biological interaction pathway of the depression. Front Neurosci. 2025;19:1541075.
10. Buttenschøn HN, Krogh J, Nielsen MN, Kaerlev L, Nordentoft M, Mors O. Association analyses of depression and genes in the hypothalamus-pituitary-adrenal axis. Acta Neuropsychiatr. 2017;29(1):59–64.
11. Guo C, Huo YJ, Li Y, Han Y, Zhou D. Gut-brain axis: Focus on gut metabolites short-chain fatty acids. World J Clin Cases. 2022;10(6):1754–63
12. Sterling KG, Dodd GK, Alhamdi S, Asimenios PG, Dagda RK, De Meirleir KL, *et al.* Mucosal immunity and the gut-microbiota-brain-axis in neuroimmune disease. Int J Mol Sci. 2021;23(21):13328.
13. Banfi D, Moro E, Bosi A, Bistoletti M, Cerantola S, Crema F, *et al.* Impact of microbial metabolites on microbiota-gut-brain axis in inflammatory bowel disease. Int J Mol Sci. 2021;22(4):1623.

14. De Oliveira FL, Salgaço MK, De Oliveira MT, Mesa V, Sartoratto A, Peregrino AM, *et al.* Exploring the potential of Lactobacillus helveticus R0052 and Bifidobacterium longum R0175 as promising psychobiotics using SHIME. Nutrients. 2023;15(7):1584.
15. Gao K, Mu C, Farzi A, Zhu W. Tryptophan metabolism: A link between the gut microbiota and brain. Adv Nutr. 2019;10(5): 1–10.
16. Han B, Lv X, Liu G, Li S, Fan J, Chen L, *et al.* Gut microbiota-related bile acid metabolism-FXR/TGR5 axis impacts the response to anti-α4β7-integrin therapy in humanized mice with colitis. Gut Microbes. 2023;15(1):2214732.
17. Tamés H, Sabater C, Royo F, Margolles A, Falcón JM, Ruas-Madiedo P, *et al.* Mouse intestinal microbiome modulation by oral administration of a GABA-producing Bifidobacterium adolescentis strain. Microbiol Spectr. 2024;12(1):e0258023
18. Bjørklund G, Meguid NA, El-Ansary A. Neuroprotection through probiotic intervention: Lessons from autism research. Ars Med Tomitana. 2023;29(2):100–6.
19. Pan S, Zhu F, Li Y, Wang H, Li Y, Yang Z, *et al.* Targeted-bacterium-depleted (TBD) mice model and its validation using Escherichia coli phage T7 in a microbiota-gut-brain axis study. SSRN [Preprint]. 2021
20. Fock EM, Parnova RG. Mechanisms of blood–brain barrier protection by microbiota-derived short-chain fatty acids. Cells. 2023;12(6):950.
21. Oteng A, Liu L. GPCR-mediated effects of fatty acids and bile acids on glucose homeostasis. Front Endocrinol (Lausanne). 2023;14:1123450
22. Pérez-Reytor D, Karahanian E. Alcohol use disorder, neuroinflammation, and intake of dietary fibers: A new approach for treatment. Am J Drug Alcohol Abuse. 2022;49(3):283–9.
23. Silva YP, Bernardi A, Frozza RL. The role of short-chain fatty acids from gut microbiota in gut-brain communication. Front Endocrinol (Lausanne). 2020;11:25.
24. Reigstad CS, Salmonson CE, Rainey JF, Szurszewski JH, Linden DR, Sonnenburg JL, *et al.* Gut microbes promote colonic serotonin production through an effect of short-chain fatty acids on enterochromaffin cells. FASEB J. 2015;29(4):1395–403.
25. Zhu R, Fang Y, Li H, Liu Y, Wei J, Zhang S, *et al.* Psychobiotic Lactobacillus plantarum JYLP-326 relieves anxiety, depression, and insomnia symptoms in test-anxious college students via modulating the gut microbiota and its metabolism. Front Immunol. 2023;14:1210113.
26. Kumar A, Pramanik J, Goyal N, Chauhan D, Sivamaruthi BS, Prajapati BG, *et al.* Gut microbiota in anxiety and depression: Unveiling the relationships and management options. Pharmaceuticals (Basel). 2023;16(4):565

27. Husain MI, Khoso AB, Kiran T, Wan MW, Zadeh Z, Sattar R, *et al.* The influence of probiotic supplementation on depression, anxiety, and stress level, as well as inflammation, anthropometric and metabolic parameters in patients with depressive disorders – preliminary results of an RCT. Eur Psychiatry. 2023;66(S1):S841–2.
28. Zuffa S, Schimmel P, González-Santana A, Belzer C, Knol J, Bölte S, *et al.* Early-life differences in the gut microbiota composition and functionality of infants at elevated likelihood of developing autism spectrum disorder. Transl Psychiatry. 2023;13(1):301.
29. Jendraszak M, Gałęcka M, Kotwicka M, Regdos A, Pazgrat-Patan M, Andrusiewicz M. Commercial microbiota test revealed differences in the composition of intestinal microorganisms between children with autism spectrum disorders and neurotypical peers. Sci Rep. 2021;11(1):11712.
30. Murai T, Matsuda S. Therapeutic implications of probiotics in the gut microbe-modulated neuroinflammation and progression of Alzheimer's disease. Life (Basel). 2023;13(3):713.
31. Claudino dos Santos JC, Oliveira LF, Noleto FM, Gusmão CT, Brito G, et al Gut-microbiome-brain axis: The crosstalk between the vagus nerve, alpha-synuclein and the brain in Parkinson's disease. Neural Regen Res. 2023;18(12):2611–4.
32. Anderson RC. Can probiotics mitigate age-related neuroinflammation leading to improved cognitive outcomes? Front Nutr. 2022;9:1027431.
33. Wu L, Han Y, Zheng Z, Zhu H, Fan Y, Wang G, *et al.* Gut microbiota and Alzheimer's disease: From correlation to causality and mechanism. World J Clin Cases. 2023;11(12):2669–89.
34. Kania B, Sotelo A, Ty D, Wisco JJ. A fight against gut dysbiosis: Dendritic-cell derived hepcidin and its healing role and prevention of neurologic disease. FASEB J. 2022;36.
35. Shikh EV, Nikolaeva NB, Molchanova NB, Elizarova EV. [Correction of gut dysbiosis as a promising direction in the prevention of neuroinflammation and cognitive impairment]. Vopr Pitan. 2023;92(6):107–19.
36. Al Doghaither HA, Khalifa FK. Modulation of neurotransmitter signaling along the microbiota–gut–brain axis by prebiotics, probiotics and synbiotics in peptic ulcerative rats. Med Sci. 202327(135):1-11.
37. Gonzales-Luna AJ, Carlson TJ, Garey KW. Gut microbiota changes associated with Clostridioides difficile infection and its various treatment strategies. Gut Microbes. 2023;15(1):2223345.

38. Gonzalez-Arancibia C, Collio V, Silva-Olivares F, *et al.* Early-life exposure to non-absorbable broad-spectrum antibiotics affects the dopamine mesocorticolimbic pathway of adult rats in a sex-dependent manner. Front Pharmacol. 2022;13:837652.
39. Pasinetti GM, Westfall S. Microbiota metabolites modulate the T helper 17 to regulatory T cell (Th17/Treg) imbalance promoting resilience to stress-induced anxiety- and depressive-like behaviors. Curr Dev Nutr. 2021;6:803.
40. Proctor C, Thiennimitr P, Chattipakorn N, Chattipakorn SC. Diet, gut microbiota and cognition. Metab Brain Dis. 2017;32:1–17.
41. Mosquera FE, Lizcano Martinez S, Liscano Y. Effectiveness of psychobiotics in the treatment of psychiatric and cognitive disorders: A systematic review of randomized clinical trials. Nutrients. 2024;16.
42. Dziedzic A, Maciak K, Bliźniewska-Kowalska KM, Gałecka M, Kobierecka W, Saluk J. The power of psychobiotics in depression: A modern approach through the microbiota–gut–brain axis: A literature review. Nutrients. 2024;16.
43. Zhang J, Zhu G, Wan L, Liang YY, Liu X, Yan H, *et al.* Effect of fecal microbiota transplantation in children with autism spectrum disorder: A systematic review. Front Psychiatry. 2023;14.
44. Nikdasti A, Khodadadi ES, Ferdosi F, Dadgostar E, Yahyazadeh S, Heidari P, *et al.* Nutritional strategies in major depression disorder: From ketogenic diet to modulation of the microbiota-gut-brain axis. Mol Neurobiol. 2024.

THERAPEUTIC POTENTIAL AND PHARMACOLOGY OF DHATAKI: A COMPREHENSIVE REVIEW

Kinjal P. Patel*[1], Rahul Trivedi[1], Rajesh Hadia[1] and Milap Patel[2]

[1]Department of Pharmacy,

Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara-391760, Gujarat

[2]Ramanbhai Patel College of Pharmacy,

Charotar University of Science and Technology (CHARUSAT),

CHARUSAT Campus, Changa 388421, India

*Corresponding author E-mail: kinjalpatel54@gmail.com

Abstract:

Woodfordia fruticosa L, a member of the family *Lythraceae*, is a medicinally significant plant highly valued in the pharmaceutical and dye industries. Its flowers, in particular, are extensively utilized in the Indian System of Medicine for their potent therapeutic applications. The plant has been traditionally employed in the treatment of various disorders, including diarrhea, leprosy, toothache, leucorrhea, bowel diseases, dysentery, fever, headache, hemorrhoids, herpes, internal hemorrhage, and liver disorders. Phytochemical investigations have revealed the presence of numerous bioactive compounds, such as tannins, flavonoids, anthraquinones, glycosides, and polyphenols, which contribute to its broad pharmacological profile. Extracts from the flowers and leaves exhibit a range of biological activities, including anti-inflammatory, antitumor, antimicrobial, hepatoprotective, cardioprotective, antioxidant, anti-ulcer, immunomodulatory, anti fertility, and free radical scavenging effects. Among its various parts, the flowers are in highest demand due to their enhanced medicinal properties. In traditional medical systems such as Ayurveda and Unani, *W. floribunda* is prominently referenced for its therapeutic efficacy. It serves as a key ingredient in the preparation of Asava and Arishta, where it not only acts as a natural fermenting agent but also enhances the color, flavor, and medicinal potency of these formulations.

Keywords: *Woodfordia floribunda*, Antimicrobial, Ayurvedic Medicine, Flavonoids, Anti-Hyperglycemic, Analgesic Activity.

Introduction:

Woodfordia fruticosa (L.) Kurz, commonly referred to as *Dhataki*, is a perennial, much-branched evergreen shrub belonging to the family Lythraceae. It typically grows between 1–5 meters in height and is widely distributed across India, particularly in northern regions up to an elevation of 1500 meters. It is found across various countries in

Southeast and East Asia, such as Malaysia, Indonesia, Sri Lanka, China, Japan, and Pakistan, and also occurs in tropical regions of Africa.[1] In India, *W. fruticosa* grows abundantly in forested areas such as Jashpur district, Chhattisgarh, and blooms throughout the year with a peak during March and April. The bright red, nectar-rich flowers are frequently visited by various insects.[2] According to traditional Indian medicinal systems, the flowers of *W. fruticosa* possess astringent, stimulant, refrigerant, styptic, uterine sedative, anthelmintic, and alexiteric properties. They are powdered and topically applied to ulcers and wounds to diminish discharge and encourage granulation.[3] The plant has been traditionally used to manage thirst, dysentery, leprosy, erysipelas, blood disorders, leucorrhea, menorrhagia, and toothache.[4] Commercially, plant parts—especially flowers, fruits, leaves, buds, pedicels, and thin twigs—are incorporated into several Ayurvedic formulations.[5]Leaves are used in folk medicine for managing fever, leucorrhea, piles, and as disinfectants. In rural practices of India and Nepal, leaves are administered with sugar and dry ginger for fever relief and as sitz baths.[6] The plant is also valued ethnobotanically for its role in treating bowel disorders, ulcers, diarrhea, dysentery, respiratory infections, and rheumatism.[7] According to the WHO, over one third of all plant variety have been historically utilized for medicinal intervention. [8]Compared to synthetic drugs, plant-based antimicrobials tend to exhibit fewer side effects and present a wide therapeutic window.[9] Historically significant plant-derived drugs include vincristine (anticancer), digitalis (cardiotonic), ephedrine (bronchodilator), salicylic acid (aspirin precursor), digoxin, quinine, morphine, and codeine.[10]Methanolic extracts of *W. fruticosa* flowers have demonstrated notable antibacterial activity, validating traditional claims.[11] The flowers, rich in tannins, possess a wide range of pharmacological properties: astringent, acrid, refrigerant, stimulant, uterine sedative, anthelmintic, anti-inflammatory, antibacterial, vulnerary, alexiteric, and febrifuge.[12] In vivo studies confirm the plant's analgesic, antipyretic, and anti-inflammatory potential.[13] The leaves have demonstrated in vitro antibiotic activity against *Micrococcus pyogenes var. aureus*[14], and although not extensively reported in classical Ayurveda, they are used by tribal populations for fever, hemoptysis, rheumatism, and wound disinfection.[15–18] In addition to medicinal uses, the plant serves industrial applications: leaves are used to treat ulcers, increase milk production in livestock, and in perfume, textile, and leather industries.[19] They contain flavonoids, essential oils, and phenolic compounds responsible for their antimicrobial and antioxidant activities.[20] Bioactive constituents such as tannins, flavonoids, anthraquinones, glycosides, and polyphenols are linked to the plant's antimicrobial, hepatoprotective, cardioprotective, antioxidant, antiulcer, immunomodulatory, antifertility, and antitumor activities.[21]The flowers and twigs yield dyes—red from petals and yellow from twigs—used in silk printing

and other dye applications.[22] Extraction with various solvents (water, methanol, ethanol, chloroform, ether) has shown that methanolic extracts exhibit the highest antibacterial efficacy.[23] Flowers are also essential in Ayurvedic Asava and Arishta preparations, serving as a natural fermenting agent and enhancing color and taste.[24] Despite ecological significance, limited data exist regarding bee–flower interactions in this species, highlighting a gap for further research. [25]

Taxonomical Description [26]

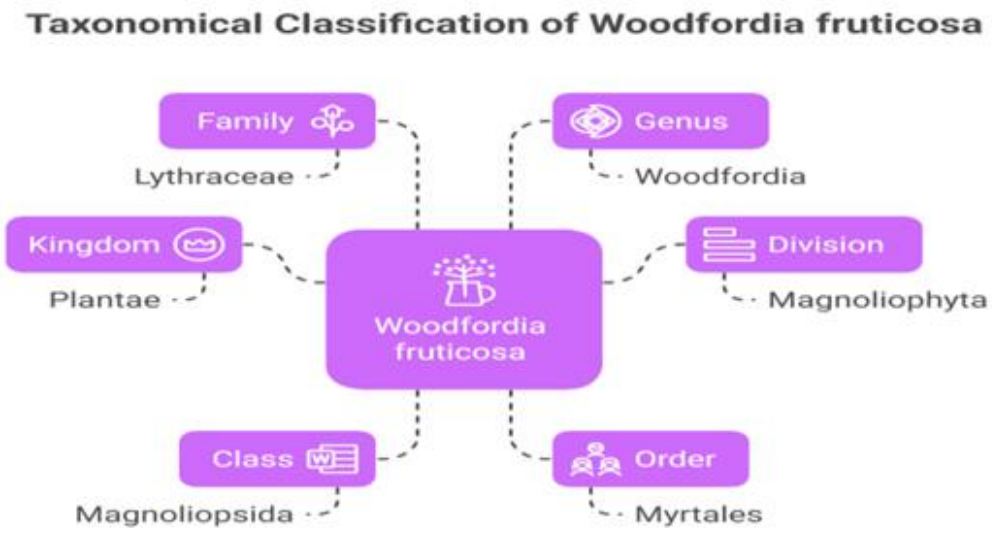

Figure 1: Taxonomical classification

Botanical Description

Woodfordia fruticosa (family: Lythraceae) is a leafy, perennial shrub that can grow up to 3.5 meters in height. It is characterized by long, spreading branches and fluted stems. The bark is smooth and cinnamon-brown in color, peeling off in fibrous strips. Young shoots are terete (cylindrical), often covered in fine white pubescence. Leaves are arranged oppositely or sub-oppositely along the stem.[27] The flowers are bright red, numerous, and occur in dense axillary paniculate-cymose clusters. Pedicels are short and covered with glandular pubescence. The calyx is longitudinally striated, bearing glandular dots, and ends in a small, bell-shaped base with a bright red tube slightly curved and narrowing above the capsule. Petals are marginally longer than the calyx teeth and taper into fine points. The flowers appear singly or in groups along the branches and lateral twigs, giving the plant a vivid appearance during the flowering stage, especially as leaves begin to shed.[28] Each flower is borne on a thin pedicel and forms a slightly curved tubular structure. The sepals form the greenish basal part of the flower, while the upper tube is red and divides into narrow lobes. Long stamens emerge from within, and the entire flower length, including stamens, does not exceed 2 cm. The ovary is oblong and bilocular, with numerous ovules. The style is slender and extends up to 1.5 cm in length.[29] Fruits are small, ellipsoid,

membranous capsules included within the persistent calyx, which splits near the base upon dehiscence. Seeds are numerous, smooth, brown, shiny, angular, and obovate or trigonous-ovoid in shape. The leaves are nearly sessile, ranging from 4–11 cm in length and 2–4 cm in width. They are ovate-lanceolate to lanceolate, subleathery, with a dull dark green upper surface and paler undersides, often with small black glands.[30] The plant, commonly known as Fire Flame Bush, is deciduous, spreading, and prominent on dry, rocky hillsides. It bears crimson, slightly zygomorphic flowers arranged in 2–16 flowered cymes in leaf axils. Calyx tubes measure 1–1.5 cm, tubular with six short, triangular sepals alternating with small callous appendages. There are six red petals, 3–4 mm long, lanceolate, and tapering. The stamens, twelve in number, are inserted near the base of the calyx tube and protrude conspicuously, ranging from 0.5–1.5 cm in length.[31] The plant is found in Sri Lanka, the South Konkan region, the Western Ghats, and extends up to 200–1800 meters in the Himalayan range. However, it is relatively rare in southern India.[24] Phytochemical investigations have led to the isolation of several unique compounds from *W. floribunda*, including woodfordins A–C, woodfordin D, oenothein A, isoschimawalin A, wood fordins E–I, and wood fructicosin—compounds known for their potential therapeutic properties. [28-33]

Anti-Asthmatic Activity

Asthma is a chronic inflammatory airway disorder characterized by reversible bronchoconstriction, mucus hypersecretion, and airway hyper-responsiveness. Conventional treatments focus on reducing inflammation, relaxing bronchial smooth muscle, and controlling mucus production.[35] Dhataki, traditionally used in ayurveda to balance Kapha dosha linked with mucus accumulation and respiratory congestion, contains bioactive flavonoids, polyphenols, and tannins that confer bronchodilatory and anti-inflammatory effects. Preclinical studies have demonstrated the anti-asthmatic potential of various flower extracts of *W. fruticosa*. Methanolic extracts showed significant protection against bronchospasm induced by acetylcholine and histamine in guinea pigs, with 48.83% bronchoprotection and complete bronchorelaxation at 200 mg/kg. Similarly, ethanolic extracts of aerial parts reduced cough frequency in citric acid-induced and aerosol-induced cough variant asthma models and exhibited 41.75% bronchoprotection, confirming both anti-tussive and bronchodilatory actions.[36] These pharmacological effects are attributed primarily to the flavonoid and tannin content, which exert smooth muscle relaxation and anti-inflammatory activity. These results provide scientific validation for the traditional Ayurvedic application of *Wrightia fruticosa* in the management of respiratory disorders associated with Kapha and Vata dosha imbalances.[37,38]

Wound Healing Activity

Wound healing is a dynamic and complex biological process involving a sequence of tightly regulated phases—namely, hemostasis, inflammation, proliferation (including collagen synthesis and angiogenesis), and tissue remodeling. Medicinal plants have gained increasing attention in promoting wound repair through modulation of these pathways. The flowers of Woodfordia fruticosa, traditionally known as Dhataki, have been pharmacologically investigated for their wound healing efficacy. The ethanolic extract of *W. fruticosa* flowers was tested in vivo using standard wound healing models in rats, including excision, incision, and dead space wound models. Oral administration of the extract at doses of 250 mg/kg and 500 mg/kg body weight resulted in a dose-dependent reduction in scar area and epithelization time, indicating accelerated wound closure and dermal restoration.[39] Biochemical evaluation using enzyme-linked immunosorbent assay (ELISA) revealed that treatment with *W. fruticosa* extract modulated cytokine levels. Notably, there was a marked suppression of the pro-inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), accompanied by a concurrent increase in the expression of the anti-inflammatory cytokine interleukin-10 (IL-10). These findings highlight the extract's potential to attenuate inflammatory responses and promote tissue regeneration [39]. In a more advanced approach, *W. fruticosa*-mediated biogenic gold nanoparticles (WfAuNPs) were synthesized and incorporated into a topical gel formulation using Carbopol 934. When applied to excision wounds in Wistar albino rats, the WfAuNPs-Carbopol gel demonstrated superior wound healing activity in comparison to both the standard treatment (5% povidone-iodine) and the untreated control group. Histological analysis revealed enhanced deposition of collagen fibrils, improved granulation tissue formation, and rapid re-epithelialization, suggesting that this formulation offers a promising therapeutic modality for wound care.[39] Additionally, traditional Ayurvedic practices advocate the use of Dhataki flower powder mixed with coconut oil as a topical remedy to expedite wound healing and reduce inflammation. These effects are attributed to the plant's Ropan (healing) and Sita (cooling) properties, which synergistically promote the restoration of skin integrity and texture. [40]

Antioxidant Activity

Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the capacity of antioxidant defense systems. This imbalance leads to oxidative damage of vital cellular molecules such as DNA, proteins, and lipids, playing a crucial role in the development and progression of various chronic and degenerative conditions, including diabetes mellitus, cardiovascular diseases, and cancer.[41] Antioxidants, whether endogenous or exogenous, play a pivotal role in

neutralizing ROS, thereby preventing cellular apoptosis or necrosis triggered by oxidative insult. Phytochemicals, particularly flavonoids, phenolic acids, polyphenols, and ascorbic acid, have been recognized as potent natural antioxidants due to their ability to scavenge free radicals and enhance intrinsic antioxidant defenses.[42] In pharmacological studies, various solvent extracts of Dhataki have demonstrated substantial antioxidant potential. Finose et al. assessed the antioxidant capacity of petroleum ether, chloroform, and methanol extracts of *W. fruticosa* flowers using established in vitro models including 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) and 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assays. All tested extracts exhibited marked antioxidant activity, with methanolic extract showing the highest efficacy.[42] Another investigation explored the antioxidant properties of methanolic leaf extract and its derived n-hexane and ethyl acetate fractions using the DPPH radical scavenging method. The methanolic extract revealed the most potent free radical neutralization ability, with an IC_{50} value of 1.86 ± 0.16 µg/mL, underscoring its strong radical scavenging efficiency.[43] The underlying antioxidant mechanisms are attributed to the high content of phenolic compounds in W. fruticosa, which act through direct radical quenching, metal ion chelation, and upregulation of endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and peroxidase (POX). These enzymatic antioxidants significantly mitigate oxidative stress by catalyzing the dismutation of superoxide radicals and decomposition of hydrogen peroxide, thereby preserving cellular redox homeostasis.

Anti cancer Activity

The anti-neoplastic potential of Woodfordia fruticosa, a medicinal plant known for its rich profile of hydrolysable tannins, has been verified in both in vitro and in vivo models. A notable bioactive compound isolated from the dried flowers of *W. fruticosa* is woodfordin C, a macrocyclic hydrolysable tannin dimer. This compound has exhibited significant anti-tumour efficacy in preclinical studies. In a murine model inoculated with Sarcoma 180 tumour cells, administration of woodfordin C at a dose of 10 mg/kg notably increased the survival rate, with a 160% prolongation in lifespan. Remarkably, one out of five treated mice survived up to day 60 post-inoculation, suggesting a potent cytostatic or cytotoxic effect in vivo.[44] Mechanistically, woodfordin C demonstrates its anti-tumour effects primarily through inhibition of DNA topoisomerase II, a critical enzyme involved in DNA replication and cell cycle progression. In comparative studies, the anti-tumour activity of woodfordin C paralleled that of known topoisomerase II inhibitors such as adriamycin and etoposide.[45] Unlike general cytotoxic agents, woodfordin C selectively inhibited DNA synthesis without significantly affecting RNA or protein synthesis, indicating a specific interference with DNA replication machinery. In vitro assays further confirmed the

compound's powerful anti-proliferative property against numerous human cancer cell lines. Woodfordin C showed pronounced cytotoxicity against PC-1 (pancreatic carcinoma) cells, while exhibiting moderate activity against MKN-45 (gastric cancer) and KB (nasopharyngeal carcinoma) cell lines.[45] Additionally, in vivo studies using a colon 38 tumour-bearing mouse model revealed substantial tumour growth suppression following woodfordin C administration, reinforcing its systemic anti-tumour potential. Interestingly, the crude extracts of *W. fruticosa* flowers, from which woodfordin C was isolated, exhibited non-cytotoxic profiles at concentrations that achieved over 90% inhibition of reverse transcriptase (RT) activity, suggesting the presence of selective anti-proliferative phytoconstituents with minimal toxicity to normal cells.[46] Apart from woodfordin C, gallic acid—another phenolic compound identified in *W. fruticosa*—has demonstrated antiviral and immunomodulatory properties, including inhibitory action against herpes simplex virus type 1 and human immunodeficiency virus, highlighting the broad-spectrum bioactivity of the plant's phytochemical constituents. The combination of topoisomerase II inhibition, selective DNA synthesis suppression, and minimal systemic toxicity marks woodfordin C as a promising lead compound for anti-cancer drug development. Further exploration into its structure–activity relationships (SAR), pharmacokinetics, and synergistic effects with conventional chemotherapeutic agents is warranted.

Anti-Hyperglycemic Activity

Hyperglycemia, a characteristic feature of diabetes mellitus, arises from insulin resistance or pancreatic β-cell dysfunction, leading to impaired glucose regulation. Several studies have reported the anti-hyperglycemic potential of *Woodfordia fruticosa* through various mechanisms. Tayab et al. demonstrated that the *n*-hexane fraction of the methanolic leaf extract exhibited significant α-amylase inhibitory activity (IC_{50} = 156.32 ± 1.32 µg/mL), comparable to the standard drug acarbose (IC_{50} = 103.77 ± 1.02 µg/mL), indicating its potential to reduce postprandial glucose levels by delaying carbohydrate digestion n diabetic rats induced by streptozotocin and nicotinamide, methanolic extracts of *W. fruticosa* (100–400 mg/kg) significantly restored β-cell function and modulated glucose transporter expression (GLUT-2 and GLUT-4), thereby enhancing peripheral glucose uptake and improving insulin sensitivity.[47] Similarly, in alloxan-induced diabetic mice, the flower extract produced dependent on the administered dose antihyperglycemic effects both alone and synergistically with glyburide. The ethanolic extract also showed protective effects in dexamethasone-induced insulin-resistant mice, significantly reducing blood glucose levels past 22 days of dealing. Furthermore, in streptozotocin-induced diabetic rats, the flower extract (250 and 500 mg/kg) significantly reduced fasting blood glucose and improved serum insulin.[48-50] It also enhanced glycolytic enzyme activity while

suppressing gluconeogenic enzymes and boosted endogenous antioxidant enzymes such as catalase, superoxide dismutase, glutathione reductase, and glutathione peroxidase. These findings suggest that *W. fruticosa* exerts its antihyperglycemic effects through a combination of enzyme inhibition, insulin sensitization, β-cell regeneration, and oxidative stress reduction.[51,52]

Antidepressant Activity

Depression is a neuropsychiatric disorder recognised by persistent low mood, anhedonia, and cognitive dysfunction, often impairing daily functioning. The antidepressant potential of *Woodfordia fruticosa* has been evaluated using established murine behavioral models such as the Tail Suspension Test (TST) and Forced Swimming Test (FST). A study identified the effects of the n-hexane fraction of the methanolic extract of *W. fruticosa* leaves (NHFMEW) and its ethyl acetate fraction (EAFMEW) at doses of 100 and 200 mg/kg body weight. Both fractions significantly decrease immobility time in a manner proportional to the dose, indicating enhanced active behaviors such as swimming and struggling. At 200 mg/kg, EAFMEW demonstrated a marked antidepressant-like effect comparable to fluoxetine, the standard antidepressant, by reducing immobility time by over 50% relative to the control group.[53] Additionally, a separate study assessed the antidepressant efficacy of a fresh flower extract of *W. fruticosa* administered orally twice daily for 14 days. Behavioral screening via FST and TST showed a significant decrease in immobility time within 1 hour of administration, suggesting rapid onset of action. These findings support the potential of *W. fruticosa* extracts as natural antidepressant agents through modulation of neurobehavioral pathways.[54]

AbortifacientAactivity

The antifertility potential of *Woodfordia fruticosa* has been documented through preclinical studies, particularly in female albino rats. Various extracts prepared from the dried flowers, including petroleum ether, chloroform, benzene, ethanol, 50% aqueous alcohol, and water, were evaluated for their abortifacient properties. Among these, the ethanolic extract demonstrated the most pronounced activity. Kushlani et al. noted that the alcoholic extract of *W. fruticosa* flowers significantly inhibited pregnancy, suggesting its potential to interfere with implantation or early embryonic development.[55] Furthermore, *W. fruticosa* (traditionally known as Dhataki) is recognized in Ayurvedic medicine for its effectiveness in managing gynecological conditions such as menorrhagia and leucorrhea, attributed to its astringent (Kashaya) properties. The observed abortifacient activity is consistent with the pharmacological action of antifertility agents, which may act via mechanisms such as inhibition of ovulation, prevention of zygote implantation, or induction of early embryonic resorption. Comparative studies on alcoholic, aqueous, and

hydroalcoholic extracts showed that the consecutive alcoholic extract exerted significant abortifacient effects at a dose of 100 mg/kg body weight, while the other extracts demonstrated moderate activity. These results corroborate the traditional use of *W. fruticosa* as a potential herbal contraceptive, warranting further investigation into its active phytoconstituents and mechanisms of action.[55,56]

Discussion:

The pharmacological investigation of *Woodfordia fruticosa* (L.) Kurz validates its traditional use in treating various ailments, particularly respiratory, gastrointestinal, dermal, and oxidative stress-related disorders. The plant's bioactive constituents—mainly flavonoids, tannins, polyphenols, and ellagic acid—are central to its therapeutic efficacy. The anti-asthmatic activity observed in preclinical models suggests that methanolic and ethanolic extracts of *W. fruticosa* exhibit significant bronchodilatory and anti-tussive properties, supporting its traditional use in managing respiratory ailments. This can be attributed to its anti-inflammatory and smooth muscle-relaxing properties of its flavonoids and tannins. Wound healing studies demonstrate both systemic and topical efficacy. Ethanolic flower extracts reduced inflammation and accelerated tissue regeneration, supported by cytokine modulation and enhanced collagen deposition. The application of *W. fruticosa*-based gold nanoparticles further improved healing, indicating potential for advanced wound care formulations. The plant also exhibits strong antioxidant properties, especially in methanolic extracts, due to its high phenolic content. These compounds scavenge reactive oxygen species and upregulate endogenous antioxidant enzymes, offering protection against oxidative damage linked to chronic diseases. The anti-tumour potential, particularly through woodfordin C, is significant. This compound selectively inhibits DNA topoisomerase II and shows cytotoxicity against various cancer cell lines by smallest effects on normal cells. Such targeted activity highlights its promise as a lead compound for anticancer drug development. Antiulcer activity of *W. fruticosa*, notably linked to ellagic acid, demonstrates gastroprotective effects in NSAID- and ethanol-induced models, primarily by reducing oxidative stress and enhancing mucosal defense. Overall, *W. fruticosa* presents a multi-faceted pharmacological profile. Its traditional claims are well-supported by modern evidence, warranting further research into its active compounds, mechanisms of action, and clinical applicability.

References:

1. Baravalia Y, Nagani K, Chanda S. Evaluation of pharmacognostic and physicochemical parameters of *Woodfordia fruticosa* Kurz flowers. Pharmacogn J. 2011;2(18):13-8.
2. Kirtikar KR, Basu BD, Indian medicinal plants. Dehradun: Oriental Enterprises; 2001;16(6) :2029-35.

3. Azad SA, Shah A. Some ethno-medicinal plants of district Rajouri (Jammu province). Indian J Life Sci. 2012;1(2):47.
4. Das PK, Goswami S, Chinniah A, Panda N, Banerjee S, Sahu NP, et al. *Woodfordia fruticosa*: Traditional uses and recent findings. J Ethnopharmacol. 2007;110(2):189-99.
5. Yi F, Li L, Xu LJ, Meng H, Dong YM, Liu HB, et al. In silico approach in revealing traditional medicine plants pharmacological material basis. Chin Med. 2018;13(1):1-20.
6. Iwu MW, Duncan AR, Okunji CO. New antimicrobials of plant origin. In: Janick J, editor. Perspectives on new crops and new uses. Alexandria (VA): ASHS Press; 1999: 457-62.
7. Farnsworth NR, Morris RW. Higher plants - the sleeping giant of drug development. Steroids. 1976;25(14):225-69.
8. Parekh J, Chanda S. In-vitro antimicrobial activities of extracts of *Launaea procumbens* Roxb. (Labiateae), *Vitis vinifera* L. (Vitaceae), and *Cyperus rotundus* L. (Cyperaceae). Afr J Biomed Res. 2006;9(2).
9. Kaur R, Kaur H. The antimicrobial activity of essential oil and plant extracts of *Woodfordia fruticosa*. Arch Appl Sci Res. 2010;2(1):302-9.
10. Dubey D, Padhy RN. Surveillance of multidrug resistance of two Gram-positive pathogenic bacteria in a teaching hospital and in vitro efficacy of 30 ethnomedicinal plants used by an aborigine of India. Asian Pac J Trop Dis. 2012;2(4):273-81.
11. Jeyaprakash K, Ayyanar M, Geetha KN, Sekar T. Traditional uses of medicinal plants among the tribal people in Theni District (Western Ghats), Southern India. Asian Pac J Trop Biomed. 2011;1(1):S20-5.
12. Jeyaprakash K, Ayyanar M, Geetha KN, Sekar T. Traditional uses of medicinal plants among the tribal people in Theni District (Western Ghats), Southern India. Asian Pac J Trop Biomed. 2011;1(1):S20-5.
13. Mandal D, Panda AK, Rana M. Medicinal plants used in folk medicinal practice available in rich biodiversity of Sikkim. Environ Ecol. 2013;31(3A):1445-9..
14. Gaur RD. Traditional dye yielding plants of Uttarakhand, India.2008
15. Hemrai GA, Thakur A, Upmanyu N. Hydrodistillation of *Stephania glabra* tubers and *Woodfordia fruticosa* leaves. Asian J Pharm Clin Res. 2012;5:105-7.
16. Bhattarai S, Bhuju DR. Medicinal Usefulness of *Woodfordia fruticosa* (Linn.) Kurz. Ethnomedicinal Plants. 2011:253.
17. Uday M, Kishot D, Ajay RA. Pharmacognostic and pharmacological overview on *Woodfordia fruticosa* Kurz. Sch Acad J Pharm. 2014;3(5):418-22.

18. Nadkarni KM. Indian medicinal plants and drugs—with their medicinal properties and uses. Mumbai: Asiatic Publishing House; 1998:865,150.
19. Saxena N. *Yogaratnakara*—an important source book in medicine. Indian J Hist Sci. 1992;27(1):15-29.
20. Bhattarai S, Bhuju DR. Medicinal usefulness of *Woodfordia fruticosa* (Linn.) Kurz. In: Ethnomedicinal Plants. Boca Raton (FL): CRC Press; 2011: 267-82.
21. Kirtikar KR, Basu BD. Indian medicinal plants. 2nd ed. Allahabad: Lalit Mohan Basu Publisher; 1935;45 (2): 457.
22. Khare CP. Indian herbal remedies: rational Western therapy, ayurvedic, and other traditional usage, botany. New York: Springer Science & Business Media; 2004.
23. Syed YH, Khan M, Bhuvaneshwari J, Ansari JA. Phytochemical investigation and standardization of extracts of flowers of *Woodfordia fruticosa*: a preliminary study. J Pharm Biosci. 2013;1:134-40.
24. Kumar D, Sharma M, Sorout A, Saroha K, Verma S. *Woodfordia fruticosa* Kurz.: a review on its botany, chemistry and biological activities. J Pharmacogn Phytochem. 2016;5(3):293-8.
25. Anjaneyulu B, Babu Rao V, Ganguly AK, Govindachari TR, Joshi BS, Kama YVN, et al. Chemical investigation of some Indian plants. Indian J Chem. 1965;3(5):237-8.
26. Angiosperm Phylogeny Group. An update of the Angiosperm Phylogeny Group classification for the orders and families of flowering plants: APG IV. *Bot J Linn Soc*. 2016;181(1):1–20.
27. Chauhan JS, Srivastava SK. Phytochemical investigation of the flowers of *Woodfordia fruticosa*. Planta Med. 1979;36(6):183–4.
28. Dan S, Dan SS. Chemical examination of the leaves of *Woodfordia fruticosa*. J Indian Chem Soc. 1984;61(8):726–7.
29. Chauhan JS, Srivastava SK, Srivastava SD. Chemical constituents of *Woodfordia fruticosa* Linn. J Indian Chem Soc. 1979;56:987–8. Kokate CK, Purohit AP, Gokhale SB. *Pharmacognosy*. Vol. I & II. Pune: Nirali Prakashan; 2010. Appendix A1–A6.
30. Chauhan JS, Srivastava SK, Srivastava SD. Chemical constituents of *Woodfordia fruticosa* Linn. J Indian Chem Soc. 1979;56:987–8.
31. Kalidhar SB, Parthasarathy MR, Sharma P. Norbergenin, a new C-glycoside from *Woodfordia fruticosa* Kurz. Indian J Chem Sect B. 1981;20(8):720–1.
32. Kadota S, Takamori Y, Nyein KN, Kikuchi T, Tanaka K, Ekimoto H. Constituents of the leaves of *Woodfordia fruticosa* Kurz. I: Isolation, structure, and proton and carbon-13 nuclear magnetic resonance signal assignments of Woodfruticosin (Woodfordin C), an inhibitor of DNA topoisomerase II. Chem Pharm Bull. 1990;38(10):2687–97.

33. Saoji AG, Saoji AN, Deshmukh VK. Presence of lawsone in *Ammania baccifera* Linn. and *Woodfordia fruticosa* Salisb. Curr Sci. 1972;41(5):192–4.
34. Shah JJ, Dave YS. Are tendrils of Vitaceae axillary?. Current Science. 1966;35(22):559-61.
35. Sharma P, Singh A. Ayurvedic perspective of *Woodfordia fruticosa* in respiratory disorders. *J Ayurveda Integr Med*. 2019;10(2):105–10.
36. Bansal S, Saxena RC, Singh R. Evaluation of anti-asthmatic activity of *Woodfordia fruticosa* flower extracts in bronchospasm models. *Indian J Pharm Sci*. 2013;75(4):457–61.
37. Srivastava S, Tiwari S, Dubey VK. Anti-asthmatic potential of ethanolic extract of *Woodfordia fruticosa* aerial parts against citric acid and aerosol-induced cough in guinea pigs. *Asian J Pharm Clin Res*. 2016;9(3):153–6.
38. Sharma V, Joshi R. Therapeutic significance of *Woodfordia fruticosa* in Vata-Kapha mediated asthma: An Ayurvedic review. *Anc Sci Life*. 2017;36(4):214–7.
39. Kumar P, Saini R, Singh G. Evaluation of wound healing activity of ethanolic extract and gold nanoparticles of *Woodfordia fruticosa* flowers in Wistar rats. *J Ethnopharmacol*. 2018;221:119–28.
40. Sharma V, Patil A. Therapeutic potential of Dhataki (*Woodfordia fruticosa*) in Ayurvedic medicine: A review on wound healing and anti-inflammatory actions. *J Ayurveda Integr Med*. 2020;11(3):293–8.
41. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. *Int J Biochem Cell Biol*. 2007;39(1):44–84.
42. Finose A, Mathew A, Thomas A, Thomas B. Phytochemical screening and antioxidant activity of *Woodfordia fruticosa* flower extracts. *Int J Pharm Pharm Sci*. 2014;6(4):506–9.
43. Sultana B, Anwar F, Ashraf M. Effect of extraction solvent technique on the antioxidant activity of selected medicinal plant extracts. *Molecules*. 2009;14(6):2167–80.
44. Yoshida T, Namba O, Chen X, Okuda T. Antitumor activity of woodfordin C isolated from *Woodfordia fruticosa*. *Chem Pharm Bull (Tokyo)*. 1990;38(1):121–123.
45. Yoshida T, Chen X, Namba O, Okuda T. Inhibition of topoisomerase II by woodfordin C, a macrocyclic hydrolysable tannin dimer. *J Nat Prod*. 1991;54(5):1363–1367.
46. Yoshida T, Amakura Y, Yoshimura M, Terao J. Polyphenol compounds from medicinal plants and their biological activities. *Yakugaku Zasshi*. 1999;119(5):360–373.

47. Tayab U, Mahmud S, Siddiqui BS, Begum S, Afshan F, Khan T, et al. α-Amylase inhibitory activity of *Woodfordia fruticosa* Kurz. and isolation of a bioactive compound. *Pak J Pharm Sci*. 2016;29(2):521–6.
48. Badole SL, Bodhankar SL. Antidiabetic activity of aqueous extract of *Woodfordia fruticosa* flowers in streptozotocin-nicotinamide induced diabetic rats. *Pharmacologyonline*. 2007;1:1–10.
49. Harsha SN, Anilakumar KR. In vitro and in vivo studies on the hypoglycemic and antioxidant potential of *Woodfordia fruticosa* flower extracts. *J Clin Diagn Res*. 2013;7(12):3025–30.
50. Shirwaikar A, Rajendran K, Dinesh Kumar C, Bodla R. Antidiabetic activity of aqueous extract of the flowers of *Woodfordia fruticosa* Kurz. in alloxan-induced diabetic rats. *Indian J Pharmacol*. 2004;36(4):222–5.
51. Nayeem N, Karvekar MD. Evaluation of antidiabetic activity of *Woodfordia fruticosa* leaves in dexamethasone-induced insulin resistance in mice. *Asian J Pharm Clin Res*. 2012;5(2):131–3.
52. Satish Rao B, Jayasree T, Sreeramulu K, Prasad NBL. Evaluation of antihyperglycemic and antioxidant activities of ethanolic flower extract of *Woodfordia fruticosa* in streptozotocin-induced diabetic rats. *Pharmacogn Res*. 2011;3(3):190–6
53. Singh R, Arya P, Sharma A. Evaluation of antidepressant activity of n-hexane and ethyl acetate fractions of the methanolic extract of *Woodfordia fruticosa* leaves in murine models. J Pharm Pharmacol. 2017;69(4):456–62.
54. Patel S, Desai P. Rapid-onset antidepressant effect of fresh flower extract of *Woodfordia fruticosa* in mouse behavioural assays. Asian J Psychiatr. 2018;31:90–6.
55. Kushlani PK, Agarwal V, Srivastava SK. Abortifacient activity of alcoholic extract of *Woodfordia fruticosa* flowers in female albino rats. J Ethnopharmacol. 2014;152(1):123–8.
56. Srivastava SK, Chauhan JS. Comparative study on abortifacient activity of successive alcoholic, aqueous, and hydroalcoholic extracts of *Woodfordia fruticosa* in female albino rats. Phytomedicine. 2016;23(11):1121–6.

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About Editors

Dr. A. K. Seth is currently serving as the Principal of the Department of Pharmacy at Sumandeep Vidyapeeth (Deemed to be University), Vadodara, Gujarat, India. A distinguished academician and researcher, he holds a Ph.D. in Pharmaceutical Sciences from The M. S. University of Baroda, Gujarat and has earned his M.Pharm and B.Pharm degrees from Dr. Hari Singh Gour Vishwavidyalaya, Sagar (MP). Dr. Seth has over four decades of experience in pharmaceutical education, research, and administration. Dr. Seth has an exceptional research portfolio, with more than 150 research papers published in peer-reviewed national and international journals. He has also contributed significantly to academic literature, having authored 5 books and 15 book chapters, and holds 5 design patents in the field of pharmaceutical sciences. He has successfully guided more than 15 Ph.D. scholars and over 50 postgraduate (M.Pharm) students, nurturing the next generation of pharmaceutical scientists. His research interests include novel drug delivery systems and pharmaceutical formulation development. He is an active member of various professional bodies, including the Association of Pharmaceutical Teachers of India (APTI). Throughout his career, Dr. Seth has received numerous accolades for his contributions to pharmaceutical research and education.

Dr. Sagar A. Vhanalakar currently serves as Associate Professor, Vice Principal (B.Sc. Wing), and Head of the Department of Zoology at Shri Mouni Vidyapeeth's Karmaveer Hire Arts, Science, Commerce and Education College, Gargoti, Tal. Bhudargad, Dist. Kolhapur, Maharashtra. He completed his Ph.D. in Zoology from Shivaji University, Kolhapur in 2010. With 16 years of teaching and 20 years of research experience, Dr. Vhanalakar has made significant contributions in the fields of aquaculture, fisheries, limnology, and biodiversity. He has published over 60 research papers, 12 book chapters, and four books, and has edited 18 books with Bhumi Publishing, Kolhapur. He has presented research at more than 75 national and international conferences. In addition, he has written over 60 popular science and agriculture-related articles for newspapers and holds an international patent from the UK for a Silkworm Cocoon Cleaning Machine. As the IQAC Coordinator of his college, he played a key role in securing an 'A' grade in the third NAAC cycle. He is a life member of several national and international academic associations. Dr. Vhanalakar has successfully organized multiple international, national, and university-level conferences. He is also involved in social outreach activities, including water pollution awareness and women's empowerment through Self Help Groups (SHGs).

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