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Nanoencapsulation of Plant Volatile Organic Compounds to Improve Their Biological Activities

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ABSTRACT

Plant volatile organic compounds (volatiles) are secondary plant metabolites that play crucial roles in the reproduction, defence, and interactions with other vegetation. They have been shown to exhibit a broad range of biological properties and have been investigated for antimicrobial and anticancer activities. In addition, they are thought be more environmentally friendly than many other synthetic chemicals [1]. Despite these facts, their applications in the medical, food, and agricultural fields are considerably restricted due to their volatilities, instabilities, and aqueous insolubilities. Nanoparticle encapsulation of plant volatile organic compounds is regarded as one of the best strategies that could lead to the enhancement of the bioavailability and biological activity of the volatile compounds by overcoming their physical limitations and promoting their controlled release and cellular absorption. In this review, we will discuss the biosynthesis and analysis of plant volatile organic compounds, their biological activities, and limitations. Furthermore, different types of nanoparticle platforms used to encapsulate the volatiles and the biological efficacies of nanoencapsulated volatile organic compounds will be covered.

Introduction

VOCs comprise a chemically diverse group of organic compounds. They have high vapour pressure under ambient conditions as a consequence of low boiling points. This causes large numbers of molecules to evaporate or sublimate from the liquid or solid form of the compound into the air [2]. Many plants release diverse blends of VOCs from nearly all organs to attract pollinators, prevent attacks from pathogens and herbivores, and communicate with the surrounding environment [3–5]. Plant VOCs account for about 1% of plant secondary metabolites currently known and typically comprise low molecular weight metabolites (< 300 Da) with fairly low boiling points (e.g., 236.8 °C for carvacrol, 225 °C for citral, and 198 °C for linalool) [6]. The lipophilic nature of plant VOCs enables them to travel freely across cellular membranes and disperse into the surrounding atmosphere. Since most plant VOCs do not cause serious toxicity to the environment, they have been classified as GRAS and listed in EAFUS [7].

Plant VOCs are known to have a diverse array of biological properties, including antibacterial [8,9], antifungal [10], antiviral [11], anticancer [12,13], insecticidal [14], anti-inflammatory [15], antidiabetic [16], neuroprotective [17], and antihepatotoxic activities [18]. Such properties can be applied in medical, food, and agricultural fields. However, many of their biological activities are prevented from wide scale use because of the short lifetimes of the active components due to volatility. Protection and controlled

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ABBREVIATIONS

CEO	clove essential oil
Ch-NPs	chitosan nanoparticles
DEN-2	dengue virus type 2
EAFUS	Everything Added to Foods in the United States
FMO	frankincense and myrrh essential oils
GRAS	Generally Regarded as Safe
HSV-1	herpes simplex virus type 1
HSV-2	herpes simplex virus type 2
JUNV	Junin virus
LOX	lipoxygenase
MDGC	multidimensional gas chromatography
MEP	methylerythritol phosphate
MFCs	minimum fungicidal concentrations
MICs	minimum inhibitory concentrations
MLVs	multilamellar nanoliposomes
MNPs	metal nanoparticles
MRSA	methicillin-resistant *Staphylococcus aureus*
MSNPs	mesoporous silica nanoparticles
MVA	mevalonic acid
NEs	nanoemulsions
NLCs	nanostructured lipid carriers
$O_2(^1\Delta_g)$	singlet oxygen
$O_2(^3\Sigma_g\text{-})$	triplet oxygen
PCL	poly-ε-caprolactone
PFEO	pepper fragrant essential oil
PLGA	poly (lactic-co-glycolic acid)
ROS	reactive oxygen species
SLNs	solid lipid nanoparticles
SUVs	unilamellar nanoliposomes
TGA	thermogravimetric analysis
TPF	thermoplastic flour
VOCs	volatile organic compounds

release of VOCs via nanoencapsulation could increase the utility of these compounds [19]. In this study, the comprehensive literature survey was implemented utilising the Scopus and Pubmed (MEDLINE) databases from inception to June 10, 2020. English language papers published as primary documents, meta-analyses, reviews, and systematic reviews were included for the investigation. The title and abstract key words employed during the search are as follows: plant volatile organic compounds; essential oil; synthesis; analysis; antimicrobial activity; anticancer activity; applicational limitation; nanoparticle encapsulation; enhanced bioavailability; enhanced biological activity. In terms of the enhanced biological activity of encapsulated plant VOCs, we focused on the improved antibacterial, antifungal, antivirus, and anticancer activities of essential oils upon nanoparticle encapsulation.

Biosynthesis of plant volatile organic compounds

Plant VOCs are synthesised from primary metabolites through enzymatic modifications, including oxidation, hydroxylation, acetylation, and methylation. The three main groups of plant VOCs (terpenoids, phenylpropanoids/benzenoids, and fatty acid derivatives) are generated via several metabolic pathways such as the MVA, MEP, the shikimate/phenylalanine, and LOX pathways (▶ **Fig. 1**) [20].

Terpenoids originate from the universal five-carbon building components isopentenyl diphosphate and its allylic isomer dimethylallyl diphosphate [2]. Two metabolic pathways such as the MVA (▶ **Fig. 1**, green highlighted box) and MEP pathways (▶ **Fig. 1**, pink outlined box) are involved in the synthesis of hemiterpenes (C5), monoterpenes (C10), sesquiterpenes (C15), and diterpenes (C20). The MVA pathway is thought to take place in the cytosol, endoplasmic reticulum, and peroxisomes to generate sesquiterpenes, while the MEP pathway occurs only in plastids and synthesises the terpenoids having C5, C10, and C20 [21].

The biosynthesis of phenylpropanoid and benzenoid compounds is initiated by the condensation of phosphoenolpyruvate and erythrose 4-phosphate, and the subsequent shikimate pathway mediates the generation of phenylalanine (▶ **Fig. 1**, blue highlighted box) [22]. Cinnamic acid converted from phenylalanine undergoes many enzymatic reactions such as methylation and acetylation to generate cyclic volatiles, including eugenol and benzyl benzoate [23, 24].

Volatile fatty acid derivatives are generated from C_{18} fatty acids, i.e., linoleic acid or linolenic acid, which are subjected to peroxidation at the C_9 or C_{13} position by LOXs, leading to the production of two kinds of compounds, the 9-hydroperoxy and 13-hydroperoxy derivatives of polyenoic fatty acids (▶ **Fig. 1**, yellow highlighted box) [25]. These intermediates undergo metabolic modifications via two branches of the LOX pathway, which are the oxide synthase pathway and hydroperoxide lyase pathway, and they are converted to fatty acid derivatives such as methyl jasmonate and green leaf volatiles [26].

Analysis of plant volatile organic compounds

Quantification or qualification of plant VOCs is difficult due to their presence in small amounts and close similarity between molecules. Although a number of analytical methods including organoleptic, physical, chemical, and spectroscopic techniques are available for the characterisation of the plant VOCs [27], the chromatographic techniques have been extensively used due the ability to mediate comprehensive separation and identification of plant VOCs [28, 29]. GC is thought to be the most suitable platform for analysing plant VOCs due to their volatility and low molecular weights [30]. In particular, multidimensional GC (MDGC), which combines several columns with different stationary phases, e.g., nonpolar and polar phases, can improve the efficiency of separation and authentication of enantiomeric plant VOCs [31]. Liquid chromatography is also employed as an alternative platform to GC for analysing thermally labile or less volatile compounds [32].

Biological Activities and Limitation of Plant Volatile Organic Compounds

Biological activities

Antimicrobial activities

Plant VOCs have a broad range of antimicrobial activities because plants have evolved their volatiles to defend themselves against

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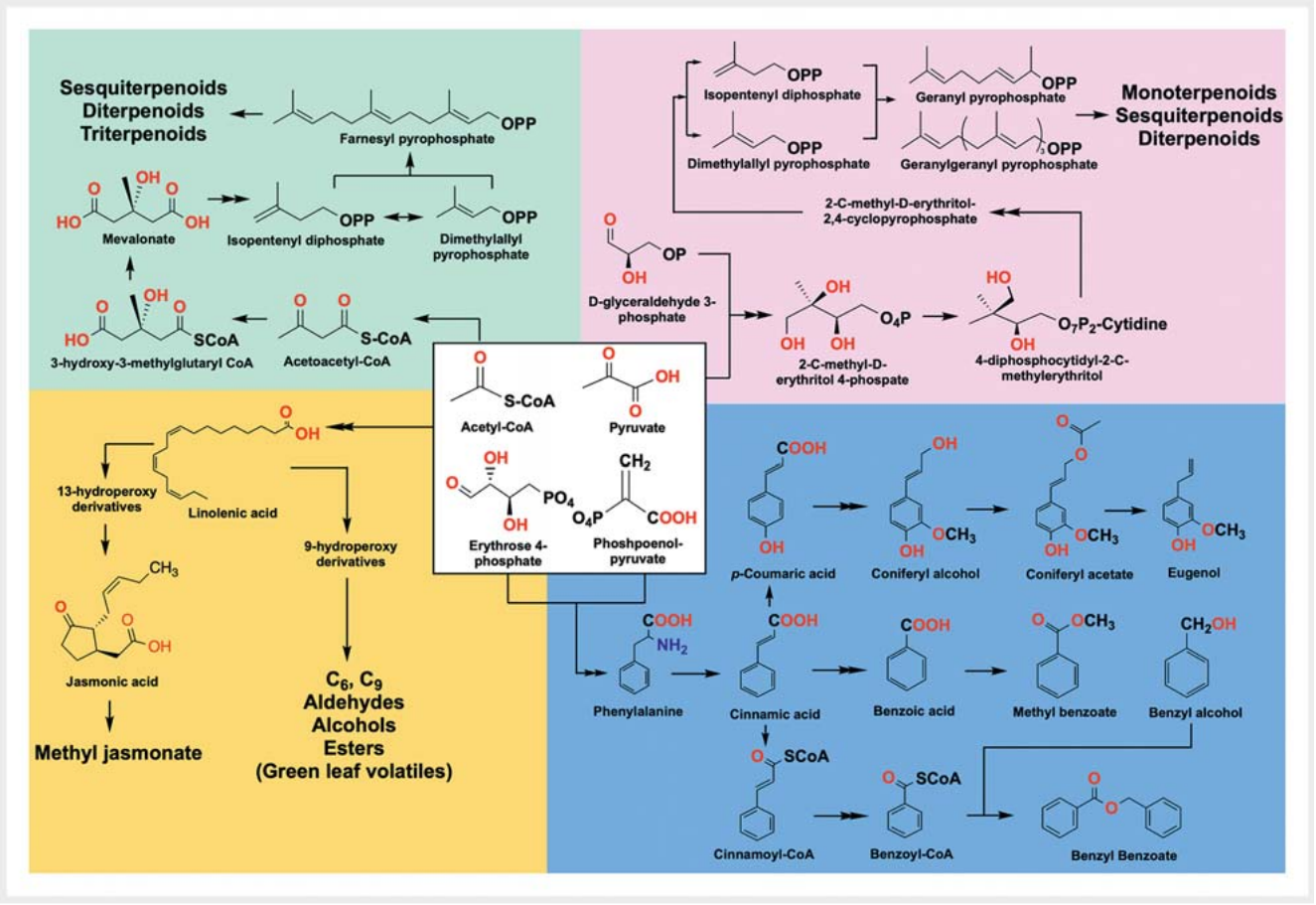

▶ **Fig. 1** Biosynthesis of plant VOCs. The biosynthesis pathways of terpenes are highlighted in blue and green, where the green background indicates the MVA pathway and the pink background shows the MEP pathway. The blue highlighted boxes and yellow highlighted boxes illustrate the phenylpropanoids/benzenoids and fatty acid derivatives biosynthesis, respectively. Acetyl-CoA, pyruvate, phosphoenolpyruvate, and erythrose 4-phosphate, which are the fundamental materials for the generation of plant VOCs, are held in the middle rectangular box. Here, the stacked arrows indicate the involvement of multiple conversion reactions.

deleterious bacteria, fungi, and viruses. The volatile compounds could be used to replace many synthetic drugs that are hindered by high toxicities and low efficacies. However, this is dependent upon the bioavailabilities of the VOCs being improved [33].

Antibacterial activity

Antibacterial properties of plant VOCs against both gram-positive and gram-negative bacteria have been demonstrated through a number of studies [34–39]. Essential oils extracted from several plants such as *Origanum* species have highly active VOCs that exert activity against multidrug-resistant bacteria, including *Acinetobacter baumannii* and *Pseudomonas aeruginosa* with MICs of 0.08–0.64 mg/mL [40]. Soković et al. reported that carvacrol possessed higher antibacterial activity towards gram-negative and gram-positive bacteria with a MIC of 0.13–1.00 µg/mL than streptomycin (MIC = 1.0–3.0 µg/mL). Gram-negative bacteria appeared to be resistant to the volatiles that they had examined, e.g., the inhibition zone of carvacrol against *P. aeruginosa* (22 mm) was smaller than those against gram-positive bacteria [36]. In a study that assessed the antibacterial potentials of citral, carvacrol, geraniol, terpineol, perillaldehyde, eugenol, linalool, and citronellal against foodborne pathogens, citral and carvacrol exhibited the highest inhibitory activities against *Escherichia coli, Salmonella typhimurium, Listeria monocytogenes,* and *Vibrio vulnificus* among all the volatiles, e.g., MICs of citral and carvacrol against *V. vulnificus* were 100 and 250 µg/mL, respectively [41]. Plant VOCs with long complex chain alcohols, and aldehydes such as citral, were shown to be effective in inhibiting the growth of gram-positive bacteria, including *L. monocytogenes* [42].

It is thought that VOCs exert their activities by means of their hydrophilic or lipophilic properties. Many studies have demonstrated that functional groups, including phenols, ketones, aldehydes, and oxides, of volatile compounds are related to the antimicrobial activities of plant VOCs [43]. Phenolic alcohol groups of terpenoids, for instance, may block the activity of membrane-related enzymes [44]. Another study revealed that monoterpenoids possessing phenol groups could prevent the synthesis of flagellin, which is the component of the flagella used for bacterial movement [45]. VOCs have also been shown to cause membrane protein denaturation, subsequent potassium efflux, and cell lysis

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[46]. Furthermore, many plant VOCs might directly affect the synthesis of DNA, RNA, and proteins in microbes [47,48]. Vulgarone B, for example, is a constituent VOC produced in *Artemisia iwayomogi*, which has been proven to introduce single nicks in DNA strands of *Staphylococcus aureus* [49].

Antifungal activity

VOCs originating from plants such as oregano, rosemary, thyme basil, citrus, and fennel have been proven to have antifungal activities against *Candida albicans, Aspergillus niger, Cryptococcus neoformans*, and *Fusarium oxysporum* [50–53]. Moghadam et al. reported *Ziziphora clinopodioides* VOCs inhibited the growth of *Aspergillus flavus* and *Aspergillus parasiticus* with MFCs of 0.78 and 0.39 mg/mL within 2 days on Muller-Hinton agar plates each, and also substantially hindered aflatoxin B_1 production from those fungi at 6.25 and 3.12 mg/mL after 29 days of incubation in maize, respectively [54]. Plant VOCs from *Mentha x piperita* displayed significant fungicidal activities, in which MICs of volatiles against *Candida* species ranged from 0.25–1.00% (v/v). Fungistatic activities of the compounds against dermatophytes [MIC = 0.125–0.5%, (v/v)] was evaluated to be higher than those of azole drugs, with MICs up to 4% (v/v) [55].

Bona et al. investigated the antifungal activities of 12 essential oils against *C. albicans* while comparing them to synthetic antifungal drugs such as clotrimazole, fluconazole, and itraconazole. This showed that pathogenic yeasts were more susceptible to plant VOCs compared to conventional treatments, and, in particular, plant VOCs from oregano and winter savoury showed fungal inhibition rates that were more than 200% that of clotrimazole. It was suggested that the VOCs mostly affected the cell wall and membranes of the fungi [56]. Indeed, plant VOCs might demolish the fungal cell wall and cytoplasmic membranes, leading to a leakage of the cytoplasm and its coagulation [57]. Eugenol and carvacrol were observed to cause mycelial deformation of *Cladosporium herbarum* when they inhibited the growth of the fungi. The morphological deformations might be correlated with the action of the compounds on cell wall enzymes involving chitinases and glucanases [58].

Antiviral activity

Many plant VOCs have demonstrated antiviral properties against HSV-1, HSV-2, poliovirus, coxsackievirus B1, avian influenza virus, rhinovirus, and DEN-2 [59–63]. HSV-1 and HSV-2 are very common viruses that are estimated to infect 60–95% of the adult human population and have been extensively studied for their susceptibility to plant VOCs. Plant VOCs of *Hyptis mutabilis* [64], *Glechon marifolia* [65], and *Artemisia arborescens* [66] suppressed the replication of HSV-1. *M. piperita* VOCs exhibited high levels of virucidal activity against HSV-1 and HSV-2, and against an acyclovir- (an antivirus drug) resistant strain of HSV-1 [67]. Anti-influenza viral properties of *Pogostemon cablin* VOCs against H1N1 and H2N2 were elucidated by Li et al. [68] and Wu et al. [69]. García et al. screened essential oils obtained from several aromatic plants for the virucidal activity against HSV-1, JUNV, and DEN-2 and concluded that *Lippia junelliana* and *Lippia turbinata* essential oils possessed potent inhibitory activities against JUNV, while *Artemisia douglasiana* and *Eupatorium patens* essential oils had distinguishable effects on DEN-2 infectivity [70]. Hammami et al. also claimed that *Teucrium pseudochamaepitys* VOCs can give rise to the significant reduction of coxsackievirus B virus infectivity of human endothelial type 2 (Hep-2) cells grown *in vitro* [60].

Anticancer activity

The preventive and suppressive effects of plant VOCs on various cancers such as brain, breast, colon, liver, lung, mouth, and prostate cancers and leukaemia have been proven in a number of studies [71,72]. Plant VOCs are able to prevent carcinogenesis through their antimutagenic and antioxidant capacities. Turmeric essential oil has been shown to exhibit significant antimutagenic activities against mutagens, including sodium azide [73]. *β*-Caryophyllene was also evaluated to possess strong antimutagenic activity against 2-nitrofluorene, because the compound might inactivate mutagens and block DNA damages *in vitro* [74]. Plant VOCs can also induce apoptosis and cell cycle arrest in cancer cells [75]. Apoptotic cell death may arise from the increased levels of ROS as a result of exposure to plant VOCs. *Schisandrae semen* VOCs demonstrated an immediate generation of ROS in human leukaemia U937 cells, and triggered the mitochondria-dependent apoptotic signalling pathways [76]. Pavithra et al. suggested that *Pamburus missionis* VOCs increased the intracellular ROS level in epidermoid cancer cells and that inhibition of the VOC-induced ROS production resulted in a decrease in apoptosis [77]. Plant VOCs can be involved in the regulation of signalling pathways such as the NF-*k*B, PIK/AKT/mTOR, ERK1/2-Bcl-2/survivin, and MAPK pathways in cancer cells to induce cell death (▶ **Fig. 2**). Zito et al. reported that *Cyphostemma juttae* VOC can cause a substantial reduction of NF-*k*B activation and downregulate the NF-*k*B target genes in breast cancer cells [78]. It had been determined that VOCs of three *Salvia* species, i.e., *Salvia aurea, Salvia Judaica*, and *Salvia viscosa*, increased the Bax/Bcl-2 expression ratio in prostate cancer cells [79], *Litsea cubeba* VOCs dephosphorylated Ser473 and Thr308 of Akt through the suppression of mTOR and pPDK1 in lung cancer cells [80], and curcumol inhibited the expression of phosphorylated STAT3 via the JAK1/2 and Src pathways and blocked the synthesis of HIF-1*α* via the mTOR and MAPK pathways to suppress the growth of hepatic cancer cells [81]. Cell cycle arrest in cancer cells by plant VOCs is also believed to be one line of therapeutic strategies where many genes involved in cancer cell cycles can be hampered. *β*-Caryophyllene, for example, has been proven to regulate G1 cell cycle progression by decreasing the expression of CDK2, CDK4, CDK6, cyclin D1, and cyclin E and increasing the levels of p21 and p27 in lung cancer cells [82]. Furthermore, the metastasis and angiogenesis processes of cancer cells were constrained by plant VOCs such as D-limonene [83] and *Tridax procumbens* VOCs [84].

Limitations

Plant VOCs can be easily dissipated through evaporation [85], and degraded (oxidised [86], isomerised [87], dehydrogenised [86], or polymerised [88]) by light, heat, or air unless they are protected by external factors [89]. The insolubility of plant VOCs in the aqueous phase may also restrict their applications [90].

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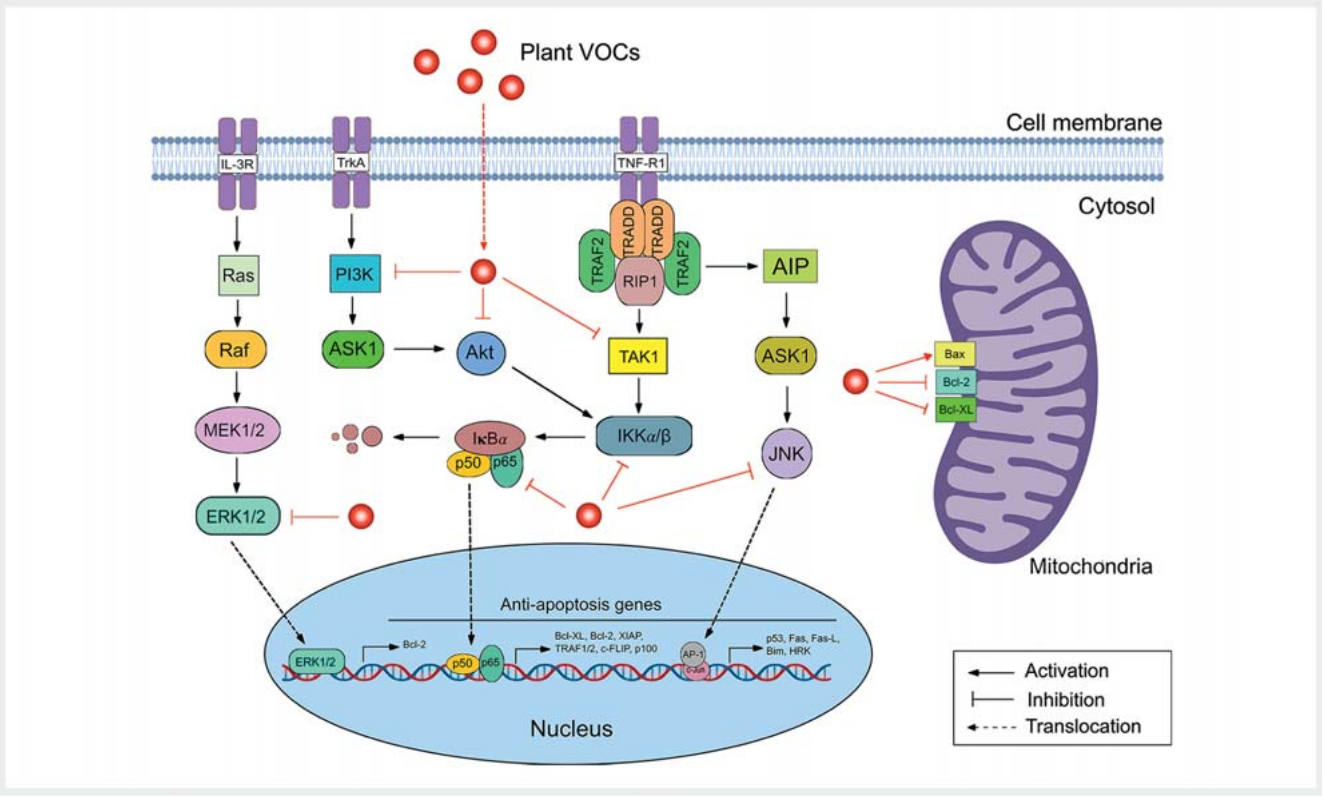

▶ **Fig. 2** Schematic illustration of action of plant VOCs on antiapoptotic pathways in cancer cells.

Deactivation by light

Ultraviolet light and visible light are able to induce the excitation of a quantum state of sensitisers such as riboflavin, and the transition energy from an excited state to ground state causes the autoxidation of plant VOCs [91]. During the autoxidation process, molecules may accept a proton or an electron from other molecules and, as a result, radicals can be produced in volatile molecules [88]. Beltrame et al. reported that essential oils of Marjoram (*Origanum majorana*) were likely to undergo rapid photodegradation and exhibit the dramatic change in their chemical profiles even in 5 min under UV light. The main components of the essential oils degraded by the light were *p*-diisopropyl-benzene, 2-undecanone, and *m*-diisopropyl-benzene [92]. The extent of degradation of individual VOCs is likely to depend on the antioxidant level in the surrounding environment. According to work done by Turek et al., the *α*-terpinene component of rosemary oil was reduced to 16.4% upon light exposure for 12 weeks, while there was no decrease of the volatile compound in the dark condition. However, under the same conditions, *α*-terpinene in thyme oil had been reduced from 91.5 to 73.3%, indicating that there is a lower degree of photodegradation in thyme oil than in rosemary oil. Thus, it could be considered that the antioxidant components of thyme oil such as thymol and carvacrol could prevent photoautoxidation of *α*-terpinene more effectively than those in rosemary oil [93]. The involvement of [$O_2(^3\Sigma_g^-)$] in photooxidation was recently identified by Dimarco Palencia et al. Oregano essential oil, whose major ingredients are carvacrol and thymol, was shown to be photodegraded through the excitement of endogenous sensitisers such as flavins, NADH/NADPH, and urocanic acid and the formation $O_2(^1\Delta_g)$ followed by the oxidation of VOCs by $O_2(^1\Delta_g)$ [94].

Deactivation by heat and air

It is predictable that the degradation of essential oils could be hastened with an increase in temperature, since chemical reactions such as oxidation and decomposition accelerate with heat. Many studies found that plant VOCs change their compositions under high temperature conditions during storage. Analysis of the thermal stability of laurel, oregano, and rosemary VOCs showed that all terpenes indicated a likelihood of thermo-degradation and monocarbonyl compounds, and hexanal, 2-hepaenal, and 2,4-decadienal appeared as a result of autoxidation [95]. Hădărugă et al. also reported that terpenes, including sesquiterpenes, had a greater susceptibility to degradation than the corresponding alcohols, and as such epoxidated sesquiterpenes and monoterpenes were found to be abundant after high temperature treatment [96]. The degradation of VOCs can result in a reduction in their bioactivities, for example, their antioxidant capacity. Indeed plant VOCs used in food preservations have been shown to have decreased antioxidant capacity after heating [97–99].

Since oxidation reactions account for the main degradation of plant VOCs, their access to oxygen has a crucial impact on stability. As a consequence, plant VOCs are less likely to be degraded in an environment with low oxygen levels [88]. It has been reported

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that lavender and thyme oil that had been stored for 72 weeks at low temperature were degraded as a result of large amounts of dissolved oxygen that contributed to peroxide generation. This is in agreement with Henry's law, which shows that oxygen solubility in liquid is high at low temperature [93]. In order to prevent the oxidation of VOCs by oxygen, inert gases such as argon might be employed in the storage of essential oils. With regards to temperature-dependent degradation, alkyl or hydroxy radicals within plant VOCs are responsible for oxidation at high temperatures due to the limited amount of oxygen [100].

Insolubility in water

Plant VOCs, which are mostly soluble in organic solvents, have poor solubility in water and body fluids such as blood. This is one of the main reasons why plant VOCs have not been widely applied in medical, food, and agricultural fields [43, 101, 102]. Samperio et al. analysed the aqueous solubility of over 20 plant VOCs at 25 °C for 24 h, shaking at 250 rpm, and found that their solubility ranged from 1.6 to 1282.2 mg/L (eugenol). In particular, nonanoic lactone, *β*-pinene, benzyl cinnamate, (R)-limonene, cyclohexane butyric acid, methyl nonanoate, propyl benzoate, and trans, trans-2,4-decadienal were almost insoluble in distilled water; less than 0.01 % (v/v) in water [103]. The insolubility of VOCs in water could be improved; the limitation of thyme white essential oil, for example, has been overcome through encapsulation into cellulose nanocrystals generating a natural antimicrobial agent [104].

Nanoencapsulation of Plant Volatile Organic Compounds and Their Improved Biological Activities

Encapsulation of bioactive compounds can be defined as a process of surrounding droplets of the compounds with coatings, or immersing them in heterogeneous or homogeneous matrices [105]. Nanoencapsulation of plant VOCs can decrease the volatility of bioactive compounds, protect them from external factors such as oxygen, light, moisture, and pH, and increase their solubilities. Encapsulated plant VOCs are likely to possess higher biological activities than free compounds, as the nanoparticles can mediate the controlled release and increased cellular accessibility of the volatiles [106].

Nanoencapsulation systems for carrying plant volatile organic compounds

Several types of nanoencapsulation platforms have been used to increase the availability of plant VOCs in pharmaceutical, food, and agricultural areas, including polymer-based, lipid-based, and inorganic nanoparticle systems. It is thought that plant VOCs form hydrophobic interactions with the hydrophobic cavities of nanocapsules, or the polymers of nanocapsules and nanospheres. They may also interact with the surfactants of nanoliposomes or lipid phases of NEs, SLNs, and NLCs. The interaction of VOCs with inorganic nanoparticle systems is likely to be *via* van der Waals bonds, or electrostatic interactions in the case of metal nanoparticles (▶ **Fig. 3**).

The encapsulation of plant VOCs in organic nanostructured systems, i.e., polymer- or lipid-based nanoparticles, has been extensively discussed by de Matos et al. [107]. Among those platforms, Ch-NPs have been most widely applied mainly due to their good physicochemical properties and intrinsic antimicrobial potentials. Ch-NPs have drawn attention as a non-parenteral delivery formulation of plant VOCs to treat various diseases, including cancers. Initial drawbacks such as low encapsulation efficiency of Ch-NPs can be improved by employing inclusion complexes such as *β*-cyclodextrin (▶ **Fig. 4**) [108]. Other commonly used systems for the encapsulation of volatiles are MSNPs (Mesoporous silica nanoparticles) and MNPs (metal nanoparticles).

MSNPs possess honeycomb-like structures with a large number of pores, whose diameters range between 2–50 nm and are characterised by a high specific surface area, adjustable particle diameter, and pore size, and the feasibility of the surface functionalisation [109]. The fabrication of MSNPs is principally based on the hydrolysis and condensation of alkoxysilanes. Surfactants or block copolymers can formulate the meso-structures above the critical micelle concentration, which is followed by condensation of silica precursors on the surface of the micelles, and the micelles are removed during the fabrication process [110, 111]. Among several types of MSNPs, MCM-41 nanoparticles with a hexagonal structure and mesopores with a diameter of 2.0–6.5 nm have often been employed to encapsulate plant VOCs [112]. Jin et al. synthesised MCM-41 nanoparticles with an average size of 717 nm and a zeta potential of − 43.9 mV and loaded PFEO (pepper fragrant essential oil) into the hollow MSNPs by stirring *n*-hexane solution containing the volatiles and nanoparticles for 24 h. PFEO laden nanoparticles demonstrated improved antimicrobial activity against foodborne bacteria compared to PFEO, e.g., the total inhibitory concentrations of the nanoformulation and free compounds against *S. aureus* were 20.0 and 22.5 mg/mL upon 48 h treatment, respectively [113]. Solvent immersion appeared to be the best way to load volatiles into MSNPs, as the other methods such as the melting process might result in a loss of VOCs during the loading process. *Thymus eriocalyx* and *Thymus kotschyanus* VOCs, for example, were loaded into MCM-41 nanoparticles by submerging the MSNPs in an acetone solution containing the cargo VOCs. The MSNPs encapsulation increased the mite mortality rates of *T. eriocalyx* and *T. kotschyanus* VOCs up to 2.5 and 3.2 times, respectively [114].

MNPs are nanoscale entities composed of pure metals such as gold, silver, titanium, zinc, and platinum or their compounds, e.g., oxides, hydroxides, sulphides, and chlorides [115]. MNPs can be formed from "magic clusters", where the cluster consists of definitive number of atoms, resulting in exceptional stability, but they might be easily coalesced due to the deficiency of repellent forces between metal nanoclusters unless the nanoparticles are stabilised. The stabilisation of MNPs could be accomplished by applying capping agents that are able to generate an electrostatic repulsion or a steric hindrance between nanoparticles [116]. Plant VOCs have been exploited as the capping or reducing agents in the formation of MNPs and have increased the innate biological activities of the MNPs. *Nigella sativa* VOC-coated gold nanoparticles were fabricated by using the VOCs as the capping agent; these were spherical, and the particle size ranged between 15.6–

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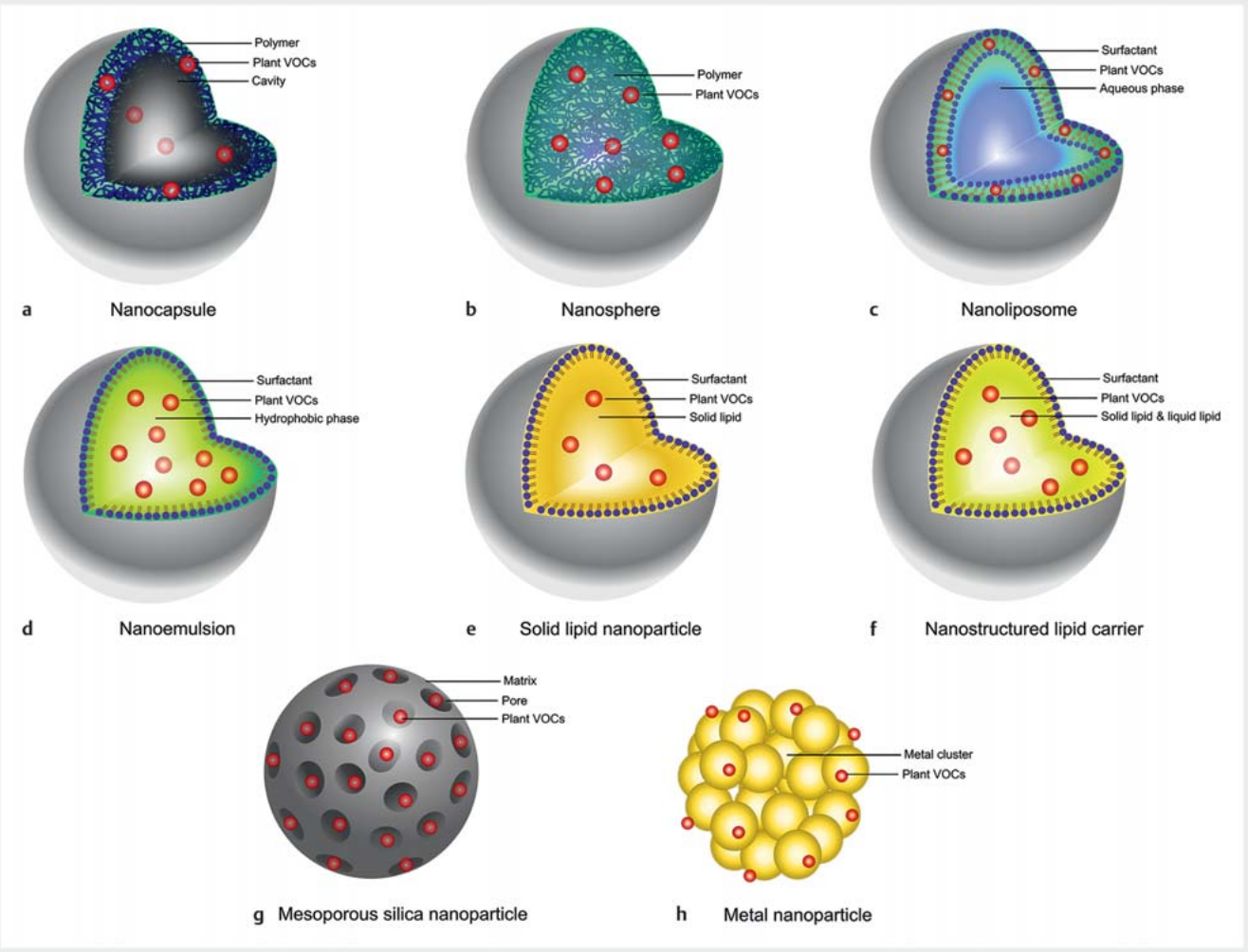

▶ **Fig. 3** Structures of nanoparticle platforms carrying plant VOCs. Nanocapsule (**a**) and nanosphere (**b**) are the polymer-based nanoparticles, while nanoliposome (**c**), nanoemulsion (**d**), solid lipid nanoparticle (**e**), and nanostructured lipid carrier (**f**) are constructed from lipid to form the lipid-based nanoparticle system. The inorganic nanoparticle system includes mesoporous silica nanoparticles (**g**) and metal nanoparticles (**h**).

28.4 nm. To do so, the volatile compounds were added to chloroauric acid ($HAuCl_4{\cdot}3H_2O$) and heated at 100 °C under agitation, leading to the rapid reduction of Au^{3+} to Au° [117]. Sheny et al. suggested that terpenoids, including spathulenol, globulol, muurolol, and cadinol, can utilise their tertiary hydroxyl groups to reduce gold ions in the presence of acetone at a high temperature and the oxidised terpenoids attach around the gold nanoparticles through the carboxylate ions, although further investigations are needed to elucidate the exact mechanism [118]. Gold reduction by plant VOCs originated from *Artemisia vulgaris* and *Ferula persica* has been achieved after incubation at ambient temperatures for 24 h [119, 120]. Green synthesis of silver nanoparticles using plant VOCs has also been reported in several studies using plant VOCs as reducing agents [121, 122].

Bioavailability and biological activity of nanoencapsulated plant volatile organic compounds *Bioavailability of nanoencapsulated plant volatile organic compounds*

Improvement of photostability

The autoxidation of plant VOCs, which is triggered by UV or visible light, can be prevented through nanoencapsulation. Sebaaly et al. reported that eugenol-laden liposomes showed a significant photostability compared to free eugenol. After exposing samples to UV light for 10 h, 95% of eugenol remained in lipoid S100 liposomes, whereas more than 40% of free eugenol had been degraded under the same conditions [123]. Resveratrol, an unstable VOC that can easily be converted to its *cis* form under illumination, was loaded into nanoliposomes to improve its photostability. Nanoliposomes maintained 70% of the active (*trans*-) resveratrol after 16 min of UV exposure, whereas only 10% of volatiles in the free form remained [124]. Nootkatone, a volatile sesquiterpenoid compound, was encapsulated in cyclodextrins complexes to improve its photostability. A photodegradation assay showed that free nootkatone was subject to almost complete degradation

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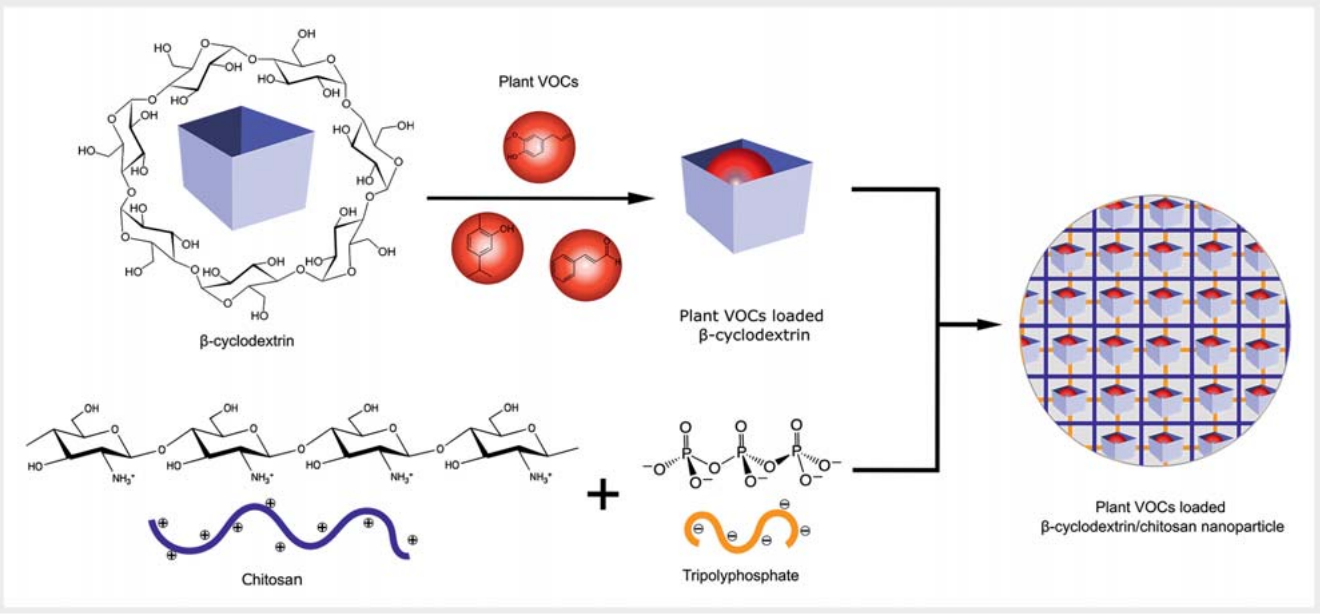

▶ **Fig. 4** Schematic representation of the formation of *β*-cyclodextrin/chitosan nanoparticles carrying plant VOCs.

(96%) after 60 min of UV irradiation, compared to 63% after encapsulation [125]. Kumar et al. found out that cyclodextrin-based nanosponges carrying Babchi (*Psoralea corylifolia*) essential oil protected cargo compounds from photodegradation such that the photodegradation rate constants exhibited by pure and encapsulated compounds were $6.909 \times 10^{-3} \cdot min^{-1}$ and $2.303 \times 10^{-3} \cdot min^{-1}$ in a pseudo-first-order kinetic model upon UV exposure, respectively [126]. Photodegradation of *Zanthoxylum riedelianum* VOCs by UV radiation was significantly reduced after their encapsulation into PCL nanospheres. Pereira et al. indicated that only 43% of the encapsulated VOCs were degraded upon 9 h of UV radiation exposure, while free VOCs were degraded by 76% [127]. Similarly, PCL nanospheres protected *Zanthoxylum rhoifolium* VOCs from photodegradation, so that the encapsulated volatiles showed only 44.76% photodegradation, whereas the free VOCs suffered 94.33% degradation after 7 h exposure to light [128].

Improvement of thermostability

Nanoencapsulation of plant VOCs into polymer-based nanoparticles such as chitosan and PLGA gelatin/gum arabic nanoparticles has been shown to increase thermostability. Essential oils of *M. piperita* and *Camellia sinensis* were loaded into Ch-NPs and the thermal stability of nanoencapsulated essential oils was investigated via TGA. Pure essential oils exhibited temperatures of a maximum degradation rate (T_d) of 160 and 200 °C, while the nanoparticles had a T_d of 350 °C, indicating an enhancement in thermostabilities of encapsulated compounds by 2.18- and 1.75-fold, respectively [129]. Upon chitosan nanoparticle encapsulation, the thermal stability of eugenol was investigated through its extrusion at 155 °C with TPF (thermoplastic flour). TPF containing encapsulated eugenol showed an 8-fold higher remaining compound content than that containing free eugenol [130].

Almeida et al. optimised the PLGA nanoparticle fabrication process using the Box-Behnken design, so that they could increase the thermal stability of the cargo VOCs from the volatilisation point of 102.4 to 133.0 °C [131]. Heat-resistant flavour nanocapsules carrying jasmine essential oil were also reported by Lv et al. Their results showed that the cross-linking of jasmine oil with gelatin/gum arabic nanoparticles by transglutaminase enabled the cargo essential oil to endure a water bath of 80 °C for several hours [132]. Zein nanoparticles have also been assessed with regard to increasing the thermal stability of thymol and carvacrol. TGA results indicated that the degradation of unloaded thymol and carvacrol took place at approximately 140 °C, whereas the major degradation of plant VOCs loaded into nanoparticles occurred at around 450 °C [133].

Improvement of aqueous solubility

Poor aqueous solubility of plant VOCs has been improved through encapsulation into nanoparticles, especially lipid-based systems such as NEs and SLNs. Upon NE encapsulation, plant VOCs dissolve in hydrophobic phases stabilised by hydrophilic surfactants, increasing their solubility in the aqueous phase. Carvacrol, limonene, and cinnamaldehyde were encapsulated in the sunflower oil droplets of NEs to overcome their own hydrophobic chemical nature. This resulted in an increase in the water solubility of carvacrol, cinnamaldehyde, and limonene by up to 2-, 6-, and 20-fold, respectively [134].

SLNs (solid lipid nanoparticles) have been used for loading FMO (Frankincense and myrrh essential oils) and were effectively dispersed into the water phase, resulting in better bioavailability of FMO and an increased *in vivo* anticancer efficacy against mouse hepatoma cells [135]. Polymer-based particles have been investigated with, for example, menthone and citral encapsulation into starch nanoparticles. Menthone-loaded nanoparticles, in particu-

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▶ **Table 1** Biological activities of nanoparticles carrying plant VOCs.

Bioactive compounds	Nanoparticles	Biological activities	References
Lemongrass essential oil	Polylactic acid nanocapsule	Antibacterial	[159]
Origanum majorana VOCs	Polycaprolactone nanocapsule	Antibacterial	[160]
Carvacrol	Chitosan nanoparticle	Antibacterial	[161]
Carum copticum VOCs	Chitosan nanoparticle	Antibacterial	[162]
Cinnamon essential oil	Nanoliposome	Antibacterial	[138]
Tea tree essential oil	Nanoliposome	Antibacterial, antifungal	[163]
D-limonene	Nanoemulsion	Antibacterial	[164]
Cuminum cyminum VOCs	Nanoemulsion	Antibacterial, anticancer	[156]
Thyme essential oil	Nanoemulsion	Antibacterial	[165]
Carvacrol	Nanoemulsion	Antibacterial, antifungal	[166]
Cymbopogon densiflorus VOCs	Nanoliposome, nanoemulsion	Antibacterial, antifungal	[145]
Eugenia caryophyllata VOCs	Solid lipid nanoparticle	Antibacterial, antifungal	[147]
Rosmarinus officinalis VOCs	Nanostructured lipid carrier	Antibacterial	[139]
Citral	Nanostructured lipid carrier	Antibacterial, antifungal	[140]
Eucalyptus & rosemary VOCs	Solid lipid nanoparticle Nanostructured lipid carrier	Antibacterial	[167]
Cinnamaldehyde, allyl isothiocyanate, Ajwain essential oil	Mesoporous silica nanoparticle	Antibacterial	[7]
Pepper VOCs	Mesoporous silica nanoparticle	Antibacterial	[113]
Coleus aromaticus VOCs	Silver nanoparticle	Antibacterial	[168]
Eugenia caryophyllata VOCs	Chitosan nanoparticle	Antifungal	[143]
Carvacrol	Nanoemulsion	Antifungal	[169]
Zataria multiflora VOCs	Solid lipid nanoparticle	Antifungal	[146]
Cymbopogon citratus VOCs	Poly (D,L-lactide-co-glycolide) nanoparticles	Antiviral	[148]
Artemisia arborescens VOCs	Nanoliposome	Antiviral	[149]
Santolina insularis VOCs	Nanoliposome	Antiviral	[150]
Curcuma longa & *Cymbopogon citratus* VOCs	Chitosan-alginate nanocapsule	Anticancer	[151]
Ocimum Gratissimum VOCs	Chitosan nanoparticle Trimethyl chitosan nanoparticle	Anticancer	[152]
Citral	Bovine serum albumin nanoparticle	Anticancer	[154]
Citrus bergamia VOCs	Nanoliposome	Anticancer	[155]
Ginger & frankincense VOCs	Nanoemulsion	Anticancer	[157]
Origanum glandulosum VOCs	Sodium alginate nanocapsule, nanoemulsion	Anticancer	[158]
Mentha spicata VOCs	Nanoemulsion	Anticancer	[170]
Citral	Solid lipid nanoparticle	Anticancer	[171]
Nigella sativa VOCs	Gold nanoparticle	Anticancer, antibacterial	[117]

lar, were completely dispersed into aqueous media, whereas free menthone was insoluble in water. Here, the hydrophilic shell material of the nanoparticles played a role in improving the solubility of cargo VOCs [136].

Biological activity of nanoencapsulated plant volatile organic compounds

In addition to the role of nanoparticles in improving the stability of volatile compounds, nanoencapsulation may also improve the bioavailability and bioactivity of active compounds (see ▶ **Table 1** for summary). This may be due to enhanced cellular absorption, and/or controlled release of plant VOCs.

Antibacterial activity

Various antibacterial, antifungal, and antiviral activities of plant VOCs could be considerably increased upon nanoparticle encapsulation. Ch-NPs loaded with VOCs from *Carum copticum* showed increased antibacterial activity against *S. aureus, Staphylococcus epidermidis, Bacillus cereus, E. coli, Salmonella typhimurium*, and *Proteus vulgaris*. Polycaprolactone nanocapsules loaded with *O. majorana* VOCs also exerted higher antibacterial activity against *Aeromonas hydrophila*, an infectious bacterium for silver catfish, than free compounds. Similar antimicrobial effects were obtained at a 50-fold lower dose when the compound was encapsulated within nanocapsules. The ability to treat the bacterial in-

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fection of catfish with a very low concentration (5 µL/L) of volatiles is more environmentally safe and cost-effective [137]. The antibiofilm effects of free cinnamon oil and nanoliposomes carrying the oil were tested against MRSA by Cui et al. The logarithmic value of a viable MRSA population in the biofilms treated with cinnamon oil was decreased by 1.49 times whereas those treated with cinnamon oil-loaded nanoliposomes led to the reduction of MRSA cells by 2.45 times. The researchers claimed that the boosted antibiofilm activity could be attributed to the improved stability of the plant VOCs by nanoencapsulation [138]. Rosemary essential oil-loaded NLCs were reported to possess antibacterial activity against gram-positive bacteria including *S. epidermidis* and reduce the rate of tissue bacterial colonisation and wound size, leading to an acceleration in healing the infected wound [139]. The antibacterial activities of NLCs and NEs carrying citral have been tested against *S. aureus, B. cereus*, and *E. coli*. Average MICs of citral-loaded NLCs were significantly lower than those of citral emulsion (e.g., MIC of emulsions against *S. aureus* was 500 µg/mL, whereas that of NLCs was 125 µg/mL), suggesting that the NLCs are likely to be the better choice to enhance the antimicrobial activity of cargo compounds than NEs [140]. Bravo Cadena et al. investigated the encapsulation of cinnamaldehyde, allyl isothiocyanate, and Ajwain essential oil into MSNPs to enhance their antibacterial activities. They revealed that cinnamaldehyde-loaded MSNPs could increase its antibacterial activity by 10-fold compared to the free compound, and eliminate over 95% of bacterial growth of five different bacterial species, including *Pseudomonas syringae* [7]. Cinnamaldehyde-load MSNPs were further incorporated into pea seed coatings, which increased the number of symptomless plants against pea bacterial blight by 143% after a 20-day cultivation compared to seed coatings without the nanoparticles [141]. Chan et al. reported that MSNPs carrying allyl isothiocyanate could maximise antimicrobial potential of the cargo compound against *P. aeruginosa* biofilm by decreasing the biofilm thickness from 100 ± 13 to 8 ± 1 µm for 24 h at a concentration of 2 mg/L. By comparison, 350 mg/L free allyl isothiocyanate only resulted in a reduction of biofilm thickness to 31 ± 4 µm under the same conditions [142].

Antifungal activity

Ch-NP encapsulation was shown to improve the antifungal activity of plant VOCs by Hasheminejad et al. They reported that free CEO could not inhibit the growth of *A. niger* at a concentration of 3 mg/mL, yet CEO-laden Ch-NPs demonstrated the complete inhibition of the fungus at a 2-fold lower concentration, i.e., 1.5 mg/mL [143]. The enhanced antifungal activity of CEO-loaded Ch-NPs could be related to the fact that the nanoparticles mediate the controlled release of VOCs and possess their own antimicrobial activity as well [144]. Lipid-based nanometric systems, i.e., NEs and nanoliposomes, containing *Cymbopogon densiflorus* VOCs were investigated for improved antifungal activities against five fungi such as *C. albicans* and *Candida parapsilosis*. Both formulations showed improved antifungal potential of up to 5 times that of free compounds and nanoliposomes carrying the plant VOCs seemed to be more effective in suppressing the growth of fungi than NEs loaded with the same volatiles. The MIC of free plant VOCs for *C. albicans* was 0.5 mg/mL, while those of NEs and nanoliposomes were 0.2 and 0.1 mg/mL, respectively [145].

Zataria multiflora VOC-loaded SLNs were also demonstrated to improve the efficiencies of plant VOCs in controlling several fungal pathogens including *Aspergillus ochraceus* and *A. niger*. Their results demonstrated a 79% inhibition on the growth of fungal pathogens with the volatiles loaded SLNs, while free plant VOCs exhibited only a 54% inhibition [146]. The antifungal activity of SLNs loaded with *Eugenia caryophyllata* VOCs against *C. albicans* (MIC = 0.10 µg/mL) have been proven to be much higher than that of free volatiles (MIC = 0.25 µg/mL). The encapsulation of volatile compounds into SLNs was proposed to enhance the antimicrobial activity through promoting the passive cellular absorption of plant VOCs into pathogens [147].

Antivirus activity

The elevated antiviral activities of plant VOCs by nanoencapsulation have been confirmed through many studies. Poly (D, L-lactide-co-glycolide) nanoparticles carrying *Cymbopogon citratus* VOCs showed a strong inhibition of HSV-1 and HSV-2 at a noncytotoxic concentration, which was 42 times lower than that of free compounds. The incorporation of the volatile compounds in the nanoparticles provided a greater contact area, resulting in a better interaction with viral membranes, and also sustained drug release from the formulation and protection of the compounds from volatilisation [148]. Antiherpetic activity was also investigated in MLVs and SUVs loaded with *A. arborescens* VOCs. *In vitro* antiviral assays based on the cytopathic effect inhibition method demonstrated that free VOCs and SUVs induced approximately 20% inhibition against HSV-1 at 100 µg/mL, while MLVs encompassing VOCs caused more than 60% viral inhibition at the same concentration [149]. However, liposome-incorporated plant VOCs do not always show higher activity than free compounds. Valenti et al. reported that *in vitro* antiherpetic activity of free *Santolina insularis* VOCs was worse in liposomal VOCs, i.e., free VOCs and MLVs exhibited 50% HSV-1 inhibition at 0.88 and 4.6 µg/mL, respectively. Although the liposomal incorporation of the VOCs did not contribute to an improved antiviral activity, the vesicular inclusion substantially improved the stability of the cargo compounds, leading to efficacy after 1 year of storage [150].

Anticancer activity

Antitumour properties of plant VOCs could also be enhanced via nanoencapsulation by improving stability and cellular absorption. *In vitro* experiments on human lung adenocarcinoma epithelial (A549) cells showed that turmeric oil- and lemongrass oil-loaded alginate and chitosan nanocapsules have higher antiproliferative activity than free compounds. The viabilities of cancer cells were decreased by 40 and 20% upon 24 h treatment of 0.4 mg/mL turmeric oil- and lemongrass oil-loaded nanocapsules, respectively, while the same concentration of free oils showed less than 10% inhibitory activity [151]. Trimethyl Ch-NPs carrying *Ocimum gratissimum* VOCs, and free volatile compounds, were tested for impact on cell viability and antiproliferation of breast cancer (MDA-MB-231) cells. After 48 h incubation, the viability of MDA-MB-231 cells was reduced to approximately 40% in response to treatment of 50 µg/mL of volatile-laden Ch-NPs, which exhibited more cytotox-

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icity against cancer cells than free volatiles, causing about 70% cell viability at the same concentration [152]. It is thought that the Ch-NPs could penetrate the cancer cell membranes and cause DNA damage, leading to defects in the cellular genes [153]. White et al. found that bovine serum albumin nanoparticle encapsulation could increase the cytotoxicity of citral against rhabdomyosarcoma cells. The viability of RH30 cells was decreased to approximately 40% of the control for the nanoparticle encapsulated citral, compared to an equivalent amount (500 µM) of free citral, after which 70% of cells remained viable. The citral-laden nanoparticles were also loaded into a biodegradable polyanhydride wafer for slow release at the tumour bed after a surgery. The wafer system was tested *in vitro* and exhibited 50% degradation over 25 days, therefore releasing citral. This could ultimately be employed to prevent locoregional recurrence of the cancer [154]. Nanoliposomes were used to encapsulate VOCs from *Citrus bergamia*, which have poor water solubility, low stability, and limited bioavailability. The encapsulated compounds were tested against human neuroblastoma (SH-SY5Y) cells at 0.01% (v/v) for 72 h and showed a 40% cytotoxicity rate compared to free volatiles, which caused the death of less than 10% of cells under the same conditions [155]. NEs carrying *Cuminum cyminum* VOCs [156] and ginger and frankincense essential oils [157] were noted to have *in vitro* antitumour activities against human tongue carcinoma (SAS) cells (IC_{50} = 1.5 µL/mL) and breast adenocarcinoma (MCF-7) cells (IC_{50} = 20.5 µg/mL), respectively. Ali et al. encapsulated *Origanum glandulosum* VOCs into sodium alginate nanocapsules and NEs and evaluated the cytotoxic effect of encapsulated volatiles and free compounds on human hepatocellular carcinoma (HepG2) and normal liver (THLE2) cells. Nanocapsules carrying the VOCs possessed higher cytotoxicity against liver cancer cells, with an IC_{50} of 54.93 µg/mL compared to an IC_{50} of 73.13 µg/mL for free compounds and 131.6 µg/mL for NEs. The low anticancer efficacy of the NEs might be correlated with their thermodynamic instability. In terms of the cytotoxicity against normal cells, the nanocapsules exhibited almost 2-fold higher IC_{50} values than the others. This result indicates that *O. glandulosum* VOC-laden nanocapsules are able to target hepatic cancer cells without causing toxicity towards healthy liver cells [158]. Gold nanoparticles have also been investigated: *N. sativa* VOCs were coated onto the particles to investigate controlling human lung cancer (A549). *In vitro* antitumour assays showed that IC_{50} values against A549 cells of bulk gold, free volatile compounds, and gold nanoparticles coated with the VOCs were 87.20, 64.15, and 28.37 µg/mL, respectively [117]. This leads to the hope that metal nanoparticles could be used as effective therapeutics to treat lung cancer in the future.

Concluding remarks

Volatile compounds derived from plants possess beneficial biological properties, including antimicrobial and anticancer activities, and do not cause serious toxicity towards the human body or the environment. Nevertheless, their usage in therapeutics, food, and agricultural settings are being inevitably restricted by the volatile, unstable, and hydrophobic attributes with which VOCs are endowed. The encapsulation of these compounds in nanostructured formulations, i.e., polymer- or lipid-based nanoparticles and inorganic nanoparticles, has been shown to increase their biological activities by improving the physicochemical properties, bioavailability, sustained release, and cellular absorption of plant-derived VOCs. Commercial applications of plant-derived VOCs are anticipated to achieve more wide scale use as the field of nanotechnology develops further.

Contributors' Statement

Conceptualization: H. E. T.; writing-original draft preparation: H. M.; writing-review and editing: H. E. T., H. M.; supervision: H. E. T.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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