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HARNESSING ESSENTIAL OILS THROUGH NANOTECHNOLOGY-BASED DRUG DELIVERY SYSTEMS FOR BIOMEDICAL APPLICATIONS: CURRENT TRENDS AND FUTURE PROSPECTS

Laxmi Gharti[1], Neelam Kumari[2], Vishal Sharma[3], Navneet Kumar Upadhyay[4], Hemlata Kaurav[1]*

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ABSTRACT
Background: Essential oils (EOs) have been used in therapeutic applications for centuries and continue to be popular in modern complementary and alternative medicine. EOs are highly concentrated, plant-derived volatile components with a wide range of biological activities, including analgesic, antibacterial, antifungal, antiviral, anti-inflammatory, and antioxidant activities. This study aims to review novel drug delivery systems enriched with essential oils to improve therapeutic outcomes, overcoming the limitations of the phytoconstituents, including high volatility, hydrophobicity, instability, and toxicity. **Methodology:** A literature review was conducted using globally recognized scientific research databases, including Google Scholar, PubMed, and Scopus. Studies were selected for their enhanced therapeutic applications of essential oils through novel drug delivery systems. The search strategy included keywords such as "essential oils", "nanoformulations", "nanoemulsions", "liposomes", and "solid lipid nanoparticles", combined using Boolean operators (AND/OR). Articles published in English between 2021 and 2026 were considered. **Result and Discussion:** Encapsulation of EOs in nanocarriers and lipid-based vesicle systems enhances their bioavailability, improves their stability, and controls their release profile. The progressive nanotechnologies in the drug delivery system have advanced EO's potential therapeutic approach for treating various disorders such as microbial diseases, pain, stomach disorders, depression, cancer, and many more. This review describes the potential of novel drug delivery systems to overcome the existing challenges associated with phytoconstituents. **Conclusion:** Novel drug delivery systems for EOs have the potential to improve the efficacy and safety of EO-based therapeutics. In this review, various novel drug delivery systems that have been reported to enhance the therapeutic potential of EOs by overcoming their limitations are highlighted.

[1]*Department of Pharmaceutics, School of Pharmaceutical Sciences, Shoolini University of Biotechnology and Management Sciences, Solan 173229, Himachal Pradesh, India.*
[2]*Department of Plant Pathology, Yashwant Singh Parmar University of Horticulture and Forestry, Nauni, Solan 173230, Himachal Pradesh, India.*
[3]*Immacule Lifesciences Private Limited, Nalagarh, Solan 174101, Himachal Pradesh, India.*
[4]*Amity Institute of Pharmacy, Amity University Rajasthan, Jaipur 303002, Rajasthan, India.*

For Correspondence: **kaurav.hem.88@gmail.com**

INTRODUCTION

For over 5,000 years, essential oils (EOs), or natural oils, have been integral to various Indian medicinal systems [1]. EOs have long been used worldwide, and their popularity continues to grow as demand for pure natural substances in the pharmaceutical industry increases. They are frequently used in food, beverages, fragrances, pharmaceutical products, and cosmetics [2–4]. Natural oils can be extracted from aromatic herbs through steam distillation or by pressing the bark. Approximately 3,000 essential oils have been extracted, with over 2,000 species, and 300 are available commercially [5]. EOs are complex mixtures of low molecular weight chemical compounds, including alcohols, polyphenols, terpenoids, aliphatic, and carbonyl compounds, with monoterpenes and sesquiterpenes being the most prevalent [6].

Additionally, other compounds like phenylpropanoids, fatty acids, and their esters, as well as nitrogen and sulfur-containing compounds, are also present in EOs [7]. These oils are susceptible to environmental degradation due to external factors like heat, light, oxidation, and hydrolysis, which affect their long-term stability [8]. Although EOs can be administered through various routes, such as oral, topical, and inhalational, they face several challenges and limitations in their delivery. Absorption of EOs via the oral route is limited by their hydrophobicity, poor chemical and biological stability (due to hydrolysis and oxidation), high volatility, and toxicity risks. Hence, this route is used sparingly [9,10]. For the oral administration of EOs, research primarily focuses on encapsulating EOs using novel drug delivery systems (NDDS) techniques. The alternative route preferred after oral administration is topical use; however, direct exposure of EOs to the skin can result in significant systemic absorption, skin irritation, and darkening due to UV sensitivity, which can lead to major adverse effects. Strong oils are also not recommended for direct inhalation, as they may irritate the eyes [11]. Consequently, researchers are focusing on enhancing the stability and delivery of EOs while accounting for their unique characteristics. The development of NDDS for the administration of EOs is an exciting field of study with a wide range of potential applications, including reducing degradation and harmful side effects, increasing bioavailability via multiple delivery pathways, and implementing drug-targeting systems [8]. NDDS such as liposomes, ethosomes, niosomes, microemulsions, nanoemulsions, solid dispersions, self-emulsifying drug delivery systems, enteric-coated systems, nanoparticles, and hydrogels have been extensively researched to improve the delivery of these compounds [12]. Figure 1 depicts various novel drug delivery systems being explored for the effective delivery of essential oils. This review discusses notable advancements in the therapeutic delivery of EOs via novel drug-delivery approaches across various routes of administration.

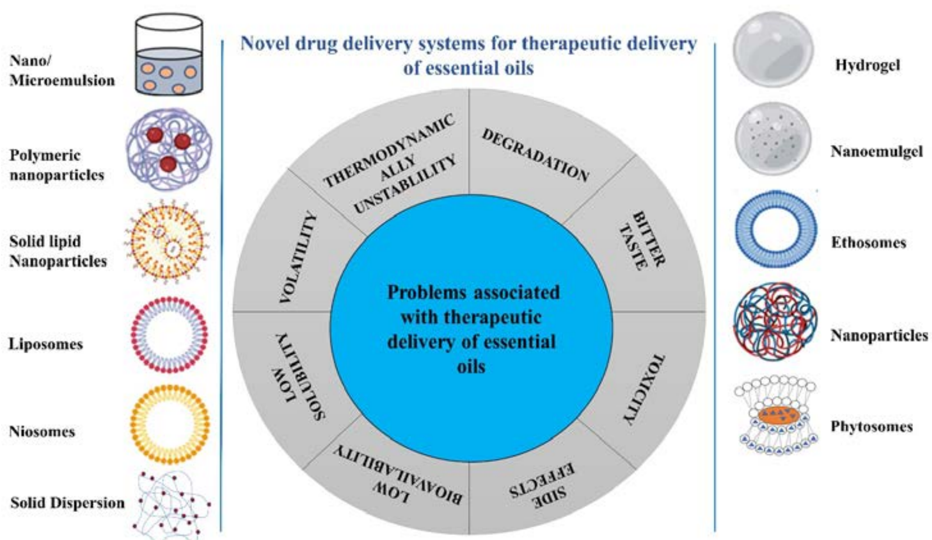

Figure 1: Novel platforms for controlled and efficient delivery of essential oils

MATERIALS AND METHODS

Literature Search Strategy

A systematic literature search was conducted to identify the most relevant publications on the formulation development, characterization, and therapeutic applications of nanoformulations loaded with essential oils. Major scientific databases, including PubMed, Scopus, and Web of Science, were thoroughly searched to ensure comprehensive coverage of peer-reviewed literature. The search strategy employed combinations of keywords and Boolean operators, including: "essential oils" AND "nanoformulation"; "nanoencapsulation" OR "nanocarriers"; "nanoemulsion"; "liposomes"; "solid lipid nanoparticles"; and "polymeric nanoparticles". The search was restricted to English-language articles published between 2021 and 2026, reflecting the most recent advances in nanotechnology-based delivery systems for essential oils.

STUDY SELECTION AND ELIGIBILITY CRITERIA

Inclusion criteria

Studies reporting nanoformulations containing essential oils.

Research articles describing formulation, physicochemical characterization, or biological evaluation.

Studies focusing on pharmaceutical, biomedical, or therapeutic applications.

Exclusion criteria

Studies involving non-nano formulations of essential oils,

Conference abstracts, editorials, and non-peer-reviewed articles.

Articles lacking sufficient experimental or methodological details.

Data Extraction and Analysis

Relevant data from the selected studies were systematically extracted, including the type of essential oil used, class of nanocarrier (nanoemulsion, liposome, SLN, polymeric nanoparticle, etc.), particle size, polydispersity index (PDI), zeta potential, encapsulation efficiency, and loading capacity, as well as biological or therapeutic outcomes. The collected data were qualitatively synthesized to compare formulation strategies, performance characteristics, and application areas.

Study Screening Process

The identification, screening, and selection of studies were carried out in multiple stages, including duplicate removal, title and abstract screening, and full-text assessment for eligibility. The overall selection workflow is illustrated in Figure 2.

ESSENTIAL OIL IN THERAPEUTICS

The potential significance of essential oils in disease management is occasionally investigated, and some research suggests they may offer specific therapeutic benefits. More research is required to completely understand the safety and usefulness of EOs, which are often used in complementary medicine. EOs are rich sources of phytoconstituents, which further possess varying pharmacological activities, making them a novel area of interest for therapeutic applications [13]. The reported literature indicates that EOs primarily possess antimicrobial, anti-inflammatory, antioxidant, analgesic, anxiolytic, anticancer, and wound-healing properties (Table 1). These pharmacological activities of EOs are well-reviewed and discussed by Bapista-Silva et al. (2020) and Cimino et al. (2021) earlier [6,11].

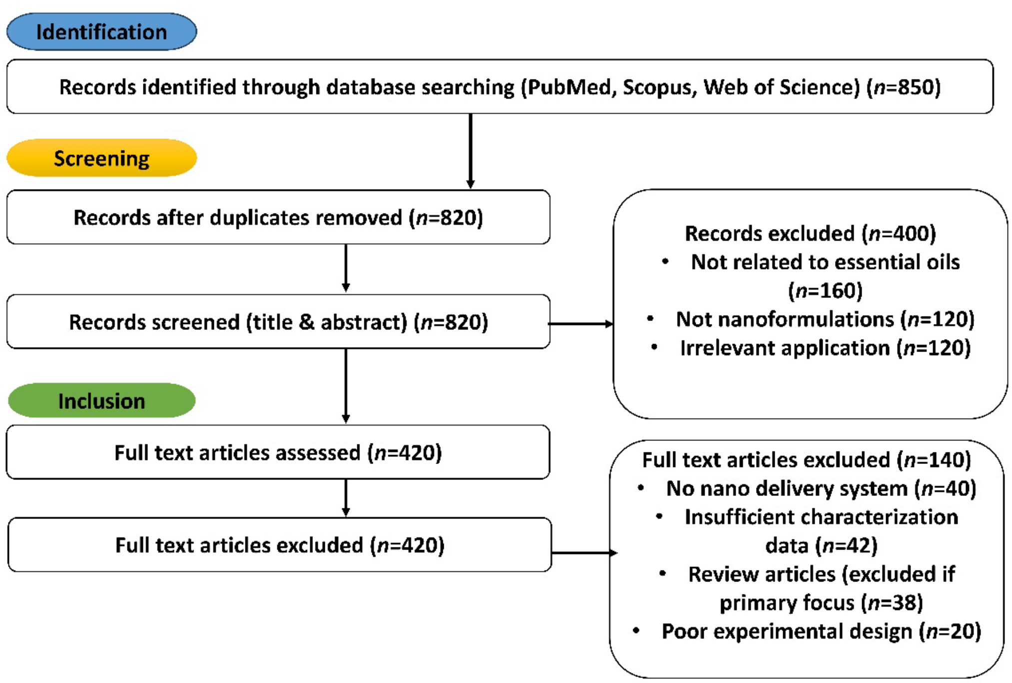

Figure 2: PRISMA flow diagram of literature for selection of studies on nanotechnology-based delivery of essential oils

Table 1: Some reported medicinal plants containing essential oil as a major phytoconstituent

SN	Plant source	Common name	Phytoconstituents	Therapeutic use	Nanoformulation	Ref.
1.	*Cinnamomum zeylanicum/ C. verum/ C. cassia*	Cinnamon; Chinese cinnamon	Cinnamyl acetate; eugenol; cinnamic aldehyde, cinnamyl aldehyde and tannins	Anti-microbial, anti-diabetic, antioxidant, anti-inflammatory and anticancer effects	Chitosan nanoparticles	[14, 15]
2.	*Commiphora myrrha*	African myrrh	2-cyclohexen-1-one and 4-ethynyl-4-hydroxy-3,5,5-trimethyl	Liver cancer and cervical cancer	Nanosilver	[16, 17]
3.	*Salvia officinalis*	Common sage	Hydrocarbons, monoterpene, oxygenated monoterpenes, sesquiterpene and diterpenes	Human breast cancer, prostate cancer and kidney cancer	PEGylated chitosan Biodegradable nanoparticles	[18, 19]
4.	*Cymbopogon citratus*	Lemon grass	Geranial, neral, β-myrcene and geranyl acetate	Anti-inflammatory	-	[20]
5.	*Blumea balsamifera*	Sambong	Borneol, caryophyllene, ledol and caryophyllene oxide	Anti-inflammatory	Nanoemulsion	[21–23]
6.	*Nepeta leucophylla; N.ciliaris; N.elliptica;*	Catmint	Caryophyllene oxide, Iridodial β-monoenol, Acetate; β-Caryophyllene, β-Sesquiphellandrene, Caryophyllene oxide; β-Sesquiphellandrene, Actinidine and Germacrene D	Anticarcinogen, antioxidant, anticonvulsant, analgesic, anti-inflammatory and antidepressant	Silver and gold nanoparticles	[24, 25]
7.	*Syzygium aromaticum*	Clove	Betulinic acid and triterpenes	Human breast cancer	Nanoemulsion	[26–28]
8.	*Anethum graveolens*	Dill	α-Phellandrene, limonene, dill ether and α-pinene	Anti-inflammatory	Nanoemulsion	[29, 30]
9.	*Pogostemon cablin*	Patchouli	Patchoulol	Colds, headaches, fever, nausea, vomiting, diarrhea, abdominal pain, insect and snake bites	Nanoemulsion	[31, 32]
10.	*Laportea aestuans*	West Indian woodnettle	Methyl salicylate, fenchol, (1,2-cyclohexanedione dioxime), (1,4-octadiene) and linalool	Abortifacient, laxative, pain-killer, febrifuge, eye treatment and pulmonary	-	[33]
11.	*Ocimum basilicum*	Basil	Linalool, methyl chavicol and 1,8-cineole	Headaches, coughs, diarrhea, constipation, warts, worms and kidney malfunctions	SNEDDS, Microemulsion	[34, 35]
12.	*Aquilaria crassna*	Agarwood	β-Caryophyllene, 1-phenanthrenecarboxylic acid, α-caryophyllene and azulene benzenedicarboxylic acid	Colorectal/colon carcinoma and pancreatic cancer	Nanoemulsion	[36]
13.	*Myrtus communis*	Common myrtle	(1,8-cineole), linalool, myrtenyl acetate and myrtenol	Blood cancer (leukemia)	Nanoemulsion	[37]
14.	*Eucalyptus citriodora*	Lemon scented gum	Pulegol, citronellol and citronellil acetate	Anticancer, antimalarial, antidiabetic	Nanocapsules	[38, 39]
15.	*Phyllanthus muellerianus*	Mbolongo, mijiriyar kurumi	Isoelemicinb, caryophyllene oxide, α-Cadinol and 2-isopropyl benzoic acid	Anti-inflammatory	Alginate based microcapsules	[40, 41]
16.	*Plectranthus amboinicus*	Indian borage	Carvacrol and thymol	Antimicrobial, antiinflammatory, antitumor, anti-epileptic, larvicidal, antioxidant and analgesic activities	-	[42]

SN	Plant source	Common name	Phytoconstituents	Therapeutic use	Nanoformulation	Ref.
17.	*Globba sessiliflora*	Kattinji	β-Eudesmol, (E)-β-caryophyllene, caryophyllene oxide and T-muurolol	Anti-inflammatory	-	[43]
18.	*Pulicaria inuloides*	False fleabane	4,5-dimetiltiazol-2-il and 2,5-difeniltetrazólio	Breast cancer	-	[44]
19.	*Teucrium ramosissimum*	Germanders	δ-Cadinene, δ-cadinol, β-eudesmol, γ-gurjunene and cedrene	Anticancer	Silver nanoparticles	[45, 46]
20.	*Salvia lavandulifolia*	Spanish sage	Camphor, 1,8-cineole, camphene and α-pinene	Spasmolytic, antiseptic, analgesic, sedative, and anesthetic activities	-	[47]
21.	*Rosmarinus officinalis*	Rosemary	α-Pinene, 1,8-cineole and camphor	Dysmenorrhea, epilepsy, rheumatic pain, spasms, memory enhancer, hysteria and depression	Chitosan crosslinked with TPP nanoparticles	[48, 49]
22.	*Hedychium coronarium*	Butterfly Ginger Lily	β-Pinene, coronarin-E, α-pinene; p-cymene, γ-terpinene, 10-*epi*-γ-eudesmol, eucalyptol and linalool	Anti-rheumatic, against bronchitis and tonsillitis	-	[50]

Drug delivery approaches for improving the therapeutic profile of essential oils

Since ancient times, EOs have been utilized for their therapeutic benefits; however, their inherent difficulties often restrict their clinical utility. These challenges include hydrophobicity, instability, volatility, susceptibility to environmental degradation, and toxicity (at high concentrations or upon direct application to the skin). Additionally, these factors can hinder effective drug delivery and targeted therapeutic applications. EOs often contain multiple bioactive compounds, making it difficult to target specific therapeutic effects [6]. To enhance the therapeutic profile of EOs for medication delivery, issues such as volatility, potential cutaneous irritation, and controlled release must be addressed. Overcoming these obstacles and improving the therapeutic profile of EOs is achievable through novel drug delivery strategies. Various methods have been investigated to enhance the distribution of EOs within the biological system. Depending on the route of administration, some of the most promising approaches include microencapsulation, nanoencapsulation, prodrug strategies, solid dispersions, cyclodextrin complexes, and delivery through nanocarriers such as liposomes, ethosomes, solid lipid nanoparticles, and polymeric nanoparticles; these are discussed further.

Oral Drug Delivery System for Essential Oils

Drug absorption through the oral route is governed by physicochemical properties of the drug, mainly its solubility, permeability, and gastrointestinal stability [51]. Due to their poor water solubility and instability, the clinical efficacy of EOs is limited by oral administration. Researchers are thus focusing on novel formulations that use nanotechnology to encapsulate EOs to improve therapeutic efficacy. Nanocarrier drug delivery systems like nanoparticles, solid lipid nanoparticles, dendrimers, liposomes, micelles, and nanoemulsions are extensively used for encapsulation in drug delivery, as these improve drug dissolution, which enhances the bioavailability, reduces drug dose, side effects, and toxicity of therapeutics [52].

Nano/microemulsions for oral administration of essential oils

Nanoemulsions (NEs) and microemulsions (MEs) are increasingly recognized as effective systems for EOs delivery [53]. These colloidal dispersion systems enhance the palatability and bioavailability of hydrophobic EOs by forming nanometer-sized droplets in aqueous solutions, thus overcoming solubility challenges. NEs and MEs protect EOs from environmental degradation, prolonging their shelf life while maintaining their therapeutic potential. Nanoemulsions can be designed to provide a controlled and sustained release of essential oils [54,55]. The growing number of studies addressing EO-based MEs and NEs is evidence that interest in these encapsulation strategies is increasing. To illustrate, a formulation consisting of curcumin encapsulated in geranium oil microemulsion was developed, and the results showed elevated antibacterial, antioxidant, anti-inflammatory, and anticancer activities [56]. Essential oil of Chuanxiong Rhizome and Angelicae Sinensis Radix combination (CA-VO) was developed for oral administration. Enhanced oral bioavailability was concluded from the Parkinson's disease model [57]. Rosemary essential oil microemulsion (REO-ME) was formulated and evaluated for its anti-inflammatory potential in a murine model of dextran sodium sulfate (DSS)- induced ulcerative colitis. The therapeutic efficacy was evident from REO-ME's ability to target multiple inflammatory factors, including IL-6, IL-1β, and TNF-α [58]. Similarly, a nanoemulsion (NE) of *Cleome viscosa* EO was developed and evaluated for its *in vitro* antibacterial activity against drug-resistant (DR) bacterial pathogens. Study findings indicate that the *Cleome viscosa*-loaded nanoemulsion was effective against DR bacteria and works by preventing DR strains from using their drug efflux mechanisms [53]. Cinnamon and clove oils, which possess antimicrobial properties, were formulated into a nanoemulsion as a polyherbal mouthwash to treat a range of oral pathogenic diseases [59].

Another study in 2020 formulated and evaluated a nanoemulsion of cumin seed oil, demonstrating potential for cytotoxicity against tongue cancer cell lines [60]. A microemulsion-based oral spray comprising clove oil for treating oral candidiasis was developed, which demonstrated better stability and antifungal activity against *Candida albicans* compared to pure oil [61]. Similarly, the anticancer efficacy of *Z. ottensii* EO (ZOEO) and its nanoformulations (nanoemulsion, microemulsion, nanoemulgels, and microemulgels) were developed, wherein nanoemulsion and microemulsion outperformed other nanoparticles in cancer cell permeation [62]. Another study formulated PLGA-based nanoparticles of *Laurus nobilis* L. EO (LNEO) to improve its oral bioavailability for treating cancer by showing a controlled release profile [63]. Yet another study evaluated monoterpene-loaded microemulsions composed of thymol, carvacrol, and geraniol, which were proven to be potential scolicidal agents [64].

In recent studies, an oregano oil nanoemulsion was formulated to treat oral cavity infections. Researchers are continually working to develop novel oral formulations of EOs to enhance their therapeutic efficacy. Advancements in oral nanoemulsion and microemulsion systems have demonstrated their effectiveness in overcoming the poor aqueous solubility and limited gastrointestinal stability of hydrophobic compounds. For instance, curcumin-loaded microemulsions formulated using geranium oil, Tween 80, and propylene glycol have shown enhanced dispersibility, improved permeation, and increased biological activity compared to free curcumin. This microemulsion system exhibited nanoscale droplet size, optimal physicochemical stability, and significantly improved antioxidant, antibacterial, and anti-inflammatory responses. Such findings highlight the ability of nanoemulsion-based carriers to enhance solubilization, protect labile compounds from degradation, and promote sustained release. Such examples reinforce the growing evidence that lipid-based nanocarriers are promising oral delivery platforms for poorly soluble phytoconstituents [56]. The growing recognition that EOs can perform on par with, or better than, pharmaceuticals made by chemical means has led researchers to focus on developing new technologies to ensure EOs' stability, bioactivity, and bioavailability.

NANOPARTICLES

Polymeric nanoparticles

Nanoparticles have been proposed as potential nanocarriers for loading a variety of essential oils to modify their therapeutic profile in terms of increased bioavailability and stability [10]. Prompted by the growing importance of nanotechnology in medicine in recent years, polymeric nanoparticles (PNP) have gained attention, particularly in pharmaceuticals, cosmetics, food science, and agriculture [13]. These nanoparticles are designed to encapsulate, protect, and deliver EOs in a controlled and targeted manner, improving therapeutic outcomes. Chitosan nanoparticles of *Ferulago angulata* (FAEO-CSNPs) were developed and investigated for antimicrobial effects. The formulation showed stronger antibacterial activity owing to the successful encapsulation of EO within the delivery system [65].

Cuminum cyminum and *Zataria multiflora* EOs loaded alginate nanoparticles were comprehensively characterized for human skin cancer cell lines and antimicrobial study, demonstrating significantly higher efficacy against [66]. Similarly, polycaprolactone nanoparticles entrapped with palmarosa (*Cymbopogon martini*) EO were formulated, containing geraniol as a primary component possessing antimicrobial and antioxidant activities [67]. Similarly, *M. chamomilla* essential oil (CEO) loaded nanocapsules for the treatment of fungal diseases with enhanced bioavailability and efficacy [68].

Further, in another study, Trachyspermum ammi seed EO (TSEO-PNP) nanoparticles were developed for targeting colorectal cancer in a dose- and time-dependent manner [69] and evaluated. Yet another study demonstrated better anti-angiogenic effects when chitosan/TPP nanoparticles loaded with *Boswellia sacra* EO (BS-CNPs) were developed, owing to their selective cytotoxicity on HepG2 cells [70]. Yet another study demonstrated enhanced antibacterial activity, notably against *P. aeruginosa*, by developing multiple lipid nanoparticles (MLNs) of rosemary EO (REO) [71]. Two critical parameters used to evaluate these systems are loading efficiency and polydispersity index (PDI). Loading efficiency for a nanoformulation reflects the proportion of essential oil successfully entrapped within the polymeric matrix and is directly associated with therapeutic potency and formulation cost-effectiveness [72].

Reported loading efficiencies for EO-loaded polymeric nanoparticles typically range from moderate to high, depending on the polymer type and preparation method. The PDI, obtained from dynamic light scattering analysis, indicates the uniformity of particle size distribution; values below 0.3 are generally considered indicative of monodisperse and physically stable formulations [73]. Together, these parameters provide essential insight into formulation quality, stability, and scalability. Research in this area is ongoing to optimize the encapsulation efficiency, release profiles, and safety of nanoparticles for therapeutic applications. However, the development and utilization of polymeric nanoparticles for EOs require careful consideration of factors such as the selection of suitable polymers, encapsulation methods, stability, biocompatibility, and controlled-release mechanisms. The synthesis methods and particle characteristics can significantly influence the efficiency and application of these nanocarriers.

Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) loaded with EOs represent another advanced and efficient delivery system for bioactive phytoconstituents. SLNs, composed of solid lipids, saturated fatty acids, glycerol monostearate, and waxes or steroids, are another generation of nanoparticles having potential application in EOs delivery [74] whereas nanostructured lipid carriers (NLCs) contain the liquid lipid (oil) additionally [75]. These nanocarriers can load hydrophilic and hydrophobic chemicals, escape from liver or spleen filtration, have excellent bioavailability, and low toxicity [76]. NLCs containing *Pterodon pubescens* fruit oil for the targeted treatment of colon cancer. *P. pubescens* fruit oil possesses antinociceptive, anti-inflammatory, and antiproliferative activities, which were developed and optimized [77]. SLNs of *Croton argyrophyllus* (CA) Kunth essential oil (CAEO) for treating neurodegenerative disorders were developed that retained the antioxidant activity with reduced cytotoxic effects *in vitro* against a neuroblastoma cell line [78].

Similarly, SLNs of *Eucalyptus globulus* EO (EGEO) [79] and *Satureja khuzistanica* EO-loaded SLNs were assessed for selective toxicity against breast cancer cells using MCF-7 cell lines [76]. Quercetin, a highly volatile and water-insoluble EO, was encapsulated into SLNs by Weerapol et al. (2022). Evaluation results showed a sustained release profile of quercetin with higher cytotoxicity compared to pure oil [80]. SLNs loaded with *Pistacia atlantica* EO (PAEO) showed enhanced apoptosis in breast cancer cell lines MDA-MB-231 compared to the bare oil [81]. Additionally, SLNs loaded with *Mentha longifolia* and *Mentha pulegium* EOs outperformed by exhibiting greater cytotoxicity against human melanoma and breast cancer cell lines than their pure counterparts [82]. *Ferula assafoetida* seed oil (FSEO) was encapsulated into SLNs to evaluate its apoptotic and anti-angiogenic potential by Sadat et al. (2022), revealing a noteworthy cell-growth suppressive impact on the human NT-2 cancer stem cell line [83]. *Cinnamon verum* EO (CO) loaded SLNs were formulated, and the antibacterial activity of CO-SLNs against drug-resistant *E. coli* strains was evaluated, wherein MIC and MBC values for CO-SLNs and CO were reduced significantly [84]. Conclusively, the nanocapsulation method can be employed to load these EOs and develop a more effective delivery system to combat many diseases. As with polymeric nanoparticles, the development of SLNs involves careful selection of lipids, encapsulation techniques, particle-size control, stability, and release mechanisms. Optimizing these parameters is essential to ensure the efficiency and safety of these delivery systems across different applications.

Liposomes for oral delivery of essential oils

Liposomes are lipid-based vesicles that can be used as carriers for delivering various therapeutic agents, including essential oils. Their hydrophilic outer layer enhances the absorption of the encapsulated EO. Surface modifications of liposomes enable the targeted delivery of EOs to specific tissues or cells. This can improve treatment efficacy while minimizing potential side effects. *Thymus capitatus* EO-loaded nano-liposomes were formulated and evaluated, which improved growth rate, antioxidant capacity, and disease resistance in the fish model.

The slow degradation of the essential oil enables controlled release and improves its interaction with biological membranes, thereby amplifying its functional benefits [85]. Similarly, a mouthwash containing liposomes loaded with Citrus limon var. pompia EO was developed, thereby enhancing stability throughout the storage period [86]. Yet another study investigated the anticancer effect of *Lavandula angustifolia* EO (LAEO) loaded nano-liposomes on HER-2 and Caspase-3 gene expression in MCF-7 and SK-BR-3 cell lines. LAEO dramatically increased the relative expression of the caspase-3 gene while significantly lowering the expression of HER-2, showing significant reductions in cell proliferation [87]. Moreover, cyclodextrin-in-liposomes encapsulating *Lippia sidoides* and *Syzygium aromaticum* were developed to enhance their stability and control release profiles [88]. Ongoing research explores liposomal delivery systems for EOs, highlighting their potential to enhance therapeutic efficacy while considering factors such as the specific EO, liposome composition, and intended use. In Table 2, various novel drug delivery systems reported to improve the therapeutic efficacy of EOs via the oral route are discussed.

Table 2: Delivery of essential oils by oral route

SN	Essential oil	Therapeutic use	Problem associated with oil	Delivery System	Study Outcomes	Ref.
1.	Turmeric oil and lemongrass oil	Antiproliferative activity	Low stability	Chitosan alginate nanocarrier	Improved stability and hemocompatibility	[89]
2.	Peppermint oil	Antioxidant, anti-inflammatory activity and antibacterial	Low bioavailability, high volatility, variable efficacy and tolerability	Alginate microbeads	Sustained release profile, improved stability, bioavailability and improved antibacterial activity	[90]
3.	*Ocimum basilicum L. leaf* oil	Antibacterial, antioxidants, and larvicidal activity against *C. quinquefasciatus*	Low stability and high volatility	Nanoemulsion	Improved stability and larvicidal activity	[91]
4.	*Eugenia globulus* essential oil	Antibacterial and antifungal activity	Hydrophobic character and volatility	Solid lipid nanoparticle	Improved antimicrobial properties	[79]
5.	*Trachyspermum copticum* essential oil	Antioxidant and anticancer effects	Bioavailability, taste and color	Niosomes	Elevated cellular toxicity against hepatocellular carcinoma and antioxidant activity	[92]
6.	Oleocanthal olive oil	Prevention of human triple-negative breast cancer	Low melting point and poor dissolution	Solid dispersion	Improved dissolution and pharmacodynamic profiles	[93]
7.	Cumin oil	Anti-inflammatory activity and antidiabetic activity	Low stability	Silver nanoparticle	Enhanced anti-inflammatory activity, controlled postprandial hyperglycemia, and improved stability	[94]
8.	Black seed oil	Antihypertensive, antimicrobial, antihistaminic, antidiabetic, lipid-lowering and anti-inflammatory	Poor bioavailability	pH-sensitive drug delivery	Increased bioavailability and targeted intestinal delivery	[95]
9.	*Lavandula angustifolia* essential oil	Antioxidant and anticancer	Low stability and high volatility	Liposomes	Improved stability and efficacy	[96]
10.	*Croton argyrophyllus* Kunth EO	Antiproliferative, anti-inflammatory, antinociceptive and anticancer	Cytotoxicity	Solid lipid nanoparticle	Free radical scavenger and reduced risk of cytotoxicity	[78]

SN	Essential oil	Therapeutic use	Problem associated with oil	Delivery System	Study Outcomes	Ref.
11.	Soyabean oil and Coconut oil	Mosquito repellent, atopic dermatitis treatment	Slow lipid digestion	Solid lipid particles	Digestion and absorption of saturated FAs* in the intestine	[97]
12.	Thyme, Rosemary, and Basil oil	Antimicrobial, antioxidant, and anticancer effects, antipseudomonal activity	Low aqueous solubility, stability and high volatility	Nanoparticles	Enhanced antimicrobial activity and improved bioavailability	[71, 98]
13.	Eugenol and Ylang-Ylang EOs	Antimicrobial, antioxidant, antianxiety and antihypertensive activity	Low solubility	Nanoparticles	Enhanced antioxidant effect after conjugation on Fe_3O_4-Lax composites	[99]
14.	*Zingiber ottensii*	Stomachache and hemorrhoids, improve blood circulation and muscular pain	Low stability, poor bioavailability and high volatility	Nano-emulsion/ micro-emulsion	Enhanced cytotoxicity against MCF-7(Michigan Cancer Foundation-7)	[62]

Topical Drug Delivery System for Essential Oils

Topical drug delivery is a versatile and widely used method for localized and, in some cases, systemic therapeutic effects. The direct topical use of EOs is limited by various factors, including skin irritation, allergic responses, and photosensitization, even though there are many intriguing medicinal possibilities. Novel approaches for loading these EOs are being explored to address these issues related to the topical administration of EOs directly (Table 3). Advances in drug delivery systems and formulation science continue to contribute to the development of more effective and patient-friendly topical drug delivery systems for treating various diseases with positive outcomes. These include hydrogels, microemulsions, nanoemulsions, liposomes, ethosomes, nanoparticles, and many more.

Table 3: Novel topical formulations of essential oils

SN	Essential oil	Therapeutic use	Problem associated with oil	Delivery System	Study Outcomes	Ref.
1	Citronella oil	Mosquito repellent and antimicrobial activity	Uncontrolled release; poor stability, skin irritation and high volatility	Microencapsulation; hydrogel	Controlled release, mosquito repellent activity	[100]
2	*Ligusticum chuanxiong Hort*	Analgesic, anti-inflammatory, cardiovascular and cerebrovascular diseases	Volatile and unstable	Liposomes	Improved stability and efficacy	[101]
3	Lemongrass oil	Antimicrobial and antipathogenic activity	Skin irritation, high volatility	Topical gel	Antibacterial activity	[102]
4	Citronella EO	Mosquito repellent and antimicrobial activity	Low stability and user acceptance	Nanostructured lipid carriers	Improved stability, and patient compliance	[103]
5	*Calendula officinalis*	Cell rejuvenation, wound healing, anti-inflammatory, and soothing	High volatility and low stability	Emulsion	Enhanced permeation	[104]
6	*Vitex negundo* L leaf EO	Anti-inflammatory, expectorant, tranquilizer, antispasmodic, rejuvenating, anti-arthritic, anthelminthic, and anti-fungal	Low stability and solubility;high volatility,	Nanoemulsion	Thermodynamically stable, improved bioavailability, and biocompatibility	[105]
7	*Origanum vulgare*	Anti-acne and antimicrobial activity	High volatility, low solubility	Nanoemulsion; Chitosan nanoparticles	Improved solubility and controlled oil release	[106]

* Folic acids

SN	Essential oil	Therapeutic use	Problem associated with oil	Delivery System	Study Outcomes	Ref.
8	Coconut oil	Atopic dermatitis treatment, anti-bacterial and antimicrobial activity	Low solubility, bioavailability, permeability, and retention of active compounds	Chitosan nanoparticles	Improved solubility, bioavailability, permeability and good antibacterial and antibiofilm effects	[107]
9	Clove oil	Digestive and respiratory conditions	High volatility; Irritation potential, low stability, and efficacy	Ethosomes and microemulsion	Enhanced permeation, and fungal activity, higher efficacy, stability, and reduced irritation potential	[108]
10	Lavender EO	Sedative, analgesic, anti-depressant, anti-inflammatory and antibacterial	Poor stability, encapsulation and release of oil	Hydrogel	Improved stability during storage and controlled release	[53]
11	Chamomile oil	Wound healing, anti-inflammatory and antianxiety activity	Low physical stability and spongiosis	Nanoemulgel	Improved stability and reduction skin healing duration and no spongiosis	[109, 110]
12	*Artemisia annua* L. oil	Antimicrobial and antiprotozoal activity	High volatility and rapid deterioration	Liposomes	Improved stability and efficacy against fungal infections	[111]
13	Eucalyptus oil and orange oil	Antifungal, antibacterial	Low stability and high volatility	Nanoencapsulation	Preserved anti-fungal activity	[112]
14	Palmarosa oil and phytoncide oil	Antimicrobial, antifungal and anti-inflammatory	Secondary infection or skin disorders	Nanofiber matrix	Potential in wound dressing and controlled secondary infection or skin disorders	[113]
15	*M.chamomilla* oil	Sedative, antimicrobial, antispasmodic, antipruritic, anti-inflammatory, antigenotoxic and antioxidant	High volatility, temperature sensitive and low stability	Chitosan nanocapsule	Promising therapeutic strategy to treat leishmaniasis	[110]
16	*Pelargonium graveolens* EO	Anti-bacterial and antifungal activity	Low stability and high volatility	Nanoemulsion (Vaginal)	Improvement antifungal activity	[114]
17	Zedoary turmeric oil and tretinoin	Psoriasis	Poor water solubility and stability	Liposomes	Improved solubility and stability	[115]
18	Cumin oil	Antidiabetic, antimicrobial, and anti-inflammatory	Poor stability, encapsulation, and oil release and high volatility	Hydrogel; Nanoemulgel	Enhanced encapsulation, permeation, and stability	[116, 117]
19	Geranium EO and Calendula EO	Anxiety, depression, antibacterial, antioxidant and anti-inflammatory	Poor stability and highly volatile	Ethanolic lipid vesicles	Preserved efficiency of EOs, improved stability and reduced volatility	[118]
20	*Pterodon pubescens*	Antinociceptive, anti-inflammatory and antiproliferative activity	High volatility and low stability	Micro-encapsulation	Improved stability	[77]

Hydrogel for topical delivery of essential oils

Hydrogels are three-dimensional polymeric networks capable of retaining a considerable amount of water, making them suitable for drug delivery applications. Their porous structure can be readily manipulated by varying the cross-link density that permits the encapsulation of oil-based medications and their subsequent, controlled release [119]. For instance, a hydrogel loaded with Lavender oil (LEO) emulsion was developed that enhanced stability and delayed LEO release under dynamic conditions, suggesting its potential as a delivery system for topical application [120]. A mucoadhesive hydrogel-thickened nanoemulsion loaded with *Pelargonium graveolens* EO was formulated to treat vaginal candidiasis, demonstrating greater antifungal activity against *Candida spp* as compared to bare EO and nanoemulsion [114]. A new encapsulating technique based on calcium alginate hydrogels loaded with cumin EO was synthesized and described by Gholamian et al. (2021), highlighting their effectiveness as a suitable carrier for topical applications [116]. A delayed-release formulation of citronella oil microsponge-loaded hydrogel (HG-COMS) achieved notable mosquito repellent efficacy and antibacterial properties over pure oil [100].

A reported novel drug delivery system for citronella oil is shown in Figure 3. Furthermore, an antibacterial polysaccharide-based hydrogel incorporated with EO (Eucalyptus, Ginger, Cumin EO) promoted dermal regeneration in wound healing models [121].

In a study, chitosan nanoparticles loaded with clove and turmeric EO into poly(vinyl alcohol) hydrogel showed potential for wound management [122] and similarly, another study reported the same application of *Thymus vulgaris* EO-loaded hydrogels and *Piper aduncum* EOs for topical delivery [123,124]. In another study, a topical formulation of alginate-based hydrogel loaded with lavandin oil, linalool, and linalyl acetate was developed for the treatment of psoriasis. *In vivo* studies in an imiquimod-induced mouse model demonstrated that the hydrogel significantly reduced the ear thickness and alleviated psoriasis symptoms. Histopathological analysis revealed a decrease in CD3 and CD68 expression and reduced cell proliferation, as measured by Ki67 staining [125].

Additionally, a polymeric-micelles-based hydrogel containing *Origanum vulgare L*. EO was developed and evaluated for the treatment of fibroepithelial polyps (FPs) through cutaneous application. Anti-angiogenesis effect was also evaluated *in ovo*, suggesting a significantly higher angiogenic inhibition index for the hydrogel formulation compared to pure oil [126]. Cai et al. (2023) investigated and demonstrated the enhanced wound-healing effect of hydrogel loaded with eucalyptus EO nanoemulsions in a mouse model [127]. Numerous scientific reports support the anti-inflammatory and antibacterial activity of EOs incorporated into hydrogel-based drug delivery systems for treating wounds topically [128]. Conclusively, researchers and formulators can develop hydrogel-based systems that effectively deliver EOs for topical applications, offering potential benefits in the domains of wound healing and pain management. There's no denying that additional research on essential oil-loaded hydrogels will eventually lead to their clinical application.

Safety assessment is another concern, as concentrated EO constituents and nanoscale carriers may induce cytotoxicity or sensitization. The integration of EO-loaded nanocarriers into hydrogel systems has demonstrated promising therapeutic potential in wound healing; however, regulatory translation remains a persistent challenge. The inherent variability in EO composition is influenced by botanical origin, extraction parameters, and storage stability, representing a critical barrier to the reproducible development of hydrogel formulations [129].

The wound healing process is critically dependent on sustained antimicrobial protection and controlled anti-inflammatory responses, and such variability complicates standardization and quality control across batches. In addition, EO-loaded nanoformulations embedded within hydrogels represent complex, multi-component systems comprising natural products, nanocarriers, and polymeric matrices [130]. This structural and functional complexity makes it challenging to define critical quality attributes, including release kinetics, permeability, and long-term stability under physiological conditions.

Moreover, interactions between nanocarriers and hydrogel networks may alter therapeutic performance over time. Although hydrogels are biocompatible, the incorporation of nanoscale carriers and concentrated EO constituents raises concerns regarding cytotoxicity, skin sensitization, and long-term exposure in chronic wounds [131].

Moreover, safety evaluation, including toxicity profiling, further complicates clinical translation and approval due to the lack of a harmonized regulatory framework. Therefore, establishing standardized EO profiling methods, robust quality control strategies, and standardized regulatory guidelines is essential to facilitate the clinical translation of EO-loaded hydrogel systems.

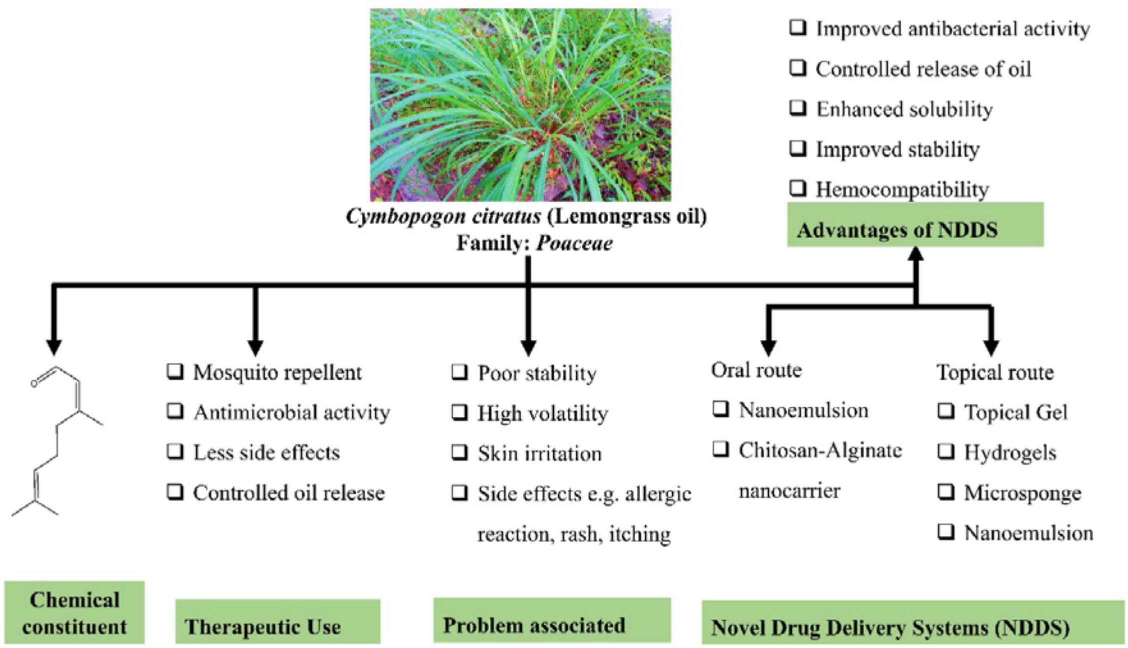

Figure 3: Novel drug delivery systems reported for therapeutic delivery of lemongrass oil

Nano/microemulsion for topical administration of essential oils

Emulsions are dispersions composed of two immiscible liquid phases stabilized by mechanical shear and emulsifying agents. The small droplet size of nano/microemulsions facilitates penetration of the EOs into the skin, improving their therapeutic efficacy. Due to their lipophilic nature and poor water solubility, EOs benefit from nano/microemulsions that increase their bioavailability and absorption. Additionally, these emulsions can mitigate skin irritation by forming a protective barrier around the oil droplets. Research highlights the versatility of nano/microemulsions in biomedical applications. For example, a nanoemulsion of *Lippia origanoides* EO was developed that demonstrated enhanced permeability in an *in-vitro* model. Results indicated its potential in topical antifungal therapy in preclinical or clinical models studies as a contribution to the treatment of topical fungal diseases caused by *Candida* spp [132]. Other studies have shown that nanoemulsions enhance wound healing and analgesic effects when loaded with various EOs, such as *Origanum vulgare*, *Citrus limonum*, licorice extract, and lavender EO (LEO) [128].

A recent study demonstrated that LEO nanoemulgels produced via ultrasonic emulsification exhibited reduced particle size, improved stability, and superior anti-melanogenic activity, alongside minimal cytotoxicity and dermal irritation. Whereas, nanoliposomes of LEO improved follicular penetration and resulted in significantly enhanced hair growth in animal models. These nanocarriers facilitate controlled release, better skin permeation, and protection of volatile EO constituents from degradation. For skin depigmentation or wound/skin therapy, nanoemulgel is efficient, whereas for hair growth and follicular targeting, nanoliposomes are more effective[133]. Similarly, a thermosensitive hydrogel consisting *Schizonepeta annua* essential oil nanoemulsions (SEO-NE-TG) was formulated. SEO-NE-TG formulation resulted as a natural alternative to conventional antimicrobial dressings with superior healing promotion capabilities as demonstrated by *in vivo* studies [134]. Chitosan nanogel was developed for SEO, which effectively enhanced the potential of SEOs. A nanoencapsulated formulation prepared from a synergistic combination of its leaf and bud demonstrated improved antimicrobial activity compared with the non-encapsulated oil blend. Physicochemical characterization further confirmed stable dispersion, suitable zeta potential, and uniform particle size, indicating good formulation stability. The sustained release, improved solubility, and increased permeability collectively contributed to its superior performance [28].In another study we prepared clove oil-loaded microemulsion-based gel for the treatment of superficial fungal infections, demonstrating comparable efficacy to the commercially available Clobet gel [108]. A study proved enhanced antichemotatic activity of *Aniba canelilla* EO (EOAC) through nanoemulsification, which effectively reduced neutrophil chemotaxis in inflamed skin animal models [135]. By enhancing the histopathological characteristics of the rats' knee joint and increasing antioxidant capacity, the topical nanoemulsion comprising EOs of peppermint and rosemary alleviates the discomfort associated with osteoarthritis [87]. A study reported that nanoemulsification improved the therapeutic potential of Niaouli EO (*Melaleuca quinquenervia L*) for the treatment of acne vulgaris topically [136] while another study highlighted the anti-inflammatory, antibacterial, and anti-diabetic activities of *Cymbopogon pendulus* EO-loaded nanoemulsion [137].

These findings suggest that EO-loaded nano/microemulsions offer enhanced stability, bioavailability, and controlled release for various topical applications. Although there are some challenges associated with the incorporation of therapeutically important EOs into nanoemulsions and microemulsions, such as limited loading capacity, compatibility, surfactant toxicity, and instability, these issues still need to be addressed carefully. Continued research is essential to optimize these formulations for specific therapeutic applications, paving the way for their clinical use in dermatology and beyond.

Liposomes for topical delivery of essential oils

Encapsulation in liposomes shields the EO from environmental degradation, improving its stability and bioavailability. Liposomes with encapsulated EOs have been explored for various therapeutic applications, including dermatology and targeted drug delivery. For example, a study developed a tea tree oil (TTO) based liposomal formulation and evaluated it for antifungal activity in an *in vivo* rat model. TTO was primarily coated by chitosan and was further incorporated in lipid bilayer and represents potential in systemic and topical fungal infections [138].

Another study reported the enhanced wound healing in rats by TTO-loaded hesperidin-loaded lipid nanoparticles (HESP-NLCs). The formulation revealed its synergistic therapeutic efficacy, proven through *in vitro* antimicrobial activity and anti-inflammatory action [139]. Yet another study reported pine green cones EO after encapsulation into liposomes, revealing strong anti-inflammatory activity of the formulation. The results indicated the potential application of liposomal formulation for topical use with enhanced bioactivity and stability [140]. Similarly,of Artemisia annua L. EO (AEO) were developed, showing a minimum fungicidal concentration (MFC) when evaluated against *C. albicans*, showing that nanoliposomes could improve their clinical efficacy against fungal infections [111].

Further, a topical liposomal gel using a combination of zedoary turmeric oil (ZTO) and tretinoin (TRE) was developed for treating psoriasis that showed enhanced skin penetration and anti-psoriatic effects in mouse models [115]. Incorporation of neem oil into liposomes and hyalurosomes, which were further modified with argan oil to develop modified argan-liposomes and argan-hyalurosomes, was formulated. *In vitro* antioxidant activity and toxicity studies on keratinocytes and fibroblasts revealed better activity in combating oxidative stress of argan hyalurosomes as compared to argan-liposomes, promoting cell proliferation and migration, causing rapid closure of wounds [141]. Lentisk oil *(Pistacia lentiscus L.*) loaded liposomes were developed for topical delivery in lesion regeneration and healing that showed enhanced keratinocyte proliferation more than the oil dispersion [142]. Al-Ogaidi et al. (2022) formulated a topical nanoliposomal formulation encapsulated with a blend of peppermint, eucalyptus, tea tree, lemon oil, and clove oils, which exhibited superior antimicrobial activity against *E. coli* and *B. subtilis* [143]. Lippia sidoides EO (LSEO) was encapsulated in nanostructured lipid carriers (NLC), wherein the formulation showed significant anti-yeast action and no toxicity in the *in vivo* model, supporting their use as a novel treatment method for treating candidemia [88]. Nano-liposomes containing *Bunium persicum* and *Trachyspermum ammi* EOs were formulated separately by green synthesis, and the effectiveness was assessed against *Trichomonas vaginalis in vitro* [113].

It can thus be concluded that topical delivery of EOs using liposomes as a vesicular system can be an effective strategy to enhance the absorption, stability, and therapeutic efficacy of these oils on the skin. Surface modifications of liposomes can also be employed to achieve targeted delivery of EOs to specific skin layers or cells, enhancing their therapeutic impact. Ongoing research focuses on optimizing liposomal formulations for specific EOs, considering factors such as size, charge, and surface modifications to improve stability and efficacy. In lipid based nanocarrier systems, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) have been extensively investigated as carriers for essential oils due to their biocompatibility, controlled release, and capacity to protect labile constituents from environmental degradation. Nevertheless, a major limitation associated with SLNs is drug expulsion during storage, which is primarily attributed to polymorphic transitions and progressive crystallization of the solid lipid matrix [144].

As the lipid transforms from metastable α and β′ forms into the more thermodynamically stable β polymorph, the crystal lattice becomes increasingly ordered, reducing available space for encapsulated molecules and forcing EO components out of the matrix. On the other hand NLCs were subsequently developed to address these shortcomings. By incorporating a fraction of liquid lipid into the solid lipid matrix, NLCs create a structurally disordered and imperfect crystalline network with greater accommodation capacity for bioactive compounds. This heterogeneous matrix not only enhances loading efficiency but also minimizes drug leakage and expulsion during long-term storage by inhibiting complete lipid recrystallization [145]. As a result, NLCs demonstrate superior physical stability, higher encapsulation efficiency, and improved retention of volatile essential oil constituents compared with SLNs, making them more suitable for formulations requiring prolonged shelf life and consistent therapeutic performance.

A comparative evaluation of nanocarriers highlights distinct advantages and limitations in delivering clove oil widely studied for antimicrobial and wound healing applications. Liposomes, being composed of phospholipid bilayers, provide effective encapsulation of both hydrophilic and lipophilic constituents and offer enhanced biocompatibility. In clove oil delivery, liposomal systems have demonstrated sustained release profiles and reduced cytotoxicity, making them particularly suitable for topical and mucosal applications [146]. However, their relatively complex preparation methods and susceptibility to physical instability caused by fusion and leakage limits their commercial upscale.

In contrast to lipid-based nanoformulations, nanoemulsions exhibit superior kinetic stability, ease of preparation, and high solubilization capacity for lipophilic compounds. Clove oil nanoemulsions have consistently shown enhanced antimicrobial activity due to improved dispersion and increased surface interaction with microbial membranes which is advantageous for both topical and oral delivery [147]. Nevertheless, nanoemulsions face challenges due to the concerns of long-term stability and require surfactants, which can raise toxicity at higher concentrations. Overall, while liposomes are preferable for controlled and biocompatible delivery, nanoemulsions offer superior simplicity and immediate bioactivity enhancement. The choice of carrier should therefore be guided by the intended route of administration and therapeutic objective, underscoring the importance of rational nanocarrier selection in essential oil-based formulations.

Ethanolic Lipid Vesicles / Ethosomes for topical delivery of essential oils

Lipid vesicles can potentially be applied to transport active components like plant extracts and phytochemicals that are otherwise insoluble, poorly absorbed, or easily degraded. The inclusion of ethanol as a penetration enhancer, distinguishes ethosomes from traditional liposomes. Ethanol imparts fluidity to the vesicular structure, increasing the flexibility of the vesicle and enhancing its ability to penetrate the skin. A study formulated a clove oil-loaded ethosomal gel, and when compared to pure clove oil, the ethosomal gel demonstrated adequate antifungal efficacy against *C. albicans,* causing cutaneous candidiasis [108]. An anti-aging topical ethanolic lipid vesicular (ELV) cream encapsulating geranium (GEO) and calendula EOs was prepared, which indicated its potential to stop skin aging while maintaining the efficacy of EOs [118]. A study demonstrated the enhanced therapeutic efficacy of *Butea monosperma* seed oil (BMSO) hydrogel incorporated with ethanolic vesicular carrier in vaginal candidiasis [148].

Nanoparticles for topical delivery of essential oils

Nanoformulation has already produced some intriguing outcomes in the development of cutting-edge phytochemical delivery systems. Nanodelivery methods also appear to resolve drug delivery limitations associated with the topical delivery of EOs. For example, mangostin extract-loaded coconut oil topical nanoemulsion and nanoemulgel were formulated, which demonstrated promising antibacterial and antibiofilm properties, making them promising candidates for acne vulgaris therapy [149]. A study demonstrated the development of nanoemulsion incorporated with EOs (palmarosa and tea tree oil). The nanoemulsions were further evaluated for antibacterial efficacy, which showed promising results [150]. In Table 3, novel formulations of essential oils for topical administration are listed.

PARENTERAL DRUG DELIVERY SYSTEM FOR ESSENTIAL OILS

Essential oils are typically utilized in topical formulations, but their parenteral delivery is an emerging area requiring careful consideration. For instance, nanoemulsion of *Syzygium Aromaticum* L. Bud EO (SABE) for parenteral delivery, demonstrating significant anti-tumor and apoptotic effects against human HT-29 colon cancer cells, with *in vitro* cytotoxicity studies showing induced apoptosis and reduced cell [151]. In another study, *Artemisia vulgaris* EO (AVEO) nanoemulsion was developed and investigations showed its cytotoxic and anti-angiogenic characteristics in MCF-7 cancer cell lines by up-regulation of Cas-9, CAT, and SOD gene expression and inhibiting VEGF expression [152]. Yet another study demonstrated enhanced bio-efficacy and a stronger inhibitory impact on cancer cells by a nanoemulsion of pine needle (*Pinus morrisonicola*) EO (PNEO) [153]. Additionally, a nanoemulsion of *Ferula gummosa* EO (FEGO-NE) showed substantial tumor inhibition *in vivo*, whereas normal cells were unaffected [154].

INTRANASAL DRUG DELIVERY SYSTEM FOR ESSENTIAL OILS

Intranasal drug delivery involves administering drugs through the nasal route. This route offers several advantages, including rapid absorption due to the highly vascularized nasal mucosa, avoidance of the first-pass metabolism, and the potential for improved patient compliance. For instance, *Ligusticum chuanxiong* essential oil liposomes (CXEO-LP) were developed to study their potential for the treatment of cerebral ischemia-reperfusion injury (CIRI) in a mouse model. CXEO-LP showed a prolonged and slow-release profile with no toxicity to the vital organs, indicating higher efficiency of CXEO-LP than CXEO only [101]. Yet another study fabricated and characterized a Limonene-based microemulsion (PRO-ME) in a nanogel system incorporated with propranolol. The *ex vivo* study and histopathological evaluation of sheep nasal tissue revealed its safety profile in addition to the improved passage through blood–brain barrier [155]. Chitosan-coated nanoemulsions (NEs) of *Thymus vulgaris* and *Syzygium aromaticum* EOs were developed to combat multidrug-resistant brain infections through the intranasal route [156] while another study was focused on NLCs for intranasal administration of EOs (*Lavandula*, *Mentha*, and *Rosmarinus*) in the treatment of neurodegenerative disorders, showing sustained drug release [157]. Lastly, a study introduced a *Geophila repens* phytosome-loaded intranasal gel (MEGR-PG) with a better nasal penetration profile for treating Alzheimer’s disease, highlighting improved nasal penetration and brain targeting capabilities [158] An intranasal nanoemulsion formulation for *Lavandula angustifolia* (lavender) was reported with high encapsulation efficiency and controlled oil release. Intranasal drug delivery of EOs can be a viable and effective option for certain therapeutic applications. However, it requires careful consideration of formulation aspects, safety, and regulatory requirements to ensure successful and safe delivery.

Critical Comparison of Nanocarriers for Essential Oil Delivery

Through thorough investigations in nanotechnology, a comparative evaluation of different nanocarriers highlights notable differences in their suitability for essential oil (EO) delivery. For instance, clove oil and lavender oil have been incorporated into various nanocarrier systems and can be compared to assess the better delivery system among them. Liposomes offer a phospholipid bilayer structure that closely resembles biological membranes, enabling efficient encapsulation of both lipophilic EO constituents and improved interaction with skin and mucosal tissues. This property makes them especially advantageous for follicular targeting and transdermal applications. In contrast, nanoemulsions provide superior kinetic stability, high surface area, and enhanced solubilization of volatile EO components, leading to improved antimicrobial and antioxidant activity. Studies have demonstrated that clove oil nanoemulsions exhibit stronger and more rapid antimicrobial effects due to better dispersion and penetration, whereas liposomal formulations of lavender oil show enhanced sustained release and reduced irritation. Therefore, nanoemulsions are often preferred for rapid bioactivity and food preservation, while liposomes are better suited for controlled delivery and dermal therapeutic applications, underscoring the importance of carrier selection based on the intended route and therapeutic objective.

CONCLUSION

Advancements in drug delivery systems for the therapeutic delivery platform of EOs have the potential to revolutionize the way these natural compounds are used for various therapeutic uses. They have been used extensively for centuries in traditional medicine and aromatherapy for their therapeutic properties.

However, the evolution of advanced drug delivery systems offers several advantages for the pharmacological potential of EOs in a more controlled and clinically relevant manner. Encapsulation within nano-carrier systems has been shown to improve the physicochemical stability of volatile EO constituents, enhance their solubility in biological environments, and enable sustained or site-specific release profiles. These developments have broadened the therapeutic landscape of EOs, supporting their investigation across diverse areas, including but not limited to antimicrobial, anti-inflammatory, and anticancer therapies. Nevertheless, the transition of EO-based delivery systems from experimental research to clinical implementation remains limited owing to the scarcity of comprehensive long-term toxicity, pharmacokinetic, and biodistribution studies, particularly in clinical settings. EO composition varies with its botanical origin and extraction methods, complicating formulation standardization and reproducibility. At the same time, prolonged storage stability, scalability, and the lack of standardized regulatory pathways further impede their translation into approved therapeutic products. Therefore, future investigations should focus on systematic safety assessment, robust clinical validation, and the establishment of standardized quality control parameters for EO-loaded delivery systems. Integrating these techniques with advances in formulation design and regulatory science will be pivotal in bridging the existing gap between laboratory-scale innovation and real-world therapeutic application. Systematic mitigation of these barriers will be essential for the widespread implementation of EO-based nanoformulations within mainstream drug development. We may anticipate that systematic mitigation of these barriers for the widespread implementation of EO-based nanoformulations within mainstream drug development as research progresses.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Laxmi Gharti performed literature review, data collection, and drafting of the original manuscript. Neelam Kumari contributed to the botanical and phytochemical aspects, interpretation of plant-based data. Vishal Sharma collected data and prepared tables and figures. Navneet Kumar Upadhyay drafted and edited the manuscript and proofread it. Hemlata Kaurav conceptualized, supervised, and guided critical revision of the manuscript for intellectual content and guidance on drug delivery system concepts. All authors have read, reviewed, and approved the final version of the manuscript.

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