JOURNAL OF NATURAL REMEDIES
DOI: 10.18311/jnr/2025/50284
REVIEW ARTICLE

The Molecular Pharmacology of *Tulsi* (*Ocimum sanctum*): A Review of its Historical Use and Current Understanding

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Abstract

This comprehensive literature review synthesizes the historical medicinal perspective and current scientific understanding of *Tulsi* (*Ocimum sanctum*), a highly esteemed adaptogenic herb. Rooted in ancient *Ayurvedic* texts as a "*Rasayana*" for promoting longevity and treating diverse ailments, modern phytochemical analysis reveals over 100 bioactive compounds, including eugenol, rosmarinic acid, and various flavonoids, whose synergistic interactions drive its therapeutic effects. Molecular investigations elucidate *Tulsi*'s multi-target actions: Inhibiting NF-κB and activating Nrf2 for potent anti-inflammatory and antioxidant responses; inducing apoptosis in cancer cells *via* mitochondrial and PI3K/AKT pathways; and modulating glucose and lipid metabolism through AMPK and HMG-CoA reductase. Clinically, *Tulsi* demonstrates significant efficacy in managing respiratory conditions, mitigating stress, improving cardiovascular parameters (lipids, blood pressure), and regulating metabolic disorders (Type 2 diabetes, weight). With a well-documented favourable safety profile, *Tulsi* holds immense therapeutic potential. Future research should focus on systems biology, personalized medicine, standardized extracts, and nanotechnology to optimize its clinical translation.

Major Findings: *Tulsi* exhibits multi-target therapeutic actions through NF-κB inhibition, mitochondrial apoptosis induction, and comprehensive antioxidant mechanisms, validating traditional uses while revealing novel therapeutic potentials for modern healthcare applications.

Keywords: Anti-inflammatory, Antioxidant, Molecular Mechanisms, *O. sanctum* (*Tulsi*), Therapeutic

1. Introduction

Ocimum sanctum Linn., commonly known as *Tulsi* or Holy Basil, represents one of the most extensively studied and therapeutically significant medicinal plants in traditional and modern medicine. This aromatic perennial herb, belonging to the *Lamiaceae* family, has garnered unprecedented scientific attention for its diverse pharmacological properties and molecular mechanisms of action[1]. Indigenous to the Indian subcontinent and widely cultivated across tropical regions, *Tulsi* has transcended its cultural and religious significance to emerge as a promising therapeutic agent in evidence-based medicine[2]. The plants journey from ancient *Ayurvedic* manuscripts to contemporary molecular research laboratories exemplifies the successful integration of traditional knowledge with modern scientific methodology[3].

The increasing global burden of lifestyle-related chronic diseases has renewed interest in traditional medicinal systems, particularly those emphasizing preventive healthcare and natural therapeutics[4]. The predominant cause of global morbidity and mortality is lifestyle-related chronic diseases, many of which

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Article Received on: 19.06.2025 Revised on: 20.08.2025 Accepted on: 30.08.2025

can be addressed through *Ayurveda* with its focus on healthy lifestyle practices and regular consumption of adaptogenic herbs[5]. Among the vast pharmacopeia of *Ayurvedic* herbs, *Tulsi* occupies a unique position due to its broad spectrum of therapeutic applications and well-documented safety profile[6]. Recent advances in phytochemistry, molecular biology, and systems pharmacology have provided unprecedented insights into the molecular mechanisms underlying *Tulsi*'s therapeutic effects, validating many traditional uses while revealing novel therapeutic potentials[7].

The contemporary relevance of *Tulsi* extends beyond its traditional applications, as modern research has identified specific molecular targets and pathways through which its bioactive compounds exert therapeutic effects. Many *in vitro*, animal and human studies attest to *Tulsi* having multiple therapeutic actions, establishing a robust scientific foundation for its clinical applications[8]. This literature review aims to provide a comprehensive examination of *Tulsi*'s historical medicinal perspective, contemporary molecular mechanisms, and clinical applications, synthesizing traditional knowledge with current scientific understanding[2].

2. Historical Medicinal Perspective

The medicinal legacy of *Tulsi* spans over five millennia, deeply embedded within the traditional medicine systems of the Indian subcontinent. Ancient *Sanskrit* texts, including the *Charaka Samhita, Sushruta Samhita*, and *Atharva Veda*, extensively document *Tulsi*'s therapeutic properties, establishing it as one of the most revered plants in *Ayurvedic* pharmacology[9]. The plant's *Sanskrit* name "Tulasi" derives from "*Tul*", meaning to lift or elevate, reflecting its perceived ability to elevate physical and spiritual well-being[2]. Traditional practitioners classified *Tulsi* as a "*Rasayana*", a category of herbs believed to promote longevity, enhance vitality, and prevent age-related diseases.

The historical documentation of *Tulsi*'s medicinal properties reveals a sophisticated understanding of its therapeutic applications across different organ systems. Ancient *Ayurvedic* texts describe *Tulsi* as possessing "*Ushna*" (hot) potency with "*Tikta*" (bitter), "*Katu*" (pungent), and "*Kashaya*" (astringent) tastes, making it particularly effective for treating respiratory ailments, digestive disorders, and metabolic imbalances[8]. The plant was traditionally classified under multiple therapeutic categories, including "*Deepana*" (digestive stimulant), "*Pachana*" (carminative), "*Shwasahara*" (anti-asthmatic), and "*Jwarahara*" (antipyretic), demonstrating its multisystem therapeutic applications.

Traditional formulations systematically utilized different parts of the *Tulsi* plant for specific therapeutic purposes, reflecting empirical knowledge of organ-specific bioactive compound concentrations. The leaves, constituting the most commonly used part, were primarily employed for respiratory disorders, including cough, bronchitis, asthma, and common cold. Historical texts describe elaborate preparation methods for leaf-based formulations, including fresh juice extraction, decoction preparation, and powder formulations combined with honey, ghee, or warm water depending on the specific therapeutic indication[10].

The seeds of *Tulsi*, known as "*Tukmaria*" or "*Sabja*", were historically utilized for urinary tract disorders, digestive complaints, and skin conditions. Ancient practitioners recognized the mucilaginous properties of *Tulsi* seeds, employing them as demulcents and cooling agents during febrile conditions. The roots found specific application in treating malaria, intermittent fevers, and certain skin disorders, while the flowers were used in formulations targeting cardiovascular and nervous system disorders[11].

The integration of *Tulsi* into daily life through religious and cultural practices inadvertently created a comprehensive system of preventive medicine. The tradition of daily consumption of *Tulsi* leaves, preferably on an empty stomach, cultivation in household courtyards, and incorporation into various ceremonial activities ensured regular exposure to its bioactive compounds throughout the population[8]. This cultural framework established *Tulsi* as both a therapeutic agent for treating existing ailments and a prophylactic substance for maintaining health, a concept that aligns remarkably with modern understanding of functional foods and nutraceuticals.

Historical polyherbal formulations frequently combined *Tulsi* with other medicinal plants to create synergistic therapeutic effects, demonstrating traditional understanding of combination therapy principles. Classical formulations such as "*Tulsi-Ghanvati*", "*Dashmoolarishta*", and various "*Churnas*"

(powdered preparations) incorporated *Tulsi* as a key ingredient alongside complementary herbs. These combinations were specifically designed to address complex pathological conditions requiring multi-target therapeutic approaches, a strategy that modern pharmacology now recognizes as potentially superior to single-compound therapies for treating multifactorial diseases[12].

3. Phytochemical Profile and Bioactive Compounds

Modern phytochemical analysis has validated the traditional therapeutic claims of *Tulsi* by identifying a complex array of bioactive compounds responsible for its diverse pharmacological properties (Table 1). Comprehensive chemical profiling has revealed over 100 distinct compounds in various parts of the plant, with significant variation in concentration and composition based on geographical origin, climatic conditions, harvesting time, and post-harvest processing methods[13]. The primary categories of bioactive compounds include phenolic compounds, terpenoids, flavonoids, essential oils, and various secondary metabolites that collectively contribute to *Tulsi*'s therapeutic efficacy[14].

The essential oil composition of *Tulsi* represents one of its most pharmacologically significant components, with eugenol serving as the predominant compound in most chemotypes. Eugenol (4-allyl-2-methoxyphenol) typically constitutes 70-85 % of the essential oil content and serves as a major contributor to *Tulsi*'s therapeutic properties[15]. Eugenol, the active ingredient present in *Tulsi*, is a l-hydroxy-2-methoxy-4-allylbenzen, which exhibits potent antimicrobial, anti-inflammatory, and antioxidant properties. Other significant essential oil components include methyl eugenol, β-elemene, β-caryophyllene, and germacrene D, each contributing unique pharmacological properties to the overall therapeutic profile.

The chemical diversity of *Tulsi* has led to the identification of distinct chemotypes, each characterized by specific essential oil profiles that influence their therapeutic applications. The eugenol-rich chemotype, most commonly found in Indian varieties, demonstrates superior antimicrobial and anti-inflammatory properties. The camphor-rich chemotype, predominantly found in certain African varieties, exhibits enhanced respiratory and neurological effects[16]. The linalool-rich chemotype shows particularly promising anxiolytic and sedative properties, while methyl chavicol-rich varieties demonstrate notable antispasmodic effects[17].

The phenolic compound profile of *Tulsi* includes several therapeutically significant molecules that contribute substantially to its antioxidant and anti-inflammatory properties (Table 1). Rosmarinic acid, caffeic acid, chicoric acid, and isorientin represent major phenolic constituents with well-documented biological activities[18]. Rosmarinic acid, in particular, demonstrates potent antioxidant properties exceeding those of vitamin E in certain experimental systems, while also exhibiting significant anti-inflammatory effects through multiple molecular pathways[19].

Flavonoid (Table 1) compounds in *Tulsi*, including orientin, vicenin, apigenin, and luteolin, contribute significantly to its cardiovascular protective, hepatoprotective, and neuroprotective properties. These compounds demonstrate excellent bioavailability and can effectively cross biological barriers, including the blood-brain barrier, enabling them to exert systemic therapeutic effects. The glycosidic forms of these flavonoids often exhibit enhanced stability and bioavailability compared to their aglycone counterparts, explaining the traditional preference for aqueous extracts in certain therapeutic applications[20].

Triterpene compounds (Table 2), including ursolic acid, oleanolic acid, and betulinic acid, represent another important class of bioactive constituents in *Tulsi*. These compounds demonstrate significant hepatoprotective, anti-inflammatory, and anticancer properties through various molecular mechanisms. Ursolic acid, in particular, has emerged as a compound of considerable therapeutic interest due to its ability to modulate multiple cellular pathways involved in inflammation, apoptosis, and cellular metabolism[21].

The synergistic interactions between different classes of bioactive compounds in *Tulsi* create a unique pharmacological profile that distinguishes it from single-compound therapeutics. The combination of lipophilic essential oil components with hydrophilic phenolic compounds and flavonoids ensures comprehensive bioavailability and multitarget therapeutic effects. This chemical complexity explains the traditional preference

for whole plant extracts over isolated compounds and supports the modern concept of "botanical drugs" that preserve the synergistic effects of multiple bioactive constituents.

4. Molecular Mechanisms of Action

Contemporary molecular research has elucidated numerous cellular and molecular pathways through which *Tulsi* exerts its therapeutic effects, providing scientific validation for its traditional uses while revealing novel therapeutic potentials. The plant's bioactive compounds interact with multiple molecular targets, creating complex networks of interconnected pathways that collectively contribute to its pharmacological properties[22]. This multitarget approach aligns with modern understanding of complex disease pathogenesis and suggests potential advantages over conventional single-target therapies[23].

5. Anti-inflammatory Pathways and Immunomodulation

The anti-inflammatory properties (Table 2) of *Tulsi* involve complex interactions with multiple inflammatory signalling pathways, with particular emphasis on the nuclear factor kappa B (NF-κB) pathway. NF-κB serves as a central transcriptional regulator of inflammatory responses, controlling the expression of numerous pro-inflammatory cytokines, chemokines, and adhesion molecules[24]. Research has demonstrated that bioactive compounds in *Tulsi*, particularly eugenol and rosmarinic acid, effectively inhibit NF-κB activation through multiple mechanisms[25].

The molecular mechanism of NF-κB inhibition by *Tulsi* compounds involves prevention of Inhibitory protein (IκB) degradation and subsequent nuclear translocation of NF-κB subunits. Eugenol specifically interferes with the phosphorylation of IκB proteins by IκB Kinase (IKK) complex, thereby maintaining NF-κB in its inactive cytoplasmic state[26]. Additionally, direct antioxidant effects of phenolic compounds reduce Reactive Oxygen Species (ROS) levels, which serve as important secondary messengers in NF-κB activation pathways[27].

The immunomodulatory properties of *Tulsi* affect both innate and adaptive immunity, as well as its antioxidant and antiinflammatory properties[6]. Clinical studies have demonstrated that *Tulsi* extracts significantly modulate cytokine production profiles, enhancing the production of beneficial cytokines such as Interleukin-2 (IL-2), Interferon-gamma (IFN-γ), and Interleukin-4 (IL-4) while reducing pro-inflammatory mediators including Interleukin-1 beta (IL-1β) and Tumour Necrosis Factor-alpha (TNF-α)[28]. This selective cytokine modulation demonstrates *Tulsi*'s ability to fine-tune immune responses rather than broadly suppressing inflammatory pathways.

Table 1. Key bioactive compounds in *O. sanctum* and their properties

Class of Compounds	Major Bioactive Compounds	Key Properties and Mechanisms	References
Essential oils	Eugenol, Methyl Eugenol, β-Elemene, β-Caryophyllene, Germacrene D, Linalool, Camphor	Potent antimicrobial, anti-inflammatory, antioxidant; contributes to distinct chemotypes with varying therapeutic applications.	18-20
Phenolic compounds	Rosmarinic Acid, Caffeic Acid, Chicoric Acid, Isorientin	Strong antioxidant activity (scavenging free radicals, activating Nrf2 pathway), anti-inflammatory effects (inhibiting NF-κB).	21,22
Flavonoids	Orientin, Vicenin, Apigenin, Luteolin	Cardiovascular protective, hepatoprotective, neuroprotective; good bioavailability, can cross blood-brain barrier.	23,24
Triterpenes	Ursolic Acid, Oleanolic Acid, Betulinic Acid	Significant hepatoprotective, anti-inflammatory, and anticancer properties (modulating cellular pathways, inhibiting MMPs).	25,26
Other secondary metabolites	Alkaloids, Saponins, Tannins, Vitamins (C, A), Minerals (Calcium, Zinc, Iron)	Contribute to overall adaptogenic, immunomodulatory, and therapeutic effects; support general health and well-being.	27,28

The enhancement of Th1 cellular immunity through increased IL-2 and IFN-γ production supports the traditional use of *Tulsi* in treating infectious diseases and enhancing overall immune function. Simultaneously, the modulation of Th2 responses through IL-4 enhancement suggests potential applications in allergic conditions and autoimmune disorders. The ability to balance Th1/Th2 responses positions *Tulsi* as a valuable immunomodulatory agent for conditions characterized by immune imbalance[29].

6. Apoptotic and Anti-cancer Mechanisms

The anticancer properties of *Tulsi* involve multiple molecular mechanisms that collectively contribute to its ability to inhibit cancer cell proliferation, induce apoptosis, and prevent metastasis. There are now around 30 natural compounds under clinical trials for the treatment of cancer. *Tulsi*, or *Holy Basil*, of the genus *Ocimum*, is one of the most widely available natural compounds being investigated for anticancer applications. The primary mechanism involves the induction of apoptosis through both intrinsic (mitochondrial) and extrinsic (death receptor) pathways[30].

Research has demonstrated that ethanolic extracts of *Tulsi* induce apoptosis in various cancer cell lines, including lung adenocarcinoma (A549), breast cancer (MCF-7), and colorectal cancer cells, through a mitochondria-caspase-dependent pathway[31]. This process involves the disruption of mitochondrial membrane potential, release of cytochrome c into the cytoplasm, and subsequent activation of caspase cascades leading to programmed cell death. The selectivity of this process for transformed cells while sparing normal cells represents a significant therapeutic advantage[32].

Dose-dependent inhibition of cell proliferation by eugenol had been reported in breast cancer. Induction of apoptosis was in HER2 positive (SK-BR-3) and triple-negative (MDA-MB-231) breast cancer cell lines via PI3K/AKT/FOXO3a pathway inhibition[33]. The modulation of the PI3K/AKT pathway represents a critical mechanism through which *Tulsi* compounds exert anticancer effects. This pathway regulates cellular survival, proliferation, and metabolism, making it an important therapeutic target in cancer treatment[34].

The tumour suppressor protein p53 serves as another important molecular target for *Tulsi*'s anticancer effects. Bioactive compounds in *Tulsi* activate p53-mediated cell cycle checkpoints, allowing cells with DNA damage to undergo repair processes or, if repair is impossible, to undergo apoptosis[35]. This mechanism helps prevent the accumulation of genetic mutations that could lead to malignant transformation. Additionally, *Tulsi* compounds modulate the expression of cell cycle regulatory proteins, including cyclins and cyclin-dependent kinases, further contributing to their antiproliferative effects[36].

The anti-metastatic properties of *Tulsi* involve the inhibition of matrix Metalloproteinases (MMPs), enzymes responsible for degrading extracellular matrix components and facilitating cancer cell invasion and metastasis[37]. Research has shown that *Tulsi* extracts significantly reduce MMP-2 and MMP-9 activity in various cancer cell lines, thereby limiting their invasive potential. Additionally, the modulation of adhesion molecules and angiogenic factors contributes to the overall anti-metastatic effects.

7. Oxidative Stress Modulation and Antioxidant Mechanisms

The antioxidant properties (Table 2) of *Tulsi* operate through multiple complementary mechanisms that provide comprehensive protection against oxidative damage (Table 2). The primary mechanism involves direct free radical scavenging through phenolic compounds, particularly rosmarinic acid, caffeic acid, and various flavonoids. These compounds donate electrons or hydrogen atoms to neutralize Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS), thereby preventing oxidative damage to cellular macromolecules[38].

The secondary antioxidant mechanism involves the enhancement of endogenous antioxidant enzyme systems through transcriptional regulation. *Tulsi* compounds activate the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, a master regulator of Antioxidant Response Elements (AREs). Nrf2 activation leads to increased expression of antioxidant enzymes including Superoxide Dismutase (SOD), catalase, glutathione peroxidase, and glutathione S-transferase[39]. This enzymatic enhancement provides

sustained protection against oxidative stress beyond the immediate scavenging effects of phenolic compounds[40].

The modulation of cellular glutathione levels represents another important antioxidant mechanism of *Tulsi*. Research has demonstrated that *Tulsi* extracts significantly increase intracellular glutathione concentrations while enhancing the activity of glutathione-related enzymes. Glutathione serves as the primary intracellular antioxidant and plays crucial roles in detoxification processes, making its enhancement particularly important for cellular protection[41].

Metal chelation represents an additional antioxidant mechanism through which *Tulsi* compounds prevent oxidative damage. Transition metals, particularly iron and copper, catalyze the formation of highly reactive hydroxyl radicals through Fenton reactions. Phenolic compounds in *Tulsi* effectively chelate these metals, preventing their participation in radical-generating reactions and providing protection against metal-catalyzed oxidative damage[42].

8. Metabolic Pathway Modulation

Recent research has revealed *Tulsi*'s significant influence on key metabolic pathways, particularly those involved in glucose homeostasis and lipid metabolism. The hypoglycemic effects of *Tulsi* involve multiple mechanisms that collectively improve glucose tolerance and insulin sensitivity. The primary mechanism involves the enhancement of glucose uptake in peripheral tissues through activation of AMP-activated Protein Kinase (AMPK), a cellular energy sensor that promotes glucose utilization when activated[43].

Tulsi compounds also modulate insulin signalling pathways by enhancing insulin receptor sensitivity and downstream signalling cascades. This involves the phosphorylation and activation of key signalling proteins including Insulin Receptor Substrate-1 (IRS-1), Phosphoinositide 3-Kinase (PI3K), and protein kinase B (Akt)[44]. The enhanced insulin signalling promotes glucose uptake in muscle and adipose tissue while inhibiting hepatic glucose production through the suppression of gluconeogenesis enzymes.

The hypolipidemic effects of *Tulsi* involve modulation of lipid metabolism enzymes and transcriptional regulators. Research has demonstrated that *Tulsi* extracts inhibit 3-Hydroxy-3-Methylglutaryl-Coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol synthesis[6]. This inhibition leads to reduced endogenous cholesterol production and subsequent upregulation of Low-Density Lipoprotein (LDL) receptors to maintain cellular cholesterol homeostasis[45].

Additionally, *Tulsi* compounds enhance lipoprotein lipase activity, promoting the clearance of triglyceride-rich lipoproteins from circulation. The modulation of Peroxisome Proliferator-Activated Receptors (PPARs), particularly PPAR-α and PPAR-γ, contributes to improved lipid metabolism and fatty acid oxidation[46]. These nuclear receptors serve as important transcriptional regulators of genes involved in lipid metabolism, glucose homeostasis, and adipocyte differentiation.

9. Clinical Applications and Therapeutic Potential

The molecular mechanisms elucidated (Table 2) through contemporary research have provided scientific validation for numerous traditional uses of *Tulsi* while revealing new therapeutic possibilities. Many *in vitro*, animal and human studies attest to *Tulsi* having multiple therapeutic actions, establishing a robust foundation for evidence-based clinical applications[47]. The translation of molecular research findings into clinical practice has resulted in numerous human studies demonstrating *Tulsi's* efficacy across various therapeutic domains.

10. Respiratory System Applications

Clinical studies have consistently demonstrated *Tulsi*'s efficacy in treating various respiratory conditions, with mechanisms involving bronchodilation, anti-inflammatory effects, and antimicrobial activity (Table 2). Controlled trials have shown significant improvement in asthma symptoms, including reduced frequency of attacks, improved peak expiratory flow rates, and decreased requirement for conventional bronchodilator medications[48]. The bronchodilatory effects result from the relaxation of smooth muscle in airways through multiple mechanisms, including calcium channel blockade and β2-adrenergic receptor stimulation[49].

The anti-inflammatory effects in respiratory tissues involve the inhibition of inflammatory mediators responsible for airway inflammation and hyperresponsiveness. Clinical studies have documented reduced levels of inflammatory markers in sputum and serum of patients treated with *Tulsi* extracts[50]. The antimicrobial properties provide additional benefits in treating respiratory infections, with documented efficacy against both bacterial and viral pathogens commonly associated with respiratory illnesses.

Recent clinical investigations have explored *Tulsi*'s potential in treating Chronic Obstructive Pulmonary Disease (COPD) and other chronic respiratory conditions[2]. Preliminary results suggest improvements in exercise tolerance, reduced exacerbation frequency, and enhanced quality of life measures in patients receiving *Tulsi* supplementation as adjunctive therapy. The antioxidant properties appear particularly beneficial in COPD, where oxidative stress plays a central role in disease progression.

11. Stress and Adaptogenic Properties

Clinical research has validated *Tulsi*'s traditional use as an adaptogen, demonstrating its ability to help the body adapt to various stressors while maintaining physiological homeostasis[51]. Human studies have shown significant reductions in perceived stress levels, anxiety scores, and depression ratings following *Tulsi* supplementation. The adaptogenic effects involve modulation of the Hypothalamic-Pituitary-Adrenal (HPA) axis, resulting in normalized cortisol secretion patterns and improved stress response[14].

Randomized controlled trials have demonstrated *Tulsi*'s efficacy in improving cognitive function under stress conditions. Parameters including attention, memory, and executive function show significant improvement in subjects receiving *Tulsi* extracts compared to placebo controls. The neuroprotective mechanisms involve antioxidant effects in neural tissues, modulation of neurotransmitter systems, and enhancement of neuroplasticity factors[52].

Sleep quality improvements represent another well-documented clinical benefit of *Tulsi* supplementation. Clinical studies have shown reduced sleep latency, improved sleep efficiency, and decreased nocturnal awakenings in subjects with stress-related sleep disturbances. The sleep-promoting effects appear to involve GABAergic mechanisms and modulation of circadian rhythm regulatory pathways[53].

12. Cardiovascular Applications

Clinical investigations have demonstrated significant cardiovascular benefits of *Tulsi* supplementation, including improvements in lipid profiles, blood pressure regulation, and endothelial function. Controlled trials have shown reductions in total cholesterol, LDL cholesterol, and triglyceride levels, along with increases in beneficial HDL cholesterol[54]. These lipid-modulating effects result from the molecular mechanisms discussed earlier, including HMG-CoA reductase inhibition and enhanced lipoprotein metabolism[55].

Blood pressure lowering effects have been documented in both hypertensive and normotensive individuals, with mechanisms involving endothelial nitric oxide enhancement, Angiotensin-Converting Enzyme (ACE) inhibition, and direct vasodilatory effects[56]. Eugenol, a component of *Holy Basil* (*Tulsi*) and common spice clove, inhibits the interaction between SARS-CoV-2 Spike S1 and ACE2, demonstrating additional cardiovascular protective mechanisms through ACE2 modulation[57].

Antiplatelet and anticoagulant effects have been observed in clinical studies, suggesting potential benefits in preventing thrombotic cardiovascular events. These effects appear to involve modulation of platelet aggregation pathways and coagulation factor activities[58]. However, these properties necessitate careful monitoring in patients receiving anticoagulant medications to prevent potential interactions.

13. Metabolic and Endocrine Applications

Clinical trials have demonstrated significant benefits of *Tulsi* in managing Type 2 diabetes mellitus and metabolic syndrome. Studies have shown improvements in fasting glucose levels, postprandial glucose responses, and glycated hemoglobin (HbA1c) values. The mechanisms involve enhanced insulin sensitivity, improved pancreatic β-cell function, and modulation of glucose metabolism pathways as described earlier[59].

Table 2. Clinical applications and molecular mechanisms of *O. sanctum*

Clinical Application	Key Molecular Mechanisms	Observed Clinical Effects	References
Anti-inflammatory	Inhibition of NF-κB activation, reduction of ROS levels, selective cytokine modulation.	Reduced inflammation, balanced immune responses, potential in autoimmune conditions.	31,32,35
Anticancer	Induction of apoptosis, disruption of mitochondrial membrane potential, PI3K/AKT pathway inhibition.	Inhibition of cancer cell proliferation, prevention of metastasis.	36,37,40
Antioxidant	Direct free radical scavenging, Nrf2 activation, increased glutathione levels.	Protection against oxidative damage, sustained antioxidant protection	42,43,45
Metabolic modulation	AMPK activation, insulin sensitivity enhancement, HMG-CoA reductase inhibition.	Improved glucose tolerance, reduced cholesterol levels.	46,47
Respiratory support	Bronchodilation, anti-inflammatory effects, antimicrobial activity.	Improved asthma symptoms, reduced respiratory infections.	48,49
Cardiovascular health	Lipid profile improvements, ACE inhibition, antiplatelet effects.	Lowered cholesterol, regulated blood pressure.	50,51

Weight management benefits have been observed in clinical studies, with participants showing modest but significant reductions in body weight, body mass index, and waist circumference. The mechanisms appear to involve enhanced metabolic rate, improved fat oxidation, and modulation of appetite-regulating hormones[60]. These effects support the traditional use of *Tulsi* in managing obesity and related metabolic disorders.

Thyroid function modulation represents an emerging area of clinical interest, with preliminary studies suggesting potential benefits in both hypothyroid and hyperthyroid conditions[61]. The mechanisms appear to involve modulation of thyroid hormone synthesis and peripheral conversion pathways, though more research is needed to establish definitive clinical recommendations.

14. Safety Profile and Toxicological Considerations

The safety profile of *Tulsi* has been extensively evaluated through both traditional use documentation and modern toxicological studies. Millennia of traditional use provide substantial evidence of safety when used appropriately, with documented adverse effects being rare and generally mild[62]. Contemporary toxicological investigations have largely confirmed this favourable safety profile while identifying specific considerations for certain populations and clinical scenarios[63].

Acute toxicity studies in animal models have demonstrated remarkably low toxicity, with median Lethal Dose (LD50) values significantly higher than therapeutic dose ranges. Chronic toxicity studies extending up to 180 days have failed to demonstrate significant adverse effects on major organ systems, including hepatic, renal, cardiovascular, and neurological functions[64]. Reproductive toxicity studies have generally shown no adverse effects on fertility or foetal development, though some studies suggest potential effects at very high doses that exceed typical therapeutic ranges[65].

Clinical safety data from human studies consistently report excellent tolerability with minimal adverse effects. The most commonly reported side effects include mild gastrointestinal symptoms such as nausea or stomach upset, typically occurring when *Tulsi* is consumed on an empty stomach or in high doses[66]. These effects are generally transient and resolve with dose reduction or administration with food. Allergic reactions are rare but have been reported in individuals with known sensitivities to plants in the *Lamiaceae* family.

Drug interactions represent an important safety consideration, particularly given *Tulsi*'s effects on various metabolic pathways. The most clinically significant interaction involves anticoagulant medications, where *Tulsi*'s antiplatelet effects may enhance bleeding risk[2]. Patients receiving warfarin, heparin, or other anticoagulants should be monitored

closely if considering *Tulsi* supplementation. Additionally, potential interactions with antidiabetic medications may require dose adjustments due to *Tulsi*'s hypoglycemic effects.

15. Future Perspectives and Research Directions

The extensive body of research on *Tulsi* has established a solid foundation for understanding its therapeutic mechanisms and clinical applications, yet numerous opportunities exist for advancing knowledge and clinical implementation. Systems biology approaches, incorporating genomics, proteomics, and metabolomics technologies, offer promising avenues for comprehensively understanding *Tulsi*'s effects on cellular networks and identifying novel therapeutic targets. These approaches may reveal previously unrecognized mechanisms and help optimize therapeutic protocols[67].

Personalized medicine applications represent an emerging frontier in *Tulsi* research. Understanding individual variations in response to *Tulsi* compounds, potentially based on genetic polymorphisms affecting drug metabolism, receptor sensitivity, or metabolic pathways, could enable more precise therapeutic recommendations. Pharmacogenomic studies examining the relationship between genetic variants and *Tulsi* efficacy could significantly enhance therapeutic outcomes[68].

The development of standardized extracts with defined bioactive compound profiles remains a critical need for advancing clinical applications. Current research focuses on identifying optimal extraction methods, standardization markers, and quality control parameters to ensure consistent therapeutic effects[69]. Advanced analytical techniques, including High-Performance Liquid Chromatography coupled with Mass Spectrometry (HPLC-MS), are being employed to develop comprehensive chemical fingerprints for quality assessment.

Nanotechnology applications offer exciting possibilities for enhancing *Tulsi*'s therapeutic delivery and efficacy. Nanoencapsulation techniques may improve bioavailability, enable targeted delivery to specific tissues, and provide sustained release profiles[70]. These technological advances could potentially overcome current limitations related to bioavailability and dosing frequency while reducing required doses and potential side effects.

Combination therapy research represents another promising direction, examining synergistic effects between *Tulsi* and other natural compounds or conventional medications. Traditional polyherbal formulations provide templates for investigating beneficial combinations, while modern pharmacological principles guide the development of rational combination therapies for specific conditions[71].

16. Conclusion

This comprehensive literature review demonstrates that *Tulsi* (*O. sanctum*) represents a remarkable example of successful integration between traditional medicinal knowledge and modern scientific validation. The plant's journey from ancient *Ayurvedic* texts to contemporary molecular research laboratories illustrates the enduring value of traditional medicine systems while highlighting the importance of scientific investigation in understanding therapeutic mechanisms. The extensive body of research examining *Tulsi*'s phytochemistry, molecular mechanisms, and clinical applications provides compelling evidence for its therapeutic potential across multiple disease categories.

The molecular mechanisms elucidated through contemporary research, including NF-κB pathway modulation, mitochondrial apoptosis induction, comprehensive antioxidant actions, and metabolic pathway regulation, provide scientific credibility to traditional therapeutic claims while revealing novel applications. The multi target approach characteristic of *Tulsi*'s bioactive compounds aligns with modern understanding of complex disease pathogenesis and suggests potential advantages over conventional single-target therapeutics. This systems-level approach to healing, inherent in traditional medicine, offers valuable insights for developing more effective therapeutic strategies for contemporary healthcare challenges.

The clinical validation of *Tulsi's* therapeutic effects across respiratory, cardiovascular, metabolic, and neurological domains, combined with its excellent safety profile, positions it as a valuable addition to evidence-based integrative medicine approaches. The plant's adaptogenic properties, immune-modulating

effects, and broad-spectrum therapeutic activities make it particularly relevant for addressing the chronic, multi-factorial diseases that characterize modern healthcare challenges.

Future research directions, including systems biology approaches, personalized medicine applications, and advanced delivery technologies, promise to further enhance our understanding and clinical utilization of *Tulsi*'s therapeutic potential. The development of standardized preparations, comprehensive safety assessments, and rational combination therapies will facilitate broader clinical adoption while maintaining the safety and efficacy standards required for modern healthcare.

As the global healthcare landscape increasingly recognizes the value of integrative approaches combining traditional wisdom with scientific rigor, *Tulsi* stands as an exemplary model of this convergence. The extensive research documenting its molecular mechanisms and clinical efficacy provides a template for investigating other traditional medicines while demonstrating the potential for ancient healing traditions to contribute meaningfully to contemporary therapeutic approaches. The continued investigation of *Tulsi* and similar traditional medicines represents a promising pathway toward more holistic, effective, and sustainable healthcare solutions that honour both traditional knowledge and scientific excellence.

17. Author Contribution

The conceptualization, initial writing, and primary literature search were performed by SPS. RCJ and JK were instrumental in reviewing and verifying the manuscript's accuracy. Additionally, JK and CGL contributed to the editing process and conducted further literature review. All authors have read and agreed to the published version of the manuscript.

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