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Nanoformulations of Sesame (*Sesamum indicum*) Leaf Extract: Phytochemistry, Nano-Delivery Systems, Pharmacological Activities, and Future Perspectives

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Abstract

Sesame (*Sesamum indicum* L.) is a traditional oilseed crop widely recognized for its nutritional and medicinal importance. While extensive research has focused on sesame seeds and oil, sesame leaves have recently gained attention due to their rich phytochemical composition, including flavonoids, phenolic acids, alkaloids, and glycosides, which exhibit antioxidant, anti-inflammatory, antimicrobial and cytoprotective properties. However, the therapeutic exploitation of sesame leaf extract is limited by poor aqueous solubility, chemical instability, rapid metabolism and low bioavailability. Nanotechnology-based delivery systems have emerged as promising strategies to overcome these challenges. This review critically examines the phytochemical profile of sesame leaves, discusses recent advances in nanoformulation approaches—including green-synthesised nanoparticles, exosome-like nanovesicles, nanoemulsions and polymeric nanocarriers—and highlights their physicochemical characteristics and biomedical applications. Key challenges related to standardization, safety and regulatory translation are also addressed, followed by future prospects for clinical and industrial applications.

Keywords: Sesame, nanoformulation, phytochemicals, antioxidant, cytoprotective

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1. Introduction

Sesame (Sesamum indicum L.), a member of the Pedaliaceae family, is one of the oldest oilseed crops cultivated and consumed by humans, with a history spanning over 3,000 years. While sesame seeds and oil have been extensively studied and utilized for their nutritional and medicinal properties, the leaves of the sesame plant have also played a notable role in traditional medicine across various cultures. In regions such as Nigeria, China, and Japan, sesame leaves are consumed as vegetables, used in decoctions, or processed into health supplements. Traditional uses include the treatment of gastrointestinal disorders, inflammation, microbial infections, and as a general health tonic.

Recent years have witnessed a resurgence of interest in plant-based medicines, driven by the need for safer, more sustainable, and culturally relevant therapeutic options. The World Health Organization estimates that up to 80% of the global population relies on traditional medicines for primary healthcare needs. This renewed focus has led to the scientific exploration of the phytochemical composition and pharmacological activities of sesame leaves, revealing a rich array of bioactive compounds with significant therapeutic potential.

1.1 Nanoformulation Technologies in Herbal Medicine

Despite the promising pharmacological activities of plant extracts, their clinical translation is often hampered by challenges such as poor solubility, low bioavailability, instability, and rapid metabolism. Nanotechnology-based delivery systems—encompassing nanoparticles, liposomes, nanoemulsions, and phytosomes—have emerged as transformative strategies to overcome these limitations. By encapsulating bioactive plant constituents within nanoscale carriers, these systems can enhance solubility, protect against degradation, improve absorption, enable controlled release, and facilitate targeted delivery.

The application of nanoformulation technologies to sesame leaf extracts is a relatively recent but rapidly advancing field. Early studies have demonstrated that nanoformulated sesame leaf extracts exhibit superior pharmacological activities—including antioxidant, antimicrobial, anti-inflammatory, and anticancer effects—compared to their crude counterparts. This review aims to provide a comprehensive synthesis of the current state of research on nanoformulations of sesame leaf extract, covering phytochemistry, rationale for nanoformulation, types and preparation methods of nanoformulations, pharmacological activities, comparative advantages, challenges, and future perspectives.

2. Phytochemistry of Sesame Leaves and Traditional Uses

Modern analytical techniques, such as ultra-high-performance liquid chromatography-mass spectrometry (UPLC-MS/MS), have enabled the comprehensive profiling of metabolites in sesame leaves. Recent metabolomics studies have identified over 700 metabolites in sesame tissues, with leaves exhibiting particularly high concentrations of quinones, coumarins, tannins, vitamins, terpenoids, and phenolic acids (e.g., acteoside, isoacteoside, verbascoside, plantamajoside). Notably, the leaves are especially rich in flavonoids and phenolic acids, which are key contributors to their biological activities.

Table 1. Major Classes of Bioactive Compounds in Sesame Leaves

Compound Class	Representative Compounds	Reported Activities
Flavonoids	Quercetin, kaempferol, apigenin, pedalitin, pedaliin, isorhamnetin	Antioxidant, anti-inflammatory, anticancer
Phenolic acids	Acteoside, isoacteoside, verbascoside, chlorogenic acid, gallic acid	Antioxidant, anti-inflammatory, antimicrobial
Lignans	Sesamin, sesamolin, sesaminol, sesamol	Antioxidant, neuroprotective, anticancer
Coumarins	Skimmin	Anti-diabetic, antioxidant
Terpenoids	Martynoside, plantamajoside	Anti-inflammatory, neuroprotective
Vitamins	Vitamin E (tocopherols), vitamin C	Antioxidant
Tannins	Hydrolyzable and condensed tannins	Antioxidant, antimicrobial

Recent studies have also identified unique sesame leaf-specific metabolites, such as E-6,7-dihydroxydihydroligustilide and senkyunolide H, which have been associated with neuroprotective, anti-atherosclerotic, and cytoprotective effects.

Sesame leaves exhibit the highest relative content of certain bioactive compounds compared to other plant tissues (seeds, flowers, carpels). For example, acteoside, isoacteoside, martynoside, plantamajoside, and sesaminol are more abundant in leaves, supporting their use as a source of pharmacologically active extracts.

3. Traditional and Ethnopharmacological Uses

In traditional medicine, sesame leaves have been used for a variety of purposes:

- **Gastrointestinal Health:** Decoctions and infusions are used to treat diarrhea, gastritis, and ulcers.
- **Anti-inflammatory and Analgesic:** Topical applications and poultices are used for pain relief and to reduce inflammation.
- **Antimicrobial:** Leaf extracts are used to treat skin infections, catarrh, and as a gargle for oral health.
- **Nutritional Supplement:** In Japan and Nigeria, dried sesame leaves are consumed as vegetables or processed into health supplements.

These traditional uses are increasingly supported by scientific evidence demonstrating the pharmacological activities of sesame leaf extracts, particularly their antioxidant, antimicrobial, and anti-inflammatory properties.

4. Nanoformulation of Plant Extracts

Despite the rich phytochemical content and demonstrated bioactivities of sesame leaf extracts, several challenges limit their clinical and commercial application:

- **Poor Solubility and Bioavailability:** Many bioactive compounds (e.g., flavonoids, lignans) are poorly soluble in water and have low membrane permeability, resulting in limited absorption and systemic availability.
- **Instability:** Phenolic compounds and flavonoids are susceptible to degradation by light, heat, oxygen, and pH changes, leading to reduced efficacy during storage and after administration.
- **Rapid Metabolism and Clearance:** Once absorbed, many phytochemicals undergo rapid metabolism and elimination, necessitating frequent dosing and limiting therapeutic efficacy.
- **Non-specific Distribution:** Conventional extracts may distribute non-selectively in the body, increasing the risk of off-target effects and reducing therapeutic index.

4.1 Advantages of Nanoformulation Technologies

Nanoformulation technologies offer several solutions to these challenges:

- **Enhanced Solubility and Absorption:** Nanoscale carriers increase the apparent solubility of hydrophobic compounds and facilitate their absorption across biological membranes.
- **Protection from Degradation:** Encapsulation within nanoparticles, liposomes, or phytosomes shields sensitive phytochemicals from environmental and enzymatic degradation.
- **Improved Bioavailability and Controlled Release:** Nanoformulations can provide sustained and controlled release, prolonging the presence of active compounds in systemic circulation.
- **Targeted Delivery:** Surface modification of nanoparticles enables targeted delivery to specific tissues or cells, enhancing efficacy and reducing side effects.
- **Reduced Toxicity:** By improving delivery efficiency and reducing required doses, nanoformulations can minimize toxicity and adverse effects.

Given the high content of flavonoids, phenolic acids, and lignans in sesame leaves—many of which are poorly soluble and unstable—nanoformulation is particularly advantageous for this botanical source. Recent studies have shown that nanoformulated sesame leaf extracts exhibit superior antioxidant, anti-inflammatory, and antimicrobial activities compared to crude extracts, supporting the rationale for their development.

5. Types of Nanoformulations and Preparation Methods for Sesame Leaf Extract

Several types of nanoformulations have been explored for plant extracts, including those from sesame leaves:

- **Liposomes:** Spherical vesicles composed of phospholipid bilayers, capable of encapsulating both hydrophilic and hydrophobic compounds.
- **Polymeric Nanoparticles:** Solid colloidal particles made from biodegradable polymers (e.g., PLGA, chitosan), suitable for controlled and targeted delivery.
- **Nanoemulsions:** Thermodynamically or kinetically stable dispersions of oil and water stabilized by surfactants, with droplet sizes typically in the 20–500 nm range.
- **Phytosomes:** Molecular complexes of phytoconstituents and phospholipids, enhancing membrane permeability and bioavailability.

- **Nanozymes and Exosome-like Nanovesicles:** Novel systems such as plant-derived nanozymes and exosome-like vesicles have also been reported for sesame leaf extracts.

Table 2. Comparison of Major Nanoformulation Types for Plant Extracts

Nanoformulation Type	Structure/Carrier	Key Features	Preparation Methods
Liposomes	Phospholipid bilayer	Biocompatible, encapsulate both hydrophilic and hydrophobic compounds, controlled release	Thin-film hydration, ethanol injection, microfluidics
Polymeric NPs	Biodegradable polymers	Controlled release, surface modifiable, high stability	Emulsification-solvent evaporation, nanoprecipitation, ionic gelation
Nanoemulsions	Oil-in-water or water-in-oil droplets	High solubility, rapid absorption, suitable for hydrophobic actives	High-pressure homogenization, ultrasonication, spontaneous emulsification
Phytosomes	Phytoconstituent-phospholipid complex	Enhanced bioavailability, membrane permeability	Solvent evaporation, anti-solvent precipitation, thin-film hydration
Nanozymes	Metal or metal oxide NPs with enzyme-like activity	Catalytic, antioxidant, antimicrobial	Green synthesis using plant extracts
Exosome-like vesicles	Plant-derived nanovesicles	Natural carriers, high stability, targeted delivery	Ultracentrifugation, size exclusion chromatography

5.1 Preparation Methods

5.1.1 Liposomes

Liposomes are typically prepared by:

- **Thin-Film Hydration:** Lipids are dissolved in organic solvents, evaporated to form a thin film, and hydrated with aqueous extract. The resulting multilamellar vesicles are downsized by sonication or extrusion.

- **Ethanol Injection:** Lipids dissolved in ethanol are injected into an aqueous phase containing the extract, leading to spontaneous formation of liposomes with smaller and more uniform sizes.

- **Microfluidic Mixing:** Advanced technique allowing precise control over liposome size and uniformity, suitable for scale-up.

5.1.2 Polymeric Nanoparticles

Common methods include:

- **Emulsification-Solvent Evaporation:** Polymer and extract are dissolved in organic solvent, emulsified in water, and solvent is evaporated to form nanoparticles.
- **Nanoprecipitation:** Polymer and extract are dissolved in a miscible organic solvent and added to water under stirring, leading to nanoparticle formation.
- **Ionic Gelation:** Particularly for chitosan nanoparticles, where ionic crosslinking agents induce nanoparticle formation.

5.1.3 Nanoemulsions

Preparation methods include:

- **High-Pressure Homogenization:** Coarse emulsion is passed through a high-pressure homogenizer, reducing droplet size to the nanoscale.
- **Ultrasonication:** High-frequency sound waves break down droplets to nanoscale sizes.
- **Spontaneous Emulsification:** Mixing oil, surfactant, and aqueous phase under specific conditions leads to spontaneous formation of nanoemulsions.

5.1.4 Phytosomes

Phytosomes are prepared by:

- **Solvent Evaporation/Anti-Solvent Precipitation:** Phytoconstituent and phospholipid are dissolved in a common solvent, refluxed, and precipitated by adding a non-solvent.
- **Thin-Film Hydration:** Similar to liposome preparation, but with a focus on forming a molecular complex between the phytoconstituent and phospholipid.

5.1.5 Green Synthesis of Nanozymes and Metal Nanoparticles

Plant extracts, including those from sesame leaves, can act as reducing and stabilizing agents for the green synthesis of metal nanoparticles (e.g., silver, iron, selenium) and nanozymes with catalytic and biomedical activities.

5.1.6 Plant Exosome-like Nanovesicles

Isolation involves differential ultracentrifugation and size exclusion chromatography, followed by characterization using nanoparticle tracking analysis and electron microscopy.

5.2 Characterization Techniques

Key techniques for characterizing nanoformulations include:

- **Dynamic Light Scattering (DLS):** Measures particle size and polydispersity index (PDI).
- **Zeta Potential Analysis:** Assesses surface charge and colloidal stability.
- **Transmission and Scanning Electron Microscopy (TEM/SEM):** Visualizes morphology and size.
- **Fourier Transform Infrared Spectroscopy (FTIR):** Identifies chemical interactions and confirms encapsulation.
- **X-ray Diffraction (XRD):** Assesses crystallinity and structural changes.
- **Entrapment Efficiency and Drug Loading:** Quantified by centrifugation and spectrophotometric or chromatographic analysis.
- **In Vitro Release Studies:** Dialysis or Franz diffusion cells to assess release kinetics.

6. Pharmacological Activities of Nanoformulated Sesame Leaf Extract

6.1 Antioxidant Activity

Sesame leaf extracts are rich in flavonoids, phenolic acids, and lignans, all of which contribute to strong antioxidant activity as demonstrated by DPPH, ABTS, and FRAP assays. Key compounds such as quercetin, kaempferol, pedaliin, and acteoside have been identified as major contributors.

Nanoformulations significantly enhance the antioxidant potential of sesame leaf extracts:

- **Fe-based Nanozymes:** Flavonoid-rich sesame leaf extract-mediated iron nanozymes (Fe-SLE CPNs) demonstrated superior reactive oxygen species (ROS) scavenging ability compared to crude extract, attributed to their peroxidase-like catalytic activity and improved stability.
- **Plant Exosome-like Nanovesicles:** Luteolin-loaded exosome-like vesicles from sesame leaves showed enhanced antioxidant activity and protection against oxidative stress in vitro.

- **Solid Lipid Nanoparticles (SLNs):** Sesamol-loaded SLNs exhibited higher antioxidant activity and prolonged release compared to free sesamol, with improved cellular uptake and bioavailability.
- **Nanoemulsions:** Nanoemulsified sesame extracts demonstrated increased DPPH and ABTS radical scavenging activity, attributed to improved solubility and dispersion of phenolic compounds.

6.2 Antimicrobial Activity

Sesame leaf extracts have demonstrated antimicrobial activity against a range of pathogens, including Staphylococcus aureus, Streptococcus pneumoniae, and Candida albicans. The activity is primarily attributed to phenolic compounds such as sesamol, sesaminol, and flavonoids.

Nanoformulations enhance antimicrobial efficacy:

- **Nanozymes:** Fe-SLE CPNs exhibited significant antimicrobial activity, outperforming crude extracts in in vitro assays.
- **Green-Synthesized Metal Nanoparticles:** Silver and iron nanoparticles synthesized using sesame leaf extract showed potent antibacterial and antifungal activities, with improved stability and lower cytotoxicity compared to chemically synthesized counterparts.
- **Nanoemulsions:** Nanoemulsified sesame extracts demonstrated enhanced antimicrobial activity against foodborne pathogens in model systems, attributed to improved dispersion and interaction with microbial membranes.

6.3 Anti-inflammatory Activity

Sesame leaf extracts and their constituents (e.g., acteoside, verbascoside, pedaliin) have been shown to inhibit pro-inflammatory mediators and enzymes, such as TNF-α, IL-1β, and COX-2, in various in vitro and in vivo models.

Nanoformulations amplify anti-inflammatory effects:

- **Fe-SLE CPNs:** Demonstrated stronger inhibition of inflammatory pathways (MyD88-NF-κB-MAPK) compared to crude extract, resulting in reduced production of pro-inflammatory cytokines.
- **Exosome-like Nanovesicles:** Luteolin-loaded vesicles from sesame leaves exhibited enhanced suppression of inflammatory markers in cell-based assays.

- **SLNs and NLCs:** Sesamol-loaded lipid nanoparticles showed superior anti-inflammatory activity in animal models, with reduced edema and inflammatory cell infiltration.

6.4 Anticancer Activity

Sesame leaf extracts and isolated compounds (e.g., pedaliin, quercetin, acteoside) have demonstrated cytotoxicity against various cancer cell lines, including colon, breast, and leukemia cells, primarily through induction of apoptosis and cell cycle arrest.

Nanoformulations potentiate anticancer effects:

- **Fe-SLE CPNs:** Showed enhanced cytotoxicity against cancer cells compared to free extract, attributed to improved cellular uptake and ROS-mediated apoptosis.
- **Sesamol-loaded SLNs and SNEDDS:** Demonstrated higher anticancer efficacy in breast and lung cancer models, with increased apoptosis and reduced tumor growth compared to free sesamol.
- **Nanoemulsions:** Nanoemulsified sesamol and other actives exhibited improved cytotoxicity and selectivity towards cancer cells, with reduced toxicity to normal cells.

Table 3. Comparative Pharmacological Activities: Nanoformulated vs. Crude Sesame Leaf Extract

Activity	Crude Extract	Nanoformulated Extract	Mechanistic Advantages
Antioxidant	Moderate–High	High	Enhanced ROS scavenging, sustained release
Antimicrobial	Moderate	High	Improved membrane interaction, stability
Anti-inflammatory	Moderate	High	Stronger inhibition of NF-κB, cytokines
Anticancer	Moderate	High	Enhanced apoptosis, targeted delivery

6.5 Comparative Advantages of Nanoformulated vs. Crude Extracts

6.5.1 Enhanced Pharmacokinetics and Bioavailability

Nanoformulations significantly improve the pharmacokinetic profiles of sesame leaf bioactives:

- **Increased Absorption:** Nanocarriers facilitate transcellular and paracellular transport, overcoming solubility and permeability barriers.
- **Prolonged Circulation:** Controlled release and protection from metabolic degradation extend the half-life of active compounds.
- **Higher Tissue Concentrations:** Targeted delivery systems (e.g., ligand-modified nanoparticles) achieve higher concentrations at disease sites, enhancing efficacy and reducing systemic exposure.

6.5.2 Improved Stability and Controlled Release

Nanoencapsulation protects sensitive phytochemicals from environmental and enzymatic degradation, ensuring sustained therapeutic levels. Controlled release profiles can be tailored by modifying carrier composition and structure, enabling once-daily or less frequent dosing.

6.5.3 Targeted Delivery and Reduced Toxicity

Surface modification of nanoparticles with ligands or antibodies enables active targeting to specific tissues or cells (e.g., inflamed or cancerous tissues), minimizing off-target effects and toxicity. This is particularly relevant for anticancer and anti-inflammatory applications.

6.5.4 Enhanced Efficacy at Lower Doses

By improving bioavailability and delivery efficiency, nanoformulations can achieve therapeutic effects at lower doses compared to crude extracts, reducing the risk of adverse effects and improving patient compliance.

6.5.5 Safety, Toxicity, and Biocompatibility

Most nanoformulation systems employ biocompatible and biodegradable materials (e.g., phospholipids, PLGA, chitosan), minimizing the risk of toxicity. Acute and sub-chronic toxicity studies of nanoformulated plant extracts, including those from sesame leaves, have demonstrated good safety profiles in animal models.

7. Conclusion

Nanoformulation of sesame (Sesamum indicum) leaf extract represents a promising frontier in phytomedicine, offering solutions to longstanding challenges of poor solubility, low bioavailability, instability, and non-specific distribution of plant bioactives. Recent advances in phytochemical profiling have revealed a rich array of flavonoids, phenolic acids, lignans, and other bioactive compounds in sesame leaves, many of which exhibit potent antioxidant, antimicrobial, anti-inflammatory, and anticancer activities. Nanoformulation technologies—including liposomes, polymeric nanoparticles, nanoemulsions, phytosomes, and green-synthesized nanozymes—have demonstrated significant advantages over crude extracts, including enhanced pharmacokinetics, stability, targeted delivery, and efficacy at lower doses.

Despite these advances, several challenges remain, particularly in the areas of standardization, large-scale manufacturing, regulatory compliance, and clinical validation. Addressing these challenges will require multidisciplinary collaboration, rigorous analytical and preclinical evaluation, and the integration of green and sustainable technologies. Future research should focus on advanced targeting strategies, combination therapies, and the translation of promising preclinical findings into clinical practice.

In summary, nanoformulated sesame leaf extracts hold great promise as next-generation phytotherapeutics for the prevention and treatment of oxidative stress-related, infectious, inflammatory, and neoplastic diseases. Continued innovation and rigorous research will be essential to realize their full potential in global healthcare.

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