HERBAL MEDICINE FOR HEALTHY AGING AND CHRONIC DISEASES

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Preface

Global population aging has become a defining challenge of contemporary healthcare, with increased life expectancy accompanied by a rising burden of chronic, age-related diseases. Conditions such as neurodegeneration, cardiovascular disease, metabolic disorders, immune dysfunction, and chronic inflammation significantly affect functional capacity and quality of life in older adults. Addressing these interconnected challenges requires integrative approaches that emphasize prevention, biological resilience, and maintenance of physiological function throughout the aging process.

Herbal medicine has a long history of use in promoting health and longevity across diverse medical traditions. Increasing scientific interest has led to systematic investigations of medicinal plants using modern pharmacological, biochemical, and clinical methodologies. This convergence of traditional knowledge with contemporary biomedical research has enabled clearer mechanistic understanding, improved standardization, and more rigorous evaluation of herbal therapies relevant to healthy aging. This book provides a structured and evidence-informed exploration of herbal medicine in the context of aging and chronic disease. It progresses from foundational concepts of aging biology and ethnobotany to disease-specific herbal interventions and safety considerations. By integrating mechanistic insights, preclinical evidence, and emerging clinical perspectives, this book aims to support the responsible and scientifically grounded use of herbal medicine as a complementary strategy for promoting healthy aging and reducing the burden of chronic diseases.

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Chapter 1
Understanding Aging: Biological Mechanisms and Modern Theories

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ABSTRACT

Aging is a complex, multifaceted biological phenomenon characterized by progressive loss of structural and functional integrity, resulting in increased susceptibility to age-related diseases such as diabetes mellitus, cardiovascular disorders, cancer, neurodegeneration, and ultimately leading to death. The research in aging has progressed from descriptive observations to molecular investigations of the biological mechanisms governing cellular and systemic decline. Vital to our comprehension is the Hayflick Limit theory, which establishes the cellular senescence concept in human fibroblasts, demonstrating that diploid cell strains undergo a limited number of cell doublings before entering a state of senescence. Current research expands this theory by disclosing the molecular basis of organismal aging including mitochondrial dysfunction, telomere attrition, genomic instability, chronic inflammation, and epigenetic alterations. These biological traits interrelate with various lifestyle and environmental factors to accelerate or decelerate the aging process. Over the past few years, interest and attention have transformed toward interventions, predominantly herbal medicine and natural compounds that regulate these biological pathways to promote healthy aging. The incorporation of traditional herbal medicine with modern geroscience signifies a promising frontier, provides the opportunity for cross-cutting strategy that improve longevity and alleviate the risk of chronic diseases. This chapter explores classical and modern theories of aging, scrutinizes its biological mechanisms and prospects for future research and therapeutic development.

Keywords: Aging, Biological Mechanisms, Hayflick Limit theory, Cellular Senescence

1. INTRODUCTION

Aging is a natural phenomenon marked by an inevitable gradual loss of physiological integrity over time. This dynamic biological process involves not only genetic programming but also stochastic damage that accumulates throughout life (Paital & Singh, 2025; Shukla, 2023). The consequences of aging extend further beyond longevity as they affect quality of life, susceptibility to chronic diseases, medical care, and healthcare burden. Comprehending aging biological mechanisms therefore represents a cornerstone for modern medicine remarkably in communities confronting demographic shifts toward aged populations. Leonard Hayflick and Paul Moorhead (1961) first introduced the cellular senescence concept through their revolutionary research which revealed that human diploid fibroblasts can only undergo a limited number of cell divisions (i.e. 40-60 times) before ceasing proliferation. This Hayflick Limit theory proposed a cellular basis for aging and confronted the initial belief that cultured cells were eternal. The Hayflick Limit theory laid the establishment for subsequent breakthroughs linking cellular senescence and telomere shortening to organismal aging (Figure 1). Telomeres, which are repetitive nucleotide sequences safeguarding the end of chromosomes, get shortened with each cycle of deoxyribonucleic acid (DNA) replication. Cellular machinery identifies telomeres as DNA damage when they reach a critical length, thus triggering growth arrest. In the context of herbal medicine for healthy aging and chronic diseases, comprehending these vital biological mechanisms facilitates researchers in designing targeted interventions to counter cellular deterioration and improve resilience against age-associated disorders.

2. BACKGROUND AND LITERATURE REVIEW

Theories of aging have expanded from philosophical concepts of vital energy to biological pathways grounded in molecular biology. Two predominant concepts dominate the literature: genetic programmed theories that propose aging follow a genetically determined sequence of events, and stochastic damage theories which attribute aging to the buildup of molecular and cellular damage over time (Ameen & Taqa, 2024). Among these paradigms of aging, the Hayflick model remains a foundation, emphasizing that somatic cells undergo a finite number of cell divisions prior to entering cellular senescence state due to the telomere attrition (Ameen & Taqa, 2024; Chalak et al., 2024). This important breakthrough correlated molecular damage with the replicative senescence of cells and presented a mechanistic link between cellular aging and organismal aging.

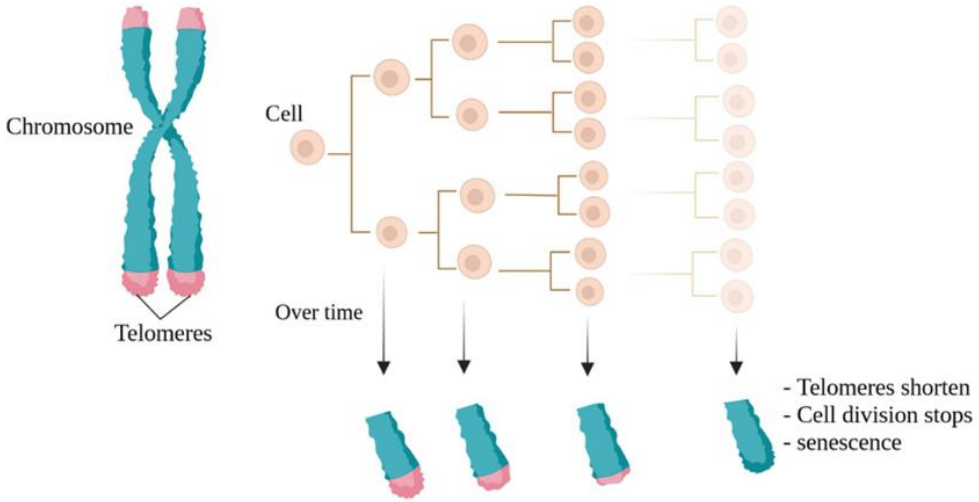

Figure 1: The Hayflick Limit theory posits that the telomeres become shorter with each cell doubling and eventually leads to cellular senescence (Chalak et al., 2024).

Beyond the Hayflick Limit model, numerous complementary theories have deepened our understanding of aging. The oxidative stress theory suggests that reactive oxygen species (ROS) accumulation damages cellular macromolecules, leading to functional decline as well as age-related disorders and ultimately death (Knoefler et al., 2013). The mitochondrial free radical theory of aging (MFRTA) extends the previous theory, proposing that free radicals damage mitochondrial DNA (mtDNA) and other cell components. This further generates a feedback loop in which mitochondrial dysfunction creates more ROS which in turn leads to further cellular damage and accelerates the aging process (Liu et al., 2014).

In addition, the immunosenescence theory emphasizes that immune competency deteriorates due to aging, resulting in increased susceptibility of infection, chronic inflammation, and cancer incidence (Franceschi et al., 2018; Liu et al., 2023). Epigenetic clock theory, which has obtained more attention recently, suggests that the biological age of organism can be determined by measuring epigenetic modifications, specifically DNA methylation. This DNA methylation data can be analyzed to track biological age with discrepancies between the estimated age and chronological age linked to numerous pathological conditions and health status (Gems et al., 2024).

The first edition of the hallmarks of aging was published by López-Otín et al. (2013) with originally nine hallmarks that serve as the foundational set of aging hallmarks. After a decade, this hallmarks of aging were expanded in López-Otín et al. (2023), outlining twelve interconnected mechanisms namely genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis (Figure 2). These hallmarks are interconnected with each other as well as to the currently proposed Hallmarks of Health, jointly represent possible targets for anti-aging interventions. Recently emerging studies revealed that certain notable phytochemical compounds such as curcumin (He et al., 2025), quercetin (Zhou et al., 2025), and resveratrol (Singh et al., 2025) can modulate a number of these pathways through various biochemical mechanisms, highlighting the significance of herbal medicine in geroscience.

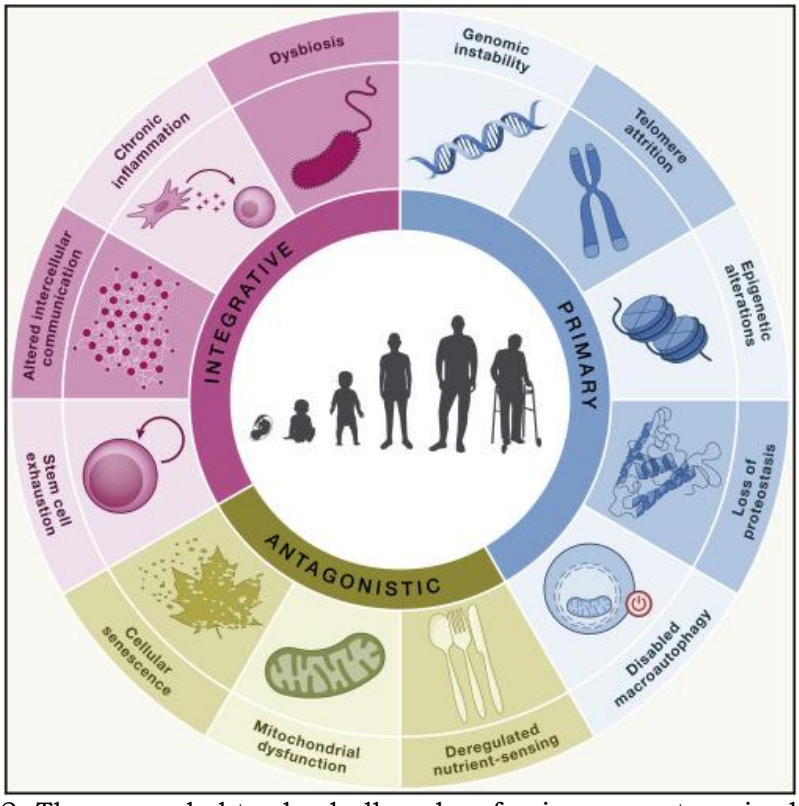

Figure 2: The expanded twelve hallmarks of aging are categorized into three classifications that are primary, antagonistic, and integrative (López-Otín et al., 2023).

3. CRITICAL ANALYSIS AND IMPLICATION

Although the Hayflick Limit theory offers a mechanistic basis for comprehending the cellular senescence concept, contemporary perspectives disclose that aging process is not exclusively and solely regulated by replicative exhaustion only. Senescent cells adopt a secretory phenotype namely the Senescence-Associated Secretory Phenotype (SASP), secreting various factors including inflammatory cytokines, growth factors, and proteases that disrupt tissue homeostasis, thereby propagating systemic aging signals (Viniak et al., 2025). This leads to 'inflammaging' which is a chronic, sterile, low-grade inflammation that expedites tissue degeneration and further predisposes individuals to age-related diseases which include cardiovascular disorder, type 2 diabetes mellitus, and Alzheimer's disease (Franceschi et al., 2018). By increasing ROS production, mitochondrial dysfunction amplifies these effects, impairing energy metabolism and thus further induce DNA damage responses.

In addition, deregulated nutrient sensing through pathways such as mechanistic target of rapamycin (mTOR), AMP-activated kinase (AMPK), and sirtuins influences biological metabolism as well as longevity (López-Otín et al., 2023). Notable phytochemicals that modulate these pathways, for instance berberine (an AMPK activator) or ginsenosides (mTOR inhibitors) prove how natural compounds can imitate caloric restriction and prolong lifespan in experimental models. Epigenetic drift depicted by global hypomethylation and site-specific hypermethylation further contributes to transcriptional noise and metabolic dysregulation, interconnecting environmental determinants with aging phenotypes. Herbal medicine abundant in polyphenols such as curcumin and green tea catechins demonstrate epigenetic-modifying properties with huge potential to reverse age-related DNA methylation.

From a translational viewpoint, comprehending these biological mechanisms offers an outline for assessing herbal therapeutic efficacy. There are numerous phytochemicals that can simultaneously aim several aging pathways, offering more advantages as compared to single-target pharmaceuticals. For example, quercetin is a promising candidate for anti-aging therapies. This is due to its dual functions as both a potent antioxidant that alleviates oxidative stress (Zhou et al., 2025), as well as a senolytic agent that selectively eliminates senescent cells (Chandrakar et al., 2024). Such dual actions illustrate the potential of phytochemical compounds in delaying aging and alleviating age-related decline.

4. FUTURE DIRECTIONS

The future geroscience research must incorporate multidisciplinary and integrative approaches. Systemic biology, transcriptomics, and metabolomics can map the complicated interconnections between genetic, lifestyle, and environmental determinants of aging. Soon, artificial intelligence (AI) and machine learning (ML) can accelerate breakthroughs by forecasting aging trajectories and discovering biomolecular targets for intervention. Additionally, there is a growing demand and trend for longitudinal, biomarker-based clinical trials to assess herbal medicine efficacy in modulating the biological age. Telomere dynamics and epigenetic clocks may serve as measurable endpoints for such research studies. The synergy between traditional herbal knowledge and advanced biomedical research provides an opportunity to design personalized interventions for healthy aging.

In the context of herbal medicine for healthy aging, ethical considerations also warrant attention and must be addressed extensively. These include guaranteeing informed consent when evidence is limited, ensuring equitable access to effective and safe interventions, and refraining from exaggerated health claims. Clinicians and researchers are responsible for explicit communication with regards to evidence, realistic benefits, and potential risks of herbal medicinal therapies. In addition, ethical sourcing of therapeutic plants must also be taken into consideration to avoid any harm to ecology and to ensure long-term availability.

Nowadays, guaranteeing access to evidence-based herbal medicine interventions becomes vital as the global populations age. Collaborative efforts between academicians, traditional practitioners, and regulatory authorities can facilitate standardization, safety evaluation, risk assessment, and clinical trial validation. Integrating public health awareness and strategies that promote healthy lifestyles alongside consumption of herbal supplements will further improve population-level outcomes.

5. CONCLUSION

Aging is a multifactorial phenomenon that involves various interactions of molecular, genetic, and environmental influences. The Hayflick Limit theory continuously serves as a fundamental framework correlating cellular replication to organismal aging, nevertheless modern theories disclose a wider, interrelated landscape encircling mitochondrial dysfunction, telomere erosion, chronic inflammation, and epigenetic remodeling. By recognizing these mechanisms, rational interventions that target the biological roots of cellular aging can be designed. Herbal

medicine with its complex phytochemical compounds provides promising and holistic strategies to modulate several hallmarks of aging concurrently.

From a clinical viewpoint, herbal medicine potential must be aligned with measurable and achievable outcomes. Herbal interventions should not be considered as anti-aging cures but rather as supplementary strategies for enhancing metabolism, diminishing inflammation, alleviating functional decline, and underpinning physiological resilience. Therefore, clinical endpoints should prioritize physical function improvement, cognitive performance enhancement, glycaemic and lipid control, and patient-reported quality-of-life measures rather than lifespan extension solely.

Significantly, herbal medicine translation into aging-related clinical practice faces various regulatory challenges. These include phytochemical composition variability due to different plant species, cultivation, harvesting, processing, and storage conditions. Inter-batch variability further complicates determination of dose, clinical findings reproducibility, and across studies comparison. Additionally, safety evaluation of herbal medicine products remains inconsistent with regards to long-term consumption in aged populations who are frequently exposed to polypharmacy. Potential herb–drug interactions, heavy metals contaminations or adulterants, and cumulative toxicity necessitate meticulous quality control, pharmacovigilance, and regulatory oversight. Thus, for future directions, we should focus more on thorough clinical assessment, mechanistic elucidation, and standardization to incorporate herbal medicine therapeutics within the conventional paradigm of geroscience. Through such interdisciplinary collaboration, it is possible to transit from extension of lifespan to optimization of health span.

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Chapter 2
Botanical Medicine and Aging: Historical and Global Perspectives

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ABSTRACT

The twenty-first century has been described as the "age of aging", reflecting unprecedented longevity alongside the global rise of chronic diseases. While advances in medicine, nutrition, and technology have extended lifespan, they have not always ensured healthspan, the years lived in good physical, mental, and social well-being. This growing imbalance has intensified interest in complementary and preventive approaches to sustain vitality and resilience throughout later life. Among these, herbal medicine, one of humanity's oldest healing traditions, offers valuable lessons through the holistic use of plants and natural compounds to restore harmony within the body, mind, and environment. This chapter explores historical and global perspectives of herbal medicine in aging populations, emphasizing three enduring traditions: Ayurveda from India, Traditional Chinese Medicine, and the Greco-Roman system that shaped Western herbalism. Each tradition upholds balance, moderation, and rejuvenation as keys to longevity, concepts now supported by modern geroscience evidence on oxidative stress, inflammation, and cellular protection. The discussion also addresses issues of safety, standardization, sustainability, and ethical integration within modern healthcare systems. By bridging cultural heritage and scientific inquiry, herbal medicine provides not only therapeutic potential but also a deeper understanding of how humans can age with dignity, connection, and purpose.

Keywords: Herbal medicine, Healthy aging, Geroscience, Traditional medical systems, Aging populations

1. INTRODUCTION

Many scholars describe the twenty-first century as the "age of aging," a term that captures both the achievements and the challenges of modern civilization. Advances in medicine, sanitation, and technology have dramatically extended human life expectancy, transforming global population structures in just a few generations. For the first time in recorded history, older adults outnumber children in many parts of the world. According to the United Nations (2023), one in six people globally will be aged 65 years or older by the year 2050. This demographic transition represents not only a medical success but also one of the most profound social, cultural, and economic transformations of our time.

Yet, while people are undeniably living longer, they are not necessarily living healthier lives. The rapid rise in chronic, non-communicable diseases, including cardiovascular disorders, type 2 diabetes, osteoporosis, arthritis, and dementia, has become a defining feature of modern aging (World Health Organization [WHO], 2022). As life expectancy continues to rise, the central question for policymakers and researchers is not merely how to prolong life, but how to extend healthspan, the period of life lived in good health, physical function, and psychological well-being.

In response to these challenges, attention has turned toward preventive and integrative approaches that can complement conventional medicine. Among these, herbal medicine, the use of plants and natural products for healing, stands out as a particularly rich and enduring resource. For thousands of years, cultures across every continent have relied on plants not only to treat illness but to sustain vitality, memory, and emotional balance. In India, Ayurvedic practitioners have long prescribed *rasāyana* formulations such as ashwagandha (*Withania somnifera*) and turmeric (*Curcuma longa*) to rejuvenate the body and mind. In East Asia, ginseng (*Panax* spp.) is regarded as a life-strengthening tonic, while in the Mediterranean region, rosemary (*Rosmarinus officinalis*) has symbolized remembrance and mental clarity. These examples illustrate that the pursuit of healthy aging is not new; it is a shared human aspiration deeply embedded in traditional medical systems.

What makes this topic especially compelling today is that modern geroscience, the interdisciplinary study of aging and longevity, has begun to uncover biological mechanisms that align remarkably well with ancient herbal wisdom. Many botanicals once valued for their restorative properties are now known to influence oxidative stress, inflammation, mitochondrial function, and stress response pathways, all of which are central to the biology of aging. This convergence between traditional practice and scientific discovery opens new pathways for evidence-based

integrative care, particularly for aging populations seeking natural, culturally meaningful approaches to wellness.

This chapter therefore explores how herbal medicine has supported aging populations throughout history, how these traditions continue to shape health practices around the world, and how emerging scientific research validates their relevance in modern contexts. By bridging cultural heritage with biomedical insight, herbal medicine offers not only therapeutic promise but also a more holistic vision of what it means to age with dignity, vitality, and purpose.

2. BACKGROUND AND LITERATURE REVIEW

2.1 Historical Foundations

The history of herbal medicine for aging begins with the world's earliest civilizations. In Ayurveda, the classical Indian medical system, the concept of *rasāyana tantra* emphasized rejuvenation and mental clarity (Sharma & Dash, 2022). Herbs such as ashwagandha (*Withania somnifera*), amalaki (*Emblica officinalis*), and turmeric (*Curcuma longa*) were prescribed to strengthen *ojas* (vital energy), delay aging, and sustain immunity. Rasāyana therapies combined herbal formulations with diet, meditation, and lifestyle discipline, anticipating today's integrative approaches.

In Traditional Chinese Medicine (TCM), aging was associated with the depletion of *jing* (essence) and the imbalance of *yin* and *yang*. *Panax ginseng*, *Astragalus membranaceus*, and *Lycium barbarum* were prescribed to tonify *qi*, improve stamina, and prevent cognitive decline (Hewlings & Kalman, 2017). Kampo medicine in Japan adapted these formulas and integrated them into the modern healthcare system (Nakashima et al., 2022).

The Greco-Roman tradition focused on humoral balance. Hippocrates and Galen viewed aging as a cooling and drying of the body that required warming herbs such as rosemary, sage, and garlic (Kuhn et al., 2023). These plants supported circulation and cognition, mirroring modern research linking them to improved vascular and memory function. Modern scientific inquiry has increasingly begun to validate many of these ancient observations, linking traditional herbal practices to contemporary concepts of cellular protection, stress regulation, and healthy aging.

2.2 Indigenous and Folk Knowledge

Beyond the classical systems, indigenous and folk traditions across Africa, the Americas, and Oceania preserved their own botanical frameworks for vitality and balance. Among the Cherokee and Iroquois, *ginkgo* (*Ginkgo biloba*) was used to enhance memory and improve blood flow, often within spiritual or communal healing ceremonies. In West Africa, the Yoruba prepared infusions of hibiscus (*Hibiscus sabdariffa*) to manage blood pressure and heart health, reflecting an intuitive understanding of cardiovascular physiology (Heinrich & Appendino, 2022). Across the Pacific, Polynesian elders consumed *kava* (*Piper methysticum*) to calm anxiety, strengthen social bonds, and promote emotional equilibrium. These diverse practices reveal an ecological and relational view of health, where physical well-being is inseparable from spiritual harmony and social connectedness.

2.3 Global Use in the Modern Era

In the contemporary world, the relevance of these herbal systems remains profound. The World Health Organization (WHO, 2022) estimates that nearly 80% of the global population relies on some form of traditional or herbal medicine. Older adults, in particular, continue to depend on botanicals for preventive care and chronic disease management, especially in communities where modern pharmaceuticals are costly or inaccessible. In Japan, Kampo formulas such as *Ninjin'yoeito* are officially covered by national insurance and prescribed for fatigue, frailty, and cognitive decline in the elderly (Nakashima et al., 2022).

Germany has institutionalized the clinical use of standardized *ginkgo* and *garlic* extracts, while in India, the Ministry of AYUSH promotes Ayurvedic formulations designed to enhance immunity and mental acuity. This enduring reliance demonstrates that traditional plant-based medicine continues to evolve alongside scientific research. Few examples are the integration of standardized Kampo formulations within Japan's national healthcare system (Nakashima et al., 2022), the development of regulatory herbal monographs by the European Medicines Agency, and an expanding body of randomized clinical trials evaluating herbs such as ginseng and ashwagandha in aging populations (Zanuso et al., 2022; Kim et al., 2025).

In Southeast Asia, particularly in Malaysia and Indonesia, traditional herbal knowledge remains deeply interwoven with daily life. Practices such as *jamu* in Indonesia and *ubat herba Melayu* in Malaysia emphasize preventive health through the use of local botanicals like *tongkat ali* (*Eurycoma longifolia*), *pegaga* (*Centella asiatica*), and *misai kucing* (*Orthosiphon stamineus*). These herbs are not only used as household remedies but are increasingly being standardized for clinical and commercial applications. Malaysia's National Policy on Traditional and

Complementary Medicine (2018) reflects the region's effort to bridge cultural heritage with modern health governance, providing an example of how traditional wisdom can coexist with biomedical practice in a regulated, evidence-based framework.

As traditional medical knowledge continues to inform modern healthcare systems, it becomes essential to critically assess how these practices align with evidence-based medicine and evolving global health priorities.

3. CRITICAL ANALYSIS AND IMPLICATIONS

3.1 Mechanistic Links Between Tradition and Science

Modern geroscience identifies nine "hallmarks of aging," including genomic instability, mitochondrial dysfunction, and chronic inflammation (López-Otín et al., 2023; Hewlings & Kalman, 2017). The active compounds in traditional herbs often target these same pathways.

A. Turmeric (*Curcuma longa*)
Curcumin acts as an antioxidant and NF-κB inhibitor, reducing oxidative stress and systemic inflammation (Khan et al., 2024).

B. Ashwagandha (*Withania somnifera*)
Withanolides regulate cortisol and improve sleep, muscle mass, and cognitive resilience in older adults (Sprenger et al., 2025; Leonard et al., 2024).

C. Ginseng (*Panax spp.*)
Ginsenosides enhance mitochondrial ATP production and modulate immune balance, explaining its reputation as a vitality tonic (Kim et al., 2025; Zanuso et al., 2022).

These herbs act through multi-targeted, synergistic mechanisms rather than single molecular pathways, supporting the idea that complex aging processes benefit from complex interventions

3.2 Integration and Policy Challenges

Despite encouraging evidence, several barriers limit herbal integration into mainstream geriatric care.

A. Safety and Polypharmacy
Older adults often take multiple medications, increasing the risk of herb–drug interactions. Turmeric may increase bleeding risk when used concomitantly with anticoagulants; ginseng can alter insulin metabolism;

and ashwagandha may interfere with thyroid medications (Wiciński et al., 2025). These potentials interactions underscore the importance of professional supervision.

B. Quality and Standardization

The herbal market is poorly regulated in many regions. Adulteration, contamination, and inconsistent potency are widespread issues (WHO, 2022). Quality assurance frameworks, such as the EMA's herbal monographs or Japan's Kampo standards, should be expanded globally.

C. Ethical and Environmental Concerns

Rising global demand threatens biodiversity. Ginseng and ashwagandha face overharvesting and habitat loss (Heinrich & Appendino, 2022). Sustainable cultivation and fair-trade certification are critical to protect both ecosystems and traditional communities.

D. Knowledge Preservation

Indigenous knowledge is often transmitted orally and risks being lost as elder healers pass away. Collaborative ethnobotanical documentation projects can preserve this heritage for future generations (Kuhn et al., 2023).

3.3 Sociocultural and Ethical Implications

Herbal medicine represents not only pharmacological but also cultural continuity. For elders, preparing herbal teas or decoctions connects them to heritage and identity. This experiential engagement fosters psychological well-being and autonomy, key dimensions of successful aging. Integrating this cultural value into modern healthcare can make geriatric care more holistic and human-centered.

Reflecting on these traditions from a Southeast Asian perspective, it becomes clear that herbal medicine functions not only as a therapeutic system but as a form of cultural resilience. In communities where aging is respected as a stage of wisdom rather than decline, the continued use of herbs reinforces identity and intergenerational connection. This human dimension is often overlooked in biomedical studies but remains central to how older adults in many Asian societies perceive well-being and dignity. Despite increasing global interest in traditional herbal medicine, challenges remain in integrating traditional knowledge with modern scientific standards. Variations in plant species, preparation methods, and dosage make it difficult to ensure consistent clinical outcomes. Moreover, many traditional systems emphasize holistic, individualized treatment philosophies that do not always fit neatly into evidence-based biomedical models. Regulatory frameworks also differ widely between countries, creating gaps in quality assurance and safety monitoring. Therefore, cross-disciplinary collaboration, standardized

research methodologies, and transparent policy frameworks are essential to bridge traditional wisdom with contemporary scientific validation.

4. FUTURE DIRECTIONS

A. Strengthening Clinical Evidence

The next frontier in botanical medicine lies in high-quality clinical trials focused on older adults. Studies should measure outcomes relevant to aging, frailty scores, cognitive performance, muscle strength, and immune resilience (Leonard et al., 2024). Trials comparing standardized herbal formulations with pharmaceuticals can clarify where integration is most beneficial.

B. Integrative and Personalized Care

Future geriatric models should merge biomedical and traditional frameworks. Japan's Kampo system and India's AYUSH network demonstrate how this integration can function at scale. Personalized herbal prescriptions informed by genetics and microbiome profiles may further optimize safety and efficacy (Zanuso et al., 2022).

C. Technology and Education

Digital health tools could empower older adults to track herbal use, check for interactions, and receive evidence-based advice. At the same time, healthcare providers need formal education in phytotherapy and cultural competence to engage confidently with herbal users (Kim et al., 2025).

D. Sustainability and Policy Collaboration

International initiatives, such as the WHO Traditional Medicine Strategy (extended to 2034), highlight the importance of conservation and equitable access. Collaborative frameworks should ensure that traditional healers, farmers, and local communities share in the benefits of global herbal trade (Heinrich & Appendino, 2022).

5. CONCLUSION

Across history, societies have turned to plants to support aging with dignity and vitality. Ayurveda's *rasāyana*, China's *qi* tonics, Greco-Roman herbals, and Indigenous decoctions all share a conviction that aging is modifiable through natural means.

Modern research confirms that many of these herbs, especially turmeric, ashwagandha, and ginseng, target fundamental aging mechanisms like inflammation, oxidative stress, and mitochondrial decline. By integrating these findings with traditional frameworks, herbal medicine can complement modern geriatric care.

Recommendations:

1. Research: Conduct large, aging-focused clinical trials using standardized herbal extracts.
2. Regulation: Enforce quality control and pharmacovigilance for herbal products.
3. Education: Train healthcare providers in integrative and culturally aware geriatric care.
4. Policy: Expand insurance coverage for evidence-based herbal therapies.
5. Sustainability: Promote ethical sourcing and biodiversity conservation.

The intersection of traditional knowledge and modern medicine offers valuable lessons for designing age-friendly health systems. When older adults are encouraged to draw on familiar herbal practices within safe, evidence-based care, it strengthens their sense of control, belonging, and trust in the healthcare process. Ultimately, aging is not merely a biological process but a narrative of continuity. By combining traditional wisdom with scientific rigor, societies can nurture an aging experience that is not only longer, but more meaningful, connected, and full of life.

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Chapter 3
Bridging Ethnobotany, Pharmacology, and Clinical Research

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ABSTRACT

Herbal medicines, rooted in traditional knowledge, serve a bridge between ancient wisdom and modern science. Ethnobotany provides a hypothesis-generating foundation. It documents centuries of medicinal plants across diverse cultures. Building on this, phytochemistry and pharmacology translate its traditional uses into standardized extracts, bioactive compounds and mechanistic insights. Finally, clinical research applies that knowledge to human health by evaluating formulation, dosage, safety, and efficacy in real-world clinical settings. Together, these disciplines create a translational framework that transforms traditional therapies into evidence-based strategies for managing chronic illnesses and promoting healthy aging. By integrating ethnobotanical insights with rigorous clinical testing and mechanistic validation, herbal medicine can evolve from informal use to precision-based therapeutics. This approach not only preserves cultural heritage but also expands the range of scientifically grounded interventions that enhance resilience, longevity, and quality of life in an aging world.

Keywords: Ethnobotany, Pharmacology, Clinical research, Phytochemistry

1. INTRODUCTION

Traditional medicine markets feature a wide variety of plants promoted for their potential to support healthy aging and longevity. However, there is still a significant discrepancy between biomedical evidence and empirical heritage in the scientific validation of these traditional remedies. An integrative framework linking ethnobotany with contemporary pharmacology and clinical research is necessary to close this gap. While pharmacological and phytochemical studies offer mechanistic insights into the active ingredients and their molecular targets, ethnobotanical knowledge acts as a storehouse of theories drawn from centuries of therapeutic observation. By linking ethnobotany with rigorous pharmacology and clinical trials, we can identify promising leads, understand how they work, and evaluate whether they truly help people age better. Closing this gap calls for a genuinely integrated approach that brings ethnobotany, pharmacology, and clinical research into the same conversation.

Traditional knowledge offers far more than cultural heritage. It provides therapeutic ideas shaped by centuries of observation and practice. Phytochemical and pharmacological studies then step in to uncover which compounds are active, how they behave in the body, and what molecular pathways they influence. Ultimately, clinical studies in humans are essential to validate these insights, determining whether these time-honoured remedies can genuinely promote health and support healthy aging. When these three fields work together, a clearer path from traditional use to scientific validation will be established. We can identify the most promising natural compounds, understand their biological mechanisms, and evaluate whether they genuinely contribute to longevity.

Aging is much more than the appearance of wrinkles. It reflects a slow, pervasive decline across multiple biological systems such as genomic instability, mitochondrial dysfunction, chronic inflammation, and the buildup of senescent cells among them (Zhang et al., 2025). Unlike many conventional drugs that target a single pathway, botanical interventions tend to act on several interconnected signalling networks simultaneously. This multimodal nature makes them especially intriguing for addressing the multifactorial processes that drive aging. New tools are also reshaping the field. Advances in multi-omics, network pharmacology, and artificial intelligence now allow researchers to map the complex interactions between plant phytochemicals and their molecular targets with a level of detail that was unimaginable even a decade ago (Chele et al., 2025). These technologies are transforming traditional remedies from broad, experience-based practices into rigorously understood therapeutic strategies.

In this rapidly evolving landscape, the convergence of ethnobotany, pharmacology, and clinical research becomes not just valuable but essential. Only through this integrative framework we can translate traditional knowledge into standardized, safe, and truly effective interventions that support healthy aging and reduce the burden of chronic diseases.

2. ETHNOBOTANICAL DISCOVERY

Ethnobotany remains the foundation of natural product research, beginning with community engagement and ethical knowledge-sharing. The discovery of these interventions does not begin in the laboratory, but in the community by listening to local healers, elders, and practitioners who, across generations, have observed how certain plants restore vitality and treat disease. These conversations grounded in respect and reciprocity has revealed far more than plant names. They uncover patterns of use, preparation techniques, dosage practices, and the cultural beliefs that shape traditional healing systems. Ethical engagement is central to this process. Ensuring informed consent, fair benefit-sharing, and formal recognition of community knowledge builds the trust needed for genuine, long-term collaboration.

Accurate documentation is equally essential. Collecting proper voucher specimens (Culley et al., 2013), verifying taxonomy, and depositing samples in recognized herbaria anchor traditional knowledge in verifiable botanical evidence. Adding detailed metadata such as species identity, locality, habitat, seasonality, and preparation method has greatly improved both reproducibility and translational value (Reyes-Garcia & McKey, 2025). Recent fieldwork illustrates how far the discipline has advanced. Jarić et al. (2024) documented medicinal plant use across several Balkan communities, linking local biodiversity to therapeutic categories. Yiblet et al. (2024) paired traditional interviews with quantitative indices like use value and fidelity level to evaluate the reliability of plant use in Ethiopia. Sameen et al. (2025) focused on plants used for diabetes management in Pakistan, showing how chronic disease patterns can be translated from ethnobotanical knowledge into pharmacological hypotheses. Together, these studies highlight the increasing rigor, professionalism, and reproducibility of modern ethnobotanical research.

Despite these advances, several challenges remain. For instance, the phytochemical profile of a plant varies depending on season, soil type, altitude, or even small climatic differences. Cultivated specimens may not mirror their wild counterparts, sometimes containing higher or lower amounts of key metabolites. Because of this, moving from an ethnobotanical observation to a consistent extract for laboratory testing

is rarely straightforward. It usually requires close coordination among ethnobotanists, phytochemists, and pharmacologists to ensure that what is tested in the lab genuinely reflects what communities use in practice. A structured checklist can help maintain this fidelity. Most researchers now document the local and scientific names, plant parts used, preparation and dosage methods, frequency of use, voucher specimen codes, and precise geolocation coordinates. Many also include notes on community rights and benefit-sharing. This level of detail not only preserves traditional knowledge ethically but also makes it far more usable for scientific work.

Ultimately, ethnobotany becomes the first bridge in the translational pathway. It connects lived human experience with biochemical analysis and, eventually, clinical evaluation. When carried out carefully and respectfully, it transforms ancestral wisdom into a credible scientific foundation for developing plant-based interventions that support healthy aging and reduce the burden of chronic disease.

3. PHARMACOLOGY: FROM EXTRACTS TO MECHANISTIC INSIGHTS

Once a botanical has been prioritised based on strong ethnobotanical evidence, the next phases of phytochemical and pharmacological investigation begin. Typically, the process starts with extract preparation using aqueous, ethanolic, or mixed solvent systems, followed by fractionation and isolation of individual compounds through techniques such as high-performance liquid chromatography (HPLC/UPLC), high-resolution mass spectrometry (MS), and nuclear magnetic resonance (NMR) spectroscopy. At this stage, rigorous dereplication is essential to avoid redundant characterization of known compounds and to streamline the discovery of novel bioactives.

Bioassay-guided fractionation continues to be a cornerstone of natural-product research, allowing researchers to pinpoint biologically active fractions using either phenotypic or target-based assays. However, the field has increasingly embraced a network pharmacology perspective, recognising that botanical extracts often contain multiple constituents that act synergistically across a spectrum of molecular targets. This approach is particularly relevant for aging and chronic disease, where interconnected molecular pathways demand coordinated, multi-target interventions rather than single-pathway modulation. For instance, recent studies on *Curcuma* highlight its anti-aging potential. The principal rhizome-derived curcuminoids such as curcumin, demethoxycurcumin, and bisdemethoxycurcumin have been shown to modulate chronic inflammation, oxidative stress, mitochondrial function, and epigenetic regulation, all of which are implicated in aging and

degenerative conditions (Elhawary et al., 2024). Similarly, recent work on natural senotherapeutics illustrates the translational promise of botanicals. Mazzone et al. (2025) reported that plant-derived terpenes such as carvacrol, thymol, eugenol, and lycopene can selectively induce apoptosis in senescent mesenchymal stromal cells via mitochondrial and SRC-signalling pathways.

Pharmacokinetics and formulation considerations such as absorption, distribution, metabolism, excretion (ADME), blood-brain barrier penetration, metabolic stability, and toxicity are not just important; they are pivotal to turning a botanical into a truly viable therapeutic. To ensure meaningful systemic exposure in humans, botanical preparations must be carefully standardized for their bioactive content and, when needed, enhanced through advanced strategies such as encapsulation or nano-formulations. When approached rigorously, these steps elevate ethnobotanical leads into highly promising, pharmacologically robust candidates, firmly advancing them toward preclinical validation and, ultimately, successful clinical translation.

4. CLINICAL RESEARCH

The field of botanical clinical research in healthy aging and chronic disease still lags behind that of synthetic small molecules, however, a gradual maturation in methodological quality is increasingly evident. The translation of novel pharmacological discoveries into human testing presents substantial logistical and ethical challenges, necessitating study designs that integrate safety assessment, mechanistic validation, and efficacy evaluation across carefully phased investigations. Phase I studies are generally designed to assess safety, tolerability, dose pharmacokinetic/pharmacodynamic relationships and also demonstrate target engagement. Later stage proof-of-mechanism and pilot efficacy studies will be conducted to determine whether botanical interventions impact functional or biochemical changes associated with aging such as enhancement of mitochondrial activity, cognitive measures, inflammatory markers, or frailty indices. Adaptive or pragmatic randomized controlled trials (RCTs) should be the next step, including standardized botanical extracts or formulations in blinded and placebo-controlled mode.

Current meta-analyses of herbal interventions for anti-aging and metabolic health consistently show strong preclinical support, yet they also underscore the limited number of large, well-controlled human studies (Wang et al., 2025). Choosing meaningful clinical endpoints is therefore essential. These can include functional outcomes such as mobility, cognitive performance, and quality of life; biomarker-based measures like oxidative stress, SASP profiles, telomere dynamics, or

metabolomic signatures; and imaging or omics-based readouts that capture system-level effects. Increasingly, multi-omics approaches by integrating transcriptomic, metabolomic, and proteomic data are being recommended to provide a comprehensive view of how botanicals influence the complex trajectories of human aging.

Regulatory and ethical considerations are equally significant. Botanical products frequently fall somewhere in between dietary supplements and pharmaceuticals, and their classification directly influences requirements for approval, labelling, and marketing claims. Modern regulatory frameworks for botanical medicines have become increasingly rigorous, emphasizing quality, safety, and consistency. Agencies such as the European Medicines Agency (EMA), the U.S. Food and Drug Administration (FDA), and the World Health Organization (WHO) now require Good Manufacturing Practice (GMP), strict botanical authentication, and standardized formulation protocols to reduce risks from dosage variability, herb-drug interactions, and inconsistent bioavailability (Karthikeyan et al., 2025). Looking ahead, the field is moving toward precision herbal medicine, reflecting the broader trend toward personalized therapeutics. By integrating genetic, epigenetic, and metabolomic profiles, it may soon be possible to tailor specific botanical formulations to an individual's unique biological signature or disease phenotype, unlocking the full potential of plant-based interventions for health and longevity. As shown in Figure 1, the integration of ethnobotanical knowledge with phytochemical, pharmacological, preclinical, and clinical research underpins the development of scientifically validated herbal therapies.

5. CONCLUSION

Integrating ethnobotany, pharmacology, and clinical research creates a vital continuum to transform traditional plant knowledge into scientifically validated interventions for healthy aging and chronic disease. Ethnobotany provides the empirical foundation, highlighting culturally validated species with therapeutic potential. Phytochemical and pharmacological studies then uncover bioactive compounds, elucidate mechanistic pathways, and reveal synergistic interactions that drive efficacy. Preclinical models and formulation studies further refine these leads, ensuring safety, stability, and optimal bioavailability. Despite growing mechanistic insight, translation into robust clinical evidence remains limited by variability in extract standardization, incomplete pharmacokinetic data, and a shortage of large, biomarker-driven trials.

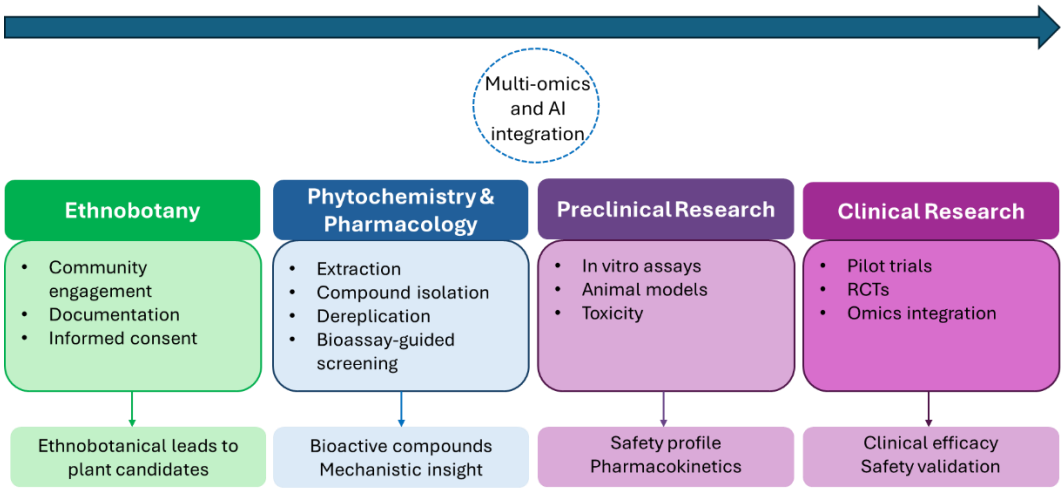

Figure 1: From traditional knowledge to clinical translation.

Addressing these challenges calls for a systems-based framework that bridges traditional knowledge with modern analytical, omics, and computational approaches. Emerging advances in network pharmacology and precision herbal medicine now offer the tools to align botanical therapies with individual biological profiles, paving the way for personalized strategies in healthy aging. While these developments highlight the potential of herbal medicine, further well-designed clinical studies are essential before such therapies can be recommended for routine clinical practice.

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Chapter 4
Mechanisms of Neuroprotection by Herbal Medicine

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ABSTRACT

Age-related cognitive decline is a major consequence of aging and a hallmark of neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. This decline is driven by oxidative stress, mitochondrial dysfunction, cellular senescence, and protein aggregation, which collectively impair synaptic plasticity and proteostasis. Current treatments offer limited efficacy and often cause adverse effects, highlighting the urgent need for safer, multi-target alternatives. Herbal medicines contain a wide range of bioactive compounds with antioxidant, anti-inflammatory, and neuroprotective properties. These compounds modulate key molecular pathways, including Nrf2 and NF-κB signalling, to protect neuronal function and mitigate cognitive deterioration. Evidence from preclinical and emerging clinical studies supports their potential in delaying neurodegeneration. Further research should focus on improving formulation, bioavailability, and clinical validation to translate these findings into effective therapies.

Keywords: Herbal medicine, Cognitive decline, Neuroprotection, Aging

1. INTRODUCTION

The global rise in the aging population is accelerating; in 2017, individuals aged 60 or older accounted for about 13% of the world's population, a proportion projected to increase sharply in the coming decades (Jongsiriyanyong & Limpawattana, 2018). Aging is the strongest risk factor for cognitive decline, defined as the gradual deterioration of mental processes such as reasoning, attention, and language (Dhakal, 2023). Although research has advanced considerably, current therapies

remain largely symptomatic and offer limited ability to halt or reverse neurodegenerative progression.

Aging triggers structural, molecular, and biochemical changes in the brain (Lee & Kim, 2022). In normal aging, these alterations are typically mild, whereas pathological aging involves protein misfolding, oxidative stress, and mitochondrial dysfunction that compromise neuronal integrity and accelerate cognitive decline (Teissier et al., 2020). Understanding these pathological mechanisms is critical for developing effective neuroprotective strategies. Pathological cognitive decline underlies conditions such as mild cognitive impairment (MCI), Alzheimer's disease (AD), Parkinson's disease (PD), and may impose substantial societal and healthcare burdens. This chapter synthesises current knowledge on the mechanisms of cognitive decline and highlights neuroprotective strategies, with emphasis on the therapeutic potential of herbal compounds.

2. MECHANISM OF COGNITIVE DECLINE

Cognitive decline arises from a network of interdependent processes in which oxidative stress, mitochondrial dysfunction, neuroinflammation, cellular senescence, and impaired proteostasis amplify one another to drive neuronal damage and loss of cognitive function.

2.1 Oxidative Stress

Oxidative stress occurs when the production of reactive oxygen species (ROS) exceeds the capacity of cellular antioxidant defences, leading to lipid, protein, and DNA damage (Guo et al., 2020; Lee & Kim, 2022). Neurons are particularly vulnerable due to high metabolic demand and relatively limited antioxidant defences (Franzoni et al., 2021). Persistent oxidative damage disrupts mitochondrial structure and function, establishing a self-perpetuating cycle in which mitochondrial impairment further elevates ROS production.

2.2 Mitochondrial Dysfunction

Mitochondrial impairment reinforces oxidative stress by increasing ROS generation, damaging mitochondrial DNA (mtDNA), and reducing cellular energy (ATP) production (Ionescu-Tucker & Cotman, 2021; Nousis et al., 2023). These changes compromise neurogenesis, impair synaptic signalling, and weaken blood-brain barrier (BBB) integrity (Anitha et al., 2023). In MCI models, elevated mitochondrial oxidative stress and reduced energy output are closely associated with memory decline (Apaijai et al., 2020). The increased ROS burden from dysfunctional mitochondria also serves as a potent trigger for neuroinflammation.

2.3 Neuroinflammation

Nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) largely drives neuroinflammation and is activated by cytokines and ROS, and regulates inflammatory gene expression through JNK, MAPK, and PI3K/Akt pathways (Kaltschmidt et al., 2022; Sun et al., 2022). Although NF-κB can initiate protective antioxidant responses, prolonged activation sustains a chronic inflammatory environment that contributes to neuronal injury and cognitive deterioration. Chronic inflammation, in turn, promotes cellular senescence.

2.4 Cellular Senescence

Cellular senescence arises from telomere erosion, DNA damage, or oncogene activation, leading to irreversible growth arrest and senescence-associated secretory phenotype (SASP) secretion via p53/p21 and p16/Rb signalling (Mylonas & O'Loghlen, 2022). Accumulated senescent cells in neural tissues release pro-inflammatory cytokines that amplify neuroinflammation and impair synaptic function, further accelerating cognitive decline (Rattanavirotkul et al., 2021). Senescence also disrupts proteostasis, increasing the burden of misfolded proteins.

2.5 Impaired Proteostasis and Protein Misfolding

Decline in proteostasis with age allows misfolded proteins such as Aβ, tau, and α-synuclein to accumulate and form toxic aggregates that compromise neuronal function (Choi et al., 2025; Kepchia et al., 2020). Defects in protein-quality control systems exacerbate oxidative stress and mitochondrial dysfunction, creating a feedback loop that promotes neuronal degeneration (Ajmal, 2023; Lenin et al., 2023).

3. EVIDENCE FOR NEUROPROTECTION BY HERBAL MEDICINE

Multiple herbal medicines have demonstrated neuroprotective effects across preclinical and clinical studies. *Ginkgo biloba* improves cognitive performance in AD mouse models. Clinical trials of EGb 761® (240 mg/day) report modest cognitive benefits (Zhu et al., 2024; Bohlken et al., 2022). *Panax ginseng* suppresses Aβ production, enhances cholinergic signalling, and promotes neurogenesis. However, clinical evidence remains limited by small sample sizes and methodological variability (Lee et al., 2022). *Curcuma longa* enhances synaptic plasticity and reduces astrogliosis. Some human studies suggest cognitive improvements at higher doses (González-Granillo et al., 2022). *Zingiber officinale* reduces oxidative stress and pro-inflammatory cytokines production in rodent models. Clinical studies similarly report cognitive enhancement with minimal adverse effects (Sutalangka & Wattanathorn,

2017). *Bacopa monnieri* improves memory and attention via antioxidant and cholinergic mechanisms. Larger and longer-term clinical trials are required to confirm efficacy (Prabhakar et al., 2020).

Centella asiatica enhances cognition and reduces neuroinflammation, with nanoparticle formulations improving bioavailability (Fitriana et al., 2021). Consumption of *Camellia sinensis* (tea) is associated with slower cognitive decline, likely due to its antioxidant and anti-inflammatory activity (Li et al., 2022). *Moringa oleifera* reduces Aβ accumulation, tau phosphorylation, and neuroinflammation in AD models, improving behavioural outcomes (Mahaman et al., 2022). Nevertheless, not all studies report consistent benefits. Several clinical trials have demonstrated modest or non-significant cognition improvements (Cave et al., 2023). These inconsistencies often arise from heterogeneity in study design, dosage, treatment duration, and extract standardisation. Overall, mixed findings highlight the need for cautious interpretation of preclinical results and further validation through well-designed clinical studies.

4. MECHANISMS OF NEUROPROTECTION

Herbal medicine exerts neuroprotective effects through multiple mechanisms. These effects are largely attributed to their active phytochemicals, which act on key molecular targets involved in cognitive decline. The mechanism of action and the corresponding bioactive compounds related to cognitive decline are presented in Table 1.

Table 1: Representative Bioactive Compounds in Herbal Medicine Associated with Cognitive Decline.

Herbal Medicine	Key Bioactive Compounds	Mechanism of Neuroprotection	Reference
Ginkgo biloba	• Flavonoids • Ginkgolides • Bilobalide • Luteolin	• Modulate PI3K/Akt/NF-kB-mediated signaling • Improve mitochondrial dysfunction • Suppress NLRP3 inflammasome and neuroinflammation	Zhu et al. (2024), Barbalho et al. (2022),
Curcuma longa	• Curcumin • Desmethoxycurcumin • Bisdemethoxycurcumin • Phenolics	• Inhibit NF-kB, AP-1, and MAPK signaling • Enhance antioxidant defense systems against ROS/RNS • Activate PI3K/Akt pathway	Kim et al. (2019), Kehinde et al. (2025)
Zingiber officinale	• 6/8-shogaol • 6-gingerol • Zerumbone	• Inhibit MAPK signalling • Antioxidant • Reduce lipid peroxidation	Zarei et al. (2021), El-hallouty et al. (2024)
Moringa oleifera	• Flavonoid • Phenolics • Alkaloids • Tannins • Vitamins	• Downregulate BACE1 and AEP • Upregulate amyloid-β clearance enzymes • Inhibit GSK-3β and AChE	Zamani et al. (2025), Mahaman et al. (2018), Mahaman et al. (2022)
Camellia sinensis	• Polyphenols • Catechins • L-theanine • Caffeine • Alkaloids • Theophylline	• Promotes a-secretase cleavage • Antioxidant • Activate neuronal survival pathways • Reduce excitotoxicity	Feng et al. (2012), Farzaei et al. (2019)

5. SAFETY AND TOXICITY

Despite these promising findings, several concerns warrant careful consideration. Elderly populations are more sensitive to pharmacological interventions due to age-related changes in pharmacodynamics and

pharmacokinetics, as well as the high prevalence of polypharmacy. Neurodegenerative disorders are multifactorial in nature; therefore, older adults often use multiple medications rather than a single therapeutic agent. Although herbal medicines are generally perceived as safe, interactions between herbal products and commonly prescribed medications, including anticoagulants, antidiabetic agents, antihypertensives, and neuropsychiatric medications, remain a significant concern. For example, *Ginkgo biloba* has been associated with increased risk of bleeding when co-administered with anticoagulants. At the same time, other botanicals may alter drug metabolism or transport pathways (Duan et al., 2025), thereby affecting therapeutic efficacy or increasing toxicity. Furthermore, variability in herbal composition and the lack of standardisation may contribute to adverse effects and inconsistent clinical outcomes. Although most studies report only transient side effects, comprehensive toxicity evaluations and long-term safety data remain limited.

6. CONCLUSION

Herbal medicines show promise as neuroprotective agents. Their multi-targeted actions help preserve synaptic function, enhance neuronal survival, and support overall brain health during aging. However, despite these promising effects, challenges remain in translating preclinical findings into clinical therapies. Limited bioavailability, lack of standardisation, and the small number of clinical studies hinder consistent outcomes. Therefore, future research should focus on optimising formulation strategies, improving compound stability and delivery, and validating their efficacy in well-designed clinical studies. By addressing these challenges, herbal-based interventions may eventually be integrated into evidence-based strategies for preventing or managing neurodegenerative disorders, offering a complementary and holistic approach for maintaining brain health across the lifespan.

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Chapter 5
Mechanistic Insights into *Centella asiatica* in Neurodegeneration

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ABSTRACT

Centella asiatica, a perennial medicinal herb, has garnered considerable attention for its neuroprotective properties, particularly its capacity to enhance cognitive function and mitigate pathological processes associated with neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. The continued absence of effective therapies capable of halting or reversing the progression of neurodegenerative diseases has redirected scientific interest toward phytopharmaceuticals as promising alternatives for drug development, owing to their broad therapeutic potential, favourable safety profiles, and high public acceptability. Among these, *C. asiatica* stands out for its multifaceted neuroprotective effects. This review provides a comprehensive synthesis of current *in vivo* and *in vitro* studies on *C. asiatica*. It highlights the key molecular mechanisms underlying its potent antioxidative and neuroprotective actions, particularly through modulation of apoptotic, inflammatory, and antioxidant signaling pathways.

Keywords: *Centella asiatica*, Neuroprotection, Alzheimer's disease, Parkinson's disease

1. INTRODUCTION

Neurodegenerative diseases are a group of disorders marked by the progressive degeneration of neurons in the central nervous system, leading to deficits in memory, motor control, and cognitive function (Gao & Hong, 2008). Alzheimer's disease (AD) and Parkinson's disease (PD) are common neurodegenerative diseases that pose significant global health challenges due to their progressive nature and affecting cognitive and motor functioning (Wilson et al., 2023). According to WHO data from 2019, AD affected approximately 55 million individuals globally, and over 8.5 million cases of PD were reported worldwide (Clare & Jeon, 2025; WHO, 2022). Given the complex and multifactorial pathological mechanisms underlying neurodegeneration, therapeutic strategies often aim for a neuroprotective approach, which includes preventing neuronal cell death and restoring function to damaged neurons (Mohd Sairazi & Sirajudeen, 2020). Despite notable progress in treatment approaches, current therapies mainly address symptoms and often come with side effects that can significantly reduce a patient's quality of life. This highlights the growing need for new therapeutic options, particularly those based on natural compounds, which offer broad, multi-targeted neuroprotective benefits (Lim et al., 2024).

2. *CENTELLA ASIATICA*

Figure 1: *Centella asiatica* (Hein et al., 2025).

Centella asiatica (L.), a member of the Apiaceae family, is commonly known as Asiatic pennywort and is locally called "*pegaga*" in Malaysia (Figure 1). The plant has a long-standing history of use in traditional medicine systems such as Ayurveda, Traditional Chinese Medicine, and

Thai medicine, where it is valued for its wide range of therapeutic benefits. In Malaysia, it is more widely known and consumed as a vegetable than as a medicinal plant. Recognizing its value, the World Health Organization (WHO) has listed it as one of the most important medicinal plants to be preserved and cultivated. In traditional Malay medicine, *C. asiatica* has been applied to wounds to help with healing, and it has also been used in beauty routines to slow skin aging. Today, it continues to gain popularity in the skincare and cosmetics industry for its natural benefits to the skin (Bakhtiar & Darnis, 2016).

Notably, *C. asiatica* is well known for its neuroprotective (Omar et al., 2011), anti-inflammatory (Hambali et al., 2024), antioxidant (Kandasamy et al. 2023), anti-bacterial (Chonsut et al., 2024), cognitive and memory enhancement (Seevaratnam et al., 2012) and wound-healing properties (Arribas-López et al., 2022). These benefits are largely attributed to its rich mix of natural compounds, especially triterpenoids, flavonoids, and phenolic compounds. Some of the most important active compounds including asiaticoside, madecassoside, asiatic acid, and madecassic acid have been widely studied for their powerful healing and protective effects. (Kunjumon et al., 2022).

3. MECHANISMS OF NEURODEGENERATIVE DISEASES

Alzheimer's disease (AD) and Parkinson's disease (PD) are both chronic and progressive neurodegenerative diseases. Although AD and PD present with distinct clinical symptoms which are cognitive impairment in AD and motor dysfunction in PD, they share several overlapping pathological mechanisms. Both conditions involve the accumulation of misfolded proteins: in AD, this includes extracellular amyloid-β plaques and intracellular tau tangles, whereas in PD, it involves the formation and accumulation of Lewy bodies, primarily composed of misfolded alpha-synuclein, which leads to the degeneration of dopaminergic neurons (Apostolova, 2016; Mhyre et al., 2012).

In addition, oxidative stress and neuroinflammation are believed to play significant roles in the pathophysiology of both diseases. An imbalance between reactive oxygen species (ROS) production and antioxidant defenses leads to oxidative stress, contributing to mitochondrial dysfunction, impaired DNA repair, and neuronal damage. This process, combined with neuroinflammation driven by activated microglia releasing inflammatory and neurotoxic factors (e.g., cytokines, COX-2), plays a critical role in the onset and progression of neurodegenerative diseases (Singh et al., 2019; Leszek et al., 2016). These overlapping pathological features suggest that targeting shared molecular pathways, such as reducing oxidative stress, modulating

protein aggregation or inflammatory pathways, may offer therapeutic potential for both disorders.

4. THERAPEUTIC EFFECTS OF *C. ASIATICA* ON ALZHEIMER'S DISEASE

Alzheimer's disease is characterized by progressive cognitive decline associated with the accumulation of amyloid-β, which triggers neuroinflammation and oxidative stress. An *in vivo* study using PSAPP mice demonstrated that long-term treatment with 2.5 g/kg of *C. asiatica* extract significantly reduced amyloid-$\beta_{1\text{-}42}$ levels in the hippocampus by 67%. This effect may be attributed to the extract's ability to influence amyloid-β pathology through multiple mechanisms, including reducing oxidative stress by inhibiting lipid peroxidation and modulating the amyloid cascade (Dhanasekaran et al., 2009). Another study also demonstrated its neuroprotective effects against $A\beta_{1\text{-}40}$-induced neuronal damage in rat PC12 pheochromocytoma and human IMR32 neuroblastoma cells by activating antioxidant defense system which leads to reduced oxidative stress (Chen et al., 2015). A recent study conducted by Liu et al. (2023) demonstrated that asiaticoside ameliorates synaptic and cognitive impairments in $A\beta_{1\text{–}42}$-induced mouse models. The study suggests that asiaticoside may improve cognitive dysfunction by modulating the p38 MAPK signaling pathway, thereby inhibiting the production of proinflammatory factors and enhancing synaptic function, ultimately leading to improved cognitive outcomes in AD mice. Other than that, a study also reported that *C. asiatica* significantly improved cognitive abilities in D-gal and AlCl3 induced rats with cognitive deficits. This cognitive enhancement was attributed to *C. asiatica*'s ability to restore cholinergic function by lowering acetylcholinesterase (AChE) levels, and to reduce oxidative stress by increasing superoxide dismutase (SOD) activity and decreasing malondialdehyde (MDA) levels. (Chiroma et al., 2019).

Various *in vitro* studies have demonstrated that *C. asiatica* exerts neuroprotective effects through the modulation of apoptosis and inflammatory pathways. Omar et al. (2011) reported that *C. asiatica* extract at low concentrations exerted neuroprotective effects against BSO-induced neuronal death. The extract significantly reduced the number of apoptotic cells by inhibiting the caspase-9–mediated apoptotic pathway, while no significant changes were observed in caspase-8 activity. Similarly in another study, asiatic acid has been shown to significantly protect SH-SY5Y cells from glutamate-induced apoptosis (Xu et al., 2012). According to Mairuae et al. (2019), treatment with *C. asiatica* extract significantly decreased nitric oxide (NO), tumor necrosis factor-alpha (TNF-α), and ROS production in lipopolysaccharide (LPS)-stimulated microglial cells. These anti-inflammatory actions were

attributed to the inhibition of NF-κB p65 nuclear translocation and the downregulation of the PI3K/AKT and ERK1/2 signaling cascades. In agreement with these findings, Hambali et al. (2024) demonstrated that *C. asiatica* extract reduced inflammatory cytokine and ROS levels in LPS-induced BV2 microglial cells through activation of the Nrf2/HO-1 pathway, significantly enhancing Nrf2 and HO-1 protein expression. Similarly, asiatic acid (Qian et al., 2018) and madecassoside (Sasmita et al., 2018) were found to reduce neuroinflammation in LPS-induced microglial cells. This was achieved by decreasing NF-κB p65 acetylation, thereby inhibiting NF-κB activation (Qian et al., 2018), along with upregulating the expression of the anti-inflammatory protein HO-1 (Sasmita et al., 2018). Additionally, a study by Song et al. (2018) reported that asiaticoside mitigated apoptosis and cytotoxicity while enhancing mitochondrial membrane potential in $A\beta_{1-42}$-induced human brain microvascular endothelial cells (hBMECs). It also significantly inhibited the translocation of NF-κB p65 from the cytoplasm to the nucleus and dose-dependently downregulated the expression of TNF-α, IL-6, TLR4, MyD88, TRAF6, and phosphorylated NF-κB p65 in hBMECs.

5. THERAPEUTIC EFFECTS OF *C. ASIATICA* ON PARKINSON'S DISEASE

Parkinson's disease is characterized by progressive mitochondrial dysfunction that leads to excessive production of ROS, resulting in oxidative stress, neuronal damage, and dopaminergic cell loss in the substantia nigra. Haleagrahara and Ponnusamy (2010) demonstrated that treatment with an aqueous extract of *C. asiatica* alleviates MPTP-induced Parkinsonism in aged Sprague–Dawley rats by restoring redox balance. MPTP is a mitochondrial complex I inhibitor which induces striatal dopamine depletion and oxidative stress. Oral administration of the extract for 21 days significantly reduced lipid peroxidation and protein oxidation while normalizing antioxidant enzyme activities, suggesting a potent antioxidative and neuroprotective effect. Further findings by Xu et al. (2012) showed that asiaticoside, ameliorated MPTP-induced motor impairments, decreased malondialdehyde (MDA) levels, preserved dopamine content, and elevated reduced glutathione (GSH), indicating modulation of oxidative and dopaminergic pathways. In a subsequent study, Xu et al. (2013) reported similar neuroprotective effects with madecassoside, accompanied by upregulation of brain-derived neurotrophic factor (BDNF) expression, highlighting its additional role in promoting neurotrophic support. Recent findings also indicate that asiaticoside demonstrated neuroprotective effects in MPTP-induced PD mice by suppressing neuroinflammation and inhibiting NLRP3 inflammasome activation. This suppression was associated with reduced dopaminergic neuronal loss and improved motor performance, indicating

that asiaticoside may serve as a potential therapeutic agent for NLRP3-mediated neuroinflammation in PD (He et al., 2024).

Moreover, ECa 233, a standardized extract of *C. asiatica*, has been reported to protect against rotenone-induced mitochondrial impairment and neuronal injury (Teerapattarakan et al., 2018). Likewise, Asiaticoside-D exhibits neuroprotective activity through the regulation of monoamine oxidase (MAO)-A and MAO-B levels, which helps attenuate ROS-mediated oxidative stress in rotenone-exposed *Lumbricus terrestris*, a mechanism believed to play a key role in preventing Parkinsonism-related neurodegeneration (Subaraja & Vanisree, 2019)

6. CONCLUSION

Extensive research has shown *C. asiatica* to be a promising candidate for therapeutic development, owing to its potent antioxidant, anti-inflammatory, and anti-apoptotic properties. Numerous pre-clinical studies have highlighted the significant neuroprotective effects of *C. asiatica* and its bioactive compounds in experimental models of neurodegenerative diseases such as AD and PD. The key signaling pathways involved in the neuroprotective actions of *C. asiatica* have been summarized and illustrated in Figure 2 (Jiang et al., 2025).

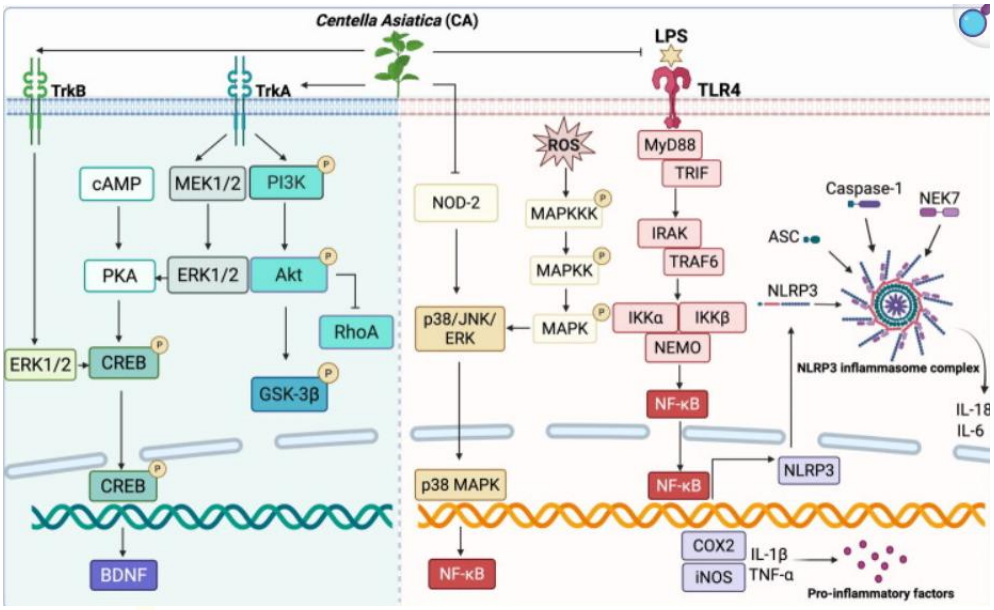

Figure 2: The cellular mechanisms and related signaling pathways involved in the neuroprotective effects of *Centella asiatica.* (Jiang et al., 2025).

Despite these promising findings, several challenges and limitations remain in optimizing clinical efficacy, safety profiles, and bioavailability. Many active compounds in *C. asiatica* are macromolecules that exhibit low water solubility and poor intestinal absorption, which substantially limits their oral bioavailability. Future investigations should aim to clarify the precise cellular and molecular mechanisms driving these effects, assess potential synergistic interactions and safety concerns, and develop strategies to enhance bioavailability and systemic absorption of *C. asiatica* derivatives. Such efforts will be crucial in unlocking the full therapeutic potential of *C. asiatica* and advancing its application in drug development.

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Chapter 6
Cardiovascular Protection by *Centella asiatica*: Preclinical Insights

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ABSTRACT

Cardiovascular diseases remain the foremost cause of mortality around the globe. For centuries, medicinal plants have been recognised as valuable sources of therapeutic agents. *Centella asiatica*, a widely used herb in traditional medicine, has gained increasing attention for its potential cardiovascular benefits. This review provides an overview of the protective roles of *C. asiatica* and its bioactive constituents in the management of cardiovascular disorders from a preclinical perspective. Relevant publications were collected from online scientific platforms including PubMed and Google Scholar, covering the years 2004 to 2025. Evidence from various *in vitro* and *in vivo* investigations suggests that *C. asiatica* and its key phytochemicals exhibit promising cardioprotective properties and beneficial effects on cardiovascular-related complications. Further clarification of the regulatory molecular mechanisms underlying *C. asiatica's* therapeutic actions on the cardiovascular system will enhance understanding of how this plant exerts its therapeutic effects.

Keywords: *Centella asiatica*, Cardiovascular, Asiatic acid, Triterpenes

1. INTRODUCTION

Cardiovascular disease (CVD) remains one of the leading contributors to illness and death across the globe (Dong et al., 2025). It poses a significant barrier to achieving healthy aging and prolonged lifespan. The global burden of CVD has risen sharply, with cases increasing from around 271 million in 1990 to approximately 523 million in 2019 (Roth et al., 2020). The major forms of CVD include ischaemic heart disease, stroke, various cardiomyopathies, cerebrovascular disorders, and rheumatic heart disease (Razali et al., 2019). Many cardiovascular conditions, such as atherosclerosis and heart failure, arise from complex interactions among metabolic dysfunction, immune responses, and neural regulation within the heart and vasculature (Mohanta et al., 2025).

Among the various risks associated with cardiovascular conditions, hypertension stands out for its strong link to serious and potentially deadly consequences. It has been determined that endothelial damage and vascular stiffness may be caused by oxidative stress and chronic inflammation (Franco et al., 2022). Oxidative stress causes endothelial dysfunction, atherosclerosis, and myocardial damage. ROS, for example, oxidise low-density lipoprotein (LDL), resulting in oxidised LDL (oxLDL), which plays an important role in atherosclerotic plaque formation. OxLDL accumulates in the arterial wall, leading to inflammation and plaque formation (Wang et al., 2022). CVD is not only the endpoint of aging or passive wear-and-tear: it is modifiable through lifestyle and targeted treatment, but the fact that it remains the leading cause of death globally underscores that current definitions may under-recognise its heterogeneity and latent progression (Netala et al., 2024). Prevention strategies largely focus on managing lifestyle-related and other changeable determinants of cardiovascular disease (Figure 1).

2. *CENTELLA ASIATICA*

Since ancient times, plants have played a pivotal role as a major resource for medicine and healthcare. *Centella Asiatica* (L.) Urban (*C. asiatica*) is a significant traditional herb in the *Umbelliferae* family (Prasad et al., 2019). *C. asiatica* also known as Gotu kola, is commonly used in Southeast Asian countries (Sun et al., 2020). It grows in tropical and sub-tropical areas up to an altitude of 600m. It thrives in shady, muddy, moist, and wet environments, like paddy fields and riverbanks, forming a dense green carpet (Devkota and Pramod, 2009).

C. asiatica is characterised by compact, fan-shaped foliage, with one to three leaves emerging from each stem node. The leaves are rounded to

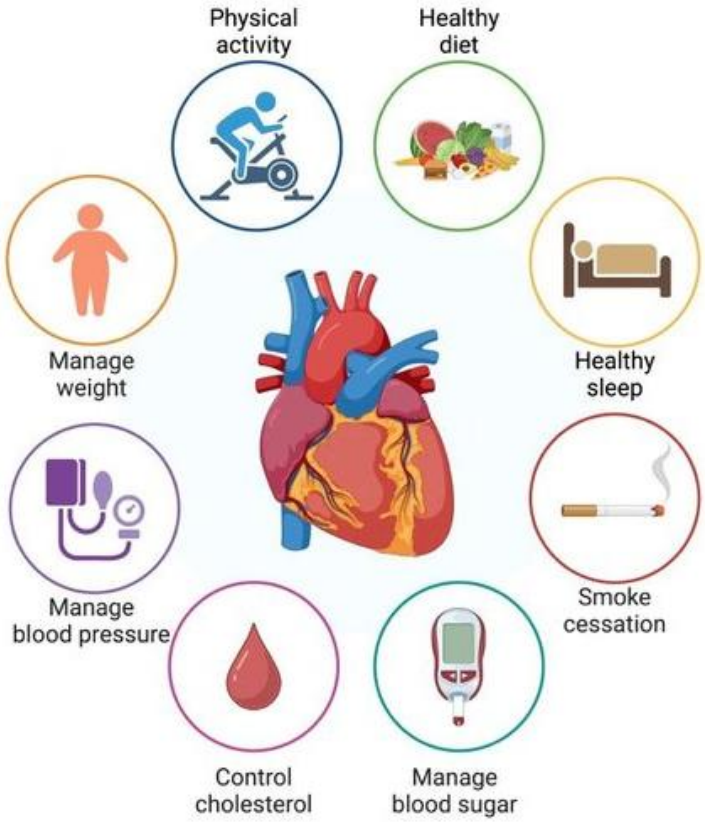

Figure 1: Modifiable risk factors for cardiovascular disease.

kidney-shaped, possess a sheathing base, and display finely scalloped margins on smooth surfaces. They are borne on slender petioles approximately 2–6 cm long, and the lamina can expand to about 15 cm in diameter. The stems are glabrous and faintly ridged, producing adventitious roots at nodal points. Inflorescences occur as small clusters of three to four flowers, which may be white, pink, or purplish in colour. Fruit formation takes place throughout the plant's growth, yielding oblong to near-spherical fruits with a thick pericarp. Roots develop from the stem nodes and typically extend 12–15 cm in length (Haritha and Rao, 2011).

Traditionally, *C. asiatica* is used to treat several chronic conditions, including Alzheimer's disease, duodenal ulcers, varicose veins, psoriasis, leprosy, some types of eczema, hypertrophic scars, and keloids (Prakash et al., 2017). Its herbal tea is commonly consumed for its antioxidant properties, which contribute to numerous health-promoting effects (Rajest et al., 2014). Additionally, this medicinal plant exhibits notable

anti-inflammatory, anti-asthmatic, antioxidant, anticancer, hepatoprotective, and neuroprotective potential (Bian et al., 2012).

C. asiatica contains a wide spectrum of biologically active molecules, with more than 130 compounds identified to date. These constituents primarily fall within the categories of triterpenoids, polyacetylenes, flavonoids, phytosterols, phenolic derivatives, and essential oils (Kunjumon et al., 2022). Terpenes, one of the major groups, are classified according to the number of carbon atoms derived from isoprene units: hemiterpenes (C5), monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), sesterterpenes (C25), triterpenes (C30), and polyterpenes with extended chains of multiple isoprene units (James & Dubery, 2009). Among these, triterpenes are the most pharmacologically significant. They are typical secondary metabolites produced via the isoprenoid biosynthetic pathway, yielding a hydrophobic aglycone core that may be linked to hydrophilic sugar groups, forming triterpenoid glycosides. Several triterpenes have been characterised in *C. asiatica*, including asiatic acid, madecassic acid, asiaticoside, madecassoside, brahmoside, brahmic acid, brahminoside, thankiniside, isothankunisode, centelloside, madasiatic acid, centic acid, and cenellic acid (Zheng & Qin, 2007).

In addition, *C. asiatica* is rich in phenolic compounds, primarily contributed by various flavonoids including quercetin, kaempferol, catechin, rutin, apigenin and naringin, as well as volatile constituents such as caryophyllene and farnesol (Chong & Aziz, 2013). These flavonoid molecules serve as important defence substances in plants, helping them cope with both environmental and biological stressors while also supporting diverse physiological processes and ecological interactions (Pourcel et al., 2007). Structurally, flavonoids contain isopentyl and methyl groups, making them hydrophobic; however, they commonly occur as glycosides in nature, where the attachment of sugar residues and hydroxyl groups increases their solubility in water (Crozier et al., 2010).

3. PRECLINICAL INSIGHTS INTO *CENTELLA ASIATICA* FOR CARDIOVASCULAR DISEASE

Cardiac failure occurs when the heart can no longer deliver an adequate blood supply to meet the body's metabolic demands. Conditions such as myocardial ischaemia and cardiomyopathy commonly promote the development of cardiac hypertrophy as a compensatory response. Accordingly, cardiac failure constitutes a complex clinical syndrome defined by myocardial hypertrophy, excessive fibrotic deposition, and impaired diastolic and/or systolic performance, pathological features that are tightly coupled with chronic inflammatory activation within the myocardium (Carter et al., 2024).

In vitro studies provide evidence that *C. asiatica* and its major triterpenoid, asiatic acid constituents protect against cardiac hypertrophy and ischemic injury (Table 1). Asiatic acid, one of the primary bioactive compounds in *C. asiatica*, appears to exert cardioprotective effects by modulating signalling cascades associated with pathological heart enlargement and ischaemia. Research using neonatal cardiomyocytes demonstrated that asiatic acid attenuated hypertrophic alterations triggered by TGF-β1. Concentrations ranging from 2.5 to 30 µM significantly reduced the increase in cell size and ANP mRNA levels stimulated by TGF-β1. The study also showed that asiatic acid suppressed p38 and ERK phosphorylation as well as NF-κB DNA-binding activity (Si et al., 2014). Supporting these findings, another investigation reported that asiatic acid counteracted IL-1β-induced cardiomyocyte hypertrophy (Xu et al., 2015). Moreover, Ma et al. (2016) demonstrated that 20 µM asiatic acid diminished angiotensin II-related hypertrophic effects by activating AMPKα while downregulating mTOR and ERK signalling pathways. In a separate experiment employing an oxygen-glucose deprivation/reoxygenation model, Huang et al. (2016) showed that asiatic acid alleviated ischaemia-reperfusion injury in H9c2 cardiomyocytes. The protective effects were associated with the stimulation of the Akt/GSK-3β/HIF-1α signalling axis. Treatment at 10 µM reduced apoptotic cell death, lowered caspase-3 and caspase-9 activities, and decreased the Bax/Bcl-2 ratio. In addition, asiatic acid helped maintain mitochondrial function by limiting excessive ROS formation and intracellular Ca^{2+} accumulation, while preserving mitochondrial membrane potential (Huang et al., 2016).

Evidence from *in vivo* studies also supports the cardioprotective potential of *C. asiatica* (Table 1). In a previous study, oral supplementation with 200 mg/kg of an aqueous extract of *C. asiatica* significantly reduced elevated levels of cardiac injury biomarkers, such as lactate dehydrogenase, creatine phosphokinase, glutamate oxaloacetate transaminase, and glutamate pyruvate transaminase, in rats treated with adriamycin (Gnanapragasam et al., 2004). The extract additionally improved myocardial antioxidant status by elevating the activities of enzymes including reduced glutathione (GSH), glutathione-S-transferase, GPx, and SOD. These findings suggest that asiatic acid improves cardiac performance and enhances antioxidant defence in myocardial tissues exposed to cardiotoxic agents. In addition to the protective effects of *C. asiatica* crude extracts, its isolated triterpenoid components also exhibit beneficial effects in preventing heart damage. Ma et al. (2016) demonstrated that administering asiatic acid orally at 10 or 30 mg/kg for seven weeks alleviated pressure overload-induced cardiac hypertrophy and fibrosis in mice by promoting AMPKα activation while suppressing ERK and mTOR signalling pathways. The involvement

of AMPKα was further supported through pharmacological inhibition and AMPKα-knockout mouse models, in which the cardioprotective effects were abolished. In another study, treatment with asiatic acid (100 mg/kg/day for 2 weeks) reduced myocardial hypertrophy and functional impairment in mice subjected to transverse aortic constriction (TAC). Furthermore, asiatic acid downregulated ANP and TGF-β1 expression in hypertrophic heart tissue and inhibited the phosphorylation of p38 and ERK1/2, as well as NF-κB activation, *in vivo* (Si et al., 2014).

Further investigations have demonstrated that oral administration of asiatic acid at 25 mg/kg improves cardiac performance and reduces adverse left ventricular remodelling in rat hearts. In myocardial infarction models, treatment with asiatic acid was associated with marked reductions in ventricular hypertrophy and interstitial fibrosis at the infarct border area (Huo et al., 2016). The same study also revealed that asiatic acid suppresses pro-inflammatory cytokines such as TGF-β1 and TNF-α, decreases NF-κB expression, and inhibits phosphorylation of p38 MAPK and ERK1/2 (Huo et al., 2016). In addition to asiatic acid, other triterpenoids derived from *C. asiatica* have demonstrated cardioprotective efficacy. Madecassoside at 50 mg/kg, administered over 2 hours of reperfusion, significantly protected Wistar rats against ischemia-reperfusion-induced myocardial infarction by decreasing lipid peroxidation, inflammation, and apoptotic markers (Bian et al., 2008). Oral dosing of madecassoside at 20 mg/kg for five consecutive days has also been shown to reduce circulating TNF-α levels, mitigate the decline in mean arterial pressure, and alleviate tachycardia in lipopolysaccharide-challenged rats. Moreover, madecassoside prevented the LPS-induced elevation of TNF-α and inhibited the activation of NF-κB, ERK, and p38 MAPK signalling pathways in neonatal rat cardiomyocytes (Cao et al., 2010).

Hypertension is defined as a persistent increase in either systolic or diastolic blood pressure beyond normal physiological limits. Asiatic acid, a major bioactive compound from *C. asiatica*, has demonstrated significant antihypertensive potential in various experimental models. In 2K-1C renovascular hypertensive rats, daily intragastric administration of 30 mg/kg for four weeks was shown to reduce elevated mean arterial pressure and heart rate to near-normal values (Maneesai et al., 2017). Similarly, in L-NAME-induced hypertensive rodents, oral intake of asiatic acid at 10–20 mg/kg/day for two weeks improved cardiovascular function and restored haemodynamics by enhancing nitric oxide bioavailability (Bunbupha et al., 2014). In another investigation, Pakdeechote et al. (2014) reported that three weeks of asiatic acid treatment corrected metabolic disturbances, including insulin resistance and dyslipidaemia, while simultaneously reducing oxidative stress and increasing nitric oxide synthase expression. Supporting these

observations, additional studies revealed that asiatic acid at 20 mg/kg/day for three weeks effectively attenuated high blood pressure and tachycardia, modulated renin–angiotensin system activation, reduced sympathetic overactivity, and improved metabolic parameters, including blood glucose, insulin, and total cholesterol levels (Maneesai et al., 2016).

Beyond their cardioprotective capabilities, *C. asiatica*-derived compounds also contribute to maintaining vascular health. For instance, asiatic acid has been shown to enhance vascular function in rat models (Maneesai et al., 2016). Expanding on this vascular benefit, Wang et al. demonstrated that asiaticoside provides protection against pulmonary hypertension. In their study, daily intragastric administration of 50 mg/kg asiaticoside for four weeks resulted in notable reductions in mean pulmonary arterial pressure, cardiac hypertrophy, and pulmonary vascular remodelling in rats exposed to chronic hypoxia (Wang et al., 2015). These improvements were associated with a downregulation of TGF-β1 and its receptor, along with suppressed Smad2/3 and phosphorylated Smad2/3 levels in lung tissues. Such outcomes indicate the therapeutic potential of asiaticoside in hypoxia-induced pulmonary hypertension. Moreover, subsequent research further confirmed its antihypertensive benefits, demonstrating enhanced nitric oxide production, increased cGMP availability, and prevention of elevated plasma endothelin-1 levels in established pulmonary hypertension (Wang et al., 2018).

Table 1: Cardioprotective effects of *Centella asiatica.*

Model	**Extract/compound**	**Effect/mechanism**	**Reference**
In vitro	Asiatic acid	Prevents cardiomyocyte hypertrophic response induced by TGF-β1	Si et al., 2014
	Asiatic acid	Inhibits cardiomyocyte hypertrophic response stimulated by IL-1β	Xu et al., 2015
	Asiatic acid	Attenuates angiotensin II-induced hypertrophy of cardiac myocytes and accumulation of collagen in cardiac fibroblasts	Ma et al., 2016
	Asiatic acid	Protects H9c2 rat cardiomyocytes from oxygen-glucose deprivation/reoxygenation injury	Huang et al., 2016

In vivo	Asiatic acid	Prevents cardiac hypertrophy and fibrosis in pressure overload-induced mice	Ma et al., 2016
	Asiatic acid	Prevents cardiac hypertrophy and dysfunction in pressure overload-induced mice	Si et al., 2014
	Asiatic acid	Improves cardiac function and inhibits cardiac hypertrophy and left ventricular remodelling following coronary artery ligation-induced myocardial infarction	Huo et al., 2016
	Asiatic acid	Improves alteration of the hemodynamics in 2K-1C hypertensive rats	Maneesai et al., 2017
	Asiatic acid	Reduces blood pressure by improving NO bioavailability in L-NAME-induced hypertensive rats	Bunbupha et al., 2014
	Asiatic acid	Improves hemodynamic abnormalities such as increased blood pressure, heart rate, and hind-limb vascular resistance in high-carbohydrate, high-fat-diet-induced metabolic syndrome rats	Pakdeechote et al., 2014
	Asiatic acid	Reduces blood pressure by decreasing renin angiotensin overactivity, sympathetic nerve overactivity and improving vascular function in high-carbohydrate and high-fat-diet-induced metabolic syndrome rats	Maneesai et al., 2016
	Asiaticoside	Reduces systemic blood pressure in hypoxia-induced pulmonary hypertensive rats	Wang et al., 2015
	Asiaticoside	Inhibits raised blood pressure and improves impaired production of NO	Wang et al., 2018

		and cGMP in hypoxia-induced pulmonary hypertensive rats	
	Medecassoside	Decreases ischemia-reperfusion injury-induced myocardial infarction	Bian et al., 2008
	Medecassoside	Reduces plasma TNF-α levels, prevents hypotension and tachycardia in LPS-induced rats	Cao et al., 2010

4. CONCLUSION

C. asiatica possesses a broad spectrum of therapeutic properties. Emerging evidence from *in vitro* and *in vivo* studies indicates that *C. asiatica* offers protection against cardiovascular disorders and their associated complications. The mechanisms underlying the cardiovascular preventive properties of *C. asiatica* have been elucidated using *in vitro* and *in vivo* models. The pharmacological properties of *C. asiatica* require thorough investigation to furnish more robust evidence for future applications.

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Chapter 7
Pharmacological Insights into *Cosmos caudatus* as a Natural Antidiabetic Agent

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ABSTRACT

Cosmos caudatus Kunth (ulam raja) is a tropical medicinal plant that has historically been consumed as a vegetable and is appreciated for its therapeutic properties. Increasing data suggest its potential as a natural antidiabetic drug, which is largely due to its high concentration of bioactive phytochemicals with antioxidant and glucose-lowering properties. This chapter examines and synthesises findings from phytochemical, *in vitro*, *in vivo*, and clinical trials on *C. caudatus* for diabetes treatment. Data were evaluated from published studies on the plant's bioactive substances, enzyme inhibition assays, antioxidant capacity, and effects on glycaemic management. Various bioactive compounds, including alkaloids, flavonoids, saponins, tannins, terpenoids, and polyphenols including α-linolenic acid, α-D-glucopyranoside, α-tocopherol, and catechin, have been associated to antidiabetic action. The 50% ethanolic extract had the best α-glucosidase inhibition and the largest phenolic content, demonstrating that moderate-polarity solvents are most effective for extracting active chemicals. LC-MS/MS profiling identified twelve main metabolites, including quercetin, oroxin B, stearidonic acid, and spathulenol, which are known for their antioxidant and enzyme-inhibiting properties. Current evidence supports its usage as a viable natural supplementary

therapy for diabetes, necessitating additional research to isolate active components and understand underlying mechanisms.

Keywords: *Cosmos caudatus*, Phytochemicals, Antidiabetic activity, α-glucosidase inhibition, Insulin sensitivity

1. INTRODUCTION

One of the most common metabolic disorders is type 2 diabetes mellitus (T2DM), which is characterised by chronic hyperglycaemia caused by pancreatic beta-cell failure and peripheral insulin resistance (Młynarska et al., 2025). This disease is a huge global health concern, impacting about 380 million people in 2014, with forecasts indicating that the figure will climb to 592 million by 2035 (Murtaza et al., 2025). Malaysia shares this global trend, with one out of every five Malaysians over the age of 30 diagnosed with T2DM (Tarmizi et al., 2025). Despite the widespread use of oral antidiabetic medications, around 78% of patients in Malaysia continue to struggle to maintain good glycaemic control, with an average HbA1c of 8.7% (Chandran et al., 2019).

T2DM pathogenesis is characterised by complicated metabolic changes such as hyperglycaemia and insulin resistance, both of which lead to pancreatic beta cell degeneration. Although long-term use of oral antidiabetic treatments like metformin and sulfonylureas can effectively lower blood glucose levels, they also entail dangers such as lactic acidosis and hypoglycaemia (Hussain et al., 2025). Given the importance of oxidative stress in T2DM problems, antioxidants have received attention for their possible protective effects in stabilising free radicals and minimising cellular damage. Herbal medicines high in antioxidant molecules have been extensively studied as complementary therapy for T2DM. *Cosmos caudatus*, often known as Ulam Raja, is a traditionally consumed herb in Southeast Asia. *Cosmos caudatus* has emerged as a promising natural agent in the therapy of type 2 diabetes due to its high antioxidant content, which may improve glycaemic control and reduce diabetes-related oxidative damage. Thus, this chapter aims to provide a full understanding of how *C. caudatus* may help with diabetes management and promote its development as a natural treatment alternative.

2. *COSMOS CAUDATUS*

Cosmos caudatus Kunth., often known as wild cosmos or ulam raja, is an Asteraceae species native to Central America. It is a short-lived perennial scented herb that grows to 1-2 meters tall. The plant has opposite, pinnate leaves divided into five leaflets. The upper surface is dark green, and the underside is paler and hairy. The pink or violet daisy-

like flowers with a cluster of yellow florets in the centre (Figure 1). *C. caudatus* is commonly used as a raw salad herb in Malaysia due to its distinct aroma and flavour, which complement local recipes. It has traditionally been used to promote blood circulation, strengthen bones, lower body temperature, slow aging, and treat illnesses. It is also thought to improve breath and strengthen bone marrow (Cheng, Barakatun-Nisak, et al., 2015). These ancient uses have sparked renewed scientific interest in its potential medical and nutraceutical benefits.

Figure 1: *Cosmos caudatus* (Ahda et al., 2023).

C. caudatus has a wide range of bioactive substances, such as ascorbic acid, quercetin, proanthocyanidin, chlorogenic acid, and catechin, which contribute to its potent antioxidant capabilities. The plant has high antioxidant capacity of 2500 mg ascorbic acid equivalent antioxidant capacity (AEAC) per 100 g fresh sample, which is much greater than that of orange or guava (Cheng et al., 2016). This powerful antioxidant activity, which is mostly due to its polyphenolic concentration, serves to minimise oxidative stress and protect cells from damage. Because oxidative stress and inadequate reactive oxygen species control play important roles in chronic diseases. Furthermore, the plant's major metabolites, flavonoids, phenolic acids, and diterpenoids, have a variety of biological activities, including antioxidant, antibacterial, antifungal, anti-inflammatory, anti-diabetic, anti-hypertensive, hepatoprotective, detoxifying, anti-osteoporotic, and anti-hyperlipidemic properties, indicating its potential as a functional medicinal and nutraceutical plant (Ahda et al., 2023).

Beyond Malaysia, the plant is culturally and medicinally significant in various regions. In Bangladesh, the flowers are utilised as ornaments in

Hindu religious rites (Rafiqul Islam et al., 2024). The aerial sections have traditionally been used to treat skin diseases such as leprosy and in herbal treatments for people with skin infections (Chan et al., 2017). *C. caudatus* has a diverse spectrum of chemical compounds, including polyphenols, which are frequently associated with antidiabetic action (Murugesu et al., 2020). Previous research has discovered various active components in this plant, including flavonoids, saponins, alkaloids, tannins, and polyphenols (Ahda et al., 2023; Firdaus et al., 2021). Furthermore, studies have indicated that water extracts of *C. caudatus* contain a high concentration of phenolic components, whilst methanol and ethanol extracts have substantial antioxidant properties (Sia et al., 2020). These features point to the plant's ability to reduce oxidative stress, a major role in diabetes progression. *C. caudatus* extracts in n-hexane and ethanol inhibit α-glucosidase and α-amylase, enzymes involved in glucose absorption and metabolism, providing direct antidiabetic actions (Firdaus et al., 2021).The inclusion of bioactive substances like catechin, α-D-glucopyranoside, and α-tocopherol reinforces its involvement in glucose regulation (Ahda et al., 2023).

3. PHYTOCHEMICAL AND ANTIDIABETIC PROPERTIES OF *COSMOS CAUDATUS*

Phytochemical studies on *C. caudatus* have identified a diverse range of bioactive compounds with significant pharmacological promise, particularly as antidiabetic drugs. Javadi et al. (2014) found α-linolenic acid, α-D-glucopyranoside, α-tocopherol, and catechin in the ethanolic extract of *C. caudatus*, which showed significant *in vitro* antidiabetic effects (Javadi et al., 2014). Loh and Hadira (2011) conducted *in vitro* studies using α-glucosidase and α-amylase inhibition tests to assess the extract's inhibitory effects on carbohydrate metabolism enzymes. These findings demonstrate the properties of *C. caudatus* to modulate postprandial hyperglycaemia via enzymatic regulation (Loh & Hadira, 2011).

Phytochemical screening of *C. caudatus* leaves revealed the presence of key types of bioactive chemicals, including alkaloids, flavonoids, saponins, tannins, and terpenoids, which is consistent with previous research (Senjaya et al., 2024). These secondary metabolites are widely known for their medicinal properties, particularly their antioxidant and antidiabetic actions. Alkaloids, for example, have antioxidant properties and operate as antidiabetic drugs by inhibiting gluconeogenic activity, lowering endogenous glucose synthesis (Muhammad et al., 2021). Flavonoids may mitigate complications associated with type 2 diabetes by suppressing the production of reactive oxygen species (ROS), promoting β-cell regeneration, and reducing oxidative stress (Caro-Ordieres et al., 2020). Saponins have both *in vitro* and *in vivo* antioxidant

properties and can lower blood glucose levels by blocking glucose transport across the gastrointestinal epithelium (Zhou & Xu, 2023). Tannins, on the other hand, have antidiabetic properties via boosting glycogenesis and decreasing intestinal glucose absorption, whilst terpenoids have been used extensively in traditional antidiabetic formulations due to their capacity to regulate glucose metabolism and insulin sensitivity (Ajebli & Eddouks, 2019).

In vitro enzymatic experiments showed that *C. caudatus* hexane extract inhibited α-glucosidase strongly and α-amylase mildly. Moderate α-amylase inhibition is therapeutically beneficial, as total inhibition may result in starch buildup and fermentation in the colon, thereby causing gastrointestinal discomfort (Firdaus et al., 2021). The only clinical study on *C. caudatus* consumption in humans found that short-term ingestion of fresh leaves dramatically enhanced insulin sensitivity in T2DM patients (Cheng, Barakatun-Nisak, et al., 2015). The hexane extracts inhibited α-glucosidase significantly, whereas the dichloromethane extract had lower activity. However, both extracts effectively inhibited α-amylase. The ethanolic extract inhibited α-glucosidase with an IC_{50} value of 59.99 μg/mL, indicating its potency in enzyme inhibition. Catechin, α-linolenic acid, α-D-glucopyranoside, and vitamin E play a key role in glucose control through complimentary processes. The 50% ethanol extract showed the highest α-glucosidase inhibition among investigated solvents, with an IC_{50} value of 77.17 ± 37.08 μg/mL (Firdaus et al., 2021). These findings indicate that the antidiabetic contents of *C. caudatus* are most soluble in a hydroethanolic solvent, supporting the use of 50% ethanol as an effective extraction medium for bioactive chemical isolation.

Liquid Chromatography-Mass Spectrometry/Mass Spectrometry (LC-MS/MS) profiling of three separate *C. caudatus* leaf extracts revealed twelve major bioactive compounds, the majority of which are secondary metabolites with antioxidant and antidiabetic effects. The aqueous extract produced two chemicals, genistin and gentiatibetine, both of which had mild antioxidant activity; however, only genistin had detectable antidiabetic potential. In contrast, the 50% ethanol extract yielded six main chemicals with varied biological functions. The major element, quercetin, is a powerful antioxidant with strong antidiabetic properties that outperform acarbose. Compounds identified include oroxin B (mild antioxidant activity), stearidonic acid and phenylpropionic acid (both with hypoglycemic effects), and 1,3,6-trihydroxy-2-methylanthraquinone-3-O-β-D-glucopyranoside, a novel anthraquinone derivative with a glucopyranoside moiety, indicating potential antidiabetic activity. Among the solvent systems studied, the 50% ethanol extract had the largest total phenolic and flavonoid content, as well as the strongest antioxidant and antidiabetic properties. LC-MS/MS analysis revealed that the extract contained the highest concentration of

quercetin, which corresponded to its greater biological efficiency (Wan-Nadilah et al., 2019). These findings show that a moderate ethanol concentration improves the extraction of both polar and nonpolar phytoconstituents important for the plant's pharmacological activity.

The promising *in vitro* results were supported by *in vivo* and clinical trials. In animal studies, *C. caudatus* extract provided to male rats at doses of 200 mg/kg and 400 mg/kg body weight (BW) significantly lowered blood glucose levels after 35 and 49 days of therapy, respectively, although a lower dose of 100 mg/kg BW had no statistically significant impact (Tandi et al., 2018). Clinical studies with type 2 diabetics who consumed 15 g of fresh *C. caudatus* leaves daily for eight weeks revealed a considerable improvement in insulin sensitivity (Cheng, Ismail, et al., 2015), confirming the preclinical findings.

The potent antidiabetic activity of *C. caudatus* is attributed to a synergistic interaction among multiple phytoconstituents, including quercetin, kaempferol, myricetin, catechin, luteolin, apigenin, quercitrin (quercetin 3-O-rhamnoside), quercetin 3-O-glucoside, quercetin 3-O-arabinofuranoside, rutin,phenolic acids (such as chlorogenic acid), α-linolenic acid, myo-inositol, diterpenoids, costunolide, and stigmasterol. Advanced metabolomic analysis revealed the existence of these chemicals, many of which have well-documented antioxidant and glucose-lowering properties. Wan-Nadilah et al. found that quercetin derivatives, in particular, play an important role in *C. caudatus*' antidiabetic effects (Wan-Nadilah et al., 2019). Nonetheless, despite these developments, isolation and structural characterisation of individual active chemicals from *C. caudatus* is still limited. As a result, future research should focus on isolating, purifying, and understanding the mechanisms of these chemicals in order to enable the development of innovative plant-derived medicinal agents for diabetes treatment.

4. TOXICITY AND SAFETY OF *COSMOS CAUDATUS*

Cosmos caudatus (ulam raja), a member of the Asteraceae family, is commonly consumed in Malaysia for its purported health benefits, including antioxidant, anti-diabetic, and circulatory-enhancing properties. Regardless of its popularity, toxicological testing is required to ensure its safety, especially at larger doses and in extract form.

Acute toxicity experiments in male rats revealed that *C. caudatus* extract is generally harmless at low to moderate doses. Administration of 50 mg/kg extract had no significant negative effects on biochemical, haematological, or organ weight parameters. Fresh *C. caudatus* leaves in doses of up to 15 g have also been shown to be safe and recommended as a dietary supplement for diabetes treatment (Amna et al., 2013).

Furthermore, aqueous extracts at 50 mg/kg demonstrated possible nephroprotective benefits in animal models, indicating enhanced kidney function. However, toxicity becomes apparent at higher doses. Acute treatment of 500-2000 mg/kg extract resulted in raised liver enzymes, including alkaline phosphatase (ALP) and alanine transaminase (ALT), as well as decreased serum albumin levels, indicating dose-dependent hepatotoxicity (Norazlina et al., 2013).

Subacute toxicity tests conducted in accordance with OECD Guidelines 407 indicated additional dose-related effects, such as altered organ weights, reduced red blood cell counts, decreased packed cell volume, and alterations in white blood cell parameters, especially at doses of 250-500 mg/kg (Amna et al., 2013). Although no severe behavioural toxicity was detected, these data suggest that continued exposure to greater dosages could cause systemic toxicity. In conclusion, *C. caudatus* appears to be safe when ingested in low amounts or fresh, while excessive doses of extracts may pose hepatotoxic and haematological concerns. Comprehensive toxicological assessments, such as chronic toxicity, mechanistic research, and evaluation of isolated bioactive chemicals, are necessary to establish safe therapeutic limits for human usage.

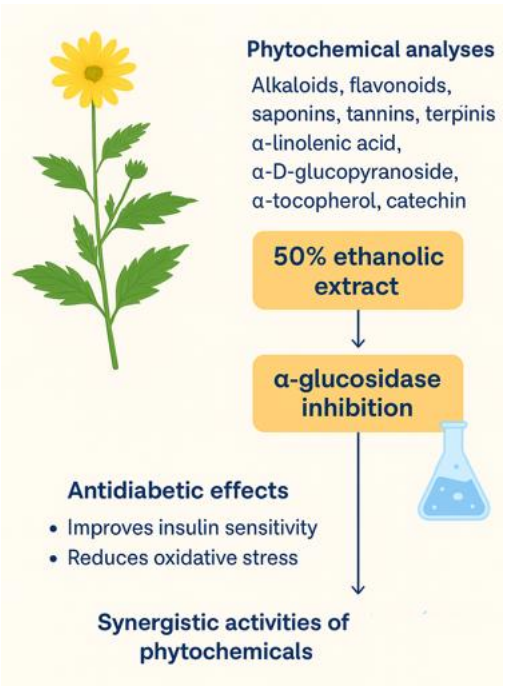

Figure 2: Mechanistic insight of *Cosmos caudatus* as a natural anti-diabetic agent.

5. CONCLUSION

C. caudatus has a wide range of bioactive phytochemicals, including flavonoids, alkaloids, saponins, tannins, terpenoids, and polyphenolic substances like quercetin, catechin, and α-linolenic acid, which contribute to its antioxidant and antidiabetic activities. Extensive *in vitro* and *in vivo* evidence shows that *C. caudatus* extracts, particularly the 50% ethanolic extract, efficiently block α-glucosidase and α-amylase activities, lowering blood glucose levels and improving insulin sensitivity. Clinical studies back up its promise as a supplementary medication in the treatment of type 2 diabetes. The antidiabetic effects are principally due to its capacity to control carbohydrate-metabolizing enzymes, enhance β-cell activity, and reduce oxidative stress (Figure 2). Overall, *C. caudatus* is a promising natural source of antidiabetic chemicals, particularly quercetin and its derivatives. However, more research into the separation, structural elucidation, and mechanistic characterisation of its active elements is required to aid in the development of standardised, plant-based medicinal medicines for diabetes treatment.

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Chapter 8
Anti-Inflammatory Herbs for Arthritis

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ABSTRACT

Arthritis is a chronic inflammatory disorder of the joints that causes pain, stiffness, and decreased mobility, with rheumatoid arthritis (RA) and osteoarthritis (OA) being the most common forms. The increase in arthritis cases around the world calls for the development of safe and effective treatments. One approach that is getting more attention is using herbal plants that have anti-inflammatory and antioxidant effects. *Tripterygium wilfordii* Hook F (TwHF) and *Curcuma longa* (turmeric) are two herbs that have shown promising therapeutic effects. TwHF suppresses inflammatory mediators such as IL-6 and CRP through immunomodulatory mechanisms, while curcumin from *Curcuma longa* inhibits the activation of the NF-κB, Akt, MAPK pathways, and the COX-2 enzyme, which plays a role in prostaglandin formation. Clinical trials and meta-analyses have shown significant reductions in inflammatory biomarkers and joint pain symptoms without serious side effects. These findings strengthen the potential of these two herbs as safe and effective complementary therapies for arthritis.

Keywords: Arthritis, Rheumatoid arthritis, Osteoarthritis, *Tripterygium wilfordii* Hook F, *Curcuma longa*.

1. INTRODUCTION

Arthritis is a condition affecting the joints, causing pain, stiffness, swelling, and decreased function due to acute or chronic inflammation. It is a leading cause of disability, imposes an economic burden, and significantly impacts the musculoskeletal system. The two most common forms are rheumatoid arthritis (RA) and osteoarthritis (OA) (Ma et al., 2009). There was a significant increase in the incidence of RA over 32 years, from 11.66 to 13.48 per 100,000 population. The number of disability-adjusted life years (DALYs) also went up, from 26.37 to 30.71 per 100,000 people, with women being more at risk (Zhang et al., 2025). OA also contributes to a relatively high incidence rate, with prevalence

reaching 19–30% in the age group above 45 years (Eze et al., 2024). Hazes et al. (2011) estimate that approximately 47% of women and 40% of men will experience OA in their lifetime.

The occurrence of arthritis usually involves several inflammatory signalling pathways (Figure 1) depending on the type of underlying trigger. Several studies have found a link between cytokines and chemokines such as tumour necrosis factor (TNF), interleukin-6 (IL-6), and granulocyte-monocyte colony-stimulating factor (GM-CSF)) that can activate immune cells in the synovium, which worsens the inflammatory condition (Derksen et al., 2017).

The increasing morbidity caused by arthritis and its complex pathogenesis necessitates the need for adequate treatment that can inhibit the inflammatory process through multiple pathways. This is expected to be the best solution to address the disease and prevent more serious problems. Researchers are currently studying several medicinal plants and herbs that show potential as antioxidants and anti-inflammatory agents. Modulating multiple inflammatory pathway targets is one of the benefits of using herbs, potentially leading to better disease-free outcomes. This chapter will discuss several herbs with known effects on arthritis.

2. INFLAMMATION PROCESS IN ARTHRITIS

Rheumatoid arthritis (RA) is classified as an autoimmune illness because of the correlation with an antibody known as rheumatoid factor (RF), which specifically targets the Fc fragment of immunoglobulin G (IgG) molecules. The most extensively researched autoantibodies are anti-citrullinated protein antibodies (ACPA). The citrullination process is essential for protein recognition, and ACPA is significantly increased in the synovial membrane during inflammation. This process initiates inflammation and accelerates bone degradation (Nithyashree & Deveswaran, 2020).

The primary lesion in rheumatoid synovitis is attributed to microvascular injury and elevated cellular infiltration in the synovial membrane, characterized by lateral perimysial infiltration of mononuclear cells. Microscopic analysis demonstrates distinctive hyperplasia and enlargement in synovial lining cells. The principal alterations in vascularization encompass emboli, ventricular injury, and the development of new vessels in regions with compromised blood supply due to trauma, accompanied by edema and infiltration of mononuclear cells, including lymphocytes, monocytes, and immature granulocytes. Endothelial cells in rheumatoid synovium display high endothelial venules, which are usually seen in lymphoid organs. This

situation alters due to cytokine exposure, which enhances cellular infiltration into the tissue, leading to a sustained rise in the quantity of adhesion molecules implicated in this process. The dimensions and content of mononuclear cells may differ based on the site of accumulation (Tanaka, 2020).

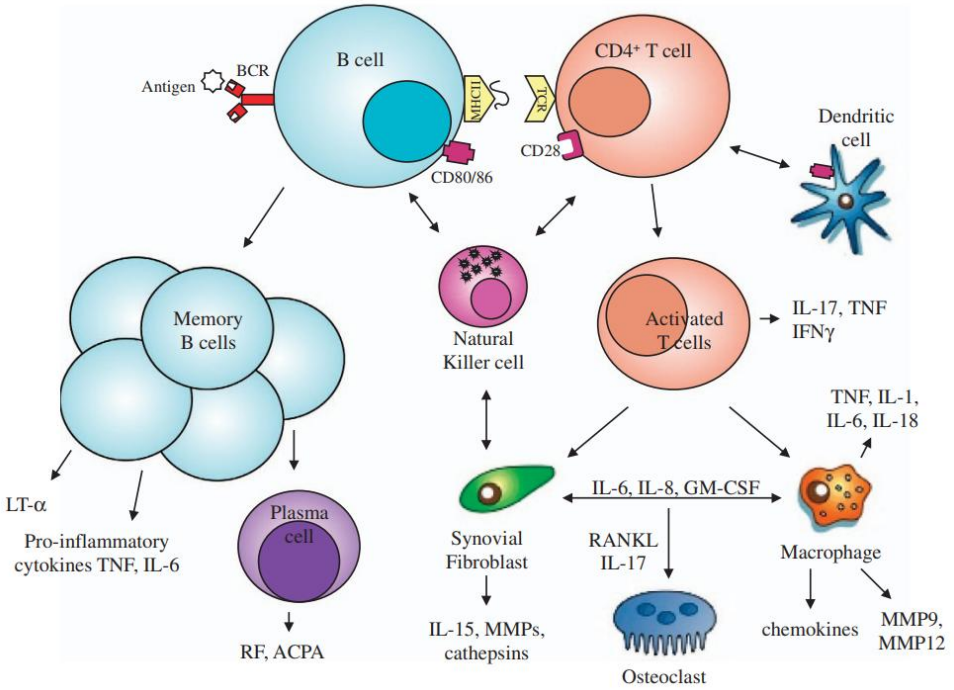

Figure 1: Immune pathways in Rheumatoid Arthritis (Chimenti et al., 2015).

T lymphocytes are the cells that most commonly infiltrate the tissue. In the synovium of individuals with rheumatoid arthritis, CD4+ memory T lymphocytes primarily accumulate near postcapillary venules, whereas CD8+ T cells are dispersed throughout the tissue. Rheumatoid synovitis is characterized by T cell proliferation as well as the invasion of many B cells and antibody-secreting plasma cells. Immune complexes are generated locally through the synthesis of polyclonal immunoglobulin (Ig) and autoantibodies (rheumatoid factor) in the synovial tissue. An elevated quantity of activated mast cells is also noted in rheumatoid synovium, where the degranulation of mast cells induces localized inflammation. Moreover, synovial fibroblasts have demonstrated the capacity to synthesize various enzymes, including collagenase and cathepsin, which contribute to the degradation of articular matrix constituents. The principal locus of bone erosion in rheumatoid arthritis is the region

inhabited by osteoclasts, which are the chief mediators of bone resorption and degradation (Chimenti et al., 2015).

3. HERBS AND ARTHRITIS

The role of herbs in healthcare is crucial, given their natural properties, which have the potential to modulate multiple inflammatory pathways and are expected to provide better disease-free outcomes. Research in the herbal field is also increasing, with increasing attention paid to safety and effectiveness. Such evidence indicates good potential for future development. Regarding arthritis, several herbs have been identified as having beneficial effects, particularly for RA and OA.

3.1 *Tripterygium wilfordii* Hook F (TwHF)

In traditional Chinese medicine, the root extract of the medicinal plant TwHF, referred to as "Lei Gong Teng" or "Thunder God Vine," has historically been utilized to address numerous inflammatory conditions, especially rheumatoid arthritis (RA). This plant is a member of the *Celastraceae* family and has garnered scientific interest owing to its extensive biological activity (Bao & Dai, 2011).

Phytochemical study reveals that TwHF comprises about 70 active components, including diterpenes, triterpenes, glycosides, and alkaloids, with roughly 95% being terpenoids (Brinker et al., 2007). Triptolide, tripdiolide, and triptonide are the predominant chemicals and are thought to significantly contribute to immunosuppressive and anti-inflammatory activities (Sarkar & Paul, 2017).

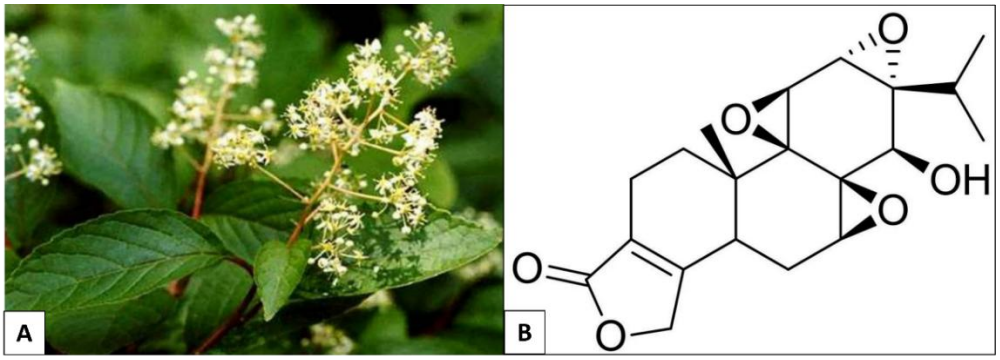

Figure 2: (A) *Tripterygium wilfordii*. (B) The chemical structure of triptolide (Sarkar & Paul, 2017).

A large, randomized clinical trial conducted at 11 medical centres in the United States compared the effectiveness and side effects of TwHF ethanol extract (180 mg/day) with sulfasalazine (2 g/day) in patients with

active rheumatoid arthritis. After 6 months of therapy, the group receiving TwHF showed rapid and marked clinical improvement, including decreased joint pain and swelling and improved general well-being. Laboratory results also showed significant reductions in inflammatory markers, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and the proinflammatory cytokine interleukin-6 (IL-6). Compared with sulfasalazine as standard therapy, TwHF provided a significantly higher clinical response based on the ACR20, ACR50, and ACR70 criteria and showed a significant improvement in the DAS28 score, indicating stronger anti-inflammatory efficacy (Goldbach-Mansky et al., 2009). However, the use of TwHF also carries the risk of side effects. Various studies have reported similar patterns of side effects in different dosage forms of the extract. The most frequently found effects include gastrointestinal disorders (especially diarrhea), decreased white blood cells (leukopenia), thrombocytopenia, skin rashes and pigmentation changes, and reproductive dysfunction in both men and women (Bao & Dai, 2011).

3.2 *Curcuma longa* (Turmeric)

Turmeric *(Curcuma longa)* is widely known as a spice that imparts a distinctive colour and aroma to various dishes. This rhizome plant is native to Southeast Asia and India and belongs to the ginger family *(Zingiberaceae)*. However, beyond its role as a culinary spice, turmeric also holds significant potential in the medical and scientific worlds (Lindler et al., 2020).

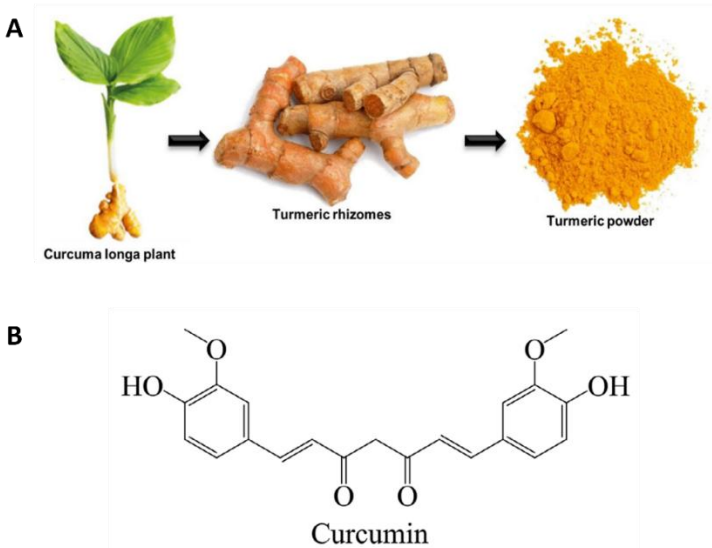

Figure 3: (A) *Curcuma longa* (Vo et al., 2021). (B) The chemical structure of curcumin (Razavi et al., 2021).

For decades, turmeric has been utilized in traditional Chinese and Ayurvedic medicine because of its curcumin content-a polyphenolic molecule demonstrated to possess potent anti-inflammatory and antioxidant properties. Curcumin operates through various pathways to inhibit inflammation. Studies indicate that curcumin extract can suppress the synthesis of inflammatory mediators, including IL-1, TNF-α, IL-8, and NO, by obstructing the activation of critical signaling pathways such as NF-κB, Akt, and MAPK. Furthermore, its inhibitory action on the COX-2 enzyme diminishes prostaglandin synthesis, hence mitigating pain and inflammation (Razavi et al., 2021).

Clinical data substantiates these advantages. A double-blind, randomized clinical research shown that a daily dosage of 1,500 mg of curcuminoids for six weeks significantly decreased levels of IL-4, IL-6, and hs-CRP in patients with mild to moderate knee osteoarthritis (Rahimnia et al., 2015). A meta-analysis of 29 studies encompassing approximately 2,400 patients with diverse forms of arthritis such as ankylosing spondylitis, rheumatoid arthritis, osteoarthritis, juvenile idiopathic arthritis, and gout, validated that the intake of curcumin and *Curcuma longa* extract is both safe and efficacious in alleviating inflammation and joint pain (Zeng et al., 2022). Turmeric is not merely a culinary spice but a "natural medicine" that demonstrates significant health benefits, particularly in the treatment of arthritis.

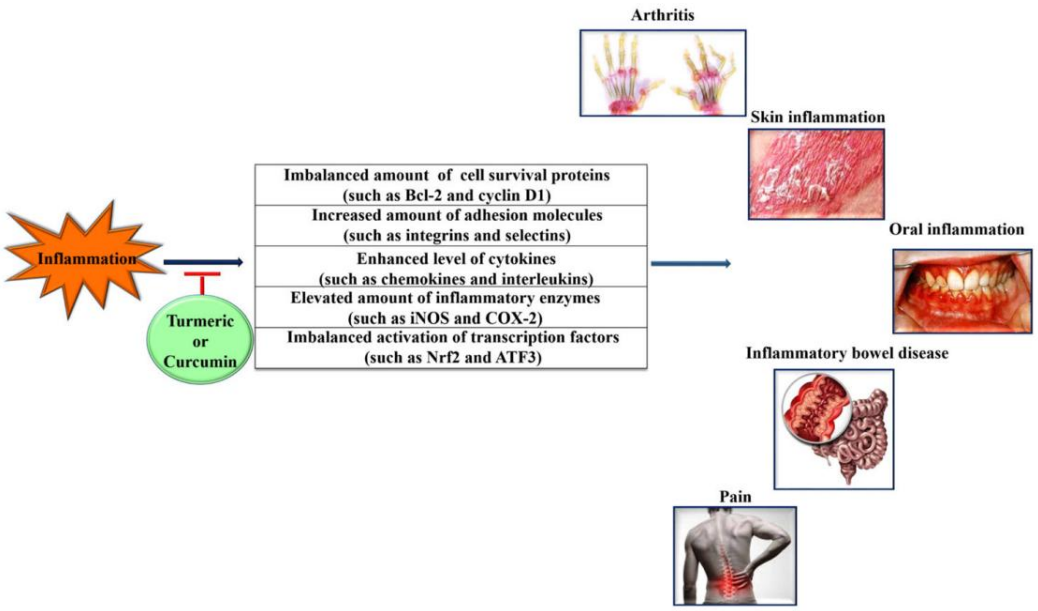

Figure 4: Anti-inflammatory mechanisms of turmeric and curcumin (Razavi et al., 2021).

4. MECHANISTIC SYNTHESIS

Rather than acting on a single mediator, both TwHF and turmeric-derived curcumin influence converging inflammatory nodes relevant to arthritis. TwHF is best characterized as an immunomodulator (particularly relevant to RA immune-cell activation), while curcumin exerts broader anti-inflammatory and antioxidant effects that converge on NF-kB-linked transcription and pain-related mediators such as COX-2 (Bao & Dai, 2011; Razavi et al., 2021). Table 1 summarizes the key pathways regulated by TwHF and *Cucuma longa.*

Table 1: Mechanistic synthesis.

Pathways	**TwHF**	***Curcuma longa***
Cytokine network (IL-6, TNF, IL-1)	Reductions in IL-6 and systemic inflammatory markers reported in RA trials (Goldbach-Mansky et al., 2009; Bao & Dai, 2011).	Reductions in hs-CRP/cytokines reported in knee OA; suppresses cytokine production in models (Rahimnia et al., 2015; Razavi et al., 2021).
NF-kB-linked signalling	Immunomodulatory mechanisms are proposed to dampen inflammatory gene programs (Bao & Dai, 2011)	Inhibits NF-kB and modulates Akt/MAPK pathways (Razavi et al., 2021)
Prostaglandins/COX-2	Indirect effects; not primarily a COX-2-directed herb	Inhibits COX-2 and prostaglandin synthesis, aligning with analgesic effects (Razavi et al., 2021).
Adaptive immunity	Stronger relevance to RA immune-cell activation and effector functions (Tanaka, 2020; Bao & Dai, 2011).	Less disease-specific immune targeting; evidence often OA or mixed populations (Zeng et al., 2022)

5. DOSAGE STANDARDIZATION, FORMULATION, AND QUALITY CONTROL

Dosage standardization is essential for integrating herbal adjuncts into arthritis management because both efficacy and toxicity are strongly exposure dependent. Unlike conventional drugs, herbal preparations can vary by plant part, extraction method, and the concentration of bioactive constituents (e.g., terpenoids in TwHF or curcuminoids in turmeric). Without clear reporting and standardization, it is difficult to compare studies or translate research doses to practice (Brinker et al., 2007; Bao & Dai, 2011). Table 2 presented the dosage that has been used in few studies.

Table 2**.** Dosage standardization.

Herb Preparation	**Dose in Study**	**Monitoring**
TwHF (ethanol extract)	180 mg/day in active RA trial (6 months)	Prefer products with quantified active constituents; monitor CBC and adverse effects; avoid in pregnancy; narrow safety margin (Goldbach-Mansky et al., 2009; Bao & Dai, 2011)
Curcuma longa (curcuminoids)	1,500 mg/day for 6 weeks in knee OA trial	Report curcuminoid content and formulation; consider bioavailability-enhanced products used in trials; monitor GI tolerance and drug interactions (Rahimnia et al., 2015; Razavi et al., 2021).

6. LIMITATIONS OF THE CLINICAL EVIDENCE

Even though clinical trials and meta-analyses point to benefits, the current body of evidence has flaws that should make strong claims about effectiveness less likely. First, a lot of studies are short compared to the long-term and changing nature of arthritis. For instance, the TwHF randomized trial monitored patients for 6 months (Goldbach-Mansky et

al., 2009), whereas frequently referenced curcuminoid trials in knee OA have a duration of approximately 6 weeks (Rahimnia et al., 2015). These durations may be inadequate for assessing enduring symptom management, structural advancement, or infrequent adverse events.

Second, the size of the sample and the characteristics of the population can cause bias. Trial participants may not accurately reflect the broader real-world populations characterized by multimorbidity, polypharmacy, or heterogeneous disease severity. Furthermore, herbal interventions are frequently evaluated as adjuncts to diverse background therapies, complicating the attribution of effects and potentially exaggerating perceived benefits.

Third, synthesis studies combine different types of medications and dosing schedules. The curcumin meta-analysis encompassed trials that addressed various arthritis phenotypes, employing diverse formulations, comparators, and outcome measures (Zeng et al., 2022). This diversity makes it hard to directly apply it to a single standardized clinical protocol. Future trials should prioritize thorough characterization of the tested product, extended follow-up periods, and clinically significant endpoints that assess both efficacy and safety.

7. CONCLUSION

The use of herbal plants such as *Tripterygium wilfordii* and *Curcuma longa* has shown positive results in suppressing the inflammatory process in various types of arthritis. The mechanisms of action of both involve inhibition of key inflammatory signalling pathways and reduction of pro-inflammatory mediators, resulting in improved clinical symptoms and improved quality of life for patients. Clinical trials confirm that herbal-based therapies are generally safe and can provide anti-inflammatory effects comparable to or even exceeding with some conventional therapies. In the future, more standardized, long-term clinical studies are needed to make sure that herbal therapies are effective, safe, and the right dose for modern medical practice.

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Chapter 9
Preclinical Insights into *Humulus lupulus* for Senile Osteoporosis

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ABSTRACT

Senile osteoporosis (SOP) is an age-related skeletal disorder characterised by reduced bone mass and impaired bone structure, mostly driven by oxidative stress, chronic inflammation, and β-amyloid (Aβ) buildup. *Humulus lupulus* L. (hops), a medicinal plant recognised for its strong antioxidant qualities, contains bioactive substances such as xanthohumol and bitter acids, which may protect against SOP. *In vitro* studies revealed that hops extract greatly increased osteoblast proliferation, differentiation, and matrix mineralisation while inhibiting osteoclast activity, cellular senescence, and apoptosis. These protective benefits were linked to increased antioxidant defence, as seen by higher levels of Nrf2, HO-1, NQO1, SOD, and CAT. Furthermore, BA induced autophagy by inhibiting the AKT/mTOR signalling pathway, hence promoting osteoblast survival under oxidative stress. *In vivo*, hops extract and xanthohumol were tested on APP/PS1 transgenic mice and D-galactose-induced SOP models. Results indicate increased bone mineral density (BMD), improved femoral microarchitecture, and decreased Aβ deposition in both brain and bone tissues. Cognitive function also increased, indicating a benefit for both skeletal and neurological health. Binding studies identified mTOR as a direct molecular target of xanthohumol, and autophagy inhibition experiments

revealed its critical role in mediating the anti-osteoporotic actions of bitter acid and xanthohumol. *Humulus lupulus* L. has multiple preventive actions against senile osteoporosis, including increasing antioxidant capacity, modulating bone metabolism, activating autophagy, and decreasing Aβ buildup. These properties make hops and its active chemicals intriguing natural candidates for the prevention and treatment of SOP, presenting a possible therapeutic strategy that addresses both bone health and age-related neurodegeneration.

Keywords: *Humulus lupulus* L., senile osteoporosis, senescence

1. INTRODUCTION

Osteoporosis is a common metabolic bone defect characterised by low bone density and degradation in bone quality, which leads to an increased risk of fractures. The disorder is typically classified into three types: postmenopausal, juvenile, and senile osteoporosis (Amarnath et al., 2023). Among these, senile osteoporosis (SOP) is a systemic bone disease linked to aging. It is defined by increasing bone mass loss, structural degeneration of bone tissue, increased bone fragility, and a much higher incidence of fractures in the aged population. With rising life expectancy and the growth of aging populations around the world, the prevalence of SOP has increased significantly. As a result, SOPs are becoming a major public health issue (Tagaev et al., 2025). Unlike postmenopausal osteoporosis, SOP is caused by more complex pathological alterations associated with aging. These include DNA damage, epigenetic changes, mitochondrial dysfunction, cellular senescence, stem cell impairment, and decreased intercellular communication. The aging skeleton has a dynamic and irreversible degenerative process that involves numerous stages, making bone repair and regeneration increasingly challenging (Li et al., 2025).

Fractures and femoral head necrosis occur often, emphasising the need for effective therapy techniques and improved biomaterials for bone healing (Hadad et al., 2025). An increasing body of evidence supports the involvement of various critical components and signalling pathways in SOP pathogenesis. These include increased oxidative stress, decreased autophagy, persistent low-grade inflammation, disturbance of the gut flora, and a drop in oestrogen levels, especially in postmenopausal women (Li et al., 2025).

In SOP, decreased bone mass is intimately related to alterations in the bone microenvironment. These include altered cytokine expression and a functional reduction in bone marrow-derived mesenchymal stem cells (BMMSCs). As people age, BMMSCs lose their osteogenic potential, which has been linked to decreased autophagy. Restoring autophagic activity

may therefore be a promising technique for improving BMMSC differentiation and recovering lost bone mass (Tian et al., 2025). Current osteoporosis prevention treatments typically include calcium-rich diets and regular physical activity, but these require long-term adherence to achieve visible results (Niedźwiedzka et al., 2025). Clinically effective treatments for boosting bone mineral density include anabolic medications such as teriparatide, abaloparatide, and romosozumab, as well as antiresorptive pharmaceuticals including bisphosphonates, SERMs, and denosumab (Jang et al., 2025). However, long-term use of these drugs is frequently associated with side effects such as gastrointestinal distress, ocular irritation, and possibly an increased risk of osteosarcoma or cardiovascular events (Wimalawansa, 2016).

As a result, the research and development of natural, safe, and effective alternatives is urgently required. In this regard, the plant *Humulus lupulus* has emerged as a possible contender. This chapter aims to explore the therapeutic potential of *Humulus lupulus* L. in the treatment of senile osteoporosis, drawing on both *in vivo* and *in vitro* preclinical trials.

2. *HUMULUS LUPULUS* L.

Humulus lupulus L. (hops) (Figure 1) is a popular medicinal and edible plant with numerous applications in the food, beverage, and pharmaceutical industries, owing to its strong antioxidant characteristics. Hops have long been used in traditional Chinese medicine to treat a variety of diseases, including digestive issues, tuberculosis, sleeplessness, and memory-related conditions (Carbone & Gervasi, 2022). It is commonly used in European herbal medicine to relieve menopausal symptoms such as hot flushes and to treat postmenopausal osteoporosis (Mohapatra et al., 2024). Recent studies have emphasised hops' high antioxidant activity, suggesting it as a viable natural source of antioxidants (Knez Hrnčič et al., 2019; Ruiz-Ruiz et al., 2020).

The cones of *Humulus lupulus* L. are abundant with secondary metabolites, particularly bitter acids (BA) and prenylated flavonoids like xanthohumol (XAN) and 8-prenylnaringenin (8-PN), which contribute significantly to the plant's numerous health benefits (Bakare & Mary, 2024). Study have shown that *Humulus lupulus* L. extracts (HLE) can successfully prevent bone loss in ovariectomised rats, most likely via reducing oxidative stress and regulating osteoblast and osteoclast activity (Xia et al., 2021). Xanthohumol has been proven to reduce Aβ-induced oxidative damage and bone degeneration in APP/PS1 mice and osteoblast models (Xia et al., 2022). Hops' beneficial effects on bone health are mostly related to bioactive chemicals, specifically xanthohumol and bitter

acids (Wanionok et al., 2025). While the anti-osteoporotic effects of hop extract and xanthohumol have been well documented (Sun et al., 2022; Xia et al., 2021), the biological activity of bitter acids is currently being investigated. Bitter acids (BA), comprising 5-20% of hop content, consist of α-acids (humulones) and β-acids (lupulones), both of which are prenylated phloroglucinol derivatives (Zhang et al., 2021). BA exhibit anticancer, anti-inflammatory, and anti-angiogenic properties, as well as strong antioxidant activity (DPPH radical scavenging capacity) (Iniguez & Zhu, 2021). Importantly, findings confirmed that BA can stimulate osteogenesis while blocking osteoclastic activity, indicating their potential involvement in bone health (Xia et al., 2024; Xu et al., 2022).

Figure 1: *Humulus lupulus* L. (Jiang et al., 2018).

3. EVIDENCE FROM *IN VITRO* STUDIES

In vitro studies have shown that *Humulus lupulus* L. extract (HLE) has favourable therapeutic potential in models with senile osteoporosis (SOP) (Table 1). HLE administration at 20 μg/mL dramatically increased osteoblast proliferation and raised the expression of major osteogenic markers, including bone morphogenetic protein-2 (BMP-2) and osteopontin. HLE at 100 μg/mL was found to stimulate ALP activity in osteoblasts, indicating early osteogenic differentiation. Notably, HLE at all tested concentrations significantly increased extracellular matrix mineralisation indicating improved osteoblast function and maturation. HLE at 20 μg/mL and 100 μg/mL concentrations inhibited tartrate-resistant acid phosphatase (TRAP) activity in osteoclasts and downregulated the expression of MMP-9 and cathepsin K, two proteolytic enzymes involved in bone resorption (Xia et al., 2021).

Humulus lupulus L. include bioactive compounds such as α-acids (humulones) and β-acids (lupulones), which contribute to their therapeutic benefits. Both components have excellent antioxidant characteristics, as demonstrated by their high oxygen radical absorption capacity and vulnerability to oxidative degradation (Astray et al., 2020). Importantly, humulone has been shown to trigger apoptosis in osteoclast

progenitors through antioxidant-mediated processes, implying a direct inhibitory effect on bone resorption (XIA, 2019). Furthermore, administration of bitter acid (BA) from *Humulus lupulus* L. was found to increase superoxide dismutase (SOD) and catalase (CAT) levels in serum, bone tissue, and osteoblast supernatants, while decreasing reactive oxygen species (ROS) and malondialdehyde (MDA) levels in D-galactose (D-gal)-induced osteoblasts (Xu et al., 2022). These findings suggest that BA's anti-SOP characteristics are directly linked to its capacity to reduce oxidative stress.

In addition to their antioxidant properties, BA have been shown to positively affect osteoblast function. In D-galactose-induced aging osteoblast models, BA increased proliferation, differentiation, and mineralisation while suppressing senescence and apoptosis. These results create an optimal cellular environment for osteoblast survival and activity. BA administration increased the nuclear translocation of nuclear factor erythroid 2-related factor 2 (Nrf2) and activated the downstream antioxidant enzymes heme oxygenase-1 (HO-1) and NAD(P)H quinone dehydrogenase 1 (NQO1 (Xu et al., 2022). Nrf2 is a crucial redox-sensitive transcription factor that regulates cellular oxidative equilibrium and protects against oxidative damage. SOD and CAT production is strongly associated to Nrf2 pathway activation, whereas HO-1 and NQO1 products are known to scavenge ROS and protect against DNA oxidative damage (Loboda et al., 2016). In SOP model, D-gal administration repressed Nrf2 nuclear translocation and decreased HO-1 and NQO1 expression, showing a deterioration in the antioxidant defence mechanism with age. However, BA therapy reversed these effects and restored antioxidant capacity. Notably, inhibiting Nrf2 reversed BA-induced overexpression of HO-1 and NQO1, indicating the Nrf2 pathway's participation in BA-mediated protection (Sun et al., 2022).

Xia et al. (2024) investigated the role of autophagy in BA-mediated bone preservation, providing additional insights into the mechanism. They used a D-galactose-induced *in vitro* SOP model to assess bone formation markers and apoptosis levels in osteoblasts. BA improved autophagy in aging osteoblasts, according to the study, which used mCherry-EGFP-LC3 adenovirus transfection and autophagic marker analysis such as beclin1 and LC3. To see if BA's bone-protective actions were dependent on autophagy, the autophagy inhibitor 3-MA was used. Inhibiting autophagy eliminated the positive effects of BA on cell proliferation, ALP activity, mineralisation, and reduction of apoptosis and senescence markers (e.g., SA-β-gal staining), demonstrating a vital role for autophagy in mediating these benefits (Xia et al., 2024).

BA has also been demonstrated to affect the AKT/mTOR signalling pathway, which is a well-known autophagy regulator. BA therapy lowered

the phosphorylation of AKT, mTOR, p70S6K, and 4EBP1, showing that this pathway is suppressed, which is often associated with autophagy inhibition. Importantly, stimulation of AKT and mTOR with agonists SC79 and MHY1485 inhibited BA-induced expression of autophagy-related proteins. These data implies that BA promotes autophagy by inhibiting the AKT/mTOR pathway, which helps osteoblasts survive and operate under oxidative stress (Xia et al., 2024). In conclusion, *in vitro* studies have shown that *Humulus lupulus* L., particularly its bitter acids, protects against senile osteoporosis by improving osteoblast function, inhibiting osteoclast activity, reducing oxidative stress, and activating autophagy via the Nrf2 and AKT/mTOR signalling pathways. These findings provide positive information on the potential of hops-derived chemicals as therapeutic agents for age-related bone loss.

Table 1: *In vitro* evidence of *Humulus lupulus L.* and its bioactive compounds in senile osteoporosis models.

Test material	**Model / Cell type**	**Key findings**	**Reference**
Humulus lupulus extract (HLE)	Osteoblasts and osteoclasts (SOP models)	↑ Osteoblast proliferation, ALP activity, BMP-2 and osteopontin expression; ↑ extracellular matrix mineralisation; ↓ TRAP activity, MMP-9 and cathepsin K expression	[Xia et al., 2021]
α- and β-acids (humulones, lupulones)	Antioxidant assays / osteoclast progenitors	High oxygen radical absorption capacity; induction of apoptosis in osteoclast progenitors	[Astray et al., 2020; Xia, 2019]
Bitter acids (BA)	D-gal-induced aging osteoblasts	↑ SOD and CAT; ↓ ROS and MDA; ↑ proliferation, differentiation, mineralisation; ↓ senescence and apoptosis	[Xu et al., 2022]
Bitter acids (BA)	D-gal-induced SOP osteoblasts	↑ Nuclear translocation of Nrf2; ↑ HO-1 and NQO1 expression;	[Xu et al., 2022; Sun et al., 2022]

		restoration of antioxidant capacity	
Bitter acids (BA)	D-gal-induced SOP osteoblasts	↑ Autophagy markers (Beclin-1, LC3); ↑ autophagosome formation; enhanced osteoblast survival	[Xia et al., 2024]
Bitter acids (BA)	D-gal-induced SOP osteoblasts (with pathway modulation)	↓ Phosphorylation of AKT, mTOR, p70S6K, and 4EBP1; autophagy inhibition reversed by AKT/mTOR agonists	[Xia et al., 2024]

Abbreviation: HLE: *Humulus lupulus* extract; SOP: Senile osteoporosis; ALP: Alkaline phosphatase; BMP-2: Bone morphogenetic protein-2; TRAP: Tartrate-resistant acid phosphatase; MMP-9: Matrix metalloproteinase-9; SOD: Superoxide dismutase; CAT: Catalase; ROS: Reactive oxygen species; MDA: Malondialdehyde; Nrf2: Nuclear factor erythroid 2-related factor 2; HO-1: Heme oxygenase-1; NQO1: NAD(P)H quinone dehydrogenase 1; BA: Bitter acids

4. EVIDENCE FROM *IN VIVO* STUDIES

Age-related disorders, such as senile osteoporosis (SOP), are linked to the buildup of β-amyloid (Aβ) and the oxidative damage it causes (Nasme et al., 2025). A recent *in vivo* study assessed the protective effects of hops extract (HLE) against SOP in APP/PS1 transgenic mice and Aβ-injured osteoblasts (Table 2). Behavioural tests using the Morris water maze demonstrated that HLE dramatically increased learning ability and memory retention in APP/PS1 mice. Histological analysis utilising Congo red staining revealed that HLE efficiently reduced Aβ deposition in the hippocampus, cortex, and femur. Furthermore, micro-CT scans showed that HLE increased bone mineral density (BMD) and femoral microarchitecture. Western blotting revealed that HLE regulates the expression of antioxidant enzymes and bone metabolism-related proteins in serum, implying a dual involvement in cognitive and skeletal health (Xia et al., 2023). Furthermore, in the same model, the osteoprotective effects of xanthohumol (XAN) were attributed to its regulation of the PI3K/AKT/Nrf2 signaling pathway in Aβ-injured osteoblasts. These findings offer valuable insights supporting the potential clinical use of XAN in the prevention and treatment of osteoporosis (Xia et al., 2022).

Expanding on this, Xia et al. (2025) employed a D-galactose (D-gal)-induced SOP mice model to test the efficacy of xanthohumol (XAN), a major prenylflavonoid in hops. Mice were administered with XAN for 12

weeks, and their responses were assessed using the Morris water maze, micro-CT, transcriptomics, and metabolomics. *In vitro*, D-gal-treated MC3T3-E1 osteoblasts were utilised to investigate the mechanism of XAN, using interventions including autophagy inhibitors (3-MA) and beclin-1 siRNA. XAN enhanced bone density and cognitive performance by activating the AKT/mTOR/p70S6K signalling pathway. XAN also improved osteoblast differentiation and mineralisation while reducing apoptosis and senescence. These effects were reversed when autophagy was inhibited, demonstrating autophagy's critical involvement. XAN boosted autophagosome formation and directly targeted mTOR, as demonstrated by molecular docking (Xia et al., 2025).

One *in vivo* study focused on how early-life isometric strength training and a long-term *Humulus lupulus* L.-enriched diet affected female rats' bone health. Rats were separated into trained and untrained groups and fed a control or hops-enriched diet for 100 weeks. While food alone had no significant impact on bone parameters, isometric training during young adulthood resulted in long-term gains in bone mineral density (BMD) and bone turnover indicators, even after training had stopped. These data show the long-term benefits of early strength training for bone health, implying that physical activity throughout youth is more effective than dietary changes in increasing peak bone mass (Figard et al., 2007).

Table 2: *In vivo* evidence of *Humulus lupulus L.* and xanthohumol (XAN) in senile osteoporosis models.

Test material	**Model / Animal**	**Key findings**	**Reference**
Humulus lupulus extract (HLE)	APP/PS1 transgenic mice; Aβ-injured osteoblasts	↑ Learning ability and memory retention (Morris water maze); ↓ Aβ deposition in hippocampus, cortex, and femur; ↑ BMD and femoral microarchitecture; regulation of antioxidant enzymes and bone metabolism-related proteins in serum	[Xia et al., 2023]
Xanthohumol (XAN)	APP/PS1 transgenic mice; Aβ-injured osteoblasts	Osteoprotective effects via PI3K/AKT/Nrf2 signaling; ↑ BMD; improved osteoblast differentiation and mineralisation; ↓ apoptosis and senescence	[Xia et al., 2022]

Xanthohumol (XAN)	D-galactose (D-gal)-induced SOP mice; MC3T3-E1 osteoblasts	↑ Bone density and cognitive performance; activation of AKT/mTOR/p70S6K signaling; ↑ autophagosome formation; effects reversed by autophagy inhibition	[Xia et al., 2025]
Hops-enriched diet + early-life isometric strength training	Female rats (100-week study)	Long-term ↑ BMD and bone turnover indicators; physical activity more effective than diet alone in increasing peak bone mass	[Figard et al., 2007]

Abbreviations: HLE: *Humulus lupulus* extract; SOP: Senile osteoporosis; Aβ: β-amyloid; BMD: Bone mineral density; XAN: Xanthohumol; D-gal: D-galactose

5. CONCLUSION

Both *in vitro* and *in vivo* studies consistently indicate that *Humulus lupulus* L. extract (HLE), particularly through major bioactive components such as xanthohumol (XAN) and bitter acids (BA), protects against senile osteoporosis (SOP). These advantages are primarily mediated by its high antioxidant, anti-inflammatory, and bone-regulatory characteristics, which all help to maintain bone health as we age (Figure 2).

In vitro studies have revealed that HLE extract increases osteoblast activity promoting cell proliferation, differentiation, and matrix mineralization while suppressing osteoclastogenesis, the process that causes bone resorption. These dual effects assist to maintain the delicate balance between bone growth and degeneration, which is frequently interrupted as we age. Treatment with HLE or BA significantly reduced reactive oxygen species (ROS) and increased the expression of key antioxidant defence proteins, including Nrf2, HO-1, NQO1, SOD, and CAT, in osteoblasts exposed to oxidative stress or β-amyloid (Aβ), which are common features of senile osteoporosis and neurodegeneration. This shows that HLE reduces oxidative damage, which is a key cause of age-related bone loss. Additionally, BA was discovered to activate autophagy, a cellular cleanup mechanism required for cell survival under stress, by inhibiting the AKT/mTOR signalling pathway. This mechanism not only decreases oxidative stress but also inhibits osteoblast apoptosis and senescence, which promotes bone growth.

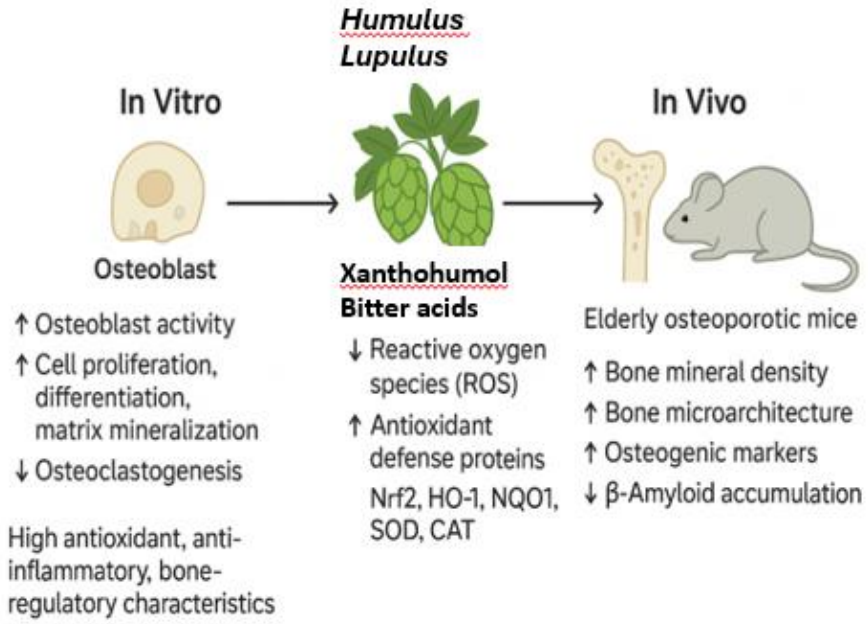

Figure 2: *Humulus lupulus* L. protects against senile osteoporosis.

In *in vivo* studies, elderly and osteoporotic mice models (e.g., APP/PS1 and D-galactose-induced models) treated with HLE or xanthohumol showed significant increases in bone mineral density (BMD) and bone microarchitecture, particularly in the femur. The improvements included increased osteogenic marker expression, improved antioxidant enzyme profiles, and decreased β-amyloid accumulation in bone and brain tissues. This combination advantage shows that hops have a unique therapeutic potential for addressing both cognitive decline and skeletal deterioration in aging. Furthermore, the identification of mTOR as a direct molecular target of xanthohumol lends evidence to its molecular function in autophagy regulation and bone homeostasis maintenance.

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Chapter 10
Protection of Visual Health with Herbal Therapies

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ABSTRACT

Vision loss from major ocular diseases such as age-related macular degeneration, diabetic retinopathy, glaucoma, and cataract affects millions worldwide. These conditions share key molecular mechanisms including oxidative stress, inflammation, mitochondrial dysfunction, and abnormal angiogenesis. The retina's high metabolic demand makes it highly susceptible to oxidative injury, leading to progressive photoreceptor and vascular damage. While conventional therapies slow disease progression, they rarely reverse cellular dysfunction. Herbal bioactives such as saffron, bilberry, and *Ginkgo biloba* provide complementary protection through pleiotropic mechanisms. These compounds enhance Nrf2 antioxidant signaling, inhibit NF-κB-driven inflammation, suppress VEGF-mediated angiogenesis, and activate SIRT1/PGC-1α pathways supporting mitochondrial renewal. Clinical studies show saffron improves visual function in macular degeneration, bilberry alleviates visual fatigue, and Ginkgo stabilizes glaucoma-related field loss. Integrating these phytochemicals with standard care may enhance retinal resilience, highlighting their translational potential as adjunct therapies in ocular disease prevention and management.

Keywords: Ocular Pharmacology, Herbal Medicine, Oxidative Stress, Neuroprotection, Nrf2, Sirt1, VEGF, Antioxidant Pathways

1. INTRODUCTION

1.1 Background

Vision loss due to ocular diseases such as age-related macular degeneration (AMD), diabetic retinopathy (DR), glaucoma, and cataract affects hundreds of millions worldwide. These disorders share common molecular denominators like oxidative stress, inflammation, mitochondrial dysfunction, and angiogenesis dysregulation. The retina, being highly metabolically active, is particularly susceptible to oxidative injury. Reactive oxygen species (ROS) generated through high light exposure and mitochondrial respiration damage the retinal pigment epithelium (RPE), photoreceptors, and vascular endothelium, initiating degenerative cascades (Ozawa, 2020).

Conventional treatments, including anti-VEGF injections, laser photocoagulation, and intraocular pressure-lowering drugs, offer symptomatic control but do not fully prevent disease progression. Thus, nutraceutical and phytochemical interventions with pleiotropic molecular actions have emerged as attractive adjuncts. Many herbs used in traditional medicine such as saffron, bilberry, and *Ginkgo biloba* are now validated by molecular and clinical evidence for protecting ocular tissues through antioxidant, anti-inflammatory, and neuroprotective mechanisms (Karakuş & Çalışkan, 2021). This chapter explores these mechanisms and compiles evidence from *in vitro*, *in vivo*, and clinical studies, with emphasis on molecular pathways and translational potential.

1.2 Selection Criteria

Herbal agents discussed in this chapter were selected using predefined scientific and translational criteria to ensure relevance and clinical applicability. A structured literature search was conducted across Web of Science, Scopus, and Google Scholar, focusing on peer-reviewed publications primarily from 2000 to 2025 to capture advances in molecular pharmacology, standardized extracts, and clinical trial design.

Selection criteria included: (i) mechanistic relevance to key pathogenic pathways in ocular diseases, particularly oxidative stress (Nrf2/ARE), inflammation (NF-κB), mitochondrial dysfunction (SIRT1/PGC-1α), angiogenesis (VEGF/HIF-1α), and neurodegeneration; (ii) preclinical evidence demonstrating retinal, RPE, or optic nerve protection in validated *in vitro* or *in vivo* ocular models; (iii) human clinical evidence, prioritizing randomized controlled trials, crossover studies, or systematic reviews reporting functional or structural ocular outcomes including visual acuity, ERG, OCT, visual field indices; (iv) use of standardized

extracts or defined bioactive constituents to enhance reproducibility and translational relevance; and (v) safety and bioavailability considerations, including documented adverse effects, drug-herb interactions, and formulation strategies to overcome poor oral absorption. Herbs lacking clinical data were included only when supported by robust molecular and animal evidence directly relevant to ocular pathology. Based on these criteria, botanicals such as *Crocus sativus, Vaccinium myrtillus, Ginkgo biloba, Lycium barbarum, Curcuma longa*, and polyphenols such as resveratrol and catechins were prioritized, as they demonstrate convergent mechanistic actions and varying degrees of clinical validation in AMD, DR, glaucoma and cataractogenesis.

2. MOLECULAR MECHANISMS OF HERBAL PROTECTION

2.1 Nrf2 and Antioxidant Defense

The Nrf2 (nuclear factor erythroid 2–related factor 2) signaling pathway regulates the transcription of antioxidant and cytoprotective genes such as heme oxygenase-1 (HO-1), superoxide dismutase (SOD), and glutathione peroxidase (GPx). Under oxidative stress, Nrf2 dissociates from Keap1 and translocates to the nucleus, promoting antioxidant enzyme expression. Herbal polyphenols such as curcumin, epigallocatechin gallate, thymoquinone, and resveratrol act as mild electrophiles that trigger Nrf2 activation (Ahmed, 2025).

In RPE cell models, saffron extracts upregulate Nrf2 and HO-1, mitigating oxidative apoptosis. Resveratrol and EGCG further enhance Nrf2-ARE binding, preventing mitochondrial collapse. These compounds stabilize redox homeostasis in photoreceptors, a crucial mechanism in preventing AMD and diabetic retinopathy.

2.2 NF-κB and Inflammation Modulation

NF-κB signalling governs inflammatory cytokine production (TNF-α, IL-1β, IL-6). Chronic activation leads to RPE and retinal endothelial cell damage. Curcumin, resveratrol, and *Ginkgo biloba* flavonoids inhibit IκB kinase, preventing NF-κB nuclear translocation. This reduces pro-inflammatory cytokine transcription and complement activation in retinal tissues.

Curcumin also suppresses COX-2 and iNOS expression in diabetic retinal cells, while *Ginkgo biloba* extract (EGb 761) reduces microglial activation in glaucoma models, supporting its neuroprotective effects (Fei et al., 2020).

2.3 SIRT1/PGC-1α Pathway and Mitochondrial Biogenesis

SIRT1, a NAD^+-dependent deacetylase, promotes mitochondrial biogenesis and cellular longevity via PGC-1α activation. Resveratrol strongly activates SIRT1, enhancing mitochondrial integrity and reducing oxidative DNA damage. In retinal cells, SIRT1-mediated deacetylation of PGC-1α boosts ATP production, improving retinal metabolism and delaying neurodegeneration (Lei et al., 2022).

Saffron and green tea catechins similarly modulate mitochondrial enzymes (complex I and IV), maintaining photoreceptor survival under oxidative load. These effects underpin their neuroprotective capacity in AMD and glaucoma.

2.4 VEGF and Angiogenesis Regulation

Pathological angiogenesis underlies neovascular AMD and DR. VEGF overexpression leads to aberrant vessel growth and retinal edema. Crocetin, EGCG, and curcumin downregulate VEGF and matrix metalloproteinases (MMP-2, MMP-9) through suppression of HIF-1α and NF-κB signalling.

In mice model of retinopathy of prematurity (ROP), resveratrol suppresses retinal neovascularization by inhibiting VEGF, VEGFR and CD31. Such anti-angiogenic activity parallels pharmacological anti-VEGF agents but with fewer side effects (Hu et al., 2022).

2.5 Neuroprotection and Retinal Signaling

Photoreceptor and ganglion cell apoptosis is a common endpoint in retinal diseases. Herbal compounds such as crocin, resveratrol, and Ginkgo flavonoids enhance expression of neurotrophic factors (BDNF, NGF) and anti-apoptotic proteins (Bcl-2). Saffron, in particular, prevents photoreceptor death by stabilizing rhodopsin and inhibiting caspase activation (Moosavi et al., 2015).

3. CLINICAL TRIAL EVIDENCE

3.1 Saffron (*Crocus sativus*)

Randomized placebo-controlled trials and systematic reviews report modest but reproducible functional improvements (including best-corrected visual acuity, focal ERG amplitude, contrast sensitivity) in early or intermediate AMD with saffron supplementation (commonly 20 mg/day of standardized saffron extract) over months. A recent systematic review and randomized trials summarize these findings and note the need

for larger, longer trials to determine durability and effect size relative to AREDS-type supplementation. Saffron's actions are consistent with antioxidant and mitochondrial-supporting mechanisms (Nrf2 activation and improved mitochondrial respiration) (Broadhead et al., 2019).

3.2 Bilberry (*Vaccinium myrtillus*)

Randomized controlled studies such as those in SBE studies show benefit for symptoms of visual fatigue and objective measures of ciliary muscle function in individuals exposed to VDT/near tasks. Doses in trials typically supply standardized anthocyanin extracts (240 to 480 mg extract daily) for 8–12 weeks. Evidence for improved night vision is older and mixed; more recent trials emphasize relief of digital eye strain and improvements in accommodative dynamics. Mechanistically, anthocyanins exert antioxidant effects and may stabilize phototransduction pigments (Kosehira et al., 2020).

3.3 *Ginkgo biloba* (standardized extract EGb 761)

Several small randomized and crossover studies in normal-tension glaucoma (NTG) and other optic neuropathies report modest improvements or stabilization of visual field indices and contrast sensitivity with EGb 761 (typical doses 120 mg/day) (Quaranta et al., 2003). Meta-analyses and reviews conclude that some patients may benefit, but results are heterogeneous and limited by small sample sizes and short follow-up; bleeding risk with anticoagulants is the main safety concern. The proposed mechanisms include improved ocular microcirculation and mitochondrial enzyme modulation.

3.4 *Lycium barbarum* (goji berry)

Randomized pilot studies report increases in macular pigment optical density and plasma zeaxanthin after daily goji intake (e.g., 15 g dried goji per day for months) (Li et al., 2021). These trials are small and often unmasked, but they align with goji's carotenoid (zeaxanthin) content and antioxidant potential. Larger, blinded RCTs are needed.

3.5 Curcumin (*Curcuma longa*)

Curcumin has compelling anti-inflammatory and anti-angiogenic mechanisms (both NF-κB and HIF-1α modulation) (Cai et al., 2024). Human ocular data are limited by curcumin's poor bioavailability; however, modern high-bioavailability formulations including phospholipid complexes and nanoparticle preparations have entered pilot clinical use and case series with signals of benefit in macular oedema and inflammatory retinal conditions. Controlled RCT evidence remains

sparse; ongoing and registered trials aim to clarify efficacy. Clinicians should note potential interactions (antiplatelet effects) and variability across formulations.

3.6 Resveratrol

EGCG and resveratrol show strong preclinical protection via Nrf2 activation and SIRT1/PGC-1α signalling, respectively (Shen et al., 2025). Human ocular trials are limited; clinicaltrials.gov lists resveratrol studies in AMD and retinal disease, but large, definitive RCTs are not yet published. Observational data suggest habitual green tea consumption correlates with modestly lower risks of cataract and some retinal conditions; randomized evidence is lacking.

3.7 Lutein & zeaxanthin

Although not a "herbal extract", lutein and zeaxanthin are plant-derived carotenoids with the most robust clinical evidence for AMD risk reduction. AREDS2 (a large multicentre RCT) showed that substituting lutein/zeaxanthin for beta-carotene and including them in the AREDS formulation reduced progression to advanced AMD in at-risk individuals. These nutrients act by filtering blue light and quenching singlet oxygen in the macula. AREDS2 remains the gold standard for nutritional prevention of AMD progression (Group, 2013).

3.8 Comparative Efficacy

Among reviewed botanicals, saffron demonstrates the strongest evidence for functional improvement in AMD, bilberry for visual fatigue, and ginkgo for glaucoma stabilization. Molecular synergy exists across compounds targeting overlapping pathways (Nrf2, NF-κB, VEGF). Integrative nutraceutical formulations combining these herbs may offer additive protection against retinal degeneration. However, clinical heterogeneity and variability in extract standardization remain major limitations.

4. BIOAVAILABILITY CONSIDERATIONS

Bioavailability remains a major limiting factor for the clinical translation of many herbal compounds used in ocular protection, as numerous phytochemicals exhibit poor aqueous solubility, rapid metabolism, and limited systemic and retinal tissue penetration following oral administration. Polyphenols such as curcumin, resveratrol, and epigallocatechin gallate demonstrate low oral bioavailability due to extensive first-pass metabolism and rapid clearance, which may partially explain the discrepancy between robust preclinical efficacy and modest

clinical outcomes (Ahmed, 2025; Kellermann & Kloft, 2011). Advances in formulation science, including phospholipid complexes, liposomal encapsulation, and nanoparticle-based delivery systems, have been shown to significantly enhance systemic exposure and ocular tissue distribution of curcumin and related bioactives in preclinical and early clinical studies (Baranauskas et al., 2024). Similarly, variability in extract standardization and marker compound content such as crocins in saffron, anthocyanins in bilberry, and ginkgolides in *Ginkgo biloba* further influences bioavailability and contributes to heterogeneity in clinical responses. Consequently, optimization of formulation strategies and use of standardized preparations are essential to maximize bioavailability and therapeutic consistency in herbal interventions targeting ocular diseases.

Table 1: Comparative clinical evidence for key herbal compounds in ocular protection.

Herb/ active compound	**Major ocular indication**	**Representative clinical design**	**Dose & duration**	**Outcome**	**Ref.**
Crocus sativus (saffron, crocins)	Early, intermediate AMD	Randomized double-blind, placebo-controlled crossover; longitudinal extension	20–30 mg/day oral, 3–14 months	↑ ERG amplitude, ↑ visual acuity, maintained retinal sensitivity	(Falsini et al., 2010; Lashay et al., 2016; Piccardi et al., 2012)
Vaccinium myrtillus (bilberry, anthocyanins)	Visual fatigue, asthenopia	Randomized crossover, healthy volunteers	12.5-50 mg/day anthocyanins, <6 weeks	↓ eye strain, ↑ accommodation recovery, improved contrast	(Kawabata & Tsuji, 2011; Nakaishi et al., 2000)
Ginkgo biloba (EGb 761)	Normal-tension glaucoma	Randomized double-blind crossover; observational follow-up	40 mg × 3/day, 4 weeks to 12 months	Visual field stabilization, mixed evidence for mean deviation	(Cybulska-Heinrich et al., 2012; Guo et

				improvement	al., 2014)
Lycium barbarum (goji berry, zeaxanthin polysaccharides)	Retinal protection, early AMD	Open-label pilot, small sample	13.7 g/day dried fruit equiv., 3 months	↑ plasma zeaxanthin, ↓ macular pigment loss	(Li et al., 2021)
Curcuma longa (curcumin)	Uveitic macular edema	Monocenter prospective observational study	60 mg, 6-12 months	↓ retinal thickness	(Allegri et al., 2022)

5. LONG-TERM SAFETY AND HERB-DRUG INTERACTIONS

Although herbal therapies are widely perceived as safe, long-term use and concurrent administration with conventional drugs raise clinically significant safety and interaction concerns, particularly in chronic ocular diseases requiring prolonged supplementation. Standardized *Ginkgo biloba* extract (EGb 761) has antiplatelet activity mediated through inhibition of platelet-activating factor and has been associated with an increased risk of bleeding when co-administered with anticoagulants or antiplatelet agents such as warfarin and aspirin, especially during long-term use (Kellermann & Kloft, 2011; Stoddard et al., 2015). Prolonged exposure to high-dose or highly bioavailable polyphenol formulations, including curcumin and green tea extracts, has been linked to rare but well-documented cases of idiosyncratic drug-induced liver injury, emphasizing the importance of dose standardization, formulation transparency, and liver function monitoring during extended use (Halegoua-DeMarzio et al., 2023).

Although clinical trials suggest that saffron is generally well tolerated at therapeutic doses used for ocular indications, toxicological studies have demonstrated uterotonic and embryotoxic effects at supratherapeutic doses, necessitating avoidance during pregnancy and caution among individuals of reproductive-age (Bostan et al., 2017; Moallem et al., 2016). Furthermore, substantial variability in extract composition, bioactive marker concentration, and manufacturing quality across commercial products complicates long-term safety assessment and may contribute to inconsistent clinical outcomes (Baranauskas et al., 2024). Therefore, long-term herbal supplementation for visual health should be guided using standardized extracts, careful patient selection,

and clinician awareness of potential herb-drug interactions, particularly in elderly patients with polypharmacy and cardiovascular comorbidities.

6. FUTURE PERSPECTIVES

Future research should prioritize multicentre RCTs with standardized extracts, long-term follow-up, and advanced imaging endpoints (OCT, mfERG). Integrative trials combining herbal antioxidants with standard therapies could clarify synergistic mechanisms. Moreover, omics-based studies may identify molecular biomarkers for personalized phytotherapy in ocular diseases.

7. CONCLUSION

Herbal compounds provide multifaceted molecular protection for ocular health, acting on oxidative, inflammatory, and mitochondrial pathways. Saffron, bilberry, and *Ginkgo biloba* are the most clinically supported, while curcumin, goji, and resveratrol demonstrate strong mechanistic potential. Combining these bioactives with conventional care may enhance visual outcomes, provided formulation and safety are standardized. The integration of molecular pharmacology and clinical science heralds a promising era for herbal vision therapeutics.

ABBREVIATIONS

AMD, age-related macular degeneration; DR, diabetic retinopathy; ROS, reactive oxygen species; RPE, retinal pigment epithelium; Nrf2, nuclear factor erythroid 2–related factor 2; ARE, antioxidant response element; HO-1, heme oxygenase-1; SOD, superoxide dismutase; GPx, glutathione peroxidase; NF-κB, nuclear factor kappa-B; TNF-α, tumor necrosis factor alpha; IL-1β and IL-6, interleukin-1 beta and interleukin-6; COX-2, cyclooxygenase-2; iNOS, inducible nitric oxide synthase; SIRT1, sirtuin-1; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1 alpha; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; HIF-1α, hypoxia-inducible factor-1 alpha; MMP-2 and MMP-9, matrix metalloproteinases-2 and -9; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor; ERG, electroretinography; OCT, optical coherence tomography; mfERG, multifocal electroretinography; NTG, normal-tension glaucoma; EGCG, epigallocatechin gallate; EGb 761, standardized Ginkgo biloba extract; VDT, visual display terminal; AREDS and AREDS2, Age-Related Eye Disease Study and Age-Related Eye Disease Study 2; RCT, randomized controlled trial; WoS, Web of Science; and DILIN, Drug-Induced Liver Injury Network.

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Chapter 11
Preserving Liver and Kidney Function with Herbal Medicine

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ABSTRACT

The liver and kidneys are central organs in maintaining metabolic balance, detoxification, and systemic longevity. They function in synergy to neutralize endogenous and exogenous toxins, regulate biochemical homeostasis, and maintain overall physiological health. However, the compounding effects of aging, environmental pollutants, and lifestyle factors on functional decline continue to contribute to the rising global burden of hepatic and renal diseases. Non-alcoholic Fatty Liver Disease (NAFLD) presently affects up to 30% of the world's population, while Chronic kidney disease (CKD) affects almost 850 million people around the world, and both are leading causes of death worldwide. These alarming statistics point to the urgent need to develop strategies for prevention and restoration of the resilience of these organs. Herbal medicine could serve as an important complementary strategy due to the various bioactive compounds it contains, such as flavonoids, polyphenols, terpenoids, and alkaloids, which demonstrate antioxidant, anti-inflammatory, antifibrotic, and cytoprotective actions. Herbs such as *Silybum marianum, Curcuma longa, Phyllanthus niruri, Boerhavia diffusa, Camellia sinensis, and Astragalus membranaceus* have been reported to depict considerable hepatoprotective and nephroprotective effects via molecular mechanism mediation, including Nrf2–Keap1, NF-κB, and SIRT1 pathways. Despite impressive preclinical evidence,

translation into clinical practise has been impeded by issues related to bioavailability, standardization, and herb-drug interactions. Further studies should combine the power of omics technologies, nanotechnology-based delivery systems, and clinical trials to support evidence-based applications. Preservation of hepatic and renal vitality, through scientifically validated herbal interventions, makes for a sustainable strategy for detoxification, healthy aging, and longevity. Merging traditional herbal wisdom with contemporary biomedical research holds great promise for the development of next-generation therapeutics that enhance health span and resilience in aging populations.

Keywords: Herbal medicine, Detoxification, Liver function, Kidney health

1. INTRODUCTION

The liver and kidneys play a pivotal role in the regulation of metabolism and the promotion and maintenance of longevity. These two organs act as the body's most important defence mechanism for protecting the body against both exogenous and endogenous compounds. While the kidney performs the task of eliminating metabolism products as well as ensuring electrolyte balance and fluid volume and acid-based equilibrium, the liver works to process nutrients, drugs, and xenobiotics through enzymatic pathways.

Detoxification represents biological processes that involve the processing and elimination of toxins. The body's ability to detoxify becomes progressively inefficient with age, resulting in the build-up of by-products of metabolism, oxidative damage, and low-grade chronic inflammation. This catalyses biological aging and the predisposition to metabolic disorders, cardiovascular disease, and neurodegeneration (Caro-Ordieres et al., 2020).

Hepatobiliary and kidney disorders have become a serious concern in terms of global prevalence. Non-alcoholic fatty liver disease, resultant upon obesity and insulin resistance, additionally affects 25-30% of the present global population, predominantly in Asia and the Middle East (Younossi et al., 2023). Chronic kidney disease currently impacts almost 850 million patients worldwide and has become one of the chief causes of death (WHO, 2024). In Malaysia, more than 15% patients are affected with chronic kidney disease, predominantly because of the aftereffects of the contemporary lifestyle.

Moreover, modern dietary patterns, environmental pollutants, and sedentary behaviours further overload the hepatic and renal detoxification systems. It is within this context that herbal medicine has regained attention. Phytochemical compounds such as flavonoids, polyphenols, terpenoids, and alkaloids have anti-oxidative, anti-inflammatory, and cytoprotective effects that could provide support for detoxification pathways and thereby repair the tissue (Ahda et al., 2023). Thus, investigating herbal medicine as a strategy for preserving liver and kidney function contributes to healthy aging and longevity.

2. BACKGROUND

2.1 Liver Detoxification and Aging-Related Dysfunction

The liver performs numerous metabolic and detoxifying processes. Nevertheless, with the advancement of age, there is a 20-40% reduction in hepatic mass, and the hepatic blood flow may decrease by about 35% above the age of 65 years (Caro-Ordieres et al., 2020).

Detoxification mechanisms primarily involve Phase I and Phase II reactions. The impairment of Phase I reactions by decreased cytochrome P450 enzymatic functioning, with advancing age, results in reduced clearance of lipophilic toxins. The Phase II conjugation system also becomes impaired by decreased glutathione levels and reduced gene expression. This results in increased levels of reactive intermediates.

Non-enzymatic pathways of antioxidant defences, glutathione, vitamin C, vitamin E, are also decreased in aging. This reduces the defence mechanism against reactive oxygen species (ROS) generated during metabolism. Deficits in detoxification mechanisms for ammonia and bilirubin conjugation also lead to conditions such as hepatic encephalopathy in elderly patients.

2.2 Kidney Detoxification and Aging-Related Dysfunction

The kidneys filter about 180 L of plasma per day. Aging is associated with progressive loss of nephrons, glomerulosclerosis, and tubular dysfunction. Glomerular filtration rate decreases about 10% per decade after middle life.

Reduced renal blood flow and impaired tubular secretion limit drug and toxin elimination. Aging kidneys also have reduced expression of detoxification enzymes, renal cytochrome P450s, and flavin-containing monooxygenases. The mitochondrial dysfunction and oxidative stress contribute to fibrosis and the reduced regenerative capacity. Such changes increase the vulnerability to nephrotoxicity, drug accumulation, and progression toward CKD, especially in those individuals who have chronic metabolic stress and/or polypharmacy.

3. HERBAL MEDICINE AND HEPATORENAL PROTECTION

3.1 Predominantly Hepatoprotective Herbs

Silybum marianum, also known as milk thistle, is one of the best-studied hepatoprotector plants. The effective flavonolignans complex in this plant, known as “silymarin,” has shown activity in protecting hepatocyte membranes, increasing glutathione in cells, and inhibiting lipid peroxide formation. The combination of all these properties has made it an effective hepatoprotector in decreasing hepatocellular damage and stimulating regenerative hepatocytes. Several studies conducted in human clinical settings demonstrated decreased levels of serum alanine and aspartate transaminases, specifically in cases of non-alcoholic fatty liver disease and toxic liver damage, thus proving its efficacy in age-related hepatopathy as well (Ahda et al., 2023).

Curcuma longa (turmeric) exerts hepatoprotective effects primarily through modulation of oxidative stress and inflammatory signaling. Curcumin activates the Nrf2 pathway, increasing the expression of endogenous antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. It simultaneously suppresses NF-κB signaling and reduces the levels of pro-inflammatory cytokines and fibrogenic mediators such as TGF-β. These mechanisms imply that curcumin can limit hepatic inflammation and fibrosis, especially in chronic liver disorders associated with both aging and metabolic stress (Zhai, 2024; Caro-Ordieres et al., 2020).

Phyllanthus niruri is traditionally used in the management of hepatobiliary disorders and viral hepatitis. The proposed mechanisms for its use in the treatment of hepatitis include antiviral properties against the hepatitis B virus, promotion of bile flow, and promotion of the expulsion of bilirubin. By alleviating cholestasis and aiding bilirubin metabolism, *P. niruri* assists in the maintenance of the liver's detoxification properties and the prevention of any complication relating to icteria related to hepatitis (Hanifah & Busman, 2024).

3.2 Predominantly Nephroprotective Herbs

Other herbs of greater nephroprotective relevance include *Boerhavia diffusa*, *Camellia sinensis*, and *Astragalus membranaceus*. These primarily target renal oxidative stress, fibrosis, and filtration defects associated with aging and chronic kidney disease.

Boerhavia diffusa, commonly known as Punarnava, has exhibited nephroprotective action, antioxidant, and diuretic activity. Punarnava diminishes the levels of serum creatinine and urea while increasing the renal clearance of metabolic wastes. Moreover, it minimizes renal oxidative stress by restoring the level of activity of the antioxidant enzyme and prevents drug-induced nephrotoxicity, especially the one caused by

cisplatin and gentamicin. These properties thereby validate its traditional use in chronic kidney disorders and states of fluid retention (Ajebli & Eddouks, 2019).

Camellia sinensis (Green Tea) has high levels of catechins, especially Epigallocatechin Gallate (EGCG), which have potent antioxidant and chelating effects. Green Tea Polypphenols exhibit renal protecting effects against heavy metals, reduce protein excretion, and increase glomerular function by activating the Nrf2 mediated antioxidant response. Regular intake has shown increased renal antioxidant response and slowing of progression of CKD by protecting against renal aging and detoxification mechanisms (Cahyani et al., 2022).

Astragalus membranaceus, a commonly employed traditional Chinese medicinal herb, has renoprotective properties attributable to the improvement of renal microcirculation and inhibition of fibrogenic signals. Polysaccharides and flavonoids in *Astragalus membranaceus* work by attenuating interstitial fibrosis and glomerulosclerosis with mitochondrial function improvement and enhancement of cellular metabolism in the context of delayed progression of chronic kidney disease in the aging population (AlAhmad et al., 2024).

3.3 Integrative Perspective

While the categorization of these herbs was based on the major targeted organs, there is an overlap in the mechanisms. Hepatoprotective herbs tend to modulate the activity of detoxification enzymes, augment antioxidant defences, and stimulate hepatocyte regeneration. Nephroprotective herbs act in preserving the filtration capacity by reducing the development of fibrosis and preserving mitochondrial integrity. This organ-specific distinction reinforces the mechanistic rationale for targeted herbal interventions in hepatic versus renal aging.

4. CRITICAL ANALYSIS AND IMPLICATION

4.1 Mechanistic Insights

Though there are overlapping functions of antioxidation and anti-inflammation pathways such as Nrf2 and NF-κB in various herbs, there are differences in their organ-targeted actions. For instance, hepatoprotective herbs are involved in increasing activities of detoxifying enzymes and hepatocyte regeneration. The other group of nephroprotective herbs acts by maintaining filtering function and mitochondrial function.

4.2 Clinical Evidence and Challenges

Evidence is mostly preliminary. Human studies demonstrate some benefit, even if supportive rather than therapeutic. Bioavailability

problems make it difficult, while variation in phytochemical content clouds the issue. More sophisticated methodologies have improved bioavailability; however, standardized preparations are still called for. Interactions between herbal medications and conventional medications are also a concern. This can be a problem in geriatric care.

4.3 Detoxification, Aging, and Longevity

Impaired detoxification leads to accelerated aging due to chronic oxidative stress, mitochondrial dysfunction, and genetic instability. Phytochemicals can activate various pathways associated with longevity, such as SIRT1, SIRT3, and AMPK, to promote autophagy and robust metabolism. Taking phytochemical-rich herbs can help promote aging health by preserving organ function.

4.4 Socio-Cultural and Economic Implications

Herbal medicine remains culturally embedded and economically significant, particularly in low- and middle-income regions. Scientific validation enhances acceptance, while sustainable cultivation supports biodiversity and local economies. Strong regulatory frameworks are required to ensure safety and quality.

5. FUTURE DIRECTIONS

Future research should prioritize standardized extracts, integrative omics approaches, and advanced delivery systems to enhance bioavailability. Gut microbiota modulation and AI-driven phytochemical modelling represent emerging frontiers. Large-scale, long-term randomized controlled trials are essential to establish efficacy, safety, and optimal dosing in aging populations.

6. CONCLUSION AND RECOMMENDATION

The liver and kidneys are essential detoxifying organs whose function declines with aging and modern lifestyle exposures. Herbal medicine offers a scientifically supported, non-invasive strategy to preserve hepatorenal health. Hepatoprotective herbs such as *Silybum marianum*, *Curcuma longa*, and *Phyllanthus niruri* primarily enhance detoxification and regeneration, while nephroprotective herbs such as *Boerhavia diffusa*, *Camellia sinensis*, and *Astragalus membranaceus* preserve filtration and reduce fibrosis. Integration of herbal therapies into preventive healthcare should be evidence-based, regulated, and guided by trained professionals. Continued interdisciplinary research will strengthen the role of herbal medicine in promoting longevity and extending health span.

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Chapter 12
Skin aging and Herbal Dermatology

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ABSTRACT

Skin aging is an inevitable biological process shaped by intrinsic genetic factors and multiple external influences, particularly ultraviolet radiation, pollution, and lifestyle habits. These cumulative stressors alter skin structure, weaken barrier function, and accelerate the development of wrinkles, dryness, and impaired repair capacity. Growing concerns about the long-term safety of synthetic skincare ingredients have renewed interest in herbal dermatology, a field that draws on the diverse bioactive compounds found in medicinal plants. This chapter reviews key herbs with documented anti-aging potential, including turmeric, thyme, sumac, coriander, rosemary, ginger, and cumin. Their extracts contain phenolics, flavonoids, terpenoids, and other secondary metabolites that exhibit antioxidant, anti-inflammatory, photoprotective, collagen-preserving, and wound-healing properties. Evidence from in-vitro, in-vivo, and limited clinical studies highlights their ability to reduce oxidative stress, inhibit matrix-degrading enzymes, improve hydration, and modulate inflammatory pathways involved in skin aging. Despite their promise, concerns remain regarding allergic reactions, systemic toxicity, and herb-drug interactions, emphasizing the need for regulated formulations and patient awareness. Future research must focus on clinical trials, long-term safety, optimized delivery systems, and better understanding of molecular mechanisms. Herbal dermatology therefore represents a valuable, evolving approach that complements modern strategies for maintaining healthy and resilient aging skin.

Keywords: Skin aging, Herbal dermatology, Clinical studies

1. INTRODUCTION

The skin is the largest organ of the human body and plays a vital role in mediating contact between the body and the external environment, including interactions with microorganisms and physical stimuli (Costa et al., 2022). Aging is characterized by a gradual decline in physiological functions, contributing to age-related syndromes and diseases such as cardiovascular disease, chronic lung disease, musculoskeletal disorders, cancer, neurological disorders, and dermatological conditions. Increasing evidence suggests that aging, geriatric syndromes, and age-associated diseases share common molecular and cellular pathways (Franceschi et al., 2018).

Skin aging is classified into two types: intrinsic aging and extrinsic aging. Intrinsic aging is driven by internal factors such as genetic and physiological changes. Epidermal thinning, reduced cellular turnover, decreased sebaceous activity, decreased elasticity, and fine wrinkles are its hallmarks. Telomere shortening, oxidative stress, DNA damage, and decreased autophagy are the main causes of this process, leading to fibroblast dysfunction and extracellular matrix breakdown. The extrinsic aging results from environmental exposures such as ultraviolet (UV) radiation, pollution, tobacco use, poor diet, alcohol consumption, harmful chemicals, and lifestyle choices. Generation of reactive oxygen species (ROS), DNA damage, and the overexpression of matrix metalloproteinases, which break down collagen and disturb the dermal extracellular matrix, are all caused by UV radiation. Clinical signs of extrinsic aging include telangiectasias, actinic elastosis, solar lentigines, coarse wrinkles, and uneven pigmentation. By causing chronic inflammation and speeding up oxidative damage, other environmental variables worsen these alterations. These factors cumulatively impact skin morphology, appearance, and function (Naharro et al., 2025). Age-related changes impair fluid balance, electrolyte and protein loss regulation, vitamin D synthesis, waste elimination, sensory perception, immune function, and barrier integrity (Ahmed et al., 2020).

2. HERBAL DERMATOLOGY

Strategies for preventing or managing skin aging include sun protection, topical antioxidants, non-invasive aesthetic procedures, invasive treatments (fillers, chemical peels, radiofrequency), systemic antioxidants, and lifestyle modifications. However, rising concerns about safety and well-being have increased demand for natural, non-invasive, and effective skincare options.

Plants remain a rich source of bioactive molecules despite the rapid growth of biotechnologies and synthetic compound development. Herbal extracts contain diverse secondary metabolites such as flavonoids,

phenolic derivatives, anthocyanidins, anthocyanins, coumarins, terpenoids, stilbenes, tannins, and alkaloids. Many standardized herbal products have established quality, safety, and efficacy profiles and are used to prevent or manage skin aging (Costa et al., 2022).

3. HERBAL COMPOUNDS WITH ANTI-AGING PROPERTIES

3.1 Turmeric *(Curcuma longa)*

Curcumin, the primary bioactive component of turmeric, exhibits antibacterial, antioxidant, antiviral, anti-inflammatory, anticarcinogenic, and antifibrotic properties. It improves skin hydration and reduces redness, making it widely used in cosmetic formulations. In a clinical study, a supplement containing glucoraphanin, sulforaphane (450 mg), and curcumin reduced UVB-induced inflammatory cytokines (Ozler et al., 2025).

Curcuma longa extracts display strong antioxidant activity in 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assays, reducing oxidative stress which is a key contributor to inflammation and aging. Its anti-inflammatory action is mediated through regulation of nitric oxide (NO) and interleukin (IL) production (Barbalho et al., 2021). A skin-on-chip study showed that *Curcuma longa* helped prevent skin aging (Kim et al., 2020). It also enhances skin hydration through increased hyaluronan production. While turmeric is generally safe, excessive use may cause irritation or allergic responses; therefore, high-quality products and recommended dosages are essential (Kim et al., 2020).

3.2 Thyme *(Thymus vulgaris)*

Thyme contains thymol and carvacrol, bioactive compounds with anticancer, antioxidant, anti-inflammatory, and antibacterial activities. *Thymus vulgaris* reduces pro-inflammatory cytokines (TNF-α, IL-6) and increases IL-10 levels. These actions reduce oxidative stress and may contribute to anti-aging benefits (Waheed et al., 2024).

A phytocosmetic formulation of lecithin and *Thymus vulgaris* increased adiponectin, stimulated adipogenesis, and reduced wrinkles in a clinical trial (Caverzan et al., 2021). Furthermore, the related species *Origanum vulgare* demonstrated anti-collagenase, anti-elastase, and anti-hyaluronidase activities, indicating protective potential against skin aging (Laothaweerungsawat et al., 2020).

3.3 Sumac *(Rhus coriaria)*

Sumac is rich in phenolic antioxidants that protect against skin aging. *Rhus coriaria* reduces UVA-induced oxidative damage and decreases pro-inflammatory mediators in keratinocytes. Its leaves possess antibacterial

and antifungal proteins that aid skin repair and wound healing. *In-vitro* studies show UV-protective properties and wound-healing activity of sumac-derived gallic acid phytocomplexes (Flieger et al., 2021; Pressi et al., 2022).

Although sumac has promising anti-aging and skin-repair potential, more research is needed to understand its mechanisms, efficacy, and practical applicability in skincare.

3.4 Coriander *(Coriandrum sativum)*

Coriander contains terpenoids, sterols, and tocols with anti-inflammatory and antioxidant effects. Its essential oil inhibits elastase and collagenase enzymes responsible for loss of elasticity and wrinkle formation. Nanoformulations containing coriander oil significantly reduced Cyclooxygenase-2 (COX-2), Prostaglandin E2 (PGE-2), Matrix metalloproteinase-1 (MMP-1), c-Jun N-terminal kinase (JNK), Activator protein 1 (AP-1), and malondialdehyde (MDA), while improving UV-induced photoaging (Salem et al., 2022).

Since advanced glycation end-products (AGEs) contribute to skin aging, coriander's anti-glycation activity further supports its protective role (Sawabe et al., 2022).

3.5 Rosemary *(Rosmarinus officinalis)*

Rosemary, from the Lamiaceae family, contains carnosic acid, ursolic acid, and carnosol compounds with antioxidant, anti-inflammatory, antibacterial, and wound-healing properties. These contribute to improved skin elasticity, reduced wrinkles, and enhanced cell activity (Nobile et al., 2016).

Topical rosemary extracts reduced UVB-induced inflammation and wrinkles in animal studies (Auh & Madhavan, 2021). It also lowered ROS, MMP-1, MMP-3, and p53 expression, potentially slowing skin aging.

3.6 Ginger *(Zingiber officinale)*

Ginger possesses anticoagulant, antioxidant, antiviral, and anticancer properties (Asoka *et al.*, 2022). Indonesian ginger varieties demonstrated anti-aging effects, particularly due to compounds such as octinoxate.

Zingiber mioga extract increased fibrillin-1, collagen, elastin, and hyaluronan synthase expression in UVB-exposed mice. It also reduced inflammatory markers, pigmentation factors, and wrinkle formation while improving skin moisture (Ozler et al., 2025).

3.7 Cumin *(Cuminum cyminum)*

Cumin contains anti-inflammatory, antioxidant, antibacterial, anticancer, and antidiabetic properties. Its antioxidants help prevent free

radical damage and maintain skin elasticity. Volatile oils such as thymol and cuminaldehyde reduce skin inflammation. Cumin also has skin-whitening potential through inhibition of tyrosinase and melanin synthesis in B16F10 melanoma cells (Singh et al., 2021).

4. SAFETY AND TOXICITY CONSIDERATIONS

Allergic contact dermatitis is the most common adverse reaction to herbal dermatologic products. Herbs such as aloe, bromelain, calendula, arnica, chamomile, goldenseal, yarrow, and tea tree oil are known sensitizers. Severe reactions including Stevens-Johnson syndrome and erythroderma have occurred with some herbal formulations. Systemic toxicity, including hepatotoxicity, has also been documented (Faghihi et al., 2011).

Topical herbs should not be ingested, and systemic herbs should not be applied to skin. Herb-drug interactions may occur, especially via immunomodulation, anticoagulant pathways, and anticonvulsant mechanisms. Use is discouraged during pregnancy, infancy, and childhood due to unpredictability of adverse reactions.

5. FUTURE DIRECTIONS

Future research should prioritize:

- Clinical trials on oral herbal intake and its effects on aging and skin health.
- Long-term studies on dietary supplements and herbal formulations assessing elasticity, wrinkles, and hydration.
- Investigation of molecular pathways and skin bioavailability of herbal bioactives.
- Exploration of synergistic effects of combined herbs and development of improved delivery systems (Ozler et al., 2025).

6. CONCLUSION

Skin aging is a multifactorial and inevitable process driven by intrinsic biological changes and accelerated by environmental stressors. Preserving skin function is essential not only for aesthetics but also for overall physiological balance. Herbal dermatology offers promising, supportive benefits in the management of skin aging. Phytochemicals such as curcumin, thymol, gallic acid derivatives, terpenoids, and carnosic acid exert antioxidant, anti-inflammatory, photoprotective, hydration-enhancing, and collagen-preserving effects. These mechanisms help mitigate early skin aging.

However, careful attention is required regarding safety, standardization, potential toxicity, and herb-drug interactions. Continued research, clinical validation, and optimized formulations will help bridge the traditional herbal knowledge with modern dermatological science. Therefore, herbal medicine should be regarded as an adjunctive option rather than primary intervention for skin aging.

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Chapter 13
Gut Health and Microbiome in Aging

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ABSTRACT

Healthy aging is closely linked to the integrity of the gut–microbiome–host axis. Aging is frequently associated with gut dysbiosis, characterized by microbial diversity imbalance, depletion of beneficial species (e.g., *Faecalibacterium prausnitzii* and *Bifidobacterium spp.*), and enrichment of opportunistic pathobionts such as *Proteobacteria*. This imbalance compromises intestinal epithelial integrity by reducing the production of protective short-chain fatty acids (SCFAs). Disruption of tight junctions increases intestinal permeability, allowing microbial products such as lipopolysaccharide (LPS) to enter systemic circulation and drive chronic low-grade inflammation (inflammaging), a key contributor to immunosenescence and age-related diseases. The systemic impact of intestinal dysfunction extends to the gut–brain axis and metabolic regulation. Dysbiosis-induced alterations in SCFA and precursor levels for central nervous system neurotransmitters are involved in accelerating neurodegeneration. Furthermore, specific microbial profiles lead to changes in bile acid metabolism and influence host energy acquisition, contributing directly to insulin resistance and metabolic syndrome. Herbal medicine provides multi-targeted approaches to restore gut homeostasis, including prebiotic herbs that enhance SCFA production, selective antimicrobials that suppress pathogenic microbes, demulcent herbs that reinforce mucosal integrity, and prokinetic agents that support gastrointestinal motility. This chapter highlights the gut microbiome as a vital, modifiable target for promoting healthy aging and disease prevention. Future directions emphasize the use of personalized, symbiotic approaches, combining steady herbal compounds with targeted probiotic strains, alongside rigorous clinical evaluation of safety, efficacy, and potential drug-herb interactions (DHIs) in the elderly.

Keywords: Gut health, Dysbiosis, SCFA, Herbal medicine

1. INTRODUCTION

1.1 Definition and Components of the Gut-Microbiome-Host Axis

The gut and human health are considerably associated with each other. Human gut coordination with microbiome provides a complex two-ways interaction system, critical to maintain host physiological homeostasis. It comprises three interconnected components of luminal content, mucosal layer and gut microbiota. The luminal content including digested food, bile acids, and secreted digestive enzymes supports microbial activity (Altshuler et al., 2013; Steigert et al, 2024). The mucosal layer together with epithelial barrier acts as the main physical and immunological barrier to provide protection from pathogens and unwanted antigens (France and Turner, 2017). The gut microbiota**,** common microorganisms found in the human guts, play a major role in maintaining physiological balance thus affecting human health. These components are believed to influence human immunity, endocrine signaling, and overall metabolic health (Juge, 2022).

1.2 Age-Related Changes (Dysbiosis)

The health of human guts is associated with aging, which is also known as gut dysbiosis – an imbalance of composition and complex function of the gut microbiota. It has been identified that this condition can be caused by several factors, including microbial and biochemical imbalance. The reduced composition of beneficial and commensal bacteria such as Bacteroidetes and well-known probiotics such as the genus *Lactobacillus* and *Bifidobacterium* was found to be significantly affecting gut health through time (Rios-Covian et al., 2013; Chen et al, 2021). Critically, there is also a significant loss of species like *Faecalibacterium prausnitzii*, producer of short-chain fatty acids (SCFA) butyrate which is known for its anti-inflammatory properties, correlating directly with immunocompromised person and human morbidity (Martín et al., 2023). Butyrate is the preferred energy source for colonocytes (epithelial cells) and is essential for maintaining the integrity of the epithelial barrier.

In spite the significant reduction of beneficial bacteria and butyrate producers, aging leads to the proliferation of potentially opportunistic or pathogenic bacteria. A recent review study conducted by Jang et al (2024) revealed that these organisms, often belonging to the *Proteobacteria* family (e.g., *Clostridium difficile* and certain *Enterobacteriaceae*), thrive in a condition of reduced microbial competition with compromised mucosal environment (Jang et al., 2024). Their prevalence contributes to inflammation and impaired intestinal function. In addition, the compositional shift results in a quantifiable reduction in the production of SCFA. Lower SCFA levels thus impair colonocyte health, diminish the

regulatory T-cell population, and induce age-related inflammation (Diwan and Sharma, 2022).

2. GUT DYSBIOSIS AND SYSTEMIC INFLAMMAGING

2.1 Increased Intestinal Permeability

The integrity of gut barrier may decrease in maintaining the composition of healthy gut structure, as proven by the correlation between gut dysbiosis and systemic aging.

i. Tight junctions composed of proteins such as occludin and zonulin, normally regulate paracellular transport. Inflammatory signals derived from an imbalanced microbiota cause the disassembling and redistribution of these components, leading to a compromised epithelial barrier function (Wu et al, 2021).

ii. Increased permeability allows the passive diffusion and active translocation of microbial components, most notably Lipopolysaccharide (LPS), an endotoxin derived from the outer membrane of Gram-negative bacteria—from the intestinal lumen into the portal circulation (An et al, 2022).

iii. Circulating LPS activates host immune cells (monocytes, macrophages) via Toll-like Receptor 4 (TLR4). This activation results in the sustained release of pro-inflammatory cytokines (IL-6, TNF-alpha, IL-1\beta). This state, characterized by persistent, poor, sterile systemic inflammation, is termed inflammaging and is a primary factor in increasing the risk of chronic disease and disable functional gut regulation in the elderly (Caldarelli et al., 2024).

2.2 The Gut-Brain Axis and Neurodegeneration

The intricate correlation of gut and brain provides a critical pathway where microbial imbalance can influence neurological and cognitive aging. The gut microbiota produces various metabolites and precursors for central nervous system neurotransmitters (e.g., serotonin, dopamine, gut-brain axis). Dysbiosis can alter the production and circulating levels of these metabolites, potentially affecting neurogenesis, synaptic function, and mood regulation. For example, the serotonin produces by gut microbiota can modulate the human enteric nervous system thus enhances the rate of gut transit (Qiu et al., 2023).

Several evidence suggest a relationship between gut dysbiosis and conditions like Alzheimer's and Parkinson's disease (Samson et al., 2017; Singh et al., 2021). Through the mechanism of chronic inflammation (inflammaging) and the misfolding/accumulation of proteins (like alpha-synuclein, which may originate in the gut), the dysbiosis state may

contribute to the initiation or acceleration of neurodegeneration (Ribeiro et al., 2020).

2.3 Role in Metabolic Syndrome and Chronic Disease

The microbial community plays a direct role in host metabolism and energy balance, impacting the onset and severity of chronic metabolic diseases associated with aging. Summary of gut-related inflammaging pathways associated with aging are provided in Table 1.

i. Certain microbial profiles, characterized by a higher *Firmicutes* to *Bacteroidetes* ratio, are associated with increased efficiency in energy extraction from the diet (Carrizales-Sánchez et al., 2021). Furthermore, the type and amount of SCFA production influences host GLP-1 secretion and subsequent insulin signaling, affecting peripheral insulin sensitivity. Dysbiosis can therefore contribute to the development of insulin resistance and Type 2 Diabetes Mellitus (Salamone, Rivellese and Vetrani, 2021).

ii. Dysbiotic gut microflora can modify the composition of bile acids, which are crucial regulators of host metabolism. These altered bile acid profiles, along with systemic inflammation, promote chronic liver stress, ectopic fat deposition, and the dysfunction of adipose tissue, leading to the development of metabolic syndrome (Sah et al., 2022).

3. HERBAL STRATEGIES FOR MICROBIOME MODULATION AND GUT INTEGRITY

Herbal medicine offers a multi-target approach to restore gut health, addressing dysbiosis, barrier function, and gut regulation simultaneously.

3.1 Prebiotic and Fiber-Rich Botanicals

Prebiotics are non-digestible food components that selectively stimulate the growth and activity of beneficial bacteria. For example, chicory root (*Cichorium intybus*) is a premier source of inulin, a fructan polysaccharide. Upon consumption, inulin is resistant to host digestive enzymes and directly intact to the colon, where it will be selectively fermented by health-promoting bacteria, primarily *Bifidobacterium* and *Lactobacillus* species (Carlson et al., 2017).

The fermentation of inulin by these organisms yields significant amounts of respective fatty acids, such as butyrate. This mechanism is crucial in which the resulting butyrate provides the vital energy source for colonocytes, promoting epithelial integrity, while the increased SCFA load contributes to a lower, more acidic environment in colon (Skinner et

al., 2025). This acidic environment is detrimental to many pathogens, effectively regulating the overall microbial ecosystem.

Table 1: Gut-related Inflammaging Pathways Associated with Aging.

Phase	**Mechanism**	**Biological Significance**	**Reference**
Microbial level	Dysbiosis & Reduced SCFAs	Loss of SCFA i.e Butyrate; rise in opportunistic Proteobacteria.	Rangareddy et al., 2025
Structural level	Tight Junction Dissolution	Increase in paracellular permeability (Leaky Gut).	Untersmayr et al., 2022; Aleman et al., 2023; Caldarelli et al., 2024
Translocation process	Endotoxemia	Migration of LPS and bacterial DNA into portal blood.	Untersmayr et al., 2022; Rosendo-Silva et al., 2023
Immunological reaction	TLR4 Activation	Chronic activation of systemic macrophages and NF-κB.	Rong et al., 2021
Systemic inflammaging	Cytokine Cascade	Sustained levels of circulating IL-6, TNF-alpha, and C-reactive protein.	Chambers and Akbar, 2020
Pathological level	Tissue Damage	Neurodegeneration, Insulin Resistance, and Sarcopenia.	Picca et al., 2018; Fu et al., 2024

3.2 Selective Antimicrobial Agents

Certain herbs possess natural compounds that can selectively target and reduce undesirable microbial populations, helping to re-balance the microflora.

i. Alkaloids like berberine, found in plants such as Goldenseal (*Hydrastis canadensis*), Barberry (*Berberis vulgaris*), and Oregon Grape (*Mahonia aquifolium*), exhibit comprehensive antimicrobial activity. Importantly, studies suggest berberine can target opportunistic pathogens while often preserving the core SCFA-producing bacteria, allowing for a targeted "weed-and-feed" approach to correcting dysbiosis (Zhang et al., 2021). Berberine also has systemic effects, improving glucose metabolism and reducing hepatic fat accumulation.

ii. Garlic (*Allium sativum*) contains organosulfur compounds, with allicin being the active compound. Allicin demonstrates significant antimicrobial and antifungal properties (Ankri and Mirelman, 1999). Furthermore, garlic extracts have been shown to modulate bacterial biofilms, a complex accumulation of microorganisms which forming a protective layer matrix that protect pathogens. Garlic extracts are also able to promote overall microbial diversity by inhibiting the overgrowth of specific opportunistic species.

3.3 Mucosal Barrier Repair and Soothing Herbs

The physical barrier of the gut requires active support and repair, especially in the context of chronic inflammation. Demulcent herbs may provide a protective coating to the respective gut composition. For instance, Slippery Elm Bark and Marshmallow Root. These demulcent herbs, derived from *Ulmus rubra* and *Althaea officinalis* respectively, are rich in complex polysaccharides and mucilage. When mixed with water, they form a thick, protective gel that coats the gastrointestinal mucosa. This coating serves as a physical protectant against irritants, aids in the repair of inflamed epithelial tissue, and can indirectly improve barrier function by creating a stable environment for healing (Aleman et al., 2023).

On the other hand, the production of amino acid L-Glutamine can be supported by herbal precursors. Glutamine is the primary metabolic fuel for enterocytes, and its supplementation is well-established in clinical settings to support rapid epithelial cell proliferation and the synthesis of tight junction proteins. Herbal approaches that reduce catabolism or enhance amino acid availability support this essential repair process (Aleman et al., 2023).

3.4 Movement and Digestive Function

Optimal gut health relies on efficient transit and digestion to prevent the decomposition of food residues and the subsequent release of toxins.

i. Ginger (*Zingiber officinale*) contains pungent compounds, gingerols and shogaols, which act as prokinetics. They promote

gastric emptying and accelerate intestinal peristalsis by stimulating receptors in the enteric nervous system. This increases the digestion which then helps in preventing intestinal stasis, reducing the time for harmful bacteria to ferment excess protein and produce potentially toxic metabolites (Drobnic et al., 2022).

ii. Herbs like Dandelion (*Taraxacum officinale*) and Artichoke (*Cynara scolymus*) are included as bitters. The bitter taste receptors on the tongue and in the gut trigger a cascade of digestive reflexes: stimulating salivary, gastric acid, and pancreatic enzyme secretion, as well as bile flow from the liver and gallbladder. This enhanced digestive efficiency ensures complete breakdown of nutrients, minimizing undigested residue that could feed opportunistic pathogens deeper in the colon (Drobnic et al., 2022).

4. CONCLUSION AND FUTURE DIRECTIONS

The gut microbiome stands as a flexible and potent determinant of the aging process. The shift from a diverse, balanced state to a pro-inflammatory, dysbiosis state is a critical factor driving inflammaging and the chronic diseases of later life.

i. The clinical priority for the elderly is to manage systemic inflammation. By addressing “leaky gut” mechanisms, the progression of cardiovascular disease can be controlled by lowering the circulating LPS thus reducing the arterial wall inflammation. Additionally, SCFAs-mediated treatment can improve insulin sensitivity in managing metabolic syndrome while modulating the gut-brain axis may reduce the risk of severe neurodegeneration.

ii. Advances in metagenomic sequencing and computational biology may become one of potential approaches in developing highly personalized intervention strategies. Future clinical protocols will involve using the individual's microbial fingerprint to design specific herbal and dietary protocols, selecting botanicals that selectively enhance deficient beneficial species or inhibit specific over-represented pathogens identified through sequencing.

iii. The most powerful therapies will increasingly employ symbiotic approaches, combining standardized, evidence-based herbal prebiotics (like inulin or specific polysaccharides) with targeted, strain-specific probiotic bacterial strains. This dual action maximizes the opportunity for microbial restoration and colonization success.

iv. A crucial consideration in the geriatric population is the potential for drug-herb interactions (DHIs). Specific herbal constituents, such as those found in St. John's Wort or high concentrations of curcumin, can influence the activity of hepatic cytochrome P450 (CYP450) enzymes. Clinicians must meticulously evaluate a patient's profile components and select herbal interventions with low DHI risk to ensure safe and effective integration into chronic disease management.

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Chapter 14
Herbal Approaches to Immune Senescence and Cancer

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ABSTRACT

Immune senescence is the loss of immune function that develops with age. This causes individuals more likely to develop cancer, chronic inflammation, and infections. The accumulation of senescent immune cells and persistent inflammation promote tumour initiation and progression. The need for safer and more comprehensive alternatives is further highlighted by the frequent progression of immune exhaustion resulting from conventional treatments. *Quercus infectoria* (QI) galls are rich in polyphenols such as gallic acid, quercetin, and ellagic acid. They have strong anti-inflammatory, immunomodulatory, and antioxidant effects. These bioactive compounds enhance immune function and inhibit tumour proliferation by modulating mTOR–AMPK pathways, attenuating NF-κB and MAPK signalling, and re-establishing redox balance. QI galls are potentially an alternative method of slowing down immune senescence and inhibit cancer from spreading through regulating metabolism, redox balance, and epigenetics.

Keywords: Immune senescence, Cancer, *Quercus infectoria,* Bioactive compounds

1. INTRODUCTION

Immune senescence, characterised by the progressive decline of immune function with increasing age, significantly contributes to higher susceptibility to infections, chronic inflammation, and cancer in older adults. This decay has been demonstrated by thymic involution, decreased antigen presentation, the buildup of old immune cells, and a pro-inflammatory signalling process that continues to occur, which is also called inflammaging (Yang et al., 2025). These changes impair immune surveillance and enable infected and malignant cells to evade the host immune system. Epidemiological data have also supported the association of aging with cancer as more than 60% of all cancers are diagnosed in people who are over 65, indicating a central role for immune dysfunction in age-related tumour susceptibility (Montégut et al., 2024).

Chemotherapy and immunotherapy are the prevalent therapies for cancer and age-associated immune dysfunction. These treatments often cause oxidative stress and exhaustion in the immune system. Herbs and natural compounds that modulate the immune system and neutralize free radicals are becoming increasingly popular as safer and higher-quality alternatives. Numerous studies have shown that herbs with high in polyphenols and tannins were able to boost the immune systems and prevent the development of cancer. In this case, the galls of *Quercus infectoria*, a medicinal plant that is well-known in traditional medicine, show a unique phytochemical profile that indicates biological markers for preventing cancer and boosting the immune system.

2. A BIOLOGICAL OVERVIEW: IMMUNE SENESCENCE & CANCER

Immune senescence is the immune system's aging-related remodelling, resulting in impaired responses to new antigens and dysregulated inflammation. Thymic involution, decreased naïve T-cell production, accumulation of senescent $CD8^+$ T cells, decrease in B-cell diversity, and modified macrophage and NK cell function are some of the main characteristics (Thomas et al., 2020; Yang et al., 2025). Meanwhile, signaling pathways of NF-κB, mTOR, p53, and Nrf2 become dysregulated at the molecular level and eventually promotes the oxidative stress and produces the inflammatory cytokine like IL-6, TNF-α, IL-1β (Liu et al., 2023; Yang et al., 2025). This on-going low-grade inflammation is a factor in inflammaging, a chronic inflammatory condition that promotes the development and progression of tumours by fostering a pro-tumorigenic microenvironment (Thomas et al., 2020).

The senescence-associated secretory phenotype (SASP), a condition in which senescent cells release cytokines, chemokines, and proteases, is a crucial connection between immune senescence and the development of

cancer. Chronic SASP signalling can sustain tissue damage, promote angiogenesis, and facilitate immune evasion, all of which contribute to carcinogenesis, even though SASP initially helps the immune system eliminate damaged cells (Fulop et al., 2010; Lian et al., 2020; Thomas et al., 2020). As a result, senescent immune and stromal cells support the development and spread of cancer by changing from a tumour-suppressive to a tumour-promoting role.

It has been shown that as the immune system declines with age, its ability to sustain effective immune surveillance diminishes. This reduction not only diminishes the capacity to eradicate damaged or altered cells but also promotes a pro-tumorigenic microenvironment. Therefore, it is important to address the question about how immunological aging makes tissues more likely to turn cancerous. In the following part, we discuss the mechanism by which these immune changes facilitate the onset and progression of cancer.

3. MECHANISMS OF IMMUNE SENESCENCE IN CANCER DEVELOPMENT

Through a number of mechanisms, immune senescence significantly affects the development and progression of cancer. To induce a stable state of cell cycle arrest, the p53/p21 pathway is activated, whereas the p16INK4A/retinoblastoma protein (pRB) pathway is inhibited (Zarneshan et al., 2023). While ER stress-induced UPR causes G2/M arrest through decreased cyclin B1 and eIF2α signalling. These pathways cooperate with CDK/cyclin complexes and the DREAM complex to control cell growth. Although this mechanism initially stops the damaged cells from proliferating, the buildup of senescent cells eventually changes their function from stopping tumours to promoting them. This can promote the growth of cancer and chronic inflammation.

Senescence-associated secretory phenotype (SASP) is a distinctive pro-inflammatory profile characterised by the secretion of cytokines, chemokines, growth factors, and proteases, serving as a significant contributor to these alterations (Lian et al., 2020; Thomas et al., 2020). SASP improves immune surveillance in its early stages by drawing immune cells to eliminate malignant or senescent cells. SASP signalling, however, takes on a harmful role when it is continuously activated, creating an environment that encourages the growth, angiogenesis, invasion, and metastasis of cancer cells. In addition to maintaining low-grade inflammation, the constant release of inflammatory mediators like TNF-α, IL-6, and IL-8 also encourages tissue remodelling and genomic instability, both of which aid in the growth of tumours (De Luca, 2023).

Senescent immune cells further impact cancer dynamics within the tumour microenvironment by changing immune regulation. By eliminating cancerous cells, these cells can either promote immunosurveillance or induce immunosuppression by releasing inhibitory cytokines and attracting regulatory immune populations that impede antitumor responses (De Luca, 2023).

Strategies that can alter these interrelated pathways are of great therapeutic interest because of the complex relationship between immune senescence and the development of cancer (Figure 1). Polyphenol and tannin-rich natural products have shown great promise in reducing oxidative stress, regulating pro-inflammatory signalling cascades, and restoring immune balance (Godos et al., 2025; Yoshimura, 2014). Due to its high phenolic content and diverse biological activities, *Quercus infectoria* (QI) galls have become a promising candidate among other natural products (Abdullah et al., 2017; Ahmad et al., 2023; Kamarudin et al., 2021; Yusof & Abdullah, 2020). There is growing evidence that QI galls and their bioactive compounds may use immunomodulatory and antioxidant properties to combat tumour-promoting inflammation and immune aging.

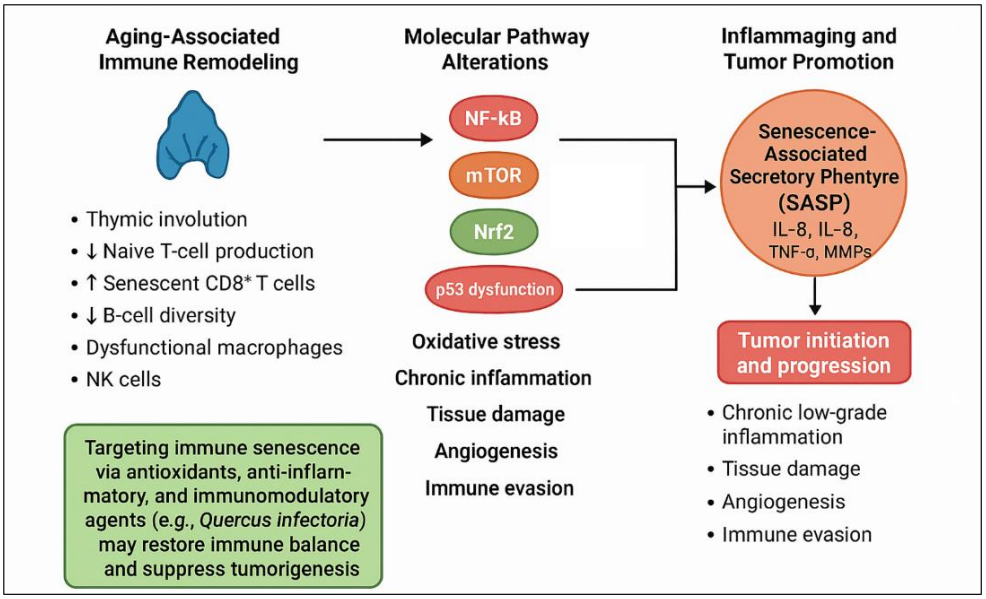

Figure 1: Mechanistic link between immune senescence and cancer development

4. *QUERCUS INFECTORIA* GALLS: HERBAL MODULATOR OF IMMUNE SENESCENCE AND CANCER

In traditional medicine, a number of native Malaysian plants are said to increase vitality, aid in recovery from illness, reduce inflammation, and extend lifespan (Manshoor et al., 2025). By investigating how these herbs may regulate immune senescence and inhibit tumorigenesis, scientific studies have recently started to support these assertions. Among these, *Quercus infectoria* (QI) galls stand out as a potentially effective herbal model for addressing the two concurrent problems of cancer progression and aging-related immune decline. The QI galls, referred to as "*manjakani*" in Malaysia and "*majuphal*" or "*machakai*" in India, have long been utilised in conventional medicine (Figure 2). They are often prepared as herbal decoctions in Malaysia to aid in the recovery of uterine elasticity as well as promote the contraction of vaginal muscles after childbirth (Syukriah et al., 2014).

The QI galls are notably rich in hydrolysable tannins, gallic acid, ellagic acid, quercetin, and syringic acid; compounds recognized for their potent antioxidant, anti-inflammatory, antimicrobial, and anticancer activities (Abdullah et al., 2017; Başyiğit et al., 2020; Hazwani et al., 2018; Ismail et al., 2021; Syukriah et al., 2014). The immunomodulatory and protective effects of QI galls are potentially more clearly identified by understanding their mechanisms of action affect molecular signalling. The main mechanisms in which QI affects the inflammation, oxidative stress, cell growth, apoptosis, and tissue repair are outlined in the following section.

Figure 2: *Quercus infectoria* galls (Amedi & Mohammad, 2021)

The QI gall extract plays an essential role in combating immune senescence due to its significant potential to modulate immune

responses. Its bioactive compounds act through diverse molecular mechanisms that regulate oxidative stress, inflammation, cell proliferation, and tissue regeneration, all of which are critical for preserving immune function regardless of age.

Previous studies have reported that QI galls possessed potent anti-inflammatory properties (Bai et al., 2024; Kaur et al., 2004). The extract of QI galls downregulates the Set7/NF-KB pathway, reducing IL-1β and TNF-α expression and mitigating chronic inflammation. It also modulates cytokine levels including IL-2, IL-5, IL-10, IL-17A, IL-23, and TGF-β1, indicating its role in immune regulation (Chokpaisarn et al., 2017; Kaur et al., 2004). Additionally, QI galls influence key signalling pathways such as AKT, MAPK, and JAK/STAT (Ahmad et al., 2023), which are central to immune regulation and inflammatory responses. Through modulation of these pathways, the galls help maintain immune homeostasis and show potential in lowering the risk of autoimmune-associated disorders.

QI galls extract also demonstrate potent antioxidant activity, contributing to the reduction of oxidative stress, a major cause of inflammatory processes (Kaur et al., 2004). The extract has anti-inflammatory properties due to the fact it scavenges reactive oxygen species (ROS) including superoxide and nitric oxide and increases the activity of antioxidant enzymes such as glutathione peroxidase and catalase (Rehman et al., 2012; Vadaga et al., 2025; Wan-Nor-amilah et al., 2021). This redox balance restoration delays telomere shortening, protects immune cells from oxidative damage, and prevents premature immune exhaustion.

Beyond their anti-inflammatory and antioxidant effects, QI galls extract influence key immunometabolic pathways associated with immune cell survival and cellular stress responses. Previous study has shown that the extract suppresses the AKT/mTOR signalling pathway in colorectal cancer (CRC) cells (Zhang et al., 2020). This finding highlights the ability of the galls to interfere with the mTOR pathway, a major regulator of cell growth and metabolism.

In addition, QI galls promote innate immune responses by increasing phagocytic activity and macrophage proliferation. Studies have demonstrated that the extract induces apoptosis in multiple cancer cell lines including cervical, lung, gastric, and oesophageal cancers, by stimulating caspase enzymes and regulating apoptosis-related genes, including BAX and BCL2 (Abdullah et al., 2021; Ahmad et al., 2024; Ismail et al., 2021; Tofigh et al., 2024; Wan-Nor-amilah et al., 2021).

QI galls have also been reported to stimulates angiogenesis, fibroblast proliferation, and collagen deposition, while reducing pro-inflammatory

cytokines, including TNF-α and IL-6, which supported wound-healing responses. This effect is especially advantageous in diabetic wound models, where excessive inflammation often impedes the healing process (Dardmah & Farahpour, 2021; Wunnoo et al., 2024). Collectively, these interactions with multiple targets suggest that QI galls could be a useful herbal modulator that uses metabolic adaptation, inflammatory control, redox balance, and epigenetic regulation to slow down immune senescence and inhibit tumour growth.

5. THERAPEUTIC PERSPECTIVES AND FUTURE DIRECTIONS

The QI galls have the potential to reduce cancer risk and delay the aging process of the immune system in older adults. Based on previous studies, they exhibit immunomodulatory, anti-inflammatory, and multi-targeted antioxidant properties making them an ideal candidate for incorporation into nutraceuticals or additional treatments which are meant to restore the immune system back to its natural state. Additionally, QI galls may enhance immunological surveillance, strengthen immune responses, and obstruct tumour-promoting pathways associated with aging by mitigating oxidative and inflammatory stress.

However, despite these promising results, most current evidence comes from *in vitro* studies and limited preclinical evaluations, with few well-designed animal studies available verify its efficacy, safety, and mechanisms *in vivo*. Addressing this research gap is critical for translating laboratory findings into clinical relevance. Subsequent investigations using robust animal models, followed by well-designed clinical studies are necessary to clarify its molecular targets, bioavailability, and synergistic effects with conventional anticancer treatments.

6. CONCLUSION

Quercus infectoria galls show promise as a natural source of bioactive compounds capable of modulating immune aging–related mechanisms, including oxidative stress, inflammatory signalling, and immunometabolic regulation. They influence pathways such as NF-κB, AKT, and MAPK suggest a potential multi-target mode of action relevant to immune function and tumour-promoting inflammation. Despite these promising properties, current evidence remains largely preclinical. Therefore, further investigations including animal studies and well-designed clinical trials are needed to clarify pharmacokinetics, determine optimal dosing, evaluate long-term safety, and assess potential interactions with existing cancer therapies to support translational application. Considering all factors, the therapeutic potential of QI galls

signifies a substantial and promising domain for future research in immunological rejuvenation and cancer prevention.

DECLARATION

AI-based language tools were employed to assist with draft and revise the article. Nonetheless, the writers take exclusive responsibility for the scientific content, interpretations, and conclusions.

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Chapter 15

South Indian Spices for Disease Prevention and Healthy Aging

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ABSTRACT

South Indian spices have been integral to daily diets and traditional medical practices for centuries, valued not only for their sensory attributes but also for their health-supporting properties. This chapter examines the role of commonly used South Indian spices as dietary components with nutraceutical potential, particularly in the context of aging and chronic disease prevention. Drawing on historical records, ethnomedical traditions, and contemporary scientific evidence, it discusses key spices such as turmeric, black pepper, cardamom, clove, cinnamon, fenugreek, cumin, coriander, mustard, and star anise. The phytochemical composition and reported biological activities of these spices, including antioxidant, anti-inflammatory, metabolic, neuroprotective, and cardioprotective effects, are critically reviewed. Attention is also given to traditional culinary practices and spice combinations, which influence bioavailability and biological efficacy. By positioning traditional knowledge alongside modern pharmacological findings, this chapter highlights the relevance of South Indian spices as functional dietary components with potential contributions to healthy aging and disease risk reduction.

Keywords: South Indian Spices, Nutraceuticals, Healthy Aging

1. INTRODUCTION

Plants offer a wide range choices like vegetables, fruits, greens, legumes, pulses, grains etc., which are packed with nutrition. Consumption of a plant-based diet have a positive correlation on the metabolic profile of individuals with reduced inflammatory effects (Herpich, Müller-Werdan, & Norman, 2022). Spices on the other hand are loaded with phytochemicals with antibacterial, anti-inflammatory, antioxidant and immune booster effects. Though used in small quantities, prolonged consumption of turmeric, black pepper, cinnamon, cardamom, ginger lowers the risk of non-communicable inflammatory diseases like cancer, heart disease, respiratory failures. The present chapter discuss about the hidden gems huddled in the jars handled down as a treasure of ancient wisdom to every household. These spices that lays in the corner of every kitchen although relished for the burst of flavours, carry assets of longevity and strength passed down from ages. This review is an attempt to highlight the potential benefits of spices found in every home of the Indian subcontinent.

2. THE SOUTH INDIAN SPICES

The spicy and aromatic South Indian foods are relished and appreciated by people all over the world not only for its taste but also for its health benefits. The southern Indian states of Kerala, Tamil Nadu, Karnataka, Andhra Pradesh, and Telangana have their own unique cuisines; the food habits are totally different from those of north India. Being tropical and receiving heavy rainfall, the soil is very fertile and is suitable for cultivating various kinds of spices, so that South India is one of the world's leading countries in growing and exporting spices. Spices such as black peppers, cardamoms, turmeric, cinnamon, cumin, coriander, fenugreek, asafoetida, and mustard seeds (Figure 1) brought unparalleled riches to the Malabar Coast through long established sea and land spice routes dating back two millennia. These spices also played a great role in shaping local food habits, customs, and legends. The historical origins of South Indian spices are interwoven with economic forces and early science (Ravindran, Sivaraman, Devasahayam, & Babu, 2024). Even before the advent of modern pharmacology, ancient medicines such as Ayurveda and Siddha perceived the overriding importance of spices not only as common food items but also as potent medicines for preventive and therapeutic uses. The old texts of the region described the wound healing property of Turmeric, remedies for lung disorders using black pepper, metabolic health property of fenugreek and digestive health property of Ginger to name a few are still practiced in modern home remedies as folksy medicine (Zachariah, 2018). Sambar, rasam along with chutneys are some of the recipes in which spices are added in an

organized way. It shows understanding of flavour which results from different proportions providing the healing touch (Ravindran, 2024). Spice blends shape the cultural core of South Indian people by using in daily food preparation and formal rituals. It is known from its inherent nature that spices are not just a flavour in the South Indian cuisine parlance but they are the essence and soul behind good health and great taste too. Many spices contain a vast array of bioactive constituents which make them as functional foods. The three components, black pepper, cumin, and turmeric are used in every day dietary pills not only for their tasty effects but also for the health promoting effects that go from their antioxidant and antimicrobial effect to modulation of digestive and metabolizing process. High prevalence of consumption of spice rich foods such as rasam, that is often called as “functional soup” is based on empiricism of centuries on prevention of diseases and promotion of good health (Sharangi & Acharya, 2018, Babu, Ravindran, Sivaraman, & Devasahayam, 2024, Sharangi, 2018).

3. HISTORICAL AND CULTURAL CONTEXT OF SOUTH INDIAN SPICES

The history of South Indian spices is linked with the world trade and cultural conversion. The southern part of the subcontinent has been a special place for spice cultivation since ancient times. Black pepper, cardamom, cinnamon, turmeric, and other spices have been used for thousands of years by the society of southern India, according to the archaeological findings and ancient literature. Spices plantations and trading settlements have been developed along the Coromandel and Malabar coast as early as 3000 BCE (Shukla, 2018). Why did so many civilizations such as Romans, Greeks, Arabs, Chinese send traders to the coast of South India? It’s because of the historic spice trade. The modern-day ruin of Muziris attests to the mythical status of pepper and other aromatic products in the ancient spice trade. The quest for South Indian spices made world history by prompting Portuguese explorers and Dutch and British traders to embark on ships that forever transformed the people and the economy of the places. Inscriptions and traveller's accounts tell us that spices from this area were valued both as status symbols and for their life-preserving properties. The stage was thus set for the complex political relationships, intercultural contact, and food heritage that we enjoy today, inter alia, due to the history of the spice trade in South India. The states of Kerala, Tamil Nadu, Karnataka, Andhra Pradesh, and Telangana have very different approaches to the use and meaning of spices in South Indian Cooking. Each of these states have developed very different spice blends and characteristic dishes due to their historical interactions, climate, and geography. Known as the "Land of Spices", Kerala's popular dishes include fish curries, coconut-based stews, Malabar biryani. The main spices here are black pepper

(often called "Black Gold"), cardamom, cinnamon, cloves, and nutmeg. Kerala has a multicultural history which includes the presence of Hindus, Christians, Muslims, and Jews with their respective cuisines.

Figure 1: Spices found in South India. A-Turmeric, B-Pepper, C-Cardamom, D-Clove, E-Cinnamon, F-Fenugreek, G-Star Anise, H-Cumin, I-Mustard, J-Coriander

Spices are used both as taste enhancers and for preserving food and the complex cuisine of Kerala has a layered history of spice blends (Sugasini, Yalagala, & Kumar, 2018). The powerful and fragrant cuisine may contain curry leaves, peppercorns, mustard seeds, fenugreek, coriander, and dry red chilies. A layered complexity of subtle and deep awareness of taste layering and synergy is seen in the characteristic use of spice blends like "sambar powder" and "rasam powder" in sophisticated Tamil Nadu cuisine. Traditional dishes like rasam, pongal, dosa and Chettinad curries are spiced up heavily. Each blend has been carefully formulated over hundreds of years for taste balance and healing properties (Ravindran, Jayashree, & Innovation Team, 2022). Karnataka cuisine, which includes "bisi bele bath," spice-infused gravies, and a range of chutneys and pickles, has been affected by a few microclimates and local traditions.

The aromatic underpinnings of both vegetarian and non-vegetarian traditional foods are mustard, curry leaves, asafoetida, and coriander, but the Malnad and coastal regions place greater emphasis on regional spice mixtures and coconut-based preparations (Tripathi, 2024). The regional cuisine of Andhra Pradesh and Telangana is renowned for its complexity and spiciness. Fresh or dried red chilies, mustard, fenugreek, cumin, coriander, ginger, garlic, and tamarind are ingredients used to

make spicy curries, chutneys, and pickles. Rich, delicious bases and a distinctive use of heat and acidity are hallmarks of Telugu cuisine. Spices play a major role in the culture and way of life of the southern states. They are utilized in temple offerings, funeral ceremonies, and large gatherings with loved ones.

4. SPICES IN AYURVEDA AND SIDDHA MEDICINE

The ancient medical systems of Siddha and Ayurveda originated and flourished in the southern regions of the Indian subcontinent. They are powerful illustrations of South Indian spices' therapeutic past. According to these outdated views, using spices is necessary to achieve equilibrium in the body, mind, and spirit. They suggest them as excellent remedies for ailments as well as daily meals (Tripathi, 2024). Traditional Ayurvedic writings describe the use of cardamom for respiratory and dental health, ginger for digestive and antiemetic effects, long pepper, and black pepper as "trikatu" to boost metabolic fire, and turmeric for its anti-inflammatory, wound-healing, and purifying properties. The medicinal and preventative qualities of spices like mustard seeds, fenugreek, cumin, and asafoetida are highly valued in the Dravidian system of Siddha, which is deeply embedded in Tamil culture. These methods use dry powders, pastes, decoctions, and infusions often in conjunction with other herbs to treat skin ailments, respiratory problems, metabolic imbalances, and digestive disorders (Ayurveda Academy of Medicine, 2023). Numerous traditional claims have been validated by contemporary phytochemical research, which has also elucidated the molecular basis of the anti-inflammatory, antioxidant, antibacterial, and immunomodulatory qualities frequently linked to South Indian spices. A common occurrence in South Indian societies is the integration of culinary and medicinal applications into daily life. This shows that the region's spice traditions are not only historical but also active examples of cultural and biological innovation (Divya, Rao, & Prasad, 2022). Several commercially and medicinally significant spices, including turmeric (*Curcuma longa*), black pepper (*Piper nigrum*), cardamom (*Elettaria cardamomum*), clove (*Syzygium aromaticum*), cinnamon (*Cinnamomum verum*), fenugreek (*Trigonella foenum-graecum*), and curry leaves (*Murraya koenigii*), are found in South India, sometimes referred to as the "land of spices”.

4.1 Turmeric

The perennial herb turmeric is a member of the Zingiberaceae family. It has mostly been used as a home remedy to treat a variety of physiological conditions from prehistoric times. The largest producer and consumer of turmeric presently in the world is India. There are currently 133 species of Curcuma known to exist in the world. Every cuisine in almost every

region of India, where food is highly valued for its medicinal qualities as well as its flavour and richness, is only effectively finished with the inclusion of fresh roots of this amazing herb, "turmeric." This herb, either by itself or in combination with other herbs, offers a medicine for everything from the head to the feet, including digestive and circulatory issues (Jikah & Edo, 2025). Turmeric has a variety of pharmacological qualities, such as antibacterial, antioxidant, anti-inflammatory, cardiovascular, antidiabetic, and anticancer benefits, mostly due to its active component curcumin.

With effectiveness on par with conventional medications, it suppresses dangerous bacteria, lowers oxidative stress, and stops inflammation. Additionally, curcumin enhances the metabolism of glucose and cholesterol, guards against platelet aggregation, and is potentially able to inhibit the growth of tumours and the development of cancer. In addition to being used to flavour food, turmeric, often known as the "Kitchen Queen," has been utilized in traditional medicine as a home cure for a number of illnesses, such as rheumatism, sinusitis, biliary disorders, anorexia, coughing, diabetic sores, and hepatic disorders. Turmeric's antioxidant and anti-inflammatory properties reverse aflatoxin-induced liver damage, exhibiting significant hepatoprotective and renoprotective benefits. Additionally, it provides neuroprotection against Alzheimer's disease by lowering inflammation and oxidative stress; dietary curcumin lowers IL-1 and oxidized proteins. Turmeric also demonstrates photo-protective properties, shielding skin from UVB rays and avoiding chromosomal changes brought on by gamma radiation. The pharmacological effect of turmeric is due to the presence of numerous phytochemicals, such as curcumin demethoxycurcumin, bisdemethoxycurcumin, zingiberene, curcumenol, curcumol, eugenol, tetrahydrocurcumin, triethylcurcumin, turmerin, turmerones, and turmeronols, are associated with turmeric. Two to five percent of turmeric contains curcumin, the spice's most active ingredient. Turmeric's yellow color comes from a phytochemical called curcumin, which is now known to be the main cause of its medicinal benefits. Because of its hydrophobic properties, curcumin is insoluble in water and easily soluble in ethanol, chloroform, acetone, and dimethylsulfoxide. The oxidation of curcumin produces vanillin. Turmeric also contains proteins, carbohydrates, alkaloids, glycosides, terpenes, steroids, flavonoids, tannins, and saponins.

4.2 Black Pepper

Black pepper reigns as the significant most liked and extensively used spice in the world. It is used in medicine and has many culinary applications for preserving and savouring processed foods. Pepper accounts for 34% of all spices traded abroad. This significant spice originated in South West India, specifically in the Western Ghats regions

of South India (Nair, 2020). Rich in piperine and essential oils, black pepper has a variety of pharmacological qualities, such as antibacterial, antioxidant, antiobesity, hypolipidemic, immunomodulatory, antitumor, anticancer, digestive, antipyretic, and antidiarrheal effects. Its wide range of therapeutic potential is further demonstrated by its analgesic, antihypertensive, antifungal, anti-inflammatory, anti-asthmatic, and insecticidal properties.

Black pepper, known as the "King of Spices," has been used in traditional medicine to cure a variety of conditions, including respiratory infections, indigestion, constipation, arthritis, toothaches, and asthma. Strong anti-inflammatory and antioxidant properties of black pepper aid in lowering oxidative stress and conditions linked to inflammation. Its traditional usage in treating infections is supported by the antibacterial and antifungal qualities of its active ingredient, piperine. By preventing tumour growth, angiogenesis, and proliferation, piperine also demonstrates anticancer potential. It is a multipurpose medicinal spice that also promotes the absorption of medications and nutrients, stimulates pancreatic enzymes and bile acids to improve digestion, and has antihypertensive, anti-diabetic, and immunomodulatory effects. The alkaloid piperine, which contributes pungency and exists in four isomeric forms; piperine, chavicine, isopiperine, and isochavicine is the primary characteristic of black pepper's phytochemistry. Only piperine is stable, while chavicine easily transforms into piperine when heated or stored. Although piperine is hydrophobic, it dissolves readily in organic solvents including ether, ethanol, and chloroform but only weakly in water (Avneet, Pal, & Singh, 2018). Piperanine, piperettine, piperolein A and B, and piperyline are minor alkaloids found in black pepper in addition to piperine. Black pepper’s pungency is caused by piperine, the main alkaloid, which also has antibacterial, anti-inflammatory, antioxidant, and bioavailability boosting qualities. Monoterpenes and sesquiterpenes, which make up the majority of the essential oil fraction, also provide antibacterial and fragrant properties. These phytochemicals work together to give black pepper its culinary and medicinal value (Zhao, Wonta, Xia, Zhong, & Sharma, 2024).

4.3 Cardamom

One of the most expensive spices in the world is cardamom. The aroma, flavour, size, and green colour of Indian cardamom are genuinely distinctive. Cardamom is used in a variety of confections and sweets and has long been utilized for its culinary and medicinal purposes. Because of its pleasant aroma, its ability to flavour a wide variety of foods and beverages and many uses in traditional cures, cardamom is referred to as the "queen of spices." Human clinical research has also looked at how cardamom affects health outcomes for several illnesses and ailments

(Ramadan, 2023). In traditional medicine, cardamom has been used to treat conditions like asthma, gum and tooth infections, cataracts, nausea, diarrhoea, and diseases of the heart, digestive system, and kidneys. Cardamom and its polyphenols have been shown in numerous studies to exhibit biological activity, including anti-inflammatory, anti-tumour, antioxidant, and metabolic regulation properties. They are well-known to be multipurpose substances that can effectively prevent or treat a range of cancerous tumours, heart ailments, chronic inflammatory diseases, digestive issues, and infectious bacterial and fungal infections. Cardamom is used extensively as a diuretic, stomachic, carminative, heart stimulant, and digestive aid. In addition to treating asthma, colds, coughs, and heart weakness, it also helps with nausea, vomiting, indigestion, flatulence, and urinary problems. With added benefits for headaches, inflammation, and general health, cardamom seeds are fragrant and tonic. For maximum results, they are sometimes mixed with other spices or honey. Essential oils, alkaloids, flavonoids, phenols, tannins, and terpenoids make up *Elettaria cardamomum*'s phytochemistry. Monoterpenes that contribute to scent and biological activity, include α-terpinyl acetate, 1,8-cineole, limonene, and sabinene, are abundant in its essential oils. Diterpenes, sterols, and alkaloids with anti-inflammatory, anti-microbial, and antioxidant qualities, such as cardamonin and velleral, are additional components.

4.4 Clove

The clove is commonly referred to as "lavang", because of its improved nutritional value and therapeutic qualities. They are used in medicine, cosmetics, nutrition, and agriculture. It is frequently used to address dental issues. Eugenol, the main bioactive component of cloves, is one of the most important sources of phenolic chemicals. It is used as an antiseptic for oral problems (Ugbogu, Emmanuel, Agi, Ibe, & Eze, 2021). The substantial eugenol content of clove is the primary cause of its many pharmacological effects. In addition to its significant antioxidant, anti-inflammatory, and analgesic properties, it exhibits powerful antibacterial and antifungal activities against microorganisms. Additionally, clove exhibits gastroprotective function by protecting the stomach mucosa, antidiabetic benefits by improving insulin sensitivity, and anticancer potential by causing apoptosis in cancer cells. It is also useful in preventing liver and heart problems because it has hepatoprotective and cardioprotective qualities (Yadav, Gupta, & Bhosale, 2020). Eugenol and other bioactive chemicals in cloves are primarily responsible for its antibacterial, antioxidant, anti-inflammatory, analgesic, antidiabetic, hepatoprotective, gastroprotective, and anticancer properties. While recent research supports its efficacy in treating oxidative stress, diabetes, and cardiovascular diseases, it has long been used to treat toothaches, sore throats, indigestion, and respiratory conditions. Clove’s

phytochemistry is characterized by essential oils and phenolic chemicals. Eugenol (70–85%), eugenyl acetate (10–15%), and β-caryophyllene (5–12%) are among the main bioactive components, as are phenolic acids including gallic, caffeic, ferulic, ellagic, and salicylic acids. Tiny levels of flavonoids like kaempferol and quercetin, along with trace amounts of methyl salicylate, benzaldehyde, and α-humulene, give them its distinctive scent. About 15–20% essential oil found in clove buds is mostly made up of eugenol. The aroma and pharmacological qualities of clove are also influenced by vanillin, tannins, triterpenoids (oleanolic acid), flavonoids (kaempferol, rhamnetin), methyl salicylate, benzaldehyde, α- and β-humulene, and trace sesquiterpenes like α-cubebene, α-copaene, γ-cadinene, and δ-cadinene (Zhao, Wonta, Xia, Zhong, & Sharma, 2024).

4.5 Cinnamon

One of the most significant and widely used spices in the world is cinnamon bark. It is utilized in both traditional and contemporary medicine in addition to cooking. Because of its aroma, it has been added to a wide range of foods, fragrances, and pharmaceutical items, cinnamon is mostly employed in the aroma and essence sectors. The most important elements of cinnamon are cinnamaldehyde and trans-cinnamaldehyde (Cin), which are present in the essential oil, therefore contributing to the smell and to the different biological activity observed with cinnamon. The most promising application of cinnamon is as a supplement to the management of type 2 diabetes mellitus; nevertheless, further research is required before firm recommendations can be made (Suriyagoda, et al., 2021). Strong anti-inflammatory, anti-ulcer, antibacterial, and anti-diabetic qualities are displayed by cinnamon (Cinnamomum verum). Clinical research supports its usefulness in diabetes, allergies, and lipid management. Its phenolics scavenge free radicals, inhibit H. pylori, control microorganisms, regulate blood glucose and lipids, and reduce inflammation. Cinnamon has a variety of therapeutic benefits. As a potent antioxidant, it shields the body from harm brought on by free radicals. Its antibacterial activity makes it efficient against germs and fungi, while its anti-inflammatory qualities aid in reducing pain and swelling. Additionally, cinnamon helps decrease cholesterol and triglycerides, which promotes heart health, and improves blood sugar regulation, which may have antidiabetic effects. It also protects the liver and stomach, and it may even help the brain work better. Essential oils, resinous chemicals, cinnamic acid, cinnamon aldehyde, and cinnamonate are all found in cinnamon. Trans-cinnamaldehyde, caryophyllene oxide, L-borneol, L-bornyl acetate, eugenol, b-caryophyllene, E-nerolidol, and cinnamonyl acetate are examples of essential oils in clove. Terpinolene, α-Terpineol, α-Cubebene, and α-Thujene are a few other components. Cinnamaldehyde gives it its

strong flavour and aroma, by the absorption of oxygen as it ages; darkens in colour and produces resinous chemicals. It was discovered to be extremely safe and helpful in treating allergy problems in clinical reports. Alkaloids, flavonoids, tannins, terpenoids, glycosides, saponins, phenols, and steroids are among the several phytochemicals found in Cinnamomum verum bark; the main bioactive substances are eugenol and cinnamon aldehyde (Khaafi, Tayarani-Najaran, & Javadi, 2023).

4.6 Fenugreek

One of the oldest medical plants is fenugreek. It has a remarkable nutritional and therapeutic profile. Fiber, phospholipids, glycolipids, oleic acid, linolenic acid, choline, vitamins A, B1, B2, C, nicotinic acid, niacin, and numerous other beneficial components are all present in significant amounts in fenugreek seeds. Fenugreek is a crucial ingredient in a number of industrial items, such as food, cosmetics, and medications (Krayem, Baydoun, Khaled, El Khatib, & Nasrallah, 2025). Numerous bioactive chemical components found in fenugreek which gives its medicinal properties. The seeds are rich in steroidal sapogenins such as diosgenin and yamogenin, which serve as precursors for steroid hormone production. It also contains alkaloids that contribute to its hypoglycemic and antioxidant qualities, including as trigonelline, flavonoids, saponins, and coumarins. Fenugreek seeds are also a good source of proteins, soluble fibres, vitamins, minerals, and amino acids, including 4-hydroxyisoleucine, which is involved in insulin secretion. Along with vital nutrients like proteins, amino acids, and carbohydrates, fenugreek seeds are abundant in a variety of phytochemicals, such as alkaloids, flavonoids, saponins, tannins, phenolic compounds, steroids, and terpenoids. The medicinal and nutritional benefits of the plant are enhanced by these bioactive substances (Faisal et al., 2024). The pharmacological properties of fenugreek are varied and include antidiabetic effects by reducing blood glucose and improving insulin sensitivity, hypocholesterolaemia action by lowering triglycerides and total cholesterol, and antioxidant activity that guards against oxidative stress. In addition, it exhibits hepatoprotective, gastroprotective, and anti-inflammatory qualities (Singh, Yadav, Kumar, & Narashiman, 2021). Its rich phytochemical content is responsible for its many therapeutic qualities. It is well known for improving glucose tolerance and increasing insulin secretion, which results in hypoglycaemic and antidiabetic effects. By lowering blood cholesterol and triglycerides, the seeds also exhibit hypocholesterolemic and cardioprotective benefits. Fenugreek has also been used traditionally to heal wounds, respiratory conditions, and digestive diseases. It also has anti-inflammatory, antioxidant, hepatoprotective, and antibacterial properties. Its galactagogue quality emphasizes even more how crucial it is for improving nursing moms' breastfeeding (Tian & Deng, 2020).

4.7 Star Anise

Native to the Southwest, star anise (*Illicium verum* Hook. f.) is a spice and medicinal plant. It is widely used in traditional medical, pharmacological, and culinary systems and is renowned for its aromatic flavour and distinctive star-shaped fruits. A popular flavouring agent and a key raw material for the manufacture of antiviral medications like oseltamivir (Tamiflu), star anise is rich in essential oils, including anethole and shikimic acid. Star anise's pharmacological capabilities, which include antibacterial, antioxidant, and anti-inflammatory qualities, as well as its varied phytochemical profile, have drawn a lot of interest as a functional food ingredient and possible source of medicinal chemicals (Huang et al., 2024). Numerous pharmacological actions, such as antibacterial, antioxidant, anti-inflammatory, antiviral, antifungal, and anticancer effects, are displayed by star anise. Its main bioactive ingredient, trans-anethole, has antibacterial and anti-inflammatory properties, and shikimic acid is essential for the manufacture of antiviral medications. Its therapeutic potential in both conventional and modern medicine is highlighted by the additional phytoconstituents that have hepatoprotective, analgesic, and immunomodulatory properties. In traditional Chinese medicine, star anise has long been used to treat respiratory infections, rheumatism, colic, and digestive disorders. These characteristics make it a promising source for drug research and therapeutic formulations in contemporary pharmaceutical science, in addition to being a traditional cure (Singh, Yadav, Kumar, & Narashiman, 2021). Numerous phytochemicals, primarily flavonoids, phenylpropanoids, lignans, and essential oils, are abundant in star anise. The scent and pharmacological activity of the essential oil are mostly attributed to trans-anethole (70–90%), coupled with estragole, limonene, linalool, and α-pinene. Quercetin, kaempferol, coumarins, phenolic acids, and shikimic acid a precursor for antiviral medications like oseltamivir are additional significant components. Together, these substances offer antibacterial, antioxidant, and medicinal qualities (Zhang et al., 2024). In addition to a variety of phytochemicals like flavonoids, tannins, alkaloids, saponins, steroids, glycosides, and phenolic compounds, star anise also includes essential oils that are primarily composed of terpenoids, anethole, and shikimic acid. It is useful in food and pharmaceutical applications because of these bioactive components, which also contribute to its medicinal, nutritional, and fragrant qualities.

4.8 Cumin

In ancient Greece, cumin was referred to be the "best of condiments" and was widely recognized for its numerous applications and extensive

medicinal value. Cumin is a necessary spice, and the plant's seeds are utilized in practically every culinary preparation to enhance the flavour of spicy foods. Cumin alcohol and cumin aldehyde are its primary component fragrance chemicals. The type of species determines the extent of each of these chemical elements. Additionally, cumin seeds contain a number of compounds with a variety of industrial uses, including food, traditional medicine, and pharmaceuticals. *Cuminum cyminum* has a variety of pharmacological properties, such as analgesic, antibacterial, anti-inflammatory, and antioxidant properties. Additionally, it exhibits immunomodulatory, hepatoprotective, gastroprotective, hypolipidemic, and antidiabetic effects. Cumin is a great medicinal spice that has also demonstrated anticancer potential, CNS-related actions like memory enhancement, and advantages for respiratory and cardiovascular health (Paul et al., 2025). Cumin's essential oils and phenolic chemicals are primarily responsible for its many therapeutic benefits. Its historical usage in treating skin conditions, respiratory issues, and digestive difficulties emphasizes its therapeutic value in contemporary pharmacology. Numerous phytoconstituents, including terpenes, flavonoids, alkaloids, phenolic compounds, and essential oils, are abundant in *Cuminum*. Cuminaldehyde, γ-terpinene, p-cymene, and β-pinene are the main volatile components that give it its distinct scent and biological activity. Strong antioxidant capacity is provided by non-volatile substances such tannins, phenolic acids (caffeic, chlorogenic, and ferulic acids), and flavonoids (apigenin, luteolin, and quercetin glycosides). Its pharmacological significance is further increased by the presence of fatty acids, alkaloids, and saponins.

4.9 Black Mustard

There are around 3000 species and 350 genera in the Brassicaceae family worldwide. The consumption of Brassicaceae is advisable due to its phytochemical richness and nutritional composition. They are rich in fibre, vitamins, and minerals and low in fat (Grygier, 2023). Black mustard's abundance of bioactive substances, including flavonoids, isothiocyanates, glucosinolates, and essential oils, allows it to display a broad spectrum of pharmacological actions. It effectively relieves joint pain, arthritis, and muscle problems because of its potent analgesic and anti-inflammatory properties. In the fight against pathogenic diseases, the seeds and their extracts exhibit strong antibacterial and antifungal qualities. Furthermore, black mustard has been shown to scavenge free radicals and exhibit antioxidant activity, reducing disorders linked to oxidative stress. Its promise as a therapeutic spice in both conventional and modern medicine is highlighted by the hypoglycaemic, cardioprotective, and anticancer effects of its bioactive ingredients. Based on its stimulating, hot, and pungent qualities, mustard has a wide range

of medical uses. It has long been used to promote circulation, increase appetite, and aid digestion. The oil and seeds of mustard are used to treat respiratory ailments such nasal congestion, asthma, colds, and coughs. Mustard poultices are applied externally to treat skin conditions, rheumatism, muscle stiffness, and discomfort. It is useful in both preventive and therapeutic settings because of its antibacterial, anti-inflammatory, and detoxifying properties. The glucosinolates found in mustard seeds, especially sinigrin and gluconapin, are hydrolysed by the enzyme myrosinase to produce biologically active compounds like allyl isothiocyanate, gives mustard its strong antioxidant potential. Additionally, mustard seeds contain omega-3 fatty acids (α-linolenic acid), tocopherols, and phenolic compounds, while the fixed oils are primarily made up of erucic acid, oleic acid, linoleic acid, and palmitic acid, while flavonoids, tannins, and alkaloids further contribute to their phytochemical diversity (Tian & Deng, 2020). The biological actions of mustard seeds are attributed to a variety of phytochemicals, such as glucosinolates, flavonoids, phenolic acids, tannins, and alkaloids. Glucosinolates are hydrolyzed by enzymes to produce isothiocyanates, thiocyanates, and nitriles, which have antibacterial, anticancer, and antioxidant properties. Additionally, mustard includes sterols, tocopherols, and carotenoids, which enhance its nutritional and medicinal benefits by lowering oxidative stress and fostering well-being.

4.10 Coriander

An annual herbaceous plant is coriander. In the Mediterranean region, entire dried seeds are pulverized and used as a spice or condiment. In Indian cuisine, they are a key component of curry powder. Additionally, seeds are used to flavour a variety of dishes, including meat, fish, and baked goods. It is interesting to note that traditional medicine has used all parts of this plant as conventional treatments for a variety of illnesses. In fact, coriander leaves increase appetite and facilitate simple digestion, while coriander seeds have been used to cure a variety of digestive issues, including indigestion, nausea, and dysentery (Iqbal, Butt, & Suleria, 2018). Numerous pharmacological characteristics of coriander include its diuretic, hepatoprotective, neuroprotective, hypoglycaemic, hypolipidemic, antioxidant, antibacterial, anti-inflammatory, and analgesic effects. It has antibacterial and anti-inflammatory properties, lowers blood glucose and lipid levels, protects the liver and nervous system, and reduces oxidative stress thanks to its essential oils, flavonoids, and phenolic components. Coriander is a remarkable medicinal plant because of its varied pharmacological activities, which support its traditional usage in treating neurological, metabolic, cardiovascular, and gastrointestinal diseases. Coriander has a wide range of therapeutic benefits, including as anxiolytic, hypoglycaemic, hypolipidemic, antibacterial, and anti-inflammatory actions. Linalool,

flavonoids, and phenolic acids are a few of its bioactive components that help protect against oxidative stress, control blood sugar and cholesterol, enhance digestion, and promote neurological health. As a natural cleansing and analgesic, coriander has long been used to treat respiratory and gastrointestinal issues, underscoring its therapeutic potential in contemporary medicine. Abundant bioactive substances, primarily phenolic acids, flavonoids, fatty acids, sterols, and essential oils, are found in coriander. Linalool, which makes up as much as 70% of the oil, is the primary component of the fraction. Other monoterpenes that make up this fraction include geraniol, camphor, borneol, citronellol, and limonene. Petroselinic acid, an uncommon fatty acid, is abundant in seeds (60–70%), but polyunsaturated fatty acids are more prevalent in leaves. Caffeic acid, chlorogenic acid, gallic acid, ferulic acid, and vanillic acid are examples of phenolic chemicals that support antioxidant action. Quercetin, rutin, apigenin, and derivatives of luteolin are important flavonoids. The plant also includes minor levels of alkaloids and tannins, sterols such as β-sitosterol, stigmasterol, and campesterol, and coumarins (umbelliferone, scopoletin). Numerous phytochemicals, including vital oils, flavonoids, phenolic acids, alkaloids, tannins, saponins, terpenoids, and sterols, are abundant in coriander. The primary volatile chemical found in the seeds is linalool, which is followed by borneol, camphor, geraniol, and limonene. The high concentration of polyphenols, carotenoids, and vitamins in leaves contributes to their remarkable antioxidant capacity. These phytochemicals support coriander's pharmacological properties, including its antibacterial, antioxidant, and digestive health-promoting properties, in addition to giving it its distinctive flavour and scent (Acharya et al., 2021).

5. SYNERGISTIC EFFECTS AND CULINARY COMBINATIONS

One characteristic of South Indian cooking is the use of complex spice combinations, which are made for both flavour and potential therapeutic benefits. Recent studies have confirmed traditional culinary knowledge by showing that interactions among the phytochemicals in spices can significantly alter their biological activity and bioavailability. The various spices used in the different cooking methods like tempering, boiling, steaming or frying has various beneficial effects to the foods. It increases the nutritional benefits to ten folds releasing micronutrients while increasing their bioavailability in the systemic circulation and some spices reduces reactive free radical species thereby downregulating the inflammation responses. The same spices in different therapeutic concentrations can provide altered benefits than consumed individually. Traditional cooking methods such as tempering (tadka) increase the release of fat-soluble compounds like carotenoids and essential oils, which improves their dispersion and absorption. Turmeric's curcumin dissolves easier when cooked in oil, but cumin and mustard seeds in oils

help distribute bioactive molecules evenly throughout meals. These techniques improve the flavour and usefulness of spices (Kaur et al., 2025). Spice mixes can have greater antibacterial activity than individual spices. In hotter regions, combining extracts of garlic, ginger, coriander, and cumin inhibits a broader range of germs, reducing food spoiling. This may explain why strongly spiced curries are still used as a cultural adaptation for food preservation (Maharjan, Thapa, & A. A., 2019). Certain bioactive compounds, such as capsaicin in chilies or eugenol in cloves, can irritate the gastrointestinal system in high amounts. Often, culinary blending counteracts these effects; for example, coriander and fenugreek mitigate the harshness of strong spices. This demonstrates how potency and safety are objectively balanced in traditional practice (Pradeep & Sharma, 2019). Increased bioavailability is one of the primary features of South Indian spice mixtures' health benefits. Many phytochemicals, such as curcumin in turmeric, have potent biological effects, but when consumed alone, they are poorly absorbed. Culinary synergy is sometimes used in traditional approaches to overcome this limitation. The most studied example is the combination of curcumin with piperine, an alkaloid present in black pepper that increases curcumin's bioavailability by over 2000% by blocking metabolic clearance routes. Cooking spices in oil enhances the absorption of lipophilic compounds such as volatile terpenes, carotenoids, and curcuminoids because the lipid medium promotes intestine absorption and solubilization. As demonstrated by pairings like ginger and garlic, which boost antimicrobial activity and possibly stabilize each other's bioactive compounds, spice-to-spice interactions also play a role. Additionally, adding turmeric to foods that are high in antioxidants, such as cardamom or cloves, helps keep curcuminoids potent by preventing them from degrading during cooking. These traditions collectively demonstrate how culinary traditions naturally optimize the transport and efficacy of phytochemicals, millennia before modern pharmacokinetics provided empirical evidence (Thatipamula, 2024). The concept of spice synergy challenges the reductionist method of looking at individual bioactive components independently. Instead, the "food matrix" method emphasizes how different elements work together to provide health advantages. The centuries-old spice combinations from South India embody this concept. The development of natural preservatives and functional foods that mimic these past synergies could come from systematic future research on the interactions between spices (Kaur et al., 2025).

6. CONCLUSION

South Indian spices are an amazing blend of chemistry, culture, and food. The future of South Indian spices from a translational perspective, lies at the intersection of ethnopharmacology, functional food innovation,

and bioprospecting. Combining traditional knowledge systems with contemporary biomedical science also promotes innovation in integrated medicine. Together, botanists, chemists, pharmacologists, and food technologists may transform centuries-old culinary wisdom into medicines that have been shown to work. The evidence synthesized in this chapter underscores that these spices are more than cultural artifacts they are reservoirs of bioactive potential with far-reaching implications for food science, pharmacology, and sustainable health systems. By bridging ethnobotanical wisdom with modern analytical rigor, South Indian spices can continue to enrich global culinary traditions while contributing to the development of safe, effective, and sustainable nutraceuticals for future generations. The knowledge and understanding of the spices and the inclusion of it in right combinations in our regular dietary routine can avert infection, prevent diseases, promote health, and subsequently delay aging process or even at times endure aging harmoniously.

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Chapter 16
How to use herbal medicine safely

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ABSTRACT

The perceived health benefits and cultural acceptance of herbal medicines have led to a significant increase in their use worldwide. However, the belief that natural products are intrinsically safe has led to unsuitable formulations, incorrect dosages, and preventable side effects. For the safe and efficient use of herbal medicines, this chapter examines important factors pertaining to formulation, dosage, and delivery methods. The chapter also emphasizes how crucial quality assurance, standardization, and new delivery methods are to increasing effectiveness while lowering toxicity. In conclusion, evidence-based formulation techniques, appropriate dosage recommendations, suitable delivery methods, and stronger regulatory oversight are necessary for the safe integration of herbal medicines into contemporary healthcare.

Keywords: Herbal medicine, Formulation, Dosage, Safety

1. INTRODUCTION

For centuries, herbal medicine which uses plant-based materials like roots, leaves, seeds, and bark for therapeutic purposes has been a crucial part of healthcare systems in many different cultures. Herbal remedies remain an important part of primary healthcare in many regions, particularly in Asia and Africa. The use of herbal medicines as complementary or alternative therapies has increased globally in recent years due to growing interest in natural and holistic treatment approaches (Tilburt & Kapchuk 2008). Even though herbal medicines are widely accepted, questions about their effectiveness, safety, and quality still exist. One common misconception is that natural products are always safe. Adverse effects, toxicity, and clinically significant herb-drug interactions can be caused by improper formulation, dosage, and delivery methods.

The possible dangers of excessive or inappropriate use are demonstrated by documented cases involving herbs like ephedra and comfrey. These difficulties highlight the necessity of standardized procedures and scientific assessment in the application of herbal medicine. Formulation plays a fundamental role in ensuring stability, consistency and bioavailability of active ingredients, thereby guaranteeing the efficacy and safety of herbal treatments. In a similar vein, choosing the right delivery method and determining the right dosage are essential for reducing risks and optimizing therapeutic benefits.

Because formulation affects stability, consistency, and bioavailability of active ingredients, it is fundamental to the safety and efficacy of herbal therapies. In a similar vein, determining the right dosage and choosing the best delivery techniques are essential for reducing risks and optimizing therapeutic advantages (Ekor 2014). This chapter reviews the fundamental principles of herbal medicine formulation, dosage calculation, and delivery systems, emphasizing their roles in supporting the safe and effective use of herbal medicines in modern healthcare systems. The key stages involved in safe herbal medicine development from traditional knowledge and scientific validation to regulatory compliance and pharmacovigilance are summarized in Figure 1.

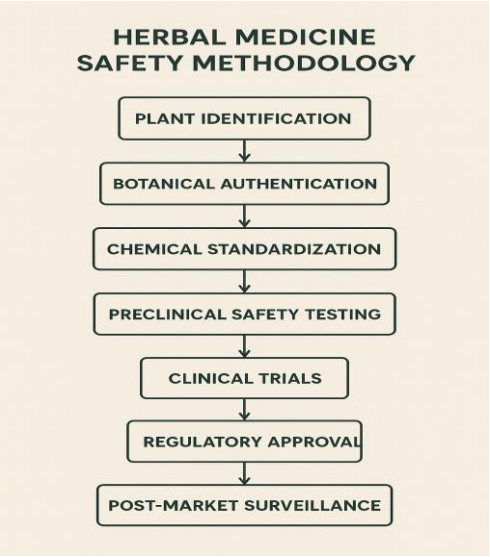

Figure 1: Systematic development of safe herbal medicines.

2. FORMULATION DEVELOPMENT

Literature has extensively addressed formulation development, which is a crucial component of the safety and effectiveness of herbal medicines. Herbal formulations, in contrast to synthetic drugs, usually contain intricate combinations of bioactive compounds, which makes quality

control and standardization especially difficult. Review studies emphasize that safety, consistency, and reproducibility should take precedence over experimental product development during formulation development. Safe herbal formulations are built on the selection and verification of medicinal plants. The literature emphasizes the significance of employing botanically validated species that have both scientific proof of their therapeutic potential and a history of traditional use.

Macroscopic and microscopic analysis, chemical profiling, and molecular methods like DNA barcoding to avoid adulteration and misidentification are examples of frequently reported authentication techniques. Phytochemical composition is also known to be greatly influenced by variables like plant part used, harvesting season, geographic origin, and storage conditions. Herbal formulations' quality is largely determined by their extraction and processing techniques. Research shows that the yield and stability of bioactive components are directly influenced by pre-processing procedures like drying and grinding, as well as the choice of suitable solvent. Depending on the polarity of the target compounds, extracts that are aqueous, alcoholic, or hydroalcoholic are frequently used. To guarantee batch-to-batch consistency and safety, standardization through phytochemical analysis using chromatographic and spectrometric techniques is commonly advised (Wang et al. 2023).

This is discussed in a variety of dosage forms, such as powders, decoctions, capsules, tablets, ointments, and tinctures, as appropriate for various therapeutic applications. Advanced formulation techniques like phytosomes, nanoformulations, and transdermal systems, which seek to improve solubility, bioavailability, and targeted delivery are also described in recent reviews. These technologies have potential benefits, but more research is needed to confirm their safety, stability, and regulatory acceptability. To ensure product quality, safety, and therapeutic reliability, formulation development in herbal medicine should be approached as a systematic, evidence-based process that integrates traditional knowledge with contemporary pharmaceutical principles.

3. DOSAGE DETERMINATION

Following formulation, dosage determination was carried out. Unlike single-entity synthetic drugs, herbal medicines often contain multiple compounds that act synergistically. Therefore, dosage decisions must be based on a combination of traditional knowledge, preclinical data, and patient-specific considerations such as age, weight, and comorbidities. Toxicity studies were performed *in vitro* and *in vivo* to establish safe dose ranges and to identify any potential organ-related side effects. Special attention was given to herbs known to cause toxicity at high doses,

ensuring that the “right dose at the right time” principle was applied. Recent work emphasizes the need for analytical standardization (marker compounds, batch profiling) and advanced chemometric methods (metabolomics, fingerprinting) to reduce batch-to-batch variability and enable reproducible dosing recommendations. Pharmacokinetic and pharmacodynamic interactions (herb–drug and herb–herb) have been increasingly documented, highlighting the importance of interaction studies and monitoring when herbal products are used with conventional medicines. Despite methodological advances such as high-throughput *in vitro* ADME assays, metabolomics-guided standardization, and improved preclinical toxicology pipelines, important gaps remain. Dose–response relationships for whole extracts are incompletely defined, clinically validated therapeutic windows for many herbs are lacking, inter- and intra-individual variability complicates generalizable dosing, and long-term safety data from large randomized controlled trials are scarce. Addressing these gaps will require coordinated efforts in standardized manufacturing, rigorous pharmacokinetics and pharmacodynamics and interaction studies, well-designed clinical trials with clear dosing rationale, and real-world pharmacovigilance to capture rare or delayed adverse events.

4. DELIVERY

The selection of delivery methods is crucial to increase their effectiveness and specificity. Conventional routes, such as oral ingestion and topical application, have been extensively compared with modernized systems like nano-encapsulation, controlled-release formulations, and transdermal patches. *In vitro* models, including dissolution studies and permeation assays, were used to test bioavailability and release kinetics. In addition, stability testing under different environmental conditions was conducted to determine appropriate shelf-life and storage requirements

Finally, the methodology should incorporate a safety and quality assessment framework. This included screening for heavy metals, pesticides, microbial contamination, and adulterants, which are common risks in poorly regulated herbal products. Potential herb–drug interactions were also investigated through *in vitro* enzyme inhibition assays and literature reviews, as these interactions can compromise patient safety when herbal products are combined with conventional medicines.

5.CRITICAL ANALYSIS AND IMPACT

The analysis of existing literature and case studies highlights that formulation, dosage, and delivery play a decisive role in determining both the therapeutic benefits and potential risks of herbal medicine. The

findings are organized under three main domains: formulation quality, dosage accuracy, and delivery efficiency.

5.1. Formulation Quality

Standardization of herbal formulations is important to ensure consistent therapeutic effects. Standardized extracts contain fixed amounts of active compounds, which helps in producing reliable and predictable results. Herbs such as *Ginkgo biloba*, *Echinacea*, and *Curcuma longa* have shown better clinical outcomes when standardized preparations are used instead of crude forms. In contrast, unregulated herbal products may have varying concentrations of active ingredients, which can lead to reduced effectiveness or safety concerns. Therefore, modern analytical methods like High-Performance Liquid Chromatography (HPLC) and DNA barcoding are used to confirm plant identity, detect adulteration, and maintain product quality.

5.2. Dosage Accuracy

Proper dosage is essential for achieving the desired therapeutic effect while avoiding adverse reactions (Busia 2024). Clinical studies on *St. John's Wort* have identified specific dose ranges that are effective for treating mild depression, whereas excessive use has been associated with harmful drug–herb interactions. Similarly, liver toxicity reported with herbs such as kava and comfrey has been linked to prolonged or high-dose consumption. These examples demonstrate that dosage should be based on scientific evidence rather than traditional use alone. Following standardized dosage guidelines helps ensure safe and effective use of herbal medicines.

5.3 Delivery Efficiency

The route of administration also plays an important role in the effectiveness of herbal remedies in the body. Conventional methods of preparation, for instance, decoctions, can easily extract water-soluble compounds in the body, although heat labile compounds can easily decompose. Capsulation techniques can prevent destruction, although the rate of absorption can potentially be slower. Modern developments, for instance, nanotechnology formulation, controlled release capsules, and transdermal patches, can increase stability, absorbency, and targeted delivery in the body, although the cost can potentially limit their use.

6. CHALLENGES AND LIMITATION

The use and safety of herbal medicines are linked to incorporating traditional practices and scientific research validation. Formulation standardization ensures standardized production, and appropriate

regulation for dosages inhibits toxicity and adverse reactions. Delivery advancements have increased bioavailability and efficacy. Despite all potential advantages, factors like government and regulatory loopholes, herbal medicinal variations, and lack of patient and medical personnel awareness influence safe use. Herb-drug interactions are particularly concerning because herbal supplements are often taken concurrently with modern medicines in medical institutions (Posadzki et a l. 2012).

Strategies to address the use of herbal medicine could involve education, regulation, and collaboration between herbalists, pharmacologists, and healthcare professionals to develop guidelines on the use of herbal medicine. The guidelines could cover herbal formulation, dosage, and interactions, as well as the cultural value placed on herbal medicine by different societies, to make herbal medicine a vital addition to modern healthcare systems by improving patient safety and outcomes associated with herbal medicines use.

7.CONCLUSION

Medicinal herbs are widely employed as major medicines as well as complementary medicines in conjunction with modern medicines in the health care system. In principle, the use of herbs as medicines is safe and effective based on their formulation, dosages, and method of administration. Variability and inconsistency should be avoided through appropriate quality control and raw material standardization. Misuse of herbs as medicines may lead to toxicity, ineffectiveness, and interactions of adverse effects when taken in conjunction with modern medicines.

Contamination, adulteration, and quality variability in improperly regulated herbal preparations are major concerns, thus underlining the imperatives of proper monitoring and evaluation. Based on traditional knowledge through scientific methods such as molecular authentication, phytochemical analysis, and toxicology studies, the safety, efficacy, and standardization of herbal medications could potentially be ensured. It is possible through these techniques to properly identify the herb as well as estimate the qualities.

Herbal medicine can be developed into reproducible, reliable, and effective therapies by merging traditional knowledge with state-of-the-art scientific technologies. With phytochemical profiling, molecular authentication, innovative delivery systems, and nano-formulations, among other modern tools, herbal remedies have gained greater credibility and global acceptance. A multidisciplinary approach has made herbal medicine one of the safest, most trusted, and accessible methods, especially in view of the increasing global demand for natural, affordable, and holistic healthcare.

8.FUTURE DIRECTIONS

With ongoing improvements in quality control and the use of evidence-based research, herbal medicines can reach their full therapeutic potential while reducing possible risks. Clear standards for identifying, extracting, and formulating medicinal plants are necessary to ensure consistent and reliable products. Well-designed clinical trials should determine safe and effective dosage ranges, supported by traditional knowledge and toxicological studies, to avoid problems such as underdosing or accidental overdosing. In addition, modern drug-delivery methods can greatly improve solubility, absorption, and targeted action of herbal remedies, including approaches such as nano-formulations and transdermal patches. Strong regulatory systems are also essential to protect the public from contamination, adulteration, and misleading health claims. Finally, healthcare professionals must be properly trained to understand herb–drug interactions and to prescribe herbal treatments responsibly. Together, these steps can help integrate herbal medicine into mainstream healthcare as a safe, effective, and sustainable option.

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Population aging is reshaping global healthcare, with increased longevity accompanied by a rising burden of chronic, age-related diseases. Addressing these challenges requires integrative, evidence-based strategies that promote healthy aging, preserve physiological function, and reduce disease risk across the lifespan.

This book provides a concise and authoritative examination of Herbal Medicine in the context of aging and chronic disease, bridging traditional medical knowledge with modern pharmacological, biochemical, and clinical research. It explores the therapeutic potential of medicinal plants in conditions such as neurodegeneration, cardiovascular and metabolic disorders, immune dysfunction, and chronic inflammation.

Integrating aging biology, mechanistic insights, safety considerations, and emerging clinical perspectives, this volume supports the responsible and scientifically grounded application of herbal medicine within contemporary healthcare.

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