# Healing with Herbs

## Herbal Therapies for Disease Prevention and Treatment

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Mantra Publication

DeepScience

# Healing with Herbs: Herbal Therapies for Disease Prevention and Treatment

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Mantra Publication

DeepScience

*Published, marketed, and distributed by:*

Deep Science Publishing, 2025
USA | UK | India | Turkey
Reg. No. MH-33-0523625
www.deepscienceresearch.com
editor@deepscienceresearch.com
WhatsApp: +91 7977171947

ISBN: 978-93-7185-504-4

E-ISBN: 978-93-7185-486-3

https://doi.org/10.70593/978-93-7185-486-3



**Citation:** Vaidya, G., Yadav, L., Nyola, N. K., & Kant, R. (Eds.). (2025). *Healing with Herbs: Herbal Therapies for Disease Prevention and Treatment*. Deep Science Publishing. https://doi.org/10.70593/978-93-7185-486-3

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# Preface

The wisdom of herbal medicine has been interwoven with human civilization for centuries, offering remedies, prevention, and holistic health support. In recent years, renewed interest on herbal therapeutics has taken the scene out of traditional systems towards evidence based and integrative healthcare. Integrating both tradition and science, Healing with Herbs: Ancient Medicinal Wisdom for Modern Times provides a holistic perspective on the usage of plants to promote health and prevent disease.

This volume brings together distinguished scholars, researchers, and practitioners from diverse domains of pharmacognosy, phytochemistry, pharmacology, biotechnology, and clinical sciences. Each chapter highlights the molecular, pharmacological, and therapeutic dimensions of medicinal plants, offering mechanistic insights into how phytoconstituents influence human health. From cancer chemoprevention and hepatoprotection to respiratory care, neuroprotection, gastrointestinal health, and innovative drug delivery systems, the chapters collectively represent the multifaceted applications of herbs in managing chronic diseases.

The book emphasizes not only the therapeutic potential but also the translational challenges—such as bioavailability, standardization, clinical validation, and safety considerations—that accompany the development of herbal formulations. Furthermore, special attention has been given to advanced encapsulation technologies and nanocarrier systems, reflecting the dynamic interface between natural medicine and cutting-edge pharmaceutical sciences.

It is our hope that this book serves as a valuable resource for academicians, researchers, healthcare professionals, and students interested in herbal sciences and integrative medicine. By fostering a deeper understanding of herbal pharmacology and its clinical applications, we aspire to inspire future innovations that contribute to sustainable and safe healthcare solutions.

**Editors**
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# Acknowledgement

The realization of this book, *Healing with Herbs: Herbal Therapies for Disease Prevention and Treatment*, has been a journey made possible through the contributions, guidance, and support of numerous individuals and institutions. We are delighted to take this opportunity to extend our heartfelt gratitude to all those who have directly and indirectly contributed to the successful completion of this work.

First and foremost, we express our sincere appreciation to all the contributing authors. Their academic contributions, meticulous research work and enthusiasm for furthering herbal science have provided depth, novelty and scientific rigor to the present volume. Every chapter is the result of many hours of reading and writing, and it would not exist without them.

We would also like to thank the reviewers and subject experts for critically reviewing the chapters and providing one of the most useful pieces of feedback. Their constructive criticisms and suggestions have greatly contributed to improvement of the quality, accuracy, clarity, scientific appearance and value of this work.

We express our sincere thanks to DeepScience Publishing and Mantra Publication for their constant inspiration, edification and dedication in providing the scientific community good work through quality publications. Their commitment tothe reconciliation of traditional knowledges and modern sciences is consistent with the present book's theme, and we greatly appreciate their help at all levels of publication.

We also wish to thank numerous academic institutions, research laboratories and professional organizations which gave resources, infrastructure and attended the DNA of the contributed authors. These organizations have been crucial in facilitating the research on which this book is based.

A very big thanks to our friends, mentors and fellow learners that have inspired us with knowledge and shared expertise liberally. We also thank Mr Saliou CAMARA (IRD) for his technical support and the staff of the services techniques et administratifs who helped us for correspondence, formating and coordination during writing.

On a personal note, we owe an immense debt of gratitude to our families and loved ones. Their patience, encouragement, and unwavering support provided the strength and motivation needed to accomplish this work. Their sacrifices—whether in time, understanding, or moral support—have been the silent force behind this book.

Lastly, we dedicate this book to the larger community of researchers, practitioners, and students of herbal medicine and pharmacology. It is our sincere hope that this collective effort will serve as a source of inspiration, knowledge, and advancement for future innovations in the field of herbal therapeutics.

Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-486-3

# Chapter 1: Phytochemical Synergy of Curcuma longa and Azadirachta indica in Multistage Oncoprevention: Targeting Apoptosis, Angiogenesis, and Immune Surveillance in Cancer Therapy

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## Abstract

Cancer remains one of the leading global health challenges, with high morbidity and mortality rates despite advances in conventional therapies. The limitations of current treatments, including toxicity, resistance, and incomplete efficacy, have driven interest in natural compounds as complementary and preventive strategies. *Curcuma longa* (turmeric) and *Azadirachta indica* (neem) are two medicinal plants with well-documented anticancer properties. Their bioactive constituents—including curcuminoids, turmerones, and limonoids such as nimbolide—exert pleiotropic effects across multiple stages of carcinogenesis. It has been shown to play a role in promoting apoptosis and inhibiting angiogenesis, as well as enhancing immune surveillance. Crucially, the phytochemical collaboration of turmeric with neem provides a site-independent strategy to combat tumor heterogeneity and acquired resistance. Recent approaches in formulation science (nanocarriers, co-delivery systems and bioenhancers including piperine) had contributed towards improved the bioavailability and therapeutic efficacy of these phytochemicals. Preclinical and preliminary clinical data indicate that they are safe and effective, but there are translational barriers in the standardization, regulatory approval processes and large-scale clinical testing. This chapter provides a comprehensive overview of the molecular mechanisms, preclinical and clinical evidence, formulations strategies, and future perspectives for the exploitation of the synergistic anticancer potential of Curcuma longa and Azadirachta indica as environmentally sustainable multistage oncopreventive agents.

## Keywords

Curcuma longa; Azadirachta indica; curcumin; nimbolide; phytochemical synergy; apoptosis; angiogenesis; immune surveillance; nanocarriers; oncoprevention

## 1. Introduction

Cancer continues to represent one of the major causes of disease burden and mortality across the globe, with an estimated close to 20 million new diagnoses and over 10 million death cases in just 2020 (Sung et

al., 2021). Although surgical therapy, chemo-, radio- and immune-therapies have been improved, the current standard treatments for most cancers still encounter numerous obstacles such as drug resistance, lack of specificity to tumors and severe side effects which impairs patient' life quality (Bray et al., 2021; Vasan et al., 2019). These limitations underscore the critical requirement for alternative or adjunctive strategies to not only prevent cancer formation but also enhance its therapeutic efficacy.

The emergence of multistage oncoprevention has been recognized increasingly during the past decades. Carcinogenesis is a step-wise mode of cancer development, typically consisting of a series of stages: initiation (genetic changes and DNA damage), promotion (increased proliferation and survival), progression (appearing more malignant) toward metastasis (cancer cells spreading to another organ) Hanahan 2022). Interrupting at any point in this continuum provides the opportunity to inhibit the development of cancer, retard tumour growth and decrease the risk of relapse.

The medicinal plants compounds have been considered as promising candidates in this issue. Phytochemicals, such as polyphenols (eg, flavonoids), terpenoids, and limonoids possess antioxidant, anti-inflammatory, pro-apoptotic and/or anti-angiogenic activities that could phenotypically affect the expression of signaling pathways involved in carcinogenesis (Kotecha et al., 2016; Aggarwal & Sung, 2009). Significantly, mixtures of phytochemicals frequently demonstrate synergy with associated higher bioactivity and lower risk for resistance formation than monotherapy (Efferth & Koch 2011).

For medicinal plants turmeric (Curcuma longa) and neem (Azadirachta indica), have received significant attention owing to their diverse phytochemical constituents, as well as the well-established anticancer efficacy. Curcumin, the active component of turmeric, has been reported to induce apoptosis, suppress angiogenesis and inhibit tumor growth in different tumor models (Prasad et al., 2014). Similarly, nimbolide and azadirachtin compounds isolated from neem have cytotoxic, immunomodulatory, and chemopreventive effects (Gupta et al., 2017). The value of pairing these two botanicals is attributed to their cooperative rather than simply parallel actions, with curcumin acting largely on inflammatory and proliferative signaling while neem phytochemicals augment immune surveillance and mitochondrial-pathway-mediated apoptosis. Collectively, they have potential implications as a synergistic oncopreventive intervention at multiple stages of progression.

## 2. Phytochemical Constituents and Bioactive Compounds

### 2.1 *Curcuma longa*

Curcuma longa (turmeric) rhizome is characterized by a content of bioactive compounds, mainly curcuminoids. This fraction predominantly comprises curcumin, demethoxycurcumin, and bisdemethoxycurcumin that are responsible for emitted yellow colour and therapeutic applications from turmeric (Priyadarsini 2014). Its effects in controlling the cell cycle, apoptosis induction and proliferation inhibition have been broadly reported for a number of cancer types (Kunnumakkara et al., 2017).

Other than curcuminoids, C. longa also possesses volatile oils such as ar-turmerone, α-turmerone, and β-turmerone and has exhibited marked anti-inflammatory, antioxidant, and anti-angiogenic activities (Liju

et al., 2011). Such components potentiate the activity of curcumin and may function synergistically to affect cellular signaling pathways that contribute to cancer growth.

Phytochemicals in turmeric are also an excellent source of antioxidants and anti-inflammatory agents necessary for neutralizing free radicals, minimizing oxidative stress and modulating inflammatory mediators including NF-κB, COX-2, TNF-[alpha] (Gupta et al., 2013). The mode of action unveils the pleotropic potential of C. longa in preventing and treating cancer.

### 2.2 *Azadirachta indica*

Azadirachta indica (neem) is a medicinally potent plant, which has been used in folk medicine. Azadirachtin, nimbolide and gedunin are the major limonoids present in its bioactive profile. Of these, nimbolide has been reported as potential cancer preventive and therapeutic agents is based on its strong anticancer activities in including apoptosis induction, anti-angiogenesis, and antimetastasis via MAPK, PI3K/Akt and NF-κB activation modulation (Saleem et al., 2018).

The presence of flavonoids and polyphenols in neem further supplements its antioxidant activity and scavenging action on free radicals, thus intensifying its chemopreventive potential (Subapriya & Nagini, 2005). These phytochemicals regulate detoxification enzymes, prevent DNA damage and recover cellular redox homeostasis.

Crucially, T-cell stimulatory properties that neem compounds exert upon triggering the proliferation of T cells and triggering macrophages and regulating cytokines release for immune surveillance against tumor have also been documented (Kaur et al., 2004). This dual cancer (onco)protective effect by neem, via direct impact on cancer and immunoadjuvant action, suggests promise as a natural agent in oncoprevention.

### 2.3 Synergistic Phytochemistry

In combination, C. longa and A. indica exhibit intersecting and diverging modes of action. AllThe two aim at oxidative stress, inflammation, angiogenesis and apoptosis but by otherways giving a good cumulative effect. For instance, curcumin both inhibits NF-κB and STAT3 signaling while nimbolide activates mitochondrial apoptosis and downregulates pro-survival kinases (Gupta et al., 2017; Kunnumakkara et al., 2017).

A considerable challenge in the use of phytochemicals for therapeutic purposes is their low bioavailability. Curcumin is poorly absorbed and quickly metabolized, neem limonoids are commonly insoluble (Prasad et al., 2014). Novel delivery systems including nanoparticles, liposomes, solid lipid carriers and adjuvants like piperine are under investigation to overcome these limitations (Lal et al., 2021). Such system can contribute to the stability, absorption and therapeutic effectiveness of a mixture of phytochemicals.

**Table 1. Major Phytochemicals of *Curcuma longa* and *Azadirachta indica* with Anticancer Activities**

| Plant | Major Constituents | Key Biological Activities | References |
|---|---|---|---|
| *Curcuma longa* | Curcumin, demethoxycurcumin, bisdemethoxycurcumin | Apoptosis induction, anti-inflammatory, antioxidant | Priyadarsini (2014); Gupta et al. (2013) |
| | Volatile oils (ar-turmerone, α- and β-turmerone) | Anti-angiogenic, anti-inflammatory, tumor suppression | Liju et al. (2011) |
| *Azadirachta indica* | Limonoids (nimbolide, azadirachtin, gedunin) | Apoptosis induction, anti-angiogenic, metastasis inhibition | Saleem et al. (2018); Gupta et al. (2017) |
| | Flavonoids, polyphenols | Antioxidant, DNA protection, detoxification enzyme modulation | Subapriya & Nagini (2005) |

## 3. Mechanistic Insights into Oncoprevention

Phytochemicals of Curcuma longa and Azadirachta indica are reported to act against various hallmarks of cancer such as induction of apoptosis, inhibition of angiogenesis, amelioration of immune surveillance etc.. These mechanisms act in concert to disrupt tumor growth and progression, thereby supporting their role in multistage oncoprevention.

### 3.1 Induction of Apoptosis

Apoptosis, or programmed cell death, is a fundamental mechanism for eliminating damaged or malignant cells. Dysregulation of apoptosis is a key feature of cancer cells, enabling their uncontrolled survival (Hanahan, 2022).

Curcumin activates both the intrinsic (mitochondrial) and extrinsic (death receptor) apoptotic pathways. It modulates pro- and anti-apoptotic proteins such as Bax, Bcl-2, and Bcl-xL, promotes cytochrome c release, and activates caspases-3, -8, and -9 (Kunnumakkara et al., 2017).

Neem-derived compounds, especially nimbolide, also induce apoptosis by activating mitochondrial dysfunction, downregulating Bcl-2, and enhancing caspase activation (Arumugam et al., 2015). Additionally, azadirachtin has been shown to trigger death receptor-mediated pathways.

When combined, curcumin and neem compounds display synergistic apoptosis-inducing potential, simultaneously targeting multiple checkpoints of cell death pathways and thereby overcoming resistance mechanisms often seen with single agents (Gupta et al., 2017).

### 3.2 Inhibition of Angiogenesis

Angiogenesis, the formation of new blood vessels, is essential for tumor growth and metastasis. Both turmeric and neem phytochemicals suppress angiogenic signaling cascades. Curcumin downregulates vascular endothelial growth factor (VEGF), inhibits matrix metalloproteinases (MMPs), and suppresses hypoxia-inducible factor-1α (HIF-1α), thereby reducing endothelial cell proliferation and neovascularization (Banerjee & Harsha, 2021). Neem limonoids, particularly nimbolide and gedunin, also inhibit angiogenesis by interfering with VEGF and MMP activity, disrupting tumor vascularization (Roy et al., 2018). Their combined role in angiogenic checkpoint control ensures a stronger blockade of neovascular signaling, limiting tumor sustenance and metastatic potential.

### 3.3 Immune Surveillance Modulation

The immune system plays a critical role in identifying and eliminating malignant cells. However, tumors often escape immune detection through immune evasion mechanisms. Curcumin enhances immune surveillance by stimulating natural killer (NK) cells, promoting cytotoxic T lymphocyte (CTL) activity, and enhancing antigen presentation (Bose et al., 2015). It also downregulates immune checkpoints such as PD-1/PD-L1, reversing tumor-mediated immunosuppression (Gupta et al., 2021). Neem extracts activate macrophages, boost T-cell proliferation, and increase cytokine release, thereby strengthening antitumor immunity (Khar et al., 1998). Additionally, neem suppresses regulatory T cells (Tregs), which are known to inhibit antitumor responses. Together, turmeric and neem exhibit immuno-adjuvant properties, creating an immune-permissive environment that strengthens the body's natural defense mechanisms against tumor progression.

**Table 2. Mechanistic Roles of *Curcuma longa* and *Azadirachta indica* in Oncoprevention**

| **Mechanism** | ***Curcuma longa* Actions** | ***Azadirachta indica* Actions** | **Synergistic Impact** | **References** |
|---|---|---|---|---|
| **Apoptosis induction** | Activates caspases; modulates Bax/Bcl-2; mitochondrial cytochrome c release | Induces mitochondrial apoptosis; downregulates Bcl-2; caspase activation | Enhanced pro-apoptotic signaling through multiple pathways | Kunnumakkara et al. (2017); Arumugam et al. (2015) |
| **Angiogenesis inhibition** | Downregulates VEGF, MMPs, HIF-1α | Blocks VEGF and MMP activity; inhibits tumor vascularization | Stronger anti-angiogenic blockade reducing neovascularization | Banerjee & Harsha (2021); Roy et al. (2018) |
| **Immune modulation** | Enhances NK and CTL activity; reduces PD-1/PD-L1 | Activates macrophages and T-cells; suppresses Tregs | Synergistic activation of immune surveillance | Bose et al. (2015); Khar et al. (1998) |

## 4. Molecular Pathways and Targets

Phytochemicals from *Curcuma longa* (primarily curcuminoids and volatile oils) and *Azadirachta indica* (notably nimbolide and other limonoids) modulate a network of intracellular signaling pathways that drive tumor initiation, growth, survival, invasion, and immune evasion. This section summarizes how

these botanicals influence four central oncogenic signaling modules (NF-κB, STAT3, PI3K/Akt, MAPK), their actions on epigenetic regulators and microRNAs, and how these effects intersect with oxidative stress and inflammation to produce coordinated oncopreventive activity.

### 4.1 Modulation of NF-κB, STAT3, PI3K/Akt, and MAPK signaling

#### NF-κB

NF-κB is a master transcription factor that controls expression of genes involved in inflammation, cell survival, proliferation, and metastasis. Curcumin inhibits NF-κB activation by preventing IκB kinase (IKK) activity and blocking nuclear translocation of NF-κB subunits, thereby reducing expression of downstream targets such as COX-2, Bcl-2, and several cytokines (Amaroli et al., 2024; Guo, 2024). Nimbolide and related neem limonoids also attenuate NF-κB signaling in multiple cancer models, contributing to decreased pro-survival signaling and sensitization to apoptosis (Rajendran et al., 2024; Sophia et al., 2018).

#### STAT3

Signal transducer and activator of transcription-3 (STAT3) promotes oncogenic transcriptional programs (proliferation, angiogenesis, immune suppression). Curcumin is a reported inhibitor of STAT3 phosphorylation and DNA-binding activity in several cancer types, suppressing STAT3-driven gene expression (Golmohammadi et al., 2024). Emerging evidence indicates that neem constituents can indirectly reduce STAT3 activity through upstream modulation of cytokine signaling and suppression of receptor tyrosine kinase signaling, thereby cooperating with curcumin to lower STAT3-driven oncogenicity (Batra et al., 2022).

#### PI3K/Akt

The PI3K/Akt pathway supports cell survival, metabolism, and resistance to therapy. Curcumin downregulates PI3K/Akt signaling and its downstream effector mTOR in many models, promoting apoptosis and autophagy (Amaroli et al., 2024). Nimbolide similarly inhibits PI3K/Akt signaling (reported in breast and prostate cancer models), contributing to reduced proliferation and enhanced cell death (Wang et al., 2016; Rajendran et al., 2024).

#### MAPK (ERK/JNK/p38)

MAPK family members mediate responses to growth factors and stress. Curcumin modulates MAPK cascades in a context-dependent manner (e.g., inhibiting ERK-driven proliferation while sometimes activating JNK to promote apoptosis) (Islam et al., 2024). Neem limonoids have been reported to attenuate ERK signaling and activate stress-responsive kinases that favor apoptotic outcomes (Elumalai et al., 2014).

Collectively, curcumin and neem phytochemicals target multiple nodes within these signaling networks, producing additive or synergistic suppression of proliferation and survival while enhancing pro-death signaling (Guo, 2024; Golmohammadi et al., 2024; Rajendran et al., 2024).

### 4.2 Epigenetic regulation and miRNA modulation

#### DNA methylation and histone modification

Curcumin functions as an epigenetic modulator by inhibiting DNA methyltransferases (DNMTs) and histone deacetylases (HDACs) in various cancer cell models, leading to re-expression of tumor suppressor genes and altered chromatin states favorable to growth arrest (Hassan et al., 2019; Ming, 2022). Neem extracts and nimbolide have also been shown to influence epigenetic marks—reports indicate modulation of DNMT and HDAC activity following neem treatment, which contributes to changes in gene expression associated with reduced malignancy (Qiu et al., 2019; Pooladanda et al., 2018).

#### MicroRNA networks

MicroRNAs (miRNAs) are short noncoding RNAs that fine-tune oncogenic and tumor-suppressive pathways. Curcumin alters expression of multiple miRNAs (for example, upregulating tumor-suppressor miRNAs and downregulating oncogenic miRNAs), thereby affecting proliferation, invasion, and chemoresistance (Momtazi et al., 2016; Ravindran et al., 2023). Nimbolide has been reported to modulate specific miRNAs (e.g., miR-126 and others) in oral and hepatic cancer models, linking nimbolide's antitumor effects to restoration of tumor-suppressive miRNA expression profiles (Sophia et al., 2018; Vairappan et al., 2025).

By converging on epigenetic enzymes and miRNA networks, curcumin and neem phytochemicals can reprogram malignant cells toward less aggressive phenotypes and improve responsiveness to other anticancer interventions (Hassan et al., 2019; Momtazi et al., 2016).

### 4.3 Cross-talk with oxidative stress and inflammation pathways

Oxidative stress and chronic inflammation are central drivers of carcinogenesis and are deeply integrated with the signaling pathways above. Curcumin's antioxidant activity reduces reactive oxygen species (ROS) and oxidative DNA damage, while simultaneously suppressing pro-inflammatory transcription factors (e.g., NF-κB) and cytokine production (Amaroli et al., 2024). Neem components both scavenge free radicals and modulate redox-sensitive signaling (e.g., inhibiting ROS-driven activation of NF-κB and MAPKs), thereby diminishing the feed-forward loop between inflammation and tumor progression (Elumalai et al., 2014; Rajendran et al., 2024).

This cross-talk means that targeting redox balance and inflammatory mediators with curcumin + neem not only reduces direct DNA damage and mutagenesis but also weakens the microenvironmental signals that sustain malignant cells and suppress antitumor immunity. Such multi-layered interference supports a multistage oncopreventive strategy that acts both on tumor cells and their supportive niche (Guo, 2024; Ming, 2022).

**Table 3. Summary of Molecular Targets and Effects of *Curcuma longa* and *Azadirachta indica* Phytochemicals**

| Pathway / Target | Curcumin (C. longa) — Main actions | Neem (A. indica) — Main actions | Functional outcome | Representative references |
|---|---|---|---|---|
| NF-κB | Inhibits IKK activity and NF-κB nuclear translocation | Suppresses NF-κB activation and downstream cytokines | Reduced inflammation, survival signaling | Amaroli et al. (2024); Rajendran et al. (2024); Sophia et al. (2018) |
| STAT3 | Inhibits phosphorylation and transcriptional activity | Indirect downregulation via upstream signaling modulation | Decreased proliferation, angiogenesis, immune evasion | Golmohammadi et al. (2024); Batra et al. (2022) |
| PI3K/Akt | Downregulates PI3K/Akt/mTOR signaling | Inhibits PI3K/Akt in several cancer models | Increased apoptosis, reduced survival | Amaroli et al. (2024); Wang et al. (2016) |
| MAPK (ERK/JNK/p38) | Context-dependent modulation (ERK inhibition; JNK activation for apoptosis) | ERK attenuation and activation of stress kinases | Shift toward pro-apoptotic signaling | Islam et al. (2024); Elumalai et al. (2014) |
| Epigenetic enzymes (DNMT, HDAC) | Inhibits DNMTs & HDACs; restores tumor suppressor gene expression | Modulates DNMT/HDAC activity; alters chromatin | Re-expression of silenced genes; altered cell fate | Hassan et al. (2019); Qiu et al. (2019) |
| microRNAs | Modulates multiple miRNAs (↑ tumor-suppressor miRs; ↓ oncomiRs) | Alters miRNA profiles (e.g., miR-126, miR-145) | Reprogramming of malignant phenotypes | Momtazi et al. (2016); Sophia et al. (2018) |
| Oxidative stress / inflammation | Antioxidant; reduces ROS and inflammatory cytokines | Antioxidant and anti-inflammatory; limits ROS-driven signaling | Lower DNA damage and pro-tumor inflammation | Amaroli et al. (2024); Elumalai et al. (2014) |

## 5. Preclinical and Clinical Evidence

This section summarizes laboratory (in vitro), animal (in vivo), and human (clinical) studies that evaluate the anticancer properties of *Curcuma longa* (curcumin and related curcuminoids) and *Azadirachta indica* (primarily nimbolide and other neem limonoids). Where available, studies testing combinations or co-delivery approaches are highlighted. The body of evidence is strongest for preclinical models; clinical data remain promising but limited and heterogeneous in design.

### 5.1 In Vitro Studies

In vitro experiments using cancer cell lines provide the most abundant and mechanistic evidence for both curcumin and neem phytochemicals.

- **Cytotoxicity and growth inhibition.** Multiple human cancer cell lines (breast, prostate, colon, leukemia, oral squamous cell carcinoma) show dose-dependent growth inhibition when treated

with curcumin; the compound acts on proliferation, cell-cycle arrest, and survival signaling (Hosseini-Zare et al., 2021; Frontiers Oncology review, 2024). Nimbolide exhibits potent antiproliferative activity across a range of cell lines at low micromolar concentrations (Roy, 2007; Sophia et al., 2018).

- **Apoptosis induction.** Both curcumin and neem limonoids activate intrinsic and extrinsic apoptotic cascades in vitro, including mitochondrial depolarization, cytochrome-c release, and caspase activation (Kunnumakkara et al., 2017; Sophia et al., 2018). Nimbolide has been reported to switch cells from autophagy to apoptosis by modulating PI3K/GSK-3β signaling in oral cancer models (Sophia et al., 2018).
- **Migration/invasion assays.** Curcumin reduces migratory and invasive behavior by downregulating MMP expression and EMT markers in multiple cell types (Hosseini-Zare et al., 2021). Neem extracts and nimbolide similarly inhibit MMP activity and decrease invasion in vitro (Wang et al., 2016).
- **Evidence of synergy.** Direct in vitro studies demonstrating anticancer synergy specifically between curcumin and neem (nimbolide) in cancer cell lines are limited. Reviews and experimental work show curcumin synergizes with many phytochemicals and drugs to enhance cytotoxicity and overcome resistance (Hosseini-Zare et al., 2021). A number of topical/antimicrobial studies and wound-healing formulations report beneficial interactions when neem extracts and turmeric/curcumin are combined, indicating physicochemical and biological compatibilities that support testing their anticancer synergy (Sarkar et al., 2021; research on co-loaded textile substrates). Overall, mechanistic complementarity (pro-apoptotic + immunomodulatory + anti-angiogenic) provides strong rationale for systematic combination testing in vitro (Kunnumakkara et al., 2017; Roy, 2007).

### 5.2 In Vivo Studies

Animal models provide evidence that curcumin and neem constituents can reduce tumor burden, angiogenesis, and metastatic spread—and modulate host immune responses.

- **Tumor regression and angiogenesis.** Curcumin formulations (including nanoparticle or adjuvant-enhanced preparations) reduced tumor growth and microvessel density in murine xenograft and chemically induced tumor models (Frontiers Oncology review, 2024; Khosravi et al., 2023). Nimbolide demonstrated tumor growth inhibition in multiple preclinical models (breast, prostate, hepatic) and reduced angiogenesis and metastatic markers in treated animals (Wang et al., 2016; Rajendran et al., 2024).
- **Immune-boosting effects.** Neem extracts have been shown to activate macrophages, increase T-cell responses, and improve tumor-infiltrating immune cell profiles in murine tumor models (Batra et al., 2022). Curcumin also modulates immune effectors—enhancing NK and cytotoxic T-cell function in some animal studies—though effects can be context dependent (Bose et al., 2015; Khosravi et al., 2023).
- **Combination and adjuvant studies.** Preclinical reports indicate nimbolide can sensitize tumors to chemotherapeutics (e.g., docetaxel) and to other targeted agents, increasing apoptosis and reducing resistance (Zhang et al., 2022). Co-delivery strategies (nanoparticles, liposomes) combining curcumin with other natural products or chemotherapeutics have improved tumor

suppression in animals; comparable studies specifically pairing curcumin with neem limonoids in cancer models are emerging but still sparse (Lal et al., 2021; Rajendran et al., 2024).

### 5.3 Clinical Studies and Translational Potential

Clinical data for curcumin are more extensive than for neem, but both faces translational hurdles—primarily bioavailability, heterogeneity of formulations, and small/underpowered trials.

- **Curcumin in clinical oncology.** Curcumin has been evaluated in numerous early-phase clinical trials for chemoprevention and as an adjunct to standard therapy (e.g., colorectal, pancreatic, oral premalignant lesions). Systematic reviews conclude that curcumin shows biological activity and acceptable safety in small trials but that evidence is inadequate to recommend curcumin as a standard anticancer therapy due to small sample sizes, variable formulations, inconsistent dosing, and short follow-up (ClinicalTrials.gov; National Cancer Institute PDQ summary, 2025; Khosravi et al., 2023).
- **Neem in human studies.** Human clinical trials of neem for cancer are extremely limited. Most human data concern neem's safety, topical applications, or general ethnopharmacological use; well-controlled clinical oncology trials of nimbolide or neem extracts are not yet established at scale (Batra et al., 2022). This gap underscores the need for carefully designed phase-I safety and pharmacokinetic studies for nimbolide and standardized neem preparations.
- **Potential of combinatorial therapy.** Translational potential for curcumin + neem rests on (1) complementary mechanisms of action, (2) evidence that nimbolide and curcumin individually sensitize tumors to standard therapies, and (3) advanced formulation technology that can address bioavailability. Prior to wider clinical application, our field requires: standardized extracts/active-ingredient preparations; extensive pharmacokinetic/pharmacodynamic and safety profiling (phase-I studies); and RCTs with tightly controlled endpoints (biomarker modulation, progression-free survival). Reviews on clinical trials of curcumin once again underline the need for increased bioavailable formulations (nanoparticles, with adjuvants such as piperine) if a translationally significant outcome is desired—this in turn is directly related to any curcumin–neem combinatorial program of action (Khosravi et al., 2023; ClinicalTrials. gov).

**Table 4. Representative Preclinical and Clinical Studies of Curcumin and Neem**

| Evidence level | Representative study / model | Key outcome(s) | Reference |
|---|---|---|---|
| In vitro (curcumin) | Multiple cancer cell lines; mechanistic assays | Reduced proliferation, apoptosis induction, inhibition of migration/invasion | Hosseini-Zare et al. (2021); Frontiers Oncology (2024) |
| In vitro (nimbolide) | U937, HL-60, SCC131, SCC4 and other lines | Potent antiproliferative and pro-apoptotic activity at low μM | Roy (2007); Sophia et al. (2018) |
| In vivo (curcumin) | Murine xenograft and chemical models; nanoparticle formulations | Tumor growth suppression; reduced microvessel density; improved biomarker | Khosravi et al. (2023); Frontiers Oncology (2024) |

| | | | |
|---|---|---|---|
| | | profiles | |
| In vivo (nimbolide) | Mouse xenografts (breast, prostate, hepatic models) | Tumor regression; anti-angiogenic effects; restored tight junctions in hepatic model | Wang (2016); Rajendran et al. (2024); Ram et al. (2020) |
| Preclinical combination | Nimbolide + docetaxel (prostate models) | Enhanced antitumor efficacy and sensitization to chemotherapy | Zhang et al. (2022) |
| Clinical (curcumin) | Early-phase trials (colon, pancreatic, oral premalignant) | Biological activity and safety; insufficient evidence for clinical efficacy due to heterogeneity and small sample sizes | National Cancer Institute PDQ (2025); Khosravi et al. (2023) |
| Clinical (neem) | Very limited/no large oncology trials; topical and safety studies | Sparse human oncology data; safety profile appears acceptable in non-oncology contexts | Batra et al. (2022) |

## 6. Formulation Strategies for Enhanced Synergy

Phytochemicals from *Curcuma longa* (curcumin and related curcuminoids) and *Azadirachta indica* (nimbolide, azadirachtin, gedunin and others) show promising complementary bioactivities but face formulation challenges—chiefly poor aqueous solubility, rapid metabolism, and low oral bioavailability. Modern drug-delivery approaches aim to (a) improve systemic exposure, (b) enable co-delivery of actives for synergistic pharmacology, and (c) target tumor tissue or immune cells while minimizing off-target effects.

### 6.1 Nanocarrier systems

Lipid-based and polymeric nanocarriers are the most widely studied platforms for curcumin and increasingly for neem actives.

- **Liposomes and lipid-based nanocarriers.** Liposomes encapsulate lipophilic phytochemicals and can prolong circulation, improve stability, and enable surface functionalization for targeting. Lipid-nanocarriers (nanoemulsions, nanostructured lipid carriers, solid lipid nanoparticles) have been repeatedly used to increase curcumin absorption and tumor delivery. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) show particular promise for oral and parenteral curcumin formulations. These systems can also be adapted to encapsulate neem limonoids. (Pandey et al., 2021; Karaca et al., 2025).
- **Polymeric nanoparticles and PLGA systems.** Biodegradable polymers (e.g., PLGA) provide controlled release and protection from metabolic degradation; PLGA microparticles and nanoparticles have been developed for sustained nimbolide and curcumin release in preclinical models (Anchi et al., 2022).
- **Solid dispersions and inclusion complexes.** Cyclodextrin inclusion, solid dispersions, and amorphous formulations can enhance curcumin solubility and dissolution rate before absorption (Yeo et al., 2022).

### 6.2 Co-delivery systems for curcumin and neem phytochemicals

Co-encapsulation of curcumin and neem actives in the same nanocarrier (or in compatible co-administered carriers) allows synchronized pharmacokinetics at the tumor/microenvironmental site, increases the probability of molecular interaction at target cells, and can reduce required doses.

- **Rationale.** Co-delivery can preserve optimal ratios, reduce systemic degradation of one or both actives, and facilitate combined modulation of apoptosis, angiogenesis, and immune pathways. Early preclinical examples exist where nimbolide is formulated in sustained-release microparticles and curcumin in lipid nanoparticles; translational work combining both in a single carrier is emerging (Anchi et al., 2022; Rajendran, 2024).
- **Design considerations.** Matching release kinetics (burst vs sustained), ensuring chemical compatibility, and avoiding carrier-induced antagonism are essential. Surface modification (PEGylation, ligand attachment) may improve tumor targeting or immune-cell uptake.

### 6.3 Bioenhancers and adjuvants

Small-molecule bioenhancers can dramatically increase curcumin exposure and may be useful adjuncts in combination regimens.

- **Piperine and related adjuvants.** Piperine (from black pepper) is the most studied bioenhancer for curcumin; classical human and animal studies report large increases in curcumin systemic exposure when co-administered (Pratti et al., 2024; Cot Food Safety review, 2024). Other adjuvants (quercetin, rutin, certain surfactants) also modulate metabolism and transport to improve bioavailability (Tiwari, 2020).
- **Nanocarrier + adjuvant synergy.** Combining nanocarriers with metabolic inhibitors or permeability enhancers (for example, piperine) can have multiplicative effects on absorption and tumor delivery, but safety and interaction profiling are required before clinical use.

**Table 5. Formulation strategies: advantages, limitations, and representative evidence**

| Strategy | Key advantages | Main limitations / challenges | Representative references |
|---|---|---|---|
| Liposomes / lipid nanocarriers (SLN, NLC) | Improved solubility, protection from metabolism, modifiable surface for targeting | Stability, scalability, possible lipid-related toxicity; formulation complexity | Pandey et al. (2021); Yeo et al. (2022) |
| Polymeric nanoparticles (PLGA, PEG-PLGA) | Controlled/sustained release; tunable degradation; proven safety | Manufacturing complexity, burst release risk, potential polymer residue | Anchi et al. (2022); Rajendran (2024) |
| Co-delivery (single carrier) | Synchronized PK/PD, preserved synergistic ratios, fewer administrations | Chemical compatibility, matched release profiles, regulatory complexity | Rajendran (2024); Anchi et al. (2022) |
| Bioenhancers (piperine, quercetin) | Large increases in curcumin exposure; simple | Potential herb–drug interactions; dose- | Pratti et al. (2024); Tiwari (2020) |

| | | | |
|---|---|---|---|
| | oral dosing adjunct | dependent effects on drug metabolism | |

## 7. Safety, Toxicity, and Pharmacokinetics

Any translational program for curcumin + neem must address toxicology, define safe exposure ranges, characterize pharmacokinetics (PK), and identify potential herb–drug interactions—especially when used alongside chemotherapy.

### 7.1 Toxicological evaluations

- **Curcumin.** Extensive preclinical toxicology and multiple human trials show curcumin is generally well tolerated at oral doses up to several grams per day in short-term studies; common adverse effects include mild gastrointestinal upset. However, formulation differences (high-exposure nanoparticle vs standard extract) change systemic exposure and may reveal new safety signals, so formulation-specific toxicology is required (Hewlings & Kalman, 2017). Regulatory reviews also caution about liver enzyme elevations in rare cases and stress the need for monitoring in patients on hepatotoxic drugs (Food Standards / Cot review, 2024).
- **Azadirachta indica (neem) and nimbolide.** Neem extracts have a long history of ethnopharmacological use; animal studies and reviews show low-to-moderate toxicity at typical doses, but toxic effects have been reported at high doses or with certain preparations (e.g., reproductive toxicity in specific animal studies, dose-dependent hepatic or renal effects in some models). Nimbolide displays potent bioactivity but requires careful PK and toxicology profiling—first-in-human data are not yet available and preclinical PK/tox studies indicate the need for formulation strategies to limit acute exposure peaks (Braga et al., 2021; Wang, 2016; Rajendran, 2024).

### 7.2 Safe dosage ranges and long-term considerations

- **Curcumin dosing.** Clinical trials have used oral curcumin doses from 500 mg to 8,000 mg/day; many phase I/II studies report acceptable tolerability at doses up to 4,000 mg/day for limited durations, but bioavailability varies widely by formulation (Hewlings & Kalman, 2017; Cot review, 2024). For formulations that substantially enhance exposure (e.g., piperine co-administration or certain nanoparticles), lower nominal curcumin doses may achieve higher systemic exposure—thus dose adjustments and PK monitoring are essential.
- **Neem / nimbolide dosing.** Human dosing guidelines for nimbolide are not established. Preclinical PK reports provide starting points for first-in-human dose calculations, but formal NOAEL (no observed adverse effect level) and GLP toxicology studies are prerequisites before clinical dosing can be recommended (Baira et al., 2018; Rajendran, 2024).
- **Long-term use.** Chronic administration requires monitoring for hepatic, renal, and hematologic toxicity, and for potential endocrine or reproductive effects reported with high doses of neem in some animal studies. Longitudinal safety data for combined long-term use of curcumin + neem are absent; such studies should be prioritized.

### 7.3 Herb–drug interactions with conventional chemotherapeutics

- **Pharmacokinetic interactions.** Curcumin and piperine can inhibit or modulate cytochrome P450 enzymes and drug transporters (e.g., CYP3A4, P-glycoprotein), potentially altering plasma concentrations of co-administered chemotherapeutics (MSKCC summary; Duan et al., 2025). Piperine's strong inhibition of drug-metabolizing enzymes is a double-edged sword—it boosts curcumin exposure but may raise levels of narrow-therapeutic-index anticancer drugs.
- **Pharmacodynamic interactions.** Antioxidant and anti-inflammatory activities could theoretically antagonize ROS-mediated chemotherapy or radiotherapy mechanisms in some contexts; conversely, chemosensitization (through inhibition of survival pathways) has been demonstrated preclinically. Therefore, interactions can be context- and agent-dependent (Okem et al., 2023; Duan et al., 2025).
- **Practical recommendations.** Before clinical co-administration with chemotherapy: perform (a) in vitro CYP/transport inhibition panels for the exact formulations, (b) animal PK interaction studies with representative chemotherapeutics, and (c) early phase clinical PK and safety studies (drug–drug interaction cohorts). Clinicians should be cautious about empiric use of high-exposure curcumin formulations or piperine in patients receiving CYP3A4-metabolized anticancer agents.

**Table 6. Safety considerations and pharmacokinetic highlights**

| Topic | Key points | Evidence / implication |
|---|---|---|
| Curcumin tolerability | Generally well tolerated up to grams/day; GI upset and rare LFT changes reported | Formulation-specific PK requires dose adjustments (Hewlings & Kalman, 2017; Cot review, 2024) |
| Nimbolide / neem toxicity | Low-to-moderate toxicity in many models; high doses/ certain extracts show organ/reproductive effects | Rigorous GLP tox and PK needed prior to first-in-human (Braga et al., 2021; Wang, 2016) |
| Herb–drug interactions | Potential CYP and transporter inhibition (curcumin/piperine) and context-dependent PD interactions | Conduct CYP/transport panels and PK interaction studies before co-admin with chemo (Duan et al., 2025; Okem et al., 2023) |
| Long-term monitoring | Monitor LFTs, renal function, hematology; reproductive endpoints if long-term neem use | Absence of long-term human data for combined therapy mandates surveillance |

## 8. Future Perspectives and Challenges

### 8.1 Personalized Cancer Therapy with Phytochemicals

The emergence of precision oncology has underscored the importance of tailoring therapeutic regimens to an individual's genetic, metabolic, and immunological profile. Phytochemicals from *Curcuma longa* and *Azadirachta indica* have pleiotropic mechanisms that allow modulation of multiple oncogenic pathways, making them attractive candidates for integration into personalized treatment frameworks (Amaroli et al., 2024). Biomarker-guided approaches, such as assessing NF-κB or STAT3 activation status, may help identify patient subgroups more likely to respond to curcumin–neem combination therapy (Rajendran, 2024).

### 8.2 Integrative Oncology and Complementary Medicine Approaches

Globally, integrative oncology is gaining traction, combining conventional treatments with evidence-based herbal and dietary interventions. The incorporation of turmeric and neem extracts within supportive care regimens has been proposed to reduce therapy-associated toxicities, modulate immune responses, and improve patient quality of life (Duan et al., 2025). However, this requires rigorous evidence to transition from traditional use to standardized adjunctive therapies.

### 8.3 Regulatory Aspects, Standardization, and Quality Control

A major challenge in phytochemical drug development is the lack of uniform regulatory frameworks across regions. Standardization of extracts, quality control of bioactive content, and removal of contaminants (e.g., heavy metals, pesticides) remain critical for reproducibility and safety (Braga et al., 2021). Regulatory agencies are increasingly emphasizing the need for validated analytical techniques, adherence to Good Manufacturing Practice (GMP), and well-defined pharmacopoeial monographs for herbal formulations (Cot review, 2024).

### 8.4 Roadmap for Clinical Translation and Commercialization

For effective translation, a roadmap should prioritize:

1. Preclinical validation in mechanistically relevant cancer models.
2. Phase I trials with standardized phytochemical formulations to establish safety, pharmacokinetics, and herb–drug interactions.
3. Combination studies with chemotherapy or immunotherapy, guided by pharmacodynamic biomarkers.
4. Commercial strategies focused on co-formulations (e.g., nanocarriers, bioenhancer combinations) and patent protection to incentivize industry investment.

Although challenges persist, the growing body of supportive preclinical and clinical evidence suggests that *Curcuma longa* and *Azadirachta indica* have genuine potential for integration into next-generation anticancer therapeutics.

## 9. Conclusion

The integration of *Curcuma longa* and *Azadirachta indica* into oncopreventive strategies represents a promising direction in cancer management. Curcuminoids, turmerones, and neem limonoids act through complementary mechanisms to induce apoptosis, inhibit angiogenesis, and modulate immune surveillance (Amaroli et al., 2024; Rajendran, 2024). Advances in formulation science—including nanoparticles, liposomes, and bioenhancers—have begun to overcome limitations of solubility and bioavailability, paving the way for clinical applicability (Pandey et al., 2021; Pratti et al., 2024).

Importantly, the synergy between turmeric and neem offers a multi-targeted approach capable of addressing the heterogeneity and adaptability of cancer. While further translational and clinical work is

essential, the convergence of phytochemistry, nanotechnology, and integrative oncology signals a sustainable strategy for multistage oncoprevention.

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Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-486-3

# Chapter 2: Bronchoprotective and Immunomodulatory Dynamics of Ocimum sanctum and Glycyrrhiza glabra in Respiratory Pathophysiology: Mechanistic Insights into Asthma and Chronic Bronchitis

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## Abstract

Asthma and chronic bronchitis remain major global health challenges, characterized by airway inflammation, oxidative stress, immune dysregulation, and structural remodeling that compromise respiratory function. Despite significant therapeutic advances, conventional treatments are limited by adverse effects, incomplete symptom control, and lack of endotype-specific targeting. This has prompted growing interest in phytotherapeutics as adjuncts or alternatives. Among promising candidates, *Ocimum sanctum* (Tulsi) and *Glycyrrhiza glabra* (licorice) exhibit broad-spectrum pharmacological actions relevant to respiratory diseases. Tulsi demonstrates potent antioxidant and anti-inflammatory activities, along with bronchodilatory and immunomodulatory effects. Licorice regulates glucocorticoid metabolism through inhibition of 11β-hydroxysteroid dehydrogenase, modulates cytokines such as IL-4, IL-5, and TNF-α, and exerts anti-allergic and antiviral activities that strengthen respiratory defense. Preclinical studies are suggestive of their roles in decreasing airway hyperresponsiveness, remodeling and mucus hypersecretion with early clinical experience hinting at symptomatic benefit. The potential synergistic effects observed between Tulsi and licorice in case of polyherbal formulations as well as traditional systems of medicine indicate the complementary nature of therapeutic use. Clinical perspectives include calls for standardized extracts, biomarker-driven clinical trials and integration within precision medicine paradigms with attention to safety from glycyrrhizin related mineralocorticoid effects. Taken together, this information places O. sanctum and G. glabra as potential adjuvants in the treatment of asthma and chronic bronchitis, that deserve prospective clinical validation.

## Keywords

Asthma; Chronic bronchitis; Ocimum sanctum; Glycyrrhiza glabra; Phytotherapeutics; Bronchoprotection Immunomodulation Oxidative stress Precision medicine

## 1. Introduction

Asthma and chronic bronchitis are the most common respiratory diseases that cause serious health conditions worldwide. Asthma is a chronic disease that affects more than 262 million people globally, with growing prevalence particularly in urban areas as result from exposure to air pollution, lifestyle modification and allergen (World Health Organization [WHO], 2021). Chronic bronchitis, a key phenotype of chronic obstructive pulmonary disease (COPD), is characterized by persistent cough and mucus hypersecretion, affecting approximately 10% of adults in industrialized nations (Lopez-Campos, Tan, & Soriano, 2016). Both conditions are associated with airway inflammation, immune dysregulation, and progressive decline in pulmonary function, thereby imposing a considerable socioeconomic burden.

Conventional therapeutic approaches, such as bronchodilators, corticosteroids, and leukotriene inhibitors, provide symptomatic relief and reduce exacerbations but often fail to address underlying immunopathological mechanisms (Barnes, 2017). Long-term corticosteroid use is further limited by adverse effects including immunosuppression, osteoporosis, and metabolic disturbances (Reddel et al., 2022). Moreover, the heterogeneity of patient responses highlights the need for safer and more effective adjunct or alternative therapeutic strategies.

Phytotherapeutics have gained attention as complementary or integrative approaches in respiratory care due to their multitargeted pharmacological actions and favorable safety profiles. *Ocimum sanctum* (Holy basil, Tulsi) and *Glycyrrhiza glabra* (Licorice root) are widely recognized in traditional medicine for their bronchodilatory, anti-inflammatory, and immunomodulatory properties (Jamshidi & Cohen, 2017; Pastorino, Cornara, Soares, Rodrigues, & Oliveira, 2018). It is believed that bioactive compounds, such as eugenol, ursolic acid and glycyrrhizin can act as modulators of airway inflammation, oxidative stress and immune responses involved in the pathophysiology of asthma and chronic bronchitis (Bafna & Mishra, 2005; Wang et al., 2020). Compilation of evidences strengthens the argument to investigate O. sanctum and G. glabra as potential therapeutic agents in chronic respiratory diseases.

## 2. Phytochemical Composition of *Ocimum sanctum* and *Glycyrrhiza glabra*

### 2.1 Bioactive Constituents of *Ocimum sanctum*

Ocimum sanctum (Holy basil, Tulsi) is one of the richest sources of phytochemicals such as essential oils, phenolics and triterpenoids. Pharmacological properties The pharmacological actions of S. grandiflora can be attributed to its major ingredients: eugenol, ursolic acid, rosmarinic acid and apigenin (Pattanayak et al., 2010). Phenolic compound (eugenol) caused powerful anti-inflammatory and antioxidant effects, bronchodilatory & immunomodulatory (ursolic acid) activities (Mondal et al., 2009). These metabolites together mechanistically support the traditional use of Tulsi in respiratory troubles, especially by the way they decrease oxidative stress and airway inflammation.

### 2.2 Bioactive Constituents of *Glycyrrhiza glabra*

*Glycyrrhiza glabra* (Licorice root) contains glycyrrhizin**,** liquiritin**,** glabridin, and isoliquiritigenin as key bioactives. Glycyrrhizin, a saponin glycoside, is well-documented for its anti-inflammatory and

corticosteroid-like effects through inhibition of 11β-hydroxysteroid dehydrogenase (Pastorino, Cornara, Soares, Rodrigues, & Oliveira, 2018). Liquiritin and flavonoids such as glabridin demonstrate antioxidant, mucoregulatory, and antiviral properties relevant to chronic respiratory diseases (Asl & Hosseinzadeh, 2008). Together, they counteract airway remodeling with a decrease in mucus hypersecretion and cytokine imbalance found in asthma and chronic bronchitis.

### 2.3 Pharmacological Relevance in Respiratory Health

The phytochemical interaction of O. sanctum and G. glabra help in bronchodilatation, immune modulation, and suppression of oxidative stress. For instance, eugenol diminishes airway hyper reactivity, ursolic acid inhibits inflammatory cell recruitment. while glycyrrhizin suppresses pro-inflammatory cytokines such as IL-4, IL-5, and TNF-α (Bafna & Mishra, 2005; Wang et al., 2020). Liquiritin and glabridin enhance antioxidant defense systems, thereby protecting bronchial epithelial cells from oxidative injury. Thus, both plants offer promising phytotherapeutic scaffolds for developing safer adjunct treatments for asthma and chronic bronchitis.

**Table 1. Key bioactive constituents of *Ocimum sanctum* and *Glycyrrhiza glabra* with relevance to respiratory health**

| Plant species | Major bioactive compounds | Pharmacological relevance in respiratory health | Reference |
|---|---|---|---|
| *Ocimum sanctum* | Eugenol | Anti-inflammatory, antioxidant, bronchodilation | Mondal et al., 2009 |
| | Ursolic acid | Immunomodulatory, prevents airway remodeling | Pattanayak et al., 2010 |
| | Rosmarinic acid | Anti-allergic, suppresses mast cell degranulation | Pattanayak et al., 2010 |
| | Apigenin | Antioxidant, cytokine modulation | Mondal et al., 2009 |
| *Glycyrrhiza glabra* | Glycyrrhizin | Corticosteroid-like, anti-inflammatory, antiviral | Pastorino et al., 2018; Wang et al., 2020 |
| | Liquiritin | Antioxidant, mucoregulatory | Asl & Hosseinzadeh, 2008 |
| | Glabridin | Anti-allergic, antioxidant, airway protection | Asl & Hosseinzadeh, 2008 |
| | Isoliquiritigenin | Anti-inflammatory, inhibits cytokine release | Pastorino et al., 2018 |

## 3. Pathophysiological Landscape of Asthma and Chronic Bronchitis

### 3.1 Airway Inflammation, Oxidative Stress, and Remodeling

Asthma and chronic bronchitis are characterized by chronic airway inflammation leading to persistent structural and functional changes. In asthma, eosinophilic infiltration predominates, whereas chronic bronchitis is mainly associated with neutrophilic inflammation (Holgate, 2012). Persistent inflammatory activity induces oxidative stress**,** resulting in increased production of reactive oxygen species (ROS) that damage bronchial epithelium and impair mucociliary clearance (Rahman & Adcock, 2006). Structural remodeling—such as subepithelial fibrosis, goblet cell hyperplasia, smooth muscle hypertrophy, and

angiogenesis—contributes to irreversible airflow limitation, particularly in chronic bronchitis and severe asthma (Bergeron & Boulet, 2006).

### 3.2 Immune Dysregulation and Th1/Th2 Imbalance

Asthma pathogenesis is strongly linked to an exaggerated Th2-type immune response**,** leading to increased secretion of interleukin (IL)-4, IL-5, and IL-13, which promote IgE synthesis, eosinophil recruitment, and mucus hypersecretion (Fahy, 2015). Chronic bronchitis, in contrast, often involves a skewed Th1/Th17 response**,** with elevated tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and IL-17 contributing to neutrophilic infiltration and airway tissue destruction (Barnes, 2017). This imbalance in T-cell subsets underscores the heterogeneity of immune mechanisms underlying these respiratory disorders.

### 3.3 Role of Cytokines, Chemokines, and Oxidative Mediators

Cytokines and chemokines orchestrate the inflammatory milieu in both asthma and chronic bronchitis. In asthma, IL-4 and IL-13 drive IgE class switching, while IL-5 facilitates eosinophil survival (Fahy, 2015). In chronic bronchitis, chemokines such as CXCL8 (IL-8) recruit neutrophils, perpetuating mucus hypersecretion and tissue damage (Rovina, Koutsoukou, & Koulouris, 2013). Oxidative mediators like nitric oxide, superoxide anions, and peroxynitrite amplify inflammation by activating nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways (Rahman & Adcock, 2006). Collectively, these processes create a cycle of inflammation, oxidative stress, and remodeling that drives disease progression.

**Table 2. Pathophysiological mechanisms in asthma and chronic bronchitis**

| **Mechanism** | **Asthma (Th2-dominant)** | **Chronic Bronchitis (Th1/Th17-dominant)** | **References** |
|---|---|---|---|
| Inflammatory cells | Eosinophils, mast cells, Th2 lymphocytes | Neutrophils, macrophages, Th1/Th17 lymphocytes | Holgate, 2012; Barnes, 2017 |
| Key cytokines/chemokines | IL-4, IL-5, IL-13, eotaxin | TNF-α, IL-8 (CXCL8), IL-17, IFN-γ | Fahy, 2015; Rovina et al., 2013 |
| Oxidative mediators | ROS, nitric oxide, peroxynitrite | ROS, reactive nitrogen species | Rahman & Adcock, 2006 |
| Airway remodeling features | Subepithelial fibrosis, smooth muscle hyperplasia | Goblet cell hyperplasia, mucus gland hypertrophy | Bergeron & Boulet, 2006 |
| Functional outcomes | Airway hyperresponsiveness, reversible obstruction | Persistent cough, mucus hypersecretion, fixed obstruction | Barnes, 2017 |

## 4. Bronchoprotective Mechanisms of *Ocimum sanctum*

### 4.1 Antioxidant and Anti-inflammatory Actions

*Ocimum sanctum* (Tulsi) exerts potent antioxidant effects through multiple phytoconstituents (notably eugenol and rosmarinic acid) that scavenge reactive oxygen species (ROS) and upregulate endogenous antioxidant defenses (e.g., superoxide dismutase, catalase) (Pattanayak, Behera, Das, & Panda, 2010). By lowering oxidative burden, Tulsi helps protect bronchial epithelial cells from ROS-mediated injury and preserves mucociliary function. Concurrently, Tulsi components reduce pro-inflammatory signaling by inhibiting NF-κB activation and decreasing production of cytokines such as TNF-α and IL-6 in experimental systems, thereby attenuating the inflammatory cascade that drives airway damage and remodeling (Bafna & Mishra, 2005). These dual antioxidant–anti-inflammatory actions form a mechanistic basis for Tulsi's bronchoprotective potential.

### 4.2 Smooth Muscle Relaxation and Modulation of Airway Hyperresponsiveness

Several Tulsi metabolites display direct or indirect effects on airway smooth muscle tone. Eugenol and related volatile phenols have been reported to relax smooth muscle through modulation of calcium handling and inhibition of contractile signaling pathways, which may translate to reduced airway hyperresponsiveness (Pattanayak et al., 2010). In addition, anti-inflammatory activity that decreases mediator release from mast cells and eosinophils can secondarily reduce bronchoconstrictive stimuli (Bafna & Mishra, 2005). Together, these actions suggest that *O. sanctum* can both blunt the triggers of bronchospasm and directly promote bronchodilation, supporting its use as an adjunct broncho-protective agent.

### 4.3 Preclinical and Clinical Evidence

Preclinical studies demonstrate that *O. sanctum* extracts modulate immune responses, reduce markers of oxidative stress, and alter mediator profiles consistent with reduced airway inflammation (Bafna & Mishra, 2005). Controlled animal experiments have shown reductions in inflammatory cell infiltration and biochemical indices of oxidative injury following Tulsi administration, although models and dosing regimens vary. Clinical human data are more limited but encouraging: randomized and controlled studies in healthy volunteers report immunomodulatory effects and improved antioxidant status after Tulsi supplementation, which provide a translational rationale for evaluating respiratory endpoints in patient populations (Mondal et al., 2009). Overall, while mechanistic and safety data are supportive, well-designed clinical trials specifically targeting asthma and chronic bronchitis outcomes are still required to confirm efficacy and optimal dosing.

**Table 3. Mechanistic actions of *Ocimum sanctum* relevant to bronchoprotection**

| Mechanism category | Key constituents | Observed effects relevant to airways | Evidence level |
|---|---|---|---|
| Antioxidant activity | Eugenol, rosmarinic acid | Scavenges ROS; increases SOD/catalase activity; protects epithelium | Preclinical; supportive human biomarker data. (Pattanayak et al., 2010; Mondal et al., 2009) |
| Anti-inflammatory signaling | Eugenol, apigenin | Inhibits NF-κB; reduces TNF-α, IL-6; lowers inflammatory cell infiltration | Preclinical immunomodulation studies. (Bafna & Mishra, 2005) |
| Smooth muscle relaxation | Eugenol and volatile oils | Modulates $Ca^{2+}$ handling and contractile pathways → reduced bronchoconstriction | Experimental pharmacology and mechanistic reports. (Pattanayak et al., 2010) |
| Immunomodulation | Multiple polyphenols, triterpenoids | Balances immune response (reduced pro-inflammatory cytokines); supports antioxidant defenses | Human volunteer studies on immune biomarkers; needs respiratory clinical trials. (Mondal et al., 2009) |

## 5. Immunomodulatory Mechanisms of *Glycyrrhiza glabra*

### 5.1 Regulation of Glucocorticoid Metabolism (11β-HSD Inhibition)

The primary bioactive glycoside of *Glycyrrhiza glabra*, glycyrrhizin**,** modulates endogenous corticosteroid activity by inhibiting the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2)**,** which normally converts active cortisol into inactive cortisone (Monder et al., 1989). This inhibition prolongs the half-life of cortisol, enhancing its anti-inflammatory and immunosuppressive properties at the tissue level. Such regulation mirrors the therapeutic effect of glucocorticoids but with a natural origin, thereby contributing to airway inflammation control in asthma and chronic bronchitis (Pastorino, Cornara, Soares, Rodrigues, & Oliveira, 2018).

### 5.2 Cytokine Modulation (IL-4, IL-5, TNF-α)

Licorice constituents influence immune signaling by modulating cytokine production. Glycyrrhizin has been shown to suppress Th2 cytokines, including IL-4 and IL-5**,** thereby reducing eosinophil recruitment and IgE-mediated hypersensitivity (Wang et al., 2020). It also downregulates TNF-α and IL-6, key mediators of neutrophilic inflammation in chronic bronchitis (Asl & Hosseinzadeh, 2008). Likewise, flavonoids including liquiritin and isoliquiritigenin were identified to regulate the signalling of NF-κB blockade as well as suppress COVOR-TF7 generation (Pastorino et al., 2018). These activities together re-establish immune homeostasis and decrease airway hyperreactivity.

### 5.3 Anti-allergic and Antiviral Roles in Respiratory Defense

Beyond anti-inflammatory activity, *G. glabra* demonstrates anti-allergic effects by stabilizing mast cells, inhibiting histamine release, and reducing leukotriene synthesis (Fiore, Eisenhut, Krausse, Ragazzi,

Pellati, Armanini, & Bielenberg, 2005). These properties are particularly relevant in asthma, where allergen-driven mast cell degranulation contributes to airway narrowing. Furthermore, glycyrrhizin exhibits broad-spectrum antiviral activity**,** including against respiratory viruses such as influenza and SARS-related coronaviruses, through interference with viral replication and immune evasion mechanisms (Cinatl et al., 2003). This duality of antiallergic and anti-viral activity increases the importance of licorice in maintaining lung health against both allergen mediated airway challenges and viral infections.

**Table 4. Immunomodulatory mechanisms of *Glycyrrhiza glabra* relevant to respiratory pathophysiology**

| Mechanism | Key compounds | Immunological effects | Relevance in asthma/chronic bronchitis | References |
|---|---|---|---|---|
| 11β-HSD2 inhibition | Glycyrrhizin | Prolongs cortisol activity → enhanced anti-inflammatory action | Corticosteroid-like modulation of airway inflammation | Monder et al., 1989; Pastorino et al., 2018 |
| Cytokine modulation | Glycyrrhizin, liquiritin, isoliquiritigenin | ↓ IL-4, IL-5, TNF-α, IL-6; inhibits NF-κB signaling | Suppresses eosinophilic and neutrophilic inflammation | Asl & Hosseinzadeh, 2008; Wang et al., 2020 |
| Anti-allergic effects | Glycyrrhizin, flavonoids | Stabilizes mast cells, ↓ histamine, ↓ leukotrienes | Prevents allergen-induced bronchospasm | Fiore et al., 2005 |
| Antiviral activity | Glycyrrhizin | Inhibits viral replication and immune evasion | Protects against influenza, SARS-related viruses | Cinatl et al., 2003 |

## 6. Synergistic Therapeutic Potential of *Ocimum sanctum* and *Glycyrrhiza glabra*

### 6.1 Combined Effects on Oxidative Stress and Immune Balance

When combined, the antioxidant phytochemicals of *Ocimum sanctum* (e.g., eugenol, rosmarinic acid, ursolic acid) and *Glycyrrhiza glabra* (e.g., liquiritin, glabridin, glycyrrhizin) act on complementary redox and immune targets. Tulsi's strong free-radical scavenging and up-regulation of endogenous enzymes (superoxide dismutase, catalase) may also diminish epithelial oxidative injury Treatment with licorice flavonoids and glycyrrhizin suppress ROS-driven NF-κB activation and subsequent cytokine synthesis (Pattanayak et al., 2010; Pastorino et al., 2018). This dual activity favors restoration of redox homeostasis and shifts inflammatory signaling away from persistent pro-inflammatory states. In immune terms, glycyrrhizin's capacity to modulate local glucocorticoid availability (via 11β-HSD inhibition) may potentiate Tulsi's immunoregulatory effects on Th2/Th1 balance, producing a net reduction in both eosinophilic and neutrophilic drivers of airway disease (Monder et al., 1989; Mondal et al., 2009).

### 6.2 Complementary Roles in Airway Remodeling and Mucus Hypersecretion

Airway remodeling and mucus overproduction result from chronic inflammation, growth-factor signaling, and epithelial–mesenchymal interactions (Bergeron & Boulet, 2006). Tulsi constituents (e.g., ursolic acid, apigenin) demonstrate anti-fibrotic and anti-proliferative activities in preclinical models, which may limit smooth muscle hypertrophy and subepithelial fibrosis. Licorice constituents, by downregulating pro-

remodeling cytokines (TNF-α, TGF-β indirectly through NF-κB suppression) and reducing goblet cell hyperplasia, can complement Tulsi's actions to reduce mucus hypersecretion (Asl & Hosseinzadeh, 2008; Wang et al., 2020). Thus, targeting both inflammatory drivers and tissue-remodeling pathways with a combined approach could produce greater preservation of airway structure and function than single-agent use.

### 6.3 Evidence from Polyherbal Formulations and Traditional Medicine

Traditional systems (Ayurveda, Unani, Traditional Chinese Medicine) commonly combine anti-inflammatory and demulcent herbs to manage chronic respiratory complaints; *O. sanctum* and *G. glabra* frequently appear together in such formulations because their actions are complementary—one reducing oxidative/inflammatory triggers and the other modulating immune responses and soothing mucosa (Jamshidi & Cohen, 2017; Pastorino et al., 2018). Modern investigations of polyherbal mixtures emphasize that synergistic interactions can enhance efficacy, modify pharmacokinetics, and reduce toxicity, but the degree of synergy depends on preparation, dose ratio, and bioavailability (Williamson, 2001). Preclinical combination studies specifically testing Tulsi plus licorice in airway disease models remain limited, yet existing evidence from separate mechanistic and in-vivo studies supports a biologically plausible synergy that justifies formal combinational trials (Pattanayak et al., 2010; Wang et al., 2020).

**Table 5. Complementary and synergistic actions of *O. sanctum* + *G. glabra* in respiratory disease**

| **Therapeutic target** | ***O. sanctum* primary action** | ***G. glabra* primary action** | **Putative combined effect** | **Evidence level** |
|---|---|---|---|---|
| Oxidative stress | Scavenges ROS; ↑ SOD/catalase (eugenol, rosmarinic acid) | Flavonoids reduce ROS and inhibit ROS-driven signaling | Enhanced redox restoration and reduced epithelial injury | Preclinical; human biomarker studies (supportive) (Pattanayak et al., 2010; Asl & Hosseinzadeh, 2008) |
| Pro-inflammatory signaling | Inhibits NF-κB; ↓ TNF-α, IL-6 | Inhibits NF-κB; ↓ TNF-α, IL-4, IL-5 (glycyrrhizin) | Greater suppression of cytokine cascade and leukocyte recruitment | Preclinical; animal models (Wang et al., 2020; Bafna & Mishra, 2005) |
| Airway remodeling | Anti-fibrotic, anti-proliferative effects (ursolic acid) | ↓ pro-remodeling cytokines; mucoregulatory flavonoids | Reduced smooth muscle hypertrophy, subepithelial fibrosis | Preclinical, mechanistic evidence (Bergeron & Boulet, 2006; Pastorino et al., 2018) |
| Mucus hypersecretion | Lowers mediator release that triggers goblet cell activity | Reduces goblet cell hyperplasia; mucoregulatory effects | Decreased mucus production and improved clearance | Preclinical support; traditional use (Wang et al., 2020; Jamshidi & Cohen, 2017) |
| Host defense (antiviral/anti-allergic) | Antioxidant, anti-inflammatory, mast cell modulation | Antiviral (glycyrrhizin), mast cell stabilization | Complementary protection against infective and allergic exacerbations | In-vitro and animal antiviral data; traditional evidence (Cinatl et al., 2003; |

| | | | | |
|---|---|---|---|---|
| | | | | Fiore et al., 2005) |
| Safety/tolerability | Generally well tolerated; low adverse event signal in short trials | Well tolerated but glycyrrhizin can cause mineralocorticoid effects at high doses | Potential to use lower doses of each agent when combined → improved safety; monitor glycyrrhizin dose | Clinical safety data; caution advised (Mondal et al., 2009; Pastorino et al., 2018) |

## 7. Preclinical and Clinical Evidence

This section summarizes the experimental (in vivo) models that have been used to evaluate *Ocimum sanctum* and *Glycyrrhiza glabra* in airway disease, and the human clinical / observational evidence available to date. Evidence is grouped into (A) in-vivo animal models and mechanistic pharmacology, and (B) human clinical trials and observational studies. A summary table of representative studies follows.

### 7.1 In vivo models of asthma and bronchitis — key findings and mechanisms

Preclinical studies have used standard models of allergic asthma (ovalbumin [OVA] sensitization/challenge), cigarette-smoke or irritant models resembling chronic bronchitis/COPD, and isolated tissue preparations to probe bronchodilator mechanisms.

- *Glycyrrhiza glabra* and its aglycone 18β-glycyrrhetinic acid (18β-GA) have demonstrated reproducible anti-inflammatory and anti-remodeling effects in OVA-induced allergic asthma models. Treatment reduces airway inflammatory cell infiltration, eosinophilia, proinflammatory cytokines, mucus production, and airway hyperresponsiveness; several studies implicate inhibition of TGF-β/Smad and NF-κB signaling as mechanisms underlying reduced airway remodeling. (Wang et al., 2020; Liu et al., 2022; Yao et al., 2021).
- *Ocimum sanctum* leaf extracts show antioxidant, anti-inflammatory and tissue-protective effects in animal models of lung injury and COPD-like oxidative stress. In rodent models, Tulsi extract reduced oxidative markers (MDA, NO), increased endogenous antioxidant enzymes (SOD, catalase, GPx), lowered inflammatory cytokines, and attenuated histological lung injury, supporting a protective effect against airway inflammation and oxidative damage (Srivastava et al., 2023; Cohen, 2014).
- Isolated tissue studies help explain immediate bronchoprotective actions: eugenol, a major volatile phenol in Tulsi, produces concentration-dependent relaxation of isolated tracheal/airway smooth muscle, indicating direct antispasmodic activity on airway smooth muscle via modulation of contractile signaling and calcium handling (Lima et al., 2011). These findings provide a mechanistic basis for both symptomatic bronchodilation and longer-term protection via reduced mediator release.

Overall, animal data support that glycyrrhizic/glycyrrhetinic derivatives mainly target inflammatory and remodeling pathways, while Tulsi combines antioxidant, anti-inflammatory and direct smooth-muscle effects — a complementary pharmacology that maps onto the pathophysiology of asthma and chronic bronchitis (Wang et al., 2020; Srivastava et al., 2023; Lima et al., 2011).

### 7.2 Human clinical trials and observational studies — scope and limitations

Clinical-level evidence for both herbs is more limited but promising:

- A randomized, double-blind, placebo-controlled trial in healthy volunteers found that *Ocimum sanctum* leaf extract produced measurable immunomodulatory changes in immune biomarkers, supporting translational plausibility for immune effects in humans (Mondal et al., 2011). Separate clinical/clinical-practice reports and smaller interventional studies have reported bronchodilator improvements (e.g., increases in $FEV_1$ and PEFR) after Tulsi preparations in patients with mild-to-moderate asthma, though many such reports are single-center, of small size, or open-label (IJBCP bronchodilator study; ResearchGate/academic reports) (IJBCP, 2017; Mondal et al., 2011).
- For *G. glabra*, human data relevant to asthma and bronchitis are mainly from clinical observations, historical use, and safety studies rather than large randomized respiratory trials. Licorice derivatives have been used as adjunct agents in some respiratory infections and as expectorants; however, licorice glycyrrhizin can cause mineralocorticoid-like adverse effects (hypertension, hypokalemia) at higher or prolonged doses, so clinical translation requires dose control and monitoring (Asl & Hosseinzadeh, 2008; Pastorino et al., 2018).
- Systematic reviews and modern clinical appraisals conclude that both herbs have biological plausibility and preliminary supportive human data (immune biomarkers, symptom reports), but high-quality randomized controlled trials focused on respiratory clinical endpoints (exacerbation rates, lung function, steroid-sparing effects) remain sparse. Safety evaluation — especially for licorice products in populations at risk for hypertension, cardiovascular disease, or on potassium-wasting diuretics — is essential in clinical development (Fiore et al., 2005; Pastorino et al., 2018).

In sum, animal models provide mechanistic and efficacy signals; human data confirm immunomodulatory and symptomatic potential but are insufficient to support routine therapeutic recommendations without larger, well-designed respiratory trials (Mondal et al., 2011; IJBCP, 2017; Pastorino et al., 2018).

**Table 6. Representative preclinical and clinical studies**

| Study (author, year) | Model / design | Intervention (typical dose) | Key outcomes | Relevance |
|---|---|---|---|---|
| Wang et al., 2020 | OVA-induced allergic asthma (mouse) | Glycyrrhizic acid (GA); dose ranges in mice | ↓ airway inflammation, ↓ airway remodeling, ↓ IL-4/IL-5, improved histology | Preclinical evidence that GA reduces eosinophilic inflammation & remodeling |
| Liu et al., 2022 | OVA asthma model (mouse) | 18β-glycyrrhetinic acid (18β-GA) | Improved lung function, reduced inflammatory infiltration and cytokines | Supports 18β-GA as active anti-asthmatic agent |
| Yao et al., 2021 | Asthmatic mice; TGF-β1/Smad pathway study | Glycyrrhizic acid | Attenuated airway remodeling via TGF-β/Smad inhibition | Mechanistic evidence for anti-remodeling effect |

| | | | | |
|---|---|---|---|---|
| Srivastava et al., 2023 | COPD/airway inflammation model (rats/mice) | Ocimum leaf extract (OLE) 200–400 mg/kg | ↓ ROS, ↓ MDA, ↑ SOD/catalase/GPx, ↓ inflammatory markers, improved histopathology | Tulsi reduces oxidative stress and lung injury in COPD-like models |
| Lima et al., 2011 | Isolated rat tracheal preparation | Eugenol (1–2000 μM) | Concentration-dependent relaxation of tracheal smooth muscle (antispasmodic) | Mechanistic basis for immediate bronchodilator effect |
| Mondal et al., 2011 | RCT, healthy human volunteers (double-blind) | Tulsi leaf extract (oral; trial dose) | Immunomodulatory biomarker changes; improved antioxidant status | Human evidence of immune modulation; supports clinical translation |
| IJBCP (2017) | Single-blind crossover study in mild–moderate asthmatics | Ocimum sanctum capsules (200 mg twice daily) vs salbutamol | Significant improvements in FEV1 and PEFR over days 4–7 | Clinical signal for bronchodilator/symptom benefit; requires larger trials |

## 8. Translational and Personalized Medicine Perspectives

### 8.1 Integration into Modern Respiratory Therapeutics

Integrating *Ocimum sanctum* and *Glycyrrhiza glabra* into contemporary respiratory care requires standardized extracts, consistent quality control, and evidence from randomized clinical trials focused on meaningful patient outcomes (symptoms, lung function, exacerbation rates). Standardization should include quantification of marker compounds (e.g., eugenol, ursolic acid, glycyrrhizin) and stability/contaminant testing to ensure reproducible pharmacology across batches (Pattanayak et al., 2010; Pastorino et al., 2018). Formulation strategies (oral standardized extracts, inhaled preparations, or adjunct lozenges/syrups) must consider bioavailability and local versus systemic effects; an inhaled or aerosolized formulation could theoretically maximize airway exposure while minimizing systemic glycyrrhizin exposure, but would require safety and aerosolization studies.

### 8.2 Potential for Adjunct Therapy with Conventional Drugs

Both herbs show pharmacologic actions that complement existing treatments: antioxidant and anti-inflammatory activity (Tulsi) and corticosteroid-like and antiviral properties (licorice) that could augment inhaled corticosteroids or bronchodilators. Potential clinical goals include symptom reduction, decreased use of short-acting bronchodilators, fewer exacerbations, and steroid-sparing effects. However, licorice's inhibition of 11β-HSD2 (prolonging cortisol action) raises the possibility of pharmacodynamic interactions with systemic corticosteroids and risk of mineralocorticoid adverse effects (hypertension, hypokalemia); therefore concomitant use requires careful dose selection and monitoring of blood pressure and serum potassium (Monder et al., 1989; Pastorino et al., 2018). Drug–herb interaction assessment (with corticosteroids, diuretics, ACE inhibitors, and potassium-wasting agents) should be built into clinical development plans and post-marketing surveillance.

### 8.3 Considerations for Precision Medicine Approaches

Precision (or personalized) respiratory therapeutics stratify patients by measurable endotypes and biomarkers rather than syndrome alone. For *O. sanctum* and *G. glabra*, the highest translational yield is likely in well-phenotyped subgroups:

- **Type-2 high asthma (eosinophilic, FeNO-high):** licorice's apparent suppression of IL-4/IL-5 and Tulsi's anti-inflammatory effects suggest potential benefit; biomarkers such as blood eosinophils, fractional exhaled nitric oxide (FeNO), and sputum eosinophils could identify responders and serve as trial inclusion criteria and outcomes (Fahy, 2015).
- **Neutrophilic or mixed COPD/chronic bronchitis endotypes:** antioxidant and mucoregulatory effects (Tulsi + flavonoids from licorice) may be relevant where oxidative stress and neutrophil-driven inflammation predominate; biomarkers could include sputum neutrophils, plasma CRP, and oxidative stress markers (Bergeron & Boulet, 2006; Rahman & Adcock, 2006).
- **Exacerbation-prone patients with viral triggers:** glycyrrhizin's antiviral activity could be targeted to patients whose exacerbations have a viral precipitant; viral PCR panels and exacerbation phenotyping should inform trial design (Fiore et al., 2005; Cinatl et al., 2003).

Clinical development should therefore incorporate: baseline endotype stratification, prespecified biomarker-defined subgroups, pharmacokinetic/pharmacodynamic (PK/PD) profiling (including glycyrrhizin exposure), and safety monitoring plans (blood pressure, electrolytes). Adaptive trial designs or enrichment strategies (enrolling patients most likely to respond based on biomarkers) can increase trial efficiency and minimize patient exposure to ineffective interventions (Reddel et al., 2022).

### 8.4 Practical and Regulatory Considerations

- **Safety monitoring:** mandatory monitoring for mineralocorticoid effects from glycyrrhizin (BP, $K^+$) and documentation of concurrent medications. Dose limits for glycyrrhizin should follow safety data and regulatory guidance.
- **Quality and standardization:** Good Manufacturing Practice (GMP) production, validated assays for active markers, and batch-to-batch consistency.
- **Regulatory path:** depending on claims, these products could be developed as botanical drugs, adjunct therapeutics, or nutraceuticals—each pathway has distinct evidentiary and labeling requirements. High-quality randomized controlled trials demonstrating clinically meaningful benefit and safety are essential for medical claims (Pastorino et al., 2018).

## 9. Conclusion and Future Directions

### 9.1 Summary of Mechanistic Insights

*Ocimum sanctum* and *Glycyrrhiza glabra* provide complementary, multi-modal biological actions relevant to asthma and chronic bronchitis: antioxidant and anti-inflammatory effects, direct airway smooth-muscle relaxation (Tulsi), corticosteroid-modulating activity via 11β-HSD inhibition (licorice), cytokine suppression (↓IL-4, IL-5, ↓TNF-α), mucoregulatory activity, and antiviral potential (Cinatl et al., 2003; Pattanayak et al., 2010; Wang et al., 2020). Preclinical models show convincing proof-of-concept

for reduction of inflammation, remodeling, and airway hyperresponsiveness; human data show immunomodulatory and symptomatic signals but are insufficient to support routine clinical use without further trials.

### 9.2 Research Gaps and Emerging Opportunities

Priority research areas include:

1. **Randomized, standardized clinical trials** evaluating respiratory endpoints ($FEV_1$, exacerbation frequency, steroid-sparing effects) with well-characterized, standardized extracts.
2. **Dose-finding and PK/PD studies** especially for glycyrrhizin to define therapeutic windows that avoid mineralocorticoid toxicity.
3. **Biomarker-driven (precision) trials** that preselect patients by endotype (Type-2 high vs Type-2 low, neutrophilic) to identify responder populations.
4. **Formulation research** (e.g., inhaled vs oral) to maximize airway targeting and limit systemic exposure.
5. **Interaction and safety studies** addressing concurrent use with corticosteroids, diuretics, antihypertensives, and other common medications.
6. **Well-controlled combination (polyherbal) studies** to quantify synergy, additive effects, and safety when Tulsi and licorice are co-administered.

### 9.3 Outlook for Clinical Integration

With rigorous standardization, careful safety characterization, and biomarker-informed clinical trials, *O. sanctum* and *G. glabra* hold promise as adjunctive agents in respiratory medicine—particularly as targeted options for biomarker-defined patient subsets (e.g., Type-2 high asthma or exacerbation-prone, virus-triggered disease). However, pretentious therapeutic claims must await high-quality efficacy and safety data. Until then, clinicians and researchers should balance biological plausibility with the necessity of rigorous evidence and vigilant safety monitoring when considering these phytotherapeutics in practice or trials.

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Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-486-3

# Chapter 3: Cardiometabolic Risk Attenuation via Bioactive Constituents of Zingiber officinale and Allium sativum: An Integrative Approach to Endothelial Function and Lipid Regulation

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**Abstract**

Cardiometabolic disorders, characterized by dyslipidemia, endothelial dysfunction, hypertension, and insulin resistance, remain leading contributors to global morbidity and mortality. Bioactive phytoconstituents of *Zingiber officinale* (ginger) and *Allium sativum* (garlic) have demonstrated promising cardioprotective potential through multifaceted mechanisms. Ginger-derived compounds such as gingerols, shogaols, and paradols exhibit antioxidant, anti-inflammatory, and lipid-lowering effects, while garlic-derived allicin, ajoene, and S-allyl cysteine contribute to cholesterol regulation, vascular protection, and nitric oxide bioavailability. Integrative use of these botanicals has been shown to modulate lipid metabolism, enhance endothelial function, attenuate oxidative stress, and regulate inflammatory cascades, thereby reducing cardiometabolic risk. This review consolidates preclinical and clinical evidence, highlighting molecular pathways such as AMPK activation, NF-κB inhibition, and eNOS upregulation as central mediators of their synergistic actions. The findings underscore the therapeutic potential of *Zingiber officinale* and *Allium sativum* as adjuncts in the prevention and management of cardiometabolic diseases, warranting further translational and clinical investigations.

**Keywords:** Zingiber officinale, Allium sativum, cardiometabolic risk, endothelial function, lipid metabolism, bioactive phytoconstituents, oxidative stress, inflammation.

## 1. Introduction

Cardiometabolic diseases such as atherosclerosis, hypertension, dyslipidemia, diabetes mellitus and metabolic syndrome are widespread public health problems. These conditions are highly interdependent and they all raise the global burden of CVD, which is an ever increasing major cause of morbidity and mortality (World Health Organization [WHO], 2023). Prevalence of metabolic syndrome has skyrocketed and has affected close to one-third of adults in the developed and developing world alike leading to increased risk for both type 2 diabetes and cardiovascular-event related morbidity (Saklayen, 2018).

One of the central pathophysiological pathways underlying the cascade leading to cardiometabolic diseases is endothelial dysfunction, which can broadly be described by poor NO bioavailability and impaired vasodilation along with enhanced oxidative stress (Daiber et al., 2019). In addition, lipid

imbalance (increased LDL-C, decreased HDL-C and increased TG) promote atherogenesis by increased oxidation of lipids and endothelial inflammation (Ference et al., 2017). Collectively, they form a cascade of vascular damage, metabolic derangement and systemic inflammation.

The most recent therapeutic approaches to control cardiometabolic risk are mainly pharmaceutical, such as statins, antihypertensive drugs and antidiabetic agents. Although effective, continuous treatment was associated with side effects and only partial prevention of vascular complications (Huang et al., 2021). In traditional medicine, plant-derived multifunctional preparations are used since ages to cope up vascular health and metabolic equilibrium.

Of these, Zingiber officinale (ginger) and Allium sativum (garlic) are particularly researched when it comes to cardioprotective effects. Ginger contains bioactive constituents like gingerols and shogaols, with antioxidant, anti-inflammatory and vasodilatory properties (Mashhadi et al., 2013). Garlic Zcontains sulphur – diarrhoe-stricken stuff like allicin and S-allyl cysteine that make your body handle fat better, help the lining of blood vessels to tell flow what to do and reducing damage caused by oxygen (Ried, 2016). Considering their combined mechanisms (ginger mainly for vascular inflammation and inhibition of platelet's aggregation, while garlic refers to lipid metabolism and vasomotor reactivity), an integrated use of these two botanicals may represent effective strategies in the management of cardiometabolic risks.

## 2. Phytochemical Composition of *Zingiber officinale* and *Allium sativum*

### 2.1 Bioactive Constituents of Ginger (*Zingiber officinale*)

Ginger rhizomes contain a diverse array of bioactive phytochemicals, primarily phenolic compounds such as gingerols, shogaols, paradols, and zingerone. The most abundant bioactive compounds in fresh ginger, which can be attributed to both its pungent taste and powerful antioxidant and anti-inflammatory capabilities, are gingerols, with [6]-gingerol as the main form (Mashhadi et al., 2013). Shogaols are dehydration products of gingerols, formed during drying or thermal processing, and demonstrate enhanced bioactivity in comparison to their precursors (Bhattarai et al., 2001). Paradols, generated through hydrogenation of shogaols, also contribute to antioxidant activity. Zingerone, another thermally generated compound, is associated with anti-inflammatory, anti-obesity, and anti-cancer effects (Dugasani et al., 2010).

### 2.2 Bioactive Constituents of Garlic (*Allium sativum*)

Garlic is particularly rich in sulfur-containing compounds, which form upon crushing or chopping the cloves. The most notable among these is allicin, produced enzymatically from alliin via alliinase activity, which is highly unstable but exhibits potent antimicrobial, antioxidant, and cardioprotective properties (Borlinghaus et al., 2014). Other important sulfur compounds include ajoene, diallyl disulfide (DADS), S-allyl cysteine (SAC), and S-allyl mercaptocysteine (SAMC). These molecules contribute to garlic's lipid-lowering, anti-thrombotic, and vasoprotective activities (Amagase, 2006). Unlike allicin, SAC and SAMC are water-soluble and more stable, making them suitable for standardized formulations and clinical applications (Iciek et al., 2009).

### 2.3 Extraction Methods and Stability of Active Constituents

The stability and yield of these bioactives are highly dependent on extraction methods. In ginger, ethanolic and supercritical $CO_2$ extractions are efficient for recovering gingerols and shogaols, while aqueous extracts tend to favor polar compounds (Ali et al., 2008). Heat processing influences ginger composition significantly—drying enhances shogaol content, whereas prolonged heating reduces gingerol levels.

For garlic, raw preparation retains unstable allicin, while aged garlic extract (AGE) is enriched with stable SAC and SAMC due to prolonged ethanol extraction (Amagase, 2006). Steam distillation yields garlic oil rich in diallyl sulfides, but volatile components degrade quickly under high temperature and oxygen exposure (Borlinghaus et al., 2014). These factors highlight the importance of standardized extraction protocols to ensure reproducibility in pharmacological studies.

### 2.4 Synergistic Interactions Among Phytochemicals

The therapeutic efficacy of ginger and garlic cannot be attributed to single compounds alone; instead, synergistic interactions among phytochemicals play a crucial role. In ginger, gingerols and shogaols work additively to enhance antioxidant and anti-inflammatory responses (Dugasani et al., 2010). Similarly, garlic sulfur compounds act synergistically to modulate lipid metabolism, inhibit platelet aggregation, and improve endothelial function (Iciek et al., 2009). Such synergism suggests that whole extracts or combination formulations may offer broader cardiometabolic protection than isolated compounds.

**Table 1. Key Bioactive Constituents of Ginger and Garlic with Their Biological Roles**

| Plant | Major Compounds | Stability | Key Biological Activities |
|---|---|---|---|
| *Zingiber officinale* (Ginger) | Gingerols, Shogaols, Paradols, Zingerone | Gingerols unstable with heat; shogaols and zingerone increase upon processing | Antioxidant, anti-inflammatory, vasodilatory, anti-obesity |
| *Allium sativum* (Garlic) | Allicin, Ajoene, Diallyl disulfide, S-allyl cysteine (SAC), S-allyl mercaptocysteine (SAMC) | Allicin unstable; SAC and SAMC highly stable in aged extracts | Lipid-lowering, anti-thrombotic, vasoprotective, immunomodulatory |

## 3. Pathophysiological Basis of Cardiometabolic Risk

### 3.1 Endothelial Dysfunction

Endothelial dysfunction represents a central mechanism in the development of cardiometabolic disorders. The endothelium regulates vascular tone, platelet activity, and leukocyte adhesion primarily through the production of nitric oxide (NO). Reduced NO bioavailability, often due to increased oxidative stress, impairs vasodilation and promotes vascular stiffness (Daiber et al., 2019). Reactive oxygen species (ROS) generated by NADPH oxidases, mitochondrial dysfunction, and uncoupled endothelial nitric oxide synthase (eNOS) further exacerbate oxidative damage. This dysfunctional state not only accelerates atherosclerotic plaque formation but also enhances thrombotic risk.

### 3.2 Dyslipidemia and Lipid Oxidation in Atherogenesis

Dyslipidemia, characterized by elevated low-density lipoprotein cholesterol (LDL-C), triglycerides, and reduced high-density lipoprotein cholesterol (HDL-C), is a well-established driver of atherosclerosis (Ference et al., 2017). Oxidized LDL (ox-LDL) plays a particularly pathogenic role by promoting foam cell formation, endothelial activation, and vascular inflammation. Lipid oxidation amplifies the inflammatory milieu, recruits monocytes to the vascular wall, and fosters plaque instability (Gisterå & Hansson, 2017). This lipid-driven mechanism represents the biochemical foundation of atherogenesis.

### 3.3 Chronic Low-Grade Inflammation in Metabolic Syndrome

Metabolic syndrome, a cluster of obesity, insulin resistance, hypertension, and dyslipidemia, is strongly associated with chronic low-grade inflammation. Adipose tissue expansion leads to macrophage infiltration and secretion of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) (Hotamisligil, 2017). These mediators impair insulin signaling, promote endothelial dysfunction, and aggravate vascular injury. Inflammatory stress thereby serves as a bridge between metabolic disturbances and cardiovascular disease progression.

### 3.4 Molecular Pathways in Cardiometabolic Dysregulation

Several molecular pathways are central to the pathogenesis of cardiometabolic disorders:

- **NF-κB (Nuclear Factor kappa B):** A master regulator of inflammation that upregulates cytokines, adhesion molecules, and oxidative enzymes, amplifying vascular injury (Baker et al., 2011).
- **AMPK (AMP-activated protein kinase):** A key energy sensor that promotes lipid oxidation, improves insulin sensitivity, and suppresses inflammation; impaired AMPK signaling is linked to obesity and diabetes (Hardie et al., 2012).
- **eNOS (Endothelial Nitric Oxide Synthase):** Critical for NO generation and vascular homeostasis. eNOS uncoupling under oxidative stress shifts its role from NO production to ROS generation (Forstermann & Sessa, 2012).
- **PPARs (Peroxisome Proliferator-Activated Receptors):** Nuclear receptors that regulate lipid metabolism, glucose homeostasis, and inflammation; dysregulation contributes to insulin resistance and atherogenesis (Ahmadian et al., 2013).
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**Table 2. Key Pathophysiological Mechanisms Underlying Cardiometabolic Risk**

| Mechanism | Molecular Mediators | Consequences |
|---|---|---|
| Endothelial Dysfunction | ROS, ↓NO, uncoupled eNOS | Impaired vasodilation, vascular stiffness, thrombosis |
| Dyslipidemia & Lipid Oxidation | LDL-C, ox-LDL | Foam cell formation, plaque buildup, vascular inflammation |
| Chronic Low-Grade Inflammation | TNF-α, IL-6, CRP, macrophages | Insulin resistance, vascular injury, atherosclerosis |

| | | |
|---|---|---|
| Molecular Pathways | NF-κB, AMPK, eNOS, PPARs | Pro-inflammatory signaling, impaired metabolism, oxidative stress |

## 4. Effects of *Zingiber officinale* on Endothelial Function

### 4.1 Overview

*Zingiber officinale* (ginger) exerts multifaceted actions that are relevant to vascular health. Its principal phenolic constituents—gingerols, shogaols and related derivatives—have demonstrated antioxidant, anti-inflammatory, and vasomodulatory activities in cellular, animal, and human studies. The combined biochemical effects translate into improved endothelial homeostasis through preservation of nitric oxide (NO) signaling, reduction of oxidative stress, and attenuation of pro-thrombotic processes (Ali et al., 2008; Mashhadi et al., 2013).

### 4.2 Antioxidant and Anti-inflammatory Properties

Ginger's phenolic compounds scavenge reactive oxygen species (ROS) and downregulate pro-inflammatory mediators. In vitro and animal experiments show that [6]-gingerol and [6]-shogaol reduce markers of oxidative damage (lipid peroxidation, protein carbonylation) and inhibit the expression of inflammatory cytokines (e.g., TNF-α, IL-6) and inducible enzymes such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) (Dugasani et al., 2010; Mashhadi et al., 2013). By lowering oxidative burden and inflammatory signaling, ginger preserves endothelial cell integrity and function—an effect conceptually aligned with therapeutic strategies that target vascular oxidative stress (Forstermann & Sessa, 2012).

### 4.3 Enhancement of NO Bioavailability and Endothelium-Dependent Vasodilation

Nitric oxide is central to endothelial-dependent vasodilation and vascular homeostasis. Preclinical studies indicate that ginger constituents can enhance NO bioavailability through two complementary mechanisms: (1) upregulation or activation of endothelial nitric oxide synthase (eNOS) and (2) indirect preservation of NO by decreasing ROS that otherwise scavenge NO (thereby preventing NO breakdown and eNOS uncoupling) (Ali et al., 2008; Dugasani et al., 2010). Animal models of hypertension and endothelial dysfunction have reported improved vasodilatory responses to acetylcholine and increased NO-mediated relaxation following ginger extract administration, supporting a physiologically meaningful improvement in endothelial function (Mashhadi et al., 2013).

Clinical evidence addressing NO-mediated vasodilation in humans is limited but suggestive. Small randomized and nonrandomized trials have reported modest improvements in brachial artery flow-mediated dilation or surrogate markers of endothelial health after short-term ginger supplementation; however, trial sizes, doses, and preparations vary, and results are not yet conclusive (Ali et al., 2008; Mashhadi et al., 2013). Well-powered, standardized clinical trials using validated endothelial function endpoints are needed to confirm translational relevance.

### 4.4 Inhibition of Platelet Aggregation

Ginger exhibits antiplatelet and anti-thrombotic properties in preclinical models. In vitro assays demonstrate that ginger extracts and isolated gingerols inhibit platelet aggregation induced by ADP and collagen and reduce thromboxane synthesis—actions that may lower the propensity for thrombus formation on dysfunctional endothelium (Dugasani et al., 2010). Animal studies corroborate reduced thrombosis tendency after ginger administration. Human data are sparse but indicate that high doses of concentrated ginger extracts can affect platelet function tests; accordingly, caution is warranted when combining potent ginger preparations with antiplatelet or anticoagulant drugs (Mashhadi et al., 2013).

### 4.5 Preclinical and Clinical Evidence — Summary

Preclinical (in vitro and animal) literature consistently supports antioxidant, anti-inflammatory, NO-preserving, vasodilatory, and antiplatelet effects of ginger phytochemicals. These findings provide biologically plausible mechanisms by which ginger may protect endothelial function and reduce vascular risk (Ali et al., 2008; Dugasani et al., 2010).

Clinical research in humans remains limited in scale. Available randomized controlled trials and small intervention studies report mixed but generally favorable effects on blood pressure, circulating inflammatory markers, and surrogate markers of vascular function; heterogeneity in ginger form (fresh, powdered, extracts), dose, duration, and endpoints hinders firm conclusions (Mashhadi et al., 2013). Safety data indicate good tolerability for culinary doses; however, concentrated extracts at pharmacological doses can alter platelet aggregation and may interact with antithrombotic medications (Mashhadi et al., 2013). Thus, while preclinical evidence is robust, translation to routine clinical recommendation awaits larger, standardized clinical trials.

**Table 3. Biological Effects of *Zingiber officinale* on Endothelial Function and Evidence Level**

| Biological Action | Mechanistic Rationale | Main Preclinical Findings | Clinical Evidence & Notes |
|---|---|---|---|
| Antioxidant activity | Scavenging ROS; reducing lipid peroxidation | Reduced oxidative markers in cells/animals (gingerols/shogaols). (Dugasani et al., 2010) | Small trials report lowered oxidative biomarkers; evidence limited. (Mashhadi et al., 2013) |
| Anti-inflammatory effects | ↓ NF-κB signaling; ↓ pro-inflammatory cytokines | Decreased TNF-α, IL-6, COX-2 in models. (Dugasani et al., 2010) | Modest reductions in CRP/IL-6 in heterogeneous small studies. (Mashhadi et al., 2013) |
| ↑ NO bioavailability / vasodilation | eNOS activation/preservation; decreased NO scavenging by ROS | Improved endothelium-dependent relaxation in animal models. (Ali et al., 2008) | Limited human data on flow-mediated dilation; promising but inconclusive. (Ali et al., 2008) |
| Antiplatelet effects | Inhibition of platelet aggregation and thromboxane synthesis | Inhibition of ADP/collagen-induced aggregation in vitro; reduced thrombosis in | High-dose extracts can affect platelet tests; clinical safety caution with anticoagulants. (Mashhadi |

| | | | |
|---|---|---|---|
| | | animals. (Dugasani et al., 2010) | et al., 2013) |

## 5. Effects of *Allium sativum* on Endothelial Function

### 5.1 Overview

Derived from the bulbous root of garlic (Allium sativum), provides vascular benefits by several nuanced, complementary mechanisms, particularly gaseous signaling molecules [hydrogen sulfide (H(2)S) and nitric oxide (NO)] modulation and antioxidant activity that suppresses low-density lipoprotein (LDLs) oxidation and also affects directly vascular cells to have anti-atherosclerotic effects. These effects have been observed in cellular and animal models, as well as human intervention studies of variable size and quality (Borlinghaus et al., 2014; Benavides et al., 2007).

### 5.2 Modulation of Vascular Tone via $H_2S$ and NO Signaling

Sulfur compounds include, but are not limited to, garlic-based sulfur-like compounds (e.g., polysulfides) that can serve as hydrogen sulfide (H2S) precursors or donors— a gasotransmitter exerting relaxation of vascular smooth muscle which cooperates the NO-mediated vasodilation pathways (Benavides et al., 2007). $H_2S$ activates $K^+$ channels and decreases intracellular $Ca^{2+}$ to induce vasorelaxation of vascular smooth muscle, while crosstalk between $H_2S$ and NO pathways may strengthen endothelial-dependent vasodilation. It is worth mentioning that garlic preparations have also been related to beneficial modulation of endothelial NO bioavailability (through preservation from oxidative inactivation, but also indirectly by counteracting inflammation and providing antioxidant activity supporting eNOS function) (Borlinghaus et al., 2014; Iciek et al., 2009).

### 5.3 Inhibition of Oxidative Stress and LDL Oxidation

(12–14) Oxidized modification of LDL is one of the initial stages in atherogenesis. Components of garlic have been shown to exert antioxidant activity both in vitro and in vivo, by scavenging ROS and activating cellular antioxidants thereby reducing LDL oxidation and foam cell formation (Iciek et al., 2009). Aged garlic preparations, which are enriched in stable sulfur amino acid derivatives (e.g., S-allyl cysteine), are particularly noted for consistent antioxidant activity that is more amenable to clinical standardization (Amagase, 2006; Borlinghaus et al., 2014).

### 5.4 Anti-atherosclerotic and Vasoprotective Mechanisms

Beyond gaseous signaling and antioxidant actions, garlic influences key processes in atherogenesis: it attenuates platelet aggregation, reduces vascular smooth muscle cell proliferation, inhibits macrophage-driven inflammation within plaques, and favorably modulates endothelial adhesion molecule expression (Borlinghaus et al., 2014). These pleiotropic effects combine to slow plaque development and stabilize existing lesions in preclinical models. Human studies, including randomized trials and meta-analyses, report modest reductions in surrogate atherosclerotic risk markers (e.g., blood pressure, LDL cholesterol)

and improvements in some measures of vascular health, although heterogeneity in preparations and dosing remains a limitation (Ried, 2016).

### 5.5 Preclinical and Clinical Evidence — Summary

Preclinical data robustly support multiple vasoprotective mechanisms for garlic, from $H_2S$/NO signaling to antioxidant and anti-inflammatory effects (Benavides et al., 2007; Iciek et al., 2009). Clinical trials and systematic reviews indicate modest but clinically relevant reductions in blood pressure and lipids with certain standardized garlic preparations; however, variability in garlic type (raw, oil, aged extract), dose and study design means that effect sizes are mixed and not uniformly reproducible (Amagase, 2006; Ried, 2016). Safety profiles are generally favorable at dietary doses, but clinicians should be alert to potential interactions with antiplatelet or anticoagulant therapies.

## 6. Lipid Regulation by Ginger and Garlic

### 6.1 Impact on Cholesterol Biosynthesis and Absorption

Bioactive compounds in ginger and garlic influence key steps in cholesterol metabolism. Gingerols and shogaols inhibit HMG-CoA reductase activity, reducing endogenous cholesterol synthesis, whereas allicin and related sulfur compounds in garlic decrease intestinal cholesterol absorption and enhance fecal sterol excretion (Ali et al., 2008; Iciek et al., 2009). These mechanisms collectively contribute to improved serum lipid profiles and decreased cardiovascular risk.

### 6.2 Regulation of LDL, HDL, VLDL, and Triglycerides

Ginger and garlic influence the key lipid-metabolizing enzymes. HMG-CoA reductase inhibitors lower cholesterol biosynthesis, and CETP modulation enhances HDL function. Lipoprotein lipase activation promotes triglyceride removal from circulation, which results in enhanced lipid homeostasis (Ali et al., 2008; Borlinghaus et al., 2014).

Consistently with such mechanistic effects, clinical experience suggests that plant-based interventions can be added to standard therapy. For example, Prakash, Goel and Verma (2020) in type-2 diabetes patients treated with metformin along with sitagliptin or glimepiride found improvement not only in the parameters of glycemic control but also of lipid so that a balance could be created between glucose and lipid metabolism. Furthermore, Prakash et al., (2024) evidenced that T.arjuna significantly decreased fasting blood sugar and lipids in diabetic patients, thus illustrating its antihyperglycemic and hypolipidemic double role.

### 6.3 Modulation of Lipid Metabolism Enzymes

Ginger and garlic modulate the function of important lipid metabolic enzymes. Inhibition of HMG-CoA reductase decreases cholesterol biosynthesis, and cholesteryl ester transfer protein (CETP) modulation improves HDL function. LPL activation results in increased clearance of triglycerides from circulation, along with better lipid homeostasis (Ali et al., 2008; Borlinghaus et al.

Consistent with these mechanistic effects, clinical evidence suggests that plant-based interventions can serve as adjuncts to traditional therapy. For example, Prakash, Goel, Verma (2020) also assessed patients of type-2 diabetes on metformin along with either sitagliptin or glimepiride and observed an improvement in glycaemic control and lipid parameters highlighting the metabolic interrelation between glucose and lipid. Equally, Prakash et al: (2024) revealed that The T. arjuna highly significantly reduces the fasting blood glucose and lipid of patient suffering from diabetes mellitus, which reflects bitherapeutic potential as antihyperglycemic and hypolipidemic properties into one single plant.

### 6.4 Comparative Effects and Synergistic Benefits

Ginger mainly has antioxidant and anti-inflammatory actions, which indirectly ameliorate lipid metabolism, whereas garlic possesses both direct lipid-lowering and endothelial-protective properties. Co-complementation approaches could provide synergistic advantages through the combined lowering of oxidative stress, inhibition of cholesterol biosynthesis, improvement in HDL function and lipid handling by endothelium. Herbal drugs combined with lifestyle modification and/or modern pharmacotherapy might therefore offer a multipronged approach to the reduction of cardiometabolic risk (Mashhadi et al., 2013; Prakash, Sehgal, Bajaj, & Singh, 2016; Prakash, Goel, Giri, & Goel 2024).

**Table 4. Comparative Clinical Effects of Herbal and Conventional Agents on Lipid Parameters**

| Intervention | Target Population | Key Findings | Reference |
|---|---|---|---|
| Ginger extract | Dyslipidemic adults | ↓ LDL, ↓ TG, ↑ HDL | Mashhadi et al., 2013 |
| Garlic (aged extract) | Hypertensive/dyslipidemic adults | ↓ LDL, ↓ TG, ↑ HDL | Borlinghaus et al., 2014 |
| Terminalia arjuna | Hyperlipidemic adults | ↓ TC, ↓ LDL, ↑ HDL | Prakash, Sehgal, Bajaj, & Singh, 2016 |
| Terminalia arjuna | Hypertriglyceridemic adults | ↓ TG, ↑ HDL | Prakash, 2019 |
| Terminalia arjuna vs Sitagliptin | T2DM adults | ↓ FBG, ↓ TC, ↓ LDL | Prakash, Goel, Giri, & Goel, 2024 |

## 7. Integrative Mechanistic Insights

### 7.1 Crosstalk Between Endothelial Function and Lipid Regulation

The endothelial function and lipid metabolism are interconnected to each other closely in the development of cardiometabolic diseases. In part, this is caused by endothelial dysfunction and oxidative lipid modification that drive atherosclerosis whereas dyslipidemia enhances endothelial damage via upregulation of reactive oxygen species (ROS) and inflammatory signaling pathways (Daiber et al., 2019; Ference et al., 2017). Both ginger and garlic are suggested to influence this crosstalk by the combined effects of increased NO bioavailability, reduced oxidative stress and modulated circulating lipid profile which in turn interferes with the loop between dyslipidemia and vascular injury.

### 7.2 Combined Roles of Antioxidant, Anti-inflammatory, and Lipid-Lowering Mechanisms

The cardiometabolic benefits of ginger and garlic arise from a coordinated action of multiple biochemical pathways. Gingerols, shogaols, and sulfur compounds exert potent antioxidant effects, scavenging ROS

and preserving NO signaling (Mashhadi et al., 2013; Borlinghaus et al., 2014). Anti-inflammatory effects through down-regulation of NF-κB lead to decreased vascular inflammation and cytokine-induced injury of the endothelium. At the same time, HMG-CoA reductase inhibition, lipoprotein lipase activity increase and LDL oxidation decrease as a whole improve lipid profile (Ali et al., 2008; Iciek et al., 2009). These additive and synergistic actions of similar mechanisms imply that botanical interventions could exert synergistic or adding benefits on cardioprotection.

### 7.3 Systems Biology Perspective on Cardiometabolic Protection

From a systems biology perspective, both ginger and garlic act on the interconnective nodes of metabolic, inflammatory and vascular networks. By engaging signaling pathways including AMPK, eNOS, PPARs and antioxidant response elements, these phytochemicals may act in concert to regulate energetics homeostasis, lipid metabolism and vascular tone (Ahmadian et al., 2013; Hardieet al., 2012). Computational simulation of these interactions can generate synergistic targets for combination therapy and optimize dosing strategies to maximize protection to endothelial and metabolic functions.

### 7.4 Potential Epigenetic and Gut Microbiome-Mediated Modulation

Recent studies have suggested that some bioactive components in ginger and garlic might also induce epigenetic changes, such as alterations in DNA methylation or histone acetylation which are associated with the regulation of genes relevant to inflammation, lipid metabolism and endothelial function (Jia et al., 2019). Furthermore, gut microbiota may biotransform phytochemicals into more bioactive derivatives that augment systemic vascular and metabolic effects. This gut–vascular axis offers a new explanation for the long-term cardiometabolic effects of diet-derived botanicals.

## 8. Translational and Clinical Perspectives

### 8.1 Human Clinical Trials on Ginger and Garlic Supplementation

The effects of ginger and garlic on cardiovascular and metabolic endpoints have been evaluated in several clinical trials and meta-analyses. Ginger supplementation has been associated with modest reductions in triglycerides, LDL cholesterol, and blood pressure, whereas garlic (particularly aged garlic extract) shows consistent LDL-lowering and blood pressure-reducing effects in adults with dyslipidemia or hypertension (Ried, 2016; Mashhadi et al., 2013). Trial heterogeneity in sample size, preparation, dosage, and duration, however, limits the generalizability of results.

### 8.2 Dose, Bioavailability, and Formulation Considerations

The therapeutic efficacy of ginger and garlic is influenced by formulation and bioavailability. Gingerols and shogaols in powdered or fresh rhizomes may differ in stability and absorption from concentrated extracts or encapsulated forms. Garlic bioactives such as allicin are unstable, whereas S-allyl cysteine in aged garlic extract is more bioavailable and suitable for standardized dosing (Amagase, 2006; Borlinghaus et al., 2014). Clinically effective doses vary but generally fall within 1–5 g/day for raw/dried ginger and 600–1200 mg/day for standardized garlic extracts.

### 8.3 Safety Profile, Adverse Effects, and Herb–Drug Interactions

Both botanicals are generally well tolerated at dietary doses. High-dose or concentrated preparations may cause gastrointestinal discomfort or interact with anticoagulants, antiplatelet drugs, or statins, leading to potential bleeding risk or additive lipid-lowering effects (Ried, 2016; Iciek et al., 2009). Clinicians should assess individual risk and monitor relevant biomarkers when recommending supplementation.

### 8.4 Potential Role in Integrative and Personalized Medicine

Ginger and garlic supplementation represents a promising adjunctive strategy in integrative cardiometabolic management. Personalized approaches considering genotype, metabolic phenotype, gut microbiota composition, and concomitant medications can optimize efficacy and safety. Integration into diet-based interventions or polyherbal formulations may enhance adherence and clinical outcomes in patients at elevated cardiometabolic risk.

## 9. Conclusion and Future Directions

### 9.1 Summary of Evidence for Cardiometabolic Risk Reduction

Cumulative preclinical and clinical evidence indicates that ginger and garlic improve endothelial function, reduce oxidative stress, modulate inflammatory signaling, and favorably influence lipid profiles. Their multifunctional mechanisms—including antioxidant, anti-inflammatory, NO- and $H_2S$-mediated vasodilation, and lipid regulation—provide a biological rationale for cardiometabolic risk attenuation.

### 9.2 Gaps in Knowledge and Limitations of Current Research

Despite promising evidence, limitations include heterogeneity in study designs, small sample sizes, variability in botanical preparations, limited mechanistic human data, and lack of long-term cardiovascular outcomes. Further studies are required to standardize formulations, clarify dose–response relationships, and establish mechanistic biomarkers.

### 9.3 Emerging Technologies and Future Prospects

Innovations such as nanodelivery systems, encapsulation, and polyherbal synergistic formulations may enhance bioavailability, stability, and targeted delivery of bioactive compounds. Epigenetic modulation and microbiome-targeted interventions also represent promising areas for research. Well-designed, multicenter clinical trials with mechanistic endpoints are needed to translate these findings into evidence-based dietary and therapeutic recommendations.

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Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-486-3

# Chapter 4: Neuroprotective Interventions with Camellia sinensis and Withania somnifera: Molecular and Antioxidant Strategies Against Cognitive Decline and Neurodegeneration

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**Abstract**

Neurodegenerative disorders, including Alzheimer's and Parkinson's disease, are characterized by progressive neuronal loss, oxidative stress, mitochondrial dysfunction, and impaired synaptic signaling. Among natural phytotherapeutics, *Camellia sinensis* (green tea) and *Withania somnifera* (Ashwagandha) have emerged as promising neuroprotective agents due to their potent antioxidant, anti-inflammatory, and cognitive-enhancing properties. Bioactive polyphenols such as epigallocatechin-3-gallate (EGCG) from *C. sinensis* and withanolides from *W. somnifera* modulate key molecular pathways, including Nrf2/ARE, NF-κB, PI3K/Akt, and MAPK, thereby attenuating oxidative stress and neuroinflammation. Preclinical and clinical studies suggest that these phytochemicals enhance neuronal survival, promote synaptic plasticity, reduce amyloid-β aggregation, and restore mitochondrial homeostasis Also, their synergistic antioxidant and immunomodulatory effects offer perspectives for integrative approaches to cognitive decline. This chapter provides an overview of the molecular areas, therapeutic potential and translational follows-up of C. sinensis and W. somnifera on neurodegeneration as a neuroprotective agent in this area.

**Keywords:** Camellia sinensis, Withania somnifera, neuroprotection antioxidants cognitive decline neurodegeneration molecular pathways oxidative stress polyphenols withanolides..

## 1. Introduction

Neurodegenerative diseases (NDs) such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS) are a serious challenge for global health caused by their progressive course and the absence of curative drugs. The incidence and prevalence of these diseases are growing, largely driven by the increase in life expectancy, thus becoming one of the most urgent problems in neurology and public health (Feigin et al., 2019). Dementia alone is estimated to be affecting more than 55 million people worldwide and almost 10 million new cases occur annually most of which are AD related (WHO, 2021). PD also has a prevalence of over 8.5 million people worldwide and is expected to increase by two-fold before 2040 (Dorsey et al., 2018). The central pathological feature

in neurodegenerative diseases is the disequilibrium between endogenous ROS production and endogenous antioxidant defense system resulting in oxidative stress.

Oxidative stress contributes to lipid peroxidation, protein misfolding, mitochondrial dysfunction, and neuronal apoptosis (Cheignon et al., 2018). In addition, neuroinflammation, largely mediated by microglial activation and pro-inflammatory cytokines, plays a synergistic role in accelerating neurodegeneration (Leng & Edison, 2021). . Taken together, oxidative stress and inflammation play a crucial role in mediating neuronal death, synaptic dysfunction and cognitive impairment which bridges the gap between the molecular pathways to clinical alterations in memory dysfunction motorics as well as behavior.

Given the multifactorial etiology of these conditions, current pharmacological interventions such as cholinesterase inhibitors for AD or dopaminergic agents for PD provide only symptomatic relief rather than halting disease progression (Yiannopoulou & Papageorgiou, 2020). This deficiency has led to the study of additional neuroprotective approaches, especially those naturally occurring and endowed with antioxidant, anti-inflammatory, and neuromodulatory effects. Cognitive well-being has been promoted for centuries by traditional medicinal systems, such as Ayurveda (in India) and Traditional Chinese Medicine (TCM), which opt for plant-based therapies. These have become scientific validated and globally accepted approaches as adjuvant therapy for neuro-degeneration in past decades (Uddin et al., 2020).

Two of naturally occurring agents, which could be particularly interesting are Camellia sinensis (green tea) and Withania somnifera (ashwagandha). Green tea polyphenols, especially epigallocatechin gallate (EGCG), have been reported to attenuate oxidative stress, prevent β-amyloid polymerization and increase synaptic plasticity (Mandel & Youdim, 2012). Potential bioactive ingredients of ashwagandha, including withanolides, also have adaptogenic and antioxidant effects, as well as neurotropic effects that can help to guard against brain cell damage so your mind stays sharp—regardless of which decade you are in (Dar et al., 2015). The combination of these pharmacological aspects place both of the plants in an important role for the chemopreventive and chemotherapeutic approaches to be used in neurodegenerative diseases.

This chapter will document the molecular and antioxidant approaches of which Camellia sinensis and Withania somnifera exercise neuroprotective. Its phytochemistry, mechanisms of action, supporting experimental and clinical evidence as well as difficulties to translate preclinical discoveries into clinical uses will be discussed. In emphasizing their therapeutic potential, this chapter draws attention to the need for combining traditional wisdom with modern neuropharmacological knowledge in managing cognitive decline and neurodegeneration.

## 2. Phytochemistry of *Camellia sinensis* and *Withania somnifera*

### 2.1. *Camellia sinensis*

The leaves of Camellia sinensis (green tea) are consumed the most universally all over the world and consist significantly of polyphenolic compounds which contribute to its neuroprotective properties. The most abundant components are the catechins, especially epigallocatechin gallate (EGCG), epicatechin gallate (ECG), epigallocatechin (EGC), and epicatechin (EC). These catechins are potent antioxidants that can scavenge reactive oxygen species, reduce lipid peroxidation and protect proteins and DNA against

damage (Cabrera eal., 2006). The most potent of these is EGCG and it represents approximately 50–60% of the total catechin content (Mandel & Youdim, 2012).

Other bioactive compounds compre¬hend theaflavins generated during black tea fermentation, caffeine with weak central stimulatory effect and L-theanine, an amino acid that is related to relaxation and attention acceleration through mediation of proteins such as dopamine, serotonin and gamma-aminobutyric acid (GABA) modulation (Unno et al., 2018). These components act together in a synergism, of which catechin antioxidants as well as anti-amyloid compounds and caffeine/theanine stimulation is related with better cognitive performance enhancement and brain protection.

### 2.2. *Withania somnifera*

*Withania somnifera*, also known as ashwagandha or Indian ginseng) is a major herb in Ayurveda prized for its adaptogen and neuroprotective affect. its major active components are withanolides, a group of steroidal lactones that exert antioxidant, anti-inflammatory and anti-apoptotic effects (Dar et al., 2015). Some compounds in the extract such as withanolide A and withanoside IV were reported to improve neurite outgrowth and synaptic regeneration that resulting in neuroregeneration (Kuboyama et al., 2005).

Furthermore, sitoindosides (glycowithanolides) are immunomodulators and antioxidants which protect from oxidative stress mediated neuronal damage. Alkaloids are found in much lower concentration but they too contribute to the pharmacological profile of the plant (anti-stress and cognitive enhancing activities) (Singh et al., 2011). These compounds act together to repair neurons, modulate the hypothalamic–pituitary–adrenal (HPA) axis and enhance cognitive resilience in neurodegenerative situations..

### 2.3. Comparative Phytochemical Insights

*Camellia sinensis and Withania somnifera* are rich in various bioactive molecules which could provide neuroprotection through anti-oxidant and anti-inflammatory mechanisms. While green tea catechins are predominantly free radical scavengers and modulators of amyloid aggregation withanolides from ashwagandha help in neuronal regeneration and synaptic plasticity (Mandel & Youdim, 2012; Dar et al., 2015).

Remarkably, they share similar properties in limiting oxidative stress and influencing neurotransmitters, though by complementary means: C. sinensis has potent polyphenolic antioxidant activity, while *W. somnifera* is characterized by adaptogenic and neuroregenerative effects. This implies the possibility of their synergy during co-administration, where while green tea catechins antagonize neuronal damage, ashwagandha facilitates recovery and repair.

**Table 1. Key Bioactive Constituents of *Camellia sinensis* and *Withania somnifera* and Their Neuroprotective Roles**

| Plant | Major Constituents | Neuroprotective Actions |
|---|---|---|
| *Camellia sinensis* | Catechins (EGCG, EGC, | Antioxidant activity, inhibition of β-amyloid aggregation, |

| | | |
|---|---|---|
| | ECG, EC) | mitochondrial protection |
| | Theaflavins | Free radical scavenging, anti-inflammatory effects |
| | Caffeine | Mild CNS stimulation, cognitive enhancement |
| | L-theanine | Neurotransmitter modulation (GABA, dopamine, serotonin), stress reduction |
| *Withania somnifera* | Withanolides | Neuroregeneration, anti-apoptotic, anti-inflammatory |
| | Sitoindosides | Antioxidant, immunomodulatory effects |
| | Alkaloids | Stress reduction, cognitive improvement |

## 3. Mechanistic Insights into Neuroprotection

Camellia sinensis and Withania somnifera provide neuroprotection via various molecular pathways including oxidative stress, mitochondrial function, inflammation, synaptic plasticity and protein aggregation. These are complementary approaches to pathogenesis of neurodegenerative diseases.

### 3.1. Antioxidant and Free Radical Scavenging Effects

Antioxidant capacities are a major mode through which the botanicals confer neuroprotection. Catechins of Camellia sinensis, specifically EGCG, are known to function as direct scavengers against reactive oxygen species (ROS) and reactive nitrogen species (RNS), thus preventing oxidative damage to lipids, proteins and nucleic acids (Mandel & Youdim, 2012). In addition, EGCG enhances the activity of endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (Gupta & Verma, 2010).

Similarly, Withanolides and sitoindosides from Withania somnifera induce antioxidant defense mechanisms including Nrf2/ARE signaling cascade, which in turn causes an increased transcription of cytoprotective enzymes (Dar et al., 2015). This bivalent antioxidant behavior is responsible for keeping the oxidative stress-induced apoptosis and neuronal degeneration under control.

### 3.2. Modulation of Mitochondrial Dysfunction

Mitochondrial dysfunction is a key driver of neuronal death in neurodegenerative diseases. EGCG has been reported to improve mitochondrial energy metabolism by maintaining ATP production and stabilizing the mitochondrial membrane potential (Wu et al., 2012). It also inhibits the release of cytochrome c and prevents activation of caspase-dependent apoptotic pathways.

Withania somnifera extracts offer mitochondrial protection by decreasing oxidative-induced damage to mtDNA and mt proteins leading to intact bioenergetics and antiapoptosis (Kumar et al., 2010). This process increases neuronal resistance to chronic stress and neurotoxicity.

### 3.3. Anti-inflammatory and Immunomodulatory Mechanisms

Neuroinflammation, mainly microglial activation and proinflammatory cytokines mediated, facilitates neuronal degradation. Green tea polyphenols suppress the expression of proinflammation mediators, including NF-κB, COX-2, TNF-α, and IL-1β to reduce inflammatory cascades in the brain (Singh et al., 2011).

Ashwagandha compounds exert immunomodulatory effects by suppressing microglial overactivation and reducing pro-inflammatory cytokine secretion. Withanolide A, in particular, attenuates NF-κB signaling and lowers iNOS and COX-2 expression, providing neuroprotection against chronic inflammation (Dar et al., 2015). Together, these effects alleviate neuroinflammation, protecting neurons from secondary damage.

### 3.4. Neurotrophic and Synaptic Plasticity Enhancement

Neurodegenerative diseases are often associated with impaired synaptic plasticity and reduced levels of neurotrophic factors. Catechins of green tea increase BDNF signaling, leading to neuron survival, neurogenesis and synaptic restoration (Mandel et al. 2006)

However, Withania somnifera also increases neurotrophic support. Withanosides also promote both neurite outgrowth and dendrite branching, which could facilitate synaptic plasticity and memory improvement (Kuboyama et al., 2005). These characteristics indicate a likely beneficial role in counteracting age- and neurodegeneration-related cognitive impairment.

### 3.5. Regulation of Protein Misfolding and Aggregation

Protein aggregation is a characteristic feature of neurodegenerative diseases including Alzheimer's disease (β-amyloid plaques) and Parkinson's disease (α-synuclein inclusions). Furthermore, to remodels misfolded proteins into nontoxic readily degradable species, this mechanism of inhibition also cause destabilization of preformed fibrils as well as the arrest of β-amyloid fibrillogenesis (Bieschke et al., 2010).

Concomitantly, withanolides from the W. somnifera protect against β-amyloid overload and tau hyperphosphorylation associated during the experimental model of Alzheimer's disease (Sehgal et al., 2012). In addition, they prevent α-synuclein aggregation in dopaminergic neurons and attenuate motor and cognitive impairment in models of Parkinson's disease.

**Table 2. Mechanistic Insights into Neuroprotection by *Camellia sinensis* and *Withania somnifera***

| **Mechanism** | ***Camellia sinensis* (Green Tea)** | ***Withania somnifera* (Ashwagandha)** |
|---|---|---|
| Antioxidant effects | Catechins (EGCG) scavenge ROS/RNS; upregulate SOD, catalase | Withanolides enhance Nrf2 signaling; increase antioxidant enzymes |
| Mitochondrial protection | Stabilizes mitochondrial membrane potential; prevents apoptosis | Prevents mitochondrial oxidative damage; sustains ATP levels |
| Anti-inflammatory action | Downregulates NF-κB, COX-2, TNF-α, IL-1β | Suppresses microglial activation; reduces pro-inflammatory cytokines |
| Neurotrophic support | Upregulates BDNF; promotes neurogenesis and synaptic repair | Withanosides induce neurite outgrowth and dendritic branching |
| Protein aggregation inhibition | Inhibits β-amyloid and α-synuclein fibrillogenesis | Reduces β-amyloid deposition and tau hyperphosphorylation |

## 4. Preclinical and Clinical Evidence

This section summarizes key preclinical (in vitro and animal) studies and human clinical evidence for *Camellia sinensis* (green tea, EGCG) and *Withania somnifera* (ashwagandha), emphasizing cognitive outcomes, biochemical markers (oxidative stress, inflammation), histopathology, and limitations in clinical translation.

### 4.1. Preclinical Studies with *Camellia sinensis*

A robust body of preclinical work (cellular and animal models) supports multiple neuroprotective actions of green tea polyphenols—principally epigallocatechin-3-gallate (EGCG). In transgenic mouse models of Alzheimer's disease (AD), EGCG reduced brain β-amyloid levels, promoted non-amyloidogenic processing of amyloid precursor protein (via enhanced α-secretase activity), and improved cognition on behavioral tasks (Rezai-Zadeh et al., 2005; Rezai-Zadeh et al., 2008). EGCG has also been shown to remodel toxic protein aggregates into less toxic conformers in vitro and to attenuate α-synuclein and Aβ fibrillogenesis in multiple models, reducing cellular toxicity (Bieschke et al., 2010; Singh et al., 2015).

EGCG and other green tea constituents improve mitochondrial function in neuronal cells and animal models by preserving mitochondrial membrane potential and ATP production while limiting cytochrome-c release and caspase activation (Wu et al., 2012). Antioxidant effects are repeatedly observed: decreased lipid peroxidation, lower ROS markers, and upregulation of endogenous antioxidant enzymes (SOD, catalase, glutathione peroxidase) have been reported across models (Singh et al., 2015; Gonçalves et al., 2021).

Preclinical evidence also indicates anti-inflammatory actions—green tea polyphenols inhibit NF-κB activation and reduce proinflammatory cytokine expression—contributing to reduced microglial activation and neuroinflammation (Mandel et al., 2006; Mancini et al., 2017). Taken together, animal studies provide mechanistic and behavioral data supporting EGCG as a neuroprotective candidate; however, many studies use doses and administration schedules that complicate direct extrapolation to humans (Zhang et al., 2020).

### 4.2. Preclinical Studies with *Withania somnifera*

Preclinical studies of *Withania somnifera* (WS) demonstrate neuroprotective, neuroregenerative, and adaptogenic properties. Withanolide A and related withanosides stimulate neurite outgrowth, enhance synaptic reconstruction, and reverse neuronal atrophy in models of neurodegeneration and cognitive impairment (Kuboyama et al., 2005). In rodent models, WS extracts have improved performance on learning and memory tasks, attenuated stress-induced cognitive deficits, reduced oxidative markers in brain tissue, and decreased inflammatory mediators (Dar et al., 2015; Lerose et al., 2024).

Mechanistically, withanolides modulate intracellular signaling involved in neuronal survival (e.g., BDNF pathways), suppress apoptotic signaling, and upregulate antioxidant responses (Dar et al., 2015). Several studies also report protection of dopaminergic neurons and reduction of protein aggregation in Parkinson's and Alzheimer's experimental paradigms (Sehgal et al., 2012). As with green tea studies,

heterogeneity in extracts, active constituent content, and dosing makes translation to human treatment regimens challenging.

### 4.3. Clinical Trials and Human Evidence

#### Green tea / EGCG — Human evidence

Human evidence for green tea and cognition includes observational studies, epidemiological meta-analyses, and a limited number of interventional trials. Meta-analytic and cohort data generally show an association between habitual green tea consumption and reduced risk of cognitive decline or dementia in older adults (Liu et al., 2017; Kakutani et al., 2019). Some randomized or controlled studies report modest cognitive benefits (attention, mood, some memory measures) after sustained consumption, but findings are inconsistent: for example, a 12-month supplementation study found limited effects on global cognitive scores though some secondary benefits were suggested (Ide et al., 2016). Recent trials exploring matcha/green tea extracts in older adults with mild cognitive decline have reported improvements in specific cognitive domains and sleep/emotional measures (Uchida et al., 2024). Overall, observational data are stronger than high-quality randomized evidence, and bioavailability/BBB penetration of EGCG in humans remains a limiting factor (Mancini et al., 2017; Zhang et al., 2020).

#### Ashwagandha — Human evidence

Clinical research on *W. somnifera* emphasizes stress reduction, anxiolytic effects, and safety; fewer high-quality trials directly target neurodegenerative diseases. Randomized, double-blind, placebo-controlled trials have demonstrated reductions in perceived stress, improved sleep, and better subjective wellbeing (Choudhary et al., 2017; Lopresti et al., 2019). Several recent placebo-controlled trials and systematic reviews conclude that ashwagandha is generally safe and can improve stress/anxiety measures, which indirectly supports cognitive health given the detrimental effects of chronic stress on cognition (Verma et al., 2021; Lopresti et al., 2019). A small number of human trials have reported improvements in memory and executive function with standardized WS extracts, but sample sizes are limited and methodologies variable; larger, disease-targeted RCTs are lacking (Lopresti et al., 2019).

#### Limitations and gaps

Across both botanicals, common translational challenges include:

- Heterogeneity of extracts and active constituent standardization (EGCG content, total withanolides).
- Bioavailability and blood–brain barrier penetration concerns for active molecules in humans.
- Differences in doses used in preclinical models versus safe, tolerable doses in humans.
- A relative paucity of large, long-duration, randomized placebo-controlled trials targeting clinically relevant cognitive endpoints (e.g., conversion from MCI to dementia, progression rate in PD).

  Consequently, although preclinical data are compelling, high-quality clinical evidence of disease-modifying benefit remains limited and requires further well-designed trials.

**Table 3. Selected Preclinical and Clinical Findings for *Camellia sinensis* and *Withania somnifera***

| **Evidence type** | ***Camellia sinensis* (Green tea / EGCG)** | ***Withania somnifera* (Ashwagandha)** |
|---|---|---|
| Key preclinical findings | Reduced Aβ accumulation and improved cognition in AD mouse models; inhibition/remodeling of Aβ and α-synuclein fibrils; antioxidant and mitochondrial protective effects. (Rezai-Zadeh et al., 2005; Bieschke et al., 2010; Singh et al., 2015) | Neuritic regeneration and synaptic reconstruction (withanolide A); improved memory/learning in rodents; antioxidant and anti-inflammatory effects. (Kuboyama et al., 2005; Dar et al., 2015) |
| Human observational / epidemiology | Cohort/meta-analysis: higher green tea intake associated with lower risk of cognitive decline/dementia in several populations. (Liu et al., 2017; Kakutani et al., 2019) | Limited observational evidence linking traditional use to cognitive resilience; more data on stress/anxiety outcomes than dementia prevention. (Lopresti et al., 2019) |
| Human interventional trials | Mixed: some small RCTs and supplementation studies show modest cognitive or mood benefits; larger RCTs with clinical endpoints are limited. (Ide et al., 2016; Uchida et al., 2024) | RCTs show stress/anxiety reduction and safety; few adequately powered RCTs directly measuring disease-relevant cognitive decline. (Choudhary et al., 2017; Lopresti et al., 2019) |
| Key translational gaps | Bioavailability, standardization, and large disease-modify RCTs. (Zhang et al., 2020) | Standardization of extracts (withanolide content), dose-finding, and large disease-specific RCTs. (Verma et al., 2021) |

## 5. Synergistic Potential of *Camellia sinensis* and *Withania somnifera*

### 5.1. Concept of Polyherbal Formulations

Polyherbal formulations are a cornerstone of traditional medicine systems such as Ayurveda, where multiple plant extracts are combined to enhance therapeutic efficacy and minimize toxicity (Patwardhan et al., 2015). The rationale is that the diverse phytoconstituents of different herbs act on complementary molecular targets, leading to synergistic or additive effects. Such formulations are gaining renewed attention in neuropharmacology because neurodegenerative diseases involve multifactorial pathophysiology, including oxidative stress, mitochondrial dysfunction, protein aggregation, and chronic inflammation (Singh et al., 2011).

Combining *Camellia sinensis* (green tea) and *Withania somnifera* (ashwagandha) presents a promising polyherbal strategy given their overlapping yet distinct mechanisms of neuroprotection.

### 5.2. Possible Synergistic Pathways

#### Antioxidant + Adaptogenic Integration

The green tea catechins, in particular EGCG, have dose-dependent strong antioxidant and mitochondria protecting activities by scavenging ROS are enhancing enzymatic anti-oxidant mechanisms (Singh et al., 2015). Concomitantly, withanolides of W. somnifera function as adaptogens that regulate the

hypothalamic–pituitary–adrenal (HPA) axis and decrease cortisol levels, thus attenuating stress-induced neuronal damage (Choudhary et al., 2017; Dar et al., 2015). Collectively, the combined actions of these two complimentary mechanisms may result in both direct antioxidant protection and systemic stress resistance.

### Anti-inflammatory and Neuroregenerative Crosstalk

EGCG inhibits the NF-κB and COX-2 signaling pathways, reducing pro-inflamma-tory cytokines (Mandel et al., 2006), while withanolides not only inhibit neuroinflammation but also promote neurite outgrowth and synaptic repair (Kuboyama et al., 2005). In an integrated context, this could potentially lead to neuroinflammation attenuation with concomitant induction of neuroplasticity and repair.

### Protein Misfolding and Synaptic Plasticity

Whereas green tea catechins reshape misfolded β-amyloid and α-synuclein aggregates (Bieschke et al., 2010), withanolides potentiate brain-derived neurotrophic factor (BDNF) expression, facilitating synaptic plasticity (Sehgal et al., 2012). Such a dual-target approach might address both pathological protein deposition and the support of functional neuronal recovery.

## 5.3. Therapeutic Prospects in Combination Therapy

The efficacy of combination of C. sinensis and W. somnifera as a therapy mainly depends on the modulation for the multifactorial effects associated with neurodegeneration. Since its constituents possess the antioxidant activity, adaptogenic, neuroregenerative and anti-inflammatory properties both in vitro and in vivo, it is possible that a polyherbal formulation offers more comprehensive protection against neurological injury than single plant products.

Potential clinical applications include:

- **Mild Cognitive Impairment (MCI):** Slowing progression to Alzheimer's disease by addressing oxidative stress and promoting synaptic plasticity.
- **Parkinson's disease:** Reducing dopaminergic neuronal loss via combined mitochondrial protection and anti-aggregation effects.
- **Stress-related cognitive decline:** Offering resilience through stress-axis modulation and antioxidant protection.

However, while theoretical and preclinical rationale is strong, clinical validation of such combinations is limited. Product standardization, pharmacokinetic profiling and randomized controlled trials are required for efficacy and safety confirmation.

**Table 4. Potential Synergistic Pathways of *Camellia sinensis* and *Withania somnifera***

| Mechanistic Axis | *Camellia sinensis* (Green tea/EGCG) | *Withania somnifera* (Ashwagandha) | Synergistic Potential |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Antioxidant defense | Potent ROS scavenger; ↑SOD, catalase, GPx (Singh et al., 2015) | Reduces oxidative stress markers; adaptogenic stress resilience (Dar et al., 2015) | Combined reduction of oxidative and stress-induced neuronal damage |
| Anti-inflammatory activity | ↓NF-κB, COX-2, TNF-α, IL-1β (Mandel et al., 2006) | Suppresses cytokines; modulates immune function (Kuboyama et al., 2005) | Stronger suppression of neuroinflammation |
| Mitochondrial protection | Preserves ATP, prevents apoptosis (Wu et al., 2012) | Enhances neuronal energy balance, reduces stress-mediated mitochondrial dysfunction (Sehgal et al., 2012) | Improved energy metabolism and neuronal survival |
| Protein misfolding/aggregation | Inhibits β-amyloid and α-synuclein aggregation (Bieschke et al., 2010) | Promotes synaptic repair, ↑BDNF expression (Kuboyama et al., 2005) | Dual action: reduced toxic aggregates + enhanced neurogenesis |

## 6. Challenges and Future Perspectives

Though Camellia sinensis (green tea) and Withania somnifera (ashwagandha have neuroprotective properties, there are various challenges to making them useful as therapeutic agents. Bioavailability and pharmacokinetics are one of the major worries, as active compounds like EGCG (epigallocatechin gallate) and withanolides can be rapidly metabolizing or have poor absorption, which leads to its diminished medicinal role (Singh et al., 2022). Lipid-based systems, nanoparticles and phytosomes have also been recommended as novel formulations to improve their solubility and tissue penetration (Shahrajabian et al., 2023).

Another difficulty is standardization and optimal dose. Coming from different plant sources, extraction methods and phytochemical concentrations may result in inconsistent therapeutic responses. Standardized combinations and measurable bioactive content in the formulations are important for reproducibility and efficacy (Kumar et al., 2021).

Safety issues and drug–herb interactions are also an issue for consideration. For example, hepatotoxicity from large doses of EGCG and potentiation of sedatives or immunomodulators by withanolides (Mishra et al., 2021). Hence, clinical safety profiling in large trials is required.

The future of nanocarrier-mediated delivery (such as the polymeric nanoparticles, liposomes and nanoemulsions) provides new strategies to enhance the stability, targeting and controlled release of the phytochemicals (Gupta & Sharma, 2022). Further studies should be directed to merge these informative techniques into clinical investigations, in the goal of filling the void between laboratory investigation and clinics.

In conclusion, despite very beneficial therapeutic potential of green tea and ashwagandha, future direction should focus on bioavailability improvements, pharmacokinetic profiling, standardization and safety confirmation to accomplish its successful application in neurodegenerative disorders.

## 7. Conclusion

The overall evidence highlights the molecular and antioxidant mediated neuroprotection of Camellia sinensis and Withania somnifera. Catechins in green tea have powerful antioxidant, anti-inflammatory

and anti-apoptotic properties, whereas withanolide act as both adaptogens and neuro-regenerative agents. (Choudhary et al., 2022; Mathur et al., 2020). Together, these botanicals enhance neuronal resilience by modulating oxidative stress, mitochondrial dysfunction, and neuroinflammatory pathways.

Preclinical and emerging clinical findings demonstrate their evidence-based neuroprotective benefits, including improved cognition, reduced oxidative damage, and protection against amyloid-beta and dopaminergic toxicity (Balkrishna et al., 2021). Importantly, their potential as adjunct therapies lies in complementing conventional pharmacological approaches, particularly in managing cognitive decline and progressive neurodegenerative diseases such as Alzheimer's and Parkinson's disease.

Thus, the combination of green tea and ashwagandha represents a promising natural therapeutic strategy. However, advancing their role from traditional remedies to clinically validated therapies will require rigorous translational research, standardized formulations, and well-designed clinical trials.

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Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-486-3

# Chapter 5: Hepatocellular Defense and Regenerative Modulation by Silybum marianum and Aloe barbadensis miller: Targeting Oxidative Stress, Fibrosis, and Detoxification Pathways in Liver Disorders write this book chapter outline

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## Abstract

Liver disorders, including non-alcoholic fatty liver disease (NAFLD), hepatitis, cirrhosis, and hepatocellular carcinoma, remain a global health burden. Oxidative stress, fibrosis, chronic inflammation, and impaired detoxification are central pathological mechanisms underlying these conditions. Natural hepatoprotective agents such as *Silybum marianum* (milk thistle) and *Aloe barbadensis* Miller (aloe vera) have demonstrated potential in mitigating liver injury through multifaceted mechanisms. Silymarin, the principal bioactive complex in milk thistle, exhibits antioxidant, anti-fibrotic, anti-inflammatory, and regenerative effects, while aloe polysaccharides and bioactive compounds provide complementary hepatoprotection via free radical scavenging, modulation of detoxification enzymes, and tissue repair. Experimental and available clinical data indicate the hepatoprotective efficacy of both plants with potential costimulatory effects in combined polyherbal preparations. Their therapeutic potential could also be improved by the development of new delivery systems based on nanocarriers, integration with regenerative medicine and computational modelling. This chapter offered a comprehensive summary on the pharmacognosy, mechanisms of action, preclinical and clinical evidences safety issues and prospect research trend in all aspects of Silybum marianum and Aloe barbadensis in hepatic safeguarding and restoration.

**Keywords:** *Silybum marianum*, *Aloe barbadensis* Miller, hepatoprotection, oxidative stress, liver fibrosis, detoxification, regenerative medicine, polyherbal therapy

## 1. Introduction

Liver diseases are a major public health challenge and leading cause of deaths throughout the world. Chronic liver diseases, such as viral hepatitis, non-alcoholic fatty liver disease (NAFLD), alcoholic liver diseases, cirrhosis and hepatocellular carcinoma (HCC), result in millions of deaths each year (Asrani et al., 2019). Liver cirrhosis alone causes over 1 million deaths per year (World Health Organization, 2018)

and the prevalence of NAFLD has escalated at an alarming rate owing to the global epidemic of obesity and diabetes (Younossi et al., 2019). In addition, hepatocellular carcinoma ranks the fifth most frequent cancer worldwide and third most common cause of death due to cancer, underlining the great demand for effective preventive and therapeutic approaches (Villanueva, 2019).

Conventional therapeutic methods for liver diseases generally include antiviral therapy, immunosuppressant agents, or in severe cases, liver transplant. Yet, these methods are costly, have side effects, and may not be widely available in low-resource settings (Wong et al., 2021). Therefore, naturally occurring hepatoprotective agents from plants are being increasingly recognized as a safer and economical alternative to orthodoxy or adjuvants in the management of liver diseases (Shen et al., 2019).

Amidst some promising candidates, Silybum marianum (milk thistle) and Aloe barbadensis Miller (aloe vera) have gained substantial attention as a result of their extraordinary phytochemical content and highly effective hepato-protective properties. Silymarin is a complex of flavonolignans (sibilin, silydianin and silychristin) present in S. marianum seeds, its hepatoprotective activity has been extensively studied in toxin-mediated as well as metabolic liver diseases (Federico et al., 2017). In contrast, the Aloe barbadensis is reported to be rich in anthraquinones, polysaccharides and vitamins and thus has been proposed to modulate oxidative stress, enhance detoxification and tissue regeneration (Surjushe et al., 2008; Salehi et al., 2018).

The reason for such a focus is due to the synergistic and complementary actions of these two botanicals that have been shown on important pathophysiological pathways contributing to liver disease such as oxidative stress, fibrosis, and dysfunctional detoxification. Although milk thistle is prominently characterized by potent antioxidant and anti-fibrotic activities, as an active constituent of the combination aloe vera acts through hepatocellular regeneration and activation of enzymatic antioxidative defence. They complement each other and represent and integrative approach in line with the strategy of integrative and regenerative hepatology (Polyak et al.

The focus of this chapter is to summarize the hepatocellular defense and regenerative regulation mediated by Silybum marianum and Aloe barbadensis, specifically targeting oxidative stress, fibrogenesis, and detoxification pathways towards hepatic disorders. Experimental and clinical evidence, synergistic potential, safety considerations, and future directions in hepatic regenerative medicine will also be reviewed in Chapter 3.

## 2. Pathophysiology of Liver Disorders

Oxidative stress, inflammation, fibrosis and poor detoxification are interwoven in the pathogenesis of liver disease. These steps lead to the disturbance of hepatocellular homeostasis and develop progressive liver injury.

### 2.1. Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress plays a pivotal role in the pathogenesis of liver damage. The excessive production of reactive oxygen species (ROS) saturates the endogenous antioxidant capacity, including, but not limited to glutathione, superoxide dismutase (SOD), and catalase thus causing lipid peroxidation, protein

oxidation and DNA damage (Zhang et al., 2016). Products of lipid peroxidation, such as malondialdehyde (MDA), cause hepatocyte apoptosis and necrosis leading to exacerbating tissue injury (Poli et al., 2004).

ROS are not only generated by but also act on mitochondria. Malfunctioning mitochondria have defective oxidative phosphorylation, ATP production and membrane potential. This bioenergetic dysfunction triggers hepatocyte loss, and advances towards chronic liver disease (Wang et al., 2020).

### 2.2. Fibrosis and Inflammatory Cascade

Fibrosis is a response to the wound that leads to abnormal accumulation of extracellular matrix (ECM) such as collagen. Stellatocyte hepatic activation (SHC) is the foundation of fibrogenesis. In oxidative and inflammatory milieu, quiescent HSC transdifferentiate to the myofibroblast-like cells that lay down the collagen type I and III (Bataller & Brenner, 2005).

The fibrogenetic pathway is controlled by cytokines and signal transduction pathways. TGF-β is the master profibrotic cytokine, promoting the synthesis of ECM and limitation of its catabolism. Nuclear factor kappa B (NF-κB) and the downstream regulation of inflammatory gene expression is responsible for secretion of pro-inflammatory mediators including TNF-α and IL-6 (Schuppan & Afdhal, 2008). Persistent activation of these pathways fosters chronic inflammation and fibrotic remodeling, which eventually progresses to cirrhosis.

### 2.3. Impaired Detoxification Pathways

The liver's primary role in detoxification involves phase I and phase II metabolism, largely mediated by cytochrome P450 (CYP450) enzymes. Dysfunction of these enzymes results in impaired clearance of xenobiotics, drugs, and endogenous toxins (Guengerich, 2019).

Phase I metabolism, dominated by oxidation reactions via CYP450 isoenzymes (e.g., CYP3A4, CYP2E1), can generate reactive intermediates that exacerbate oxidative stress if not efficiently neutralized. Phase II metabolism involves conjugation reactions (glucuronidation, sulfation, glutathione conjugation), which facilitate excretion. Disruption of either phase contributes to toxin accumulation, hepatocellular stress, and enhanced susceptibility to drug-induced liver injury (DILI) (Russmann et al., 2009).

**Table 1. Key Pathophysiological Mechanisms in Liver Disorders**

| Mechanism | Cellular/Pathway Involved | Consequences in Liver Disorders |
|---|---|---|
| Oxidative stress & mitochondrial dysfunction | ROS, lipid peroxidation, mitochondrial respiratory chain | DNA damage, apoptosis, necrosis, energy failure |
| Fibrosis & inflammation | Hepatic stellate cells, TGF-β, NF-κB, TNF-α, IL-6 | ECM accumulation, chronic inflammation, cirrhosis |
| Impaired detoxification pathways | CYP450 enzymes, phase I & II metabolism | Toxin accumulation, oxidative intermediates, DILI |

## 3. Pharmacognostic Insights into *Silybum marianum*

### 3.1. Botanical Description and Distribution

*Silybum marianum* (L.) Gaertn., commonly known as milk thistle, belongs to the family Asteraceae. It is a biennial or annual herb characterized by erect, branched stems that can reach a height of 1–2.5 meters. The leaves are large, spiny, and marbled with distinctive white veins, while the flower heads are purple and thistle-like, containing tubular florets surrounded by spiny bracts (Karkanis et al., 2011).

S. marianum natively occurs in the Mediterranean region but is found throughout Europe, Asia, North and South America, and Australia (11). It is common in sunny habitats, both as a weed of wastelands and cultivated lands (Abenavoli et al., 2018). Its ability to tolerate different climatic conditions has contributed in its widespread use worldwide as a medicinal herb and supplement.

### 3.2. Phytochemical Constituents

Fruit (seeds) of S. marianum constitutes the primary reservoir of its bioactive constituents. The leading pharmacological fraction is silymarin, which contains complex of flavonolignans and polyphenols.

- **Flavonolignans**: The chief constituents are silybin (also known as silibinin), silydianin, and silychristin. Silybin is the most abundant, constituting 50–70% of the silymarin complex and being mainly responsible for hepatoprotective effect (Kren & Walterova, 2005)
- **Antioxidant polyphenols**: The plant also contains taxifolin and other flavonoids that enhance the antioxidant and free radical scavenging capacity (Surai, 2015).
- Other compounds found in S. birrea are fixed oils (containing high levels of linoleic acid), proteins, tocopherols (vitamin E), and sterols which confer its nutraceutical usefulness (Mocan et al., 2016).

### 3.3. Traditional and Modern Uses in Hepatic Therapy

The use of *S. marianum* in liver ailments dates back more than 2,000 years. Traditionally, it was prescribed for "melancholy" and "liver congestion" in Greco-Roman medicine, and later used in European folk medicine for jaundice and gallbladder disorders (Abenavoli et al., 2010).

In modern pharmacotherapy, standardized silymarin extracts are widely employed as hepatoprotective agents. Clinical and experimental studies have demonstrated its role in:

- **Antioxidant defense**: Enhancing glutathione content and scavenging ROS (Polyak et al., 2013).
- **Anti-fibrotic activity**: Inhibiting hepatic stellate cell activation and reducing collagen deposition (Federico et al., 2017).
- **Detoxification**: Stabilizing hepatocyte membranes and modulating phase I and II metabolic enzymes (Křen & Walterová, 2005).
- **Therapeutic indications**: Management of alcoholic liver disease, NAFLD, viral hepatitis, and protection against drug- or toxin-induced liver injury (Loguercio & Festi, 2011).

**Table 2. Phytochemical Constituents and Pharmacological Significance of *Silybum marianum***

| Compound/Class | Major Examples | Pharmacological Significance |
|---|---|---|
| Flavonolignans | Silybin, silydianin, silychristin | Antioxidant, anti-fibrotic, hepatoprotective |
| Flavonoids | Taxifolin | Free radical scavenging, anti-inflammatory |
| Fixed oils | Linoleic acid, oleic acid | Nutritional value, membrane stabilization |
| Tocopherols & sterols | Vitamin E, stigmasterol | Antioxidant, membrane protection |
| Proteins & minor polyphenols | Albumin-like proteins, phenolic acids | Cellular protection, detoxification support |

## 4. Pharmacognostic Insights into *Aloe barbadensis* Miller

### 4.1. Botanical Description and Distribution

*Aloe barbadensis* Miller, commonly known as aloe vera, is a perennial, succulent plant belonging to the family Asphodelaceae. Morphologically, it has thick, fleshy, lance-shaped green leaves with serrated edges, containing a central parenchymatous tissue that stores mucilaginous gel (Surjushe et al., 2008). The outer green rind encloses vascular bundles and an inner clear gel, which is the medicinally important component.

Geographically, aloe vera is native to North Africa, the Arabian Peninsula, and the Canary Islands. However, due to its resilience and economic importance, it is now widely cultivated across tropical, subtropical, and arid regions worldwide, including India, Mexico, and parts of the United States (Hamman, 2008). Its adaptability to low-water conditions has contributed to its extensive use in traditional and modern medicine.

### 4.2. Phytochemical Constituents

*Aloe barbadensis* contains diverse classes of bioactive compounds contributing to its therapeutic versatility.

- **Anthraquinones**: Compounds such as aloin, aloe-emodin, and barbaloin exhibit laxative, antimicrobial, and hepatoprotective effects (Boudreau & Beland, 2006).
- **Polysaccharides**: Acemannan, a major polysaccharide, plays a critical role in immunomodulation, wound healing, and antioxidant defense (Choi & Chung, 2003).
- **Vitamins and minerals**: Aloe gel contains vitamins A, C, and E (antioxidant vitamins), along with B-complex vitamins and minerals such as calcium, magnesium, and zinc, which contribute to cellular defense against oxidative stress (Surjushe et al., 2008).
- **Enzymes**: Key enzymes such as catalase, peroxidase, and superoxide dismutase enhance free radical scavenging, supporting hepatocellular defense (Ni et al., 2004).

### 4.3. Traditional and Modern Uses in Hepatic Therapy

Historically, aloe vera has been used in traditional systems of medicine such as Ayurveda, Traditional Chinese Medicine (TCM), and Unani for ailments including constipation, skin diseases, and inflammatory disorders (Reynolds & Dweck, 1999). In hepatic therapy, its traditional role was associated with detoxification and relief from jaundice-like symptoms.

Modern pharmacological research validates many of these traditional claims. Aloe vera exhibits multiple hepatoprotective mechanisms:

- **Antioxidant activity**: Enhancement of endogenous antioxidant enzymes and reduction of lipid peroxidation (Rajasekaran et al., 2005).
- **Anti-fibrotic effects**: Downregulation of TGF-β and collagen synthesis, reducing hepatic fibrosis in experimental models (Salehi et al., 2018).
- **Detoxification support**: Modulation of phase I and II metabolic pathways, improving xenobiotic clearance (Hamman, 2008).
- **Regenerative properties**: Polysaccharides such as acemannan promote tissue repair and hepatocellular regeneration (Choi & Chung, 2003).

These findings suggest aloe vera as a promising adjunct in the management of chronic liver diseases, particularly when used in integrative hepatology.

**Table 3. Phytochemical Constituents and Hepatoprotective Role of *Aloe barbadensis* Miller**

| Compound/Class | Major Examples | Pharmacological Significance in Liver Disorders |
|---|---|---|
| Anthraquinones | Aloin, aloe-emodin, barbaloin | Antioxidant, anti-inflammatory, antimicrobial, hepatoprotective |
| Polysaccharides | Acemannan, glucomannan | Immunomodulation, antioxidant defense, regeneration support |
| Vitamins & minerals | Vitamins A, C, E; calcium, zinc | Antioxidant protection, cofactor role in detoxification enzymes |
| Enzymes | Catalase, peroxidase, SOD | Free radical scavenging, oxidative stress reduction |

## 5. Mechanistic Basis of Hepatoprotection

### 5.1. Antioxidant Mechanisms

Oxidative stress plays a central role in hepatocellular injury by generating reactive oxygen species (ROS), which damage lipids, proteins, and DNA. Both *Silybum marianum* and *Aloe barbadensis Miller* exert potent antioxidant effects. Silymarin, the active complex from *S. marianum*, scavenges free radicals and inhibits lipid peroxidation (Surai, 2015). Additionally, it enhances the activity of glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), which collectively protect hepatocytes from oxidative insults (Abenavoli et al., 2018). Aloe polysaccharides and vitamins (e.g., vitamin C and E) also contribute to redox balance by reducing ROS accumulation (Hamman, 2008).

### 5.2. Anti-fibrotic Pathways

Chronic liver injury activates hepatic stellate cells (HSCs), leading to fibrosis. Silymarin has been shown to inhibit TGF-β signaling and reduce HSC activation, thereby limiting extracellular matrix deposition (Polyak et al., 2010). Aloe-derived anthraquinones and polysaccharides downregulate collagen synthesis and interfere with pro-fibrotic mediators, slowing the progression of fibrosis (Chandanwale et al., 2016).

### 5.3. Detoxification Modulation

Detoxifying pathway is important for hepatic metabolism of xenobiotic compounds. Silymarin increases phase I and II detoxification enzymes such as cytochrome P450, glutathione S-transferase (GST) and UDP-glucuronosyltransferase (Zhao & Agarwal, 2018). Aloe polysaccharides also enhance detoxification through the regulation of drug-metabolizing enzymes and by stimulating conjugation reactions leading to the elimination of toxins (Gupta et al., 2006).

### 5.4. Anti-inflammatory Effects

Persistent inflammation accelerates hepatocellular injury. The NF-κB activation itself is inhibited by silymarin leading to low level expression of pro-inflammatory mediators like TNF-α, IL-6, COX-2, and iNOS (Soleimani et al., 2019). Aloe vera extracts have also supplementary anti-inflammatory functions that suppress cyclooxygenase pathways and reduce inflammatory cytokines (Chandanwale et al., 2016).

### 5.5. Hepatocellular Regeneration

Reconstruction of the function after the injury is important when considering recovery from liver injury. Silymarin increases hepatic protein synthesis and hepatocyte regeneration, thus facilitating recovery (Abenavoli et al., 2018). Aloe polysaccharides also induce hepatocellular regeneration by increasing DNA synthesis and growth factors (Hamman, 2008). As a group, they serve as synergists in the aid of regeneration and functional rehabilitation.

**Table 4. Mechanistic actions of *Silybum marianum* and *Aloe barbadensis Miller* in liver protection**

| **Mechanism** | ***Silybum marianum* (Milk thistle)** | ***Aloe barbadensis Miller* (Aloe vera)** |
|---|---|---|
| Antioxidant activity | Scavenges ROS, increases GSH, SOD, CAT, GPx | Vitamins & polysaccharides reduce oxidative stress |
| Anti-fibrotic effect | Inhibits TGF-β, suppresses stellate cell activation | Downregulates collagen synthesis, reduces fibrosis |
| Detoxification modulation | Enhances CYP450, GST, and UGT enzymes | Supports phase I/II enzymes, promotes conjugation |
| Anti-inflammatory effect | Inhibits NF-κB, TNF-α, COX-2, iNOS | Inhibits COX-2 and reduces pro-inflammatory cytokines |
| Regenerative potential | Stimulates protein synthesis and hepatocyte proliferation | Promotes hepatocyte repair and DNA synthesis |

## 6. Experimental and Clinical Evidence

### 6.1. Preclinical Studies on *Silybum marianum*

Preclinical evaluation Silybum marianum has been widely investigated in preclinical models of hepatotoxicity. Studies in vitro show that silymarin inactivates an intracellular radical produced by $CCl_4$- and ethanol-induction of hepatic oxidation, which effect is due to the inhibition of the lipid peroxidation and increasing in glutathione activity of myoglobin (Flora et al., 1998). In vivo, silymarin shows hepatoprotective effects against drugs induced injuries like acetaminophen and doxorubicin intoxication and attenuates liver enzyme expression and histopathological alterations (Abenavoli et al., 2018). Moreover, by inhibiting HSC activation and decreasing the amount of collagen fibers, silymarin has been found to have demonstrated its anti-fibrotic effect (Polyak et al., 2010).

### 6.2. Preclinical Studies on *Aloe barbadensis Miller*

Aloe's hepatoprotective effect is well-supported by animal studies. Acanthaceae Aloe polysaccharides prevent chemically-induced liver injury in mice by inhibiting oxidative stress markers and stabilizing the serum transaminase (Gupta et al., 2006). In $CCl_4$-treated rat model, aloe gel extract decreased the formation of malondialdehyde (MDA) with increased levels of antioxidant enzymes SOD and CAT were observed (Rajasekaran et al., 2005). Histological evaluations also support its potential in protecting hepatocyte architecture and alleviating necrosis.

### 6.3. Clinical Evidence and Human Trials

The clinical trials on silymarin confirm its effectives in chronic liver diseases. In patients with NAFLD, silymarin supplementation led to a significant decrease in serum ALT and AST levels, as well as oxidative stress indicators (Hajaghamohammadi et al., 2008). Trials in hepatitis C patients revealed reduced inflammation and slower disease progression with silymarin use (Fried et al., 2012). In cirrhosis, long-term silymarin administration was associated with improved survival rates (Ferenci et al., 1989).

Evidence for aloe in human liver health remains limited but promising. Small-scale studies suggest aloe supplementation may normalize liver enzymes and support detoxification (Chandanwale et al., 2016). However, more robust randomized controlled trials are needed to validate its hepatoprotective efficacy. Emerging findings indicate that combining aloe polysaccharides with silymarin may yield synergistic antioxidant and hepatoregenerative effects, warranting further exploration (Hamman, 2008).

**Table 5. Summary of experimental and clinical evidence of *Silybum marianum* and *Aloe barbadensis* in liver protection**

| Level of Evidence | *Silybum marianum* (Milk thistle) | *Aloe barbadensis Miller* (Aloe vera) |
|---|---|---|
| In vitro studies | Protects hepatocytes from $CCl_4$/alcohol-induced ROS; enhances GSH and antioxidant enzymes | Reduces oxidative stress markers, supports hepatocyte viability |
| Animal models | Restores liver enzymes, prevents fibrosis, reduces collagen deposition | Normalizes ALT/AST, reduces MDA, preserves histology |
| Clinical trials | Improves ALT/AST in NAFLD and hepatitis; slows cirrhosis progression | Limited evidence; some reports of improved liver enzymes |
| Synergistic potential | Antioxidant, anti-fibrotic, regenerative | Supports detoxification, complements antioxidant activity |

## 7. Synergistic Potential of *Silybum marianum* and *Aloe barbadensis Miller*

The combined use of *Silybum marianum* (milk thistle) and *Aloe barbadensis Miller* (aloe vera) offers promising synergistic effects in hepatoprotection. Both herbs target oxidative stress through complementary mechanisms—silymarin enhances antioxidant enzyme activity (SOD, CAT, GPx) and glutathione replenishment, while aloe polysaccharides and vitamins scavenge free radicals and reduce lipid peroxidation (Hamman, 2008; Abenavoli et al., 2018). This dual action provides superior redox balance compared to monotherapy.

Additionally, their effects on detoxification pathways are synergistic. Silymarin enhances cytochrome P450 enzymes and phase II conjugation, while aloe supports xenobiotic clearance and bile flow (Zhao & Agarwal, 2018; Gupta et al., 2006). Such complementary modulation can reduce drug-induced hepatotoxicity, particularly from chemotherapeutics, antitubercular drugs, and acetaminophen.

Future research could focus on polyherbal preparations of silymarin and aloe extracts in defined proportions. These preparations may be beneficial in the multi-targeted hepatoprotection, and could reduce dosage and increase compliance. Nevertheless, rigorous clinical trials are required to determine the safety, effectiveness and dosing (Soleimani et al., 2019).

## 8. Safety, Toxicological Considerations, and Limitations

### 8.1. Dose-related Safety of Silymarin and Aloe Extracts

Silymarin is well-tolerated and no evidence of liver damage has been found in patients taking upto 700 mg/day of silymarin (Flora et al., 1998). Aloe gel extracts are considered safe at normal/therapeutic dose levels but may cause electrolyte imbalances and diarrhea when ingested in excessive amounts (Gupta et al., 2006).

### 8.2. Herb-Drug Interactions

Silymarin and aloe vera can both influence cytochrome P450 enzymes and be responsible for interaction with drugs metabolised by CYP3A4 and CYP2C9 (Zhao & Agarwal, 2018). Silymarin might inhibit the

metabolism of anticoagulants and statins, and aloe may affect the pharmacokinetics of hypoglycemic or laxative drugs.

### 8.3. Toxicological Issues Related to Anthraquinones in Aloe

The aloe Latex has anthraquinones including aloin and emodin, with laxative activity but high doses are associated with hepatotoxicity (Park et al., 2009). Regulatory bodies, including the European Medicines Agency, caution against long-term anthraquinone use due to potential hepatotoxic and carcinogenic risks. Thus, formulations should prioritize aloe gel over latex to minimize toxicity.

**Table 6. Safety and toxicological considerations of *Silybum marianum* and *Aloe barbadensis Miller***

| **Parameter** | ***Silybum marianum* (Milk thistle)** | ***Aloe barbadensis Miller* (Aloe vera)** |
|---|---|---|
| Safe dosage range | Up to 700 mg/day of silymarin (clinical) | Gel extracts safe at therapeutic doses |
| Common side effects | Mild GI upset, headache | Diarrhea, electrolyte imbalance (high doses) |
| Herb-drug interactions | Alters CYP3A4/CYP2C9 → affects statins, warfarin | Alters drug absorption, interacts with hypoglycemics |
| Toxicological risks | Low, rare hepatotoxicity | Anthraquinones (latex) → hepatotoxicity, carcinogenic potential |
| Safety recommendation | Safe in long-term use under supervision | Use gel extracts; avoid latex in chronic therapy |

## 9. Future Perspectives in Hepatic Regenerative Medicine

Advances in hepatology are increasingly shifting toward integrative and regenerative approaches, where plant-derived compounds such as *Silybum marianum* (silymarin) and *Aloe barbadensis* are positioned as adjuncts in modern therapy.

### 9.1 Nanocarrier and Novel Drug Delivery Systems

The clinical application of silymarin and aloe bioactives is often limited by their poor solubility and bioavailability. Nanotechnology-based drug delivery systems, including liposomes, polymeric nanoparticles, and solid lipid nanoparticles, have demonstrated promise in improving oral absorption and sustained release of silymarin, thereby enhancing its hepatoprotective efficacy (Mao et al., 2021). Similarly, encapsulating aloe polysaccharides in nanoparticle formulations may ensure improved stability and targeted delivery to hepatic tissues.

### 9.2 Integration with Stem Cell Therapy and Tissue Engineering

Stem cell therapy has emerged as a frontier in treating chronic liver diseases, aiming to restore hepatocyte function and tissue architecture. The combined use of bioactive phytoconstituents such as silybin and aloe polysaccharides with mesenchymal stem cells or scaffold based tissue engineering can enhance liver

regeneration through cellular and biochemical supportive role (Yuan et al., 2020). This might accelerate repair and decelerate fibrosis contraction.

### 9.3 Systems Biology and Computational Approaches

Given that these different pathological pathways of oxidative stress, fibrosis and detoxification are interlinked, a systemic approach to examination is required. Synergistic hepatoprotection is computationally predicted by systems biology and network pharmacology in combining aloe and silymarin. Computational models of molecular interactions with targets including NF-κB, TGF-β and cytochrome P450 enzymes can identify how we should design optimised polyherbal formulations and designs of clinical trials (Hopkins, 2008).

## 10. Conclusion

Experimental and early clinical data have shown both Silybum marianum and Aloe barbadensis to offer hepatoprotection. They act by providing strong antioxidant protection, inhibition of fibrosis by blocking TGF-β signaling, regulation of detoxifying reactions as well as stimulation of hepatocyte regeneration. Although silymarin has found video-patho-clinical evidence in affections like non-alcoholic fatty liver disease (NAFLD), hepatitis, and cirrhosis, the aloe can present a complementary effect for its polysaccharides and bioactive metabolites.

The combined use of these botanicals might then be a good strategy for potential polyherbal hepatoprotective preparations especially if combined with innovative delivery systems and regenerative medicine techniques. Although there are some difficulties in this regard, including poor bioavailability the herb–drug interaction and safety concerns with anthraquinones of both herbs, they offer significant prospects for further study in integrative hepatology. Their capacities in addressing oxidative stress, fibrosis, inflammation, detoxification and regeneration makes them promising players for the future of liver therapeutics.

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Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-486-3

# Chapter 6: Dual Anti-Inflammatory and Immunosuppressive Mechanisms of Curcuma longa and Ocimum sanctum in Chronic Inflammatory Diseases: Targeting NF-κB and Cytokine Networks

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## Abstract

Chronic inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, asthma, and psoriasis are driven by persistent dysregulation of immune responses and excessive activation of pro-inflammatory signaling cascades. Central to this pathology is the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway and an imbalance between pro- and anti-inflammatory cytokine networks, which collectively perpetuate tissue damage and immune hyperactivation. Natural therapeutics have emerged as promising adjuncts for modulating these pathways, with *Curcuma longa* (turmeric) and *Ocimum sanctum* (tulsi) showing particular potential. Curcumin, the principal bioactive of *C. longa*, exerts anti-inflammatory effects through inhibition of NF-κB activation, downregulation of cytokines such as TNF-α, IL-6, and IL-17, suppression of COX-2/iNOS, and promotion of IL-10 and regulatory T-cell responses. *O. sanctum*, rich in eugenol, ursolic acid, and rosmarinic acid, complements these effects by suppressing NF-κB and STAT3 signaling, modulating Th1/Th17 vs. Treg balance, reducing dendritic cell maturation, and attenuating stress-induced immune activation. Together, these botanicals exhibit dual anti-inflammatory and immunosuppressive actions, offering synergistic modulation of NF-κB and cytokine networks. Both agents provide strong preclinical evidence of benefit in arthritis, colitis, and asthma, whereas preliminary clinical data indicates benefits on symptoms, inflammatory markers and quality of life. Nevertheless, constraints would include low bioavailability, variability in phytochemical composition and inadequate clinical trial data. New formulation approaches based on nanoparticle and phytosome delivery systems may circumvent these limitations, portending positive translational possibilities. This chapter offers an insight into mechanistic aspect, preclinical and clinical documentations along with discussing the future prospects POS as downstream modulator of both inflammation and immunity, emphasizing their possible inclusion into individualized evidence-based therapeutics of chronic inflammatory disorders.

**Keywords:** Curcuma longa; Ocimum sanctum; curcimin; eugenol; NF-κB, cytokines, chronic inflammation, rheumatoid arthritis, inflammatory bowel disease immunomodulation, phytotherapy integrative medicine

## Introduction

Chronic inflammation conditions, such as RA, IBD, asthma and psoriasis have exerted a light-and-shade influence on global health. These diseases are marked by chronic inflammation, continuous destruction of tissues, and poor quality life dispensability most times demanding longterm treatments (Medzhitov, 2008; Smolen et al., 2016). The incidence and prevalence of these diseases are increasing despite the availability of biologics and other small molecule therapies, indicating that there is a demand for safer and more effective alternative or additional treatments.

Key features in such conditions include immune dysregulation with a vicious cycle of inflammation. As a rule, inflammation is a response against harmful stimuli and serves to change the various cell types for initiating the healing process. However, in chronic inflammatory diseases, the balance between pro- and anti-inflammatory mechanisms is disrupted, resulting in persistent immune activation and tissue destruction (Hunter & Jones, 2015). Central to this dysregulation is the overproduction of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), coupled with reduced anti-inflammatory mediators such as interleukin-10 (IL-10) (Zhang & An, 2007).

At the molecular level, the nuclear factor kappa B (NF-κB) signaling pathway plays a pivotal role in orchestrating chronic inflammation. NF-κB regulates the transcription of a wide range of genes encoding cytokines, chemokines, adhesion molecules, and enzymes such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) (Lawrence, 2009). Persistent activation of NF-κB not only drives inflammatory cascades but also sustains pathogenic immune responses, thereby linking innate and adaptive immunity to chronic disease pathology (Hayden & Ghosh, 2012). Consequently, targeting NF-κB and its downstream cytokine networks has emerged as a central therapeutic strategy in managing chronic inflammatory conditions.

While synthetic drugs such as corticosteroids and biologic agents can effectively inhibit NF-κB and cytokine activity, their long-term use is associated with significant adverse effects, including immunosuppression, infections, and metabolic disturbances (Smolen et al., 2016). This has sparked a renewed interest in adjuvant-like natural products with potential immunomodulatory effects, which could exert both anti-inflammatory and immunosuppressive effects with better safety profiles. Of these, Curcuma longa (turmeric) and Ocimum sanctum (holy basil or tulsi) have been the center of attention.

*Curcuma longa:* rich in curcuminoids, including the well-known compound curcumin, which has been extensively studied for its capacity to block NF-κB activation and the expression of pro-inflammatory cytokines as well as triggering antioxidant defenses (Gupta et al., 2013). Besides, phytochemicals in Ocimum sanctum such as eugenol, ursolic acid and apigenin also regarded for their strong immunomodulating and stress-protective actions with the effect of modulating NF-κB mediated events and regulation of T-cell responses (Mondal et al., 2009). These plants combined make potentially interesting dual modulators of inflammation and immunity, with the ability to act on molecular pathways involved in chronic inflammatory disorders.

Therefore, a comparative study on the antiinflammatory and immunosuppressive potential of Curcuma longa and Ocimum sanctum in conjunction with NF-κB and cytokine network would provide an indication to their novel therapeutic potential for chronic inflammation associated disorders.

## 2. Phytochemical Composition of *Curcuma longa* and *Ocimum sanctum*

### 2.1 Major Bioactive Constituents of *Curcuma longa*

*Curcuma longa* (turmeric) contains a diverse array of secondary metabolites, the most significant being curcuminoids and volatile oils. Curcuminoids include curcumin, demethoxycurcumin, and bisdemethoxycurcumin, which are polyphenolic compounds responsible for the characteristic yellow pigment and the majority of turmeric's pharmacological activities (Gupta et al., 2013). These molecules exhibit strong antioxidant and anti-inflammatory properties by modulating multiple molecular targets, particularly NF-κB, COX-2, and iNOS (Goel et al., 2008).

Additionally, turmeric essential oil contains sesquiterpenes such as ar-turmerone, α-turmerone, and β-turmerone, which have been shown to enhance the bioavailability of curcumin and independently exert immunomodulatory effects (Jiang et al., 2006). The combined presence of curcuminoids and turmerones provides a synergistic contribution to *C. longa*'s therapeutic potential in chronic inflammatory disorders.

### 2.2 Major Bioactive Constituents of *Ocimum sanctum*

*Ocimum sanctum ((holy basil or tulsi)* contains various phytochemicals, including phenolics, flavonoids and terpenoids. Eugenol, a phenylpropanoid, is one of the most studied compounds, showing potent anti-inflammatory effects by inhibiting NF-κB activation and downregulating pro-inflammatory cytokines such as TNF-α and IL-6 (Cohen, 2014). Ursolic acid, a triterpenoid, has demonstrated immunosuppressive properties through modulation of T-cell activity and inhibition of STAT3 signaling (Shanmugam et al., 2013).

Flavonoids such as apigenin and rosmarinic acid contribute to antioxidant defense and cytokine regulation, while unique glycosidic compounds like ocimumosides have been shown to exert adaptogenic and anti-stress effects, indirectly supporting immune homeostasis (Mondal et al., 2009). Collectively, these bioactive molecules position *O. sanctum* as a broad-spectrum immunomodulator.

### 2.3 Comparative Analysis of Chemical Scaffolds Relevant to NF-κB and Cytokine Regulation

In both C. longa and O. sanctum, structurally different phytochemicals are present that modulate multiple inflammatory pathways. Curcuminoids are therefore diarylheptanoids with conjugated double bonds, which accounts for the ability to quench free radicals and interact at crucial transcription factors in particular NF-κB (Gupta et al., 2013). O. sanctum extracts compounds like eugenol (phenolic), apigenin (flavone) on the other hand show significant efficacy mainly through signalling cascades (MAPK, STAT3, NF-κB) along with cytokines in response to one or more antigens from pathogen that result in protective immunity.

Despite structural diversity (diarylheptanoids for turmeric versus phenolic, terpenoid and flavonoid moieties for tulsi), several routes are tractable to both types of compounds. Such complementary chemical diversity would likely result in a more widely and robustly immunomodulatory effect, when used in combination.

### 2.4 Synergistic Potential of Combining Both Herbs

The combination use of C. longa and O. sanctum could bring together some advantages of both components for potential synergy in the management of chronic inflammatory conditions. The potent inhibitory activity of curcumin on NF-κB-mediated pro-inflammatory gene expression might be enhanced by the suppression of eugenol on cytokines and T-cell regulation from ursolic acid. Get this: Tulsi itself has adaptogenic properties that could mitigate stress-induced immune activation, and turmeric supports antioxidant defenses and tissue-recovery factors."

Together, these herbs may provide a holistic therapeutic approach by:

- Suppressing pro-inflammatory cytokine storms (TNF-α, IL-1β, IL-6).
- Enhancing anti-inflammatory mediators (IL-10, TGF-β).
- Influencing both innate and adaptive immune reactions..
- Enhanced bioavailability of curcumin with essential oils (Jiang et al., 2006).

This potential synergy qualifies the turmeric-tulsi combination as one of the best candidates for integrative medicine approaches in autoimmune and chronic inflammatory diseases.

**Table 1. Major Bioactive Constituents of *Curcuma longa* and *Ocimum sanctum* and Their Reported Biological Activities**

| Plant | Major Phytochemicals | Chemical Class | Key Biological Activities Related to NF-κB and Cytokines |
|---|---|---|---|
| *Curcuma longa* | Curcumin, Demethoxycurcumin, Bisdemethoxycurcumin | Curcuminoids (polyphenols) | Inhibition of NF-κB, downregulation of TNF-α, IL-6, iNOS, COX-2 |
| | Turmerones (ar-, α-, β-turmerone) | Sesquiterpenes | Enhances bioavailability of curcumin, immunomodulation |
| *Ocimum sanctum* | Eugenol | Phenylpropanoid | NF-κB inhibition, suppression of TNF-α, IL-6 |
| | Ursolic acid | Triterpenoid | T-cell regulation, STAT3 inhibition |
| | Apigenin | Flavonoid | Antioxidant, cytokine regulation |
| | Rosmarinic acid | Polyphenolic ester | Anti-inflammatory, antioxidant |
| | Ocimumosides | Glycosides | Adaptogenic, stress-induced immune regulation |

## 3. NF-κB Pathway in Chronic Inflammation

### 3.1 NF-κB Family Members and Canonical vs. Non-Canonical Pathways

The nuclear factor kappa B (NF-κB) family comprises transcription factors that regulate diverse biological processes, including immune responses, cell proliferation, and inflammation. The five main family members are RelA (p65), RelB, c-Rel, NF-κB1 (p50/p105), and NF-κB2 (p52/p100). These proteins form homo- or heterodimers, with the RelA–p50 heterodimer being the most abundant and functionally relevant in inflammation (Hayden & Ghosh, 2012).

NF-κB activation occurs through two distinct pathways: the canonical and non-canonical. The canonical pathway, which is rapid and transient, is mainly triggered by microbial products and pro-inflammatory cytokines. It involves phosphorylation and degradation of inhibitor of κB (IκB), allowing NF-κB dimers (e.g., p65/p50) to translocate into the nucleus (Lawrence, 2009). The non-canonical pathway is slower, activated by developmental signals such as lymphotoxin-β and BAFF, and primarily involves p52/RelB dimers (Sun, 2017). Both pathways ultimately converge on the regulation of inflammatory and immune gene expression, but the canonical route is considered the primary driver in chronic inflammatory diseases.

### 3.2 NF-κB Activation by Pro-Inflammatory Stimuli (LPS, TNF-α, IL-1β)

A variety of stimuli can activate NF-κB, linking innate and adaptive immunity. Lipopolysaccharide (LPS), a bacterial endotoxin, engages Toll-like receptor 4 (TLR4), leading to recruitment of MyD88 and activation of the IκB kinase (IKK) complex (Kawai & Akira, 2010). Similarly, pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) activate NF-κB via TNF receptor-associated factors (TRAFs) and receptor-interacting protein kinases (RIPKs), which also converge on the IKK complex. Activated IKK phosphorylates IκB, leading to its ubiquitination and degradation, thereby freeing NF-κB dimers for nuclear translocation (Liu et al., 2017).

### 3.3 Role of NF-κB in Transcription of Cytokines, Chemokines, and Adhesion Molecules

Once in the nucleus, NF-κB binds to κB motifs in DNA and promotes transcription of a wide range of genes involved in inflammation. These include pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), chemokines (CCL2, CXCL8), adhesion molecules (ICAM-1, VCAM-1), and enzymes like COX-2 and iNOS (Lawrence, 2009). The sustained expression of these mediators amplifies inflammatory cascades, recruits immune cells to inflamed tissues, and perpetuates chronic inflammation. In autoimmune diseases such as rheumatoid arthritis and inflammatory bowel disease, NF-κB-driven transcription is a critical driver of disease pathogenesis (Liu et al., 2017).

### 3.4 NF-κB as a Therapeutic Target

Given its central role in orchestrating inflammatory and immune responses, NF-κB is an attractive therapeutic target. Pharmacological inhibitors that block IKK activity, proteasome-mediated IκB degradation, or NF-κB DNA binding have shown promise in preclinical models (Hayden & Ghosh, 2012). Clinically, biologics such as TNF-α inhibitors indirectly reduce NF-κB activity by blocking

upstream cytokine signaling. However, systemic NF-κB inhibition poses challenges, as this pathway also regulates cell survival and host defense. Thus, selective modulation rather than complete suppression of NF-κB is considered a more viable strategy in chronic inflammatory diseases (Sun, 2017).

**Table 2. Overview of NF-κB Pathways, Stimuli, and Major Targets**

| Pathway | Key Stimuli | Main Dimers Involved | Target Genes Regulated | Clinical Relevance in Inflammation |
|---|---|---|---|---|
| Canonical | LPS, TNF-α, IL-1β | p65/p50 | TNF-α, IL-1β, IL-6, COX-2, iNOS, ICAM-1, VCAM-1 | Major driver of chronic inflammatory diseases |
| Non-canonical | Lymphotoxin-β, CD40L, BAFF | RelB/p52 | Genes for lymphoid organogenesis, B-cell survival | Supports adaptive immune regulation |

## 4. Cytokine Networks in Chronic Inflammatory Diseases

### 4.1 Pro-Inflammatory Cytokines (TNF-α, IL-1β, IL-6, IL-17, IFN-γ)

Pro-inflammatory cytokines are central mediators of chronic inflammatory responses. Tumor necrosis factor-alpha (TNF-α) is produced by macrophages, T cells, and dendritic cells and amplifies inflammation by inducing adhesion molecules, chemokines, and additional cytokines (Bradley, 2008). Interleukin-1 beta (IL-1β) promotes leukocyte recruitment, activates endothelial cells, and drives the expression of cyclooxygenase-2 (COX-2) and matrix metalloproteinases, contributing to tissue degradation (Dinarello, 2011). Interleukin-6 (IL-6) plays a dual role, acting both pro- and anti-inflammatory, but in chronic diseases its persistent activation via the JAK/STAT3 pathway enhances B-cell activation, Th17 cell differentiation, and systemic inflammation (Hunter & Jones, 2015).

Interleukin-17 (IL-17), secreted by Th17 cells, recruits neutrophils and synergizes with TNF-α and IL-1β to sustain chronic inflammation (Korn et al., 2009). Interferon-gamma (IFN-γ), produced mainly by Th1 cells and natural killer (NK) cells, activates macrophages and perpetuates antigen presentation, driving autoimmune responses in diseases like rheumatoid arthritis and multiple sclerosis (Billiau & Matthys, 2009).

### 4.2 Anti-Inflammatory Cytokines (IL-10, TGF-β)

In contrast, anti-inflammatory cytokines play essential roles in restoring immune homeostasis. Interleukin-10 (IL-10) is secreted by regulatory T cells (Tregs), macrophages, and B cells. It suppresses pro-inflammatory cytokine production, inhibits antigen presentation, and promotes immune tolerance (Saraiva & O'Garra, 2010). Transforming growth factor-beta (TGF-β) regulates immune cell differentiation, promotes Treg induction, and limits T-cell proliferation, thereby preventing excessive tissue injury (Li et al., 2006).

Although these cytokines are critical for resolution of inflammation, their activity is often insufficient in chronic inflammatory diseases due to overwhelming pro-inflammatory signaling or resistance at the receptor level.

### 4.3 Imbalance Between Pro- and Anti-Inflammatory Cytokines in Disease Progression

Chronic inflammatory diseases arise when the balance between pro- and anti-inflammatory cytokines shifts toward persistent activation of immune pathways. Elevated TNF-α, IL-6, and IL-17 levels drive autoimmune pathology, while inadequate IL-10 and TGF-β fail to control the inflammatory response (O'Shea & Murray, 2008). For example, in rheumatoid arthritis, excessive TNF-α and IL-1β induce joint destruction, whereas insufficient IL-10 activity exacerbates inflammation. In inflammatory bowel disease, Th1/Th17-associated cytokines predominate, overwhelming regulatory cytokine mechanisms (Neurath, 2014). This imbalance creates a self-perpetuating cycle of inflammation and tissue damage.

### 4.4 Cytokine-Driven Immune Cell Activation and Tissue Damage

Cytokines directly shape immune cell recruitment, differentiation, and effector function. Pro-inflammatory cytokines promote macrophage activation, neutrophil infiltration, and T-cell polarization toward pathogenic Th1 and Th17 subsets (Korn et al., 2009). These activated immune cells release reactive oxygen species, proteolytic enzymes, and additional cytokines, amplifying inflammation and damaging host tissues. Over time, this leads to fibrosis, loss of organ function, and systemic complications, as seen in chronic conditions such as asthma, IBD, and psoriasis (Zhang & An, 2007).

**Table 3. Major Cytokines in Chronic Inflammatory Diseases and Their Roles**

| Cytokine | Source Cells | Primary Function | Role in Chronic Inflammation |
|---|---|---|---|
| TNF-α | Macrophages, T cells | Induces adhesion molecules, cytokines | Joint destruction in RA, gut inflammation in IBD |
| IL-1β | Macrophages, dendritic cells | Leukocyte recruitment, COX-2 induction | Tissue degradation, fever, systemic inflammation |
| IL-6 | Macrophages, fibroblasts | B-cell activation, Th17 differentiation | Systemic inflammation, autoimmunity (RA, IBD) |
| IL-17 | Th17 cells | Neutrophil recruitment, synergy with TNF-α | Chronic neutrophilic inflammation, autoimmunity |
| IFN-γ | Th1, NK cells | Macrophage activation, antigen presentation | Autoimmune diseases (RA, MS, psoriasis) |
| IL-10 | Tregs, macrophages, B cells | Suppresses pro-inflammatory cytokines | Insufficient levels promote unchecked inflammation |
| TGF-β | Tregs, epithelial cells | Treg induction, immune suppression | Dysregulation leads to tissue fibrosis and autoimmunity |

## 5. Anti-Inflammatory Mechanisms of *Curcuma longa*

### 5.1 Inhibition of NF-κB activation and nuclear translocation

Curcumin, the principal curcuminoid in *Curcuma longa*, exerts a potent inhibitory effect on the NF-κB signaling axis, a central regulator of inflammatory gene expression. Mechanistically, curcumin interferes

with upstream activators of NF-κB by inhibiting the IκB kinase (IKK) complex, preventing phosphorylation and subsequent proteasomal degradation of IκBα; this retains NF-κB dimers (primarily p65/p50) in the cytoplasm and reduces their DNA binding in the nucleus (Gupta et al., 2013; Goel et al., 2008). By blocking NF-κB translocation, curcumin suppresses the transcriptional program that drives sustained production of pro-inflammatory mediators in chronic inflammatory tissues.

### 5.2 Downregulation of pro-inflammatory cytokines (TNF-α, IL-6, IL-17)

Downstream of NF-κB inhibition, curcumin reduces expression and secretion of multiple pro-inflammatory cytokines implicated in chronic inflammatory diseases. Preclinical studies demonstrate curcumin-mediated decreases in TNF-α and IL-6 production from activated macrophages and synovial cells, and evidence also indicates attenuation of Th17-associated cytokines such as IL-17 in animal models of autoimmunity (Gupta et al., 2013). This pleiotropic cytokine suppression reduces leukocyte recruitment and the positive feedback loops that sustain tissue inflammation.

### 5.3 Upregulation of anti-inflammatory mediators (IL-10)

Beyond suppression of pro-inflammatory signals, curcumin can enhance anti-inflammatory pathways. Several studies report increased expression of IL-10 and other regulatory molecules in curcumin-treated immune cells and disease models, suggesting that curcumin helps restore the pro/anti cytokine balance rather than producing indiscriminate immunosuppression (Goel et al., 2008). This dual action—dampening inflammatory drivers while supporting regulatory mediators—may underlie curcumin's ability to resolve inflammation with a relatively favorable safety profile.

### 5.4 Suppression of COX-2, iNOS, and ROS production

Curcumin attenuates enzymatic mediators of inflammation by downregulating cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) expression, both of which are NF-κB target genes. Reduction of COX-2 lowers pro-inflammatory prostaglandin synthesis, while suppressed iNOS reduces excessive nitric oxide production that contributes to oxidative and nitrosative stress in inflamed tissues (Gupta et al., 2013). In parallel, curcumin acts as a scavenger of reactive oxygen species (ROS) and induces phase II antioxidant enzymes (e.g., heme oxygenase-1, glutathione S-transferases), which together limit oxidative damage that amplifies inflammatory signaling (Goel et al., 2008).

### 5.5 Modulation of T-cell and macrophage responses

Curcumin modulates both innate and adaptive immune cells. In macrophages and dendritic cells, curcumin reduces antigen-stimulated production of pro-inflammatory cytokines and decreases expression of costimulatory molecules, leading to attenuated T-cell priming. In T-cell compartments, curcumin inhibits pathogenic Th1/Th17 differentiation while favoring regulatory T-cell (Treg) phenotypes in several experimental systems, thereby shifting immune responses toward tolerance and limiting autoimmune tissue injury (Gupta et al., 2013; Goel et al., 2008). These immunoregulatory effects complement curcumin's molecular inhibition of NF-κB and cytokine production and are central to its efficacy in animal models of chronic inflammatory disease.

**Table 4. Major Anti-inflammatory Actions of Curcumin and Representative Evidence**

| Mechanistic target | Cellular / molecular effect | Representative functional outcome | Evidence type (examples) |
|---|---|---|---|
| NF-κB / IKK | Inhibits IKK activity; prevents IκBα degradation and NF-κB nuclear translocation | Reduced transcription of pro-inflammatory genes | In vitro cell studies; animal models. (Gupta et al., 2013) |
| Pro-inflammatory cytokines | Lowers TNF-α, IL-6, IL-17 expression/secretion | Decreased leukocyte recruitment and inflammation | In vitro and in vivo studies. (Goel et al., 2008) |
| Anti-inflammatory mediators | Upregulates IL-10 and regulatory signals | Restores cytokine balance, promotes resolution | Animal and ex vivo immune cell studies. (Goel et al., 2008) |
| COX-2 / iNOS / ROS | Downregulates COX-2 and iNOS; scavenges ROS; induces antioxidant enzymes | Less prostaglandin and nitrosative stress; reduced tissue damage | Biochemical and animal inflammation models. (Gupta et al., 2013) |
| Immune cell modulation | Suppresses macrophage activation; shifts T-cell polarization (↓Th1/Th17, ↑Treg) | Reduced autoimmunity and chronic tissue injury | Animal autoimmune/inflammatory disease models. (Gupta et al., 2013) |

## 6. Immunosuppressive Mechanisms of *Ocimum sanctum*

### 6.1 Regulation of T helper subsets (Th1, Th17 vs. Treg balance)

*Ocimum sanctum* (tulsi) contains multiple phytochemicals that influence T-cell differentiation and effector function. Experimental and clinical reports indicate that tulsi extracts can downregulate pathogenic Th1 and Th17 responses—both implicated in autoimmunity and chronic inflammation—while favoring regulatory pathways that enhance Treg numbers or function. This shift is mediated by suppression of pro-inflammatory cytokines (e.g., IL-6, IL-17, IFN-γ) and by promoting anti-inflammatory mediators such as IL-10, helping to rebalance adaptive immunity toward tolerance rather than aggression (Mondal et al., 2009; Cohen, 2014). Such reprogramming of T helper subsets reduces tissue-directed immune damage in models of chronic inflammation.

### 6.2 Inhibition of NF-κB and STAT3 pathways

Key tulsi constituents (for example, eugenol and ursolic acid) interfere with intracellular signaling cascades that sustain inflammation. Several studies and reviews report that these phytochemicals inhibit NF-κB activation—limiting nuclear translocation of NF-κB subunits and downstream transcription of pro-inflammatory genes—and can also modulate STAT3 signaling, which is central to IL-6–driven inflammation and Th17 differentiation (Cohen, 2014; Shanmugam et al., 2013). By attenuating both NF-κB and STAT3 axes, *O. sanctum* acts upstream of cytokine amplification loops that maintain chronic disease.

### 6.3 Modulation of B-cell activation and antibody production

Tulsi extracts have been reported to modulate humoral responses, including effects on B-cell activation and antibody generation. The net effect described in the literature is context-dependent: in models of

hyperactive humoral immunity, tulsi components reduce excessive antibody production and lower pro-inflammatory isotypes, while in immunodeficient settings tulsi may support normal antibody responses (Mondal et al., 2009; Cohen, 2014). These modulatory actions appear mediated through altered cytokine milieus (less IL-6 and IL-21) and reduced antigen-presenting cell stimulation, thereby indirectly downshifting B-cell hyperactivation.

### 6.4 Reduction in dendritic cell maturation and antigen presentation

Dendritic cells (DCs) are gatekeepers of adaptive immunity; their maturation state determines the strength and quality of T-cell responses. Constituents of *O. sanctum* have been shown to impair DC maturation markers and co-stimulatory molecule expression in vitro and in some animal studies, leading to reduced capacity for naive T-cell priming and decreased inflammatory T-cell polarization (Cohen, 2014). By limiting DC maturation and antigen presentation, tulsi lowers the initiation and perpetuation of pathogenic adaptive responses.

### 6.5 Attenuation of stress-induced immune hyperactivation

Tulsi is classically described as an adaptogen; experimental and clinical evidence supports its capacity to blunt physiological stress responses (e.g., glucocorticoid and sympathetic activation) that otherwise exacerbate immune activation. Stress hormones and neuroimmune pathways potentiate NF-κB and pro-inflammatory cytokine production; tulsi's adaptogenic and antioxidant properties therefore indirectly reduce stress-linked immune hyperactivity and downstream tissue inflammation (Mondal et al., 2009). This neuroimmune modulation contributes to tulsi's overall immunosuppressive profile in chronic inflammatory contexts.

## 7. Dual Mechanistic Interplay: Synergistic Modulation of NF-κB and Cytokine Networks

### 7.1 Convergent pathways targeted by *Curcuma longa* and *Ocimum sanctum*

Although their dominant phytochemical classes differ, *Curcuma longa* (curcuminoids/turmerones) and *Ocimum sanctum* (phenylpropanoids, triterpenoids, flavonoids) converge functionally on several core inflammatory pathways. Both attenuate NF-κB activation and downstream transcription of pro-inflammatory genes; both reduce key cytokines such as TNF-α and IL-6; and both modulate immune cell phenotypes (macrophages, T cells, dendritic cells) toward a less inflammatory state (Gupta et al., 2013; Cohen, 2014). Because they act at overlapping but not identical molecular nodes (for example, curcumin strongly scavenges ROS and inhibits COX-2/iNOS, while tulsi constituents more robustly affect adaptogenic and some STAT3-dependent processes), their combination can produce broader pathway coverage than either herb alone.

### 7.2 Complementary suppression of cytokine storms and chronic inflammation

In acute hyperinflammatory states ("cytokine storms"), rapid suppression of cytokine production and blockade of positive feedback loops is critical. Curcumin's capacity to quickly inhibit NF-κB, COX-2, and ROS generation can blunt initiation and amplification of cytokine release, while tulsi's modulatory effects on STAT3, DC maturation, and stress axes can prevent continued cytokine propagation and

adaptive immune overdrive. In chronic disease, where low-grade but persistent cytokine production sustains pathology, the paired herbs may (a) lower basal pro-inflammatory tone, (b) promote regulatory mediators such as IL-10 and TGF-β, and (c) restore immune homeostasis more effectively than monotherapy (Goel et al., 2008; Mondal et al., 2009).

### 7.3 Potential benefits in autoimmune and inflammatory diseases (RA, IBD, lupus, psoriasis)

Mechanistically, the combined targeting of innate drivers (macrophage cytokine release, NF-κB) and adaptive effectors (Th17/Th1 polarization, DC priming, B-cell activation) suggests translational utility across diverse chronic inflammatory conditions. Preclinical models support efficacy of curcumin in arthritis, colitis, and psoriasis-like inflammation, and tulsi has shown immunomodulatory benefits in experimental and small clinical studies; together they could reduce disease activity, lower required doses of conventional immunosuppressants, and improve symptom control with fewer side effects (Gupta et al., 2013; Mondal et al., 2009). However, rigorous randomized clinical trials of combined therapy are sparse and necessary to validate these potential benefits.

### 7.4 Comparative effectiveness with conventional immunosuppressants

Compared with conventional immunosuppressive drugs (corticosteroids, calcineurin inhibitors, biologic cytokine blockers), curcumin and tulsi offer advantages in safety, pleiotropy of action, and cost. They typically produce more moderate immunosuppression and act across multiple pathways rather than blocking a single cytokine receptor, which may reduce the risk of opportunistic infections associated with deep, targeted immunosuppression (Smolen et al., 2016). Conversely, their potency and bioavailability are lower, effects can be slower to manifest, and variability in extracts/dosing complicates direct comparisons. Therefore, herbal adjuncts are best conceptualized as complementary agents that may permit dose reduction of conventional drugs or provide maintenance support, rather than as replacements for potent, life-saving immunosuppressants in severe disease (Hayden & Ghosh, 2012; Gupta et al., 2013).

**Table 5. Summary of Complementary Mechanisms and Potential Clinical Roles of *Curcuma longa* and *Ocimum sanctum***

| **Mechanistic domain** | ***Curcuma longa* (curcumin, turmerones)** | ***Ocimum sanctum* (eugenol, ursolic acid, flavonoids)** | **Complementary/Combined clinical role** |
|---|---|---|---|
| NF-κB inhibition | Direct IKK inhibition; prevents NF-κB nuclear entry (strong) | Inhibits NF-κB activation via multiple phytochemicals | Broader blockade of NF-κB signaling |
| STAT3 / Th17 axis | Indirectly reduces IL-6 and Th17 responses | Direct modulation of STAT3 and Th17/Treg balance | Enhanced suppression of Th17-mediated pathology |
| Oxidative stress / COX-2/iNOS | Robust antioxidant, COX-2/iNOS suppression | Antioxidant support; reduces DC maturation | Reduced tissue oxidative damage and inflammatory enzyme activity |
| Immune cell modulation | Shifts macrophages and T cells toward regulatory phenotypes | Suppresses DC maturation, modulates B cells and Tregs | Multi-level immune reprogramming |

| | | | |
|---|---|---|---|
| Clinical advantages | Well-studied, pleiotropic, antioxidant | Adaptogenic, immunoregulatory, stress-modulating | Potential to lower drug doses and improve tolerability |
| Limitations | Low oral bioavailability; variable formulations | Variable extract composition; potency variability | Need for optimized formulations and clinical trials |

## 8. Preclinical and Clinical Evidence

### 8.1 In vitro studies (immune cells, cytokine assays)

In vitro work has extensively characterized how curcuminoids and *Ocimum sanctum* phytochemicals modulate immune cells and cytokine production. Curcumin reduces NF-κB DNA binding in macrophages and dendritic cells, lowers LPS-induced TNF-α and IL-6 secretion, inhibits COX-2 and iNOS expression, and attenuates ROS production in multiple cell lines (Gupta et al., 2013; Goel et al., 2008). Similarly, tulsi constituents such as eugenol and ursolic acid suppress pro-inflammatory cytokine release from macrophages, inhibit DC maturation markers in vitro, and alter T-cell cytokine profiles in culture, favoring IL-10 production in several experimental setups (Cohen, 2014; Mondal et al., 2011). Collectively, these mechanistic studies provide molecular rationale for anti-inflammatory and immunoregulatory effects observed in vivo.

### 8.2 In vivo models of chronic inflammation (arthritis, colitis, asthma)

Preclinical animal models demonstrate therapeutic benefits of both agents across diverse inflammatory disease models. Curcumin reduces joint swelling, inflammatory cell infiltration, and cartilage damage in rodent arthritis models, and lowers colonic inflammation in chemically induced colitis models through inhibition of NF-κB and suppression of Th17 responses (Gupta et al., 2013). Tulsi extracts have shown reduced inflammatory markers and improved histopathology in models of arthritis and experimentally induced inflammation; tulsi's adaptogenic effects also reduce stress-exacerbated inflammation in animal studies (Cohen, 2014; Mondal et al., 2011). Several studies used formulations (nanoparticles, phospholipid complexes) to improve curcumin exposure and thereby efficacy (Tabanelli et al., 2021).

### 8.3 Clinical studies on *Curcuma longa* supplementation

Clinical trials and systematic reviews indicate potential benefit of curcumin formulations as adjunctive therapy for some chronic inflammatory conditions, although study quality and formulations vary. Notable trials include Hanai et al.'s ulcerative colitis maintenance trial that reported higher remission rates with curcumin add-on therapy (Hanai et al., 2006), and randomized trials in rheumatoid arthritis and osteoarthritis showing improved symptoms and inflammatory markers with bioavailable curcumin preparations (Amalraj et al., 2017; Zeng et al., 2022). Systematic reviews conclude curcumin is generally safe and can improve disease activity in selected trials, but emphasize heterogeneity in dose, formulation, and study size (Coelho et al., 2020; Zeng et al., 2022).

### 8.4 Clinical studies on *Ocimum sanctum* supplementation

Human evidence for tulsi is smaller but supportive of immunomodulatory and safety signals. A well-known randomized, double-blind, crossover trial in healthy volunteers reported immunomodulatory effects (changes in selected immune markers) following ethanolic tulsi extract administration (Mondal et al., 2011). Broader clinical reviews report tulsi as generally safe in human studies and suggest benefits for stress reduction, metabolic parameters, and mild anti-inflammatory effects, but high-quality randomized trials in chronic inflammatory disease populations remain limited (Jamshidi & Cohen, 2017).

### 8.5 Combination or co-administration evidence

Direct clinical trials evaluating combined curcumin + tulsi therapy in chronic inflammatory diseases are sparse. Some small pilot studies have explored topical or local combinations (for oral conditions, periodontal adjuncts, or mucosal applications) with promising preliminary outcomes (Rahalkar et al., 2021; Srivastava et al., 2015). Preclinical combination data suggest additive or synergistic suppression of NF-κB and inflammatory cytokines, but robust randomized clinical trials testing systemic co-administration for RA, IBD, or psoriasis are presently lacking.

**Table 6. Representative preclinical and clinical studies of *Curcuma longa* and *Ocimum sanctum***

| Model / Study type | Intervention (representative dose/formulation) | Key outcome(s) | Reference |
|---|---|---|---|
| Ulcerative colitis — RCT (maintenance) | Curcumin 1 g/day (adjunct to standard therapy) | Greater remission rates vs placebo | Hanai et al., 2006 |
| Rheumatoid arthritis — RCT (bioavailable curcumin) | Curcumin matrix formulation 250 mg twice daily | Improved DAS28, CRP, ESR vs placebo | Amalraj et al., 2017 |
| Healthy volunteers — randomized crossover | Tulsi ethanolic extract 300 mg capsule | Changes in immune markers; tolerability good | Mondal et al., 2011 |
| Systematic review — curcumin in arthritis/IBD | Various curcumin formulations | Generally safe; symptom/inflammation improvement in many trials but heterogeneity present | Zeng et al., 2022; Coelho et al., 2020 |
| Periodontal local delivery — pilot | Local curcumin + tulsi gel | Improvement in periodontal parameters (pilot data) | Rahalkar et al., 2021 |

## 9. Challenges and Future Perspectives

### 9.1 Bioavailability and pharmacokinetics of curcumin and tulsi phytochemicals

A major translational barrier for curcumin is low oral bioavailability due to poor aqueous solubility, rapid metabolism, and systemic elimination; consequently, plasma levels after standard oral doses are low (Tabanelli et al., 2021). Tulsi phytochemicals also exhibit variable absorption and metabolic profiles that

depend on extract composition. These pharmacokinetic limitations complicate dose selection and reproducibility across clinical trials (Bertoncini-Silva et al., 2024).

### 9.2 Strategies for enhanced delivery (nanoparticles, liposomes, phytosome complexes)

Multiple formulation strategies have been developed to overcome curcumin's bioavailability problems: nanoencapsulation (PLGA, solid lipid nanoparticles), liposomes, phospholipid complexes (phytosomes), micellar systems, and complexation with piperine or turmeric essential oils (to enhance absorption) (Tabanelli et al., 2021; Bertoncini-Silva et al., 2024). Recent studies demonstrate that optimized nano- or matrix formulations yield higher plasma curcuminoid levels and improved clinical endpoints in pilot trials (Amalraj et al., 2017; Han et al., 2024). Comparable pharmaceutical optimization for tulsi phytochemicals (standardized extracts, enriched fractions) is less mature but progressing.

### 9.3 Safety, dosage, and long-term immunosuppressive concerns

Overall, curcumin and tulsi have favorable safety profiles in clinical studies, with few serious adverse events reported at commonly studied doses; nevertheless, long-term immunosuppression risks are understudied. Because both agents modulate immune responses, caution is warranted when combining them with potent immunosuppressants or in populations at high risk for infection. Standardized reporting of adverse events, drug-herb interaction studies, and long-term safety monitoring are essential prior to recommending broad use in immunocompromised patients (Jamshidi & Cohen, 2017; Zeng et al., 2022).

### 9.4 Integrative medicine approaches – combining phytotherapy with standard drugs

The most pragmatic translational path is integrative: using curcumin and tulsi as adjuncts to reduce disease activity and potentially lower required doses of conventional drugs (e.g., steroids, biologics), thereby minimizing side effects. Pilot trials show adjunctive benefit in IBD and arthritis, but rigorous randomized controlled trials with standardized extracts, appropriate endpoints, and pharmacokinetic/pharmacodynamic co-assessments are required to define optimal combinations and timing (Coelho et al., 2020; Zeng et al., 2022).

### 9.5 Future directions in personalized medicine and immunomodulatory therapy

Future research should prioritize: (a) standardized, bioavailable formulations with reproducible pharmacokinetics; (b) mechanistic biomarker-driven trials that link target engagement (e.g., NF-κB activity, cytokine panels) to clinical outcomes; (c) dose-finding and drug-interaction studies for safe co-administration with immunosuppressants; and (d) stratified or precision approaches that identify patient subgroups (biomarker signatures, genetic polymorphisms) most likely to benefit. Combination trials directly testing curcumin + tulsi versus monotherapy, and head-to-head comparisons with standard agents (or steroid-sparing designs), would meaningfully advance clinical translation.

## 10. Conclusion

The accumulated evidence highlights *Curcuma longa* and *Ocimum sanctum* as promising immunomodulatory botanicals with complementary mechanisms of action. Both agents regulate key

immune pathways, including NF-κB signaling, STAT3 activation, and cytokine production, while also influencing T-cell subset balance, dendritic cell function, and stress-associated immune hyperactivation. Preclinical studies consistently demonstrate anti-inflammatory and immunosuppressive effects in models of arthritis, colitis, and airway inflammation, and early-phase clinical studies suggest potential benefits in chronic inflammatory disorders such as ulcerative colitis, rheumatoid arthritis, and stress-related immune dysfunction.

Despite encouraging findings, translation into mainstream clinical use remains limited by poor bioavailability, variability in extract composition, and the scarcity of high-quality randomized trials, especially for tulsi. Advances in formulation science—including nanoparticle delivery, phytosome complexes, and synergistic co-administration strategies—are addressing pharmacokinetic challenges and may help realize the full therapeutic potential of these botanicals.

Taken together, curcumin and tulsi represent a rational pair of phytotherapeutic agents capable of targeting overlapping and convergent immune pathways, with possible applications as adjuncts in autoimmune and inflammatory diseases. Future research should focus on standardized bioavailable formulations, mechanistic biomarker-driven clinical trials, and integrative medicine approaches that combine these botanicals with conventional therapies in a safe and evidence-based manner. With such advances, *Curcuma longa* and *Ocimum sanctum* could transition from traditional remedies to scientifically validated tools in modern immunomodulatory therapy.

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Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-486-3

# Chapter 7: Botanical Modulation of Cutaneous Inflammation and Microbial Dysbiosis by Azadirachta indica and Glycyrrhiza glabra: A Phytotherapeutic Approach to Dermatoses and Wound Healing

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## Abstract

Cutaneous inflammatory disorders and microbial dysbiosis, including acne, eczema, psoriasis, and chronic wounds, present significant global dermatological challenges. Conventional therapies such as corticosteroids, antibiotics, and antifungals often have limitations including resistance, adverse effects, and incomplete efficacy. Phytotherapeutics offer a promising alternative, with *Azadirachta indica* (neem) and *Glycyrrhiza glabra* (licorice) emerging as potent botanicals for skin health. Neem contains bioactives such as nimbidin, azadirachtin, and nimbolide, exhibiting anti-inflammatory, antimicrobial, antioxidant, and wound-healing effects. Licorice provides glycyrrhizin, glabridin, and liquiritigenin, contributing anti-inflammatory, corticosteroid-mimetic, melanogenesis-regulating, and photoprotective properties. The synergistic application of these botanicals enables dual modulation of inflammation and microbial dysbiosis. Modern delivery systems, including nanoemulsions, liposomes, hydrogels, and topical films, enhance bioavailability and therapeutic efficacy. Preclinical, in silico, and clinical evidence support their role in managing dermatoses and promoting tissue regeneration. While generally safe, attention to dosage, standardization, and potential adverse effects is critical. Integration with microbiome-targeted therapies and personalized phytodermatology represents a promising future direction for sustainable and evidence-based dermatological care.

**Keywords:** *Azadirachta indica*, *Glycyrrhiza glabra*, dermatoses, wound healing, phytotherapy, microbial dysbiosis, anti-inflammatory, antioxidant, topical formulations

## 1. Introduction

Cutaneous inflammatory disorders and microbial dysbiosis represent a significant global health burden, affecting millions of individuals across diverse age groups and geographical regions. Skin conditions such as acne, eczema, psoriasis, atopic dermatitis, and chronic wounds not only impair physical appearance but also compromise the skin's essential barrier and immunological functions, leading to pain, itching,

secondary infections, and reduced quality of life (Hay et al., 2014). In many low- and middle-income countries, microbial dysbiosis, including colonization by *Staphylococcus aureus*, *Candida albicans*, and resistant bacterial strains, exacerbates these conditions, making their management increasingly challenging (Byrd et al., 2018).

Conventional therapies for skin disorders largely depend on corticosteroids, antibiotics, antifungals, and immunosuppressants. While these interventions often provide short-term relief, their prolonged use is associated with substantial drawbacks. Corticosteroids may cause skin thinning, telangiectasia, and systemic side effects such as adrenal suppression (Ference & Last, 2009). Also, the extensive usage of antibiotics in dermatology has led to antimicrobial resistance with common bacteria causing disease becoming less susceptible to treatment (Walsh & Wuthrich, 2020). Despite their efficaciousness, antifungals often encounter problems of resistance and relapse, especially in chronic or immunocompromised individuals (Arendrup 2014). These limitations highlight an urgent demand for new and adjunct therapeutic strategies that not only are effective, but also have long term safety profile.

Phytotherapeutics, which are formulated by medicinal plants products, have become the subject of interest in dermatology because of their multi-targeted pharmacological activities and high safety profile along with natural abundance and historical usage in traditional medicine. Pharmaceutical applications in cutaneous diseases Conventionally, the use of plant-derived bioactives/delivery system offers anti-inflammatory, antimicrobial, antioxidant and woundhealing effects to tackle various aspects of skin pathology (Mukherjee et al., 2011). In contrast to single-target synthetic drugs, phytochemicals commonly function synergistically and can act on complex molecular pathways and the skin microbiome with minimal side effects. This broader perspective has made the botanicals as a hope potential for treatment of dermatoses and healing process.

In this aspect, Azadirachta indica (Neem) and Glycyrrhiza glabra (Licorice) are two such botanicals of high dermatological consequence. Neem Neem is one of the most respected plants of Ayurveda, having a rich source of bioactives namely; nimbidin, azadirachtin and quercetin which exert potent anti-inflammatory, antimicrobial, and wound-healing activities (Subapriya & Nagini., 2005). Licorice The root is a popular ingredient in Unani and traditional Chinese medicine, with glycyrrhizin, liquiritigenin and glabridin identified as corticosteroid-mimeticanti-inflammatory agents, antioxidants and depigmenting agents (Asl & Hosseinzadeh 2008). Crucially, both plants reshuffle skin microbial ecologies when stimulating tissue regeneration, rendering them potent alternatives to treat dermatoses linked to inflammation and dysbiosis.

The aim of this chapter was to investigate how these two botanicals can reduce cutaneous inflammation and microbial dysbiosis, either when used alone or in combination. Based on their phytochemistry, mechanisms of action, preclinical and clinical evidences and incorporation into cutting edge delivery systems, this review emphasizes that the use of neem and licorice cuts across the past to become sustainable evidence-based dermatological and wound care phytomedicines.

## 2. Pathophysiology of Cutaneous Inflammation and Microbial Dysbiosis

### 2.1. Skin as an Immunological Organ

The skin is the largest organ of the body, functioning as a physical and immunological interface between the host and external environment. It contains a wide array of immune cells such as keratinocytes, Langerhans' cells, dermal dendritic c ells, macrophage sand T cell that represent the first and second line

of immune response (Paspa rakis et al., 2014). Keratinocytes can secrete cytokines and AMPs, the contributing factors of pathogen defense and inflammation control. Skin associated lymphoid tissue (SALT) is the major effector and surveillance frontier of host cells for tolerance towards commensal, but recognition and reactions against invading pathogens (Nguyen & Soulika 2019)..

### 2.2. Molecular Pathways in Skin Inflammation

Inflammation of the skin disorders is characterized by disruption in several signaling pathways. Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) could activate the nuclear factor kappa B (NF-κB) pathway, which further induces the expression of pro-inflammatory cytokines including IL-1β, TNF-α and IL-6 (Liu et al., 2017). Similarly, the mitogen-activated protein kinase (MAPK) pathway, including ERK, JNK, and p38 cascades, contributes to the release of inflammatory mediators, keratinocyte proliferation, and dermal remodeling (Zhang & Dong, 2021). Moreover, eicosanoids from arachidonic acid including prostaglandins and leukotrienes further escalate inflammation and pain in skin lesions (Dennis & Norris, 2015). Deregulation of these pathways occurs in acne, psoriasis, and atopic dermatitis leading to chronic inflammation and tissue destruction.

### 2.3. Microbial Dysbiosis in Skin Diseases

The skin microbiome, which consists of bacteria, fungi, viruses and mites is indispensable for cutaneous homeostasis. An imbalanced microbial community (dysbiosis) plays a crucial role for the development, maintenance and resolution of cutaneous pathology (Belkaid & Segre, 2014). In acne vulgaris, C. acnes strains carrying virulence genes induce the inflammation by activation of toll-like receptor (TLR) and NF-κB signalling pathways (Fitz-Gibbon et al., 2013). Staphylococcus aureus overgrowth in atopic dermatitis: a summary of the current information The increased Staphylococcus aureus burden observed in AD has both negative impact on barrier function and Th2 biased immune responses (Nakatsuji et al. Psoriasis is associated with changes in Firmicutes and Actinobacteria that are proportional to disease severity (Yan et al., 2020). Chronic wounds typically contain polymicrobial biofilms, such as Pseudomonas aeruginosa and methicillin-resistant S. aureus (MRSA), that impede healing and are resistant to standard antibiotics (James et al., 2008).

### 2.4. Role of Oxidative Stress in Dermatoses and Delayed Wound Healing

Reactive oxygen species (ROS) are essential signaling molecules in host defense and wound repair; however, excessive ROS production leads to oxidative stress, DNA damage, and lipid peroxidation. In inflammatory skin diseases such as psoriasis and atopic dermatitis, elevated oxidative stress exacerbates keratinocyte dysfunction and cytokine release (Kurutas, 2016). During wound healing, high ROS levels impair fibroblast migration, collagen synthesis, and angiogenesis, resulting in delayed tissue repair (Schäfer & Werner, 2008). The interplay between oxidative stress and microbial infection further aggravates chronic wound pathology, as pathogens often exploit oxidative environments to establish biofilms.

**Table 1. Key Factors in Cutaneous Inflammation and Microbial Dysbiosis**

| Pathological Factor | Key Mechanism | Associated Disorders |
|---|---|---|
| NF-κB activation | Induces pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) | Acne, psoriasis, eczema |
| MAPK signaling | Promotes keratinocyte proliferation and inflammation | Psoriasis, atopic dermatitis |
| Eicosanoid production | Prostaglandins/leukotrienes amplify pain and inflammation | Dermatitis, wounds |
| Microbial dysbiosis | Overgrowth of pathogenic microbes, loss of commensal balance | Acne (*C. acnes*), eczema (*S. aureus*), chronic wounds (biofilms) |
| Oxidative stress | ROS-induced cellular and tissue damage | Psoriasis, delayed wound healing |

## 3. Azadirachta indica (Neem): Phytochemistry and Dermatological Applications

### 3.1. Botanical Description and Ethnomedicinal Use

*Azadirachta indica* A. Juss, commonly known as neem, belongs to the family Meliaceae. It is a fast-growing evergreen tree native to the Indian subcontinent and widely cultivated across tropical regions (Subapriya & Nagini, 2005). Traditionally, neem has been used in Ayurvedic, Unani, and folk medicine for managing skin infections, inflammation, and wounds. Neem leaves, bark, seeds, and oil are applied topically or ingested for their therapeutic properties, including antimicrobial, anti-inflammatory, antipyretic, and immunomodulatory effects (Biswas et al., 2002).

### 3.2. Bioactive Constituents

Neem contains a diverse array of bioactive compounds, primarily terpenoids, flavonoids, and fatty acids, which contribute to its dermatological potential. Key constituents include:

- **Nimbidin**: Anti-inflammatory and immunomodulatory effects
- **Azadirachtin**: Antimicrobial and insecticidal properties
- **Nimbolide**: Potent antioxidant and anti-inflammatory agent
- **Quercetin and other flavonoids**: Free radical scavenging and anti-inflammatory activity
- **Fatty acids**: Contribute to skin barrier repair and hydration (Subapriya & Nagini, 2005; Biswas et al., 2002)

### 3.3. Mechanisms of Action in Skin Health

**Anti-inflammatory Signaling Modulation**
Neem bioactives inhibit NF-κB and MAPK signaling pathways, reducing the production of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) and suppressing chronic inflammation in dermatoses (Saini et al., 2018).

**Antimicrobial and Antibiofilm Properties**
Neem extracts demonstrate activity against Gram-positive and Gram-negative bacteria (*Staphylococcus*

*aureus*, *Escherichia coli*) and fungi (*Candida albicans*). Biofilm formation is inhibited by nimbolide and azadirachtin, reducing microbial colonization in wounds (Chattopadhyay et al., 2004).

**Antioxidant Activity and Free Radical Scavenging**

Flavonoids and phenolic compounds in neem neutralize reactive oxygen species (ROS), preventing oxidative damage to keratinocytes and fibroblasts, which is critical in inflammatory skin disorders and wound repair (Saini et al., 2018).

**Wound-Healing and Tissue Regeneration**

Neem promotes fibroblast proliferation, collagen deposition, and angiogenesis, accelerating the repair of cutaneous wounds. The combined antioxidant, anti-inflammatory, and antimicrobial effects synergistically enhance tissue regeneration (Kumar et al., 2011).

### 3.4. Evidence from In Vitro and In Vivo Studies

In vitro studies demonstrate neem leaf and bark extracts inhibit pro-inflammatory cytokine production in keratinocyte cultures and suppress microbial growth (Chattopadhyay et al., 2004). In vivo animal models reveal that topical neem formulations accelerate wound closure, increase collagen content, and reduce inflammatory cell infiltration in excision and burn wound models (Kumar et al., 2011). Neem oil and aqueous leaf extracts show protective effects against UV-induced skin damage and oxidative stress in experimental studies (Saini et al., 2018).

### 3.5. Clinical Applications in Dermatology

Neem has been explored in several clinical contexts:

- **Acne vulgaris**: Topical neem gel reduces lesion counts and inflammation in mild-to-moderate acne patients (Kumar et al., 2011).
- **Eczema and psoriasis**: Neem-based ointments decrease erythema, scaling, and pruritus, likely through immunomodulatory and anti-inflammatory effects (Biswas et al., 2002).
- **Wound healing**: Neem formulations, including gels and oils, promote faster epithelialization and reduce infection rates in chronic wounds (Chattopadhyay et al., 2004).

**Table 2. Major Bioactive Constituents of *Azadirachta indica* and Their Dermatological Actions**

| Bioactive Compound | Mechanism of Action | Dermatological Relevance |
|---|---|---|
| Nimbidin | Inhibits NF-κB, MAPK pathways | Anti-inflammatory, reduces cytokine-mediated skin inflammation |
| Azadirachtin | Antimicrobial, antibiofilm | Controls bacterial/fungal skin infections |
| Nimbolide | Antioxidant, anti-inflammatory | Prevents oxidative stress and inflammation |
| Quercetin/Flavonoids | Free radical scavenging, anti-inflammatory | Protects keratinocytes, promotes wound healing |
| Fatty acids | Skin barrier repair, hydration | Enhances tissue regeneration and |

| | | |
|---|---|---|
| | | barrier function |

## 4. Glycyrrhiza glabra (Licorice): Phytochemistry and Dermatological Applications

### 4.1. Traditional Medicinal Uses in Skin Ailments

*Glycyrrhiza glabra* L., commonly known as licorice, belongs to the Fabaceae family. Licorice has been used in traditional medicine systems, including Ayurveda, Unani, and Traditional Chinese Medicine, for centuries to manage skin conditions such as eczema, dermatitis, psoriasis, melasma, and burns (Asl & Hosseinzadeh, 2008). Topical applications of licorice root extracts and formulations have historically been employed to reduce inflammation, lighten hyperpigmented lesions, and promote wound healing.

### 4.2. Bioactive Constituents

Licorice contains diverse bioactive molecules with significant dermatological potential. Key constituents include:

- **Glycyrrhizin**: Triterpenoid saponin with anti-inflammatory and corticosteroid-like effects
- **Liquiritigenin**: Flavonoid with antioxidant and anti-inflammatory properties
- **Glabridin**: Isoflavonoid known for melanogenesis inhibition and skin-lightening activity
- **Other flavonoids and saponins**: Contribute to antimicrobial, antioxidant, and photoprotective actions (Asl & Hosseinzadeh, 2008; Fiore et al., 2008)

### 4.3. Mechanisms of Action in Skin Health

**Anti-inflammatory and Corticosteroid-Mimetic Effects**
Glycyrrhizin inhibits pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 via modulation of NF-κB signaling, mimicking corticosteroid activity without the adverse effects associated with synthetic steroids (Fiore et al., 2008).

**Modulation of Microbial Growth and Biofilms**
Licorice extracts exhibit antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*. Saponins disrupt biofilm formation, enhancing the efficacy of topical antimicrobial therapy in chronic wounds and infected dermatoses (Park et al., 2016).

**Skin Depigmentation and Melanogenesis Regulation**
Glabridin inhibits tyrosinase activity and melanogenesis, reducing hyperpigmentation and melasma. It also protects melanocytes from oxidative stress, contributing to a more uniform skin tone (Hwang et al., 2011).

**Antioxidant and Photoprotective Effects**
Flavonoids and polyphenols in licorice neutralize reactive oxygen species (ROS), protecting keratinocytes from oxidative damage. Licorice extracts also reduce UV-induced erythema and DNA damage, providing photoprotective benefits (Asl & Hosseinzadeh, 2008).

### 4.4. Preclinical and Clinical Evidence

Preclinical studies demonstrate that licorice root extracts reduce inflammation, enhance wound closure, and protect against oxidative stress in animal models of dermatitis, burns, and UV-induced skin damage (Fiore et al., 2008). Clinical trials have proven licorice to be effective in the treatment of hyperpigmentation, melasma severity and inflammation in patients with eczema and atopic dermatitis. The application of topical preparations containing glabridin and glycyrrhizin have resulted in a significant increase in the improvement of lesion appearance, pigmentation homogeneity and general skin condition compared to placebo without any major side effects (Hwang et al., 2011; Park et al., 2016).

**Table 3. Major Bioactive Constituents of *Glycyrrhiza glabra* and Their Dermatological Actions**

| Bioactive Compound | Mechanism of Action | Dermatological Relevance |
|---|---|---|
| Glycyrrhizin | Inhibits NF-κB, mimics corticosteroids | Anti-inflammatory, reduces cytokine-mediated skin inflammation |
| Liquiritigenin | Antioxidant, anti-inflammatory | Protects keratinocytes, reduces oxidative damage |
| Glabridin | Tyrosinase inhibitor, melanogenesis regulation | Skin-lightening, reduces hyperpigmentation |
| Flavonoids & Saponins | Antimicrobial, antibiofilm, ROS scavenging | Controls infections, enhances wound healing and photoprotection |

## 5. Synergistic Potential of *A. indica* and *G. glabra* in Dermatology

### 5.1. Complementary Phytochemical Actions

Neem and licorice contain bioactive compounds with overlapping and complementary dermatological activities. Neem is rich in terpenoids (nimbidin, azadirachtin, nimbolide) and flavonoids, whereas licorice contains saponins (glycyrrhizin) and isoflavonoids (glabridin, liquiritigenin) (Subapriya & Nagini, 2005; Asl & Hosseinzadeh, 2008). Combined, this allows them to work together and produce anti-inflammatory, antioxidant, antimicrobial and wound healing actions. For example, neem efficiently modulates microbial biofilms and attenuates tissue restoration; while licorice optimizes antioxidant defenses and melanogenesis regulation, synergistically supplement each other in dealing with difficult conditions of dermatoses.

### 5.2. Potential for Dual Modulation of Inflammation and Dysbiosis

The synergistic combination of neem and licorice can target both cutaneous inflammation and microbial dysbiosis simultaneously. Neem's terpenoids suppress NF-κB and MAPK pathways, reducing cytokine-mediated inflammation, while licorice's glycyrrhizin acts as a corticosteroid-mimetic to further attenuate inflammatory signaling (Saini et al., 2018; Fiore et al., 2008). Meanwhile, the two plants also possess antimicrobial and antibiofilm activities for bacteria (S. aureus, C. acnes) and fungi (C. albicans), which modulate normal flora on skin (Chattopadhyay et al., 2004; Park et al., 2016). Such dual modulation is highly advantageous when treating chronic wounds, acne, eczema, and psoriasis in which inflammation and microbial dysbiosis are present..

### 5.3. Formulation Strategies Combining Neem and Licorice Extracts

Some of the potential Topical and advanced delivery systems used to combined effect of neem and licorice were discussed below:

- **Creams and Ointments** Basic formulation for your mild to moderate dermises acting as an antiinflammatory and antimicrobial
- **Gels and Hydrogels** Aid patient acceptance, promote percutaneous absorption and create moist wound healing conditions.
- **Nanoparticles and Nanoemulsions**: improve the bioavailability and stability of the phytochemicals; enable targeted drug-delivery; allow sustained-release over a period of time, and facilitate skin penetration for target delivery to deeper dermal layer

These strategies maximize therapeutic efficacy while minimizing systemic exposure and adverse effects.

### 5.4. In Silico, In Vitro, and Translational Evidence of Synergism

Computational docking analysis show that azadirachtin and glycyrrhiza bioactives can simultaneously dock with inflammatory mediators (NF-κB, COX-2, IL-6) and microbial proteins indicating combined inhibitory effects (Saini et al., 2018). In vitro studies demonstrate that neem and licorice extracts, when combined, are more effective in inhibiting microbial growth compared to single preparations, reduce the production of pro-inflammatory cytokines in keratinocyte culture as well as increase fibroblast proliferation (Chattopadhyay et al., 2004; Park et al. Animal wound models from some translation research confirm that the combination application results in a faster restoration time, lesser inflammatory infiltration and greater collagen content deposition. These results indicate a multi-targeted, synergistic strategy applicable for clinical translation in dermatology.

**Table 4. Synergistic Effects of Neem and Licorice Bioactives in Skin Health**

| Phytochemical Source | Primary Bioactives | Mechanisms of Action | Dermatological Relevance |
|---|---|---|---|
| *Azadirachta indica* | Nimbidin, Azadirachtin, Nimbolide | Anti-inflammatory, antimicrobial, antioxidant, wound-healing | Reduces skin inflammation, controls biofilms, promotes tissue repair |
| *Glycyrrhiza glabra* | Glycyrrhizin, Glabridin, Liquiritigenin | Anti-inflammatory, antioxidant, melanogenesis regulation, antimicrobial | Reduces inflammation, oxidative stress, hyperpigmentation, and microbial dysbiosis |
| Combined Application | All above bioactives | Dual modulation of inflammatory pathways and microbial biofilms, enhanced antioxidant defense | Effective management of acne, eczema, psoriasis, chronic wounds, and hyperpigmentation |

## 6. Delivery Systems for Botanical Bioactives in Skin Disorders

### 6.1. Challenges: Poor Solubility, Stability, and Bioavailability

Azadirachta indica and Glycyrrhiza glabra have been reported to possess strong anti-inflammatory, antimicrobial, antioxidant, and wound-healing abilities; however their clinical usefulness has remained somewhat restricted due to low solubility, chemical instability and poor skin penetration. Hydrophobic and photo oxidatively labile bioactive constituents (i.e. nimbolide, azadirachtin, glycyrrhizin and glabridin) of plants are the limiting factor, as their poor solubility in aqueous vehicles also reduces the availability for topical application (Moghassemi & Hadjizadeh, 2014). Moreover, stratum corneum constitutes an effective barrier against dermal absorption and also a prohibitive factor of therapeutic effects.

### 6.2. Modern Approaches for Enhanced Delivery

#### Nanoemulsions

Nanoemulsions are dilute dispersions of one liquid phase in another that exhibit droplets at the nanometer scale. They also increase water solubility, protect bioactives from decomposition and facilitate transdermal delivery across the stratum corneum. Studies in preclinical settings have demonstrated that neem- and licorice-based nanoemulsions exhibited enhanced antimicrobial efficacy and faster wound healing abilities (Pandey et al., 2018).

#### Liposomes, Phytosomes, and Ethosomes

Liposomes are vesicular systems composed of phospholipids and are used for encapsulating hydrophilic as well as lipophilic drugs with advantages such as improved drug stability and targeted drug delivery. Phytosomes are phospholipids complexes of plant bioactives for better bioavailability. Ethosomes loaded with ethanol, are also improve the transderma delivery by skin lipid bilayer fluidization (Jain et al., 2016). These vesicular systems have been successfully used for trans-epidermal transport of neem flavonoids and licorice glycyrrhizin.

#### Hydrogels and Biopolymeric Scaffolds

Hydrogels offer moisture condition for wound healing and controlled release of bioactives. Biopolymeric scaffolds primarily comprised of chitosan, alginate, and cellulose can support tissue regeneration while providing controlled delivery. Hydrogels containing neem and licorice enhanced wound healing, along with increased fibroblast proliferation, collagen deposition and antimicrobial activities in animal wound models (Kumar et al., 2019).

#### Topical Films and Dressings

NE and LE containing films and dressings ensure that the skin takes advantage of a longer contact time while protecting wounds from microbial insult, thereby bolstering localized drug delivery. These systems are beneficial especially for chronic ulcers, burns and dermatoses wherein prolonged antiinflammatory and anti microbial effects are necessary..

## 7. Safety, Toxicology, and Regulatory Perspectives

### 7.1. Safety Profile of Neem and Licorice in Topical and Systemic Use

*Azadirachta indica* and *Glycyrrhiza glabra* are generally regarded as safe when used topically at recommended concentrations. Topical neem formulations rarely produce systemic toxicity and are well-tolerated in dermatological applications, including acne, eczema, and wound healing (Subapriya & Nagini, 2005). Licorice-containing topical formulations are also widely used for hyperpigmentation and inflammatory skin conditions, with minimal adverse effects (Asl & Hosseinzadeh, 2008). Oral or systemic use requires caution, as high doses can lead to dose-dependent toxicities.

### 7.2. Known Toxicities and Contraindications

**Neem:** Oral ingestion of high doses may cause gastrointestinal upset, hepatic effects, or nephrotoxicity in sensitive individuals. Topical use can occasionally trigger contact dermatitis in susceptible patients (Biswas et al., 2002).

**Licorice:** Excessive intake of glycyrrhizin can produce mineralocorticoid-like effects, leading to hypertension, hypokalemia, and fluid retention. Allergic reactions and contact dermatitis have also been reported for topical applications (Fiore et al., 2008).

Clinicians must consider patient-specific factors, including age, comorbidities, and concurrent medications, when recommending systemic use or high-concentration formulations.

### 7.3. Regulatory Approval Status and Pharmacopoeial Standards

Neem and licorice are recognized in multiple pharmacopoeias, including the Indian, European, and British Pharmacopoeias, which provide guidelines for identification, purity, and quality of plant materials and extracts (Subapriya & Nagini, 2005; Asl & Hosseinzadeh, 2008). Some countries classify standardized extracts as cosmetic ingredients, while concentrated preparations may require regulatory approval for medicinal claims.

### 7.4. Challenges in Standardization, Quality Control, and Dosage Optimization

The therapeutic efficacy of neem and licorice depends on consistent phytochemical composition, which can vary due to geographic origin, harvesting season, and extraction methods. Standardization of bioactive content (e.g., nimbidin, glycyrrhizin, glabridin) is critical to ensure reproducible effects. Quality control measures, including chromatographic profiling and bioassays, are essential for dosage optimization and minimizing adverse events. Advanced formulation strategies, such as nanoencapsulation, may help overcome variability and enhance bioavailability (Moghassemi & Hadjizadeh, 2014).

## 8. Future Prospects and Research Directions

### 8.1. Multi-Targeted Phytotherapy for Chronic Dermatoses

Combining neem and licorice bioactives provides a multi-targeted approach to managing inflammation, oxidative stress, and microbial imbalance. Future research should focus on identifying optimal synergistic ratios and formulation strategies for chronic skin disorders such as psoriasis, atopic dermatitis, and acne.

### 8.2. Integration with Microbiome-Targeted Therapies

Given the role of skin microbial dysbiosis in dermatoses, integrating phytotherapeutics with microbiome-modulating approaches (probiotics, prebiotics, or microbial metabolites) could enhance therapeutic outcomes and restore skin homeostasis (Belkaid & Segre, 2014).

### 8.3. Advances in Personalized Phytodermatology

Emerging technologies such as genomic profiling, metabolomics, and skin microbiome mapping may allow customization of neem- and licorice-based therapies according to individual patient phenotypes, optimizing efficacy and minimizing adverse reactions.

### 8.4. Gaps in Clinical Evidence and Translational Research Needs

Despite promising preclinical data, large-scale, randomized clinical trials are limited. Evidence gaps include long-term safety, standardized dosing, comparative efficacy with conventional therapies, and mechanistic studies on synergistic interactions. Addressing these gaps is critical for translating phytotherapeutics into mainstream dermatological care.

## 9. Conclusion

*Azadirachta indica* and *Glycyrrhiza glabra* offer significant therapeutic potential for the management of inflammatory and dysbiotic skin disorders. Their multi-targeted bioactive compounds confer anti-inflammatory, antioxidant, antimicrobial, melanogenesis-regulating, and wound-healing effects, making them valuable alternatives or adjuncts to conventional therapies. Advanced formulation strategies and integration with microbiome-targeted and personalized approaches may further enhance efficacy and safety. Systematic clinical evaluation and standardization are essential to establish evidence-based protocols for widespread dermatological application. Overall, neem and licorice represent safe, effective, and sustainable options in phytotherapeutic dermatology.

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Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-486-3

# Chapter 8: Endothelial Stabilization and Antihypertensive Potential of Allium sativum and Camellia sinensis: Mechanistic Evaluation of Nitric Oxide Modulation and Vascular Remodeling

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## Abstract

Hypertension remains a leading contributor to global morbidity and mortality, with endothelial dysfunction and vascular remodeling recognized as central hallmarks in its pathogenesis. The endothelium-derived mediator nitric oxide (NO) plays a pivotal role in vascular tone regulation, and its impaired bioavailability contributes significantly to hypertensive progression. Natural phytotherapeutics have emerged as promising adjuncts in cardiovascular disease prevention. Among them, *Allium sativum* (garlic) and *Camellia sinensis* (green/black tea) exhibit potent antioxidant, anti-inflammatory, and vasoprotective effects. Garlic-derived organosulfur compounds such as allicin and S-allyl cysteine enhance NO synthesis and improve endothelial relaxation, while tea catechins, especially epigallocatechin gallate (EGCG), upregulate endothelial nitric oxide synthase (eNOS) activity and mitigate oxidative stress. There is also an inhibition of vascular remodeling by both botanicals with the decrease in arterial stiffening, fibrosis and inflammation signaling. Comparative mechanistic analyses elucidate parallelizing pathways, hinting at possible cooperating in terms of endothelial stabilization and blood pressure control. This chapter supplies the comprehensive of molecular mechanisms, experimental and clinical work, and translation aspects regarding Allium sativum and Camellia sinensis in antihypertensive treatment especially in the modulation of NO as well as vascular remodeling.

## Keywords

Allium sativum; Camellia sinensis; endothelial dysfunction; nitric oxide; vascular remodeling; hypertension; antioxidant, eNOS activation; nutraceuticals, cardiovascular protection

## 1. Introduction

Cardiovascular diseases (CVD) are one of the biggest killers with nearly 1 in every 3 deaths occurring due to CVD each year worldwide. Hypertension specifically is one of the greatest known and modifiable risk factors for developing CVD, stroke, renal disease, and HF (World Health Organization [WHO],

2021). Given that traditional pharmacological treatments have failed to curb the increasing prevalence of hypertension, alternative and complementary approaches aimed not only at controlling blood pressure but also cardiovascular health at molecular level are required

Endothelial dysfunction, a hallmark of hypertension, disrupts the exquisite balance between vasodilatory and vasoconstricting factors in the circulation.. The vascular endothelium regulates vascular tone primarily through nitric oxide (NO), a potent vasodilator synthesized by endothelial nitric oxide synthase (eNOS Decreased NO availability, in great part due to oxidative stress, inflammation and metabolic abnormalities, is a key factor in the genesis of vascular stiffness, remodeling and hypertension (Gimbrone& García-Cardeña, 2016). Therefore, efforts to regain endothelial function and correct NO signaling are important for controlling and preventing hypertension.

Natural products gain more and more attention in the past years as they are rich source for bioactive compound with multiple functions, which could be beneficial to cardiovascular health. Contrary to arthetores youri drugs, that address one reaction at a time cellulose is asungitire marshastere antioxidants action antiinflammatory (synergistic vaspotectives tically normalize endothelium functions (Orekhov et al., 2020). This has stimulated investigation of diet-based interventions and nutraceutical preparations as additions to antihypertensive treatment.

Of the natural agents, Allium sativum (garlic) and Camellia sinensis (green and black tea) have been extensively investigated for their cardioprotective efficacy. Garlic contains organosulfur compounds, including allicin, S-allyl cysteine and diallyl disulfide, that have been reported to promote NO generation as well as function as free radical scavengers and vasodilators for regulation of blood pressure (Ried et al., 2016). In the same way, tea polyphenols especially catechins such as epigallocatechin gallate (EGCG) protect endothelial cells through eNOS activation, antioxidant damage and vascular inflammation inhibition (Peng et al., 2014). Garlic and tea also affect vascular remodeling, a key factor in the regulation of blood pressure over time and arterial health.

Because they are mechanistically plausible and widely ingested as part of human diet, A. sativum and C. sinensis have the potential to test the hypothesis regarding natural products for endothelial homeostasis and anti-hypertensive therapy. The purpose of this chapter is an attempt to emphasise their impact on NO modulation, vascular remodelling, and the implications for cardiovascular protection.

## 2. Endothelial Dysfunction in Hypertension

### 2.1 Structure and Function of the Vascular Endothelium

The vascular endothelium is a single layer of cells that covers the lumenal side of blood vessels and provides a dynamic interface between blood in circulation and the underlying vascular smooth muscle. It modulates vascular tone, haemostasis, immune response and angiogenesis by releasing bioactive mediators including nitric oxide (NO), prostacyclin and endothelin (Rajendran et al., 2013). Healthy endothelial cells contribute to the vascular homeostasis through vasodilation, inhibition of platelet

aggregation and inflammation. Disruption of these functions predisposes individuals to hypertension and cardiovascular diseases.

### 2.2 Pathophysiological Mechanisms of Endothelial Injury

Endothelial dysfunction refers to a shift in the balance of endothelial mediators toward reduced vasodilation and increased pro-inflammatory and pro-thrombotic signaling. In hypertension, hemodynamic stress, dyslipidemia, and exposure to reactive oxygen species (ROS) impair endothelial integrity and signaling. Damage to endothelial cells leads to impaired vasodilatory responses, increased vascular permeability, and enhanced leukocyte adhesion, creating a pro-atherogenic environment (Gimbrone & García-Cardeña, 2016).

### 2.3 Role of Oxidative Stress, Inflammation, and Vascular Remodeling

Oxidative stress is a central driver of endothelial dysfunction. Excess ROS, generated by NADPH oxidase, mitochondrial dysfunction, and xanthine oxidase, inactivates NO and forms peroxynitrite, which damages cellular proteins and lipids (Förstermann et al., 2017). Chronic oxidative stress initiates vascular inflammation, characterized by upregulation of adhesion molecules, cytokines, and activation of nuclear factor-kappa B (NF-κB) pathways. These processes contribute to vascular remodeling—structural changes including intimal thickening, smooth muscle cell proliferation, and extracellular matrix deposition—which worsen arterial stiffness and elevate blood pressure (Intengan & Schiffrin, 2001).

### 2.4 Importance of Nitric Oxide in Vascular Homeostasis

Nitric oxide is one of the most critical vasodilators produced by the endothelium through the action of endothelial nitric oxide synthase (eNOS). NO diffuses into vascular smooth muscle cells, activating soluble guanylate cyclase (sGC), which increases cyclic guanosine monophosphate (cGMP) and promotes relaxation. In hypertension, decreased NO bioavailability is caused by eNOS uncoupling, oxidative degradation, and reduced substrate or cofactor availability (Moncada & Higgs, 2006). Restoring NO signaling is therefore essential for maintaining vascular homeostasis and preventing hypertension-related complications.

**Table 1. Major Mechanisms of Endothelial Dysfunction in Hypertension**

| Mechanism | Key Features | Consequences on Vascular Function |
|---|---|---|
| Oxidative stress | Excess ROS generation, NO degradation | Impaired vasodilation, peroxynitrite formation |
| Inflammation | Upregulation of cytokines, NF-κB activation | Endothelial activation, leukocyte adhesion |
| Vascular remodeling | Smooth muscle proliferation, ECM deposition | Arterial stiffness, narrowed lumen |
| NO dysregulation | eNOS uncoupling, reduced cGMP signaling | Loss of vascular tone regulation |

## 3. Nitric Oxide (NO) Modulation in Vascular Health

### 3.1 Biosynthesis of NO via Endothelial Nitric Oxide Synthase (eNOS)

Nitric oxide (NO) is synthesized in endothelial cells by endothelial nitric oxide synthase (eNOS), which catalyzes the conversion of L-arginine into L-citrulline and NO in the presence of cofactors such as tetrahydrobiopterin (BH4), flavins, and NADPH (Forstermann & Sessa, 2012). eNOS activity is tightly regulated by calcium-calmodulin binding, phosphorylation states, and interactions with regulatory proteins. Adequate eNOS coupling ensures continuous NO production, which is critical for vascular homeostasis.

### 3.2 NO Signaling in Vasodilation and Vascular Tone Regulation

After its production, NO diffuses into neighboring vascular smooth muscle cells and stimulates soluble guanylyl cyclase (sGC). This enzyme hydrolyzes guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP), which signals for the activation of protein kinase G (PKG). PKG reduces the concentration of intracellular Ca and mediates smooth muscle relaxation that results in vasodilation (Moncada & Higgs, 2006). According to this pathway, NO is the key mediator of the regulation of vascular tone, blood pressure, and cardiovascular health.

### 3.3 Impaired NO Bioavailability in Hypertension

NO bioavailability is significantly diminished in hypertensive conditions through several mechanisms, such as oxidative destruction of NO by ROS (reactive oxygen species), eNOS uncoupling, and the deficiency of cofactors like BH4 (Guzik et al., 2000). The resultant dysregulation tilts the balance towards vasoconstriction, endothelium inflammation and vascular remodeling which drive deterioration of the hypertensive phenotype. Moreover, oxidative stress by angiotensin (ANG) II leads to exasperation of eNOS dysfunction leading to a negative feedback process of endothelial dysfunction (Touyz and Schiffrin, 2004).

### 3.4 Strategies to Restore NO Activity

To restore NO activity, several dietary and therapeutic strategies have been investigated. Pharmacological interventions also include inhibitors (ACE inhibitors and ARBs) as well as modifiers of statin, ACE-inhibitor/ARB therapy that increase endothelial health and NO signaling (Davignon, 2004). Both L-arginine and a closely related amino acid, L-cittrulline have shown to enhance eNOS activity (Machha & Mustafa, 2005) and the combined effect of increasing these by dietary supplementation can be additive or synergistic in ameliorating NO production as antioxidants like vitamin C and polyphenols are also known to prevent oxidative inactivation of NO. Lifestyle changes are also known to improve NO bioavailability, including routine exercise with associated shear stress-induced eNOS expression (Green et al., 2017).

**Table 2. Mechanisms Affecting NO Bioavailability and Potential Restorative Strategies**

| Mechanism of Impairment | Effect on NO Signaling | Restorative Strategy |
|---|---|---|
| Oxidative stress (ROS) | NO degradation, peroxynitrite formation | Antioxidants (vitamin C, polyphenols) |
| eNOS uncoupling | Superoxide generation instead of NO | BH4 supplementation, statins |
| Reduced L-arginine availability | Impaired NO synthesis | L-arginine or L-citrulline supplementation |
| Angiotensin II overactivation | Increased NADPH oxidase activity, NO reduction | ACE inhibitors, ARBs |
| Endothelial dysfunction | Decreased eNOS expression and activity | Exercise, dietary interventions |

## 4. *Allium sativum* (Garlic) and Endothelial Protection

### 4.1 Phytochemical Composition

Garlic (Allium sativum) contains several bioactive sulfur compounds that have the ability to modify cardiovascular risk factors. The major ones are allicin, which is produced enzymatically by alliinase from alliin, and other stable metabolites such as S-allyl cysteine, S-allyl mercaptocysteine, diallyl disulfide and thus diallyl trisulfide (Banerjee & Maulik 2002). These are the compounds that give garlic its antioxidant, anti-inflammatory, and vasodilatory effects. Hydrophilic ingredients such as S-allyl cysteine exhibit high bioavailability and are thus especially important for maintaining cardiovascular health in the long-term (Amagase et al., 2001).

### 4.2 Antioxidant and Anti-inflammatory Mechanisms

Oxidative stress and inflammation represent important causes of endothelial dysfunction in hypertension. Organosulfur compounds in garlic are powerful scavengers of free radicals and stimulate activities of endogenous antioxidant enzymes, in particular superoxide dismutase, catalase and glutathione peroxidase (Borek, 2006). Moreover, garlic also inhibits pro-inflammatory mediators including TNF-α and IL-6 and down-regulates NF-κB-dependent signalling pathways (Qidwai & Ashfaq, 2013). These effects contribute to reduce vascular inflammation, and to preserve endothelial continuity.

### 4.3 Evidence of NO-Enhancing Effects

There is evidence that garlic improves the bioavailability of NO through eNOS expression and decreasing oxidative inactivation of NO Allicin and its derivatives enhance production of NO by endothelial cells, resulting in improved vasodilation and regulation of blood pressure (Ginter & Simko, 2010). It has been reported that garlic supplementation elevates the circulating NO metabolites, an observation associated with improved vascular reactivity (Ried et al., 2013).

### 4.4 Effects on Vascular Smooth Muscle Relaxation

Garlic also has a direct vasorelaxant action on vascular smooth muscle. Diallyl disulfide and diallyl trisulfide are doners of hydrogen sulfide (H2S), an agent that activates potassium channels in cells of vascular smooth muscle, leading to relaxation effect (Benavides et al., 2007). Such NO and $H_2S$ double reactional modulation does endow garlic with a special advantage in vascular tone regulation and arterial stiffness reduction.

### 4.5 Clinical and Experimental Evidence of Antihypertensive Properties

Animal models of hypertension have consistently shown that garlic has hypotensive properties via protecting the endothelium and relaxation response of the vasculature (El-Sayed et al., 2017). Several clinical trials also promote its antihypertensive properties. A meta-analysis conducted by Ried (2016) indicated that garlic supplementation produced a statistically significant decline in systolic and diastolic pressure of hypertensive patients similar to those of standard first-line antihypertensive drugs. Long-term garlic consumption was further associated with better arterial compliance and lower levels of oxidative biomarkers, supporting its prolonged cardioprotective effects.

**Table 3. Bioactive Compounds of Garlic and Their Endothelial Effects**

| Compound | Mechanism of Action | Endothelial/Vascular Effect |
|---|---|---|
| **Allicin** | Enhances NO production, antioxidant activity | Improved vasodilation, reduced oxidative stress |
| **S-allyl cysteine** | Free radical scavenging, increases eNOS expression | Endothelial protection, blood pressure reduction |
| **Diallyl disulfide** | $H_2S$ donor, potassium channel activation | Smooth muscle relaxation, vasodilation |
| **Diallyl trisulfide** | Antioxidant, anti-inflammatory | Reduced vascular inflammation, arterial stiffness |
| **S-allyl mercaptocysteine** | Anti-inflammatory, NF-κB inhibition | Suppression of cytokine-mediated endothelial injury |

## 5. *Camellia sinensis* (Green/Black Tea) and Vascular Modulation

### 5.1 Key Phytoconstituents (catechins, EGCG, theaflavins)

*Camellia sinensis* has a complex polyphenolic composition which varies according to processing: green tea is abundant in monomeric catechins (epicatechin [EC], epigallocatechin [EGC], epicatechin-3-gallate [ECG] and, epigallocatechin 3-gallate [EGCG]), whereas black tea contains oxidized polyphenols imparted during fermentation, such as theaflavins and thearubigins (Cabrera et al., 2006). EGCG is the most intensively studied catechin and has been implicated in many of the vascular effects attributed to tea. In addition to polyphenols, tea provides small amounts of caffeine, L-theanine, and micronutrients that may modulate bioactivity (Khan & Mukhtar, 2013).

### 5.2 Antioxidant Defense and Free-Radical Scavenging

Tea polyphenols act as direct free-radical scavengers and also upregulate endogenous antioxidant defenses. Catechins neutralize reactive oxygen species (ROS) and can chelate transition metals, limiting Fenton chemistry. They also influence expression and activity of antioxidant enzymes such as superoxide dismutase and glutathione peroxidase, thereby reducing oxidative degradation of nitric oxide (NO) and protecting endothelial cells from ROS-mediated injury (Cabrera et al., 2006; Khan & Mukhtar, 2013). These combined actions help preserve NO bioavailability and attenuate redox-driven inflammatory signaling in the vessel wall.

### 5.3 Role in eNOS Activation and NO Production

Multiple experimental studies indicate that tea polyphenols enhance endothelial NO signaling. EGCG has been shown to stimulate eNOS phosphorylation via upstream kinases (e.g., Akt/PI3K pathway) and to increase eNOS expression in cultured endothelial cells, leading to higher NO release (Khan & Mukhtar, 2013). In addition, by reducing ROS levels, polyphenols prevent NO scavenging and formation of peroxynitrite, indirectly preserving NO function. These molecular effects translate into improved endothelium-dependent vasodilation in ex vivo vessel preparations and in vivo models (Cabrera et al., 2006).

### 5.4 Modulation of Vascular Remodeling and Arterial Stiffness

Beyond acute vasodilation, tea polyphenols influence long-term structural changes in the vasculature. Antioxidant and anti-inflammatory actions reduce smooth muscle cell proliferation, extracellular matrix (ECM) deposition, and collagen crosslinking—processes central to medial hypertrophy and arterial stiffening (Hodgson & Croft, 2010). EGCG and theaflavins inhibit pro-fibrotic signaling (e.g., TGF-β pathways) and matrix metalloproteinase activity in experimental systems, thereby limiting maladaptive remodeling that contributes to sustained increases in vascular resistance and pulse-wave velocity (Hodgson & Croft, 2010).

### 5.5 Clinical and Experimental Evidence of Antihypertensive Activity

Preclinical studies consistently report that green and black tea extracts improve endothelial function and lower blood pressure in rodent models of hypertension via NO-dependent mechanisms and reduced oxidative stress (Khan & Mukhtar, 2013). Human studies show more mixed but encouraging results. A meta-analysis of randomized controlled trials found that regular green tea consumption is associated with modest reductions in systolic and diastolic blood pressure, particularly with longer duration and higher polyphenol doses (Peng et al., 2014). Several controlled trials of black tea have also reported improved flow-mediated dilation and small decreases in ambulatory blood pressure, although effects depend on baseline risk, dose, and caffeine content (Hodgson & Croft, 2010). Overall, clinical evidence supports a role for tea intake as an adjunctive lifestyle measure to improve endothelial function and modestly lower blood pressure, with greater effects seen in individuals with hypertension or endothelial dysfunction.

### Table 4. Major Tea Phytoconstituents and Their Vascular Actions

| Phytoconstituent | Principal Vascular Mechanisms | Expected Vascular Outcome |
|---|---|---|
| EGCG (catechin) | eNOS phosphorylation/activation; antioxidant; anti-inflammatory | ↑ NO bioavailability; improved endothelium-dependent dilation |
| Other catechins (EC, EGC, ECG) | ROS scavenging; inhibit NF-κB signaling | Reduced oxidative stress & inflammation |
| Theaflavins (black tea) | Antioxidant; inhibit smooth muscle proliferation | Attenuated vascular remodeling, decreased arterial stiffness |
| Caffeine (minor) | Transient sympathetic stimulation; adenosine receptor antagonism | Short-term BP variability; confounds acute effects |
| Theanine & micronutrients | Modulate endothelial signaling and oxidative balance | Supportive, indirect vascular protection |

## 6. Comparative Mechanistic Insights: Garlic vs. Green Tea

### 6.1 Shared Molecular Pathways

Both *Allium sativum* (garlic) and *Camellia sinensis* (tea) converge on several conserved mechanisms that protect the endothelium and support blood-pressure regulation. They act as antioxidants that scavenge reactive oxygen species (ROS) and upregulate endogenous antioxidant defenses, thereby preventing oxidative inactivation of nitric oxide (NO) and limiting peroxynitrite formation (Benavides et al., 2007; Cabrera et al., 2006). Anti-inflammatory actions are also common: organosulfur compounds and polyphenols suppress proinflammatory cytokines and inhibit NF-κB signaling, reducing endothelial activation and leukocyte adhesion (Qidwai & Ashfaq, 2013; Khan & Mukhtar, 2013). Crucially, both agents enhance NO-mediated vasodilation — garlic by promoting eNOS expression/activity and providing complementary $H_2S$-mediated vasorelaxation, and tea by stimulating eNOS phosphorylation via PI3K/Akt and protecting NO from oxidative loss (Forstermann & Sessa, 2012; Benavides et al., 2007; Khan & Mukhtar, 2013). These overlapping pathways explain why both botanicals improve endothelial function and may lower blood pressure in experimental and clinical settings (Ried, 2016; Peng et al., 2014).

### 6.2 Distinct Phytochemical Profiles and Vascular Outcomes

Although their downstream vascular effects overlap, garlic and tea possess distinct chemical repertoires that give rise to complementary actions:

- **Garlic** is dominated by organosulfur compounds (allicin, S-allyl cysteine, diallyl disulfide/trisulfide). These molecules act as direct antioxidants, modulate redox-sensitive signaling, and — importantly — can release hydrogen sulfide ($H_2S$), a gaseous mediator that produces vasorelaxation through potassium-channel opening and synergizes with NO signaling (Benavides et al., 2007; Banerjee & Maulik, 2002). Garlic's metabolites also exhibit favorable pharmacokinetics (e.g., water-soluble S-allyl cysteine) that support sustained biological activity (Amagase et al., 2001).

- **Tea** contains polyphenolic catechins (EGCG, EGC, ECG) in green tea and oxidized dimers (theaflavins) in black tea. These polyphenols are potent radical scavengers and modulate kinase cascades (e.g., Akt) that increase eNOS phosphorylation and expression, thereby raising NO output. Polyphenols also inhibit matrix-remodeling enzymes and profibrotic signaling (e.g., TGF-β), contributing to reduced arterial stiffening (Cabrera et al., 2006; Hodgson & Croft, 2010).

Because garlic supplies $H_2S$ donors in addition to NO-supporting activity, its acute vasodilatory profile can differ from tea's primarily NO-focused effects; conversely, tea polyphenols may exert stronger influence on intracellular kinase signaling and long-term anti-fibrotic remodeling.

### 6.3 Potential Synergistic Roles in Endothelial Stabilization

Mechanistic complementarity suggests potential synergy when garlic and tea are combined. Garlic's $H_2S$ release can potentiate NO signaling by preventing eNOS uncoupling and by directly modulating smooth-muscle cell ion channels, while tea polyphenols protect NO from oxidative degradation and activate upstream kinases that increase eNOS activity. Together, these effects could (a) amplify acute vasodilation, (b) reduce chronic oxidative/inflammatory burden, and (c) attenuate maladaptive vascular remodeling more effectively than either agent alone. Preliminary combinatorial concepts are supported by the idea that multi-target phytotherapy often yields additive or synergistic benefits because each phytochemical fraction targets different nodes within the endothelial signaling network (Ried, 2016; Khan & Mukhtar, 2013). However, rigorous experimental and clinical combination studies are limited; dose, formulation, and interaction with conventional antihypertensives require systematic evaluation.

### 6.4 Metabolomic and Systems Biology Insights

Metabolomics and systems biology offer tools to map the complex biochemical fingerprints that underlie garlic's and tea's vascular effects. Untargeted metabolomic profiling can reveal circulating biomarkers of endothelial response (e.g., nitrite/nitrate, oxidative stress metabolites, $H_2S$-related thiol pools) and detect metabolic shifts in lipid, amino-acid, and polyphenol metabolic pathways after intervention (Wishart, 2016). . Systems pharmacology offers an opportunity to analyze transcriptomic, proteomic and metabolomic data in one system analysis for identification of network hubs (e.g., eNOS, NADPH oxidase subunits or TGF-β signaling nodes), modulated by phytochemicals as well as prediction of synergistic combinations (Orekhov et al., 2020). These integrative studies also provide insights into interindividual diversity (pharmacometabolomics), which may lead to more specific nutraceutical advice and hypothesis-driven combination trials. Overall, systems biology can make possible for the field from descriptions of single pathways to dynamic network models that provide mechanistic insight into how garlic and tea work together to protect the endothelium and reduce hypertension risk.

**Table 5. Comparative Overview — Garlic vs. Tea: Key Compounds and Vascular Actions**

| Feature / Endpoint | Garlic (*Allium sativum*) | Tea (*Camellia sinensis*) |
|---|---|---|
| Dominant compounds | Allicin, S-allyl cysteine, diallyl disulfide/trisulfide | EGCG, EGC, ECG (green); theaflavins (black) |
| Primary vascular mechanisms | Antioxidant, anti-inflammatory, $H_2S$ donation, eNOS upregulation | Antioxidant, anti-inflammatory, eNOS phosphorylation via Akt/PI3K |
| NO pathway effects | Increases eNOS expression/activity; reduces NO scavenging; $H_2S$–NO crosstalk | Enhances eNOS activation and protects NO from ROS |
| Vascular remodeling impact | Reduces inflammation and fibrosis; improves arterial compliance | Inhibits SMC proliferation, ECM deposition; anti-fibrotic signaling |
| Clinical evidence (BP effects) | Meta-analyses show modest but significant BP reductions in hypertensives (Ried, 2016) | Meta-analyses and RCTs suggest modest BP lowering and improved endothelial function (Peng et al., 2014) |
| Synergy potential | Complements NO with $H_2S$ signaling; sustained metabolites support chronic effects | Protects kinase-mediated eNOS activation and limits remodeling — complementary to garlic |
| Systems biology readouts | Changes in sulfur-related metabolites, thiol pools, antioxidant enzyme markers | Changes in polyphenol metabolites, oxidative stress markers, kinase/phosphoprotein signatures |

## 7. Vascular Remodeling and Long-Term Cardioprotection

### 7.1 Mechanisms of Vascular Remodeling in Hypertension

Hypertensive vascular remodeling is a complex phenomenon that develops in a non-acute fashion and also includes structural and cellular alterations of the arterial wall. Central to these are SMC hypertrophy and hyperplasia, augmented deposition and cross-linking of extracellular matrix (ECM) proteins (collagens, fibronectin), endothelial-to-mesenehymal signaling, and inflammatory cell invasion (Intengan & Schiffrin 2001). Hemodynamic (increased pressure and altered shear stress) and neurohormonal mediators, including angiotensin II and aldosterone, drive profibrotic pathways (eg, TGF-β signaling) as well as matrix metalloproteinase (MMP) remodeling that result in increased media thickness, smaller lumen diameter, and increased stiffness—changes that help maintain elevated systemic vascular resistance (Intengan & Schiffrin, 2001; Forstermann & Sessa 2012).

### 7.2 Role of *Allium sativum* and *Camellia sinensis* in Preventing Structural Vascular Changes

Preclinical and clinical evidence indicates that garlic and tea interfere with several pro-remodeling mechanisms. Garlic-derived organosulfur compounds (e.g., allicin, S-allyl cysteine, diallyl polysulfides) reduce oxidative stress and inflammation, inhibit SMC proliferation, and modulate profibrotic signaling pathways (e.g., TGF-β, NF-κB), thereby attenuating ECM accumulation (Sleiman et al., 2024; Frontiers review, 2022). Garlic metabolites also provide $H_2S$ or $H_2S$ signaling, which can counteract vasoconstrictive and profibrotic stimulants (Benavides et al., 2007).

Tea polyphenols – in particular EGCG and other catechins – also decrease oxidative stress, inhibit proinflammatory transcription factors and down-regulate pathways promoting SMC proliferation and collagen expression (Cabrera et al., 2006; Hodgson & Croft, 2010). EGCG also disrupts MMP/TIMP balance, and TGF-β signaling in experimental models resulting in reduced fibrosis and the maintenance of vascular compliance (Cabrera et al., 2006).

These two botanicals, together, also act on upstream (oxidative stress and inflammation) and downstream (SMC proliferation and extracellular matrix remodeling) focal points in the remodelling process that would underline beneficial effects in vascular structure herein reported by both animal models and some human trials (Benavides et al., 2007; Sleiman et al., 2024).

### 7.3 Impact on Arterial Stiffness, Fibrosis, and Angiogenesis

It is an important clinically measurable consequence of remodeling and a risk factor for cardiovascular events. Multiple RCTs and intervention studies with aged garlic extract (AGE) (Kyolic/AGE studies) have found positive effects on pulse-wave velocity (PWV), central blood pressure, and other stiffness indices after supplementation 26 \(Moreno? et al.; see clinical reviews. Likewise, green tea and EGCG have been associated with reduced arterial stiffness and improved flow-mediated dilation, particularly when caffeine confounding is controlled (Peng et al., 2014; recent EGCG trials). Both agents also modulate collagen synthesis and MMP activity, reducing fibrosis in preclinical models, while some data indicate modulation of angiogenic signaling (relevant for repair and microvascular integrity) — usually toward normalization rather than pathological neovascularization (Frontiers review, 2022; Peng et al., 2014).

### 7.4 Integration with Antihypertensive Pharmacotherapy

Garlic and tea are predominantly adjunctive — they may complement conventional antihypertensives by improving endothelial function and reducing stiffness, potentially allowing better blood-pressure control and cardiovascular risk reduction. However, attention to interactions and additive effects is necessary: for example, garlic can potentiate antiplatelet effects and may interact (mildly) with ACE inhibitors or diuretics in some contexts, while high doses of tea or EGCG can influence drug-metabolizing enzymes and transiently affect sympathetic tone because of caffeine (Drugs.com interaction summaries; Sleiman et al., 2024). Clinically, combining well-standardized garlic extracts (e.g., AGE) with standard therapy has shown modest additive BP lowering in trials, but formal interaction studies and long-term outcome data remain limited (Ried, 2016; Sleiman et al., 2024).

## 8. Clinical Evidence and Translational Potential

### 8.1 Summary of Clinical Trials and Meta-analyses

Meta-analyses and RCTs point to modest but clinically meaningful benefits of garlic and green tea on blood pressure and vascular function:

- **Garlic:** Multiple meta-analyses and RCTs report that standardized garlic preparations (notably aged garlic extract) lower systolic and diastolic blood pressure in hypertensive subjects, often by

a magnitude comparable to first-line agents in some trials (average SBP reductions ~8–10 mmHg in uncontrolled hypertensives in several studies when using 1.2–2.4 g AGE formulations) and improve arterial stiffness markers (Ried, 2016; recent meta-analyses and Nutrients review) (Ried, 2016; Sleiman et al., 2024; PubMed meta-analysis). Recent randomized trials of optimized aged-black-garlic extracts reported small but significant reductions in DBP in hypercholesterolemic subjects and small BP reductions in grade I hypertensives with low SAC doses (MDPI trials) (MDPI randomized trials; turn3search2).

- **Green/Black Tea:** Systematic reviews and meta-analyses find that green tea consumption modestly lowers SBP and DBP (pooled SBP reduction ~1.5–2.0 mmHg), with stronger effects in longer-duration studies, lower catechin doses (to avoid caffeine confounding), and in individuals with prehypertension or stage 1 hypertension (Peng et al., 2014). Black tea trials show mixed results but improvement in endothelial function parameters (flow-mediated dilation) has been documented (Peng et al., 2014; Hodgson & Croft, 2010).

Overall, clinical data support adjunctive use of both botanicals for vascular protection, with stronger evidence for standardized aged garlic extracts in hypertensive patients and modest but consistent signals for tea polyphenols.

### 8.2 Dosage, Bioavailability, and Safety Considerations

- **Dosage & formulations:** Effective garlic doses in RCTs have varied: many studies used aged garlic extract (AGE) at 600–1,200 mg/day (yielding ~1.2–2.4 mg SAC/day) or similar preparations; some optimized ABG trials show effects with much lower SAC content when formulation is standardized (Ried, 2016; MDPI trials). For tea, effective regimens in trials ranged from 300–800 mg/day of green-tea catechins (EGCG content variable), or habitual intake of 2+ cups/day in epidemiological studies (Peng et al., 2014).
- **Bioavailability:** Water soluble garlic components (mainly S-allyl cysteine) show good oral bioavailability and stability, which support sustained efficacy (Amagase et al., 2001; ScienceDirect review). Tea catechins have different but variable absorption and are rapidly metabolized (glucuronidation/sulfation) – formulation (decaffeination, extract vs beverage) influences exposure and effects (Khan & Mukhtar, 2013).
- **Safety & interactions:** Both agents are generally well tolerated. Garlic may increase bleeding risk (antiplatelet effects) and has mild interactions with some antihypertensive drugs; caution is warranted in patients on anticoagulants or those awaiting surgery (Sleiman et al., 2024; Drugs.com interaction summaries). High doses of concentrated EGCG have been associated with rare hepatotoxicity; confounding by caffeine can transiently raise BP in some individuals (Peng et al., 2014; Khan & Mukhtar, 2013). Long-term safety data are encouraging but further large outcome trials are needed.

### 8.3 Nutraceutical Formulations and Dietary Interventions

Standardized extracts (e.g., AGE, aged black garlic, decaffeinated green tea extracts) yield more reproducible clinical effects than raw food interventions. Formulation strategies that improve stability, control SAC or EGCG dose, and minimize caffeine are preferred for trials and clinical use (Ried, 2016;

Peng et al., 2014). Dietary interventions combining habitual intake of tea (decaffeinated where appropriate) and culinary garlic, or using standardized supplements as adjuncts to pharmacotherapy, are translationally attractive because of accessibility and low cost; however, regulation, batch-to-batch standardization, and quality control remain essential.

### 8.4 Limitations and Controversies in Current Evidence

Key limitations include heterogeneity in botanical preparations, variable dosing and study duration, small sample sizes in many RCTs, and inconsistent control for confounders such as caffeine, diet, and concurrent medications. Publication bias and variable product standardization limit generalizability (Peng et al., 2014; Sleiman et al., 2024). Mechanistic gaps remain — particularly regarding optimal combinations, long-term hard cardiovascular outcomes (e.g., MI/stroke reduction), and precise interaction profiles with polypharmacy. Finally, interindividual variability (pharmacometabolomics, gut microbiome influences) may explain differing responses and requires more personalized investigations (Wishart, 2016; Orekhov et al., 2020)

**Table 6. Vascular Remodeling Endpoints and Evidence for Garlic & Tea**

| Remodeling Endpoint | Evidence for Garlic | Evidence for Tea | Translational Note |
|---|---|---|---|
| Arterial stiffness (PWV, pulse pressure) | Several RCTs with aged garlic extract report ↓ PWV, central BP, improved arterial compliance. (AGE/Kyolic trials; MDPI trials). | Moderate evidence—longer green tea interventions and decaffeinated extracts show small ↓ stiffness metrics. (Peng et al., 2014) | Clinically measurable; responsive to standardized formulations |
| Fibrosis / ECM deposition | Preclinical studies show ↓ TGF-β signaling and collagen deposition; some animal cardiac/vascular remodeling data (allicin, SAC). | EGCG inhibits profibrotic pathways and MMP dysregulation in preclinical models. | Strong preclinical support; limited direct human histologic data |
| SMC proliferation / medial hypertrophy | In vitro/in vivo inhibition of SMC growth reported with organosulfur compounds. | Catechins suppress SMC proliferation via antioxidant/kinase modulation. | Mechanisms complementary — potential for combination therapy |
| Angiogenesis / microvascular integrity | Garlic modulates angiogenic factors; effects appear normalizing rather than pro-angiogenic. | Tea polyphenols modulate VEGF/TGF pathways; context-dependent effects. | Relevant for microvascular complications; more clinical data needed |

## 9. Challenges and Future Perspectivess

Despite promising evidence supporting the antihypertensive and endothelial protective roles of *Allium sativum* and *Camellia sinensis*, several challenges hinder their broader clinical application.

**Standardization of phytochemical content.** Both garlic and tea contain diverse bioactive compounds whose concentrations vary depending on cultivation, processing, and preparation methods. For garlic, allicin and its derivatives degrade rapidly, making it difficult to ensure consistent therapeutic potency

(Amagase, 2010). Similarly, catechins in green tea and theaflavins in black tea are sensitive to oxidation, requiring improved methods of stabilization and formulation (Yang et al., 2020).

**Long-term safety and efficacy studies.** Although short-term clinical trials have demonstrated blood pressure–lowering effects, large-scale and long-duration studies are still limited. Potential interactions with conventional antihypertensive drugs, variability in patient response, and concerns about gastrointestinal tolerance and hepatotoxicity (especially in high-dose tea extracts) warrant further research (Hu et al., 2018).

**Personalized medicine and nutrigenomics.** Advances in nutrigenomics suggest that individual genetic variations influence response to dietary bioactives. For instance, polymorphisms in nitric oxide synthase genes or antioxidant enzymes may determine the extent to which garlic or tea exerts vascular benefits (Corella & Ordovás, 2014). Understanding these interactions could pave the way for precision nutrition approaches in hypertension management.

**Prospects for combined phytotherapy.** Integrating garlic and tea in synergistic formulations offers a novel therapeutic strategy. Their complementary mechanisms—garlic's sulfur compounds enhancing NO bioavailability and tea polyphenols providing antioxidant defense—could collectively improve vascular outcomes. Systems biology and metabolomics approaches will be crucial in mapping these interactions and guiding the development of next-generation nutraceuticals (Afzal et al., 2020).

## 10. Conclusion

Endothelial dysfunction remains a central driver of hypertension and cardiovascular disease progression. Restoration of nitric oxide signaling and prevention of vascular remodeling are key strategies in maintaining vascular homeostasis.

*Allium sativum* and *Camellia sinensis* have emerged as potent natural agents that modulate these pathways through antioxidant, anti-inflammatory, and NO-enhancing mechanisms. Garlic's organosulfur compounds and tea's catechins/theaflavins not only improve endothelial function but also reduce arterial stiffness, fibrosis, and oxidative stress, providing long-term cardioprotection.

Clinical evidence, though encouraging, highlights the need for standardized formulations, robust safety evaluations, and personalized approaches to maximize therapeutic benefits. These natural interventions are best viewed as complementary strategies alongside pharmacotherapy, contributing to integrative cardiovascular medicine.

Looking forward, advances in nutrigenomics, phytochemical standardization, and multi-omics technologies hold promise for optimizing garlic and tea–based therapies. Together, they represent valuable tools in the fight against hypertension and a step toward holistic cardiovascular health management.

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Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-486-3

# Chapter 9: Adaptogenic and Neuroendocrine Regulatory Effects of Withania somnifera and Zingiber officinale: A Comprehensive Analysis of Stress Axis Modulation and Anxiolytic Efficacy

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## Abstract

Stress-related disorders are closely linked to dysregulation of neuroendocrine systems, particularly the hypothalamic–pituitary–adrenal (HPA) axis and the sympatho–adrenal–medullary (SAM) system. Chronic activation of these pathways results in maladaptive cortisol and catecholamine responses, contributing to anxiety, depression, and immune imbalance. Adaptogens, a class of natural substances, have shown promise in restoring homeostasis by modulating stress axis function. Among them, *Withania somnifera* (Ashwagandha) and *Zingiber officinale* (Ginger) stand out for their multifaceted roles in neuroendocrine regulation and anxiolytic activity. W. somnifera produces various withanolides that reduce cortisol levels and enhance resistant to stress, whereas Z. officinale contains the bioactive gingerols and shogaols which exert neuroprotective, anti-inflammatory and mood-modulating properties. Preliminary preclinical and clinical studies support the ability of such botanicals to help augment adaptogenic tone, lessen anxiety, and reinforce general vitality. This chapter offers a critical appraisal of their phytochemical profiles, mechanisms of modulation of stress axes, anxiolytic efficacy and therapeutic applications as well as the future prospects and limited gaps concerning integrative adaptogenic medicine.

**Keywords:** Adaptogens; Withania somnifera; Zingiber officinale; HPA axis; SAM system; cortisol regulation; neuroendocrine system, anxiety disorders and phytotherapy and stress mechanisms.

## 1. Introduction

The notion of adaptogens has received much attention in integrative medicine and neuropharmacology because of their ability to provide resistance against nonspecific stress factors, resulting in the stabilization homeostasis. Adoptogens are naturally occurring agents that enhance the body's ability to cope with environmental stress, by adjusting neurological responses together with neuroendocrine, and immune and metabolic functions (Panossian & Fishman, 2010). While traditional anxiolytics are known to primarily target a single neurotransmitter system, adaptogens regulate the function of the hypothalamic–pituitary–adrenal (HPA) axis and sympatho–adrenal–medullary (SAM) systems, having

multi-target effects which result in improved resilience during chronic stress, as well as alleviation of stress-related pathologies (Boonen & Oswald, 2020).

Modulation of stress axes is one of the main mechanisms for adaptogenic properties. Disruption of HPA axis activity is characterized by prolonged cortisol release, resulting in anxiety, depression, immune suppression as well as metabolic dysregulation (Chrousos, 2009). Conversely, hyperactivity in the SAM system leads to an increased catecholamine release that further intensifies cardiovascular and emotional stress responses (McEwen, 2017). Thus treatments that correct basic alterations in these systems are likely to have significant effects on mental and physical health.

In this context, Withania somnifera (Ashwagandha) and Zingiber officinale (Ginger) have gained attention as potential botanical supplements in adaptogenic and anxiolytic domain. Based on its withanolide-rich phytochemistry, known for redaction of stress and cortisol regulation as well as enhancement in cognitive and affective functioning (Singh et al., 2011), W. somnifera is a rule herb in Ayurvedic practice. Z. officinale has been used since ancient times as a digestive, anti-inflammatory and more recently acknowledged for its neuroprotective and mood-modulating aspect of bioactive compounds like gingerols and shogaols (Mohd Sahardi & Makpol, 2019). Collectively, these botanicals hold a double therapeutic promise of the modulation of neuroendocrine stress response and anxiolytic effects.

The aim of the present chapter is to offer a comprehensive overview on W. somnifera and Z. officinale in their adatopgenic and endocrine regulation effects, with a focus on stress axis modulation and anxiolytic efficacy. This chapter discusses their phytochemical profiles, mechanisms of action on HPA and SAM systems, clinical evidence for the use of such herbs, and prospects for their integration into therapeutic approaches to stress-induced disorders. This review intends to underscore the translational implications of these plants in the evolution of adaptogenic medicine and in promoting safe, effective approaches in managing stress and anxiety-related disorders.

## 2. Phytochemical Profile of *Withania somnifera* and *Zingiber officinale*

### 2.1. Key Bioactive Constituents of *Withania somnifera*

*Withania somnifera (Ashwagandha)* is a source of steroidal lactones referred to as withanolides, and are the active constituents responsible for its adaptogenic and neuroprotective effects. These compounds have cortisol-reducing, anti-inflammatory and anxiolytic activities (Singh et al., 2011). In addition to withanolides, the plant is rich in alkaloids like somniferine, anaferine, cuscohygrine and such alkaloids are believed to be responsible for its neuroendocrine-modulating activity (Dar et al., 2015). A group of glycowithanolides, sitoindosides, contribute to the anti-stress and immunomodulatory potential of plant (Verma & Kumar, 2011). Simultaneously, these compounds are responsible for the herb's well-documented effect of modulating hypothalamic–pituitary–adrenal (HPA) axis and enhancing resistance to chronic stress.

### 2.2. Bioactives of *Zingiber officinale*

*Zingiber officinale (Ginger*) contains an impressive and substantial amount of phenolic components referred to as gingerols, the predominant and pharmacologically active phytochemicals. Gingerols, in particular [6]-gingerol have antioxidant, anti-inflammatory and neuroprotective effects (Ali et al., 2008). 8 When heat treated or during long storage, gingerols are turned into shogaols with even greater anti-inflammatory and anxiolytic effects (Mohd Sahardi & Makpol, 2019). Other components including paradols and zingerone are also involved in anti-stress and adaptogenic activities that are attributed to the modulation of neurotransmitter system and reduction of oxidative stress (Semwal et al., 2015).

### 2.3. Comparative Phytochemical Insights Relevant to Adaptogenic Activity

These two plants have a distinct phytochemical composition, yet both possess adaptogenic properties by acting on the stress axis. W. somnifera exerts its effect mainly via steroidal lactones (withanolides), which control cortisol levels and GABAergic signalling (Choudhary et al., 2015). On the other hand, Z. officinale is capable of influencing serotonin and dopamine neurotransmission as well as oxidative stress through its phenolic compounds, mainly gingerols and shogaols. Therefore, the two plants are synergistic in mediating stress in terms of action as *W. somnifera* aims at endocrine while Z. officinale targets neuroinflammatory and neurotransmitter pathways.

### 2.4. Synergistic Potential of Combining *W. somnifera* and *Z. officinale*

Taken together these botanicals may have a synergistic and adaptogenic effect. The withanolides of W. somnifera attenuate hypercortisolemia and stabilize the HPA axis, whereas gingerols and shogaols present in Z. officinale potentiate antioxidant defense alongside neurotransmitter equilibrium. When combined, these approaches have the potential to promote wider neuroendocrine resistance through their effects on hormonal as well as neural stress pathways. It also indicates a potential role in combination with other plant adaptogens in multi-herbal adaptogenic preparations against anxiety and stress-related disorders (Panossian & Wikman, 2010).

**Table 1. Major Phytochemicals of *Withania somnifera* and *Zingiber officinale* and Their Adaptogenic Relevance**

| Plant | Major Phytochemicals | Biological Activities Relevant to Adaptogenesis |
|---|---|---|
| *Withania somnifera* | Withanolides (withaferin A, withanolide D), Alkaloids (somniferine, anaferine), Sitoindosides | Cortisol regulation, anti-stress, neuroprotection, immunomodulation |
| *Zingiber officinale* | Gingerols ([6]-gingerol), Shogaols, Paradols, Zingerone | Antioxidant activity, neurotransmitter modulation, anxiolytic and anti-inflammatory effects |

## 3. Mechanisms of Stress Axis Modulation

### 3.1. Overview of HPA Axis Regulation

The hypothalamic–pituitary–adrenal (HPA) axis is the principal neuroendocrine system that coordinates the body's response to stress. Activation begins with hypothalamic secretion of corticotropin-releasing hormone (CRH), which stimulates pituitary release of adrenocorticotropic hormone (ACTH) and finally prompts adrenal cortisol synthesis and secretion. Cortisol exerts widespread effects on metabolism, immunity, and brain function and participates in negative feedback at the pituitary and hypothalamus to restrain further HPA activation (Chrousos, 2009). Chronically elevated HPA tone and sustained cortisol exposure are associated with impaired stress resilience, mood disorders, immune dysregulation, and cognitive deficits (McEwen, 2017). Effective modulators of the stress response therefore act by restoring appropriate HPA responsiveness and strengthening feedback control mechanisms (Panossian & Wikman, 2010).

### 3.2. Role in Neuroendocrine Balance, Cortisol Control, and Stress Resilience

Neuroendocrine balance depends on tight cross-talk among the HPA axis, the sympatho-adrenal-medullary (SAM) system, and central neurotransmitter circuits. Adaptive stress responses produce transient increases in cortisol and catecholamines followed by rapid normalization; maladaptation arises when these responses are exaggerated or prolonged (McEwen, 2017). Restoring resilience can be achieved by (a) reducing baseline hypercortisolemia, (b) normalizing stress-induced peaks, and (c) improving central feedback sensitivity (Chrousos, 2009; Panossian & Wikman, 2010). Botanicals with adaptogenic properties exert multi-level effects — endocrine, immune, and neuronal — that collectively improve behavioral and physiological coping with stress.

### 3.3. Molecular Signaling Pathways Influenced by *Withania somnifera* and *Zingiber officinale*

Both *Withania somnifera* (Ashwagandha) and *Zingiber officinale* (Ginger) engage multiple intracellular signaling networks implicated in stress, inflammation, and neuronal survival. Key pathways and putative actions include:

- **Glucocorticoid signaling and HPA feedback:** Withanolides and related glycowithanolides from *W. somnifera* have been linked to normalization of HPA function and attenuation of corticosterone/cortisol responses in preclinical models, suggesting improved negative feedback or reduced CRH/ACTH drive (Panossian & Wikman, 2010; Dar et al., 2015).
- **NF-κB and MAPK (pro-inflammatory) pathways:** Both ginger constituents (gingerols, shogaols) and withanolides inhibit NF-κB activation and can down-regulate MAPK signaling, thereby reducing production of proinflammatory cytokines (Semwal et al., 2015; Dar et al., 2015). Because inflammation potentiates HPA dysregulation, anti-inflammatory action contributes indirectly to HPA stabilization.
- **Oxidative stress and cytoprotective responses (Nrf2):** Ginger phenolics and some withanolides enhance cellular antioxidant defenses and may activate Nrf2-dependent transcriptional programs, protecting neurons from stress-induced oxidative damage (Semwal et al., 2015; Mohd Sahardi &

Makpol, 2019). Reduced oxidative load supports neuronal resilience and preserves feedback signaling within stress circuits.

- **Heat-shock proteins and cellular stress sensors:** Adaptogens in general (including *W. somnifera*) have been reported to influence molecular chaperones and heat-shock protein expression, which buffer cellular stress and help restore homeostasis following insult (Panossian & Wikman, 2010).
- **Monoaminergic modulation via intracellular cascades:** By modulating kinases and second-messenger systems, both botanicals can influence synthesis, release, or receptor sensitivity of monoamines (see section 3.4), thereby affecting mood and stress reactivity (Panossian & Wikman, 2010; Semwal et al., 2015).

These intersecting molecular actions provide a rationale for how botanical constituents translate biochemical modulation into improved organismal stress responses.

### 3.4. Impact on Neurotransmitters: GABA, Serotonin, Dopamine

Neurotransmitter systems are central to behavioral and emotional responses to stress; adaptogens often exert anxiolytic and mood-stabilizing effects by modulating these systems:

- **GABAergic system:** Evidence from mechanistic reviews indicates that *W. somnifera* can potentiate GABAergic signaling (directly or via GABA-mimetic effects of certain constituents), producing calming and anxiolytic effects without the sedative liabilities of classical benzodiazepines (Panossian & Wikman, 2010; Singh et al., 2011). Enhanced GABA tone dampens HPA activation and reduces physiological arousal.
- **Serotonergic pathways:** Gingerols and related phenolics exert modulatory effects that may influence serotonergic neurotransmission (e.g., altering synthesis or receptor responsiveness), which is relevant to mood regulation and anxiety (Semwal et al., 2015; Mohd Sahardi & Makpol, 2019). *W. somnifera* extracts have also been associated with changes in central serotonin dynamics in preclinical assessments (Panossian & Wikman, 2010).
- **Dopaminergic signaling:** Both botanicals show neuroprotective and neuromodulatory actions that can stabilize dopaminergic circuits implicated in motivation and stress coping. Anti-inflammatory and antioxidant effects preserve dopaminergic neuron function, while some phytochemicals may directly influence dopamine turnover or receptor activity (Dar et al., 2015; Semwal et al., 2015).

By acting across these neurotransmitter systems, the two plants help attenuate hyperarousal, reduce anxious behavior, and support adaptive emotional processing — effects that complement their endocrine-directed actions on the HPA and SAM systems.

**Table 2. Summary of Major Mechanistic Targets and Evidence for Stress-Axis Modulation**

| Target / System | Principal Botanical Actions | Mechanistic Rationale | Representative Evidence (reviews) |
|---|---|---|---|
| HPA axis / cortisol | Attenuation of stress-induced cortisol/corticosterone responses; improved feedback | Withanolides modulate endocrine signaling and stress hormone output | Panossian & Wikman (2010); Dar et al. (2015) |
| Pro-inflammatory signaling (NF-κB, MAPK) | Inhibition of NF-κB and downstream cytokine production | Reduces inflammation that exacerbates HPA dysregulation | Semwal et al. (2015); Dar et al. (2015) |
| Oxidative stress / Nrf2 | Enhancement of antioxidant defenses; reduced ROS | Protects neurons and preserves signaling in stress circuits | Semwal et al. (2015); Mohd Sahardi & Makpol (2019) |
| GABAergic neurotransmission | Potentiation of GABAergic tone (anxiolytic effects) | Lowers neuronal excitability and HPA activation | Panossian & Wikman (2010); Singh et al. (2011) |
| Monoaminergic systems (5-HT, DA) | Modulation of serotonin and dopamine availability/receptor function | Improves mood regulation and stress coping behavior | Semwal et al. (2015); Panossian & Wikman (2010) |

### 3.5. Integrative Perspective

The mechanistic profile of *W. somnifera* and *Z. officinale* is inherently polypharmacological: endocrine modulation (direct HPA effects), anti-inflammatory and antioxidant protection (indirectly stabilizing neuroendocrine circuits), and neurotransmitter modulation (behavioral outputs). This multi-pronged action is characteristic of adaptogens and underlies their potential to restore physiological set-points disrupted by chronic stress (Panossian & Wikman, 2010). While preclinical and mechanistic reviews provide strong conceptual support, translation into clinical practice requires standardized extracts, rigorous dosing studies, and biomarkers that directly link molecular changes to improved stress resilience in humans.

## 4. Anxiolytic and Antidepressant Potential

### 4.1. Preclinical Evidence: *Withania somnifera*

Preclinical studies consistently demonstrate that *Withania somnifera* (Ashwagandha) exerts anxiolytic-like effects across multiple animal models. Standard behavioral assays—such as the elevated plus maze (EPM), open field test (OFT), and light–dark box—show increased exploratory behavior and reduced anxiety-like avoidance following administration of root extracts or isolated withanolides (Dar, Hamid, & Ahmad, 2015; Panossian & Wikman, 2010). In models of chronic stress, Ashwagandha attenuates stress-induced elevations in corticosterone and protects against stress-related neuronal atrophy in hippocampal and prefrontal regions, effects that align with improved behavioral outcomes (Dar et al., 2015). Forced-swim and tail-suspension tests used to screen antidepressant-like activity also report reduced immobility after Ashwagandha treatment, indicating potential antidepressant-like properties in rodents (Panossian & Wikman, 2010). Mechanistically, these behavioral benefits are attributed to combined modulation of the

HPA axis, enhancement of GABAergic tone, antioxidant effects, and anti-inflammatory actions (Singh, Bhalla, de Jager, & Gilca, 2011; Dar et al., 2015).

### 4.2. Antidepressant-like Effects and Mood Regulation

Evidence for mood modulation by Ashwagandha spans molecular, neurochemical, and behavioral domains. Preclinical work indicates normalization of stress hormone profiles (corticosterone/cortisol), upregulation of neurotrophic factors, and reduction in proinflammatory cytokines after chronic administration—changes that parallel improvements in depression-like behavior (Panossian & Wikman, 2010; Dar et al., 2015). Human clinical trials, though limited, have reported reductions in perceived stress and anxiety scores with standardized Ashwagandha extracts; some randomized, placebo-controlled studies showed clinically meaningful improvements in stress and mood scales (Chandrasekhar, Kapoor, & Anishetty, 2012; Choudhary, Bhattacharyya, & Bose, 2017). While these findings are promising for depressive symptoms, larger and longer-duration randomized controlled trials that use standardized diagnostic and biomarker endpoints are needed to establish Ashwagandha's antidepressant efficacy and optimal dosing.

### 4.3. *Zingiber officinale* (Ginger): Neuroinflammation, Oxidative Stress, and Mood

Ginger's principal bioactives (gingerols, shogaols, paradols) produce robust anti-inflammatory and antioxidant effects that are relevant to mood regulation. In animal models, ginger extracts reduce neuroinflammation (e.g., lower brain cytokine expression), protect against oxidative damage, and improve behavioral indices of anxiety and depression (Mohd Sahardi & Makpol, 2019; Semwal et al., 2015). These effects are hypothesized to arise from suppression of NF-κB signaling, enhancement of endogenous antioxidant systems (e.g., Nrf2 activation), and indirect stabilization of monoaminergic neurotransmission. Human data on ginger for mood disorders remain sparse, but the mechanistic profile supports its potential as an adjunctive agent to reduce neuroinflammatory contributors to anxiety and depressive symptoms (Mohd Sahardi & Makpol, 2019).

### 4.4. Comparative Efficacy with Conventional Anxiolytic Agents

Direct head-to-head comparisons between these botanicals and conventional anxiolytics (benzodiazepines, barbiturates, SSRIs/SNRIs) are limited. Important distinctions include:

- **Onset and mechanism:** Benzodiazepines produce rapid anxiolysis via direct positive modulation of GABA_A receptors, while SSRIs modulate serotonin over weeks. Adaptogens like Ashwagandha have multi-target actions (HPA stabilization, GABAergic modulation, anti-inflammatory and antioxidant effects) and typically show a more gradual onset but broader physiological normalization (Panossian & Wikman, 2010).
- **Efficacy:** Some clinical trials report significant reductions in stress and anxiety scales with Ashwagandha compared to placebo (Chandrasekhar et al., 2012; Choudhary et al., 2017). However, there are few robust RCTs directly comparing Ashwagandha or ginger with benzodiazepines or SSRIs; therefore, claims of equivalence are premature.

- **Safety and tolerability:** Botanical adaptogens generally display favorable safety profiles with fewer reports of sedation, tolerance, or dependence compared with benzodiazepines. This safety advantage may support their use as adjuncts or for long-term management of chronic stress (Dar et al., 2015; Panossian & Wikman, 2010).
- **Adjunctive potential:** Given complementary mechanisms (endocrine vs. receptor-centric), Ashwagandha and ginger may augment conventional therapies or allow dose reduction of pharmaceuticals, but formal trials assessing combination strategies, interactions, and biomarker outcomes are required.

In summary, botanical interventions show promising anxiolytic and mood-supportive effects and may offer improved tolerability, but definitive statements about equivalence to standard pharmacotherapies require more rigorous comparative research.

### 4.5. Limitations of Existing Evidence and Research Needs

Major limitations include heterogeneity of extracts (standardization issues), variable dosing regimens, small sample sizes in clinical trials, and reliance on symptom scales without concurrent biomarker assessments. Preclinical models are informative but do not fully replicate human affective disorders. Future work should prioritize: standardized extract characterization, dose-finding studies, adequately powered RCTs with active comparators, and incorporation of neuroendocrine (e.g., cortisol), inflammatory, and neuroimaging biomarkers to link mechanistic effects with clinical outcomes.

**Table 3. Summary of Key Evidence on Anxiolytic/Antidepressant Effects**

| Evidence Domain | *Withania somnifera* | *Zingiber officinale* | Strength of Evidence |
|---|---|---|---|
| Preclinical anxiety models (EPM, OFT) | Reproducible anxiolytic-like effects; reduced stress hormones | Anxiolytic-like effects; reduced neuroinflammation | Strong (animals) |
| Antidepressant-like behavior (FST, TST) | Reduced immobility; neurotrophic and anti-inflammatory changes | Improved depression-like behavior in some models via antioxidant/anti-inflammatory effects | Moderate (animals) |
| Human clinical trials (stress/anxiety scales) | Several RCTs showing reduced perceived stress/anxiety vs. placebo | Sparse clinical mood trials; mostly mechanistic/adjunct evidence | Limited-moderate (humans) |
| Comparative head-to-head vs. benzodiazepines/SSRIs | Largely lacking; some trials vs. placebo only | No robust head-to-head trials | Insufficient |
| Safety & tolerability | Favorable; low incidence of sedation/dependence | Favorable; gastrointestinal effects most reported | Good |

## 5. Immunomodulatory and Anti-inflammatory Cross-talk

### 5.1. Stress–Immune–Inflammation Axis and Its Relevance in Anxiety

Chronic stress activates the HPA and SAM axes, which in turn influence immune function. Prolonged stress elevates glucocorticoids and catecholamines, leading to dysregulated cytokine production and low-

grade systemic inflammation (Chrousos, 2009). Elevated pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), have been linked to anxiety and depressive disorders, highlighting the bidirectional communication between stress and immune pathways (Miller, Maletic, & Raison, 2009). Modulating this stress–immune–inflammation axis is critical for restoring both psychological and physiological resilience.

### 5.2. *Withania somnifera* as an Immunoadaptogen

*Withania somnifera* exhibits immunomodulatory effects that extend its adaptogenic properties. Preclinical studies report that withanolides and sitoindosides reduce pro-inflammatory cytokine levels (IL-6, TNF-α) while enhancing anti-inflammatory cytokines such as IL-10, promoting a balanced immune response (Dar et al., 2015; Singh et al., 2011). Such modulation mitigates inflammation-driven HPA dysregulation and contributes to improved behavioral outcomes in anxiety and stress models.

### 5.3. Anti-inflammatory and Antioxidant Roles of *Zingiber officinale*

Ginger and its bioactive constituents (gingerols, shogaols, paradols) exert robust anti-inflammatory effects by inhibiting NF-κB and MAPK pathways, thereby reducing the expression of IL-6, TNF-α, and other pro-inflammatory mediators (Semwal et al., 2015; Mohd Sahardi & Makpol, 2019). Additionally, ginger's antioxidant properties reduce oxidative stress in neuronal and peripheral tissues, preventing cellular damage that can exacerbate stress and mood disorders.

### 5.4. Integration of Immune and Neuroendocrine Resilience

The complementary immunomodulatory and anti-inflammatory actions of *W. somnifera* and *Z. officinale* enhance neuroendocrine resilience. By reducing pro-inflammatory signaling and oxidative stress, both botanicals indirectly stabilize HPA axis activity and improve neurotransmitter balance. This integration of immune and neuroendocrine regulation forms a mechanistic basis for their anxiolytic and adaptogenic efficacy (Panossian & Wikman, 2010).

**Table 4. Immunomodulatory and Anti-inflammatory Actions of W. somnifera and Z. officinale**

| Plant | Key Bioactives | Immune/Inflammatory Targets | Mechanistic Effects |
|---|---|---|---|
| *W. somnifera* | Withanolides, Sitoindosides | IL-6 ↓, TNF-α ↓, IL-10 ↑ | Balances immune response, mitigates inflammation-induced HPA dysregulation |
| *Z. officinale* | Gingerols, Shogaols, Paradols | IL-6 ↓, TNF-α ↓, NF-κB/MAPK inhibition | Reduces neuroinflammation and oxidative stress, stabilizes neurotransmitter signaling |

## 6. Clinical Evidence and Human Trials

### 6.1. Key Randomized Controlled Trials on *Withania somnifera*

Several RCTs have assessed the efficacy of *W. somnifera* in stress and anxiety management:

- **Chandrasekhar et al. (2012):** 64 adults received 300 mg of standardized root extract twice daily for 60 days. Results showed significant reductions in perceived stress scores and serum cortisol compared to placebo.
- **Choudhary et al. (2017):** 50 participants showed improvements in stress, anxiety, and cognitive parameters after eight weeks of standardized Ashwagandha extract. No serious adverse events were reported, indicating safety and tolerability.

These studies support Ashwagandha's role in modulating both subjective stress and physiological markers (cortisol), reinforcing its adaptogenic properties.

### 6.2. Clinical Studies on *Zingiber officinale*

Evidence for ginger in cognitive and mood modulation is less robust but promising:

- Trials on older adults and healthy volunteers indicate improved cognitive function, reduced fatigue, and lower markers of systemic inflammation following ginger supplementation (Liu et al., 2018; Mohd Sahardi & Makpol, 2019).
- Although direct RCTs on anxiety or depression are limited, mechanistic insights from anti-inflammatory and antioxidant effects suggest potential benefits in mood disorders.

### 6.3. Comparative Clinical Effectiveness and Safety

- **Effectiveness:** Ashwagandha has more consistent evidence in stress/anxiety reduction, while ginger demonstrates potential in neuroprotection and cognitive support.
- **Safety:** Both botanicals show favorable safety profiles with minimal adverse effects. No serious drug interactions have been consistently reported, making them suitable for adjunctive use.
- **Limitations:** Heterogeneity in extract standardization, small sample sizes, short trial durations, and limited head-to-head comparisons with conventional anxiolytics reduce generalizability (Panossian & Wikman, 2010; Semwal et al., 2015).

### 6.4. Limitations of Existing Studies

- Lack of standardized dosing across trials.
- Small cohort sizes and short durations.
- Predominantly subjective outcome measures without robust biomarker correlation.
- Limited trials directly comparing botanical interventions with pharmaceutical anxiolytics or antidepressants.

## 7. Formulation Strategies and Therapeutic Applications

### 7.1. Synergistic Formulations Combining *W. somnifera* and *Z. officinale*

The combination of Ashwagandha (*W. somnifera*) and Ginger (*Z. officinale*) offers a multi-targeted approach to stress modulation. Preclinical evidence suggests that the HPA-regulatory and anti-inflammatory effects of Ashwagandha complement the antioxidant and neuroprotective properties of Ginger, resulting in enhanced adaptogenic and anxiolytic outcomes (Panossian & Wikman, 2010; Semwal et al., 2015). Synergistic formulations can be designed to optimize bioactive concentrations, improve bioavailability, and target both neuroendocrine and immune pathways.

### 7.2. Dosage Forms

Various dosage forms have been developed to facilitate administration and ensure consistent dosing of bioactives:

- **Standardized extracts:** Root extract of Ashwagandha standardized to withanolide content; Ginger extract standardized for [6]-gingerol and shogaols.
- **Capsules/tablets:** Convenient oral delivery systems for single or polyherbal combinations.
- **Polyherbal adaptogenic formulations:** Blends incorporating Ashwagandha, Ginger, and other adaptogens (e.g., *Bacopa monnieri*, *Rhodiola rosea*) to target multiple stress-related pathways.

### 7.3. Functional Foods, Nutraceuticals, and Integrative Medicine

The bioactive potential of these botanicals supports their incorporation into functional foods (e.g., fortified beverages, teas) and nutraceuticals for daily stress management. Integrative medicine strategies may include the use of Ashwagandha or Ginger as complementary supplements to conventional treatments for anxiety, depression and cognitive impairment, taking advantage of their minimal adverse effects and multi-system benefits (Dar et al., 2015; Mita Mohd Sahardi & Makpol, 2019).

### 7.4. Safety Considerations, Contraindications, and Interactions

Ashwagandha and Ginger are safe for most people. The most frequent adverse effects are mild gastrointestinal symptoms. Precautions include:

- **Pregnancy and lactation:** Limited data; consult healthcare provider before use.
- **Drug interactions:** Ashwagandha -may enhance the effects of sedatives or thyroid hormone replacement therapy; Ginger may interact with anticoagulants and antiplatelet drugs (Dar, et al., 2015; Semwal, et al., 2015).
- **Long-term safety:** Generally favorable, but standardized extracts should be used to minimize variability in bioactive content.

**Table 5. Formulation Strategies and Therapeutic Applications of Ashwagandha and Ginger**

| Formulation Type | Key Bioactives | Therapeutic Application | Advantages |
|---|---|---|---|
| Standardized Extracts | Withanolides, Gingerols/Shogaols | Stress/anxiety modulation, neuroprotection | High bioactive concentration, consistent dosing |
| Capsules/Tablets | Combination extracts | Adaptogenic supplementation | Convenient, easy dosing |
| Polyherbal Formulations | Ashwagandha + Ginger + Other adaptogens | Multi-target stress management | Synergistic effects, broader neuroendocrine coverage |
| Functional Foods/Nutraceuticals | Bioactive-enriched foods/beverages | Daily stress support, cognitive enhancement | Consumer-friendly, preventive approach |

## 8. Conclusion and Future Directions

### 8.1. Summary of Adaptogenic and Anxiolytic Effects

*Withania somnifera and Zingiber officinale* are complimentary adapatogens with anxiolytic and neuroprotective actions, respectively. While Ashwagandha acts to modulate the HPA axis, GABAergic signaling, and cortisol levels, Ginger works as an antioxidant, anti-inflammatory and also monoaminergic modulation (Dar et al., 2015; Semwal et al., 2015). Together, these botanicals support several physiological and molecular pathways involved in stress-related disease.

### 8.2. Potential Clinical Relevance in Stress-Related Disorders

RCT and mechanistic trial data indicate that Ashwagandha decreases perceived stress, anxiety, and cortisol, whereas Ginger may enhance psychology and mood through anti-inflammatory/antioxidation modulating factors). On the whole, these botanicals can be considered as adjuvant treatments for anxiety, depression and stress-induced neurocognitive deficits (Chandrasekhar et al., 2012; Mohd Sahardi & Makpol, 2019).

### 8.3. Gaps in Research

Although there are encouraging data, limitations include the fact that:

- The synergistic mechanism at the molecular level is not fully understood.
- Long-term trials with well defined extracts are scarce.
- Dosage optimization, improved bioavailability and standardised biomarker end-points remain to be explored.
- Comparative studies versus conventional pharmacotherapy are sparse.

### 8.4. Future Perspectives in Personalized Medicine and Phytopharmacology

Future research should focus on:

- Personalized adaptogenic regimens based on individual stress profiles, genetics, and biomarker signatures.
- Advanced delivery systems (nanoparticles, functional foods) to improve bioavailability and therapeutic efficacy.
- Integration of Ashwagandha and Ginger into multi-modal interventions combining lifestyle, nutrition, and pharmacotherapy.
- Systems biology approaches to map the multi-target effects of these botanicals on neuroendocrine-immune networks.

The convergence of phytopharmacology, precision medicine, and integrative strategies may enable optimized botanical interventions for stress resilience, mood stabilization, and cognitive enhancement.

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Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-486-3

# Chapter 10: Gastrointestinal Cytoprotection and Antiulcerogenic Properties of Aloe barbadensis miller and Silybum marianum: Molecular Targets in Mucosal Integrity and Inflammatory Regulation

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**Abstract**

Gastrointestinal disorders, particularly peptic ulcers, are a prevalent health concern arising from the disruption of mucosal integrity and the imbalance between protective and aggressive factors in the gastrointestinal tract. Oxidative stress and inflammatory processes play critical roles in ulcer pathogenesis by damaging epithelial cells and impairing mucosal healing. Herbal therapeutics, notably *Aloe barbadensis* Miller (Aloe vera) and *Silybum marianum* (milk thistle), have demonstrated significant gastroprotective properties through antioxidant, anti-inflammatory, and cytoprotective mechanisms. Aloe vera contributes to mucosal repair by enhancing mucus secretion and scavenging reactive oxygen species, while silymarin, the active constituent of milk thistle, modulates inflammatory pathways and supports epithelial regeneration. The present chapter reviews current ortcomes of the molecular targets responsible for mucosal protection and antiulcerogenic activity of these plants as well as -candidates to be used in a complementary or alternative form of treatment for gastrointestinal diseases.

**Keywords:** Gastrointestinal disorders Peptic ulcers Mucosal integrity Oxidative stress Inflammation Aloe barbadensis Silybum marianum Gastroprotection Herbal therapeutics

## 1. Introduction

Gastrointestinal (GI) diseases such as peptic ulcer disease, are a highly prevalent health problem worldwide that cause the break in the lining of stomach or duodenum. Such conditions are usually due to disequilibrium between aggressive substances (e.g., gastric acid and pepsin) and defensive agents (e.g., mucus secre-tion, bicarbonate buffering) existing in the body. Helicobacter pylori infection, NSAID use and lifestyle stressors resulting in mucosal injury and inflammation are the factors involved in pathophysiology of ulcers (Malik, 2023).

Integrity of the mucosa is essential for the health of gut. Composed of dense mucus–epithelial cells and tight junctions, the mucosal barrier acts as a forefront physical barrier against pathogen's adhesion or invasion as well as harmful chemicals (pathogens and toxins) and mechanical stress in general (Okumura et al. During such times of disturbance the integrity of barrier can be disrupted leading to increased

permeability, where toxins and noxious agents incite the inflammation, leading to ulceration (Okumura; 2024).

Oxidative stress and inflammation are key factors in ulcer formation and its progression. ROS and pro inflammatory cytokines are capable of causing cellular damage, delay healing processes, and leave a vicious cycle of injury/ inflammation within GI (Albalawi, 2025). Antioxidants and anti-inflammatory factors are key to alleviate these effects and encourage mucosal healing.

Phytotherapeutics have been studied for their role in GI protection. Aloe barbadensis Miller (Aloe vera) and Silybum marianum (milk thistle) are two plants reported to possess gastroprotective effects. Since aloe vera gel is anti-inflammatory and anti-oxidant, it has potential mucosal healing and protective properties (Huang et al. 2024). Likewise, silymarin, the main bioactive compound in milk thistle possesses anti-inflammatory and antioxidant effects by which it maintains liver and gastrointestinal health (Khazaei, 2021). These phytotherapeutical agents provide interesting adjuvants for the traditional treatment and underlie the significance of plant products in current drug development.

## 2. Phytochemical Profile of *Aloe barbadensis* Miller

*Aloe barbadensis Miller*, commonly referred to as Aloe vera is a succulent member of the lily family and one of most popular medicinal plants, with extracts taken from the fresh green leaves. Over 200 compounds have been identified in the inner gel of the leaves, such as polysaccharides, anthraquinones, flavonoids and phenolic acids, enzymes and vitamins that many of them have been well-studied for their pharmacological effects with a focus on gastrointestinal (GI) health.

### 2.1 Major Bioactive Compounds

- **Polysaccharides:** A well-known polysaccharide in Aloe vera, acemannan is widely recognized for its immunomodulatory and anti-inflammatory qualities. It is said to stimulate macrophage activity, aid in the immune response of the body and promote wound healing (Matei et al., 2025).
- **Anthraquinones:** Main components are aloe-emodin and aloin, they have laxative activities, and also possess antimicrobial activity. These compounds are responsible for the ability of the plant to relieve constipation and fight gastrointestinal infections (Kaur, 2024).
- **Flavonoids:** Aloe vera also contains flavonoids such as quercetin and kaempferol that have antioxidant and anti-inflammatory properties. These phytochemicals play a role in the decrease of GI tract oxidative stress and inflammation (Hęś, 2019).
- **Phenolic Acids:** Phenolic compounds including chlorogenic acid and caffeic acid are responsible for the antioxidant property of Aloe vera, as they scavenge free radicals and protect cells from oxidative stress (Iosageanu et al., 2024).
- **Enzymes and Vitamins:** Aloe vera gel is a rich source of enzymes, for example amylase and lipase which help in digestion as well the vitamins A, C and E that are beneficial for our cellular health and immune system (Verywell Health, 2025).

### 2.2 Pharmacological Relevance in Gastrointestinal Protection

The bioactive compounds in Aloe vera play significant roles in maintaining and restoring gastrointestinal health:

- **Anti-inflammatory Effects:** Anti-inflammatory PatternsActive flavonoids and phenolic acids from Aloe vera inhibit the synthesis of proinflammatory cytokines in diseases such as colitis or inflammatory bowel disease (Hęś, 2019).
- **Antioxidant Activity:** Polysaccharides and phenolic compounds scavenge reactive oxygen species, protecting the gastrointestinal mucosa from oxidative damage and promoting healing (Iosageanu et al., 2024).
- **Mucosal Protection:** Aloe vera has been shown to stimulate mucus secretion (Wu et al, 2035) and stabilise cell membranes, thereby providing a protective surface that can protect against irritants and aid in the repair of tissue damage (Verywell Health, 2025).

### 2.3 Antioxidant, Anti-inflammatory, and Mucoprotective Effects

The pharmacological efficacy of Aloe vera in gastrointestinal diseases is multidimensional as follows:

- **Antioxidant Effects:** Aloe vera contains phenolics and flavonoids that makes it the source of antioxidant which scavenges free radicals and mitigates the oxidative stress induce during a number of gastrointestinal disorders (Iosageanu et al., 2024).
- **Anti-inflammatory Effects:** The aloe vera plant has been found to interfere with inflammatory cascades resulting in downregulation of proinflammatory cytokines and enzymes, which subsequently decreases inflammation in the gut (Hęś, 2019).
- **Mucoprotective Effects:** The polysaccharides in Aloe vera stimulate mucus production and stabilize the gastric mucosal barrier which can help reduce the occurrence of ulcers and heal current sores (Verywell Health, 2025).

**Table 1: Major Bioactive Compounds in *Aloe barbadensis* Miller and Their Gastrointestinal Effects**

| Compound | Gastrointestinal Effect |
|---|---|
| Acemannan | Immunomodulation, anti-inflammatory |
| Aloin | Laxative, antimicrobial |
| Aloe-emodin | Antimicrobial, anti-inflammatory |
| Quercetin | Antioxidant, anti-inflammatory |
| Kaempferol | Antioxidant, anti-inflammatory |
| Chlorogenic acid | Antioxidant, anti-inflammatory |
| Caffeic acid | Antioxidant, anti-inflammatory |
| Amylase | Aids in carbohydrate digestion |
| Lipase | Aids in fat digestion |
| Vitamins A, C, E | Support cellular health and immune function |

## 3. Phytochemical Profile of *Silybum marianum*

*Silybum marianum* (milk thistle) is a traditional plant used as a hepatoprotective and gastroprotective drug. The therapeutic value of milk thistle is mainly due to its bioactive compounds, including silymarin, a mixture of flavonolignans. These compounds have a variety of pharmacological effects beneficial to the health of digestive organs.

### 3.1 Major Bioactive Compounds

The principal bioactive constituents of *Silybum marianum* include:

- **Silymarin**: A flavonolignan complex comprising approximately 65–80% of the extract. It includes silybin (also known as silibinin), silychristin, silydianin, isosilybin, and taxifolin (Surai, 2015).
- **Silybin**: he major active ingredient of silymarin; and it is composed of the mixture of stereoisomers, silybin A and silybin B, which are the compound enhancing main pharmacological effects in this plant (Surai, 2015).
- **Flavonoids and Polyphenols**: Other ingredients are the flavonoids (taxifolin) and polyphenolic compounds responsible for the antioxidant properties, as well to their anti-inflammatory action exerted by the plant Surai 2015).

### 3.2 Hepatoprotective and Gastroprotective Relevance

Bioactive compounds of Silybum marianum as an indicator for revealing the protecting effect of its administration on liver and gastrointestinal tract:

- **Hepatoprotective Effects**: :CR has been found to lower liver enzyme levels (ALT, AST), reduce liver oxidative stress and boost hepatocyte turnover; it is potentially useful in treating hepatic diseases (VargasMendoz et al., 2014).
- **Gastroprotective Effects**: A study by (Bittencourt et al., 2020) has demonstrated that silymarin possesses cytoprotective actions via strengthening gastric mucosal barrier, decreasing gastric acid secretions and inducing mucosal regeneration which provides protection against peptic ulcer.

### 3.3 Anti-inflammatory, Antioxidant, and Cytoprotective Properties

The pharmacological effects of Silybum marianum are ascribed to its antioxidant, anti-inflammatory and cytoprotective efficacy:

- **Antioxidant Activity**: Flavonolignans like silybin scavenge free radicals and inhibit lipid peroxidation, protecting cells from oxidative damage (Surai, 2015).
- **Anti-inflammatory Effects**: Silymarin modulates inflammatory pathways by inhibiting pro-inflammatory cytokines and enzymes, thereby reducing inflammation in the gastrointestinal tract (Zhao et al., 2024).
- **Cytoprotective Effects**: Silymarin stabilizes cell membranes, promotes protein synthesis, and enhances cell regeneration, contributing to tissue repair and protection (Surai, 2015).

**Table 2. Major Bioactive Compounds in *Silybum marianum* and Their Gastrointestinal Effects**

| Compound | Gastrointestinal Effect |
|---|---|
| Silybin | Antioxidant, anti-inflammatory, hepatoprotective |
| Silychristin | Antioxidant, anti-inflammatory |
| Silydianin | Antioxidant, hepatoprotective |
| Isosilybin | Antioxidant, anti-inflammatory |
| Taxifolin | Antioxidant, anti-inflammatory |
| Polyphenols | Antioxidant, anti-inflammatory |

## 4. Mechanisms of Gastrointestinal Cytoprotection

The GI cytoprotection is defined as the phenomenon that is able to protect upper and lower mucosa of stomach against damage induced by noxious factors like gastric acid, pepsin, ROS (reactive oxygen species) or inflammatory mediators. Phytotherapeutics such as that sourced from Aloe barbadensis Miller and Silybum marianum have protective effects by various mechanisms on the mucosal barrier leading to healing (Miller & Vescovi, 2023).

### 4.1 Enhancement of Mucosal Barrier and Mucus Secretion

The mucosal barrier serves as the primary interface between primal aggressors in the lumen. Cytoprotective compounds promote mucus and bicarbonate secretion that prevents direct contact of gastric acid with the epithelial cells (Shukla et al., 2022). Aloe vera polysaccharides and silymarin enhance synthesis and secretion of the protective mucus, which leads to an improvement in the resistance of the gastric mucosal barrier, decreasing its exposure to ulceration (Hęś, 2019; Surai, 2015).

### 4.2 Modulation of Gastric Acid Secretion

Gastric acid is an important regulator of cytoprotection. Some of these herbal mixtures may act on parietal cells, such as to prevent them from producing too much acid, but at the same time not impairing digestion. Silymarin has exhibited an inhibitory effect on acid secretion of histamine, and Aloe vera gel decreases acid output and enhances mucosal resistance to acid injury (Bittencourt et al., 2020; Matei et al., 2025).

### 4.3 Scavenging of Reactive Oxygen Species (ROS)

Free radicals are an important cause of mucosal damage. ROS damage lipids, proteins and DNA and reduce the capacity for tissue repair. Aloe vera (phenolics, flavonoids) and Silybum marianum (sillybin, fl avonolignans) bioactives elimiate ROS directly, elevate the activity of the endogenous antioxidant enzyme (SOD, catalase and glutathione peroxidase), and attenuate oxidative stress-induced mucosal damage (Iosageanu et al., 2024; Zhao et al., 2024).

### 4.4 Regulation of Prostaglandins and Nitric Oxide in Mucosal Defense

PGs and NO are important mediator for mucosal defence. They promote mucus and bicarbonate secretion, increase mucosal blood flow, and stimulate cicatrization. Herbal bioactives including silymarin and Aloe

polysaccharides enhance the generation of PG protective and modulate NO formation, thereby keeping mucosal homeostasis and cytoprotection (Khazaei, 2021; Hęś, 2019).

### 4.5 Role of Growth Factors in Epithelial Regeneration

Epithelial cell proliferation, migration and angiogenesis during tissue repair all depend on growth factors such as the epidermal growth factor (EGF), vascular endothelial growth factor (VEGF). Aloe vera gel promotes the liberation of growth factors, which contributes to accelerate the epithelial regeneration and healing of ulcers, while silymarin supports cell proliferation and wound repair in injured mucosa (Matei et al., 2025; Surai, 2015).

**Table 3. Mechanisms of Gastrointestinal Cytoprotection Mediated by Herbal Bioactives**

| Mechanism | Key Bioactive Agents | Protective Effect |
|---|---|---|
| Mucosal barrier enhancement & mucus secretion | Aloe polysaccharides, silymarin | Strengthens barrier, prevents ulceration |
| Modulation of gastric acid secretion | Silymarin, Aloe vera gel | Reduces acid output, protects mucosa |
| Scavenging of ROS | Phenolics, flavonoids, silybin | Reduces oxidative stress, prevents tissue damage |
| Regulation of PGs and NO | Aloe polysaccharides, silymarin | Enhances mucus, blood flow, mucosal repair |
| Growth factor-mediated epithelial regeneration | Aloe vera gel, silymarin | Promotes cell proliferation, angiogenesis, healing |

## 5. Molecular Targets in Ulcer Prevention and Healing

There are numerous complex molecular pathways that determine ulcer prevention and healing, which control inflammation, oxidative stress, apoptosis and tissue repair. The epithelial defense and repair pathways may be targeted by bioactive compounds derived from Aloe barbadensis Miller and Silybum marianum (Miller & Vescovi 2023).

### 5.1 Anti-Inflammatory Signaling Pathways (NF-κB, MAPK)

NF-κB and MAPK pathways are key regulators of gastric mucosal inflammation. Activation of NF-κB induces transcription of pro-inflammatory cytokines and enzymes including COX-2 and iNOS that aggravate mucosal lesions. Aloe polysaccharides and silymarin suppress NF-κB activation and also decrease expression of inflammatory mediators (Hęś, 2019; Surai, 2015). In addition, the down-regulation of MAPK (ERK, JNK and p38) by these compounds leads to lessen inflammatory signaling and cellular protection (Khazaei, 2021).

### 5.2 Oxidative Stress-Related Targets (Nrf2/HO-1 Pathway)

The Nrf2/HO-1 signal pathway acts as a protective role in oxidative injury. Activation of Nrf2 leads to expression of antioxidant enzymes, such as heme oxygenase-1 (HO-1), and superoxide dismutase (SOD) and glutathione peroxidase that antagonize ROS-mediated damage. Aloe and silymarin together increase

Nrf2 translocation into the nucleus, elevate expression of cytoprotective genes, and reduce lipid peroxidation in gastric tissue (Iosageanu et al., 2024; Zhao et al., 2024).

### 5.3 Apoptosis and Cell Survival Pathways (Bcl-2, Bax, Caspases)

The apoptotic and cell survival counterbalance is essential for the maintenance of mucosal integrity. Increased levels of pro-apoptotic proteins (Bax, caspase-3) and down-regulation of anti-apoptotic proteins (Bcl-2) result in epithelial cell death. These pathways are also affected by bioactives in Aloe vera, as well as silymarin that up-regulates Bcl-2 and inhibits the Bax and caspase activation leading to cell survival and mucosa healing (Matei et al., 2025, Surai, 2015).

### 5.4 Cytokine Modulation (TNF-α, IL-6, IL-1β)

Cytokines such as TNF-α, IL-6, and IL-1β have their proinflammatory effects on mucosal injury and delayed ulcer healing. These cytokines are inhibited by aloe polysaccharides and silymarin, thus reducing inflammation and contributing to tissue regeneration (Hęś, 2019; Zhao et al., 2024).

### 5.5 Role in Angiogenesis and Tissue Remodeling

Angiogenesis and modification of tissue are necessary for the healing process of ulcer. Aloe vera and silymarin promote the release of VEGF other than growth factors that increase endothelial cell proliferation, neo-vascularization and tissue remodelling in injured gastric mucosa (Matei et al., 2025; Khazaei, 2021).

## 6. Experimental Evidence

### 6.1 In Vitro Studies on Gastric Epithelial Cells

Researches with gastric mucosal epithelial cell lines prove that Aloe polysaccharides and silymarin can prevent oxidative stress and inflammation injury. Treatment decreases ROS accumulation, prevents NF-κB overlooking and in the shift increases membrane viability in ethanol or inflammatory treated models (Iosageanu et al., 2024; Hęś, 2019).

### 6.2 Animal Models of Gastric Ulceration

The gastroprotective effects of Aloe and silymarin have also been demonstrated in animal models with ethanol, NSAIDs, and stress-induced ulcers.. Administration of these bioactives reduces ulcer index, increases mucus secretion, restores antioxidant enzyme activity, and lowers pro-inflammatory cytokine levels (Bittencourt et al., 2020; Matei et al., 2025).

### 6.3 Comparative Efficacy of *Aloe barbadensis* and *Silybum marianum*

Comparative studies suggest that both herbs exert similar gastroprotective effects, though silymarin may show stronger antioxidant and anti-inflammatory activity, whereas Aloe polysaccharides are particularly effective at enhancing mucosal barrier function (Hęś, 2019; Surai, 2015).

### 6.4 Synergistic or Combinatorial Effects in GI Protection

Recent research highlights the potential of combining Aloe and silymarin for synergistic effects. Co-administration in animal models results in enhanced mucosal protection, greater reduction in ROS, and more effective cytokine suppression than individual treatments, suggesting complementary mechanisms of action (Matei et al., 2025; Zhao et al., 2024).

**Table 4. Molecular Targets and Experimental Outcomes of Aloe and Silymarin in Gastroprotection**

| Molecular Target / Pathway | Effect of Bioactives | Experimental Evidence |
|---|---|---|
| NF-κB, MAPK | Anti-inflammatory | Reduced COX-2, iNOS expression (Hęś, 2019) |
| Nrf2/HO-1 | Antioxidant defense | Increased SOD, catalase, HO-1 activity (Zhao et al., 2024) |
| Bcl-2/Bax, Caspases | Anti-apoptotic | Enhanced cell survival, decreased apoptosis (Matei et al., 2025) |
| TNF-α, IL-6, IL-1β | Cytokine suppression | Lowered inflammatory cytokine levels (Hęś, 2019) |
| VEGF, Growth Factors | Angiogenesis, tissue remodeling | Accelerated ulcer healing in animal models (Khazaei, 2021) |

## 7. Clinical Evidence and Translational Potential

### 7.1 Human Clinical Studies and Case Reports

Clinical studies investigating *Aloe barbadensis* Miller and *Silybum marianum* have provided evidence for their gastroprotective potential. Aloe vera gel has been evaluated in patients with functional dyspepsia and mild gastritis, showing improvement in symptom scores and reduction in gastric mucosal inflammation (Hęś, 2019). Silymarin has been studied primarily in hepatic disorders but also demonstrates protective effects in patients with NSAID-induced gastric mucosal damage, reducing ulcer incidence and enhancing healing (Surai, 2015). Case reports further support the use of these herbal bioactives in enhancing mucosal integrity and reducing gastrointestinal discomfort.

### 7.2 Safety and Tolerability

Both Aloe vera and silymarin are generally well tolerated when administered orally in therapeutic doses. Aloe gel may occasionally cause mild gastrointestinal effects such as diarrhea when consumed in excess (Verywell Health, 2025). Silymarin has demonstrated a favorable safety profile with minimal adverse effects, including mild nausea or headache in rare cases (Vargas-Mendoza et al., 2014). Importantly, long-term studies have not shown significant hepatotoxicity or systemic toxicity, supporting their use as complementary therapies in gastrointestinal disorders.

### 7.3 Limitations and Gaps in Clinical Translation

Despite encouraging findings, clinical translation faces several challenges. Most studies are limited by small sample sizes, short duration, and variability in herbal preparation standardization. Furthermore, mechanistic studies in humans are limited, and there is insufficient data on combinatorial effects of Aloe

and silymarin in controlled trials (Khazaei, 2021). Standardized dosing, long-term safety, and multicenter clinical trials are required to validate efficacy and establish evidence-based guidelines.

## 8. Formulation Strategies for Gastroprotective Applications

### 8.1 Oral Formulations (Capsules, Extracts, Gels)

Oral administration remains the most common route for delivering Aloe and silymarin. Aloe gel can be administered directly or incorporated into capsules and liquid extracts, ensuring convenient dosage and patient compliance (Matei et al., 2025). Silymarin has often been incorporated into the standardized capsules or tablets (to facilitate uniform bioactive content and enhanced stability)..

### 8.2 Controlled-Release and Targeted Delivery Approaches

Controlled-release systems are designed to be kept therapeutically-effective over the prolonged periods in the GI tract. Encapsulation of Aloe polysaccharides or silymarin within entericcoated tablets avoids early breakdown in the stomach and improves delivery to small intestine (Bittencourt et al., 2020). Such patient-targeted delivery systems are particularly useful for site-specific cytoprotection in ulcer-susceptible sites.

### 8.3 Nanocarriers and Bioavailability Enhancement

Nanotechnological delivery systems like nanoparticles, liposomes, and solid lipid carriers have been investigated to enhance the bioavailability and efficacy of herbal bioactives. These systems protect the compounds against gastrointestinal degradation, increase absorption and offer controlled release (Iosageanu etal., 2024). The nanocarrier systems of silymarin and Aloe polysaccharides were more effective gastroprotective agents in pre-clinical animal models than formulations such as solutions.

**Table 5. Clinical and Formulation Strategies for Gastroprotective Herbal Bioactives**

| Aspect | Details / Examples |
|---|---|
| Human studies | Aloe vera gel improves gastritis and dyspepsia symptoms (Hęś, 2019); silymarin protects against NSAID-induced gastric injury (Surai, 2015) |
| Safety profile | Generally safe; mild gastrointestinal discomfort for Aloe, rare nausea for silymarin (Verywell Health, 2025) |
| Formulations | Capsules, liquid extracts, gels |
| Controlled-release approaches | Enteric-coated tablets, sustained-release delivery systems (Bittencourt et al., 2020) |
| Nanocarriers | Nanoparticles, liposomes, solid lipid carriers to enhance bioavailability (Iosageanu et al., 2024) |

## 9. Future Directions and Research Perspectives

### 9.1 Molecular Profiling and Target Identification

A more detailed molecular characterization of Aloe barbadensis Miller and Silybum marianum are the aim for future studies to decipher novel bioactive compounds and their particular target molecules. Sophisticated procedures, including high throughput screening and application of proteomics- and metabolomics-based analyzers offer the possibility to disclose overlapping pathways implicated in gastrointestinal cytoprotection and inflammatory or oxidative stress-induced apoptosis with desirable specificity (Khazaei, 2021; Iosageanu et al., 2024).

### 9.2 Personalized Medicine Approaches in Gastroprotection

The differences in patient responsiveness highlight the possibility of individualized medicine paradigms when considering herbal therapeutics. Genetic and microbiome profiling may help assist with the choice and dose of Aloe- or silymarin-based products for implementation of personalized interventions and reduction of side effects. This approach is coherent with an overall trend of specialized therapy in gastroenterology (Miller & Vescovi, 2023).

### 9.3 Integrating Herbal Therapeutics with Conventional Antiulcer Agents

The co-administration of herbal bioactives with the classical antiulcer drugs like proton pump inhibitors or H2-receptor antagonists have potential to improve treatment efficacy. Synergistic effects in animal models have been observed with the combination of the parasite extract and other drugs, which are related to improved protection against gastric mucosa disruption caused by parasites, reduced oxidative stress, and healing rate improvement (Bittencourt et al., 2020). Prospective clinical trials of these combinations may set the standard for evidence-based, combination therapy.

### 9.4 Emerging Technologies: Omics, Systems Pharmacology, and AI-Driven Discovery

New approaches, such as genomics, proteomics, metabolomics, systems pharmacology and AI-enabled drug discovery have the potential to speed up the discovery of bioactive compounds and molecular mechanisms. Computational modeling can enable to predict molecules interactions, formulate strategies and expedite preclinical and clinical assessments (Matei et al., 2025; Zhao et al., 2014).

## 10. Conclusion

### 10.1 Summary of Cytoprotective and Antiulcerogenic Effects

*Aloe barbadensis Miller and Silybum marianum* have gastroprotective and antiulcerogenic properties by a number of mechanisms; enhancement of the mucosal barrier function, antisecretory activity on gastric acid formation, ROS scavenging, regulation of inflammatory cytokines, and the promotion of epithelial regeneration (Hęś, 2019; Surai, 2015).

### 10.2 Potential as Complementary Therapies

Aloe and silymarin has antioxidant, anti-inflammatory, cytoprotective effects so these agents have the potential therapeutic application as adjuvant treatment to concomitant antiulcer drugs. Their advantageous safety profiles and bioactive diversity additionally suggest their application in clinical practice as a tool to manage gastrointestinal health (Verywell Health, 2025; Bittencourt et al., 2020).

### 10.3 Implications for Future Research and Clinical Practice

Future studies should aim to standardize formulations, optimize dosages, and evaluate combinatorial strategies with conventional therapies. Incorporation of personalized medicine, omics technologies, and AI-driven approaches will facilitate the translation of preclinical findings into effective, evidence-based clinical interventions for gastrointestinal disorders (Khazaei, 2021; Miller & Vescovi, 2023).

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Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-486-3

# Chapter 11: Liposomal and Nanoparticle-Based Systems for Efficient Herbal Drug Delivery: Advanced Formulation Strategies and Therapeutic Applications

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## Abstract

Herbal medicines are an integral part of traditional and modern healthcare systems due to their wide spectrum of therapeutic properties, including antioxidant, anti-inflammatory, antimicrobial, and anticancer activities. However, the clinical translation of herbal compounds remains limited owing to poor solubility, low bioavailability, rapid metabolism, and instability under physiological conditions. Nanotechnology-based delivery systems have emerged as a promising strategy to overcome these challenges and enhance the pharmacological efficacy of phytoconstituents. Among these, liposomal and nanoparticle-based carriers have gained significant attention due to their ability to encapsulate hydrophilic and lipophilic compounds, protect bioactives from degradation, enable controlled release, and facilitate targeted delivery. Liposomes (with biocompatible bilayer structure) and nanoparticles, such as solid lipid nanoparticles, polymeric nanoparticles, and nanostructured lipid carriers, are superior dosage forms that have potential enhancement effect on therapeutic performance of herbal drugs. This chapter offers an extensive discussion on the shortcomings of traditional herbal drug delivery system, recent progress on liposomal and nanoparticle-based systems, formulation approaches, pharmacokinetic enhancement, and therapeutic uses in cancer, neuroprotection, infectious diseases and inflammatory diseases. Issues related to scale-up production, regulatory considerations and future directions are also considered in order to illustrate the ability of these state-of-the-art systems to become translationally relevant platforms for modern medicine.

**Keywords:** Herb-based drugs; Microfluidics Summary With advances in nanoscience and technology, the branch of herbal medicine/herbal drugs has not remained untouched.

## 1. Introduction

Herbs are known to have been widely used for many years as specific therapeutic remedies in the prevention and treatment of various diseases. They are also abundant in phytochemicals including

alkaloids, flavonoids, terpenoids, and phenolics that possess various pharmacological activities such as antioxidant, anti-inflammatory, antimicrobial and anticancer activity (Ekor 2014; Yuan et al., 2016). As these NP compounds are naturally derived and have less side effects they are still at the forefront of modern integrative medicine and drug discovery.

However, these traditional herbal drug delivery systems have some drawbacks. Many herbs-derived bioactive compounds possess low water solubility, poor membrane penetration, and instability upon storage as well as high rates of metabolism in the body and restricted oral bioavailability which greatly all mire their clinical efficacy (Patra et al., 2018; Pandey et al., 2020). As an example, curcumin, silymarin and qurcetine all exhibit interesting pharmacological actions in vitro and despite their potential beneficial properties, they are not reaching the necessary plasma concentrations to elicit effects in vivo due to degradation occurring too fast and low bioavailability (Mishra et al., 2022). These difficulties underscore the demand for novel formulation strategies to improve pharmacokinetic and pharmacodynamic features on herbal therapeutics.

There is growing interest in the use of nanotechnology as a platform technology to provide targeted, controlled, and sustained release of bioactive compounds. Nano systems, especially liposomes and Nanoparticles are able to encapsulate phytoconstituents leading not only to protection against enzymatic degradation, but also an increased solubility and permeability across biological membranes (Bhattacharya et al., 2020; Shah et al., 2022). In addition, the surface modification of nanocarriers facilitates site-specific targeting and prolonged circulation while reducing systemic toxicities leading to better therapeutic effects.

One of the popularized drug delivery system by mean of herbal drug is nanocarriers, in which liposomal and nanoparticle-based formulations are receiving more success among them. Liposomes containing phospholipid bilayer could entrap hydrophilic and lipophilic phytochemicals, and therefore higher stability and controlled-release patterns can be achieved. Likewise, nanoparticles including solid lipid nanoparticles, polymeric based nanoparticles and nanostructured lipid carriers are reported to elevate the bioavailability as well as therapeutic potential of herbal drugs (Patra et al., 2018; Shah et al., 2022). These are a great leap of development in the application of herbal medicines between the traditional medicine and modern nanomedicines.

## 2. Limitations of Conventional Herbal Formulations

However, the clinical application of the traditional herbal decoction is severely limited by multiple adverse factors. All these shortcomings including poor aqueous solubility, instability of phytoconstituents, non-specific targeting and quick systemic clearance collectively decrease the pharmacological response of extracts.

### 2.1 Low Aqueous Solubility and Poor Absorption

Several bioactive cells in the herbal extract, e.g., curcumin, quercetin, and silymarin have low solubility in water which makes their dissolution in GI fluids poor as well as subpar adsorption through biological membrane (Samanta et al., 2018; Sharma et al., 2020). This low solubility generally equates to in

adequate plasma concentrations which may not be effective for therapeutic purposes. For example, curcumin has potent antioxidant and anticancer activities but has very limited oral bioavailability because of high insolubility and fast metabolism (Yallapu et al., 2012).

### 2.2 Poor Stability and Degradation of Phytoconstituents

A number of phytochemicals are chemically unstable and undergo rapid degradation under environmental/physiological factors like light, temperature, pH and enzyme mediating conditions. Molecules such as epigallocatechin gallate (EGCG) and resveratrol are easily oxidized and/or hydrolyzed, thus suffering from marked activity loss during formulation, storage, circulation in body (Pangeni et al., 2016; Zhang et al., 2020). Such instability not only diminishes shelf life, but also impacts therapeutic efficacy.

### 2.3 Limited Target Specificity and Bioavailability

The conventional herbal preparations may not have potential to accumulate selectively at the site of disease. Consequently, supraphysiological doses are necessary to induce pharmacologic actions that may predispose to systemic toxicity (Patra et al., 2018). Additionally, first pass metabolism also lowers the bioavailability of several herbal constituents settling their limited clinical potential (Gupta et al., 2021). One such example is resveratrol given orally, a significant component of which undergoes extensive hepatic metabolism with little reaching the therapeutic plasma concentration (Tomé-Carneiro et al., 2013).

### 2.4 Rapid Clearance from Systemic Circulation

Even if taken up, most phytoconstituents are quickly eliminated from circulation by enzymatic biotransformation and renal excretion (Sharma et al., 2020). This short half-life requires frequent administration which is not always convenient, and may lead to lack of compliance by the patient. For example, flavonoids and polyphenols are characterised by rapid clearance from plasma, which limits their prolonged therapeutic effect (Pangeni et al., 2016).

## 3. Nanotechnology-Based Herbal Drug Delivery Systems

Nanotechnology-based drug delivery Despite the incredible scientific breakthroughs that have taken place in recent years, delivering herbal bioactives is no exception to this recent flood of development and innovation in nanotechnology drug delivery. In addition, they aid to enhance the solubility, stability, permeability and therapeutic potential of the phytoconstituents by protecting them from degradation and assists their controlled or site-specific release (Bhattacharya et al., 2020; Patra et al., 2018). Liposomes and nanoparticles are two of the most frequently studied nanocarriers capable of modifying pharmacokinetic as well as pharmacodynamic effects of herbal drugs.

### 3.1 Liposomes

#### Structure and Composition

Liposomes are circular vesicles that are formed by one or more phospolipid bilayers enclosing an aqueous core. This particular feature of this structure enables the encapsulation of hydrophilic drugs in an aqueous inner portion and lipophilic ones in a lipid bilayer (Akbarzadeh et al., 2013). Cholesterol is frequently added to the bilayer in order to enhance rigidity and stability.

#### Advantages in Encapsulating Herbal Compounds

Due to their capacity to accommodate a variety of phytoprinciples, liposomes are well suited for herbal formulations. Both hydrophilic (e.g., polyphenols) and hydrophobic (curcumin) compounds can be optimally loaded in the particles, which overcomes solubility and stability issues (Shah et al., 2022).

#### Stabilization and Controlled Release Mechanisms

Encapsulation in liposomes also shelters the labile phytochemicals from enzymatic degradation, oxidation and hydrolysis. Surface alterations, including PEGylation (attachment of polyethylene glycol), could prolong the vascular half-life, while ligand-modified liposomes allow intratumoral selective accumulation (Bozzuto & Molinari, 2015). Controlled release by liposomes permits continuous drug supply, enhancing the therapeutic effect and leading to decrease in frequency of dosing.

### 3.2 Nanoparticles

#### Types of Nanoparticles

Nanoparticles represent a diverse class of carriers that include:

- **Polymeric nanoparticles:** Produced with biodegradable polymers such as PLGA and chitosan, which provides control of the release of these formulations as well as biocompatibility.
- **Solid lipid nanoparticles (SLNs):** Composed of solid lipids, providing high stability and controlled release of lipophilic phytoconstituents.
- **Nanostructured lipid carriers (NLCs):** Second-generation lipid carriers with improved loading capacity and release kinetics.
- **Metallic nanoparticles:** Gold and silver nanoparticles synthesized with herbal extracts possess antimicrobial and anticancer properties.
- **Dendrimers:** Highly branched, tree-like structures allowing multiple functional groups for drug loading and targeting (Mukherjee et al., 2019; Gupta et al., 2021).

#### Biocompatibility and Biodegradability

Nanoscale drugs made of biodegradable natural or synthetic materials are nontoxic and biocompatible. Polymeric NPs and lipid-based vehicles disintegrate into naturally occurring components without induced systemic side effects (Pangeni et al., 2016).

### Enhanced Solubility, Protection, and Targeted Delivery

Poorly water-soluble herbal ingredients greatly benefit from solubility and dissolution rates of nanoparticles. Protection by encapsulation Encapsulation protect bracketed polyphenolic from chemical degradation and metabolism leading to their stability. Moreover, introduction of ligands or antibodies onto nanoparticle surface facilitates active targeting of nanoparticles to certain tissues or receptors, and therefore improves therapeutic specificity (Bhattacharya et al., 2020; Shah et al., 2022).

**Table 1. Comparison of Liposomes and Nanoparticles in Herbal Drug Delivery**

| Feature | Liposomes | Nanoparticles |
|---|---|---|
| Structure | Phospholipid bilayer vesicles with aqueous core | Solid or polymeric colloidal particles |
| Encapsulation | Hydrophilic (core) and lipophilic (bilayer) compounds | Primarily lipophilic, but adaptable for both |
| Stability | Sensitive to oxidation and fusion; requires stabilization | Higher stability with longer shelf life |
| Release profile | Controlled and sustained; modifiable by PEGylation | Controlled and sustained; tunable via polymers or lipids |
| Targeting | Surface modification (ligands/PEGylation) | Ligand conjugation, magnetic or metallic targeting |
| Clinical use | Widely studied, some approved formulations | Increasing clinical interest, ongoing trials |

**Table 2. Examples of Herbal Compounds in Nanoformulations**

| Herbal Compound | Nanocarrier Type | Therapeutic Application | Reference |
|---|---|---|---|
| Curcumin | Liposomes, SLNs, Polymeric nanoparticles | Anticancer, anti-inflammatory | Yallapu et al., 2012 |
| Silymarin | NLCs, Liposomes | Hepatoprotective, antioxidant | Pandey et al., 2020 |
| Resveratrol | Polymeric nanoparticles, Liposomes | Cardioprotective, anticancer | Pangeni et al., 2016 |
| Quercetin | Liposomes, Metallic nanoparticles | Antioxidant, anticancer | Mukherjee et al., 2019 |
| Ginsenosides | Liposomes, Polymeric nanoparticles | Neuroprotective, immunomodulatory | Bhattacharya et al., 2020 |

## 4. Advanced Formulation Strategies

The success of the herbal drug delivery system via nanotechnology relies on the strategies of formulation. Progresses in the methods to prepare liposomes and nanoparticles have brought higher encapsulation efficiency, stability and therapeutic efficacy. In addition, surface engineering methods yield site-specific

delivery and extended circulation time – important aspects in optimising therapeutic index of herbal bioactives (Akbarzadeh et al., 2013; Patra et al., 2018).

### 4.1 Liposomal Formulations

#### Thin-Film Hydration

One of the most popular methods to prepare liposomes is the thin-film hydration technique. In this method, the phospholipids and cholesterol are dissolved in an organic solvent, dried by evaporation to a thin lipid film and then hydrated with aqueous solution of herbal drug (Bozzuto & Molinari, 2015). This technique permits the encapsulation of hydrophilic as well as lipophilic phytochemicals.

#### Reverse-Phase Evaporation

The formulation includes emulsification of an aqueous drug solution with phospholipids dissolved in organic solvents. Liposomes Self-assemble on Solvent Removal. The encapsulation efficiency by this method is better, especially for hydrophilic compounds like polyphenols (Akbarzadeh et al., 2013).

#### Ethanol Injection

Lipid dissolved in ethanol is injected into an aqueous solution of drug. The direct spread of ethanol forms a small unilamellar liposome. The method is easy, reproducible and can be performed in a scale-up manner (Patra et al., 2018).

#### Surface Modification with Ligands

Site-specific delivery of lipophilic botanicals can be realized through conjugation of ligands (folate, antibodies or peptides) on the surface of the liposomes. This promotes the site-specific drug delivery in the body specifically at tumor sites containing receptor over-expression, which enhance the uptake of conjugate (Shah et al., 2022).

#### Stealth Liposomes (PEGylation)

“Stealth” liposome technology refers to PEGylation or coating of the liposomes with polyethylene glycol (PEG) that weaken RE recognition and extend circulation time. This approach improves therapeutic efficiency through longer drug circulation in the system (Bozzuto & Molinari, 2015).

### 4.2 Nanoparticle Formulations

#### Nanoprecipitation and Emulsification–Solvent Evaporation

Nanoprecipitation is a common method for making polymeric nanoparticles. It requires the dissolution of polymer and drug in a water-miscible organic solvent, which is then added to an aqueous phase under controlled condition resulting in nanoparticle formation (Mukherjee et al., 2019). The process of

emulsification–solvent evaporation has been used to encapsulate active compounds from the herbs into biodegradable polymers, such as PLGA and chitosan in similar studies.

### High-Pressure Homogenization for Lipid-Based Nanoparticles

This approach is frequently used for the production of SLNs and NLCs. Lipid and drug combinations are dispersed in an aqueous surfactant solution under high pressure resulting in stable nanosized particles with high encapsulation efficiency (Gupta et al., 2021).

### Green Synthesis Approaches for Herbal-Loaded Nanoparticles

Green synthesis of metal nanoparticles with the help of herbal extract become an advanced approach. The phytochemicals play their role as natural reducing and stabilizing agents in the synthesis which does not require toxic chemicals. These green-synthesized nasties are especially gold and silver nano- particles, and they have antimicrobial and anticancer activities (Sharma, Sharma & Rohit, 2019).

### Functionalization with Targeting Ligands

For selective delivery, they are functionalized with target moieties including monoclonal antibodies (mAbs), peptides and folate. Such ligands bind to receptors that are overexpressed on diseased cells, leading to higher target specificity and lower off-target effects (Bhattacharya et al., 2020).

### Table 3. Common Methods for Liposomal Herbal Formulations

| **Method** | **Key Principle** | **Advantages** | **Limitations** | **Example Herbal Drug** |
|---|---|---|---|---|
| Thin-film hydration | Hydration of lipid film with aqueous drug solution | Simple, widely used, versatile | Low encapsulation efficiency for hydrophilic drugs | Curcumin |
| Reverse-phase evaporation | Emulsion formation followed by solvent evaporation | High encapsulation efficiency | Requires organic solvents | Quercetin |
| Ethanol injection | Rapid injection of lipid-ethanol solution into aqueous medium | Reproducible, scalable | Produces small vesicles only | Silymarin |
| PEGylation (Stealth liposomes) | Surface coating with PEG | Prolonged circulation, reduced RES clearance | Costly, possible immune response | Resveratrol |

**Table 4. Nanoparticle Formulation Approaches in Herbal Drug Delivery**

| Nanoparticle Type | Preparation Method | Advantages | Example Herbal Compound |
|---|---|---|---|
| Polymeric nanoparticles | Nanoprecipitation, emulsification–solvent evaporation | Controlled release, biocompatible | Resveratrol |
| SLNs | High-pressure homogenization | High stability, sustained release | Silymarin |
| NLCs | Hot/cold homogenization | High drug loading capacity | Curcumin |
| Metallic nanoparticles | Green synthesis using herbal extracts | Eco-friendly, antimicrobial, anticancer | Gold nanoparticles with tea polyphenols |
| Dendrimers | Stepwise polymerization | High drug loading, functional groups for targeting | Quercetin |

## 5. Pharmacokinetic and Pharmacodynamic Improvements

Chemodiagnostic applications of MNP-based DDSs It is well established that single Holistic and management strategy for ASD using nanoparticles oral dose of herbal medicines do not lead to significant therapeutic effect in prevention of ASD. Liposomes and nanoparticles increase therapeutic efficacy and decrease toxicity due to an alteration in absorption, distribution, metabolism, and excretion (ADME) processes.

### 5.1 Enhanced Oral Bioavailability of Poorly Soluble Herbal Compounds

The most important benefit of liposomal and nanoparticle mediated approaches is the increase in oral bioavailability of hydrophobic phytoconstituents such as curcumin, resveratrol, and silymarin (Ganesan et al., 2018; Yallapu et al., 2012). Lipid nanocarriers, such as solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), are able to enhance dissolution in gastrointestinal fluids and promote lymphatic transport avoiding hepatic first-pass metabolism (Kumar et al., 2019). For example, the bioavailability of curcumin nanoparticles has increased almost 10 times as compared to conventional suspensions (Prasad et al., 2014).

### 5.2 Sustained and Controlled Drug Release Profiles

Nanocarriers facilitate encapsulation of herbal actives in protective matrices that result in controlled and sustained release leading to the maintenance of therapeutic levels for a longer duration (Patra et al., 2018). Liposomes and polymeric nanoparticles offer customized release profile through adjustment of polymer composition, lipid bilayer characteristics or surface coatings. Such sustained release is advantageous in that it decreases dosing frequency and increases patient convenience. For instance, silymarin nanoparticles exhibited an extended hepatoprotective effect as compared to silymarin alone and thus indicated their sustained-release profile (Maiti et al., 2014).

### 5.3 Improved Blood–Brain Barrier (BBB) Penetration

A major obstacle is the restricted penetration of herbal compounds into the central nervous system (CNS) behind the BBB. Polymeric nanoparticles, dendrimers and PEGylated liposomes have been reported to transverse the BBB well, and deliver neuroprotective phytochemicals (Tapeinos & Battaglini, 2015). For example, curcumin-loaded NP have shown increased brain uptake and therapeutic efficacy in models for Alzheimer's disease (Bisht et al., 2011). These delivery strategies are promising tools for the treatment of neurodegenerative diseases targeting herbal bioactives with low CNS penetration.

### 5.4 Reduced Toxicity and Side Effects Compared to Crude Extracts

Phytochemicals encapsulated in nanocarriers reduce systemic toxicity owing to shielding of non-target organs from unnecessary drug exposure (Zhou et al., 2018). The use of ligand-coated NPs for localized delivery largely reduces non-specific binding and improves therapeutic selectivity. For example, the anticancer activity of resveratrol was found to be higher as a component of the nanoparticles (less toxic against normal cells) than free resveratrol (Pangeni et al., 2016). Also, PEGylated liposomes will minimize immune recognition system and systemic clearance when using in large doses of drug treatment to reduce the production of toxic effect.

## 6. Therapeutic Applications of Herbal Nanoformulations

The use of nanotechnology for herbal formulations has potential therapeutic applications in various disease conditions, such as cancer, neurodegeneration, infections and chronic inflammatory diseases. Liposomal and nanoparticle-based carriers improve the pharmacological potential of herbal bioactives through better solubility, stability, site-specific delivery, and bioavailability.

### 6.1 Anticancer Applications

Herbal agents, including curcumin, resveratrol, quercetin and ginsenosides have potent antitumor efficacy; however, they are limited by poor solubilization as well as bioavailability. Liposomal and nanoparticle-based formulations resolve these limitations, enhance clinical application (Yallapu et al., 2012; Patra et al., 2018).

- **Curcumin liposomes and nanoparticles**: Liposomal curcumin enhances apoptosis in cancer cells by modulating caspase activation and downregulating NF-κB signaling (Prasad et al., 2014). Nanocurcumin also demonstrated greater cytotoxicity for breast and prostate cancer cells than free curcumin (Bisht et al., 2011).
- **Resveratrol and quercetin nanoformulations**: Both compounds exhibit improved anticancer efficacy when delivered via polymeric nanoparticles, inducing apoptosis and inhibiting angiogenesis (Pangeni et al., 2016).
- **Ginsenoside nanoformulations**: Encapsulation of ginsenosides enhances their stability and cytotoxic effects, promoting cell cycle arrest and reducing metastasis (Zhou et al., 2018).

**Mechanisms of action include:** By inducing apoptosis, inhibiting angiogenesis and tumor proliferation, and decreasing the metastatic potential.

### 6.2 Neuroprotective Applications

Herbal neuroprotective agents are hard to deliver into the brain owing to the blood–brain barrier (BBB). Nanocarrier systems have promoted brain-targeted delivery of phytochemicals in neurological diseases, including Alzheimer's and Parkinson's disorders (Tapeinos & Battaglini, 2015).

- **Curcumin nanoparticles** enhance cognitive functions and reduce amyloid plaque accumulation in Alzheimer's models (Maiti et al., 2014).
- **Resveratrol nanoformulations** improve mitochondrial function and reduce oxidative stress in Parkinson's disease models (Neves et al., 2016).
- **Ginsenoside-loaded nanoparticles** enhance cholinergic transmission and neuroprotection against dopaminergic neurodegeneration (Kumar et al., 2019).

Therefore, nanoherbal formulation increases CNS penetrability and decreases oxidative stress, which in turn increase neuronal survival.

### 6.3 Antimicrobial and Antiviral Applications

Herbal nanoformulations have also been explored for their potential in infectious diseases. Encapsulation improves antimicrobial potency by enhancing solubility, protecting active components, and enabling targeted delivery.

- **Antibacterial applications**: Nano-curcumin and nano-catechins exhibit strong antibacterial effects against *Staphylococcus aureus* and *Escherichia coli* (Khan et al., 2019).
- **Antiviral applications**: Nanoparticle-encapsulated glycyrrhizin and quercetin demonstrated inhibitory effects against influenza and herpes viruses (Ganesan et al., 2018).
- **Synergistic effects**: Herbal nanoformulations enhance the efficacy of conventional antibiotics and antivirals, reducing drug resistance (Patra et al., 2018).

### 6.4 Anti-inflammatory and Antioxidant Applications

Chronic inflammation and oxidative stress play a key role in the development of cancer, cardiovascular, and neurodegenerative diseases. Herbal nanoformulations have shown strong anti-inflammatory and antioxidant effects.

- **Curcumin liposomes** reduce pro-inflammatory cytokine expression and oxidative stress (Yallapu et al., 2012).
- **Boswellic acid nanoparticles** exhibit enhanced anti-arthritic and anti-inflammatory activity compared to free boswellic acid (Sharma et al., 2020).
- **Catechin nanoformulations** protect against oxidative damage and reduce inflammation in cardiovascular disorders (Zhang et al., 2020).

These effects are mediated through modulation of NF-κB, COX-2, and antioxidant defense pathways.

## 7. Case Studies and Recent Advances

Nanotechnology-based delivery of herbal compounds has moved from laboratory research toward clinical applications, with several formulations undergoing trials or achieving market approval. These case studies highlight the translational potential of liposomal and nanoparticle-based herbal systems.

### 7.1 Marketed Liposomal Herbal Formulations

Some herbal-based liposomal products have entered the nutraceutical and pharmaceutical markets.

- **Liposomal curcumin** formulations are available as dietary supplements for antioxidant and anti-inflammatory benefits, demonstrating improved absorption compared to crude extracts (Yallapu et al., 2012).
- **Liposomal silymarin** products (e.g., *Siliphos*®) are marketed for hepatoprotection, offering enhanced oral bioavailability of silybin compared to conventional formulations (Maiti et al., 2014).
- **Liposomal artemisinin** supplements are also being developed for adjunctive therapy in malaria and cancer treatment (Efferth et al., 2019).

### 7.2 FDA-Approved and Clinically Investigated Herbal Nanoformulations

Although no herbal liposomal product has yet gained full FDA approval as a drug, several formulations are under clinical evaluation.

- **Curcumin nanoparticles** have been investigated in clinical trials for colorectal cancer and pancreatic cancer, with results showing improved systemic exposure and tolerability (Kanai et al., 2013).
- **Resveratrol nanocarriers** are being studied for cardiovascular and metabolic disorders, demonstrating higher plasma concentration and enhanced therapeutic effects compared to free resveratrol (Neves et al., 2016).
- **Green tea polyphenol EGCG nanoparticles** are under preclinical and clinical investigation for their anticancer and neuroprotective properties (Sharma et al., 2020).

### 7.3 Examples from Recent Research

- **Curcumin**: Polymeric and lipid-based nanoparticles have shown improved anticancer efficacy and enhanced brain delivery in Alzheimer's models (Bisht et al., 2011).
- **Artemisinin**: Nanocarriers improved its stability and antimalarial activity while enabling targeted tumor therapy through ROS generation (Efferth et al., 2019).
- **Silymarin**: Solid lipid nanoparticles enhanced hepatoprotective effects and improved pharmacokinetics (Maiti et al., 2014).
- **Berberine**: Nanoformulations enhanced oral absorption and demonstrated superior antidiabetic and anticancer activity (Kumar et al., 2019).

## 8. Challenges and Limitations

Notwithstanding these significant progresses, the clinical translocation of herbal nanomedicine meets several challenges. These are related to manufacturing scale-up, regulatory hurdles, stability concerns and cost considerations.

### 8.1 Scale-Up and Manufacturing Challenges

Scale-Up and Manufacturing Barriers It is well established that laboratory preparation of herbal nanoparticles has been around for quite some time, also the large-scale production of these materials are still complex [232]. High-pressure homogenization, solvent evaporation and nanoprecipitation need to be optimized for scaling up without deterioration of the quality (Patra et al., 2018). Quality consistency is also compromised by lot-to-lot variability and reproducibility in clinical approved formulations.

### 8.2 Regulatory Concerns and Safety Evaluation

Safety Evaluation and Regulatory Concerns There is no established regulatory approval for herbal nanomedicine, so the safety becomes a concern. Toxicologcial consideration is important since receptor size can be changed by the nanoparticles and this might alter pharmacokinetics and biodistribution of herbal compounds, which may induce unforseen side effects (Zhou et al., 2018). Regulatory guidelines are being developed for nanopharmaceuticals by FDA and EMA but since herbal materials are highly variable, more strict regulation is needed.

### 8.3 Stability, Storage, and Cost-Effectiveness Issues

Stability, Storage and Economic Issues Nanocarriers like liposomes and SLNs undergo the problems of aggregation, drug leakage from/on particles surfaces as well as degradation during storage (Kumar et al., 2019). Lyophillization, cryoprotector additives or more advanced packaging are necessary for achieving long-term stability, but the latter entail high costs. Furthermore, production costs render nanoformulations more expensive compared to classical herbal supplements possibly preventing patient availability.

### 8.4 Limited Clinical Translation of Herbal Nanomedicine

Poor Clinical Application of Herbal Nanomedicine An exclusive trial on herbal nanoformulations, as potential products of the future, remains missing in late-stage clinical investigations despite promising results obtained at the preclinical level. Its limitations are heterogeneity of herbal raw materials, lack of standardization in preparation methods, ethical issues and less commercial interest (#GRIFFIN et al., 2014). Narrowing this gap is dependent on adequate regulations, new clinical trial designs, and cooperation between the industry and academics.

## 9. Future Perspectives

Herbal nanomedicine is an emerging field with many advances in recent years, however there are still some unmet challenges that need to be addressed for successful clinical translation. Furthermore, potential investigation should focus on developing cost-effective and reproducible scalable techniques for the large-scale production of herbal nanoformulations.The stability studies and quality control testing must also need some more attention (Kumar et al., 2021). Integrated artificial intelligence (AI) and

machine learning could also help expedite formulation development by predicting nanoparticle–phytoconstituent interactions and drug pharmacokinetic optimization (Singh et al., 2023). Individualized nanomedicine which is designed based on the personal genetic and metabolic composition of patients have potential to improve therapeutic efficacy as well as reduce side effects. In addition, hybrid nanocarriers that can leverage the advantages of liposomes, polymeric nanoparticles and metallic systems may potentially provide multifunctional platforms with enhanced targeting, imaging and therapeutic electronic supplementary material (Zhang et al. Synchronized regulation, chronic impact analysis, and combination with emerging drug delivery systems including 3D printing and injectable nanodevices will be the mainstream of future herbal nanomedicine.

## 10. Conclusion

Phytotherapeutics have great therapeutic potentials but suffers from poor solubility, bioavailability, stability and targeted delivery. Liposomal and nanoparticle systems have emerged as potential strategies to cross such barriers with better pharmacokinetics, controlled release, better tissue targeting profile and less toxicity. Their promise in oncology, neurology, infectious and inflammatory diseases is documented both in preclinical and clinical studies. However, challenges related to large-scale manufacturing, regulatory approval, and long-term safety must be addressed to fully realize their translational value. With the integration of nanotechnology, biotechnology, and personalized medicine, herbal drug delivery is poised to transition from traditional use toward evidence-based, globally accepted therapeutic interventions.

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Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-486-3

# Chapter 12: Advanced Encapsulation Techniques for Herbal Drugs: Innovations from Microencapsulation to Nanocarriers for Enhanced Bioavailability, Targeted Delivery, and Therapeutic Efficacy

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## Abstract

Herbal drugs have long been recognized for their therapeutic potential; however, their clinical application is often limited due to poor solubility, instability, low bioavailability, and lack of targeted delivery. Advanced encapsulation technologies provide innovative solutions to overcome these limitations by protecting bioactive phytoconstituents, enabling controlled release, and enhancing therapeutic efficacy. This chapter explores the progression of encapsulation techniques from conventional microencapsulation approaches, such as spray drying and coacervation, to state-of-the-art nanocarrier systems, including liposomes, polymeric nanoparticles, solid lipid nanoparticles, and nanoemulsions. Emphasis is placed on how these systems improve pharmacokinetics, enhance bioavailability, and facilitate targeted delivery to specific tissues or organs. The use of new distribution technologies such as stimuli-responsive carriers, phytosomes, and green nanotechnology is also emphasized in relation to sustainable formulations with a focus on the patient. Considering safety, regulatory aspects and technological hurdles of encapsulated herbal products are also mentioned in the chapter. Through the present chapter, an insight into the recent advancements from micro- to nano -scale in delivery of herbal drugs is provided which highlights that encapsulation technologies have potential to change the landscape of traditional drug delivery and prepare them for their transformation in modern therapeutics.

## Keywords

Herbal drugs have an impressive remedy on the human health, due to their use in traditional system of medicine from prehistoric times.

## 1. Introduction

Plants have been used as medicines for thousands of years by people all over the world, and they have played a vital role in the treatment and prevention of diseases due to various bioactive phytoconstituents including alkaloids, flavonoids, terpenoids, phenolic compounds found within them. These natural

options have gained significant attention in contemporary health care for their pharmacological properties (such as antioxidants, anti-inflammatory, antimicrobial and anticancer) (Ekor, 2014). Different from the synthetic drugs, herbal preparations tend to have multi-target effects on treatment, which will be especially valuable in treatment of chronic and complex diseases.

Although herbal drugs have attracted much attention as therapeutic agents, their clinical application is hindered by some important obstacles. Majority of the phytoconstituents have poor water solubility, instability under physiologic condition and rapid metabolism leading to low systemic bioavailability and poor pharmacological action (Kumar & Jena, 2017). In addition, the pharmacokinetics of herb compounds is highly variable and contributes to the variability in therapeutic effects (Patra et al., 2018). These restrictions impede the potential of herbal drugs for wider use in today mainstream clinical practice, although their pharmacological profiles continue to appear interesting.

To address these challenges new encapsulation and controlled-drug-release modes are developed. Encapsulation strategies including microencapsulation and nanocarrier-based systems provide protective matrices for the unstable herbal parts, leading to protection from degradation as well improving their solubility and stability (Shah et al., 2019). Furthermore, such systems offer controlled release and targeted delivery, that enhance therapeutic efficiency and reduce side effects. 89Nanotechnology-based carriers especially have shown the capability of delivering herbal drugs through difficult biological barriers such as BBB owing to which they have gained wider clinical applications (Ansari et al., 2016).

It may, therefore, be a promising approach for the development of herbal drug formulations that correspond with modern pharmaceutical requirements. These breakthroughs, if the problems in terms of stability, solubility and bioavailability can be solved, have a great potential to increase the therapeutical value of herbal drugs as well as their safe usage and utilization in modern medical practice.

## 2. Fundamentals of Encapsulation in Herbal Drug Delivery

### 2.1 Principles of Encapsulation

Encapsulation is the entrapment of an active pharmaceutical ingredient (API) including herbal bioactives in a protective sheath or matrix to protect it from physical, chemical and physiological degradation as well as enhancing its stability, solubility and pharmacological activity. The notion is based on the trapping of labile molecules into carriers, to safeguard them from light, heat, oxygen and enzymatic breakdown (Jyothi et al., 2010). This not only maintains the physiological action of herbal drugs, but also leads to controlled and sustained release at the site. Particle size, morphology, surface characteristic and microenvironment conditions are modulated by encapsulation of compounds and thus can have a significant effect on release kinetics and in vivo availability of these components (Desai & Park, 2005).

### 2.2 Materials Used in Encapsulation

The selection of encapsulating material is extremely significant to the capability to perform, but yet has not been described in detail. A high range of materials is applied that accounts for the physicochemical properties of the herbal bioactive and its targeted therapeutic application:

- **Polymers**: Synthetic and natural polymers are widely employed in encapsulation. Synthetic polymers, including polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA), and

poly(ethylene glycol) (PEG), offer good biocompatibility, biodegradability and the possibility of targeted controlled release (Danhier et al., 2012). Naturally occurring polymers such as alginate, chitosan, starch are preferred due to thier biocompatibility and non-toxic nature along with the advantage in the ability to form hydrogels for herbal drug encapsulation (Sharma et al., 2016).

- **Lipids**: For lipophilic herbal actives, lipid-based carriers like SLNs and NLCs are the most common. They increase the solubility and bioavailability as well as achieve the sustained release of poorly water-soluble phytochemicals (Mehnert & Mäder, 2012).
- **Proteins**: Proteins like gelatin, albumin and soy protein are also considered potential encapsulating agents because they are natural, biodegradable materials and can assemble into stable matrices. Proteinaceous encapsulation delivery systems are particularly effective for proteins, highly sensitive herbal actives that need protection against enzymatic degradation (López-Rubio et al., 2006).
- **Natural Carriers**: cyclodextrins, gums (acacia, guar), and other natural materials are also used for encapsulation. They can enhance the water solubility of hydrophobic herbal components in their aqueous environment, and represent a safer option for nutraceutical or for pharmaceutical products (Duchêne & Ponchel, 2003).

### 2.3 Role of Encapsulation in Herbal Drug Delivery

The general advantages of encapsulation for improving the therapeutic promise of herbal formulations include:

- **Stability Enhancement**: Most of the phytoconstituents like polyphenols, flavonoids are easily deteriorated by exposure to heat, light and oxygen. Depending on the MDF design, these molecules may also be encased to protect them in situ from environmental and physiological factors leading to degradation, and hence increase shelf life and biological activity (Gouin, 2004).
- **Controlled and Sustained Release**: Encapsulation allows for the manipulation of drug release kinetics which in turn offers a constant therapeutic concentration within systemic circulation. This leads to a reduced dose frequency and improved patient compliance (Saraf, 2010). For instance, polymeric nanoparticles sustain release of herbal drugs for long periods that tends to avoid fast metabolism.
- **Masking Taste and Odor**: Many herbal preparations usually have bad taste and unpleasant smell. Encapsulation obscures these unfavorable organoleptic characteristics leading to better patient compliance, in particular the paediatric and geriatric patients (Patel et al., 2012).

The encapsulation in herbal drugs delivery systems, is really a versatile tool for improving the drug efficiency that can overcome important problems of traditional formulations. Suitable encapsulating materials and procedures may offer improved stability, site-specific delivery, and efficacy relating to herbal bioactives.

## 3. Microencapsulation Techniques for Herbal Formulations

### 3.1 Spray Drying

Spray drying is one of the most common microencapsulation methods used in pharmaceutical and nutraceutical fields. This technology consists on the atomisation of a liquid herbal extract or suspension through a hot dry air stream, resulting in rapid solvent evaporation and microcapsules formation in the dried state (Gharsallaoui et al., 2007). This method has the advantages of scalability, cost-efficiency and generation of stable microparticles with tunable particle size. Spray drying technology has been successfully used for encapsulation of herbal actives like curcumin and polyphenols which hindering the degradation of these compounds and enhancing their solubility (Desai & Jin Park, 2005).

### 3.2 Coacervation

Coacervation relies on the phase separation of polymer solutions, resulting in the formation of a polymer-rich coacervate phase that encapsulates the herbal bioactive. It is further divided into simple and complex coacervation based on whether one or two polymers are employed (Jyothi et al., 2010). Coacervation has high encapsulation efficiency and homogeneous particle morphology. This approach has been used to encapsulate essential oils and flavonoids achieving better stability against oxidation (Jain et al., 2015) and light-induced degradation.

### 3.3 Solvent Evaporation

Solvent evaporation has been widely use to encapsulate hydrophobic herbal compounds. This consists in dissolving both the herbal drug and a polymer in a volatile organic solvent, and emulsifying into an aqueous phase. Upon solvent evaporation, solid microcapsules are obtained (Soppimath et al., 2001). This approach has also been extensively applied for the encapsulation of plant components such as quercetin and resveratrol to enhance their release and bioavailability (Liu et al., 2013).

### 3.4 Extrusion Method

Extrusion is a mechanism, which involves forcing the polymer-herbal drug blend through a needle into a hardening medium to form microspheres in spherical shape (Madene et al., 2006). This method is well-suited for encapsulation of thermosensitive herbal bioactives as it does not involve the use of elevated temperature. Applications may include encapsulation of probiotics and herbal polyphenols in which extrusion can increase stability and provide for sustained release (Rosenberg & Sheu, 1996).

### 3.5 Advantages in Protecting Sensitive Phytoconstituents

Microencapsulation is beneficial in various aspects in the preparation of herbal formulations. It provides a protection to sensitive phytochemicals, like polyphenolics, flavonoids and essential oils from environmental degradation (light, heat and oxygen), enhances their solubility/bioavailability profiles and offers controlled delivery for the purpose of an extended therapeutic outcome (Gouin, 2004). Further, microencapsulation enables suppression of bitter taste and odor, thus improving patient adherence to the treatment regimen.

### 3.6 Case Studies of Microencapsulated Herbal Drugs

Several herbal actives were successfully microencapsulated through different methodologies. For instance, the spray-dried curcumin microcapsules were more stable and bioavailable than free curcumin (Tonnesen & Karlsen, 2002). Microencapsulation of green tea polyphenols by coacervation as a novel formulation for controlled release and delivery against cancer (oxidative damage): in vitro & ex-vivo study. Resveratrol has also been encapsulated with solvent evaporation method to improve its oral bioavailability (Liu et al., 2013). These examples highlight the use of microencapsulation in the formulation of stable, effective and patient-friendly plant-based formulations.

**Table 1. Comparison of Microencapsulation Techniques for Herbal Drug Delivery**

| Technique | Principle/Process | Advantages | Applications (Examples) |
|---|---|---|---|
| Spray Drying | Atomization and rapid solvent evaporation | Scalable, cost-effective, stable particles | Curcumin, polyphenols |
| Coacervation | Phase separation of polymer solution | High encapsulation efficiency, uniformity | Essential oils, flavonoids |
| Solvent Evaporation | Polymer-drug dissolved in volatile solvent, evaporated | Suitable for hydrophobic drugs, controlled release | Quercetin, resveratrol |
| Extrusion | Forcing drug-polymer mixture through nozzle | Mild process, suitable for heat-sensitive actives | Probiotics, polyphenols |

## 4. Nanocarrier-Based Encapsulation Systems

### 4.1 Liposomes

Liposomes are small spherical vesicles made up of one or more phospholipid bilayers with an internal aqueous space. Due to amphiphilic natures, they can encapsulate both hydrophilic and lipophilic herbal bioactives, therefore, act as versatile carriers (Bozzuto and MolinariCited by:, - Hervera Trends Food Sci. They are soluble, bioavailable and stable stoichiometric substitutes for plant metabolites thus liposomalize labile phytocontents and develop surface-modified targetable drug carriers in vitro. For instance, curcumin encapsulated in liposomes has demonstrated improved oral bioavailability and enhanced anticancer activity (Rafiee et al., 2019).

### 4.2 Niosomes

Niosomes are non ionic surfactant derived vesicles structurally similar to liposomes but possessing higher physical stability and lower cost. They also protect the LAB cells against the harsh conditions by preventing any degradation as well as enabling controlled release of cell contents (Moghassemi & Hadjizadeh, 2014). Some of the herbal drugs such as esculin and silymarin have been encapsulated in niosomes, demonstrating better hepatoprotective activity and bioavailability with respect to their pure form (Kumar et al., 2012).

### 4.3 Polymeric Nanoparticles

Polymeric nanoparticles (PNPs) Colloidal carriers made up of biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA), chitosan, and alginate. They improve drug stability, controllable release, and can be programmed for targeted therapy (Danhier et al., 2012). Herbal bioactives such as resveratrol-loaded PLGA nanoparticles have shown enhanced pharmacokinetic profiles and antioxidant action (Neves et al., 2013).

### 4.4 Solid Lipid Nanoparticles (SLNs)

SLNs are lipid nanoparticles comprising solid lipids stabilized with surfactants. They take advantage of the strengths of both liposomes and polymeric nanoparticles but circumvent some drawbacks of those such as polymer toxicity. SLNs elevate the solubility of phytoconstituents with poor water solubility and provide controlled release of drug (Mehnert & Mäder, 2012). The encapsulation of quercetin in SLNs greatly improved its oral bioavailability and antioxidant activity (Ganesan et al., 2017).

### 4.5 Nanostructured Lipid Carriers (NLCs)

NLCs are second generation lipid nanoparticles prepared by combining solid and liquid lipids. Such structure can also possess the relatively high drug-loading capacity and the low drug expulsion occurring during storage (Pardeike et al., 2009). Berberine as one of the drug ingredients of herbal medicine could be successfully delivered by NLCs for enhancing its intestinal absorption and therapeutic efficacy (Zhang et al., 2019).

### 4.6 Mechanisms of Enhancing Solubility and Bioavailability

Nanocarriers improve the therapeutic potential of herbal drugs through multiple mechanisms:

- **Enhanced solubility**: Reduction of particle size to the nanoscale increases surface area, improving dissolution of poorly water-soluble phytoconstituents (Saraf, 2010).
- **Improved stability**: Encapsulation protects bioactives from enzymatic, oxidative, and photolytic degradation (Shah et al., 2019).
- **Controlled and sustained release**: Nanocarriers provide predictable release profiles, reducing dosing frequency and enhancing therapeutic efficiency (Danhier et al., 2012).
- **Targeted delivery**: Surface modifications (e.g., PEGylation, ligand attachment) allow specific delivery to organs, tissues, or cells (Bozzuto & Molinari, 2015).

### 4.7 Examples of Herbal Drugs Delivered via Nanocarriers

A number of herbal bioactives have been effectively encapsulated with nanocarriers to enhance their poor bioavailability. Liposomal formulations of curcumin exhibit improved anticancer activity (Rafiee et al., 2019) and resveratrol-encapsulated PLGA nanoparticles feature higher antioxidant effects (Neves et al., 2013). Similarly, quercetin SLNs had higher oral bioavailability (Ganesan et al., 2017), while berberine NLCs had better intestinal absorption and hypoglycemic effects (Zhang et al., 2019).

**Table 2. Nanocarrier-Based Systems for Herbal Drug Delivery**

| Nanocarrier Type | Structural Feature | Mechanism of Improvement | Example Herbal Drug (Effect) |
|---|---|---|---|
| Liposomes | Phospholipid bilayer vesicles | Solubility enhancement, targeted delivery | Curcumin (anticancer activity) |
| Niosomes | Non-ionic surfactant vesicles | Stability, controlled release | Silymarin (improved hepatoprotection) |
| Polymeric Nanoparticles | Biodegradable polymer matrix (PLGA, chitosan) | Controlled release, site-specific delivery | Resveratrol (enhanced antioxidant activity) |
| Solid Lipid Nanoparticles (SLNs) | Solid lipid matrix stabilized by surfactants | Solubility, stability, sustained release | Quercetin (improved oral bioavailability) |
| Nanostructured Lipid Carriers (NLCs) | Blend of solid and liquid lipids | Higher drug loading, reduced expulsion | Berberine (enhanced absorption & hypoglycemic effect) |

## 5. Advanced and Emerging Encapsulation Strategies

### 5.1 Nanoemulsions

Nanoemulsions Kinetic stable colloidal dispersions of oil, water, surfactant and coxurfactants with droplet size size between 20-200nm. They are of special importance in herbal drug delivery due to their potential for solubility enhancement, absorption improvement and onset of action (Gupta et al., 2016). For instance, curcumin-loaded nanoemulsions have demonstrated enhanced oral bioavailability and improved therapeutic efficacy as opposed to conventional curcumin formulations (Kumar et al., 2019).

### 5.2 Dendrimers

Dendrimers are densely branched, nanoscale macromolecules which have precisely controlled structure and surface functionality. They offer high drug-loading ability, site-specific targeting and controlled release, which are suitable for delivering poorly soluble phytoconstituents (Boas & Heegaard, 2004). The successful encapsulation of herbal bioactives like resveratrol (Japani et al., 2008) and quercetin in dendrimers has resulted in better stability as well as therapeutic activity (Patel et al., 2019).

### 5.3 Phytosomes

Phytosomes are the complexes of herbal drugs/extract or their phytoconstitunets with phospholipids that were developed to enhance the lipophilicity and cellular membrane permeability. They improve the pharmacokinetics of hydrophilic herbs, generating lipid-system-compatible molecular complexes (Bombardelli, 2005). Well-established examples were silymarin and ginkgo biloba phytosomes, that showed greater absorption and therapeutic effects (Yanyu et al., 2006).

### 5.4 Hybrid Systems

Hybrid encapsulation systems are those composed of two or more types of nanocarriers (e.g., liposomes and polymeric nanoparticles), in order to take advantage of the combined benefits thereof. These systems enhance stability, extent the circulation time, allow for multifunctional delivery (Souto et al., 2020).

Combined formulations of herbs A hybrid of herbal formulation can provide a multiple combination of the phytoconstituents at the same time and it may give the combinatorial therapeutic benefits.

### 5.5 Stimuli-Responsive and Smart Delivery Systems

More recent advances in encapsulation are external-stimulus (e.g., pH, temperature, light or enzyme) responsive systems. These intelligent carriers afford site directed/Site specific and controlled on demand release of herbal drugs reducing systemic side effects (Mura et al., 2013). For instance, pH-sensitive nanocarriers have been investigated for the delivery of polyphenols during tumor therapy utilizing acidic microenvironment in tumors to release drugs (Zhao et al., 2020).

### 5.6 Integration with Green and Sustainable Approaches

Demand for the field from eco-friendly point of view has led to use of biodegradable, renewed and natural encapsulation material. The tendency today is towards green synthesis, in which plant-extract-mediated nanoparticle formation one potential alternative to decrease toxicity and environmental hazard (Iravani 2011). This will help herbal drug delivery more in conformity with environment and regulation in current green chemistry trend.

**Table 3. Emerging Encapsulation Strategies for Herbal Drugs**

| Encapsulation System | Key Features | Examples of Herbal Drugs | Advantages |
|---|---|---|---|
| Nanoemulsions | Oil-in-water nanosized dispersions | Curcumin, quercetin | Enhanced solubility, rapid absorption |
| Dendrimers | Branched polymeric carriers with functional ends | Resveratrol, quercetin | High drug loading, targeted delivery |
| Phytosomes | Phospholipid complexes of phytoconstituents | Silymarin, ginkgo biloba | Improved absorption and bioavailability |
| Hybrid Systems | Combination of nanocarriers | Multi-component herbal extracts | Stability, multifunctional delivery |
| Stimuli-responsive systems | pH/temperature/enzyme/light-sensitive carriers | Polyphenols, flavonoids | Site-specific and controlled release |
| Green encapsulation approaches | Biodegradable and eco-friendly carriers | Various plant bioactives | Sustainable, low-toxicity systems |

## 6. Applications in Targeted Delivery and Therapeutic Enhancement

### 6.1 Organ- and Tissue-Specific Targeting

Encapsulation techniques help to direct herbal drugs toward the target organ/tissue, and in this way improve therapeutic effects while minimizing general exposure. Liposomes containing silymarin have already been established to target the liver and were observed to enhance hepatoprotective activity in drug-induced models of hepatotoxicity (Tiwari et al., 2021). In addition, curcumin nanoformulations have been developed for targeted cancer cell treatment based on the functionalization of nanoparticles with

ligands such as folic acid, which specifically interacts with the folate receptor over-expressed in tumor cells (Kumar et al., 2016). In the field of cardiovascular disease, resveratrol-containing NP exhibited superior cardioprotective efficacy over free drug attributed to controlled release and myocardium targeting (Neves et al., 2013).

### 6.2 Encapsulation for Crossing Biological Barriers

One of the main challenges associated with herbal drug delivery is that several bioactives fail to permeate essential biological barriers, including the blood–brain barrier (BBB). Encapsulation approaches with liposomes, polymeric nanoparticles and dendrimers have been effectively offered in the context of this hurdle. The same is the case of nanoparticles loaded with quercetin, which have better penetration into the brain and greater neuroprotective activity in experimental models of Alzheimer's disease (Ghosh et al., 2018). Nanoemulsions of baicalein also displayed augmented crossing the BBB and might have an indicative role in neurodegenerative diseases (Chen et al., 2021).

### 6.3 Enhanced Therapeutic Efficacy with Reduced Toxicity

Enhanced therapeutic efficacy and diminished toxicity are one of the major advantages of encapsulation. Herb bioactives often need to be administered at high doses, which may cause adverse effects. [7] Encapsulation offers sustained and controlled release, decreasing the frequency of dosing and side effects. For instance, berberine-loaded solid lipid nanoparticles showed enhanced antihyperglycemic effects at about lower doses than free berberine, also decreased gastrointestinal irritation (Zhang et al., 2019). Moreover, andrographolide-loaded formulations have shown better anti-inflammatory as well as anticancer potentials with reduced systemic toxicity (Chung et al., 2020).

**Table 4. Applications of Encapsulated Herbal Drugs in Targeted Therapy**

| Target Site | Herbal Drug | Encapsulation System | Therapeutic Application | Outcome |
|---|---|---|---|---|
| Liver | Silymarin | Liposomes | Hepatoprotection | Improved bioavailability & liver targeting |
| Brain (BBB penetration) | Quercetin | Polymeric nanoparticles | Neuroprotection (Alzheimer's) | Enhanced brain delivery |
| Cancer cells | Curcumin | Folic acid-modified nanoparticles | Anticancer therapy | Selective tumor targeting, higher efficacy |
| Cardiovascular tissue | Resveratrol | Polymeric nanoparticles | Cardioprotection | Sustained release, improved outcomes |
| Systemic circulation | Berberine | Solid lipid nanoparticles | Antidiabetic therapy | Reduced dose, minimized side effects |
| Inflammation sites | Andrographolide | Nanocarriers | Anti-inflammatory/anticancer | Potent effect with reduced toxicity |

## 7. Challenges, Safety, and Regulatory Perspectives

### 7.1 Scale-Up Challenges and Industrial Feasibility

Although many encapsulation approaches have shown promise in preclinical applications, their large scale production remains highly challenging. Lack of reproducibility, high cost and process optimization are challenges for industrial scale-up (Mishra et al., 2018). Technologies such as spray drying or solvent evaporation are scalable, but they depend on careful process parameters control to ensure particle and drug loading size, and stability (Bhattacharjee et al., 2020). Moreover, the expense of nanomaterials, strict quality control and variations on the raw materials in herbs have made the development no longer to be a commercial product straightforward.

### 7.2 Safety, Toxicity, and Biocompatibility Concerns

Although herbal bioactives are of natural origin, their encapsulation by nanocarriers introduces safety fears. Problems are the long term toxicity, bio accumulation, and unanticipated immunogenesis (Sharma et al., 2015). For example, metallic nanoparticle carriers with drug delivery potential could possibly cause oxidative stress and organ toxicity. Biodegradable polymers and lipid-based systems are regarded as a safer alternative, while their biocompatibility needs to be assessed thoroughly by extensive in vivo studies (Sharma et al., 2019). No standardized protocols are available for assessment of toxicity of herbal nanomedicines that makes it difficult to determine their safety.

### 7.3 Global Regulatory Landscape for Herbal Nanoformulations

Regulations and Policies Regulations regarding herbal nanomedicines are still evolving. In the United States, FDA reviews nanotechnology-based products just like it would any other drug under established regulations for drugs not dependent on an IND filing (WHO, 2007); whereas, botanical nanoformulations are sometimes found in a regulatory gray area between dietary supplement and therapeutic drug depending on their intended use (FDA, 2022). The European Medicines Agency (EMA) and World Health Organization (WHO) predicates requirements on safety, efficacy and quality without offering special guidelines for herbal nanocarriers (Chaudhry et al., 2017). In India, regulatory measures are taking shape under AYUSH; but there is a requirement for uniform international guidelines for approval and commercialization.

## 8. Future Prospects and Conclusion

### 8.1 Integration of Nanotechnology, Biotechnology, and Personalized Medicine

The next generation of herbal drug delivery is at the intersection of nanotechnology, biotechnology, and personalized medicine. With the progress of bioinformatics and pharmacogenomics, designing individualized herbal compounds can be achieved through encapsulation according to genetic profile, disease condition, metabolic pattern (Ventola, 2017). Furthermore, the combination of biosensors and intelligent nanocarriers could potentially facilitate the monitoring of drug release and therapeutic status in real time.

### 8.2 Role of Encapsulation in Next-Generation Herbal Therapeutics

Encapsulation is and will still be in the future of utmost need for the production of advanced herbal drugs with improved stability, targeted delivery profiles, and low toxicity. Strategies like stimulus-responsive nanocarriers, hybrid encapsulation of platforms and green synthesis technology, would enable a sustainable and enhanced safety profiles of herbal therapeutics (Patra et al., 2018). Through combining ancient herbal wisdom with cutting-edge pharmaceutical technology, encapsulation can release the full therapeutic potential of phytoconstituents.

### 8.3 Concluding Remarks on Clinical Translation and Commercialization

Although there are problems, but encapsulation techniques offer the potential for a new direction to transfer herbal medicine from bench to bedside. The latter's clinical achievements (for example, with silymarin and curcumin phytosomes) can be seen as proof of concept with regard to this drug delivery approach (Yanyu et al., 2006). Further developments will be determined based on resolving safety issues, establishing cost-efficient and scalable techniques, and the international uniformity of regulations. Given the continued trends in research and regulatory support, encapsulated herbal medicines could become leading treatment options that offer both efficacy and safety as well as environmental sustainability.

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