NANOFORMULATIONS OF *OCIMUM SANCTUM* (TULSI) BIOACTIVES FOR ENHANCED THERAPEUTIC DELIVERY: A REVIEW

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Graphical Abstract

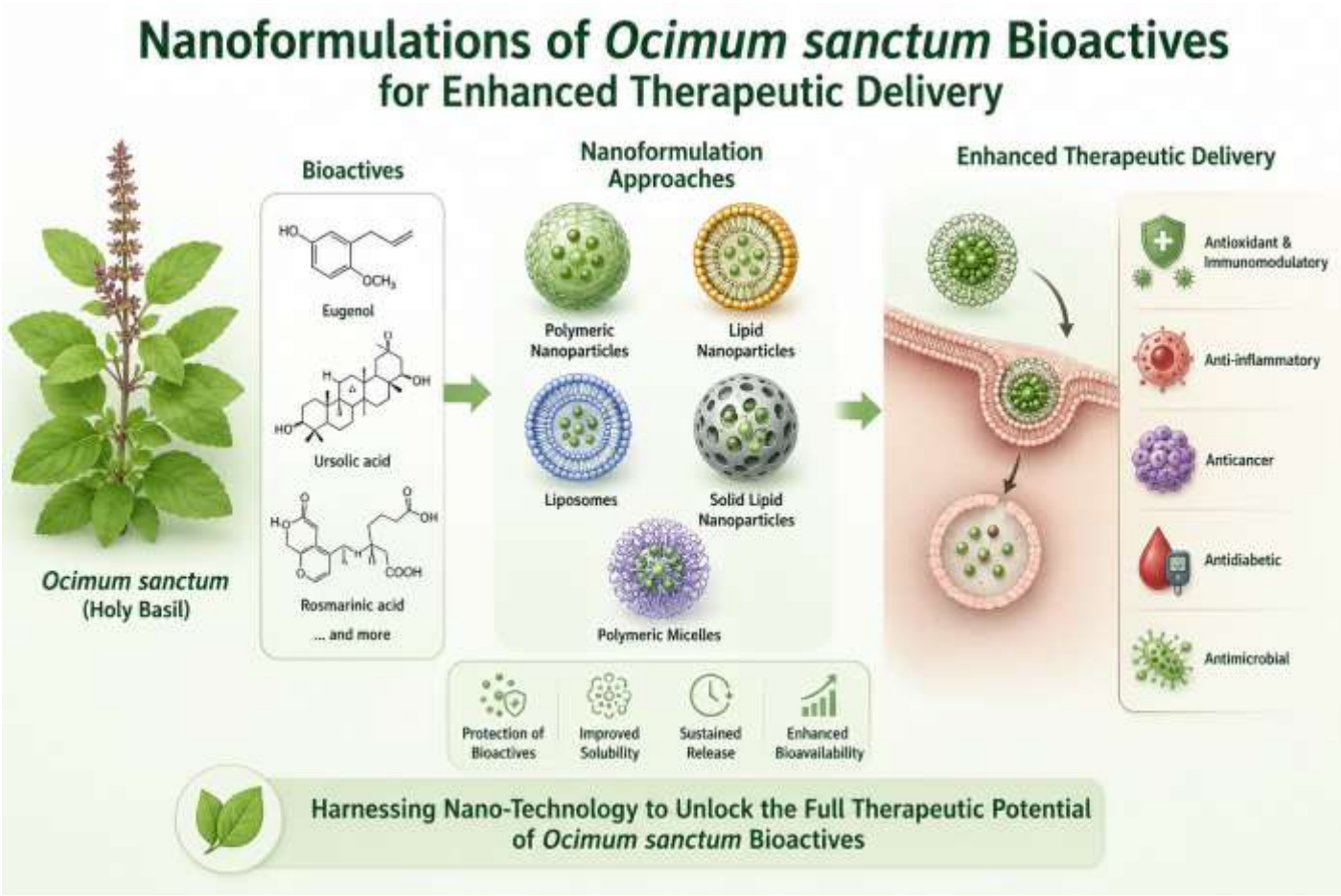

Fig. 1 Graphical Abstract

Abstract

Ocimum sanctum Linn. (Tulsi), a medicinal plant belonging to the family Lamiaceae, has gained considerable scientific attention owing to its broad spectrum of pharmacological activities and diverse phytochemical composition. The plant contains numerous bioactive constituents, including eugenol, ursolic acid, rosmarinic acid, apigenin, orientin, vicenin, and linalool, which exhibit antioxidant, anti-inflammatory, antimicrobial, antiviral, anticancer, antidiabetic, neuroprotective, and immunomodulatory properties. Despite these promising therapeutic effects, the clinical application of Tulsi phytoconstituents is often limited by poor aqueous solubility, low oral bioavailability, rapid metabolism, chemical instability, and inadequate tissue targeting. Recent advances in pharmaceutical nanotechnology have provided innovative strategies to overcome these limitations through the development of nano-based drug delivery systems such as liposomes, phytosomes, polymeric nanoparticles, nanoemulsions, solid lipid nanoparticles, nanostructured lipid carriers, nanogels, and green-synthesized metallic nanoparticles. These nanocarriers enhance drug solubility, improve pharmacokinetic behavior, provide sustained and controlled release, increase cellular uptake, and facilitate targeted delivery, thereby significantly improving therapeutic efficacy while minimizing systemic toxicity. The present review comprehensively discusses the botanical profile, phytochemical composition, pharmacological activities, limitations of conventional delivery, and recent developments in nanoformulations of *Ocimum sanctum* bioactives. Furthermore, the review critically evaluates the mechanisms of enhanced therapeutic delivery, pharmaceutical applications, safety considerations, regulatory challenges, research gaps, and future prospects for the clinical translation of Tulsi-based nanomedicines. This review aims to provide researchers with an updated scientific overview of the current progress and future opportunities in the development of nano-enabled herbal therapeutics.

Keywords

Ocimum sanctum; Tulsi; Nanoformulation; Herbal Drug Delivery; Phytochemicals; Nanomedicine; Phytosomes; Liposomes

1. INTRODUCTION

Medicinal plants have served as one of the primary sources of therapeutic agents since ancient times and continue to play a vital role in modern healthcare systems. According to the World Health Organization (WHO), a significant proportion of the global population relies on herbal medicines for primary healthcare, particularly in developing countries where medicinal plants remain affordable, accessible, and culturally accepted **[1]**.

The increasing prevalence of chronic diseases, including cancer, diabetes mellitus, cardiovascular disorders, microbial infections, and neurodegenerative diseases, has renewed scientific interest in plant-derived bioactive compounds as safer and more effective therapeutic alternatives **[2]**. Unlike many conventional synthetic drugs that often target a single molecular pathway, phytochemicals possess multitarget pharmacological properties by simultaneously modulating oxidative stress, inflammation, apoptosis, immune responses, and cellular signaling pathways **[3]**.

Among the medicinal plants extensively investigated worldwide, *Ocimum sanctum* Linn., commonly known as Tulsi or Holy Basil, occupies a unique position because of its extensive traditional use and broad therapeutic spectrum. Belonging to the family Lamiaceae, Tulsi has been revered in Ayurveda as the "Queen of Herbs" owing to its remarkable medicinal value and adaptogenic properties **[4]**.

Traditionally, Tulsi has been used for the management of respiratory disorders, fever, skin diseases, gastrointestinal disturbances, diabetes mellitus, cardiovascular disorders, inflammatory conditions, microbial infections, and stress-related illnesses. Modern pharmacological investigations have validated many of these traditional claims by demonstrating antioxidant, anti-inflammatory, antimicrobial, antiviral, antifungal,

hepatoprotective, cardioprotective, nephroprotective, neuroprotective, immunomodulatory, and anticancer activities of Tulsi extracts and isolated phytoconstituents **[5]**.

The remarkable therapeutic potential of *Ocimum sanctum* is primarily attributed to its chemically diverse phytochemical composition. The plant contains several biologically active constituents including eugenol, ursolic acid, rosmarinic acid, apigenin, orientin, vicenin, linalool, β-caryophyllene, and numerous phenolic acids, flavonoids, and terpenoids. These compounds exhibit significant pharmacological activities through synergistic modulation of multiple biochemical and molecular pathways **[6]**.

Despite the promising biological activities of Tulsi bioactives, their clinical translation remains limited because of several pharmaceutical challenges. Many phytochemicals possess poor aqueous solubility, low gastrointestinal absorption, rapid first-pass metabolism, chemical instability, short biological half-life, and inadequate tissue-specific distribution. Consequently, conventional dosage forms often fail to achieve optimal therapeutic concentrations at the target site, thereby reducing treatment efficacy **[7]**.

Recent advances in pharmaceutical nanotechnology have emerged as promising solutions to overcome these limitations. Nano-based drug delivery systems, including liposomes, phytosomes, polymeric nanoparticles, nanoemulsions, solid lipid nanoparticles, nanostructured lipid carriers, nanogels, and metallic nanoparticles, have demonstrated significant improvements in drug solubility, stability, bioavailability, controlled release, and tissue-specific targeting. These delivery systems not only enhance therapeutic efficacy but also reduce systemic toxicity and improve patient compliance **[8]**.

The present review aims to provide a comprehensive overview of the botanical characteristics, phytochemical composition, pharmacological activities, and nanoformulation strategies developed for *Ocimum sanctum* bioactives. Particular emphasis is placed on recent advances in nanotechnology-based drug delivery systems, mechanisms of enhanced therapeutic delivery, pharmaceutical applications, safety considerations, regulatory challenges, and future perspectives for the clinical translation of Tulsi-derived nanomedicines.

2. BOTANICAL PROFILE OF *Ocimum sanctum*

2.1 Taxonomy

Ocimum sanctum Linn., currently accepted by many botanical databases as *Ocimum tenuiflorum* Linn., belongs to the family **Lamiaceae**, which comprises more than 7,000 species of aromatic and medicinal plants distributed worldwide. The genus *Ocimum* contains over 60 species, among which *Ocimum sanctum* is the most extensively investigated because of its remarkable medicinal, pharmaceutical, and ethnobotanical significance **[9]**.

Taxonomic Classification

- **Kingdom:** Plantae
- **Division:** Magnoliophyta (Angiosperms)
- **Class:** Magnoliopsida (Dicotyledons)
- **Order:** Lamiales
- **Family:** Lamiaceae
- **Genus:** *Ocimum*
- **Species:** *Ocimum sanctum* Linn. (*Ocimum tenuiflorum* Linn.)

Two principal varieties of Tulsi are commonly cultivated. **Rama Tulsi (Sri Tulsi)** possesses bright green leaves and is extensively cultivated throughout India, whereas **Krishna Tulsi** is characterized by purple leaves

and stems and generally contains higher concentrations of essential oils and phenolic compounds. A third variety, **Vana Tulsi**, grows wild in several tropical regions and is also recognized for its medicinal importance **[10]**.

2.2 Geographical Distribution

Ocimum sanctum is native to the Indian subcontinent and has been cultivated for thousands of years because of its medicinal, religious, and cultural significance. Today, the plant is widely distributed throughout tropical and subtropical regions including India, Nepal, Bangladesh, Sri Lanka, Pakistan, Thailand, Malaysia, Indonesia, China, Africa, Australia, and South America **[11]**.

Tulsi grows optimally in warm climates with temperatures ranging from **20°C to 35°C** and requires well-drained fertile loamy soil with a pH of **5.5–7.5**. The plant thrives under adequate sunlight and moderate rainfall, producing higher concentrations of essential oils under favorable environmental conditions.

Several environmental factors including altitude, seasonal variation, cultivation practices, irrigation, harvesting stage, and post-harvest processing significantly influence the phytochemical composition of Tulsi. Such variations may alter the concentration of bioactive constituents including eugenol, ursolic acid, rosmarinic acid, and linalool, thereby affecting the therapeutic efficacy of herbal formulations **[12]**.

2.3 Morphological Characteristics

Ocimum sanctum is an erect, aromatic, perennial shrub that generally attains a height of **30–90 cm**. The plant possesses a highly branched quadrangular stem, which is a characteristic feature of members belonging to the Lamiaceae family.

The leaves are simple, opposite, ovate to elliptic, measuring approximately **2–5 cm** in length with serrated margins and acute apices. Numerous glandular trichomes are distributed over the leaf surface and serve as specialized secretory structures responsible for the synthesis and storage of essential oils.

The flowers are small, purplish-white or lavender in color, bisexual, and arranged in terminal racemes. Flowering occurs throughout most of the year under suitable climatic conditions. The fruits are small nutlets containing dark brown to black seeds with excellent germination capacity under appropriate environmental conditions.

The characteristic aroma of Tulsi is primarily due to the presence of volatile essential oils rich in eugenol, methyl eugenol, linalool, and β-caryophyllene, which contribute significantly to the medicinal value of the plant **[13]**

2.4 Traditional Medicinal Uses

Ocimum sanctum has occupied a central position in Ayurveda, Siddha, and Unani systems of medicine for more than 3,000 years. In Ayurvedic literature, Tulsi is described as an **"Elixir of Life"** because of its ability to promote longevity, improve immunity, enhance mental health, and maintain overall physiological balance.

Traditionally, fresh leaves, leaf juice, seeds, roots, and essential oils have been utilized for the treatment of respiratory disorders such as cough, cold, bronchitis, asthma, influenza, and sore throat. Tulsi decoctions are also commonly administered for the management of fever and infectious diseases.

In addition, Tulsi has been widely employed for the treatment of gastrointestinal disorders including indigestion, gastric ulcer, abdominal pain, diarrhea, and intestinal infections. The essential oil is extensively used as a natural antiseptic for wound healing and management of various skin diseases.

Traditional practitioners have also recommended Tulsi for diabetes mellitus, hypertension, arthritis, cardiovascular diseases, liver disorders, kidney diseases, stress, anxiety, insomnia, and several inflammatory

conditions. These diverse ethnomedicinal applications have been scientifically supported by numerous pharmacological investigations conducted during the past few decades **[14]**.

2.5 Ethnopharmacological Importance

The ethnopharmacological significance of *Ocimum sanctum* extends beyond its therapeutic applications. In Indian culture, Tulsi is regarded as one of the most sacred medicinal plants and is cultivated in millions of households. Daily consumption of fresh Tulsi leaves is traditionally believed to improve immunity, enhance physical endurance, reduce stress, and protect against infectious diseases.

Different parts of the plant, including leaves, stems, flowers, roots, and seeds, have been incorporated into numerous traditional herbal formulations either individually or in combination with other medicinal plants. Such widespread ethnobotanical utilization has inspired extensive scientific investigations leading to the discovery of several pharmacologically active compounds.

Recent studies have demonstrated that Tulsi possesses antioxidant, anti-inflammatory, antimicrobial, antiviral, antifungal, hepatoprotective, nephroprotective, cardioprotective, neuroprotective, antidiabetic, anticancer, immunomodulatory, and adaptogenic properties. These biological activities result from the synergistic interaction of multiple phytochemicals rather than a single active constituent, emphasizing the importance of preserving phytochemical complexity during pharmaceutical formulation development **[15]**.

The growing demand for evidence-based herbal medicines has further increased the commercial importance of Tulsi in pharmaceutical, nutraceutical, cosmetic, and functional food industries. Consequently, *Ocimum sanctum* has become one of the most extensively investigated medicinal plants for the development of advanced herbal drug delivery systems, particularly nanotechnology-based formulations designed to improve stability, bioavailability, and therapeutic efficacy.

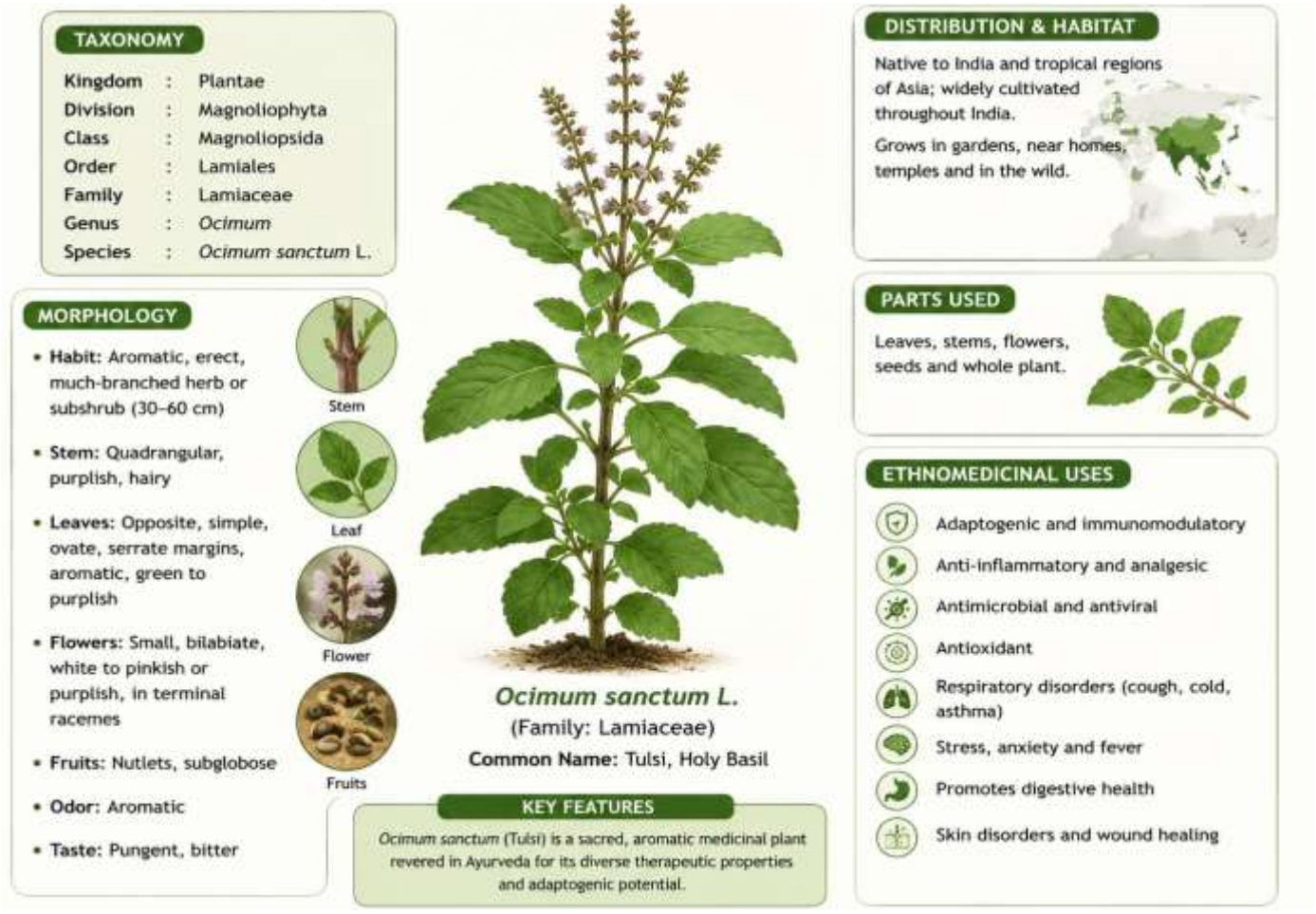

Fig. 2 Botanical Profile of Ocimum Sanctum (Tulsi)

3. PHYTOCHEMICAL CONSTITUENTS OF *Ocimum sanctum*

Ocimum sanctum is recognized as one of the richest medicinal plants because of its chemically diverse phytoconstituents. More than 200 bioactive compounds have been identified from different parts of the plant, including leaves, stems, flowers, seeds, and roots. These phytochemicals belong to several chemical classes, including phenylpropanoids, flavonoids, phenolic acids, terpenoids, triterpenoids, tannins, saponins, alkaloids, glycosides, and volatile essential oils **[16]**. The pharmacological efficacy of Tulsi is attributed not only to individual compounds but also to the synergistic interactions among these bioactive constituents, which collectively contribute to its broad therapeutic spectrum **[17]**.

The phytochemical composition of *Ocimum sanctum* is influenced by several factors, including geographical location, climatic conditions, soil composition, cultivation practices, harvesting season, plant maturity, and extraction techniques. Consequently, standardization of herbal formulations remains an important consideration during pharmaceutical development **[18]**.

Among the numerous phytochemicals identified in Tulsi, eugenol, ursolic acid, rosmarinic acid, linalool, apigenin, orientin, vicenin, β-caryophyllene, carvacrol, methyl eugenol, cirsimaritin, and various phenolic compounds have received considerable scientific attention because of their potent biological activities **[19]**.

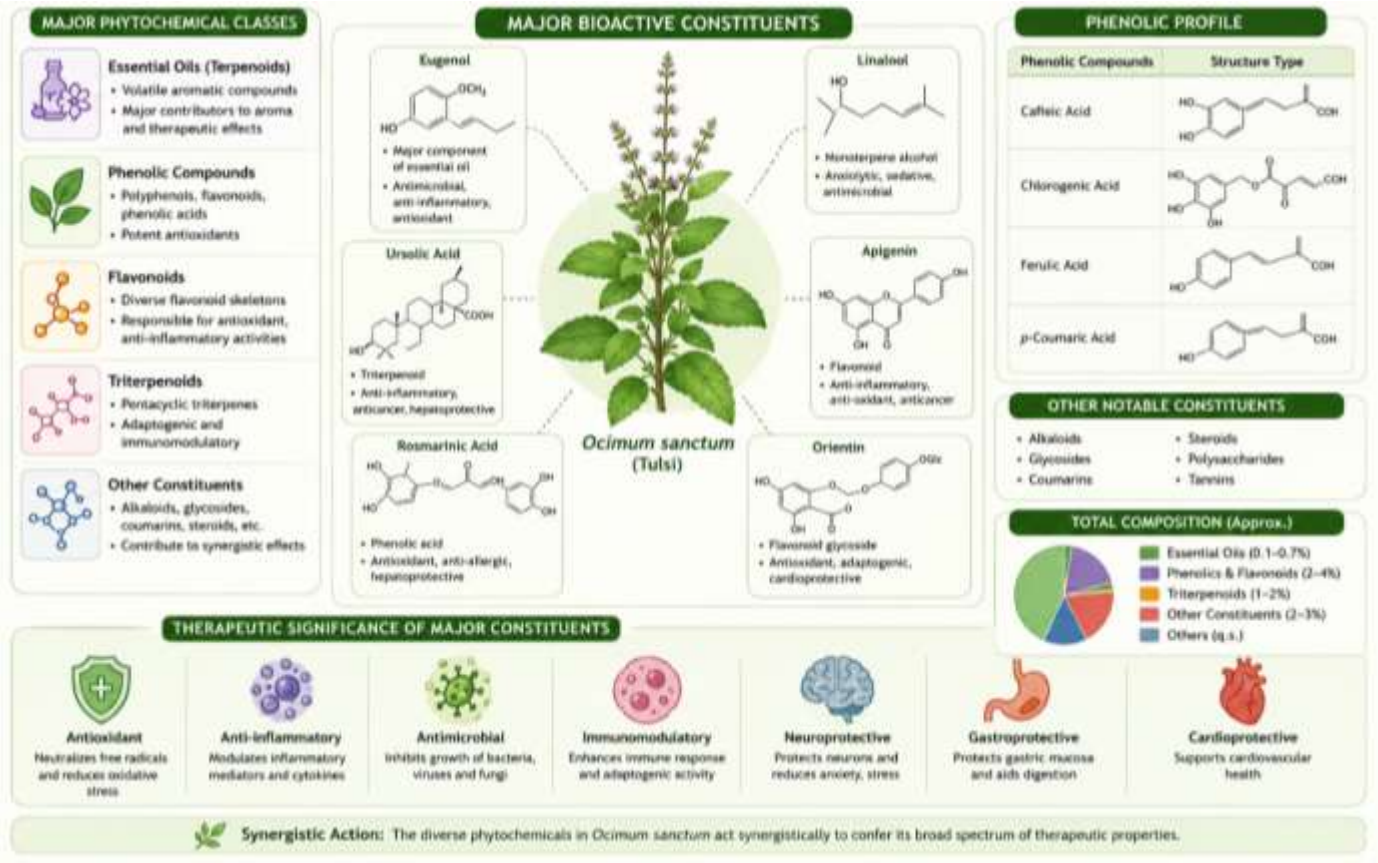

Fig. 3 Phytochemical Composition and Bioactive Constituents of Ocimum Sanctum

3.1 Eugenol

Eugenol is the principal phenolic constituent of Tulsi essential oil and is primarily responsible for the characteristic aroma of the plant. Chemically, eugenol belongs to the phenylpropanoid class and exhibits remarkable antioxidant, anti-inflammatory, analgesic, antimicrobial, antiviral, and anticancer activities **[20]**.

The biological activity of eugenol is mainly attributed to its ability to scavenge reactive oxygen species, inhibit lipid peroxidation, suppress cyclooxygenase (COX-2) activity, reduce prostaglandin synthesis, and regulate nuclear factor-kappa B (NF-κB) signaling pathways. Experimental studies have also demonstrated that eugenol induces apoptosis in several cancer cell lines through mitochondrial dysfunction and activation of

caspase-dependent pathways. Because of its excellent pharmacological profile, eugenol has emerged as one of the most promising candidates for nano-based drug delivery systems.

3.2 Ursolic Acid

Ursolic acid is a naturally occurring pentacyclic triterpenoid abundantly present in Tulsi leaves. It possesses a wide range of pharmacological activities including antioxidant, anti-inflammatory, hepatoprotective, cardioprotective, antimicrobial, antidiabetic, and anticancer properties **[21]**.

Ursolic acid exerts its therapeutic effects by modulating several intracellular signaling pathways, including PI3K/Akt, MAPK, NF-κB, STAT3, and apoptotic pathways. It suppresses inflammatory cytokine production, inhibits tumor cell proliferation, induces programmed cell death, and protects normal tissues against oxidative injury. However, its poor aqueous solubility and limited oral bioavailability have encouraged researchers to develop lipid-based and polymeric nanoformulations for enhanced therapeutic delivery

3.3 Rosmarinic Acid

Rosmarinic acid is one of the most abundant phenolic acids present in *Ocimum sanctum*. It is well known for its exceptional antioxidant capacity owing to the presence of multiple hydroxyl groups capable of neutralizing reactive oxygen species. In addition to its antioxidant activity, rosmarinic acid exhibits anti-inflammatory, antiviral, neuroprotective, cardioprotective, and immunomodulatory effects **[22]**.

Recent molecular investigations have shown that rosmarinic acid inhibits oxidative stress-mediated cellular damage by activating the Nrf2 antioxidant pathway while simultaneously suppressing NF-κB-mediated inflammatory signaling. These dual mechanisms make rosmarinic acid an attractive therapeutic candidate for chronic inflammatory disorders and neurodegenerative diseases.

3.4 Linalool

Linalool is a naturally occurring monoterpene alcohol present in the essential oil of Tulsi. It contributes significantly to the pleasant fragrance of the plant and exhibits antimicrobial, anti-inflammatory, anxiolytic, analgesic, and sedative activities **[23]**.

Linalool disrupts microbial cell membranes, inhibits bacterial enzyme systems, and suppresses inflammatory mediator production. Furthermore, experimental studies have demonstrated its neuroprotective effects through modulation of neurotransmitter systems and reduction of oxidative stress in neuronal tissues. These pharmacological properties have encouraged the incorporation of linalool into nanoemulsions and lipid nanoparticles for improved therapeutic performance.

3.5 Apigenin

Apigenin is a naturally occurring flavonoid widely distributed in medicinal plants, including *Ocimum sanctum*. It possesses significant antioxidant, anti-inflammatory, anticancer, antidiabetic, and neuroprotective properties **[24]**.

Apigenin inhibits cellular proliferation, induces apoptosis, suppresses angiogenesis, and modulates multiple signaling pathways including PI3K/Akt, MAPK, and Wnt/β-catenin. Its anti-inflammatory activity results from inhibition of pro-inflammatory cytokines and cyclooxygenase enzymes. Owing to its poor aqueous solubility, several nanoformulation approaches have been investigated to improve its bioavailability and therapeutic efficacy.

3.6 Orientin and Vicenin

Orientin and vicenin are flavonoid glycosides abundantly present in Tulsi leaves. These compounds are recognized for their potent antioxidant, radioprotective, cardioprotective, hepatoprotective, and neuroprotective activities **[25]**.

Experimental studies have demonstrated that orientin and vicenin effectively scavenge free radicals, reduce oxidative DNA damage, stabilize mitochondrial membranes, and enhance endogenous antioxidant enzyme activity. Their ability to protect normal tissues against radiation-induced injury has attracted considerable attention in pharmaceutical research. Furthermore, these flavonoids contribute significantly to the adaptogenic and immunomodulatory properties traditionally associated with Tulsi.

Other Bioactive Constituents

In addition to the major phytochemicals described above, *Ocimum sanctum* contains numerous biologically active compounds including β-caryophyllene, carvacrol, methyl eugenol, cirsimaritin, cirsilineol, caffeic acid, chlorogenic acid, luteolin, rutin, tannins, saponins, alkaloids, and various volatile terpenoids. Although present in relatively smaller quantities, these constituents contribute synergistically to the broad pharmacological profile of Tulsi and enhance the therapeutic efficacy of the whole plant extract.

The combined action of these phytochemicals provides multiple pharmacological benefits, including antimicrobial, antifungal, antiviral, antioxidant, anti-inflammatory, hepatoprotective, cardioprotective, nephroprotective, neuroprotective, immunomodulatory, and anticancer effects. Consequently, preservation of the complete phytochemical profile is considered essential during the development of pharmaceutical formulations, particularly nano-based drug delivery systems designed to maximize therapeutic outcomes.

Table 1. Major Bioactive Constituents of *Ocimum sanctum* and Their Pharmacological Activities

Bioactive Constituent	Chemical Class	Major Pharmacological Activities	Potential Nanoformulation
Eugenol	Phenylpropanoid	Antioxidant, Anti-inflammatory, Antimicrobial, Anticancer	Liposomes, Nanoemulsion, SLN
Ursolic Acid	Pentacyclic Triterpenoid	Anticancer, Hepatoprotective, Anti-inflammatory	Polymeric NP, NLC, Phytosomes
Rosmarinic Acid	Phenolic Acid	Antioxidant, Neuroprotective, Antiviral	Liposomes, Polymeric NP
Linalool	Monoterpene Alcohol	Antimicrobial, Analgesic, Sedative	Nanoemulsion, Lipid NP
Apigenin	Flavonoid	Anticancer, Anti-inflammatory, Antioxidant	Phytosomes, Polymeric NP
Orientin	Flavonoid Glycoside	Radioprotective, Antioxidant, Cardioprotective	Liposomes
Vicenin	Flavonoid Glycoside	Neuroprotective, Antioxidant	Polymeric NP
β-Caryophyllene	Sesquiterpene	Anti-inflammatory, Analgesic	Nanoemulsion

Carvacrol	Monoterpenoid Phenol	Antimicrobial, Antifungal	Nanoemulsion
Methyl Eugenol	Phenylpropanoid	Antimicrobial, Insecticidal	Liposomes

5. LIMITATIONS OF CONVENTIONAL DELIVERY OF *Ocimum sanctum* BIOACTIVES

Although *Ocimum sanctum* possesses remarkable pharmacological potential, its successful clinical application remains limited because of several pharmaceutical challenges associated with its bioactive constituents. Most phytochemicals present in Tulsi exhibit poor physicochemical and pharmacokinetic properties, resulting in inadequate therapeutic efficacy following conventional administration. These limitations have encouraged researchers to develop novel drug delivery systems capable of improving the stability, bioavailability, and tissue distribution of Tulsi bioactives **[36]**.

5.1 Poor Aqueous Solubility

Many pharmacologically active constituents of *Ocimum sanctum*, including ursolic acid, eugenol, β-caryophyllene, and several terpenoids, exhibit poor aqueous solubility because of their hydrophobic chemical structures. Poor solubility restricts dissolution in gastrointestinal fluids following oral administration, thereby limiting drug absorption and reducing systemic bioavailability.

Incomplete dissolution also leads to significant variability in therapeutic response among patients. Consequently, relatively high doses are often required to achieve therapeutic plasma concentrations, increasing the possibility of adverse effects and poor patient compliance. Enhancement of aqueous solubility therefore remains one of the primary objectives during formulation development of Tulsi bioactives **[37]**.

5.2 Poor Oral Bioavailability

Oral administration is the most preferred route for herbal medicines because of its convenience and patient acceptability. However, most Tulsi phytochemicals exhibit poor oral bioavailability due to inadequate gastrointestinal absorption, limited membrane permeability, and extensive first-pass metabolism.

Lipophilic compounds such as ursolic acid and eugenol demonstrate limited intestinal absorption, whereas several flavonoids undergo rapid metabolic transformation within the liver before reaching systemic circulation. Consequently, only a small fraction of the administered dose becomes pharmacologically available at the target site, significantly reducing therapeutic efficacy **[38]**

5.3 Rapid Metabolism and Elimination

Another major limitation associated with conventional delivery of Tulsi bioactives is their rapid metabolic degradation and systemic elimination. Following absorption, many phytochemicals undergo extensive Phase I and Phase II biotransformation reactions, including oxidation, glucuronidation, sulfation, and methylation.

Rapid metabolism shortens the biological half-life of active constituents, resulting in reduced plasma concentrations and shorter therapeutic duration. Consequently, repeated administration becomes necessary to maintain effective drug levels, which may negatively affect patient adherence to therapy **[39]**.

5.4 Chemical Instability

Several phytochemicals present in *Ocimum sanctum* are chemically unstable and susceptible to degradation under environmental conditions such as heat, moisture, oxygen, ultraviolet radiation, and pH variation. Oxidative degradation of essential oil components may significantly reduce their biological activity during storage.

Furthermore, degradation products formed during processing and storage may alter the safety and efficacy of herbal formulations. Therefore, development of stable pharmaceutical dosage forms capable of protecting these bioactive compounds has become an important area of pharmaceutical research **[40]**

5.5 Poor Tissue Targeting

Conventional herbal formulations generally distribute phytochemicals non-selectively throughout the body following systemic administration. Such non-specific distribution reduces drug accumulation at diseased tissues while increasing exposure of healthy organs to bioactive compounds.

Poor tissue targeting decreases therapeutic efficacy, particularly in diseases requiring localized drug delivery such as cancer, inflammatory disorders, neurological diseases, and skin infections. Therefore, targeted drug delivery systems capable of selectively delivering Tulsi bioactives to pathological sites are highly desirable for improving therapeutic outcomes **[41]**.

6. NANOTECHNOLOGY-BASED DRUG DELIVERY SYSTEMS

6.1 Introduction to Nanomedicine

Nanotechnology has revolutionized modern pharmaceutical sciences by providing innovative strategies for improving the delivery of therapeutic agents. Nanomedicine involves the application of nanoscale materials, generally ranging from **10 to 1000 nm**, for diagnosis, treatment, and prevention of various diseases. Nano-sized carriers possess unique physicochemical properties, including high surface area, enhanced permeability, controlled drug release, and improved interaction with biological membranes.

For herbal medicines, nanotechnology offers an effective approach to overcome limitations such as poor solubility, instability, rapid metabolism, and inadequate tissue targeting. Encapsulation of phytochemicals within nanocarriers protects them from degradation while enhancing absorption and therapeutic efficacy **[42]**

6.2 Advantages of Nanoformulations

Nanoformulations provide numerous pharmaceutical advantages over conventional dosage forms. Encapsulation of Tulsi bioactives within nanocarriers significantly enhances aqueous solubility and dissolution rate, thereby improving oral bioavailability. Nanocarriers also protect phytochemicals from enzymatic degradation and premature metabolism, resulting in prolonged systemic circulation.

Controlled and sustained drug release minimizes fluctuations in plasma drug concentration, reduces dosing frequency, and improves patient compliance. Furthermore, the small particle size facilitates enhanced cellular uptake through endocytosis, increasing intracellular drug accumulation and therapeutic efficacy.

Targeted delivery using ligand-modified nanoparticles enables selective drug accumulation at diseased tissues, reducing systemic toxicity and improving treatment outcomes. These advantages have established nanotechnology as one of the most promising approaches for herbal drug delivery.

6.3 Mechanisms of Enhanced Drug Delivery

Nanoformulations enhance therapeutic delivery through several complementary mechanisms. First, reduction of particle size increases the surface area available for dissolution, leading to improved drug solubility and faster absorption.

Second, encapsulation within lipid or polymeric matrices protects sensitive phytochemicals from degradation caused by enzymes, gastric acid, oxidation, and environmental factors.

Third, nanoparticles improve permeation across biological barriers such as intestinal epithelium, skin, and blood-brain barrier, thereby increasing drug availability at target tissues.

Finally, controlled-release characteristics of nanocarriers maintain therapeutic drug concentrations for prolonged periods, reducing dosing frequency and improving overall therapeutic effectiveness.

Collectively, these mechanisms contribute significantly to enhanced pharmacokinetic performance and superior clinical potential of nanoformulated Tulsi bioactives.

7. NANOFORMULATIONS OF *Ocimum sanctum* BIOACTIVES

Nanotechnology-based delivery systems have emerged as highly effective approaches for improving the pharmaceutical performance of Tulsi bioactives. Nanoformulations enhance aqueous solubility, protect phytochemicals from degradation, improve membrane permeability, prolong systemic circulation, and facilitate controlled as well as targeted drug delivery. Consequently, nano-enabled delivery systems have attracted considerable attention for maximizing the therapeutic potential of *Ocimum sanctum* phytoconstituents **[43]**.

7.1 Liposomes

Liposomes are spherical vesicular systems composed of one or more phospholipid bilayers surrounding an aqueous core. These carriers are capable of encapsulating both hydrophilic and lipophilic phytochemicals, thereby improving drug stability and bioavailability.

Liposomes containing eugenol, rosmarinic acid, and Tulsi essential oil have demonstrated enhanced antioxidant, antimicrobial, and anti-inflammatory activity compared with conventional formulations. The phospholipid membrane facilitates improved interaction with biological membranes and promotes cellular uptake, resulting in enhanced therapeutic efficacy.

Furthermore, liposomal formulations provide sustained drug release and reduced systemic toxicity, making them attractive candidates for oral, topical, and parenteral delivery of Tulsi bioactives.

7.2 Phytosomes

Phytosomes are advanced lipid-based delivery systems formed through complexation of phytochemicals with phospholipids. Unlike conventional liposomes, phytosomes establish molecular interactions between phytoconstituents and phospholipid molecules, resulting in improved stability and absorption.

Several poorly soluble Tulsi bioactives, particularly ursolic acid and flavonoids, have shown enhanced gastrointestinal absorption following phytosomal formulation. Increased membrane permeability and improved pharmacokinetic behavior contribute to superior therapeutic outcomes. Phytosomes are especially useful for oral delivery of hydrophobic phytochemicals exhibiting poor bioavailability **[44]**.

7.3 Nanoemulsions

Nanoemulsions are thermodynamically stable colloidal systems consisting of oil droplets dispersed within an aqueous phase or vice versa, typically possessing droplet sizes below 200 nm. Because Tulsi essential oil contains several lipophilic constituents, nanoemulsions have become one of the most promising delivery systems for its administration.

Nanoemulsion formulations significantly improve dissolution, absorption, dermal penetration, and antimicrobial efficacy of essential oil components such as eugenol, linalool, and β-caryophyllene. Their small droplet size facilitates greater surface area, improved stability, and enhanced biological activity.

Additionally, nanoemulsions are particularly useful in topical formulations developed for wound healing, acne management, fungal infections, and inflammatory skin disorders.

7.4 Polymeric Nanoparticles

Polymeric nanoparticles are prepared using biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA), chitosan, alginate, and polycaprolactone. These carriers provide controlled drug release, improved stability, and enhanced targeting capabilities.

Tulsi phytochemicals encapsulated within polymeric nanoparticles have demonstrated prolonged circulation time, enhanced cellular uptake, and superior therapeutic efficacy compared with free compounds. Chitosan-based nanoparticles are especially attractive because of their mucoadhesive properties and ability to improve intestinal absorption of poorly permeable phytochemicals.

Polymeric nanoparticles have shown significant potential for delivery of ursolic acid and flavonoids intended for anticancer, anti-inflammatory, and neuroprotective applications **[45]**.

7.5 Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles are submicron colloidal carriers prepared using physiologically compatible solid lipids. These systems provide improved drug stability, controlled release, and enhanced protection of sensitive phytochemicals against degradation.

SLNs have been extensively investigated for the delivery of lipophilic Tulsi constituents such as eugenol and ursolic acid. Encapsulation within a solid lipid matrix improves bioavailability while reducing degradation caused by environmental and biological factors.

The excellent biocompatibility and scalability of SLNs make them promising candidates for commercial development of herbal nanomedicines.

7.6 Nanostructured Lipid Carriers (NLCs)

Nanostructured lipid carriers represent the second generation of lipid nanoparticles and consist of mixtures of solid and liquid lipids. Compared with SLNs, NLCs exhibit greater drug-loading capacity and reduced drug expulsion during storage.

NLC-based formulations have demonstrated enhanced encapsulation efficiency and prolonged release of Tulsi bioactives. The imperfect lipid matrix created within NLCs provides additional space for drug accommodation, thereby improving formulation stability and therapeutic performance **[46]**.

7.7 Nanogels

Nanogels are three-dimensional nanoscale hydrogel systems capable of absorbing large amounts of water while maintaining structural integrity. Their high biocompatibility and controlled release characteristics make them attractive carriers for topical and transdermal delivery.

Tulsi-loaded nanogels have demonstrated significant potential in wound healing, burn management, skin infections, and inflammatory dermatological conditions. The sustained release of phytochemicals from nanogels enhances therapeutic effectiveness while reducing dosing frequency.

Furthermore, nanogels improve skin penetration of Tulsi bioactives and maintain prolonged residence time at the site of application.

7.8 Metallic Nanoparticles

Metallic nanoparticles synthesized using plant extracts have attracted considerable interest because of their unique physicochemical and biological properties. Silver, gold, zinc oxide, and copper nanoparticles synthesized using Tulsi extracts exhibit potent antimicrobial, antifungal, antioxidant, and anticancer activities.

These nanoparticles benefit from the combined therapeutic effects of metallic nanostructures and plant-derived phytochemicals. Enhanced cellular interaction, increased reactive oxygen species generation within microbial cells, and membrane disruption contribute to their biological activity **[47]**.

7.9 Green-Synthesized Nanoparticles

Green nanotechnology has emerged as an environmentally friendly alternative to conventional nanoparticle synthesis methods. Tulsi extracts contain reducing and stabilizing phytochemicals capable of converting metal ions into nanoparticles without the need for toxic chemicals.

Green-synthesized silver nanoparticles prepared using *Ocimum sanctum* extracts have demonstrated remarkable antimicrobial, antifungal, antiviral, and anticancer activities. Such approaches reduce environmental impact while simultaneously enhancing the therapeutic value of the resulting nanomaterials **[48]**.

8. MECHANISMS OF ENHANCED THERAPEUTIC DELIVERY

Nanoformulations improve the therapeutic delivery of Tulsi bioactives through several complementary mechanisms. Reduction of particle size increases surface area and dissolution rate, leading to enhanced absorption. Encapsulation protects phytochemicals from degradation and premature metabolism, thereby improving systemic availability.

Nanocarriers also facilitate improved permeation across biological barriers, including intestinal epithelium, skin, and blood-brain barrier. Enhanced cellular uptake through endocytosis increases intracellular drug accumulation and therapeutic efficacy. Controlled-release characteristics maintain therapeutic concentrations for prolonged periods, reducing dosing frequency and improving treatment outcomes **[49]**.

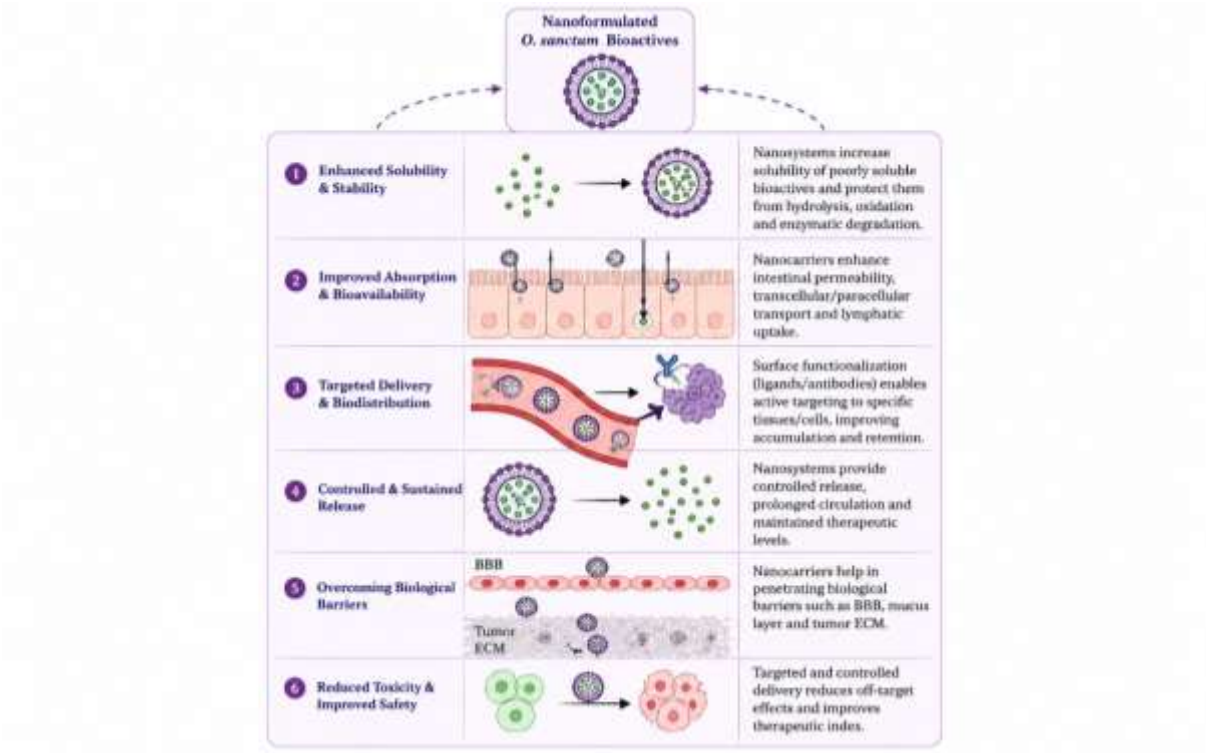

Fig.4 Mechanisms of Enhanced Therapeutic Delivery

9. THERAPEUTIC APPLICATIONS OF NANO-TULSI SYSTEMS

Nanoformulations of Tulsi bioactives have shown considerable potential in the treatment of infectious diseases, inflammatory disorders, cancer, diabetes mellitus, cardiovascular diseases, neurological disorders,

respiratory conditions, and dermatological infections. Improved bioavailability, enhanced targeting, and controlled drug release contribute significantly to their superior therapeutic performance.

Particularly promising applications include anticancer therapy, wound healing, antimicrobial treatment, neuroprotection, and management of chronic inflammatory disorders. Continued advances in formulation technology are expected to expand the clinical utility of nano-Tulsi systems in the coming years **[50]**.

Table 2. Nanoformulations Developed for *Ocimum sanctum* Bioactives

Formulation Type	Bioactive Used	Therapeutic Application	Major Advantages
Liposomes	Eugenol, Rosmarinic Acid	Anti-inflammatory, Antimicrobial	Improved stability and cellular uptake
Phytosomes	Ursolic Acid, Flavonoids	Oral Delivery	Enhanced bioavailability
Nanoemulsions	Tulsi Essential Oil	Antimicrobial, Dermatological Applications	Improved penetration and absorption
Polymeric Nanoparticles	Ursolic Acid	Anticancer Therapy	Controlled release
Solid Lipid Nanoparticles	Eugenol	Anti-inflammatory Therapy	Improved stability
Nanostructured Lipid Carriers	Multiple Bioactives	Sustained Delivery	Higher drug loading
Nanogels	Tulsi Extract	Wound Healing	Prolonged local action
Silver Nanoparticles	Tulsi Phytochemicals	Antimicrobial Therapy	Strong microbial inhibition
Gold Nanoparticles	Tulsi Extract	Anticancer Applications	Enhanced cellular targeting
Green-Synthesized Nanoparticles	Whole Plant Extract	Multifunctional Therapy	Eco-friendly synthesis

10. SAFETY, TOXICITY AND REGULATORY CONSIDERATIONS

10.1 Safety and Toxicity of *Ocimum sanctum* Nanoformulations

Although *Ocimum sanctum* has been consumed safely for centuries as a medicinal herb, incorporation of its bioactive compounds into nanocarriers may alter their pharmacokinetic behavior, biodistribution, and biological interactions. Therefore, comprehensive safety evaluation of nanoformulations is essential before clinical application **[51]**.

Several preclinical studies have demonstrated that lipid-based nanoparticles, polymeric nanoparticles, and phytosomes containing Tulsi bioactives exhibit good biocompatibility and low toxicity when prepared using biodegradable pharmaceutical excipients. However, toxicity may vary depending on particle size, surface charge, composition, dose, route of administration, and duration of exposure. Extremely small nanoparticles may cross biological barriers and accumulate in organs such as the liver, spleen, kidneys, lungs, and brain, necessitating careful toxicological evaluation.

Green-synthesized metallic nanoparticles prepared using Tulsi extracts have demonstrated promising antimicrobial and anticancer properties. Nevertheless, metallic nanoparticles require detailed investigation regarding long-term toxicity, biodistribution, biodegradation, and elimination. Future studies should include acute toxicity, repeated-dose toxicity, genotoxicity, reproductive toxicity, immunotoxicity, and pharmacokinetic investigations to establish their safety profile.

10.2 Regulatory Challenges

Despite significant advances in herbal nanomedicine, regulatory approval remains one of the major challenges limiting commercialization of nanoformulated herbal products. Variability in phytochemical composition, lack of standardized extraction methods, inadequate characterization of nanocarriers, and insufficient clinical evidence contribute to regulatory uncertainty.

Regulatory agencies require comprehensive documentation regarding botanical authentication, phytochemical standardization, manufacturing processes, quality control, stability, pharmacokinetics, toxicology, and clinical efficacy before approval of herbal nanomedicines. Adoption of Good Manufacturing Practices (GMP), Quality by Design (QbD), and robust analytical methods is essential to ensure product consistency and reproducibility **[52]**

10.3 Quality Control Requirements

Quality control plays a crucial role in ensuring the safety, efficacy, and reproducibility of nanoformulations containing Tulsi bioactives. Standardization should include authentication of plant material, determination of marker compounds, evaluation of particle size distribution, zeta potential, encapsulation efficiency, drug loading, in vitro release profile, stability testing, and microbiological quality.

Advanced analytical techniques such as high-performance liquid chromatography (HPLC), liquid chromatography–mass spectrometry (LC-MS), gas chromatography–mass spectrometry (GC-MS), Fourier-transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), scanning electron microscopy (SEM), and transmission electron microscopy (TEM) should be employed for comprehensive characterization of both phytochemicals and nanocarriers.

11. CURRENT RESEARCH GAPS AND FUTURE PERSPECTIVES

Although substantial progress has been made in the development of nanoformulations of *Ocimum sanctum* bioactives, several scientific and technological challenges remain to be addressed before successful clinical translation.

One of the major research gaps is the limited availability of well-designed clinical trials evaluating the efficacy and safety of Tulsi nanoformulations in humans. Most published studies remain confined to in vitro experiments or animal models, highlighting the need for multicenter randomized clinical investigations.

Another important challenge is the lack of standardized formulations. Variability in extraction procedures, phytochemical composition, nanoparticle preparation methods, and characterization protocols makes comparison among different studies difficult. Development of standardized manufacturing protocols will facilitate reproducibility and regulatory approval.

Artificial intelligence (AI), machine learning (ML), and computational modeling represent emerging technologies with considerable potential for herbal nanomedicine. AI-assisted formulation design may accelerate optimization of formulation variables, predict physicochemical properties, improve quality control, and reduce formulation development time **[53]**.

Personalized herbal nanomedicine is another promising area of future research. Integration of nanotechnology with pharmacogenomics and precision medicine may enable development of individualized therapeutic strategies tailored to patient-specific genetic and metabolic characteristics.

Future investigations should also focus on multifunctional nanocarriers capable of simultaneous drug delivery, diagnostic imaging, and targeted therapy. Such advanced systems may significantly improve treatment outcomes for cancer, neurological disorders, infectious diseases, and chronic inflammatory conditions.

12. CONCLUSION

Ocimum sanctum (Tulsi) remains one of the most valuable medicinal plants owing to its diverse phytochemical composition and broad spectrum of pharmacological activities. Bioactive compounds such as eugenol, ursolic acid, rosmarinic acid, apigenin, orientin, vicenin, and linalool exhibit antioxidant, anti-inflammatory, antimicrobial, antiviral, antidiabetic, neuroprotective, immunomodulatory, and anticancer properties through multiple molecular mechanisms **[54]**.

Despite these promising therapeutic effects, conventional formulations of Tulsi bioactives are limited by poor aqueous solubility, low bioavailability, rapid metabolism, and inadequate tissue targeting. Pharmaceutical nanotechnology offers effective strategies to overcome these limitations through the development of liposomes, phytosomes, nanoemulsions, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, nanogels, and green-synthesized metallic nanoparticles.

Nanoformulations improve drug stability, enhance cellular uptake, prolong systemic circulation, enable controlled drug release, and increase therapeutic efficacy while reducing systemic toxicity. These advantages position nano-enabled Tulsi formulations as promising candidates for the management of infectious diseases, inflammatory disorders, cancer, diabetes, neurological disorders, and cardiovascular diseases.

Although encouraging preclinical findings have been reported, successful clinical translation requires standardized formulations, comprehensive toxicological evaluation, robust regulatory frameworks, and well-designed clinical trials. Continued interdisciplinary collaboration among pharmacognosists, pharmaceutical scientists, nanotechnologists, clinicians, and regulatory authorities will be essential to realize the full therapeutic potential of Tulsi-based nanomedicines **[55]**.

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