Review article

Polymeric nanoparticles for enhanced delivery and improved bioactivity of essential oils

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ABSTRACT

Essential oils are volatile constituents that give aromatic plants their characteristic odour. The application of these plant actives in food, agriculture, pharmaceutics, and cosmetics has been widely studied. Aromatherapy, a complementary therapy involving the use of essential oils to treat several diseases ranging from microbial infections to metabolic dysfunctions, has been utilised for centuries. Anticancer, antimicrobial, and anti-inflammatory activities are well-established among other pharmacological properties of these aromatic oils. The oils, which are composed mainly of terpene-based compounds, have also been explored as nutraceuticals, alternative green preservatives, and functional additives in foods. However, due to their physicochemical properties, viz high volatility and low aqueous solubility, essential oil delivery to target receptors were challenging when administered as chemotherapeutics. Hence, formulating essential oils with suitable excipients to enhance their delivery and bioavailability, invariably improving their bioactivity and therapeutic efficacy becomes expedient. Nanotechnology presents a unique strategy to develop a particulate delivery system for the controlled, sustained, and extended release of essential oils. In this review, we examine and summarize the trends and developments in the formulation of essential oils using polymeric nanoparticles.

1. Introduction

Paracelsus Von Hohenheim of Switzerland termed essential oil in the sixteenth century after being produced from the medicine *Quinta essentia* [1]. Essential oils (EOs) are volatile, naturally occurring chemicals with a potent odour that aromatic plants produce as a by-product of their secondary metabolism. They are extracted from aromatic plants typically found in temperate to warm and tropical regions, where they form a vital component of the ancient pharmacopoeia [2]. Various cultures have employed essential oils for thousands of years for medicinal and therapeutic purposes. Significant amounts of EOs are discovered in oil sacs or glands at various

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depths in the fruit peels, particularly the flavedo and cuticle [3].

Additionally, they are aromatic oily liquids derived from various plant parts, including leaves, barks, seeds, flowers, and peels [4]. Depending on the method, they can be expressed, effervesced or fermented. Steam distillation and hydro-distillation are the most used techniques for the industrial manufacture of essential oils [5,6].

EOs are used in aromatherapy, a natural way of healing a person's mind, body, and soul [7]. Many ancient civilisations have used aromatherapy as a popular and sought-after complementary and alternative therapy for about 6000 years [8,9]. Essential oils are administered in small quantities via various methods such as inhalation, massage, and simple application on the skin but are rarely taken internally [10,11]. Several aromatherapy classes have been employed in treating various disease conditions. The categories include cosmetic aromatherapy, massage aromatherapy, medical aromatherapy, olfactory aromatherapy, and psycho-aromatherapy.

EOs can be classified based on chemical composition, extraction methods, and aroma therein [12]. The class of EOs based on chemical composition is attributed to the plant where they are found. For instance, oils from *Citrus* and Pine contain hydrocarbon made up of only carbon and hydrogen, making them different from oils found in coriander, tea, and peppermint [12]. Essential oils are complex mixtures that may contain more than 300 different compounds [13]. Many of these chemicals have been discovered and characterised as terpenes, the most common type of terpene in essential oils [14]. Characterization of essential oils is mainly via the Gas Chromatographic (GC) techniques for the separation of individual terpene and other components based on partition coefficients and retention time between the gaseous mobile phase and the liquid or solid stationary support. Most GC uses mass spectrometry (MS) for the detection of each chemical entity and flame ionization detectors (FID) detectors are also coupled with GC [15]. Aldehydes, ketones, esters, amines, amine-amide, phenols, and heterocyclic hydrocarbons are other chemical classes to which EOs belong [16]. Alcohols have an attached hydroxyl group to the terpene structure, which is present in coriander and peppermint. Citronella, lemon balm, and lemon myrtle contain terpenoids containing a carbonyl group (C=O) and a hydrogen-bonded carbon containing aldehyde [17]. Ketone comprises a carbonyl group connected to two carbon atoms; Thuja, Sage, and *Eucalyptus radiata* possess this type of essential oil [18,19]. Phenols contain a hydroxyl group attached to a benzene ring found in Thyme and Oregano [20].

EOs have found usage in the cosmetic, food, and pharmaceutical industries because of their potent therapeutic efficacy [21,22]. EOs are utilised as an expectorant against bronchitis and cough, carminative, antimicrobial, and pain reliever [23].

This review further expatiates EO's bioactivity and delivery which are enhanced using polymeric nanoparticles.

2. Bioactivity of essential oils

In the scientific space, EOs have remained relevant due to their flexibility and usefulness and the increasing demand for natural products. They are rich sources of phytoconstituents whose pharmacological activities account for their numerous applications [24]. Essential oils are composed mainly of terpenoids and non-terpenoid compounds, which give their characteristic aroma. Biological activities such as antibacterial, antifungal, anticancer, antiviral, and antioxidant have been described for many EOs [25]. They may typically have about 20–60 components at varying concentrations. While some components have as high as 20–70% concentration, others are in minute quantities [2]. The bioactivity exhibited by these oils is not solely due to only one main active component, as inactive components' synergistic and antagonistic impact is quite significant. Such impacts affect their absorption, bioactivity, and reaction rate [26,27]. However, the main components remain essential for their bioactivity [28]. The bioactivities discussed here include antioxidant, phytotoxic, acaricidal, antimicrobial, anticancer, and antidepressant (Fig. 1).
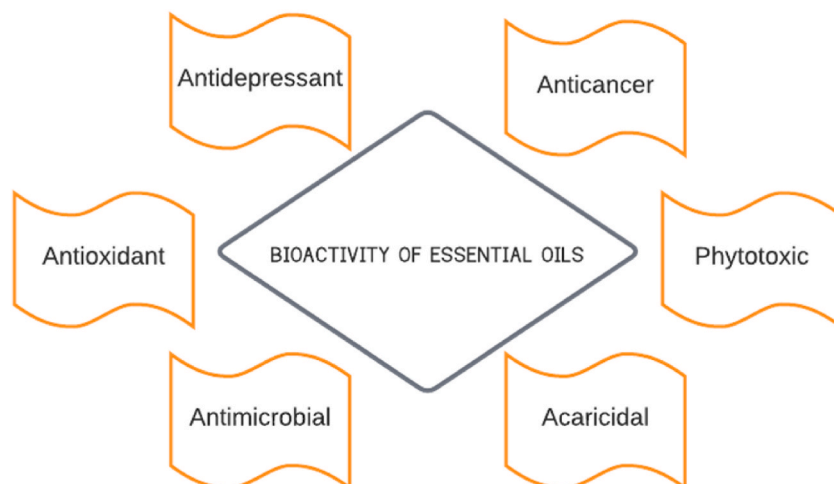

Fig. 1. Various bioactivities of essential oils.

2.1. Antioxidant activity

A vital factor which diminishes the shelf-life of many food products is oxidative degradation – a process whereby macromolecules break down due to the action of oxygen-releasing free radicals. Many aromatic plants have produced essential oils with significant potential for delaying or hindering chemical deterioration in fat-containing food systems. Effective in small quantities, these essential oils are increasingly being studied due to undesirable side effects obtained from using synthetic antioxidants to prevent such deterioration [29]. EOs are now being added to edible products either as coatings and inactive packaging or indirectly mixed to prolong shelf life and avert autoxidation [30].

EOs of spices *Thymus vulgaris* (thyme), *Syzygium aromaticum* (clove), *Rosmarinus officinalis* (rosemary), *Origanum vulgare* (oregano), and *Salvia officinalis* (sage) have all been reported to show varying forms of antioxidant activity. These include iron chelation, DPPH radical, and TBARS inhibition [29]. Iron chelation is an antioxidant mechanism where transition metal ion (iron) forms stable complexes to prevent their participation in generating free radicals [31]. The build-up of free radicals in neurons has been reported as a major event in the development and progression of Parkinson's disease [32]. Other degenerative disorders such as carcinogenesis, mutagenesis, and cardiovascular issues are also caused by free radicals [33].

In a study highlighting the antioxidant significance of some widely used spice EOs, clove EO inhibited DPPH radical at 98.74% (the highest of the five EOs screened), while thyme EO inhibited TBARS the most at 89.84%. Although all the EOs chelated iron, the highest effect was displayed by rosemary EO at 76.06% [29].

2.2. Phytotoxic activity

The phytotoxic effect of *Monarda didyma* EO on germination and the initial radical growth of *Avena fatua* L. (wild oats; a popular weed), *Taraxacum officinale F.H.* Wigg (dandelions), *Lepidium sativum* L. (garden cress), and *Papaver rhoeas* L. (red poppies) were examined. The EO inhibited the germination of red poppy seeds at 1.250 μg/mL. As for dandelion seeds, their germination was also totally inhibited by the EO at the same concentration. However, only 50% and 80% inhibition were achieved on the germination of garden cress and wild oats, respectively, at that concentration [34]. Although the inhibitory reaction mechanism of EOs remains unclear, there are reports of a hindrance to apical meristems' cell division. Reactive Oxygen Species (ROS) production causing membrane disruption or DNA synthesis inhibition is probably responsible [35].

2.3. Acaricidal activity

EOs extracted from various species of *Eucalyptus* have shown acaricidal activity, warding and fighting off ticks and mites. *E. staigeriana* and *E. citriodora*'s EOs brought about 100% mortality on ticks larvae at 10% concentration while *E. globulus* did the same at 20% [36]. At low concentrations, EOs of *E. maidenii*, *E. bicostata*, *E. approximans* and *E. sideroxylon* showed significant acaricidal effects on *Tetranychus urticae* (spider mite) with high mortalities [37]. On other mite species such as *Amblyomma cajennense, Anocentor nitens,* and *D. gallinae*, mortality rates of 53%, 100%, and 85% respectively were observed following exposure to *E. citriodora* EO [38, 39].

2.4. Antimicrobial activity (antibacterial, antifungal, and antiviral)

The menace of increased antibiotic resistance has necessitated further studies on the potentials of EOs. Research works on the antimicrobial activity of various EOs, both *in vitro* and *in vivo,* have been carried out [40]. While some of these works centered on an individual EO, other works have been on blends of EOs. Extraction of the main compounds in these oils was also done using several methods. In oregano plants (*Origanum vulgare*), the main compounds, thymol and carvacrol show high antimicrobial activity. Antiparasitic, antibacterial, and antifungal activities have been reported *in vitro* for oregano EO [41]. 64% of infected patients with enteric parasites (*Entamoeba hartmanni, Endolimax nana,* and *Blastocystis hominis*) showed improvement when treated with oregano EO [42].

A mild effect was exerted *in vitro* on strains of *Plasmodium falciparum* that were resistant to chloroquine. This suggests further studies into a potential malaria treatment through EOs [43]. *Thymus vulgaris* EO (of Iranian roots) was reported *in vitro* to be highly potent against *Entamoeba histolytica* trophozoites which cause amoebiasis [44]. The effects of these EOs on antibiotic-resistant Gram-positive and Gram-negative bacteria have also been documented [45].

In vitro antifungal activity of *Calamintha nepeta* (L.) Savi subsp. *glandulosa* (Req.) obtained from Tarquinia in Italy against *Candida albicans* was explained in a comprehensive study. Although pulegone (a monoterpene ketone) was the major essential oil component, it was not the only component responsible for this activity. Following the steam distillation process, the extracted EO showed - very significant antifungal activity. Minimum Inhibitory Concentration (MIC) of both the extracted EO and miconazole (a common synthetic antifungal drug) were compared to test anti-*Candida* efficacy. A notable antifungal activity against candidiasis was confirmed [46].

Due to their antimicrobial and antioxidant properties, EOs have also been explored in the food industry mainly to increase shelf-life and maintain food quality in active packaging. While they add fragrance to fabrics in the textile industry, they also work as antimicrobials [24].

2.5. Anticancer activity

Cancer is currently the leading cause of death worldwide. With cancer cells invading and growing uncontrollably, a potent cancer therapy would involve inhibiting the multiplication of cancer cells [47]. *In vitro* and *in vivo* studies of EOs from *Cymbopogon flexuosus*, a variety of lemongrass against a dozen human cell lines have been reported. *In vitro*, visible effects against different human cancer cell lines were observed, denoting cytotoxicity. In addition, the oil inhibited several tumour growths at varying doses in 180 model mice. The EO activated the apoptotic process, which resulted in the loss of viable tumour cells. Therefore, oil is seen as a promising anti-cancer candidate [48].

Limonene is a major component of citrus EO procured through distillation. It inhibited the multiplication of 22RV-1 (a prostate cancer cell line), and A549 (a human lung cancer cell line). Therefore, its potential for prostate and lung cancer therapy usage was reported [49]. Similarly, another component of citrus EO, pinene, inhibited non-small-cell lung carcinoma cells [50].

2.6. Antidepressant activity

An estimate of one in every 20 individuals has depression worldwide, with an almost double prevalence among females than males [51]. Depression affects relationships and work output, causing distress to many people. Thus, the search for efficient depression therapies is important [52]. The high cost of depression pharmacotherapy coupled with side effects, intolerance to treatment, and an exhibition of partial or no remission pose challenges to managing depression. Hence, the need for new antidepressants with fewer side effects, more efficiency, and a swifter response [53]. Experimental works on the antidepressant properties of EOs and their components have been reported Preclinical testing of many EOs (and components) on their antidepressant activities have shown that these oils might relieve vital depression symptoms, presenting a complimentary source of therapy [52]. Clinical trials have recently revealed that EOs, whether taken orally or inhaled, enter the bloodstream and exert specific effects. These effects include improving sleep, reducing anxiety, treating post-traumatic stress disorder, and reducing nicotine cravings [54–56].

Lavender, which has been most studied for its anxiolytic properties, displayed significant effects on mood in humans [57]. It was found that inhaling lavender oil for 3 min every day for three days resulted in decreased depression and a calm sensation in healthy adults. Furthermore, when diagnosed, depressed patients with psychomotor agitation, insomnia, and anxiety were given lavender oil capsules for three weeks, anxiety, sleep disturbance, and psychomotor agitation were significantly reduced [58].

According to a research investigation, EOs can also aid with mild to moderate postpartum depression and anxiety. Women diagnosed with postpartum depression (showing anxiety and depression) were given a mix of EOs of *Rose otto* and *Lavandula angustifolia* to inhale or apply topically. There were no reported adverse effects by all the 28 patients tested, interestingly. The four weeks treatment, remarkably relieved both the symptoms of anxiety and depression as scored by a Generalised Anxiety Disorder Scale (GAD-7) and Edinburgh Postnatal Depression Scale (EPDS), respectively [59]. This blend of two EOs (rose and lavender) provided another practical approach to managing and treating the symptoms of depression and anxiety.

Furthermore, many animal studies have described the antidepressant-like effects of several essential oils from plants. These include *Zingiber officinale* Roscoe (Zingiberaceae), *Rosmarinus officinalis* L. (Lamiaceae), *Syzygium aromaticum* (L.) Merr. & L.M. Perry (Myrtaceae), *Eugenia uniflora* L. (Myrtaceae), *Citrus limon* (L.) Osbeck (Rutaceae), and *Valeriana wallichii* DC. (Caprifoliaceae) [53].

3. Nanotechnology: polymeric nanoparticles

Nanotechnology is fast evolving and leads to various significant technological advancements in many interdisciplinary areas such as chemistry, material science, engineering, physics, and medicine. Specifically, for medical applications, different types of nano-particles such as inorganic, lipid-based, and polymers have been exploited for drug delivery and enhancing effectiveness of drugs [60]. Polymeric nanoparticles (PNPs) offer superior advantages of being accessible to functionalised (i.e., tailor their biological, physical, and chemical properties), ability to release encapsulated compounds at a controlled rate, and proper action on specific sites [61,62]. Driven by the significance of nanotechnology in medicine in the past few years, the adoption of PNPs has played a crucial role as a therapeutic strategy for developing several medicinal agents. This is due to their efficacy and bioavailability, enhancement over drug administration, easy integration into biological matrices, and active ingredient transport to the target site of action with specified concentration, stability, and more extended activity period, especially for volatile active agents. Thus, they are considered ideal candidates for efficient drug delivery [60].

Furthermore, the formulation of any given nano-drug depends on the choice of a suitable polymer system based on factors such as maximum encapsulation efficiency, bioactivity, retention time, bioavailability and enhancement of intracellular penetration, applicability, safety, biocompatibility, and cost [63,64]. It is worth noting that aside from drug loading efficiencies, the choice of PNPs is a major factor upon which the drug release mechanism depends [63]. Additionally, the synthesis and selection of PNPs are predicated on the bioactive molecule to be loaded. Drug loading on PNPs can be achieved either by surface adsorption after the production of PNPs or by encapsulation during PNP synthesis [65]. In the past, freeze-drying was used to increase the long-term stability of polymeric nanoparticles while also improving handling and storage. However, this was associated with stress throughout the process [66]. More recent studies revealed the lyophilisation of polymeric nanoparticles as a more efficient means of obtaining a good and stable lyo-philizate for drug delivery [67]. Physicochemical properties of formulations and the engineering principle of a cycle are vital considerations to obtaining a good lyophilizate and preservation of the nanoparticles.
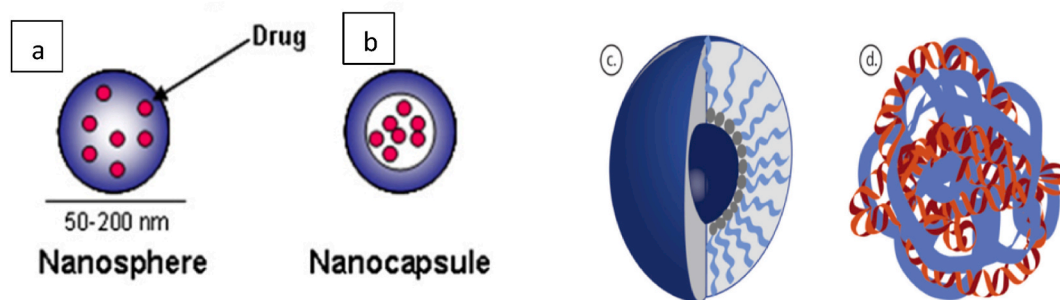
Fig. 2. Schematic illustration of PNPs in the form of (a) nanosphere, (b) nanocapsule, (c) Polymeric micelles and (d) polyplex nanoparticles [61,65].

3.1. Classification of polymeric nanoparticles

PNPs have been classified according to different criteria. The structural organisation is formulated as nanocapsules, nanospheres, nano-ellipsoids and oval nanoparticles, polymeric micelles, and polyplex nanoparticles [67,68]. Their structures depend on preparative methods. When drugs are entrapped as core in a nanoparticle shell, they are regarded as "nanocapsules", and when adsorbed on the surface of the matrix, they are referred to as "nanospheres", as illustrated in Fig. 2 [61,65]. PNPs have also been grouped based on formulations into sizes and shapes such as micelles, vesicles, stars, and inorganic-polymer hybrids [69].

Based on absorptivity, PNPs are categorised as biodegradable (which could be natural or synthetic-based) and non-biodegradable polymers (such as polyacrylates, polystyrene, polyacrylamide, poly (methyl methacrylate) and many more [70,71]. Owing to the limitations and associated risks of non-biodegradable PNPs like low absorptivity and poor degradability in body matrices, chronic toxicity, poor excretion ability and inflammatory reaction [71], biodegradable PNPs remain most attractive. They enhance the therapeutic value of drugs and bioactive ingredients by improving bioavailability, solubility and retention time [72]. Natural biodegradable polymeric nanoparticles have their sources from naturally occurring materials formed during lifecycles of living organisms such as green plants, animals, bacteria and fungi. They are further classified as polysaccharides- and proteins-derived [73]. Polysaccharides could be from the plant (such as pectin, cellulose & derivatives, starch and derivatives, Arabic gum, and alginate), animal or microbial origin (e.g. xanthan gum, gellan gum and chitosan). Also, protein sources include albumin, gelatin, soy protein, hydrolysate, and casein. Explicitly, natural PNPs are normally biodegradable and biocompatible and are eliminated from the body by natural metabolic pathways [74,75]. In addition, they are non-toxic, non-immunogenic, have high binding capacity, are well-tolerated with no serious side effects and are widely applicable [76]. Nevertheless, they can be mildly immunogenic with their uses limited due to batch-to-batch variation in properties. They also often require surface modification to act as nanocarriers [74]. Synthetic PNPs are widely known for their controlled chemical composition and are scalable for large-scale production and low batch-to-batch variability [77]. Nevertheless, they may be cytotoxic or immunogenic due to unintended degradation [61]. Poly lactic-co-glycolic acid (PLGA), Cyclodextrin, Polylactide (PLA), Poly ε-caprolactone (PCL), and Poly β-amino ester (PBAE) are examples of synthetic polymeric nanoparticles.

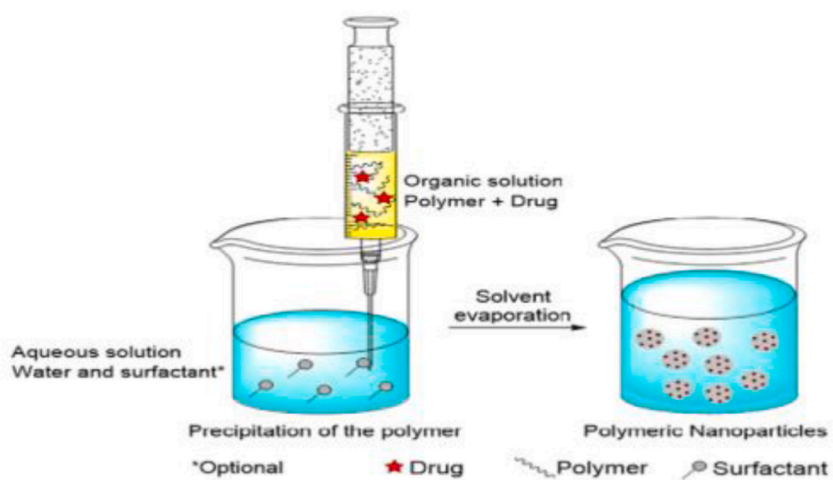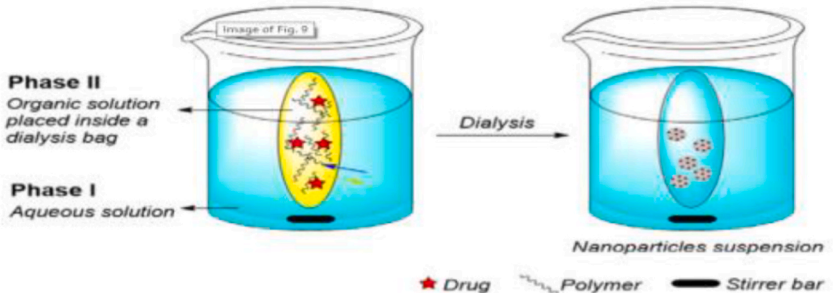*3.2. Synthesis approaches of polymeric nanoparticles*

The method selection for synthesising PNPs depends on the physical and chemical properties of interest and the applications. The preparation methods have been categorised into two: those based on the polymerisation of monomers (which comprise microemulsion, emulsion, mini-emulsion, controlled/living radical and interfacial polymerisation techniques), and those based on the dispersion of preformed polymers (which include emulsification-solvent evaporation, nanoprecipitation, dialysis, salting out and supercritical fluid technology) [78]. The methods based on the polymerisation technique have been reported to be inferior and less attractive over those based on preformed polymers due to their non-biocompatibility, non-biodegradability, and toxic residue formation [79]. Ref. [74] classified the PNP synthesis approach into one-step and two-step procedures. The one-step approach (nanoprecipitation, dialysis, supercritical fluid technology) does not involve the preparation of the emulsification system before the formation of nanoparticles while the emulsification system is prepared followed by the formation of nanoparticles in the two-step approach (such as emulsification-solvent evaporation, emulsification solvent diffusion and Emulsification-reverse-salting out). Table 1 presents a comprehensive description, applications, advantages and limitations of each method and Fig. 3 shows a typical scheme for the synthesis of nanospheres.

4. Polymeric-essential oil nanoparticles

A wide range of techniques (physical, chemical, and mechanical processes) are employed to develop essential oil formulations. EOs are a unique class of phytochemicals that require specific protection from light, heat, and other oxidative processes. This is because they are labile, insoluble in water, and volatile like many other bioactives. Although the volatile nature of EOs is explored in aromatherapy and the treatment of respiratory diseases such as sinusitis and asthma, this unique property is also a limiting factor for
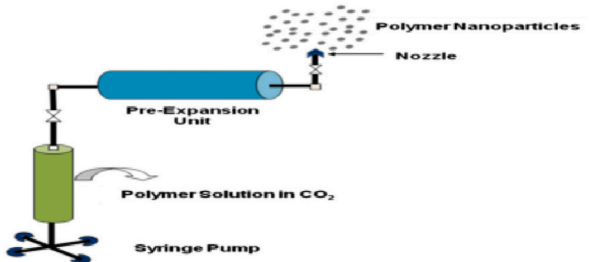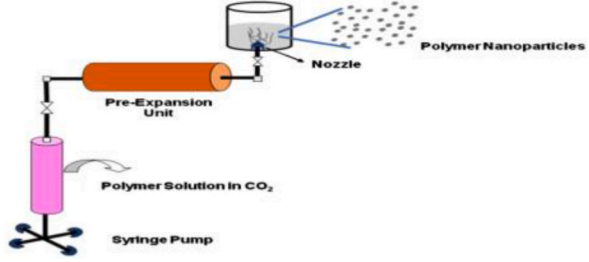
Table 1

Summary of methods of polymeric nanoparticles preparation based on preformed polymers, application, advantages, and limitations [74,78].

METHODS	DESCRIPTION	SELECTED APPLICATIONS	ADVANTAGES	LIMITATIONS	SCHEMATIC ILLUSTRATION
1. DISPERSION OF PREFORMED POLYMERS					
(a) One-step route (involving a direct formation of nanoparticles)					
(I) Nano-precipitation (or solvent displacement)	This method is based on the interfacial deposition of the polymer after displacement of the organic solvent from lipophilic solution to the aqueous phase. First, a polymer solution with water-miscible solvent of intermediate polarity is formed and added to a stirring aqueous phase in one shot, stepwise, dropwise or in a controlled addition rate through spontaneous diffusion to form the nanoparticles instantaneously to prevention water molecules	Several PLGA- and PLA-based nanoparticles are synthesised employing this technique [80–83].	The process is simple, quick and reproducible;	Finding of drug/polymer/solvent/non-solvent system, which allows nanoparticle production and drug encapsulation challenging	
(II) Dialysis	Polymer is first dissolved in an organic solvent, placed inside a dialysis membrane and then dialysed against a non-solvent.	Several PLGA-, PGGA-, PPA- and PMMA-based nanoparticles have been prepared with this technique [84–86].	Requires no surfactant; PNPs prepared are of small or narrow nanoparticles	Weak loading efficiency	
(III) Supercritical fluid technology (RESS and RESOLV)	Supercritical fluids are used. The most common technologies are RESS and RESOLV	Employed to produce drug-loaded nanoparticles [87–90].	This method is usually adopted in biomedical and environmental fields because surfactants or organic solvent is not applied for	Most polymers are poorly soluble or even non-soluble in supercritical fluids using RESS or RESOLV; Requires a high	

Table 1 (*continued*)

METHODS	DESCRIPTION	SELECTED APPLICATIONS	ADVANTAGES	LIMITATIONS	SCHEMATIC ILLUSTRATION
			PNPs preparation; easy to scale up; environmentally friendly because no surfactant and organic solvent required; suitable for the production of high purity nanomedicine with tunable structural homogeneity	investment for high-pressure equipment	
(i) RESS	PNPs are formed by dissolving the solute in a supercritical fluid to form a solution, followed by a rapid expansion of the solution across an orifice or a capillary nozzle into ambient air	A few methods have demonstrated the use of RESS for the production of PNPs based on Poly (perfluoropolyether diamide), PLLA, etc. [91,92].	No surfactant and organic solvent required	Major products of this technique are in micro-scales rather than nano-scales	
(ii) RESOLV	It is a modification of RESS method. The second step involves a rapid expansion of the formed supercritical solution into a liquid solvent rather than ambient air. The liquid solvent acts as a suppressant of particle growth, making the final product in the form of nano-sized.	A few reports on the production of PLLA, PMMA and PHDFDA nanoparticles using supercritical fluids by RESOLV have been reported [93,94].	The technique solved the problem of micro-scale product formed using RESS	Most polymers are poorly soluble or even non-soluble in supercritical fluids	

(b) Two-step route (involving the preparation of emulsification system followed by the formation of nanoparticles)
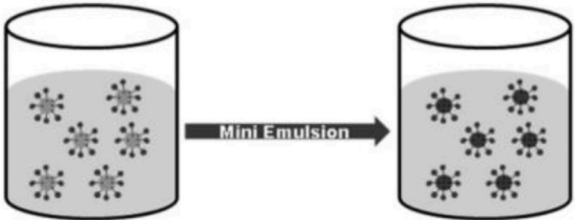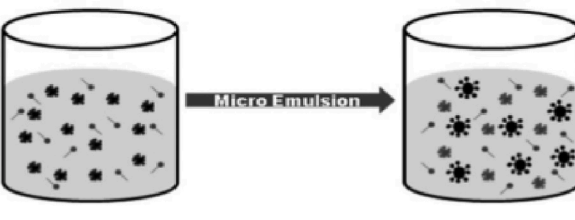
Table 1 (*continued*)

METHODS	DESCRIPTION	SELECTED APPLICATIONS	ADVANTAGES	LIMITATIONS	SCHEMATIC ILLUSTRATION
(I) Solvent evaporation	Polymer is dissolved in a volatile solvent. The organic solution is emulsified either by single emulsion (oil-in-water) or double emulsion (water-in-oil)-in water in the aqueous phase, and the mixture is processed by a surfactant followed by homogenisation yielding a dispersion of nanodroplets. The polymer solvent is then evaporated to form nanoparticles, followed by further post-synthesis treatment and finally, the product is lyophilised.	They are widely applied in the preparation of several synthetic polymeric nanoparticles with diameter that falls within 60 to about 300 nm using appropriate solvent systems and stabiliser [95–101].	The method is simple and versatile	It is time-consuming; possible coalescence of nanodroplets during evaporation process may affect morphology and particle size; applied only to liposoluble drugs; for scale-up, an alternative method using low-energy requirement in homogenisation is preferred	
(II) Solvent diffusion	In this method, a partially water-miscible solvent containing the polymer, and an aqueous solution, containing a surfactant yields the formation of o/w emulsion. Solvent diffusion from the dispersed droplets into the external phase is induced by sequential dilution with an extensive amount of water, resulting in colloidal particle formation.	Nanospheres are generally produced by this method [102, 103]. Also, by adding little amount of oil, nanocapsules can be prepared [104,105].	High yield of product obtained; easy to scale up; no need for high-pressure homogeniser or ultra-sonication; good encapsulation efficiencies; batch-to-batch reproducibility	A high volume of water is usually eliminated from the suspension; there is the possible leakage of water-soluble drugs into the external phase throughout the emulsification step	

Table 1 (*continued*)

METHODS	DESCRIPTION	SELECTED APPLICATIONS	ADVANTAGES	LIMITATIONS	SCHEMATIC ILLUSTRATION
(III) Reverse-salting out	An emulsion is formulated from a water-soluble polymer solvent (such as acetone) and an aqueous gel containing the salting-out agent (calcium chloride) and a colloidal stabiliser	Various PLGA and PLA nanoparticles are produced [106,107].	Hazardous solvents are not required.	Exclusive application in encapsulating lipophilic drugs; intensive purification step due to the use of salts	
2. POLYMERISATION OF MONOMERS					
(I) Emulsion polymerisation	Most common method use for the production of, many speciality polymers			Water is used as the dispersion medium, making the process eco-friendly; Characterised by excellent dissipation of heat in the course of the polymerisation	
(i) Conventional emulsion polymerisation	Surfactants are utilised in the process, and the nature of the surfactants determines the diameter of the PNP produce. Using this approach, water, a monomer of low water solubility, a water-soluble initiator is the precursors required for the reaction. PNPs of about 100 nm are usually obtained.	The majority of the poly (alkylcyanoacrylate) nanoparticles are obtained through anionic polymerisation [108–113]	Well-defined nanoparticles are obtained	Surfactants used are not easily eliminated, thus may pose some toxicity effect; Surfactant removal is time-consuming, and that increases the cost of production	

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Table 1 (*continued*)

METHODS	DESCRIPTION	SELECTED APPLICATIONS	ADVANTAGES	LIMITATIONS	SCHEMATIC ILLUSTRATION
(ii) Surface-free emulsion polymerisation	No surfactant required. The ingredients used are deionised water, a water-soluble initiator and monomers	Several PS, PMMA, PECA nanoparticles have been prepared [114–117]	The process is surfactant-free, no environmental and economic concern; time-saving for PNPs production because there is no removal of surfactant	A challenge of preparing mono-dispersed and precisely controlled particle size is a challenge	
(II) Mini-emulsion	Water, a mixture of monomer, co-stabiliser, surfactant and initiator, are the typical formulation of this method. Low molecular weight compounds are used as compounds. A high-shear device (e. g. ultrasonication machine) is used; Droplets formed range between 20 and 200 nm; Particle sizes fall within 10 nm–30 nm. Polydispersity is very low. Stability period range from hours to months upon appropriate storage conditions	PMMA and poly (n-butylacrylate) nanoparticles were prepared using SLS/DDM and S.L.S./hexadecane as surfactant/co-stabiliser systems respectively [118, 119].	Utilises a small amount of surfactant	Although little quantity of surfactants are used in the process, some amount remains in the polymer matrix	
(III) Micro-emulsion	The mechanism of the process involves the formation of nanodroplets of about 10 nm followed by growth in particle size due to the osmotic and elastic influence of the chain. Like the emulsion polymerisation method, colloidal polymer nanoparticles of high molecular mass are produced; they are	Production of co-polymer nanoparticles made of MMA and NMA using AOT as surfactant. Poly (dimethylsiloxane) nanopolymer) (12–80 nm) can be produced using cationic surfactants. Poly (hexylmethacrylate) of 38–53 nm can be produced using DTAB and DDAB as stabiliser and VA-044 as the initiator [120–122].	Very effective for the parathion of nano-sized particles	A large ratio of surfactant to monomer is required for polymer stability and thus may be difficult to eliminate	

Table 1 (*continued*)

METHODS	DESCRIPTION	SELECTED APPLICATIONS	ADVANTAGES	LIMITATIONS	SCHEMATIC ILLUSTRATION
	kinetically different. Polydispersity is very low. Particle sizes may fall within 30–100 nm; They are thermodynamically unstable; Infinity stability upon constant storage conditions				
(IV) Interfacial polymerisation	A reaction occurs at the interface of two liquids in which the two reactive monomers needed for the reactions dissolve, respectively	Several PNPs have been prepared using a wide range of continuous and dispersed phases	A well-established process of producing PNPs	The process is expensive; Environmental concerns; various membranes with different sizes of inner pores are required to control the size of the product	N/A
(V) Controlled/ Living radical polymerisation (NMP, ATRP and RAFT)	Three approaches are involved (NMR, ATRP and RAFT)	Preparation of poly (n-butylacrylate) nanoparticles of about 300 nm size [123].	Polymeric nanoparticles with precise particle size and size distribution control can be achieved	Lack of control over molar mass; molar mass distribution, end-functionalities and macro-molecular architecture due to unavoidable fast radical-radical termination reactions; residua control agent are usually contained in the product; challenging to remove mediating agents from the aqueous dispersion	N/A

RESS: Rapid expansion of a supercritical solution; RESOLV: Rapid expansion of a supercritical solution into liquid solvent; PS: Polystyrene; PMMA: poly (methylmethacrylate); PECA: Poly (ethyl-cyanoacrylate); NMP: Nitroxide-mediated polymerisation; ATRP: Atom transfer radical polymerisation; RAFT: Reversible addition and fragmentation transfer chain polymerisation.
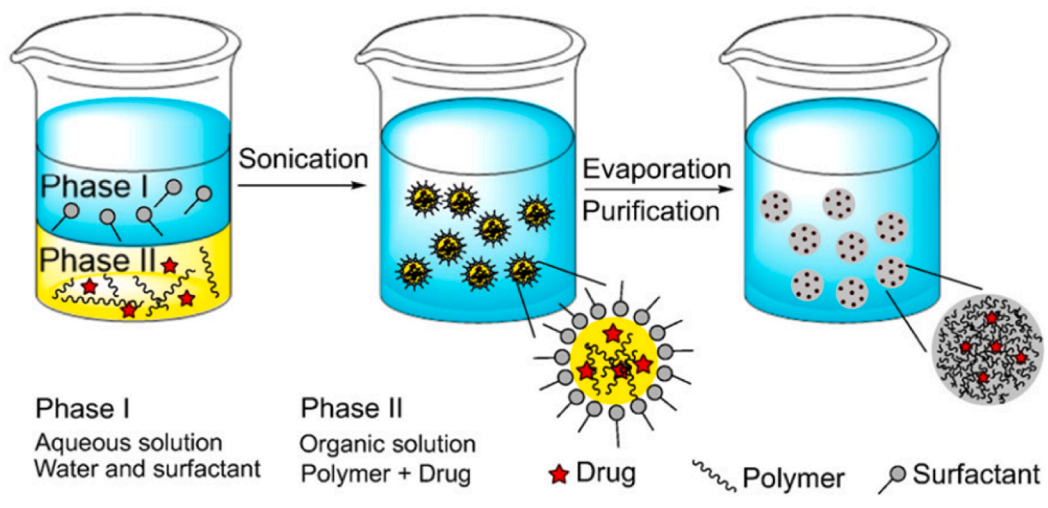
Fig. 3. Schematic illustration of the synthesis of nanosphere PNPs [74].

applying EOs as chemotherapeutics despite their wide range of medicinal properties. Thus, there is a need to develop new advanced formulations for augmented protection and enhanced delivery of EOs.

In recent years, advances in nanotechnology have spurred interest in the use of nanoparticles to improve the bioactivity of EOs via encapsulation in polymeric matrices. Polymeric nanoparticles are sub-micron particles (<1000 nm in size) that have found extensive medical applications in drug delivery, targeting, imaging, and diagnostics. Bioactives can either be encapsulated in or adsorbed on these polymeric materials. The polymers conferred new characteristics on the actives, protecting them from degradation to more minor or inactive derivatives, improving their half-life in circulation when administered and serving as a platform for controlled delivery, and ultimately enhancing their targeted bioavailability and bioactivity in a sustained manner.

As highlighted in the previous sub-section, polymers can either be from natural or synthetic origins. Nanoparticles prepared from pharmaceutically approved synthetic polymers such polyethylene glycol (PEG), polylactic acid (PLA), polycaprolactone (PCL), polyvinyl alcohol (PVA) and their respective co-polymers, PLGA (poly(lactic-co-glycolic acid)), EVA (poly(ethylene-co-vinyl acetate)) among others are used as delivery systems for EOs [124–128]. Similarly, polymers from natural sources such as starch, cellulose, alginate, chitosan, cyclodextrins, gum arabic, and their derivatives and polycomplexes have been demonstrated as micro to nano-particulate platforms for EOs formulations [129]. These polymeric nanoparticles were formed using various techniques that include melt-dispersion, antisolvent precipitation, ionic gelation, polyelectrolyte complexation, spray-drying, and supercritical fluid technology. This section will briefly discuss some of the advances in the formulation of polymer-essential oil nanoparticles based on the type of materials employed, with more focus on those from natural sources (Table 2).

4.1. Synthetic polymer-essential oil nanoparticles

PEG is a polyether compound generated from petroleum by-products that comes in a wide range of molecular weights and is used in various industrial applications. It's a versatile excipient utilised in cosmetics, pharmaceuticals, food, and agriculture as an additive, binder, and emulsion. Ref. [128] employed the melt-dispersion approach to make polymer-essential oil nanoparticles with PEG 6000 (g/mol). The EO was loaded into the polymer at a 1 to 9 ratio, nanoparticles with sizes <240 nm were produced, and 80% oil loading efficiency was achieved. Due to the gradual release of the EO from the polymeric nanoparticles, the oil's anti-insecticidal action against *Tribolium castaneum* (red flour beetle) was boosted seven times and maintained for five months.

In another study, PLA-lemon grass (*Cymbopogon citratus*) EO nanocapsules were produced by solvent/antisolvent precipitation method [127]. PLA is a linear aliphatic polyester of lactic acid, which is strongly hydrophobic. [127] prepared the functional nano-capsules by mixing the lemon-grass oil with PLA in acetone and then dispersing the water solution. The precipitated PLA nanoparticles were ~240 nm and increased in size to ~300 nm when the lemongrass oil was incorporated. The PLA nanoparticles were shown to possess inherent antimicrobial activities against four bacteria strains viz *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Candida albicans.* The incorporation of lemongrass EO enhanced the antimicrobial properties of the nanocapsules.

Other synthetic polymers such as PCL and co-polymers such as PLGA can also formulate a polymeric-essential oil delivery system. Ref. [125] prepared PCL-nanocapsules for thyme and oregano EO using the nanoprecipitation method. The polymeric nanoparticles showed uniform size distribution (170–175 nm) with very high encapsulation efficiency. In addition to the improved antimicrobial activities against *S. aureus* and *E. coli*, PCL nanocapsules conferred higher anti-oxidant activity on *Cymbopogon martini,* palmarosa EO [126]. PLGA nanoparticles containing lemongrass oil were optimised using the oil-in-water emulsion/solvent diffusion method [124]. GC/MS analysis of the optimised formulation showed that only citral was incorporated in the nanoparticles. The PLGA-citral nano-particles had a mean size of 277 nm and an encapsulation efficiency of about 73%. The bioactive component, citral, demonstrated a

Table 2
Biopolymeric nanoparticles loaded essential oils for different biological applications.

PNPs	Essential oil (EO)	Support materials	Method of synthesis	Morphology of NPs	Biological Application	References
Starch	Menthone EO	–	Nanoprecipitation	Spherical	Antioxidant and antimicrobial activities	[130]
Zein	Clove EO	–	Electro-spraying	Spherical wrinkle	edible coating and bio-preservative in perishable food products	[131]
Potato starch	*Zataria multiflora* EO	Apple peel pectin/ZrO₂ NPs	–	Spherical pores	Anti-microbial packing for quail meat	[132]
Starch	Clove EO	CaCO₃ NPs	Templating approach	Honeycomb	Natural food preservatives and anti-microbial activity	[133]
Chitosan	Tumeric EO	Magnetic-Silica NPs	Core-shell	Oval and round	Packaging material for prolonged shelf-life of surimi	[134]
Glycyrrhiza polysaccharide	Tea tree EO	Gliadin NPs	–	Spherical	Meat preservation	[135]
Starch	Thyme EO	Nano-silica	–	Coarse surface	Slow-releasing and antimicrobial packaging materials	[136]
Chitosan	Thymol EO	–	–	Spherical	Inhibit chestnuts decay during storage	[137]
Konjac glucomannan	Oregano EO	Zein–pectin	Pickering emulsions	Homogeneous and smooth	Food preservation/packaging	[138]
Whey and mung bean proteins	Industrial hemp EO	–	Nanoprecipitation	Spherical	Natural preservative for coating fishes	[139]
Alginate- chitosan	Turmeric oil- and Lemongrass oil-	–	Emulsification	Spherical	Nanocarriers with antiproliferative properties	[140]
Calcium alginate	Thyme EO	Acetic or propionic acids, and Tween®80	–	Porous fibrous	Maintaining the microbial quality of ground meat	[141]
β-cyclodextrin/chitosan	*Cinnamomum zeylanicum* EO		Ionic gelation	Spherical	Ocular mucosa, cornea, or transdermal delivery	[142]
Chitosan	Thyme EO	β-cyclodextrin	Freeze drying	Dense and irregular	Antibacterial and antioxidant	[143]
Chitosan	*Geranium maculatum,* and *Citrus bergamia*	PEG	Dispersion	–	Mosquito control	[144]
Zein	Clove EO	–	Antisolvent precipitation	–	Insecticides for crop protection	[145]
Chitosan	Peppermint EO	–	Ionic gelation	Spherical	Stored food pest management	[146]
Chitosan	Garlic EO	TPP	Ionic gelation	Spherical	Seed dressing agent	[147]
Chitosan/pullulan	Clove EO	Chitosan-ZnO	Solvent casting	Rough surface	Active food packaging	[148]
Chitosan	Clove EO	–	Emulsion-ionic gelation	Spherical	Antioxidant and antibacterial activities	[149]
Chitosan	Summer savory	–	Ionic gelation	Spherical	Antioxidant and antibacterial delivery	[150]

biphasic release pattern with an initial 50% burst release within 1 h in saline-phosphate buffer (pH 6.8). Astoundingly, encapsulation in PLGA nanoparticles eliminated the cellular toxicity of citral-rich oil against human keratinocytes by attenuating its effect on mitochondrial dehydrogenase activity. These investigators showed that polymeric nanoparticles could improve activity and reduce the toxicity of EOs. The antimicrobial and antioxidant bioactive compounds in Palmarosa (*Cymbopogon martinii*) EO was entrapped in poly-ε-caprolactone nanoparticles prepared by the nano-precipitation method [126]. The entrapped compounds demonstrated intriguing antioxidant capacity by DPPH assay, and antimicrobial activity against *Escherichia coli* and *Staphylococcus aureus* and are considered as a material suitable in perfumery, cosmetics, and in the pharmaceutical industries. In addition, the electrospinning of polycaprolactone blended with gold nanoparticles (AuNPs) and spearmint oil nanoemulsion was also explored for wound dressing [151]. The blended compounds also displayed brilliant antimicrobial prospects against wound-associated microbes such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Candida albicans*. The potential pharmaceutical application of *Cymbopogon citratus* EO loaded into poly (D,L-lactide-co-glycolide)-nanoparticles was reported [124]. The characterization of the compound revealed the incorporation of citral as a nanocarrier, with a biphasic pattern sustained-release depending on diffusion from the polymeric matrix. A composite material of thyme essential oil (TEO) loaded in electrospun porous poly(lactic acid) nanofibers and coated with poly(vinyl alcohol)/poly(ethylene glycol) blend was prepared for humidity-controlled TEO release [152]. The bioactive packaging film showed an excellent >99% inhibition of *Escherichia coli* and *Staphylococcus aureus* as well as minimal weight loss and good firmness of strawberries packaged with the composite material. The *in vitro* release behaviours of TEO could be controlled by adjusting the humidity (20% RH to 80% RH).

4.2. Natural polymer-essential oil nanoparticles

Chitosan is a natural polymer derived from the deacetylation of chitin. It is a polycationic macromolecule that is readily functionalised for the targeted delivery of bioactive agents. It also has exceptional mucoadhesive properties. Hence, its application as an oral to gastrointestinal delivery of poorly diffused drugs across the intestinal epithelium. Polymeric encapsulation of EOs in a chitosan-based delivery system is well-established in the literature. Ionic gelation with polyphosphate is the most common method for synthesising chitosan-essential oil nanoparticles because it is generally organic solvent-free. Ref. [129] successfully encapsulated Oregano EO in chitosan nanoparticles using the oil-in-water emulsion method followed by ionic gelation with tripolyphosphate. The nanoparticles were spherical with a size range of 40–80 nm. The influence of pantasodium tripolyphosphate (TPP) and sodium hexametaphosphate (HMP) showed that oil loaded in chitosan-TPP nanoparticles had higher loading capacity and encapsulation efficiency than those prepared with HMP. The bioactivities of the EO were not affected following loading in chitosan nanoparticles. For applications in food preservation, films made from or coated with chitosan-essential oils nanoparticles were also shown to improve the shelf life and quality of perishable foods such as fruits and meats [153]. Chitosan nanoparticles loaded with cinnamon EOs exhibited unusual antimicrobial and antioxidant activities. The loading capacity of the oil was directly dependent on the size of the nanoparticles [153]. The cumulative amount of oil released was higher in acidic pH when compared to those released at normal or basic pH [129]. Chitosan disintegrates easily in acidic solutions, thus the need for co-polymerisation with other acid-tolerant polymers such as alginate in other to extend retention coefficients of chitosan-based nanoparticles in the gastric environment. The antifungal properties and half-life of thyme EOs in nanogel formulation of chitosan and benzoic acid were examined by Ref. [154].

The *in vivo* analysis displayed an increased half-life and remarkable anti-fungal properties against *Aspergillus flavus* at elevated concentrations above 700 mg/l. Ref. [155] revealed that the semi-solid hydrogels fabricated from polyvinyl alcohol incorporated into chitosan-loaded clove EO or turmeric EO are promising candidates for wound management. This is because the hydrogel assisted in sustaining the prolonged-release rate of the bioactive essential oil compounds for wound treatment and is non-toxic to both NCTC clone 929 and normal human dermal fibroblasts (NHDF) cells. To improve the anti-cancer activity of celandine roots and leaves oil, Ref. [156] extracted the essential oils and loaded them into chitosan nanoparticles. The loaded compounds displayed a dose-dependent effect on the MCF-7 cell line with inhibitory concentration (IC50) values of 77.6, and 41.5 μg/mL for the loaded roots oil and leaves oil respectively; as well as 63.73% apoptosis for the loaded leaves oil. Meanwhile, in the dental industry, nanogel was fabricated from *Mentha piperita* EO (MPEO) loaded with chitosan [157]. The nanogel was deployed as an antibiofilm agent against *Streptococcus mutans* (dental plaque agent). The maximum release of MPEO was about 50% during 360 h in a hydroalcoholic solvent at ambient temperature. The adherence of bacterial cells showed high sensitivity to the nanoformulation compared with unloaded chitosan-nanogel. The antibiofilm inhibition of *S. mutans* occurred in 50 and 400 μg/mL for loaded and unloaded-nanogel respectively. For the control of dengue vector, Ref. [158] prepared chitosan-cashew gum beads loaded with *Lippia sidoides* EO. The oil loading ranged from 2.4% to 4.4% and the diffusion coefficient was as low as 2×10^{-15} m^2/s. The *in vivo* release studies show good larvae control of the dengue vector and its successful elimination in 72 h.

5. Conclusions

The integration of EOs into the health care delivery system worldwide is increasing, and enhancing their delivery is of utmost importance. Essential oils used chiefly in aromatherapy can be repurposed, and their delivery into the patient's system is enhanced using nanotechnology. EOs are reportedly antioxidant, phytotoxic, acaricidal, antimicrobial, anticancerous, and antidepressant. Integrating nanotechnology into the healthcare delivery system is an evolving area of drug delivery. However, formulating any nano-drugs depends on choosing a suitable polymer system. EOs from several medicinal plants have been produced in synthetic polymer nanoparticles, which has reportedly increased the efficacy and shelf-life of the polymer-essential oil nanoparticles. Also, natural polymers have been employed to produce polymer-essential oil nanoparticles, increasing their effectiveness.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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