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# Nature’s nano–shield: plant–based essential oil nano–emulsions as potent defenders against microbial invaders and skin wounds

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Review

# Nature's nano-shield: plant-based essential oil nano-emulsions as potent defenders against microbial invaders and skin wounds

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## ABSTRACT

As the demand for safer and more natural skincare solutions grows, the fusion of ancient botanical wisdom with cutting-edge nanotechnology is unlocking unprecedented potential in skin therapeutics. Plant-based essential oils, long revered for their healing properties, have transcended traditional uses in massage and beauty treatments to emerge as powerful bioactive agents against microbial infections and skin disorders. However, their volatile nature and limited stability have posed significant challenges until now. This review explores the innovative field of essential oil nano-emulsions, in which natural substances are encapsulated within nanoscale systems to amplify their efficacy, stability, and skin penetration. Through in-depth investigation and comprehensive presentation, the presence of monoterpenoids that contribute to both the aroma and biological activities of essential oils is documented. The subsequent analysis introduces advanced methods used to create nano-emulsions containing essential oils, the pivotal role of surfactants, and the exceptional antimicrobial, anti-inflammatory, and wound-healing properties exhibited by these nano-emulsions. This is the first review that comprehensively presents essential oil nano-emulsions as a promising approach to address the imminent risks of skin infections and chronic wounds, thereby offering a bold new frontier in combating complex skin disorders. The future of skincare is unfolding, and it promises to be both natural and revolutionary.

## 1. Introduction

A vast array of natural medications and therapeutic agents can be found in the fascinating field of plants and botany. Herbal essential oils are nature-based products derived from numerous plant parts, including leaves, roots, flowers, fruits, peel, buds, wood, and seeds [1, 2]. The use of essential oils dates back to the Pharaonic era (3000 BCE), when ancient Egyptians utilised various essential oils for perfumes, body treatment, and mummification [3, 4]. The most common reason for using essential oils was their pleasant and elegant fragrance, which works as an aromatherapy approach to control stress and depression and to improve mental health [5–8]. Nowadays, essential oils are widely incorporated into the ingredients of numerous gel, cream, lotion, and ointment products in the global cosmetic industry for softening, nourishing, and moisturising human skin and hair [9–11]. Plant-based essential oils were reported to have antiseptic, antibacterial, and anti-inflammatory properties that are beneficial for burn care, wound healing, and acne treatment [10, 12–14]. Furthermore, essential oils are commonly used in food industry for food preservation, food colouring [15], and food packaging [16], as well as in some medical fields like pain relief [17, 18] and bone repair [19].

Human skin, which consists of three individual layers of adipose tissue, dermis, and epidermis, serves as a physical barrier between the human body and the external environment and comes into contact with microorganism colonies. The human body acts as a host, supplying nourishment through sebum, sweat mineral salts, and cell debris to internal microbes (collectively referred to as the microbiome), which is shaped by genes, skin microenvironment, and external environment; in turn, this microbiome helps to train the human immune system and prevent pathogen invasion [20, 21]. Most skin issues are caused by microbiome imbalance and dysbiosis, which leads to colonisation and dominance of external microbes on human skin, for instance, acne caused by *Propionibacterium acnes* (*P. acnes*) [22], tissue damage by *Cutibacterium acne* (*C. acne*) [23], and chronic wounds by *Staphylococcus aureus* (*S. aureus*) [24]. Nano-sized antimicrobial materials have been developed for skin treatment, for instance, metallic (Au and Ag) and metal oxide (ZnO, CuO, and MgO) nanoparticles with inherent antimicrobial properties [25, 26]. Polymeric nanocomposites using polymers like poly (hydroxyl ethyl methacrylate) (pHEMA), poly(methyl methacrylate) (PMMA), polycaprolactone (PCL), and poly(lactic-co-glycolic acid) (PLGA) have been used as drug carriers to deliver the antimicrobial metal/metal oxide nanoparticles and bioactive agents [27–31]. However, the penetration of metals and metal oxides into human skin leads

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to a range of side effects including allergies, oxidative stress, cell apoptosis, and DNA damage [32, 33]. More seriously, human skin may suffer a variety of acute wounds by incidents, as well as chronic wound including ulcers [34], surgery wounds [35], burns [36], and bacterial-infected wounds [37]. Several antibiotics have been utilised in skin treatment against bacterial infections, for instance, oxacillin, cefazolin, clindamycin, ceftaroline, daptomycin, and contezolid [38, 39]. Nevertheless, some antibiotics can cause substantial adverse effects on human health, such as allergic reactions, vomiting, diarrhoea, unpleasant mouth taste, abnormal urine colours, and even encephalopathy [40, 41]. Therefore, the use of nature-based substances for skin treatment, which have fewer negative impacts on human health, is a major concern. A number of natural materials have been employed to address skin problems, for example, polysaccharides such as chitosan, alginate, and hyaluronic acid for wound healing; probiotics for atopic dermatitis treatment [42]; bioactive compounds like curcumin for inflammation control, lutein for skin aging reduce, and quercetin for skin cancer treatment [43].

Currently, herbal essential oils are extensively utilised in skin therapeutic products. Both essential oils and their individual components function as active pharmacological agents and offer a wide range of biological and cosmeceutical actions [9, 44]. However, essential oils contain organic components that are volatile and unstable upon exposure to light, moisture, air, and heat [45, 46]. Some constituents of essential oils are also capable of producing odoriferous and potentially toxic derivatives [47]. Furthermore, the limited ability of essential oils to dissolve in water hinders their application in therapeutic settings [48]. To address the as-mentioned issues, nano-encapsulation is regarded as a valuable method for containing and delivering essential oils. A number of nanoscale delivery systems for essential oils have been developed based on polymeric materials [49, 50], liposomes [51], metal nanoparticles [52, 53], and nano-emulsions [54]. Among these nanocarriers, nano-emulsions possess the capacity to ameliorate the stability and physico-chemical characteristics of essential oils by rendering them aqueous dispersibility, decreasing their volatility, and preventing their interaction with the environment or other substances [55, 56]. In addition, nano-emulsion technology facilitates the control of the discharge of active compounds found in essential oils onto specific substrates [57]. It also enables a profound infiltration of essential oils into microorganisms at the cellular level due to its minuscule droplet size [58]. The present review is the first thorough investigation of nano-emulsion systems loaded with plant-derived essential oils as skin therapeutics. It begins with a summary of the monoterpenoids that predominate in essential oils. The review also sheds light on various low- and high-energy techniques used to produce essential oil nano-emulsions. Owing to their antimicrobial, anti-inflammatory, and wound-healing activities, essential oil nano-emulsions have the potential to be used as skin treatment materials in cases of microbial infections and wounds. This review places particular emphasis on these uses.

## 2. Monoterpenoids as predominant essential oil components

Herbal essential oils can be obtained from different parts of plants, including roots, rhizomes, flowers, leaves, fruits, peel, and seeds. Essential oils represent the most extensive category of organic compounds in nature, comprising approximately 30 000 identified structures [59]. Each type of essential oil comprises up to 100 constituents that are by-products of plant metabolism, mostly low-molecular-weight compounds with poor water dispersibility. These constituents are predominantly terpenes in the form of sesquiterpenes ($C_{15}H_{24}$) and monoterpenes ($C_{10}H_{16}$) and low concentrations of phenols, ketones, esters, acids, oxides, alcohols, and aldehydes [60, 61].

Considering the typical essential oil plants, those belonging to the Rutaceae family are known for having a significant amount of limonene (32%–98%) in their essential oils [62, 63]. Noticeable amounts of the zingiberene-based compounds were detected in the essential oils of ginger (*Zingiber officinale* Roscoe, Zingiberaceae family). A concentration of 23.9% α-zingiberene was found in the essential oil extracted from fresh ginger rhizomes in Brazil. In comparison, the concentration of α-zingiberene in the essential oils from fresh ginger rhizomes in China, India, and West Africa was up to 40% [64]. Menthone, a monoterpene known for its minty aroma, is an abundant constituent with a concentration of approximately 21.8% in the essential oils of peppermint (*Mentha piperita* L.) from the Lamiaceae family [13, 65]. Other terpenoid compounds such as α-pinene, β-pinene, myrcene, linalool, neral, geraniol, and sabinene are frequently found in the essential oils derived from the leaves, fruits, and seeds of plants belonging to the Poaceae, Myrtaceae, and Apiaceae families.

It is evident that many of the main terpenes found in herbal essential oils fall within the category of monoterpenoids. Structurally, monoterpenes are composed of two isoprene units in acyclic, monocyclic, and bicyclic forms, which are observed in their oxy-functionalised states. The physicochemical and biological properties of these substances are largely determined by the monoterpene structures. Furthermore, their fragrance properties are greatly influenced by the presence of heteroatoms (namely oxygen), double bonds, and chiral centres. These factors in turn influence the spatial arrangement and interaction of these compounds with olfactory receptors [66]. Fig. 1 displays the structural formulae of common monoterpenes that are mostly found in essential oils generated from plants.

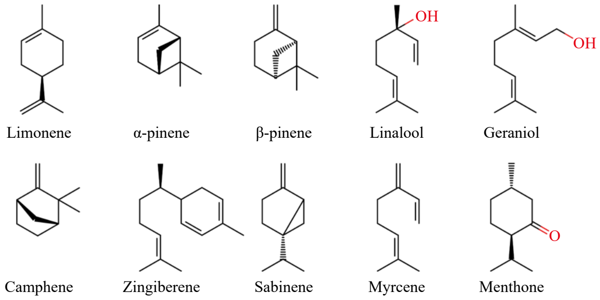

**Fig. 1** Structural formulae of some typical monoterpenes present in plant-based essential oils.

Table 1 provides a concise overview of the botanical origins, primary constituents, and potential effects of several widely used essential oils.

The majority of essential oil molecules are highly volatile and susceptible to degradation. Furthermore, the fact that they are hydrophobic and have poor solubility in aqueous media poses a significant challenge to their widespread use in the skincare field. Emerging materials are suitable delivery systems to broaden their application range and enhance their stability across the entire process of manufacturing, transportation, storage, and consumption. The delivery system also has a crucial function in minimising the likelihood of essential oil molecules reacting unfavourably with other components of skincare products. The use of nano-emulsions as a method of delivering essential oils for cosmeceutical applications is discussed in the following sections.

## 3. Preparation of essential oil nano-emulsions

Emulsions are lyophobic colloids composed of two immiscible liquids, generally water and oil. One of the two liquids is uniformly distributed within the other, forming globules. Water-in-oil (W/O) emulsions occur when an oily substance forms the continuous phase and water is dispersed within it. In contrast, oil-

**Table 1** Botanical sources, main terpenoid components, and activities of some typical herbal essential oils.

| Family | Common name | Botanical name | Plant sections | Main components | Ref. |
|---|---|---|---|---|---|
| Rutaceae | Lemon | *Citrus limon* L. | Fruit peel | Limonene, α-pinene, β-pinene, neral, linalool, terpinene, geraniol | 67–68 |
| | | | Leaves | Limonene, α-pinene, terpinene, sesquiterpene, erucamide, oxygenated compounds | 69 |
| | Lime | *Citrus aurantifolia* L. | Leaves | Limonene, α-pinene, β-pinene, β-ocimene, β-thujene, linalool, isoterpinolene, geraniol, citronellal | 70 |
| | | | Fruit peel | Limonene, camphene, sabinene, myrcene, α-phellandrene, citronellal | 71 |
| | Sweet orange | *Citrus sinensis* L. | Fruit peel | Limonene, α-pinene, β-pinene, linalool, β-myrcene | 72–73 |
| | Bitter orange | *Citrus aurantium* L. | Flowers | Limonene, β-pinene, camphene, α-farnesene, linalool | 74–75 |
| | Grapefruit | *Citrus paradisi* L. | Fruit peel | Limonene, α-pinene, β-pinene, camphene, α-copaene, linalool, neral, geraniol, γ-terpinene | 76 |
| | Mandarin | *Citrus reticulata* L. | Fruit peel | Limonene, α-pinene, β-pinene, β-myrcene, γ-terpinene, β-thujene | 77 |
| | Bergamot | *Citrus medica* L. var. sarcodactylis (Noot.) Swingle | Fruits | Limonene, α-pinene, α-myrcene, γ-terpinene, sabinene, linalool, α-bergamotene, terpinolene | 78 |
| Zingiberaceae | Ginger | *Zingiber officinale* Roscoe | Rhizomes | α-zingiberene, α-pinene, β-pinene, myrcene, geraniol, neral, citronellal, camphene, camphor | 79-81 |
| | Cardamom | *Elettaria cardamomum* L. | Seeds | α-terpineol, α-pinene, β-pinene, geraniol, photocitral A, sabinene, limonene, myrcene, neral | 82 |
| Lamiaceae | Thyme | *Thymus vulgaris* L. | Leaves | Thymol, linalool, carvacrol, γ-terpinene | 83 |
| | Lavender | *Lavandula angustifolia* Mill. | Flowers | α-pinene, β-pinene, camphene, sabinene, limonene, δ-terpinene, β-myrcene, borneol | 84 |
| | Rosemary | *Rosmarinus officinalis* L. | Leaves | 1,8-cineole, α-pinene, camphor, borneol, *ρ*-cymene-7-ol | 85–86 |
| | Peppermint | *Mentha piperita* L. | Leaves | Piperitenone oxide, menthone, isomenthone, 1,8-cineole, limonene, β-pinene, sabinene, γ-terpinene | 13, 65 |
| | Spearmint | *Mentha spicata* L. | Leaves | Carvone, 1,8-cineole, β-myrcene, γ-terpinene, sabinene, limonene | 65, 87 |
| | Sweet marjoram | *Origanum majorana* L. | Leaves | α-pinene, β-pinene, camphene, sabinene, limonene, linalool, carvone, γ-terpinene | 88 |
| | Patchouli | *Pogostemon cablin* L. | Flowers | Caryophyllene, fenchone, patchoulene | 89 |
| | | | Leaves | Caryophyllene, limonene, fenchone, patchoulene | |
| | Basil | *Ocimum basilicum* L. | Leaves | Menthone, camphor, linalool, 1,8-cineole, myrcene, camphene, sabinene, α-pinene, β-pinene | 90–91 |
| Poaceae | Lemongrass | *Cymbopogon citratus* | Leaves | Citronellal, citral, neral, isoneral, limonene, geraniol, linalool, | 92–93 |
| | Ginger grass | *Cymbopogon martinii* | Leaves, roots | Geraniol, neral, linalool, myrcene, trans-β-ocimene | 94-96 |
| | Citronella | *Cymbopogon nardus* | Leaves, stems | Citronellal, neral, geraniol, squalene, | 97 |
| Myrataceae | Tea tree | *Melaleuca alternifolia* | Leaves | 1,8-cineole, sabinene, limonene, α-pinene, α-terpinene, γ-terpinene | 98 |
| | Cajeput | *Melaleuca cajuputi* Powell. | Leaves | α-pinene, limonene, camphene, fenchone, 1,8-cineole | 99 |
| | Clove | *Syzygium aromaticum* L. | Buds | Eugenol, α-pinene, 2-pinene, valencene, α-copaene, α-humulene | 100 |
| Laurenceae | Cinnamon | *Cinnamomum verum* | Bark | α-copaene, cinnamaldehyde dimethyl acetal, cinnamic aldehyde | 101 |
| | Camphor | *Cinnamomum camphora* | Leaves | Camphene, α-pinene, β-pinene, sabinene, linalool, 1,8-cineole, α-thujene | 102 |
| | Litsea | *Litsea cubeba* Pers. | Fruits | α-pinene, camphene, limonene, myrcene, geraniol, linalool, isomenthone | 103 |
| Apiaceae | Coriander | *Coriandrum sativum* L. | Fruits | Linalool, cymene, β-myrcene, limonene, camphor, α-pinene | 104 |
| | Carrot | *Daucus carota* L. | Seeds | Carotol, α-thujene, α-pinene, β-pinene, elemicin, camphene, sabinene, γ-terpinene, limonene | 105–106 |
| | Cumin | *Cuminum cyminum* L. | Seeds | Limonene, α-pinene, β-pinene, α-terpinene, β-myrcene, α-phellandrene, *ρ*-cymene | 107 |
| Asteraceae | Roman chamomile | Chamaemelum nobile L. | Flowers | Carvone, α-pinene, β-pinene, α-thujene, camphene, myrcene | 108–109 |
| | German chamomile | *Matricaria chamomilla* L. | | | |
| | Helichrysum | *Helichrysum italicum* Roth. | Flowers | α-*cis*-bergamotene, limonene, α-pinene, nerol, α-copaene | 110 |

in-water (O/W) emulsions are characterised by the dispersion of lipid/oil molecules as the dispersed phase, while an aqueous medium serves as the continuous phase [111]. To enhance the thermodynamic stability and dispersion of two immiscible liquids, an emulsifier or surfactant is used. Emulsifiers are surface-active substances containing non-polar and polar groups. Their role is to act as a bridge between the oil and water phases, reducing the tension at the interface and preventing coalescence of emulsion droplets [112]. Nano-emulsions are a category of emulsion with droplet sizes of their dispersed phases ranging from 10 to 100 nm. Despite the large number of droplets, these droplets remain transparent or translucent to the human eye and are resistant to creaming and sedimentation. Nano-emulsions, like conventional emulsions, comprise an aqueous phase, an oil phase, and a surfactant. Typically, water is used as the aqueous phase, whereas the oily phase can include essential oils, waxes, mineral oils, and other lipophilic substances. The emulsifiers used for coating droplets in O/W nano-emulsions are hydrophilic in nature, while those used in W/O nano-emulsions are hydrophobic or lipophilic [113, 114]. This review focuses on OW nano-emulsions that utilise plant-derived essential oils as the dispersed phase.

### 3.1. Surfactants

Surfactants, or surface-active agents, are amphipathic compounds that consist of one hydrophobic tail and one hydrophilic part. This specific molecular structure allows them to remain at the interface between two immiscible liquids in essential oil-loaded nano-emulsions. In this configuration, their polar groups engage with the water phase, while their non-polar portions interact with the oily phase. During the fabrication of nano-emulsions, it is crucial for surfactants to rapidly adsorb onto the droplet surface and to ensure that the droplets remain stable even in the event of collisions. The polar groups play a crucial role in determining whether the surfactants belong to the non-ionic or ionic category, specifically cationic or anionic [56].

#### 3.1.1. Non-ionic surfactants

Non-ionic surfactants have been extensively used owing to their low toxicity and rapid adsorption onto droplet surfaces to create nano-sized droplets. These surfactants possess one hydrophobic tail and one hydrophilic head containing polar groups, such as carboxyl (–COOH), hydroxyl (–OH), and amino (–$NH_2$) groups, but lack electrically charged groups, rendering them non-ionised in aqueous systems. Sorbitan esters, produced by the esterification of sorbitol (a sugar alcohol) with fatty acids, are regarded as the predominant non-ionic surfactants [115]. For instance, in the case of preparing nano-emulsion containing spearmint essential oil, the addition of Tween 20 (polyoxyethylene (20) sorbitan monolaurate) containing lauric acid helped decrease the size of the droplets, while Tween 80 (polyoxyethylene sorbitan monooleate) containing oleic acid effectively prevented the droplets from merging together [116]. A nano-emulsion containing essential oil from the cotton-lavender (*Santolina chamaecyparissus* L.) was created in the presence of a mixture of Span 20 (sorbitan monolaurate) (0.44%) and Tween 80 (11.25%), resulting in droplets with a minimum size of 15.98 nm. This nano-emulsion remained stable at temperatures ranging from 4 to 45 °C, with no notable change in globule size after storage at 4 °C for 3 months [117]. In addition, some polymeric surfactants are used in essential oil nano-emulsion formulation. Brij-35 (polyoxyethylene 23 lauryl ether) functioned as a surfactant during the preparation of nano-emulsions containing clove and cinnamon essential oils, maintaining droplet sizes below 15 nm [118]. Brij-97 (polyoxyethylene 10 oleyl ether) was combined with Span 85 (sorbitan trioleate) in a nano-emulsion containing citral essential oil, in which its polyoxyethylene chains, together with one sorbitan ring, formed a hydrophilic region, while the fatty acid of Span 85 served as a hydrophobic head [119]. The successful formation of nano-emulsions was attributed to the capacity of these surface-active agents to reduce water–oil interfacial tension, improve droplet dispersion, and generate a protective barrier that enhanced the stability of the nano-emulsion droplets and minimised aggregation [115].

#### 3.1.2. Ionic surfactants

Ionic surfactants are used in nano-emulsion formulation by virtue of their net charge, which can be either positive or negative. Upon adsorption at the water–oil interface, these surfactants generate a charged barrier around the droplets, causing them to repel similarly charged ones, thereby preventing coalescence and aggregation [56]. Cationic surfactants, characterised by a positive charge in their polar groups, stabilise nano-emulsions by creating a positively charged surface on the droplets, thereby promoting electrostatic repulsion [120]. For example, lauric arginate (LAE) not only served as a co-surfactant to stabilise a thyme essential oil nano-emulsion through its positively charged arginine moiety, but also helped enhance the antifungal activity of the nano-emulsion through its interaction with the negatively charged components of fungal cells [121]. On the other hand, anionic surfactants possess a negatively charged polar head with groups like carboxylate, sulphonate, and sulphate [120]. Incorporation of sodium dodecyl sulphate into the formulation of a nano-emulsion containing thyme essential oil resulted in a droplet size of around 6.5 nm and a polydispersity index (PDI) of 0.219, both of which were lower than those measured in the nano-emulsion prepared with Tween 80. This outcome demonstrated the efficacy of an ionic surfactant in regulating the size and homogeneous distribution of nano-sized droplets [122]. The co-action of this anionic surfactant also enhanced the storage stability of essential oil nano-emulsions up to 50 days, owing to its ability to sustain the zeta potential and surface charge of the droplets [56, 123]. However, the potential for environmental contamination and human irritation associated with ionic surfactants necessitates their careful use and precise quantification [124, 125].

#### 3.1.3. Bio-surfactants

To mitigate the adverse effects of synthetic surfactants, a few natural substances were employed to stabilise essential oil nano-emulsions. Polysaccharides obtained from plants such as cashew gum [126], cellulose [127], pectin [128], as well as those derived from animals like chitosan [129], have demonstrated their capacity to bind oil and water through their hydrophilic and non-polar groups. They stabilise nano-emulsions by means of steric effect and electrostatic repulsion, preventing droplet coalescence. Protein-based emulsifiers like whey protein [130], soybean protein [131], and fish gelatine [132] possess both lipophilic and hydrophilic groups, allowing them to form a strong and cohesive film around nano-emulsion droplets. These proteins have large molecular sizes, which make their adsorption onto the droplet surface a time-consuming process. Nevertheless, once adsorbed, they establish a viscoelastic layer that prevents droplet aggregation and improves stability under variable conditions.

Fig. 2 exhibits a schematic illustration of surfactant structure and their role in connecting two immiscible liquid phases to establish a nano-emulsion.

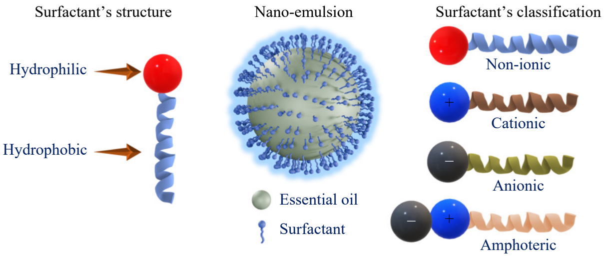

**Fig. 2** Diagrammatic presentation of surfactant structure, connection of two immiscible liquids by a surfactant, and surfactant classifications.

### 3.2. Preparation methods

Oil–water nano-emulsions are non-equilibrium systems that cannot be spontaneously established without the assistance of an adequate external energy input. This energy source can be supplied by high-energy approaches using mechanical equipment in large-scale manufacturing, which disrupt the water and oil phases and lead to the generation of minuscule oil droplets. On the other hand, low-energy techniques are primarily based on internal energy arising from the variation of nano-emulsion constituents and environmental conditions [133]. The selection of nano-emulsion production methods essentially depends on the characteristics of the oily phase, the surfactant/emulsifier, and the predicted functional performance of the final product. Fig. 3 depicts a diagrammatic description of typical approaches for the preparation of nano-emulsions containing essential oils that are discussed in this review.

### 3.2.1. High-energy approaches

High-energy procedures necessitate a substantial quantity of external energy supplied *via* machinery. Currently, high-pressure homogenisation is widely considered the predominant technique for producing nano-emulsions. This technology involves a continuous procedure that applies pressure ranging from 50 to 400 MPa to force fluids through a micrometre-scale channel. The homogeniser induces significant mechanical forces such as cavitation, shear, and turbulence, ultimately reducing the size of essential oil droplets dispersed in the aqueous phase [134]. A recent study created a nano-emulsion containing Chinese pepper essential oil by employing a high-pressure homogeniser in the presence of capric triglyceride and Tween 80 as co-emulsifiers. The experimental results indicated that the droplet size of this pepper essential oil nano-emulsion increased slightly from 125.07 nm to 134.53 nm after 31 days of storage at low temperature. This finding highlighted the benefit of using a homogeniser to achieve a uniform distribution of nano-scale droplets [135].

Another high-energy method, which harnesses high-frequency ultrasound waves typically ranging from 20 to 40 kHz, is used to either create a nano-emulsion directly or reduce the droplet size of a pre-prepared one. Ultrasonication involves cavitation to generate disturbance at the interface between the oil and aqueous phases. In particular, microbubble collapse creates an implosion that produces highly powerful waves with pressures of up to 100 MPa, which propagate throughout the material. These waves disrupt the interface between the aqueous and oily phases, leading to a reduction in droplet size [134]. In a study by Lee and coworkers, an ultrasonicated oregano essential oil nano-emulsion had a droplet size of 221.3 nm and a PDI of 0.251, whereas the non-sonicated emulsion had a larger droplet size of 1420.47 nm and a higher PDI of 0.709 [136]. Nano-emulsions of essential oils derived from artemisia (*Artemisia vulgaris*), lavender, and peppermint, which underwent ultrasonication, exhibited notable stability, whereas the non-sonicated samples experienced phase separation between the oil and water components within 24 h after preparation [137]. Song et al. [138] investigated the impact of ultrasonication settings on the characteristics of the nano-emulsion. The droplet size of a eucalyptus essential oil nano-emulsion decreased when the sonication amplitude increased and the sonication distance decreased, while the time was kept constant. However, the droplet size was larger when the sonication distance was long and the sonication time was short, while the amplitude was maintained constant.

Micro-fluidisation is another technique that uses high levels of energy to create nano-emulsions. A micro-fluidiser operates similarly to a homogeniser in terms of shear force. However, a high-pressure pump propels the fluids through an inline homogeniser to generate a coarse emulsion. The emulsion then travels to an interaction chamber via micro-channels and undergoes homogenisation under pressures reaching up to 270 MPa. The emulsion experiences an impingement process, culminating in a significant reduction of droplet size to the nano-scale [139].

### 3.2.2. Low-energy approaches

Low-energy methods require minimal or no external energy from machinery to fabricate nano-emulsions. Instead, the necessary energy is derived from internal activities of the emulsion components. The establishment of nano-emulsion systems using low-energy approaches relies on the ability of surfactants to induce phase transition processes. Specifically, an O/W system can be transformed into a W/O one and vice versa. This results in the release of chemical energy, which ultimately leads to the generation of well-dispersed droplets in the continuous phase [140].

Phase inversion temperature (PIT) refers to the temperature at which the inversion procedure is regulated by the interaction forces between the surfactants and fluids. Surfactants, particularly those responsive to temperature variation, exhibit greater affinity for water and possess a positive spontaneous curvature when exposed to low temperatures. At the PIT point, the hydrophilic–lipophilic balance of the surfactant is reached, resulting in equivalent solubility in either oil or water, while its curvature approaches zero and creates a bicontinuous emulsion. However, raising the temperature above the PIT threshold affects its head groups, diminishing hydrophilicity, generating a negative spontaneous curvature, and thus forming a W/O system [141]. Non-ionic surfactants, such as the Tween series, exhibit their lipophilicity at heating degrees because of dehydration of their polar parts, and show their hydrophilicity at lower temperatures [139]. As the temperature is progressively returned to the PIT, followed by an instantaneous ice-cooling step, the surfactant is rehydrated, its hydrophilicity is restored, and it swiftly interacts with the aqueous phase, thereby establishing the O/W emulsion [141]. However, a disadvantage of this method for producing essential oil nano-emulsions is that the heating process may cause degradation of volatile compounds, potentially affecting the desired properties of the final emulsion product [142].

Another low-energy procedure can be carried out without the use of a heating system. The phase inversion composition (PIC) technique is implemented at ambient temperature with magnetic stirring equipment. To obtain an O/W nano-emulsion by this method, a W/O system is first created by adding water dropwise to the organic phase, which is a mixture of oil and surfactants. As the concentration of the aqueous phase is gradually increased, the initial W/O system is converted into an O/W emulsion at a precise inversion point [141, 143]. In contrast to the PIC method, the spontaneous approach is implemented using a hydrophilic surfactant, which involves adding the organic phase containing oil and surfactants dropwise into the aqueous phase. When the two phases of the emulsion interact, the surfactant switches to the water phase, generating a turbulent force at the water–oil interface and expanding this interfacial area. All of this results in the formation of oil droplets in water via the budding process [141]. One drawback of these methods is that the introduc-

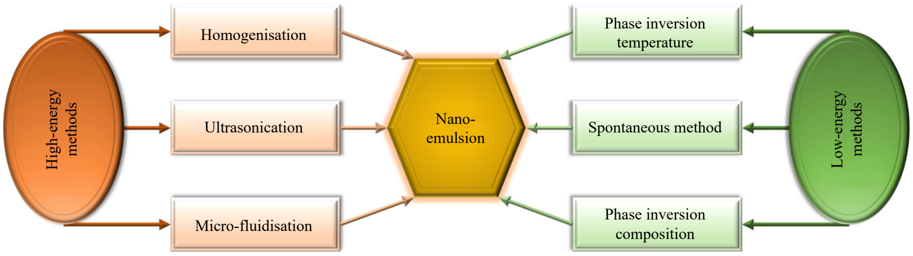

**Fig. 3** Diagrammatic representation of primary high-energy and low-energy methods for preparing nano-emulsions.

tion of the aqueous phase into the organic mixture or vice versa must be carried out in a very slow and gradual manner, making it a time-consuming procedure.

Fig.4 exhibits the proposed mechanisms of nano-emulsion formulations *via* high-energy and low-energy approaches.

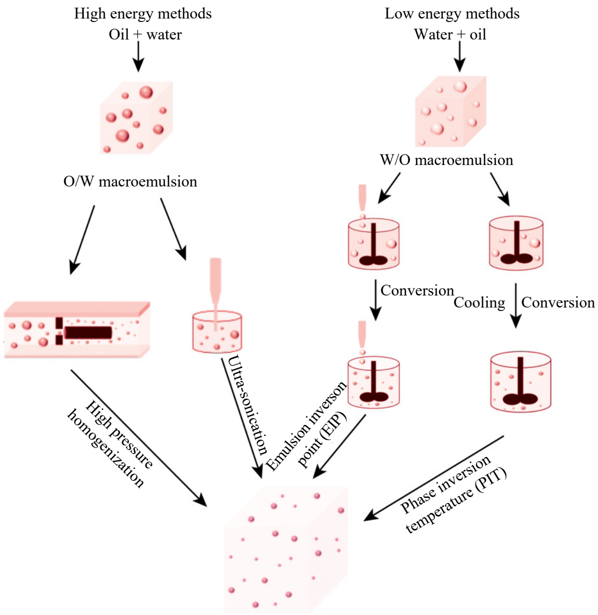

**Fig. 4** Mechanism of nano-emulsion formation by high-energy and low-energy methods.

Table 2 summaries recent investigations on the fabrication of essential oil nano-emulsions utilising various high-energy and low-energy approaches.

## 4. Essential oil nano-emulsions as skin therapeutics

Every year, treating various forms of acute and chronic wounds requires a substantial financial and technological commitment [166, 167]. Open wounds that are not adequately treated within a proper medical system may result in severe pain, microbial infection, chronic illness, and even death. Furthermore, prolonged exposure to high moisture levels delays damaged tissue regeneration, cell proliferation, and matrix formation [168, 169]. Wound care involves several obstacles, including intricate injury features, delayed treatment, a shortage of appropriate dressing materials, and the possibility of drug resistance and medication allergies in patients [170]. Therefore, producing nature-based skin therapeutics is a noteworthy and necessary strategy for reducing the need for antibiotics and analgesics in wound treatment. It has been found that using essential oils derived from plants, which possess remarkable antimicrobial, anti-inflammatory, and antioxidant properties, is a viable alternative to conventional medicines. However, the volatile nature of essential oil constituents means that they should only be used for brief periods. Furthermore, their limited solubility in aqueous media hinders their capacity to interact with biological fluids and restricts their bioavailability in transdermal application. Considering the drawbacks of essential oils, nanocarriers have been extensively researched for effective delivery of these natural substances. Essential oils in nano-emulsion formulations are proven to release in a controlled manner and are improved in terms of stability and biological performance. This section discusses the mechanisms of action of essential oils on microbes, free radicals, and inflammation, as well as the use of essential oils in nano-emulsion form in combating bacterial infections and wounds.

### 4.1. Mechanisms of biological activities of essential oils

#### 4.1.1. Antimicrobial mechanism

Plant-derived essential oils have been scientifically proven to possess diverse biological properties. The primary reason for the antibacterial efficacy of herbal essential oils is the effects of their components on various types of bacteria. The hydrophobic molecules present in essential oils can act on the lipids of cytoplasmic membranes, causing damage to the cell membranes and an increase in membrane permeability [171]. An illustrative instance of this mechanism can be observed when rose essential oil (10 mg·mL$^{-1}$) caused a notable discharge of lactate dehydrogenase (LDH) from *Pseudomonas putida* (*P. putida*) cells into external culture substance. This release occurs because of severe disruption of the bacterial cell membrane, leading to a remarkably high LDH activity of around 5.5 U·mL$^{-1}$, in contrast to the untreated cell which exhibited only about 1.8 U·mL$^{-1}$ [172]. The excessive permeability of bacterial cell membranes leads to the leakage of proteins [173], DNA [174, 175], and electrolytes such as K$^+$ and Mg$^{2+}$ [176, 177]. The loss of these intracellular contents results in the destabilisation of bacterial cell frameworks and disruption of membrane transport, ultimately culminating in nutrient deprivation and cell death. Constituents of essential oils may also disrupt the electron transport system and proton gradients (H$^+$) as well as the depletion of adenosine triphosphate (ATP), which is the primary chemical energy source for the cellular functions like DNA replication, protein synthesis, and cell signalling (Fig. 5) [134, 178].

The mechanism of the antifungal action of essential oils has been found to be closely related to their antibacterial effects. The hydrophobic compounds present in essential oils may interact with ergosterols in fungal cell membranes, suppressing their biosynthesis and resulting in changes to membrane permeability [179–181]. The action of some monoterpenes such as citral and eugenol upon *Penicillium roqueforti* (*P. roqueforti*) caused noticeable leakage of K$^+$, Mg$^{2+}$, and Ca$^{2+}$ ions. This suggests that essential oils containing these components have the potential to disturb the metabolism of fungus by destroying their cellular electrolytes [182]. Carvacrol, isolated from oregano essential oil, has been discovered to induce DNA damage in *A. flavus*, evidenced by the increased intensity of DAPI stain blue fluorescence observed in the fungal mycelia treated with carvacrol, as compared to faint fluorescence exhibited in the control group [183]. The expression of ERG4, ERG25, ERG6, FDFT1, and SMT1 genes, which play a crucial role in the steroid biosynthesis of *P. roqueforti*, was considerably suppressed by *Angelica sinensis* essential oil. This demonstrated that essential oil possesses the capacity to interfere with fungal cell membranes and cellular operations because steroids are the primary constituents of membranes and join several cellular activities like cell detoxification, nutrient transportation, and response to hosts and environmental pressure [184]. *Perilla frutescens* essential oil generated a decrease in ATP content in *A. flavus* by 19.6% and 39.1% at the MIC and 2MIC doses, individually, compared to the control group. This indicated that essential oil could demolish the key energy source of the fungus's metabolism [185]. Fig. 6 depicts the antifungal mechanism of essential oils.

Various essential oils have been documented to exhibit antiviral activity. Generally, the entry of viruses into host cells results in genetic material replication and the formation of fresh viral particles for release. Essential oils are unable to prevent the entry of viruses by obstructing the receptors on host cells. Instead, essential oils disrupt the function of virions at every stage of their infection lifecycle by altering the structure of the virus envelope or generating a mask on viral proteins, which are crucial for viruses to enter host cells [186]. For instance, the PR8 strain of the H1N1 virus showed partially and fully damaged viral envelopes when exposed to vaporised bergamot and tea tree essential

**Table 2** Recent works on essential oil nano-emulsions preparation by high and low energy methods.

| Energy level | Essential oil source | Surfactants | Methods | Optimised droplet size | Stability | Ref. |
|---|---|---|---|---|---|---|
| High energy | Sichuan pepper (*Zanthoxylum bungeanum* Maxim) | Tween 80, capric triglyceride | High-pressure homogenisation | 125.07 | Droplet size was 134.53 nm after 31 days of storage at 4 and 25 °C | 135 |
| | Ginger (*Zingiber officinale*) | Tween 20, Arabic gum | High-pressure homogenisation | 68 | 8% and 15% increase in turbidity after 2 and 3 weeks of storage at 25 °C, individually | 144 |
| | Citronella (*Cymbopogon nardus*) | Tween 60, Span 60 | High-pressure homogenisation | 79 | Droplet size was 58 and 140 nm after 28 days of storage 4 and 25 °C, individually | 145 |
| | Clove (Syzygium aromaticum) | Tween 80 | High-pressure homogenisation | 100 | Droplet size was up to 180 nm after 30 days of storage at room temperature | 146 |
| | Thyme (*Thymus* spp.) | Hexadecylpyridinium chloride monohydrate | High-pressure homogenisation | 12.61 | Droplet size was 937.4 nm after 15 days of storage due to coalescence phenomenon | 147 |
| | Rosemary (*Rosmarinus officinalis* L.) | Span 20, Tween 40 | High-speed homogenisation | 52.58 | Droplet size was 87.32 nm after thermal stress and 65 h of storage | 148 |
| | Cinnamon (*Cinnamomum cassia* L.) | Tween 80 | High-pressure homogenisation | 221.8 | No significant change in droplet size after 30 days of storage at 4 °C | 149 |
| | Litsea (*Litsea cubeba* Pers.) | Whey protein | Ultrasonication | Under 200 | Good stability under storage at low temperature (4 °C) | 150 |
| | Oregano (*Origanum vulgare*) | Tween 80 | Ultrasonication | 41.67 | Good stability after 30 days of storage at 4 °C (droplet size under 150 nm) | 151 |
| | Aromatic ginger (*Kaempferia galanga* L.) | Saponin | Ultrasonication | 71.68 | Good stability after 14 days of accelerated storage | 152 |
| | Cinnamon (*Cinnamomum* spp.) | Lauroyl arginate | High-pressure micro-fluidisation | 86.84 | Average growth rate of around 5 nm each 5-day interval in 20 days | 153 |
| | *Eucommia ulmoides* seed | Tween 80, ethanol | Dynamic high-pressure fluidisation | 179.9 | Droplet size was higher than 180−230 nm after 25 days of storage at 4, 25, and 60 °C | 154 |
| Low energy | Lemon balm (*Melissa officinalis* L.) | Tween 80 | Emulsion phase inversion | 183.8 | Good stability after 3 months of storage at 4 and 20 °C | 155 |
| | *Ocotea indecora* leaves | Sorbitan monooleate 20, polysorbate 80 | Emulsion phase inversion | 122.8 | Moderate stable after 1 year of storage at 8 and 25 °C, but a colour change and droplet size increase at 40 °C | 156 |
| | Black pepper (*Piper nigrum* L.) | Tween 20, Tween 40, Tween 60, Tween 80 | Emulsion phase inversion | 19.13 (frozen nano-emulsion) | No change in droplet size after 5 weeks of storage (droplet size: 19.60 nm) | 157 |
| | Lemongrass (*Cymbopogon densiflorus*) | Span 80, PEG 40 | Emulsion phase inversion | 65.9 | No change in droplet size after 28 days of storage | 158 |
| | Rosemary (*Rosmarinus officinalis* L.) | Polysorbate 20 | Catastrophic phase inversion | 50.15 | Droplet size was 184.0 nm after 30 days of storage at around 20 °C | 159 |
| | Cajeput (*Melaleuca quinquenervia*) | Tween 80 | Phase inversion temperature | 20.5 | Good stability after 120 days of storage at 15 °C | 160 |
| | Black pepper (*Piper nigrum* L.) | Tween 80 | Phase inversion temperature | 9.7 | Good stability after 1 month of storage at room temperature | 161 |
| | Cinnamon (*Cinnamomum* spp.) | Tween 80 | Phase inversion temperature | 100.70 | Cinnamaldehyde degradation observed after 31 days of storage | 142 |
| | Peppermint (*Mentha piperita*) | Tween 20, Tween 40, Tween 80 | Spontaneous method | Under 50 | Increase in transparency and decrease in droplet size after 90 days of storage | 162 |
| | Key lime (*Citrus aurantifolia*) | Tween 80 | Spontaneous method | 21 | No aggregation observed after 1 month of storage under low light at 25 °C | 163 |
| | Cumin (*Cuminum cyminum* L.) | Tween 20, Tween 80 | Spontaneous method | 121 | No physical change observed after 6 months of storage at 4 and 26 °C | 164 |
| | Ajwain (*Carum copticum*) | Tween 80 | Spontaneous method | 88.38 | Slight increase after 30 days of storage: droplet size was 122.5 and 91.8 nm after storage at refrigerator (4 °C) and ambient (20 °C) temperatures, respectively | 164 |
| | Mint (*Mentha longifolia*) | Tween 80 | Spontaneous method | 60.51 | Controlled release of essential oil nano-emulsion decreased the decay microbial growth of treated strawberry during 15 days of storage at 4 °C | 165 |

oils, respectively [187]. Another study investigated the effects of Chinese maqian (*Zanthoxylum* spp.) essential oil and its isolated D-limonene component on the actions of H1N1 virions in MDCK cells. The results showed a significant decrease in both the propagation of the virus and the establishment of their NS1 protein [188]. Furanodienone and curzerene components found in myrrh (*Commiphora* spp.) essential oil were claimed to decrease the relative fluorescence intensity (RFI) of hemagglutinin (HA) protein of IVA-PR8 strains to about 40% and 70%, respectively, 24 h after viral infection in MDCK cells, compared to the 100% fluorescence observed in the control [189]. Thyme essential oil, at a concentration of 27 $\mu g \cdot mL^{-1}$, reduced the viral titres of feline coronavirus (FCoV) in Crandell Reese Feline Kidney (CRFK) cell to nearly 2.25 $\log_{10}$ $TCID_{50}$/50 μL. In comparison, the control cell had higher viral titres of around 4.25 $\log_{10}$ $TCID_{50}$/50 μL [190]. It is plausible to infer that the hydrophobic molecules present in essential oils are able to interact with the lipid bilayer of viruses. This interaction affects the viral envelopes, causing leakage of cellular proteins and a decrease in viral activity [191].

### 4.1.2. Antioxidant mechanism

During ordinary metabolic processes, cells possibly create reactive oxygen species (ROS), including hydroxyl ion (OH·), singlet oxygen ($^1O_2$), hydrogen peroxide ($H_2O_2$), and superoxide ion ($O_2^-$), which may lead to the degradation of enzymes, DNA, lipids, and proteins [192]. Consequently, there is a growing need for to prevent the occurrence of lipid peroxidation and the resulting harm caused by these free radicals. A few synthetic antioxidants have been utilized, for instance, butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA) and t-butyl hydroquinone (tBHQ) in food, food packages, and cosmetics [193]. However, BHT is known to cause irritation to the skin and eyes, whilst BHA is alleged to be a suspected carcinogen [194, 195]. Therefore, there has been a substantial rise in the demand for natural antioxidants such as herbal essential oils.

The primary mechanism by which essential oils exhibit anti-

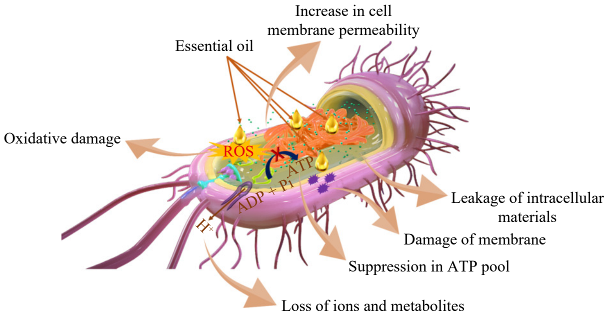

**Fig. 5** Schematic illustration of antibacterial effects of essential oils: The lipophilic essential oil constituents interact with bacterial cytoplasmic membrane lipids; increase the membrane permeability, leading to the leakage of intra-cellular materials like DNA, electrolytes, and proteins; suppress the ATP energy source, which disrupts various cellular functions (ATP: adenosine triphosphate; ROS: reactive oxygen species; ADP: adenosine diphosphate; Pi: inorganic phosphate).

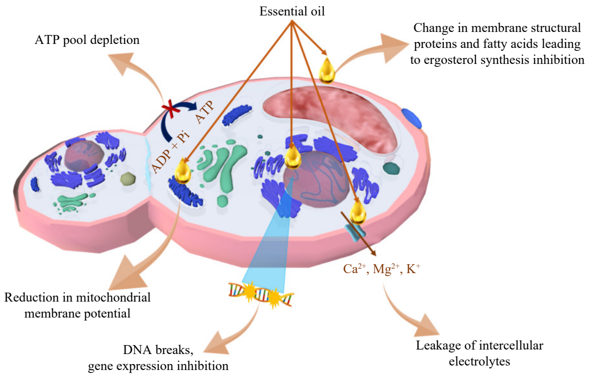

**Fig. 6** Schematic illustration of antifungal effects of essential oils: the lipophilic essential oil molecules interact with fungal membrane components (mostly ergosterols); alter the membrane permeability, cause the leakage of DNA materials and cellular ions; disrupt the gene expression; suppress the ATP energy source that disrupts various cellular activities (ATP: adenosine triphosphate; ROS: reactive oxygen species; ADP: adenosine diphosphate; Pi: inorganic phosphate; DNA: deoxyribonucleic acid).

oxidant behaviour is through their ability to scavenge free radicals [196]. For instance, the antioxidant performance of limonene-containing essential oils from four *Citrus* spp. plants, including grapefruit, sweet orange, bergamot, and lemon, were investigated by measuring their free radical scavenging with 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS). At a concentration of 144 mg·mL$^{-1}$, these essential oils exhibited DPPH scavenging percentages of approximately 10%, 30%, 60%, and 80%, respectively, while their ABTS scavenging percentages were higher than 80% at a concentration of 64 mg·mL$^{-1}$ [73]. A study conducted on essential oils from Indonesian gingers (*Zingiber* spp.) showed that the α-zingiberene component has a more potent antioxidant behaviour compared with ascorbic acid. An examination of the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of this compound revealed that the HOMO is distributed throughout the cyclic carbon chain region, which contains double bonds. Therefore, the ability of this molecule to scavenge radicals is mostly attributed to this cyclic carbon chain region [197]. Lemon balm essential oil was found to possess antioxidant properties owing to the function of its carvacrol component. Molecular docking indicated that carvacrol formed hydrogen bonds with ALA1079 and GLU802 residues, as well as hydrophobic interactions with amino acids of xanthine oxidoreductase, resulting in xanthine oxidoreductase inhibition and reduced ROS production [198]. The antioxidant activity of pineapple mint (*Mentha suaveolens*), toothpick weed (*Ammi visnaga*), and Spanish lavender (*Lavandula stoechas*) essential oils was evaluated by testing their ability to reduce ferric ion (Fe$^{3+}$) to ferrous (Fe$^{2+}$). The results showed remarkable antioxidant activity, with IC$_{50}$ values of 144.38 μg·mL$^{-1}$, 348.28 μg·mL$^{-1}$, and 192.27 μg·mL$^{-1}$ for pineapple mint, toothpick weed, and lavender essential oils, respectively [199].

### 4.1.3. Anti-inflammatory mechanism

Essential oils demonstrate the ability to prevent the onset and spread of inflammatory processes, making them an ideal approach for treating wounds. Essential oils primarily diminish the protein expression of pro-inflammatory cytokines and enhance the regulation of protein expression of anti-inflammatory cytokines, which is the most common effect they have on inflammation [200]. The *Amomum tsaoko* Crevost et Lemarie essential oil (20 μg·mL$^{-1}$) significantly reduced the levels of the IL-6, IL-1β, and TNF-α pro-inflammatory cytokines from 70.05, 258.07, and 481.44 pg·mL$^{-1}$ to 28.65, 93.55, and 163.25 pg·mL$^{-1}$, respectively, resulting in a considerable decrease in the MCP-1 pro-inflammatory chemokine level in stimulated cells. This effect was possibly attributed to the NF-κB signalling pathway [201]. Peppermint essential oil, in contrast, boosted the regulation of IL-10 anti-inflammatory cytokines, while its menthol component hindered the differentiation of Th1 cells [13]. The excessive expression of inducible nitric oxide synthase (iNOS), which is the dominant enzyme in nitric oxide production, can lead to severe inflammation. Essential oils have the ability to lower the level of intracellular iNOS, which helps attenuate inflammation generated by free radicals [202, 203]. In addition, essential oil molecules can inhibit inflammatory mediators, such as cyclooxygenase 2 (COX-2), substance P, kinins, and myeloperoxidase. This function helps lower vascular permeability and regulate excessive fluid retention in tissues, thereby alleviating oedema [204]. Fig. 7 provides a schematic representation of the proposed anti-inflammatory pathway of plant-derived essential oils.

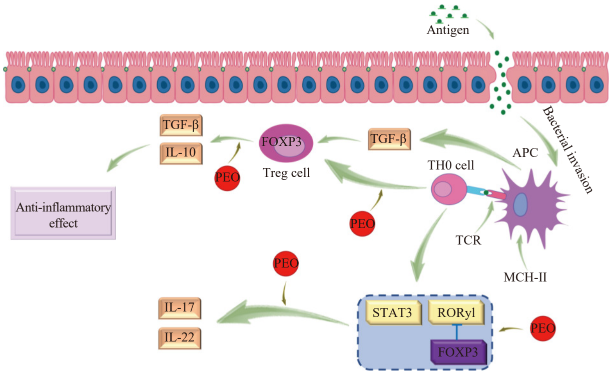

**Fig. 7** Schematic representation of anti-inflammatory effects of essential oils by suppressing pro-inflammatory cytokines and boosting the activity of anti-inflammatory cytokines and growth factors in skin tissues (PEO: plant essential oils; TGF-β: transforming growth factor beta; MHC-II: major histocompatibility complex class II; TCR: T-cell receptor; IL: interleukin; STAT3: signal transducer and activator of transcription 3; RORγt retinoic acid-related orphan receptor gamma t; FOXP3: Forkhead box protein P3; TDDS: transdermal drug delivery systems).

### 4.1.4. Tissue repair mechanism

To heal a wound, many processes rely on growth factors, which alter the wound microenvironment and promote cell differentiation, proliferation, and migration. As a growth factor that contributes to the inflammatory response, platelet-derived growth factor (PDGF) is responsible for coordinating the migration and proliferation of diverse immune cells to the wound area. In addition, the upregulation of fibroblast growth factor (FGF) in response to injury plays a crucial role in the establishment of granulation tissue, re-epithelialisation, and tissue remodelling [205]. Transforming growth factor beta (TGF-β) exerts pleiotropic actions throughout wound healing. Specifically, TGF-β1 and TGF-β2 facilitate fibroblast development and the generation of extracellular matrix, while TGF-β3 specifically inhibits scar formation [206, 207]. Essential oils have been found to potentially influence the expression levels of these growth factors when used in wound care. For instance, the administration of Salvia officinalis essential oil to a wound infected with bacteria resulted in an increase in both FGF and vascular endothelial growth factor (VEGF). This led to improved healing by boosting the spread of fibroblasts and the occurrence of angiogenesis [208].

### *4.2. Applications of essential oil nano-emulsions as skin therapeutics*

#### *4.2.1. Antimicrobial application*

Essential oil nano-emulsions have been reported to be more effective in inhibiting bacterial colonies compared with essential oils in their initial form, because the nano-sized droplets with a large surface area of the emulsions enhance the transport of essential oil molecules to microbial cell membranes and promote their strong interaction with numerous membrane molecular sites [153, 209]. Therefore, the antimicrobial effects of nano-emulsions containing essential oils have been investigated against several types of microorganisms that may cause skin issues. The antibacterial activity of a nano-emulsion containing clove essential oil was demonstrated by its ability to inhibit approximately 50% of S. aureus biofilm at a concentration of 0.5 × MIC. In addition, confocal laser scanning microscopy (CLSM) analysis revealed that the untreated *S. aureus* biofilm exhibited significant cell adhesion, while the bacterial biofilm treated with nano-emulsion showed a notable phenomenon of cell death [210]. A nano-emulsion containing linalool was found to disrupt the morphological structure of *Aeromonas hydrophila* (*A. hydrophila*); the bacterial cells appeared flattened and the boundaries between them became indistinct, reflecting the destruction of bacterial cell membranes and the loss of intracellular substances [211].

It is worth mentioning that nano-emulsions containing essential oils have been found to be an ideal approach for treating acne. Nano-emulsions of jojoba and jasmine essential oils, with the inclusion of tazarotene, exhibited excellent antibacterial activity against *P. acnes*, with MIC values of 0.78 and 3.12 μL, respectively. Due to their nano-sized droplets, both nano-emulsions enhanced drug penetration in the deeper layers of the skin, resulting in a substantial amounts of drug deposition in the dermis (around 35 and 70 μg, respectively). Furthermore, essential oils could modify the composition of lipids in the outermost layer of the skin, leading to the generation of pores that facilitate the penetration of drug into the skin [212, 213]. An additional benefit of incorporating an essential oil into the nano-emulsion formulation for acne treatment is its potential to mitigate the adverse effects of chemical acne medications, such as skin redness, dryness, erythema, and irritation [214].

When an *Ocotea indecora* essential oil nano-emulsion was present at a concentration of 2048 μg·mL$^{-1}$, it demonstrated the , whereas the essential oil alone did not exhibit any fungicidal action [215]. In another study, nano-fibres made from polycaprolactone and peppermint essential oil nano-emulsion exhibited outstanding antifungal performance by causing substantial protein leakage of around 150 and 250 μg·mL$^{-1}$ in *A. niger* and *C. albicans*, respectively, after 24 h of exposure. An elevated concentration of these nano-fibres (200 μg·mL$^{-1}$) effectively suppressed almost of 90% of the biofilm produced by these two strains of fungus [216].

#### *4.2.2. Anti-inflammatory application*

The suppression of inflammation is a crucial biological function of skin therapeutics. Several studies have reported the anti-inflammatory properties of essential oil nano-emulsions in relation to their potential for treating skin-related issues. An *in vivo* study was conducted using thyme essential oil to control inflammation cause by *C. acnes*. The thickness of the mice's ears was assessed at 24, 48, and 72 h following treatment. The results showed that the nano-emulsion of this essential oil was comparable to clindamycin in its ability to normalise skin thickness and decrease the inflammatory cells in the dermal layer [217]. An oregano essential oil nano-emulsion was found to be more effective than 2% erythromycin in suppressing the inflammation generated by *P. acnes* in mice. The nano-emulsion significantly decreased the mice's ear thickness and exhibited a notable inflammation inhibition rate of over 60%, whereas therapy with erythromycin only achieved an inhibition rate of approximately 20% [218]. A nano-emulsion of *Eugenia supra-axillaris* essential oil (100 mg·kg$^{-1}$) showed its ability to alleviate inflammation in the paws of rats. After 24 h of application, a notable inhibition rate of 53.6% was observed, which was only slightly lower than the rate reached with celecoxib (55.4%), but substantially higher than that obtained with diclofenac (38%) [219].

#### *4.2.3. Wound-healing application*

Wound healing is an essential aspect of skin treatment, particularly for open wounds, as these may cause severe issues such as persistent pain, swelling, and infection. Various nano-emulsion formulations containing essential oils have been shown to be effective in promoting wound healing. This is principally based on their antimicrobial activity in preventing the onset of external microbial invasion and inflammation. These formulations also have the capacity to stimulate tissue remodelling, granulation tissue formation, and wound contraction [220]. Furthermore, nano-emulsions accelerate wound healing processes such as re-epithelialisation, which require less time than essential oils in their initial form owing to the more efficient penetration of nano-droplets into the epidermal layers [221].

Nano-emulsions containing 2% of *Deverra tortuosa* (Desf.) DC and *Deverra. triradiata* Hochst. ex Bioss essential oils achieved proper wound closure in rats after 16 days of treatment, with impressive wound contraction rates of up to 98% and 95%, respectively [222]. A curcumin-infused essential oil nano-emulsion (Cur-NE) was shown to outperform unencapsulated clove oil and curcumin in terms of wound closure in albino rats over a 24-day period, with an outstanding wound contraction rate of nearly 95%. Histopathological investigation revealed that treatment with the nano-emulsion resulted in a small number of inflammatory mononuclear cells and evident generation of granulation tissue [223]. In another investigation, after undergoing a 16-day therapy, the wound infected by *S. aureus* was effectively cured using a hydrogel loading eucalyptus essential oil nano-emulsion (CBM/CMC/EEO NE). The healing rate was approximately 90%, a substantial improvement compared with the less favourable recovery observed in the control group. The group treated with the essential oil nano-emulsion exhibited smooth dermal cells, as well as the recovery of sweat glands and hair follicles [224]. The utilisation of scaffolds incorporating *Zataria multiflora* essential oil nano-emulsion effectively facilitated the healing of injuries in Wistar rats within 21 days, resulting in evident emergence of skin appendages. The group treated with this nano-emulsion had minimal oedema and a high rate of re-epithelialisation, close to 90%, whereas the control group had an oedema level of around 7.5% and a re-epithelialisation rate of 55% [225]. A hydrogel comprising an oregano essential oil nano-emulsion was used to treat diabetic ulcers with the support of low-level laser therapy. After 14 days, the treated group had a wound area of only 2.5%, whereas the control group and the group that underwent treatment with only low-level laser had notably larger wound areas of 24.3% and 12.9%, respectively [226]. Another study found that a starch hydrogel containing myrtle (*Myrtus* spp.) essential oil nano-emulsion (0.3%, *W/V*) achieved full healing of burn wounds with little scab formation, but the utilisation of silver sulfadiazine (1%, *W/W*) only resulted in 96% wound recovery. The bandage containing this nano-emulsion formulation could be readily peeled off from the wound area, whereas the stickiness of silver sulfadiazine made it difficult to change the bandage, potentially causing pain and delaying the healing process [227].

Plant-based essential oils in nano-emulsions appear to be a promising option for skin therapy owing to their ability to control microbial colony development, inflammation, and wound aggravation. Table 3 presents some recent research on the use of nano-emulsion formulations containing essential oils, including investigation routes, main experimental results, and measured tissue activities, which have the potential to be effective therapeutics for treating bacterial infections and skin damage. Nano-emulsions show superior therapeutic efficiency over initial essential oils by virtue of their nano-sized droplets, which allow them to rapidly penetrate microbial cells and interact with targeted substances, thereby disrupting cellular structures. These nano-scale droplets, together with increased aqueous solubility, are expected to conveniently penetrate deep skin layers, interact with biological fluids, and exhibit bioavailability in tissues.

## 5. Current concerns and clinical translation of essential oil nano-emulsions

### 5.1. Current concerns about essential oil nano-emulsions

Essential oil nano-emulsions are credited with several benefits for the treatment of skin disorders, such as controlled release of therapeutic agents, excellent skin penetration, remarkable and prolonged effectiveness, reduced adverse effects, and protection of volatile essential oil molecules from degradation. On the other hand, essential oil nano-emulsions encounter certain minor constraints that raise concerns among global experts regarding the widespread use of these formulations in dermatological treatments.

#### 5.1.1. Potential cytotoxicity

The potential cytotoxicity of nano-emulsions is a major concern in ensuring their safe use in skin treatment. As a form of nanomaterial, the features of essential oil-loaded nano-emulsions may contribute to their potential cytotoxicity, owing to their particle size, ingredients, and digestibility. Recent studies on the *in vitro* cytotoxicity of some essential oil nano-emulsions indicated that these formulations achieved nearly 100% cell viability [235] and exhibited minimal inhibition of cell proliferation at low concentrations [236], whereas the formulations with increased concentrations culminated in notable cytotoxicity. A nano-emulsion containing *Zataria* spp. plant essential oil necessitated greater dose to attain a 50% reduction in cell populations (cytotoxicity $IC_{50}$, $\mu g \cdot mL^{-1}$) compared to a marketed drug, while the emulsion with larger droplet size was even less cytotoxic than the nano-emulsion [237]. Consequently, the optimised formulations with appropriate concentration and particle sizes are essential for preparing nano-emulsions with minimised risk of cytotoxicity.

Several investigations have revealed that nano-emulsions ameliorated the bioavailability of the hydrophobic molecules [238–239]. However, some bioactive substances have been identified to induce side effects following consumption with high contents. For instance, significant levels of citronella (1000 $\mu g \cdot mL^{-1}$ and above) were seen to cause DNA disruption in human lymphocytes [240], while excessive intake of β-carotene heightened the menace of lung cancer in heavy smokers [241]. The choice of nano-emulsion ingredients is therefore critical for producing safe products that may not result in severe health issues in specific populations.

#### 5.1.2. Interactions with biological systems

Numerous studies have been conducted following standard protocols to select components, prepare formulations, characterise the materials, investigate activities, and assess toxicology with respect to the effectiveness of essential oil nano-emulsions for the treatment of skin infections and wound healing. However, nanomaterials may pose cytotoxicity risks because of their ease of penetration and uncertain digestibility. Topical nano-emulsions may facilitate penetration of essential oil molecules across biological membranes by reversibly modifying cellular organisation and enhancing interaction following solubilisation of the lipid barrier or integration of the lipid bilayer interface with cell walls [140]. However, the interplay between nano-emulsions and immunological responses remains inadequately understood, potentially leading to undesirable adverse effects on human health. Further evaluation of barrier permeability to ascertain the interaction between nano-emulsions and various tissues is a crucial step in developing appropriate delivery mechanisms and avoiding off-target effects.

#### 5.1.3. Scalability

The transition of nano-emulsion preparation from a laboratory setting to an industrial scale may result in variations in droplet features because of unintentional errors in equipment configuration and production protocols. This process culminates in the output of inadequate nano-emulsions, accompanied by undesirable phenomena such as creaming, aggregation, coalescence, and even phase inversion. To industrialise the fabrication of highly stable nano-emulsions, a high-energy technique such as homogenisation is preferable owing to its capacity to effectively create nano-sized droplets based on shear and cavitation energy. Furthermore, the micro-fluidisation method is expected to surpass homogenisation owing to its instrument design, which facilitates convenient scale-up through the multiplication of micro-fluidisation chambers, yielding nano-emulsions with particle sizes and PDI parameters comparable to those produced in laboratory settings [242–243]. Nevertheless, ultrasonication is presently unsuitable for large-scale manufacture, since it is confined to the fabrication of small material batches [244].

### 5.2. Clinical translation for essential oil nano-emulsions

#### 5.2.1. Formulation optimisation

Essential oil nano-emulsions are ideal candidates for treating skin infections and wounds by virtue of their promising efficacy demonstrated in preclinical research. The subsequent customisation and optimisation phases may enhance their safe and extensive deployment in human contexts. Statistical analyses such as response surface methodology (RSM) [245–246], Taguchi approach [247], and D-mixture optimal design [248], followed by examination using analytical software, have been favoured for assessing the impact of component ratios, equipment configuration, and processing temperature and duration, to obtain essential oil nano-emulsions with optimal droplet sizes, PDI parameters, stability, and biological functions. Industrial-scale production of nano-emulsions for clinical use requires thorough optimisation of experimental designs to determine the effects of different variables on the physicochemical and biological features of nano-emulsions, while minimising deviations.

#### 5.2.2. Pharmacokinetic and bioavailability studies

Topical essential oil nano-emulsions provide considerable advantages in dermatological therapy, including avoidance of the first-pass effect and reduced risk of enzymatic degradation in the gastrointestinal tract compared with oral delivery of drugs. Although a comprehensive understanding of the absorption, distri-

**Table 3** Recent works on essential oil nano-emulsion formulations for antibacterial, anti-inflammatory, and wound healing applications.

| Formulation | Targeted activities | Study methods | Results | Mechanisms | Ref. |
|---|---|---|---|---|---|
| Lavender essential oil nano-emulsion | Wound healing | *In vitro*, *in vivo* | 50% recovery in the scratch caused by inserts in HaCat cell monolayer after 24 h of treatment. Rabbit skin having sodium dodecyl sulphate for irritation test expressed no swelling and erythema symbols after 24 h of treatment with nano-emulsion. No sensitiveness was observed in burn wound of guinea pig rat after 48 h of treatment with 50% nano-emulsion. | Nano-emulsion prompted the expression of VEGF, IL-6, and IL-8, leading to the keratinocytes migration and promoting recovery in HaCat cell. Nano-emulsion with a low concentration of emulsifier might not interfere with outermost lipid layer of animal skin and could protect the wound area from irritants. | 228 |
| Licorice extract and lavender essential oil nano-emulsion in cream | Wound healing | *In vivo* | After 14-day treatment, the size of the wound area of the group treated with the formulation was only 0.1 cm$^{2}$, whereas that of the placebo and phenytoin-treated groups was 0.3 and 0.4 cm$^{2}$, respectively. Histopathological micrographs displayed the tissue granulation, re-epithelisation, and collagen fibre density in the group treated with the formulation. | After 14 days of application, the expression of growth factor (TGF-β1) and collagen type I of the nano-emulsion treated group was noticeably greater than that of the phenytoin-treated group. Malondialdehyde (MDA) level of the nano-emulsion treated group was around 40 nm MDA/mg protein. GPx and SOD contents of this group were approximately 4 and 48 U·mg$^{-1}$ protein, individually, which were greatly higher than those of the control and phenytoin-treated group, indicating that oxidative stress was controlled using the nano-emulsion. | 229 |
| Bitter almond essential oil nano-emulsion in hydrogel | Antibacterial, anti-inflammatory, wound healing | *In vitro*, *in vivo* | Hydrogel formulation containing 6% nano-emulsion inhibited *S. aureus*, *E. coli*, and *P. aeruginosa* with inhibition zones greater than 20 mm. Hydrogel formulation containing 6% nano-emulsion resulted in 99.75% wound closure in rat skin after 14 days of treatment. | Essential oil nano-emulsion droplets probably disrupted the bacterial cell membranes. The formulation lowered the expression of pro-inflammatory cytokines IL-1β and IL-6, promoting collagen establishment and accelerating tissue healing. | 230 |
| Chamomile essential oil nano-emulsion in polysaccharide gel | Anti-inflammatory, skin repairing | *In vivo* | Nano-emulsion gel fixed the atopic dermatitis issue in AD mice through the reduction of epidermal thickness (about 70 μm) and mass cell quantity (about 8), much lower than those of AD group (about 160 μm and 20, respectively). | The formulation effectively reduced IgE levels and pro-inflammatory cytokines (IFN-γ, TNF-α, and IL-4) in both serum and skin tissues, indicating its anti-inflammatory effect. | 231 |
| Eucalyptus essential oil nano-emulsion | Antibacterial, wound healing | *In vitro*, *in vivo* | Nano-emulsion suppressed *S. aureus* by around 85% after 48 h and eliminated biofilms by approximately 77%. After 16 days of therapy, the nano-emulsion in gel healed the wound in mice by approximately 90 and reduced the bacterial load in the infected wound to only about 3 lg (CFU·g$^{-1}$), while the control group had about more than 4 lg (CFU·g$^{-1}$). | The nano-emulsion inhibited the bacterial growth, which in turn reduced the bacterial activity in the wound area. The nano-emulsion gel decreased the expression of pro-inflammatory cytokines including TNF-α and IL-6, as well as increased the expression of the growth factors including VEGF, EGF, and TGF-β1, all of which controlled the inflammation and aided in tissue repairing. | 224 |
| Tea tree oil nano-emulsion in hydrogel | Antibacterial, wound healing | *In vitro*, *in vivo* | The formulation exhibited antibacterial percentages of around 90%, 100%, and 75% against methicillin resistant *S. aureus*, *S. aureus*, and *E. coli*, individually. After 12 days of topical application, the nano-emulsion gel healed the wound in mice by nearly 100% and minimised the bacterial load in the wound region to almost 0 (CFU·mL$^{-1}$). Histological analysis indicated a significant deposition of collagen in the infected wound area after treatment. | The antibacterial behaviour of the nano-emulsion effected the activity of the bacterial colonies in the wound area. After 12 days of treatment with the formulation, the group that received the formulation had a drop in the density of HIF-1α, which is created because of the hypoxic environment caused by excessive generation of free radicals. Due to HIF-1α's encouragement of angiogenesis through the HIF-1α-VEGF mechanism, VEGF expression was elevated throughout the early wound healing stage (6 days), suggesting the maturity of new blood vessels. The formulation's ability to promote wound healing and reduce scar establishment was demonstrated by the treated group's reduced expression of α-SMA and greater levels of PCNA and collagen type I when compared to the control. | 232 |
| Lemongrass essential oil combined with ferulic acid in nano-emulsion gel | Antibacterial, wound healing | *In vitro*, *in vivo* | The nano-emulsion demonstrated outstanding antibacterial performance against *S. aureus* with minimal inhibition concentration. The 14-day treatment of the wound in rat with the formulation resulted in notable wound closure, with around 70% wound contraction. Histopathological scans revealed healed tissues and minimal quantity of mononuclear inflammatory cells. The substantial density of collagen type I verified the presence of extra-cellular matrix. | The formulation reduced the expression of the pro-inflammatory cytokines, including IL-6 (nearly 1900 pg·mg$^{-1}$ protein) and TNF-α (about 45 pg·mg$^{-1}$ protein), compared to those of the control group (around 2200 and 75 pg·mg$^{-1}$ protein, respectively). | 233 |
| *Aniba canelilla* (Kunth) Mez essential oil nano-emulsion in hydrogel | Anti-inflammatory | *In vivo* | The formulation reduced the mice ear oedema caused by croton oil by 36.24%. Histological micrographs exhibited less quantity of inflammatory cells than the acetone-treated group. The formulation lowered myeloperoxidase enzyme activity, which is released by the infiltration of polymorphonuclear leukocyte as an inflammation biomarker, by 2.8 times lower compared to the acetone-treated group. | The formulation lessened the expression of the pro-inflammatory cytokines, such as IL-6 (approximately 1.8 pg·mg$^{-1}$) and IL-1β (approximately 0.4 pg·mg$^{-1}$), which were notably lower than those of the acetone-treated group (nearly 2.5 and 0.8 pg·mg$^{-1}$, respectively). | 234 |

bution, metabolism, and excretion of these formulations within the human body is essential for broadening their applications, only a limited number of preclinical studies have reported their plasma drug concentrations and relative bioavailability [249]. Further pharmacokinetic investigations are anticipated to thoroughly examine the appropriate dosages and therapeutic effectiveness across diverse patient populations.

### *5.2.3. Clinical trials and approval*

Nano-emulsions containing essential oils must be examined through rigorous clinical research to assess their safety and effectiveness prior to regulatory approval and practical application. A few nano-emulsion formulations for topical and transdermal administration have progressed to phase III clinical trials to evaluate their safety, metabolism, and efficacy in patients in large-scale investigations [250]. However, there is little evidence about the outcomes of clinical trials of essential oil nano-emulsions. According to the Food and Drug Administration (FDA), a recognised nanomaterial possesses a particle dimension below 100 nm, characterised by size-dependent features and specific applications [251]. The employment of some FDA-approved natural compounds like astaxanthin [252] and β-caryophyllene [253] to create nano-emulsions and investigate in vivo anti-inflammatory and wound-healing effects in diabetic models, respectively, may signify a promising opportunity for approved nano-emulsion formulations in the near future.

## 6. Conclusions and future perspectives

### *6.1. Conclusions*

Global dermatological scientists are continuously exploring the benefits of natural substances for use as multi-functional skincare materials. Despite the fact that numerous chemical cosmetics are invented and produced each year to satisfy the varying demands of the market, plant-based essential oils have proven to be a reliable ally for human skin. This review provides insight into the use of essential oils within nano-emulsion systems to overcome the limitations of these natural materials and enhance their biological efficacy. A brief overview of essential oil components shows that monoterpenes predominate and play a primary role in the bioactivities of essential oils. Various methods for preparing essential oil nano-emulsions have been reported, involving the use of either mechanical energy through external equipment or chemical energy *via* phase inversion. Nano-emulsions incorporating essential oils have demonstrated adequate anti-inflammatory, antimicrobial, and wound-healing capacities in inflamed or damaged tissues. These biological characteristics make them promising candidates for skin treatments aimed at addressing microbial infections and common wounds. The potential of essential oil nano-emulsions as skin therapeutics presents a novel frontier in dermatological management, especially for conditions caused by microbial infections and chronic wounds.

### *6.2. Future perspectives*

The development of essential oil nano-emulsions offers vast potential in the cosmetic and pharmaceutical industries. Future research should focus on optimising these formulations to target specific skin conditions, particularly viral infections and skin cancers. By fine-tuning the droplet sizes and compositions of nano-emulsions, it may become possible to enhance the bioavailability of essential oils, enabling deeper penetration into the skin and more precise delivery to target sites. Moreover, the integration of other natural compounds with essential oils in nano-emulsions could lead to synergistic effects, further amplifying their therapeutic properties. The exploration of sustainable, eco-friendly methods of producing these formulations will also be a key area of development, as consumer demand for "green" skincare products continues to grow. With advancements in nanotechnology and a deeper understanding of essential oil chemistry, future innovations may lead to next-generation skincare solutions that are both natural and highly effective. This could revolutionise not only skin treatments but also skincare design approaches, offering safer and more sustainable alternatives to chemical-based products.

## Declaration of competing interests

These authors have no conflict of interest to declare.

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