

REVIEW ARTICLE



Essential oils: a review on their salient biological activities and major delivery strategies

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Essential oils are volatile, complex products of plants as secondary metabolites and include terpenes and their oxygenated derivatives, such as alcohols, aldehydes, esters, ketones, phenols and oxides. In recent years, out of 3000 essential oils obtained from plant origin only 300 essential oils have gained extensive attention for applications in various fields. In this review, we discuss the major biological activities associated with EOs as antimicrobial, antispasmodic, antioxidant, antiviral, anti-inflammatory, anthelmintic, insecticidal, antiparasitic, and cytotoxic agents. Different routes for delivery of essential oil along with the problems associated with essential oils like high volatility, low stability, permeability, bioavailability, poor water solubility, susceptibility to oxidation, decomposition, photosensitization and skin irritation are also highlighted. Furthermore, strategies to solve the mentioned problems are suggested by different nanoencapsulating systems. These include polymer-based nanocarriers, lipid-based nanocarriers and molecular complexes. It is believed that nanoencapsulation of essential oils will improve their therapeutic activity and delivery.

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Introduction

Restoring or rectifying health with medicinal plants is as ancient as mankind itself. Nature is dependably end up being the huge source of medication for the humanity. Recognition of the usage of medicinal plants by humans is the consequences of countless years of hassle against illnesses.¹ On the report of evolving situation made in the scientific field, keen interests have been given on the therapeutic properties of plants because they exhibit relatively less adverse effects and are safe, eco-friendly and locally available.² Plants were strongly believed to have healing power in almost all ancient civilizations. Because *Homo sapiens* are omnivorous, hence take plants or plant parts as a

principle component of diet for their nutritious content and medicinal value. In drug development, either pharmacopoeial, non-pharmacopoeial or synthetic drugs, medicinal plants are considered as rich resources of ingredients and thereby making them the source to upscale supply of different types of medicines.³

Some of the drugs obtained from plant are aspirin, atropine, artemisinin, colchicine, digoxin, ephedrine, morphine, physostigmine, pilocarpine, quinine, quinidine, reserpine, taxol, tubocurarine, vincristine, vinblastine, etc. The medicinal value of plants lies in bioactive phytochemical constituents that produce definite physiological action on the human body. Some of the most important bioactive

phytochemical constituents are alkaloids, essential oils, flavonoids, tannins, terpenoids, saponins, phenolic compounds, etc.⁴

This review covers the major activities of essential oils and problems associated with delivery of essential oil. Possible solutions and delivery strategies of essential oils are also described.

Essential oil

Essential oils (EOs) are aromatic, concentrated oily liquids obtained from plant organs, i.e. seeds (e.g. *Nigella sativa*, *Anethum graveolens*), fruits (e.g. citrus fruits), fruits peel (*Citrus japonica*), flowers (e.g. *Lavandula officinalis*, *Halimondendron halodendron*), roots (e.g. *Ballota nigra*, *Valeria najatamansi*, and *Zingiber officinale*), rhizome (e.g. *Z. officinale*), buds, twigs, leaves (e.g. *Artemisia monosperma*, *Artemisia douglasiana*, *Pimenta dioica*, and *Eucalyptus citriodora*) wood or bark (*Cordia trichotoma*, *Cinnamomum cassia*).

In sixteenth century, Swiss reformer of medicine Paracelsus von Hohenheim coined the term "essential oil", derived from the term *quinta essentia*. Essential oils can be defined as either mixtures of fragrant substances or as mixtures of fragrant and odourless substances; they are also termed as volatile or ethereal oils. They are composed mainly of monoterpenes, phenylpropenes, flavonoids and polyunsaturated omega-6-fatty acids. EOs are fat soluble and are small so that they are able to pass across the membranes or the skin and reaches the systemic circulation before being entering the microcirculation.⁵⁻⁹

Sources of essential oil

There are about 3000 different plant species containing EOs have been reported out of which only 300 of them are economically important. EOs are used in the fragrance, food, pharmaceutical, agricultural, and sanitary industries. They are formed through a schizolysigenous process in cluster gland cells and accumulated in secretory cavities, cells, epidermis cells, glandular trichomes of plant organs.⁶ EOs can be extracted by several methods which involve utility of microwaves or liquid carbon dioxide, and predominantly low- or high-pressure distillation engaging heated water or hot steam.

Due to their bactericidal and fungicidal properties, pharmaceutical and food uses are more and more widespread as alternatives to synthetic chemical products. In those cases, extraction by steam distillation or by expression is preferred and for perfume uses, extraction with lipophilic solvents and sometimes with supercritical carbon dioxide is favoured. Thus, the essential oil products differ not only in their chemical profiles and in the number of molecules but also in the stereochemical types of molecules extracted, according to the type of extraction. Depending on the change in climate, soil composition, age, plant organ, assemblage time and vegetative cycle stage, the quality, quantity and composition of the extract vary considerably.⁵

Biological activities of essential oil

Various biological activities of EOs are shown in Figure 1.

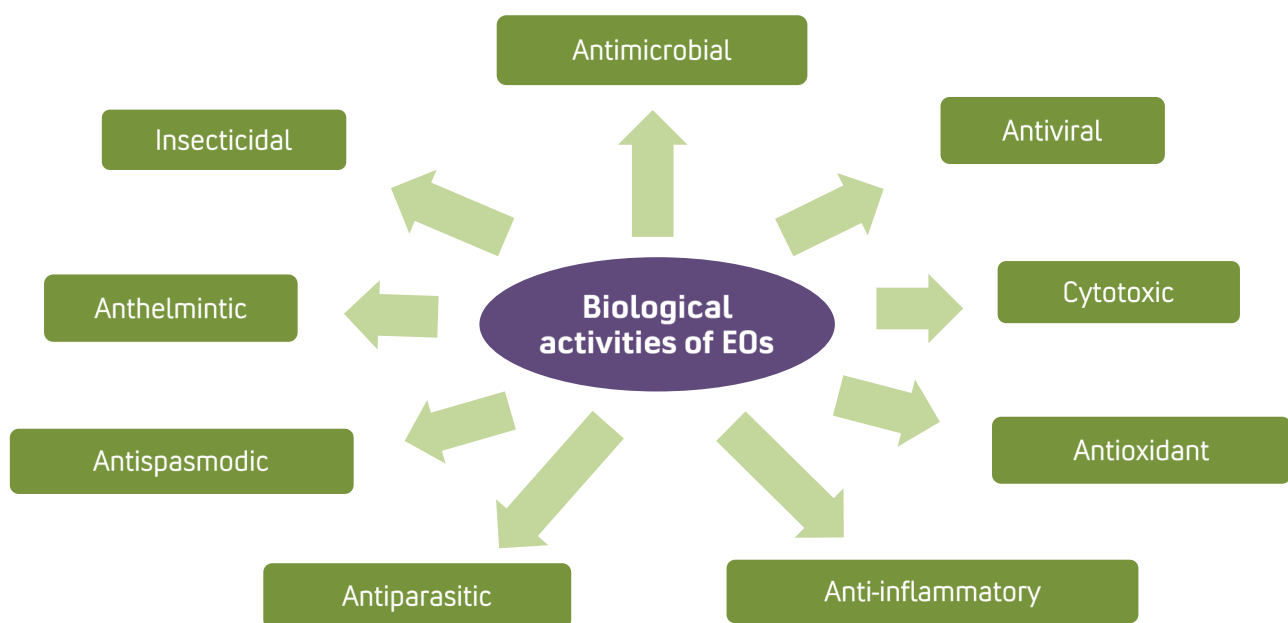


Figure 1 | Major biological activities of essential oils.

Table 1 | Plants that contain essential oils with antispasmodic activity

Plant containing EO	Mechanism of antispasmodic action*	References
<i>Acorus calamus</i>	Inhibition of Ca ²⁺ channels	13
<i>Anethum graveolens</i>	Inhibition of Ca ²⁺ channels	14
<i>Artemisia dracunculus</i>	Not found	15
<i>Carum carvi</i>	Not found	16,17
<i>Chamomile nobile</i>	Direct smooth muscle relaxation	18
<i>Chrysactinia mexicana</i>	Inhibition of Ca ²⁺ channels	19
<i>Citrus aurantifolia</i>	Not found	20
<i>Citrus aurantium</i>	Not found	21
<i>Coriandrum sativum</i>	Inhibition of Ca ²⁺ channels	22
<i>Cymbopogon citratus</i>	Inhibition of Ca ²⁺ channels	23
<i>Cymbopogon schoenanthus</i>	Not found	24
<i>Elettaria cardamomum</i>	Inhibition of Ca ²⁺ channels	25
<i>Ferula heuffelii</i>	Not found	26
<i>Foeniculum vulgare</i>	Not found	27
<i>Hofmeisteria schaffneri</i>	Not found	28
<i>Lippia alba</i>	Reduction of calcium influx, stimulation of NO production	29
<i>Lippia thymoides</i>	Not found	30
<i>Matricaria recutita</i>	K ⁺ channels activation	16
<i>Melissa officinalis</i>	Inhibition of Ca ²⁺ channels	16,31
<i>Mentha spicata</i>	Inhibition of Ca ²⁺ channels	32
<i>Mentha x villosa</i>	Not found	33
<i>Ocimum basilicum</i>	Inhibition of Ca ²⁺ channels	34
<i>Ocimum gratissimum</i>	Not found	35
<i>Ocimum selloi</i>	Inhibition of Ca ²⁺ channels	36
<i>Origanum majorana</i>	Inhibition of Ca ²⁺ channels	37
<i>Plectranthus barbatus</i>	Direct smooth muscle relaxation	38
<i>Pimpinella anisum</i>	Activation of NO-cGMP pathway	39
<i>Pistacia integerrima</i>	Inhibition of Ca ²⁺ channels	11
<i>Rosmarinus officinalis</i>	Inhibition of Ca ²⁺ channels	40
<i>Salvia officinalis</i>	K ⁺ channels activation	41
<i>Sature jahortensis</i>	Not found	42
<i>Xylopiia frutescens</i>	Inhibition of Ca ²⁺ channels; antagonism of histaminergic receptors	43
<i>Xylopiia langsdorfiana</i>	Decrease in cytosolic calcium concentration	44

Antispasmodic activity

EOs are found to possess marked antispasmodic property. There is a report on antispasmodic effect of essential oils obtained from several species of aromatic plant along with the mechanistic discussion and composition of the essential oil.¹⁰ It has been demonstrated that the presence of cymene, borneol, tetrahydrocarvone, 4-carvomenthenol, terpinenol, α -terpinene and β -caryophyllene, levo-bornyl acetate, aromadendrene in the essential oil of *Pistacia integerrima*, which are responsible for relaxing the isolated ileum and inhibiting the contraction induced by receptor-dependant and independent mechanisms.¹¹ Similarly another researcher

investigated the effect of essential oil extracted from *Croton nepetaefolius* on intestinal motility *in vivo* and on isolated preparations of gastrointestinal smooth muscle and found that it possess a potent modulator of intestinal smooth muscle.¹² Several studies confirmed the antispasmodic effect of essential oils, as listed in Table 1.

Antimicrobial activity

It has long been recognised that some EOs have antimicrobial properties, recent enhancement of interest in 'green' consumerism has led to a renewal of scientific interest in these substances.⁴⁵ Some of the essential oils along with the name of microbes

Table 2 | List of some essential oils along with the microbes they inhibit

EO or component	Microbial species	References
Clove oil	<i>E. coli</i> , <i>S. aureus</i> , <i>A. hydrophila</i> , <i>L. monocytogenes</i> , <i>Streptococcus thermophilus</i> , <i>Lactobacillus bulgaricus</i> , <i>S. typhimurium</i>	46,47
Eugenol	<i>L. monocytogenes</i> , <i>A. hydrophila</i> , <i>Microsporium gypseum</i>	48
Sage oil	<i>B. cereus</i> , <i>S. aureus</i> , <i>S. typhimurium</i>	47
Oregano oil	Natural flora, <i>Photobacterium phosphoreum</i> , <i>C. botulinum</i> , <i>L. monocytogenes</i> , <i>S. enteritidis</i> , <i>E. coli</i>	47
Coriander oil	<i>A. hydrophila</i> , <i>Salmonella choleraesuis</i> , <i>Streptococcus haemolyticus</i> , <i>Shigella sonnei</i> , <i>Shigella flexneri</i> , <i>E. coli</i> , <i>Salmonella choleraesuis</i> , <i>Corynebacterium diphtheria</i> , <i>Streptococcus haemolyticus</i> , <i>Staphylococcus aureus</i> , <i>Bacillus subtilis</i> , <i>Pseudomonas aeruginosa</i> , <i>Klebsiella</i> spp., <i>Proteus vulgaris</i>	47,49,50
Cinnamon oil	<i>Streptococcus thermophilus</i> , <i>Lactobacillus bulgaricus</i> , <i>E. coli</i>	47,51, 52
Thyme oil	<i>L. monocytogenes</i> , <i>Pseudomonas putida</i> , <i>E. coli</i>	47, 53
Cilantro oil	<i>L. monocytogenes</i>	47
Cinnamaldehyde	<i>Pseudomonas putida</i> , <i>Salmonella</i> spp.	52
Carvacrol	<i>B. cereus</i> , <i>S. typhimurium</i> , <i>E. coli</i> , <i>L. monocytogenes</i> , Natural flora	47
Citral	<i>S. typhimurium</i> , <i>L. monocytogenes</i> , <i>S. aureus</i> , <i>E. coli</i>	47
Geraniol	<i>S. typhimurium</i> , <i>E. coli</i> , <i>L. monocytogenes</i> ,	47
Thymol	<i>Salmonella</i> spp., <i>Shigella sonnei</i> , <i>S. typhimurium</i> , <i>B. cereus</i> , <i>L. monocytogenes</i> , <i>S. aureus</i>	47
Ginger essential oil	<i>Mycobacterium</i> spp.	7
<i>A. Douglasiana</i> leaf oil	<i>Bacillus cereus</i> , <i>S. aureus</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , <i>Candida albicans</i> , <i>Aspergillus niger</i>	8
Linalool	<i>Botrytis cinerea</i>	54

against which they are active are given in Table 2.

Antiviral activity

A study reported that AB1 blend (3.52 % of *Eucalyptus globules*, 3.52 % *Cinnamomum zeylanicum*, 3.00 % of *Rosmarinus officinalis*, 1.04 % of *Daucus carota*, and 88.90 % of *Camelina sativa* oils) was effective against H1N1 and HSV1 viruses.⁵⁵ Another researcher investigated the antiviral effect of 0.5 % of lemon EO, 0.1 % of orange, 0.1 % of grape fruit EOs and 0.05 % of rosemary cineole EO against *Hepatovirus A* (HAV); and reported that lemon, grapefruit, and rosemary cineole EOs significantly reduced the HAV titers on fruit surface.⁵⁶ In the same way another researcher investigated the *in vitro* antiviral activity of *Melaleuca alternifolia* essential oil (TTO) and its main components, terpinen-4-ol, α -terpinene, γ -terpinene, p-cymene, terpinolene and α -terpineol and reported that TTO has an antiviral activity against influenza A/PR/8 virus subtype H1N1.⁵⁷

Antioxidant activity

A study demonstrated the antioxidant activity of

essential oils of *Cananga odorata*, *Boswellia thurifera*, *Cymbopogon citratus*, *Marjorana hortensis*, *Ocimum basilicum*, *Rosmarinus officinalis*, *Cinnamomum zeylanicum* and *Citrus limon* in comparison with α -tocopherol and butylated hydroxytoluene.⁴⁰ There is a report on the free radical scavenging activity and antioxidant potential of EO and methanolic extract of *Zanthoxylum alatum* *in vitro* together with its scavenging ability versus DPPH, mitigating power and chelating capability on Fe^{2+} ions and found to have efficient activity.⁵⁸ Another study reported that *Thymus bovei* essential oil contains several volatile bioactive components, especially the oxygenated monoterpenoids, which showed strong antioxidant activity; so could potentially be used as natural preservatives in food and pharmaceutical industries.⁵⁹

Cytotoxic activity

A study concluded that the lavender (*Lavandula angustifolia*) oil which contain linalyl acetate and linalool as major constituent are cytotoxic to human skin cells *in vitro* (endothelial cells and fibroblasts) at a concentration of 0.25% (v/v) in all cell types tested (HMEC-1, HNDF and 153BR).⁶⁰ There is a report on

the cytotoxic effect of the essential oil from the dried leaves of *Lippia citriodora* against the P815 murine mastocytoma cell line using the MTT assay and found that the EO can induce apoptosis against P815 tumor cell line.⁶¹ An evaluation of the antitumor activity of essential oil of *Mentha crispa* found to be cytotoxic against U87 MG cells, with IC₅₀ values of 16.263.⁶² It has been reported that the essential oil of *Stachys koelzii* possess acceptable cytotoxic effects of against HeLa cell line, lower side effects on normal healthy cell lines.⁶³

Anti-inflammatory activity

There is a reported on the anti-inflammatory activity of *Cinnamomum zeylanicum* bark essential oil (CBEO) on several inflammatory biomarkers which include vascular cell adhesion molecule-1, intercellular cell adhesion molecule-1, monocyte chemoattractant protein-1, interferon gamma induced protein 10, interferon-inducible T-cell alpha chemoattractant, and monokine induced by gamma interferon. CBEO could also modulate global gene expression and can alter signalling pathways, many of which are important in inflammation, tissue remodeling, and cancer biology.⁶⁴ Another study investigated the anti-inflammatory properties of compounds found in the lavender essential oil (LEO) using two models of acute inflammation: carrageenan-induced pleurisy and croton oil-induced ear edema and the results found to be efficacious.⁶⁵

The chemical composition and anti-inflammatory activity of essential oil of *Jatropha curcas* has been studied and found that the oil contain 35.8 % of neophytadiene, 23.1 % of phytol, 12.7 % of *trans*-pinane, 12.3% of 6,10,14-trimethyl-2-pentadecanone and 11.2 % of citronellylpropanoate. The anti-inflammatory activity of oil was showed significant inhibition at a dose of 2%, v/v.⁶⁶ Similarly, another researcher investigated the anti-inflammatory, antimicrobial, antiviral, antioxidant properties of *Eugenia caryophyllata* essential oil and found to have significant effect on the increased production of several pro-inflammatory biomarkers like vascular cell adhesion molecule-1 (VCAM-1), interferon c-induced protein 10 (IP-10), interferon-inducible T-cell a chemoattractant (I-TAC), and monokine induced by c interferon (MIG). CEO also significantly inhibited tissue remodelling protein molecules, namely, collagen-I, collagen-III, macrophage colony-stimulating factor (M-CSF), and tissue inhibitor of metalloproteinase 2 (TIMP-2).⁶⁷

Antiparasitic activity

There is an investigation on the antiparasitic activity of the essential oil from the fruits of *Piper tuberculatum*, against lines of *Leishmania infantum* (MHOM/ES/92/BCN83), *Leishmania braziliensis*

(MHOM/CO/88/UA301) and *Trypanosoma cruzi* (LC-B5 clone) and reported that the essential oil possess good antiparasitic potential.⁶⁸ A researcher assessed the *in vivo* and *in vitro* antiparasitic activity of the essential oil of *Lippia sidoides* and blood and histological alterations in *Colossoma macropomum* (tambaqui) and found positive results.⁶⁹ It has been demonstrated that the antiparasitic activity of the essential oil obtained from *Phania matricarioides* against *T. cruzi*; and founded high safety of the EO when compared in mammalian cells based on the high selectivity index.⁷⁰

Anthelmintic activity

There is a report on the *in vitro* anthelmintic activity of essential oil from Brazilian red propolis (EOP) against larvae of *Toxocara cati* and 600 g/mL of the EOP showed larvicidal activity after exposure for 48 hr.⁷¹ Another study reported that the anthelmintic effects of the essential oil of *Foeniculum vulgare* showed moderate *in vitro* schistosomicidal activity against *Schistosoma mansoni*.⁷² Similarly, another researcher studied the *Thymus bovei* essential oil and revealed that the essential oil showed powerful anthelmintic effect even greater than the effect of the control drug piperazine citrate.⁵⁹

Insecticidal activity

The essential oil extracted from garlic and its constituents like diallyldisulfide, dimethyl trisulfide, diallyltetrasulfide, diallylsulfide, and 3-vinyl-[4H]-1,2-dithiin were found to be toxic to *Tenebrio molitor* Linnaeus larva, followed by pupa and adult.⁷³ It has been reported that the essential oil extracted from rhizome of *Cheilocostus speciosus* have insecticidal activity against the old-world bollworm, *Helicoverpa armigera*.⁷⁴ Another study demonstrated the insecticidal activity of essential oil, active constituents obtained from *Satureja hortensis* against *Acrobasis advenella*, and found to be useful.⁷⁵

Route of delivery of essential oils

External application

Inhalation

The absorption of essential oils in the bloodstream is intervened on two fronts via the skin respiratory system. Aromatherapy also referred to as "essential oil therapy" is a complimentary health approach that works by stimulating smell receptors in the nose and obtain an outcome in seconds. Owing to its preferential method, oil diffusion into the air takes place by utility of heat, utility of water

and atomization.⁷⁶ EOs have been broadly exploited in the treatment of ailments such as ameliorating cognitive efficiency, relieve pain, body relaxation and much more other psychological and physical conditions.⁷⁷ EOs from herbs possess antidepressant potential that can govern the brain function in many ways. Their fast-onset effect is based on the aromatic odor that can lightly activate the olfactory nerves. Due to their volatility in nature, they are considered convenient for nasal-brain targeted and inhalation delivery.⁷⁸

Mouthwashes

Several studies have shown that self-performed brushing alone is not efficacious for the withdrawal of plaque and demand improvement.⁷⁹ With this in mind, antimicrobial mouthrinses (containing essential oils, cetylpyridinium chloride, or chlorhexidine) in combination with brushing are employed and found to have better impact in the removal and disruption of the amassed plaque layers and effective against gingivitis.^{80,81} Several ingredients such as water, alcohol, buffering agents, surfactants and flavouring agents are used in the manufacturing of mouthrinses. Alcohol is often used as a preservative and solubilizer of EOs to maintain bioavailability. However, the use of alcohol have been limited due to some problems encountered as mentioned.⁸² In view of this, an alcohol-free EO mouth rinse (AFM) was developed and evaluated *in vitro* and *in vivo* and demonstrated its efficacy in reducing plaque and gingivitis in clinical trials.^{83,84}

Topical or transdermal

Topical or transdermal route of application is considered dependable for the delivery of EOs. These oils due to their volatility are able to infiltrate the skin, also, improve the infiltration of several drugs therefore topical formulation towards the lower skin layers thereby involves various mechanism of action: (i) conformational modification due to interaction with intercellular domain of protein, (ii) disintegrating the profoundly ordered intercellular lipid structure enclosed by corneocytes in stratum corneum, (iii) partitioning of the drug is enhanced.^{85,86} Even through physical techniques such as phase separation, fluidization, extraction and increased disorder, EOs can enhance the transmission of small drug compounds. Penetration of EOs through the skin membrane and then to the blood stream is problematic, they get readily eliminated with faces or urine from the body. Because of their better safety profile, the use of EOs has gained attention.^{86,87} 90% of EOs are delivered through dermal or transdermal route, which trait to non-invasive, patient's compliance and reduction of adverse effect.⁸⁸

Internal application

Oral

Generally, EOs are initially diluted with olive oil, milk and soya milk before they are orally administered. They are absorbed in the buccal mucosa at a rate of 3-9 times higher compared to the GI system absorption rate, also, having the capability of 4,000 times higher permeation rate. This makes the delivery of essential oils more efficient and reliable indicating that the ingested oils rapidly penetrate into the blood-stream after administration.⁸⁹ In a study on zedoary turmeric oil for oral delivery was prepared and reported improved aqueous stabilization, dispersity and oral bioavailability which has been carried out in rats.⁹⁰ A study was performed on *Croton cajucara* oil where the formulation was orally administered in rats and assessed. The author concluded that the essential oil exhibited low toxicity in mice and offered gastro-protective benefits.⁹¹

Problems in delivery of essential oils

The use of EOs in their free form reduces their effectiveness because they easily get volatilized and decomposed when exposed to oxygen, light, humidity, heat or irradiation.⁵³ Essential oils are unstable and possess poor water solubility. The components of EOs that belong to same chemical group are structurally similar which results easy inter conversion of the component, enzymatically or chemically triggering oxidation, isomerization, cyclization, or dehydrogenation reactions.⁹² These changes can occur during handling of the oil or during distillation, processing and storage of the plant material. Again some oil, like bergamot oil can cause photosensitization reaction and can even induce malignant change.

Sometimes aromatherapy can cause skin irritation, especially if the oils are concentrated. Even applying the concentrated oil topically, in excess amount to broken or on large surface of the skin can cause serious side effects as they undergo systemic absorption. Storing EO for long duration of time may result change in organoleptic characteristics along with change in viscosity and oxidation of terpenoids compounds results hypersensitivity reaction like allergic contact dermatitis.⁹²

Solutions suggested

An alternative to solve the problems related to stability, solubility, bioavailability of oil would be on their micro or nanoformulation, seeking protection against instability, decomposition and improves therapeutic efficacy. To preserve oil through encapsulation various colloidal systems can be used

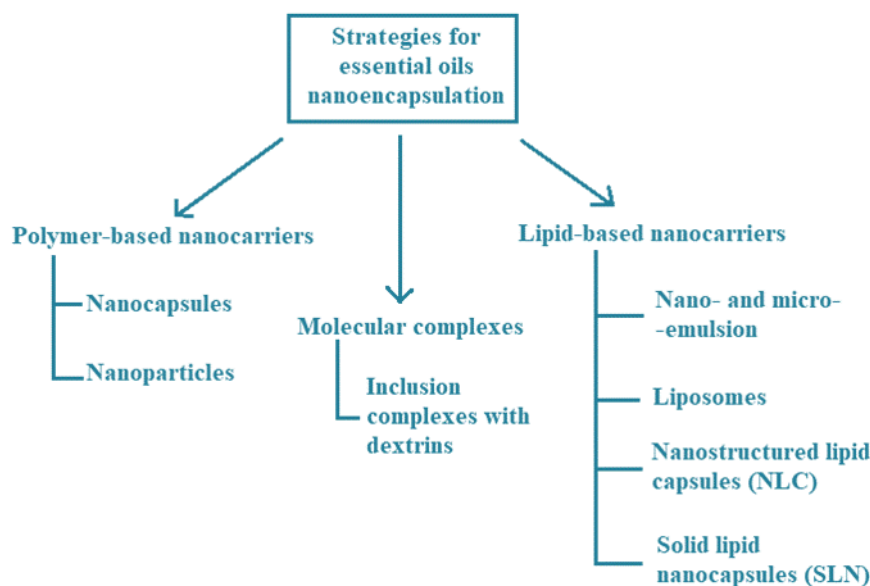


Figure 2 | Strategies involved in delivery of essential oils.

such as nanoemulsions, liposomes, microemulsion and microcapsules, etc. The proposed strategies to overcome the shortcoming of essential oils delivery are given in Figure 2.

Polymer-based nanocarriers

Nanocapsules

Nanocapsules are vesicular systems consist of nanoscale shell which is made from a nontoxic polymer and a space/core which can be aqueous or oily where the desired substance is confined. The active ingredient incorporated inside the core can be solid or liquid. If the active substance is lipophilic then it may get solubilised in the core cavity or may get adsorbed on the polymeric shell depending on its solubility.⁹³ Nanocapsules are submicroscopic colloidal drug carrier systems and its sizes range from 5 to 1000 nm, but usually the accepted range is in between 100-500 nm.⁹⁴ They can be prepared by various methods namely, nanoprecipitation, emulsion/solvent diffusion, double emulsification polymer coating, salting out, dialysis, solvent evaporation, interfacial polymerization, supercritical fluid technology. They provide good shielding environment to peptides, hormones, proteins, enzymes, drug, metabolites, or molecules against biological and chemical degradation; they can also delay the release of active ingredients and possess site specificity, therefore they attained great interest in drug delivery system.⁹⁴ The advantages of nanocapsules include, higher encapsulation efficiency, specific absorption mechanism across the GIT, sustained release, biocompatibility, biodegradability, membrane efflux transporter

inhibition, targeting potential and oral deliver ability.⁹⁵ Considering these advantages, these systems can actually provide a novel approach for delivering essential oil and overcoming its limitations.

The important ingredients used in nanocapsules formulation for delivery of oil are given in Table 3. There is a report on nanocapsules as a system for carrier of vitamin E, prepared by nanoprecipitation method for laboratory scale and pilot-scale. This method provided nanocapsules with mean diameter of 165 and 172 nm, respectively and with high entrapment efficiency i.e. of 98% and 97 % respectively.⁹⁶ It has been demonstrated that chitosan-alginate nanocapsules were developed for encapsulation of essential oil and found that the formulated nanocapsules were hemo-compatible and can be used in biomedical and pharmaceutical field.⁹⁷

Nanoparticles

Nanoparticles are sub-nanosized, solid, colloidal drug delivery systems with particle size ranges from 10 to <1000 nm,^{98,99} Nanoparticles can be developed into better systems by manipulating the size, surface characteristics and material employed, which improve therapeutic efficiency and stealth property. Again this system can deliver the drug in controlled manner and to the targeted site, which decrease the dose and dosing frequency thereby reduce toxicity and patient non-compliance.⁹⁹ Nanoparticles can break the damaged or inflamed tissue and this penetration can occur passively or actively. In passive targeting, no ligand is used and targeting is attained when nanoparticles when nanoparticles loaded drug

Table 3 | Components for formulation of nanocapsules

Component	Examples
Oils	Vegetable oil, mineral oil, etc.
Surfactant	Natural lecithins from plant or animal source, laryl sulphate, [poly (oxyethylene) poly (propylene) glycol]
Cosurfactant	Ethanol, glycerine, PEG300, PEG400, polyene glycol, poloxamer
Polymer	Polylactic acid, polyglycolic acid, polylactic-co-glycolic acid, hydroxypropylmethyl cellulose, chitosan

reaches the target through the leaky nature of the vessel. However, in active targeting, the carrier system is conjugated to a tissue or cell specific receptor using ligand. For efficient targeted drug delivery, various materials can be used that modify the physiochemical properties which increase their loading capacity, stability and intra cellular delivery.^{98,100}

Nanoparticles can also protect the essential oil from oxidation or evaporation, photo or thermal degradation which helps to extend the shelf life and therapeutic activity of the final product.¹⁰¹ These features can be considered for overcoming essential oils delivery. Ferreira *et al.* used chitosan nanoparticles for encapsulating the EO of *Siparuna guianensis* to prolong its mosquitocidal activity. This study indicates that chitosan nanoparticles are suitable system for preserving the properties of EO of *Siparuna guianensis* essential oil in an aqueous medium and protects it from degradation.¹⁰² In another study nanoparticles loaded with eucalyptus or rosemary essential oils were developed and evaluated their wound healing and antimicrobial property; and proved its efficacy and safety in *in vivo* rat model.¹⁰³

Molecular complexes

A molecular complex generally attribute to the physical union between a host and a guest molecule. In order to increase solubility and chemical stability of the active ingredient a simple strategy is to physically complex them with other molecule. For EOs the complexes are reported with cyclodextrins.¹⁰⁴

Inclusion complexes with dextrins

Cyclodextrins (CD) are a family of cyclic oligosaccharides, consisting of five or more glucopyranosyl units joined together by α -1,4-glycosidic bonds. They are also known as cycloamyloses, cyclomaltooses and Schardinger dextrins.¹⁰⁵ They consist of hydrophobic core and hydrophilic exterior, so hydrophobic drug can easily encapsulated into the core of cyclodextrins with non-covalent interaction which results in alter physical and chemical proportions and thus increase the

aqueous solubility and chemical stability of the guest molecule.¹⁰⁶ To prevent evaporation of the volatile compound, allylthiocyanate present in 'wasabi', a Japanese spice, an inclusion complex is made with cyclodextrin. In nanodelivery, cyclodextrins facilitate cellular uptake and thereby reduce toxicity. Due to their high stability and nontoxic nature they have attractive pharmaceutical applications and β forms of cyclodextrins are widely used as they improve oral bioavailability. Therefore their complexes with essential oils enhance the water solubility of the EOs; and the chemical modifications in both primary and secondary substituent further improve the solubility and biodegradability with reduced toxicity.¹⁰⁷

The advantages of CD include protection of the guest molecule against light, oxidation, thermal decomposition, evaporation or sublimation, GIT irritation, drug-drug interactions and elimination of undesired taste/odour, hygroscopicity.¹⁰⁸ These features of CD carrier system can overcome the limitations related to essential oil delivery. In a study, the physical and chemical condition of the β -cyclodextrins complexation reaction for several types of essential oils along with their release characteristic were investigated and found that encapsulation of EOs using β -cyclodextrin promote their therapeutic uses.¹⁰⁹ Encapsulation of the EO of clove in hydroxypropyl beta-cyclodextrin (CEO-HP β CD) inclusion complexes in 1:1 molecular ratio using Kneading method was performed in an experiment. The study revealed that this system increased the total phenolic content of free EO as well as total phenolic content of particles and also prolongs the shelf life of the encapsulated EO.¹¹⁰

Lipid-based nanocarriers

Nano- and microemulsions

Nanoemulsions (NE) and microemulsions (ME) are transparent, monophasic, optically isotropic colloidal dispersions consists of two immiscible phases, oil and aqueous phase, along with surfactant and co-surfactant. The difference between NE and ME are that in case of NE the colloidal dispersion is kinetically stable with droplet sizes less than 100nm while in ME the colloidal dispersion is thermodynamically stable with droplet sizes in the

Table 4 | Comparison between nanoemulsions and microemulsions

Properties/Parameters	Nanoemulsions	Microemulsions
Physical description	Colloidal dispersion	Colloidal dispersion
Particle size	<100 nm	10- 00 nm
Polydispersity	Low	Low
Thermodynamic stability	Unstable	Stable
Kinetic stability	Stable	Unstable
Preparation	Low/high energy	Low energy
Composition: surfactant to oil ratio	Moderate	Low
Loading capacity	High	Moderate
Physical appearance	Transparent	Transparent

range 10-100 nm.¹¹¹ The similarities and dissimilarities between NE and ME are summarized in Table 4.

Among NE and ME, NE are found to be more efficient for delivery of essential so, it is described further.

NE can be prepared using two preparation methods, viz. low-energy and high-energy emulsification method. The high energy emulsification method includes high-pressure homogenization, ultrasonication and membrane emulsification. The low energy emulsification method includes microfluidization, emulsion inversion point, phase transition and phase-inversion temperature method. The advantages of NE include increased rate of absorption of drug, increased drug loading, enhanced bioavailability, controlled/sustained release of drug and targeted drug delivery.

Both lipophilic and lipophobic drugs can be formulated in NE but encapsulating lipophilic drug are found to be more effective, as in this system the droplet size of the lipophilic molecule get decrease thereby enhances their solubility, stability and subsequently the biological activity. This system is nontoxic, non-irritant because the components used in this system are generally regarded as safe and

exclude the requirement of harmful co-solvents, so, they can be used for both parenteral and non-parenteral route. NE can also protect the drugs from oxidation and hydrolysis process. It can be formulated in variety of formulation such as foams, liquids, sprays and creams. Their long-term stability, ease of preparation (spontaneous emulsification), high encapsulation efficiency, high bioavailability, protection from enzymatic degradation and high solubilisation of drug molecules makes them promising as a drug delivery tool for essential oil.¹¹² The ingredients required for formulation of nanoemulsions are given in Table 5.^{113,114}

There is a report where nanoemulsions were formulated containing oil of *Cinnamomum zeylanicum* with droplet diameter of 65 nm using Tween 80 and water by ultrasonic emulsification for 30min which demonstrated bactericidal activity against food-borne pathogen *Bacillus cereus*. The study illustrated that emulsification time, oil-surfactant mixing ratio and surfactant concentration had significant effect on nanoemulsion droplet diameter and its stability.¹¹⁵ Another researcher discussed nanosystems with utility in skin delivery and focuses on the composition and characterization of microemulsion and nanoemulsion for topical and

Table 5 | Components of nanoemulsions.

Component	Examples
Oils	Castor oil, corn oil, coconut oil, evening primrose oil, linseed oil, mineral oil, olive oil. etc
Emulgent	Natural lecithins from plant or animal source, phospholipids, castor oil
Surfactant	Polysorbate20, Polysorbate80, Polyoxy60, castor oil, Sorbitanmonooleate
Cosurfactant	Ethanol, glycerine, PEG300, PEG400, Polyene glycol, Poloxamer
Tonicity modifiers	Glycerol, sorbitol, and xylitol
Additives	Propylene glycol, lower alcohol (ethanol), propylene glycol, 1, 3-butylenes glycol, sugars such as butylene glycol, sugars such as glucose, sucrose, fructose, and maltose
Antioxidants	Ascorbic acid and tocopherol

transdermal delivery.¹¹⁶ Similarly, another researcher prepared *Plai* (*Zingiber cassumunar* Roxb.) nanoemulsions under oil-in-water emulsion system by high pressure homogenization and obtained that an optimal surfactant component in formulation for fabricate Plainanoemulsion with the small droplet size and had impact in long lasting stability.¹¹⁷

Liposomes

Liposomes are considered among the finest colloidal drug delivery systems which have are developed for delivering drug to a specific site in the body as early as 1970.¹¹⁸ Liposomes are enclosed spherical vesicles, organized in one or several concentric phospholipidic bilayers with an internal aqueous phase and their diameter ranges from 80 nm to 100 μ m. They are suitable templates for drug delivery as they provide promising drug carriers due to their capability of cutaneous targeting and slow release of the drug.¹¹⁹ They are also suitable for encapsulating natural compounds like essential oil, which improve its solubility and chemical stability.¹²⁰ They prevent the encapsulated bioactive compounds from degradation and increase the solubility of lipophilic compounds. The advantages of liposomal encapsulation includes improvement of therapeutic activity and safety, local delivery of medicament at the site of action, controlled and sustained drug delivery, increased bioavailability as their surface can be modified to alter their biodistribution and pharmacokinetics.¹²¹ Liposomes can encapsulated with hydrophilic, hydrophobic and amphiphilic substances. The structural components of liposomes are phospholipids and cholesterol. Phospholipids can be natural and synthetic and the most commonly used phospholipid is known as lecithin; it is amphipathic. Cholesterol increases the stability of the lipid vesicles by modulating the fluidity of the lipid bilayer.¹²²

An investigation on the effects of core-wall ratio on the stability and antibacterial activity during storage of the encapsulated cinnamaldehyde by liposomes was performed and found that liposome-encapsulated cinnamaldehyde might still inhibit

bacteria by destroying cell membrane integrity after storage and the persistence was more efficient than that of pure cinnamaldehyde. Therefore, liposomes could improve the stability and long-term antibacterial activity of cinnamaldehyde.¹²³ There is a report where nanovesicles were developed by loading essential oils of *Salvia triloba* and *Rosmarinus officinalis*. Liposomes loaded with 100 μ L/mL of EO, were optimised for their size, polydispersity index, ζ -potential, recovery, encapsulation efficiency (EE %), release property and morphology. The prepared liposomes were stable over one month period if stored at 4°C and possessed significant antioxidant, anti-inflammatory and antibacterial activities. The findings suggest that these formulations can decrease the volatility of EOs, optimise their biological properties and defeat antimicrobial infections.¹²⁴ It has been established that phospholipid vesicle from natural soybean would increase the durability of clove essential oil and eugenol which is its main constituent. The study was performed and discovered that liposomes manifested spherical shaped and nanometre coligolamellar vesicles thereby preventing eugenol from deterioration influenced by UV exposure and also conserved the DPPH-scavenging activity of free eugenol and serve as an apt system for encapsulating the components of unstable volatile essential oil.¹²⁵

Nanostructured lipid capsules

In 1990, nanostructured lipid capsules (NLC) were first introduced as a carrier systems.¹²⁶ They are colloidal drug delivery systems consisting of a fluid lipid phase enclosed into a solid lipid matrix or confined at the surface of solid matrix and the surfactant layer. In these systems both hydrophilic and lipophilic drug can be used.¹²⁷ The structural arrangement of the lipids provides higher drug loading capacity. The spatial structure of the lipids allows greater drug loading and better stability compared to SLN. These carrier systems can improve the stability as well as bioavailability of the active compounds and they are known to possess excellent

Table 6 | Components used for formulation of NLC

Component	Examples
Liquid lipids	Lauroglycol® FCC, Capryol® 90, medium chain triglycerides, paraffin oil, 2-octyl dodecanol, Miglyol® 812, Transcutol® HP, LabrafilLipofile® WL 1349, Labrafac® PG
Hydrophilic emulsifiers	Polyvinyl alcohol, Solutol® HS15, polyglycerol methyl glucose distearate Pluronic® F68 (poloxamer 188), Pluronic® F127, Tween 20, Tween 40, Tween 80
Lipophilic emulsifiers	Span 40, Span 60, Myverol® 18-04K, Span 20
Amphiphilic emulsifiers	Phosphatidylcholines, phosphatidylethanolamines, Gelucire® 50/13, egg lecithin, soya lecithin

biocompatibility.^{128,129} NLC are easier to scale-up, sterilize, validate and approval from regulatory bodies accessible, they also provide controlled and targeted delivery of active constituent.¹³⁰ The ingredients used in this system are mentioned in Table 6.

Solid lipid nanocapsules

Solid lipid nanoparticles (SLNs) is nano-dispersion and prepared using lipids that are solid at body or room temperature. The lipid component may contain different varieties of lipid and lipid-like molecules, viz. triacylglycerols or waxes.¹³¹ SLN can increase the permeation of the active compounds as well enhance the contact time which hydrates the skin forming an occlusive barrier, so, these systems mainly used to load hydrophobic compounds like vitamin A, E and coenzyme Q that increase its stability and reduces its degradation by light and oxygen. The size of these systems varies from 50 nm to 1 µm and the active compounds get solubilised easily inside the core part or outside it.¹³² The advantages of these carrier system includes protection against chemical and physical degradation, sustained/controlled release, improve stability, immobilisation of the active compound and suitable for delivery of lipophilic substances.¹³³ Hence, it serves the purpose of overcoming the problems of EOs delivery.

Conclusion

Essential oils possesses important volatile compounds with diverse bioactivities including antimicrobial, antispasmodic, antioxidant, antiviral, anti-inflammatory, anthelmintic, insecticidal, antiparasitic, cytotoxic activity. However, the free form of the EO is prone to physical and chemical decomposition along with poor water solubility, low stability, bioavailability that limits their uses in medicines. Therefore, when EOs are delivered in the form of nano-encapsulation provides promising strategies to overcome the shortcoming of EOs. They will enhance various physiochemical and physiological properties of the EOs and thereby lower their dose, improve safety and therapeutic activity.

Conflict of interest

The authors do not have any conflict of interest.

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