5 Bioactivity of Essential Oils and Their Components

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5.1 Introduction

Essential oils (EOs) are secondary metabolites that plants usually synthesized for combating infectious or parasitic agents or generate in response to stress conditions [1]. EOs are aromatic components obtained from different plant parts such as flower, buds, seed, leaves and fruits, and they have been employed for a long time in different industries, mainly in perfumes (fragrances and aftershaves), in food (as flavouring and preservatives) and in pharmaceuticals (therapeutic action) [2].

Ten major EO crops account for 80% of the world market for EOs, the remaining 20% of the world market comprises over 150 crops. The major producers of EOs are developing or emerging countries (Brazil, China, Egypt, India, Mexico, Guatemala and Indonesia), while the major consumers are the industrialized countries (USA, western Europe and Japan). The forecasted annual growth of EO markets of around 4% is thus generating new commercial opportunities for the developing world [3]. The large volumes of EOs produced worldwide and the limited number of species in the world trade show the economic potential of EO plants as new crops [4].

The commercialization of EOs can be targeted around their bioactivity, and in this context the discovery of new uses and applications of EOs will further drive the research and development process [5]. EOs with promising activities are thus reviewed in the present work.

5.2 Antimicrobial Activity

In the last few years, there has been target interest in biologically active compounds, isolated from plant species for the elimination of pathogenic microorganisms, because of the resistance that microorganisms have built against antibiotics [6] or because they are ecologically safe compounds [7].

A wide variety of EOs are known to possess antimicrobial properties and in many cases this activity is due to the presence of active constituents, mainly attributable to isoprenes such as monoterpenes, sesquiterpenes and related alcohols, other hydrocarbons and phenols [8, 9].

The lipophilic character of their hydrocarbon skeleton and the hydrophilic character of their functional groups are of main importance in the antimicrobial action of EO components. Therefore, a rank of activity has been proposed as follows: phenols>aldehydes>ketones>alcohols>esters>hydrocarbons [10].

Some EOs containing phenolic structures, such as carvacrol and thymol, are highly active against a broad spectrum of microorganisms [10-12], including *Shigella* sp. [13]. The importance of the hydroxyl group has been confirmed [9, 14] and the relative position of the hydroxyl group on the phenolic ring does not appear to strongly influence the degree of antibacterial activity [14, 15]; however, it was reported that carvacrol is more active than thymol [9, 16–18]. Furthermore, the significance of the aromatic ring was demonstrated by the lack of activity of menthol [14]. Low activity was observed with components containing only an aromatic ring with alkyl sustituents as in *p*-cymene [9, 13, 19]. However, an aldehyde group with a conjugated double bond and a long hydrocarbon chain link to the aromatic ring might result in a better antibacterial activity [20]. Thus, cinnamaldehyde was highly effective in inhibiting the growth of several strains of bacteria [21] and fungi [22, 23]. Moreover, the strong inhibitory effect against fungi of *Cinnamomum osmophloeum* leaf oil was directly related to cinnamaldehyde content [7, 24].

High antimicrobial and antifungal activities of carvacrol have been reported [17, 25–34] with Gram-positive bacteria being the most sensible germs [35]. Thymol had potential antimicrobial and antifungal properties against plant, animal and human pathogenic fungi [36–38]. When the phenolic group was methylated, components like anethole and estragole still showed antimicrobial activity [8, 39].

EOs rich in 1,8-cineole demonstrated activity against Gram-positive and Gram-negative bacteria [39–43], including *Listeria monocytogenes* [44], against the yeast *Candida albicans* [45, 46] and against phytopathogenic fungi species [47, 48].

The aldehyde citral displayed moderate activity [49–52]. Ketones such as pulegone [53–56], fenchone [39, 57], α-thujone [58] and camphor [48–67] were reported to have antimicrobial activities.

Oxygenated monoterpenes such as menthol and aliphatic alcohols (e.g. linalool) were reported to possess strong to moderate activities against several bacteria [40, 68–73]. The position of the alcohol functional group was found to affect molecular properties of the component, such as a hydrogen-bonding capacity, and hence terpinen-4-ol was active against *Pseudomonas aeruginosa*, while *α*-terpineol was inactive [8]. The antimicrobial effects of borneol [65, 74, 75] and geraniol [76] were also reported.

Monoterpenes hydrocarbons, such as sabinene [77, 78], terpinenes [12, 31, 32, 79, 80] and limonene [30, 73, 81–83], have also shown antimicrobial properties that appear to have strong to moderate antibacterial activity against Gram-

positive bacteria and against pathogenic fungi, but in general weaker activity was observed against Gram-negative bacteria [53, 84].

The bridged bicyclic monoterpenes *α*-pinene and *β*-pinene showed considerable antifungal activity [19, 44, 67, 73, 78, 85–90]; however, there is no clear consensus yet as to which pinene isomer is more antimicrobially active [8, 44, 85, 91].

Similarly, EOs that were characterized by high levels of sesquiterpenes, such as 8-cadinene, (*Z*)-*β*-farnesene, *γ*-muurolene, spathulenol, hexahydrofarnesyl acetone and *α*-selinene, exhibited antifungal and antibacterial activity [92, 93]. In addition, caryophyllene oxide has been reported with slight antibacterial activity [55] and was inhibitory to the growth of several agricultural pathogenic fungi [94]. There are reports showing the antimicrobial activity of (*E*)-caryophyllene, [88, 95, 96], cadinanes [79, 97, 98], farnesol [99], α-eudesmol [100], *β*-eudesmol [101], *β*-phellandrene [81], biclogermacrene [102] *α*-cedrene, *β*-cedrenes and sesquithuriferol [103].

The diterpenes ferruginol and hinokiol [104, 105], geranylgeraniol, teprenone and phytol [106] showed antibacterial activity. *β*-Hydroxykaurenoic acid produced permeabilisation of the cell membrane of the fungi *Botrytis cinerea* [107, 108].

Antimicrobial activities of garlic and onion oil appeared to be determined by the concentrations of individual constituent sulfides. Sulfides with a single sulfur atom were not active, and sulfides with three or four sulfur atoms were highly inhibitory against the growth of *Candida utilis* and *Staphylococcus aureus* [109, 110].

Usually, major components are mainly responsible for the antibacterial activity in most of the EOs; however, there are some studies where whole EOs have a higher antibacterial activity than the combination of the major isolated components, indicating that minor components are critical to the activity, probably by producing a synergistic effect [111, 112]. The combination of citral with vanillin, thymol, carvacrol or eugenol was demonstrated to have synergistic effects on growth inhibition of *Zygosaccharomyces bailii* [113]. Synergistic activity between carvacrol and thymol [15] and carvacrol and cymene [14, 114] have also been described. Investigation of the two major chemical constituents of *Osmitopsis asteriscoides*, 1,8-cineole and (-)-camphor, both independently and in combination showed that synergistically they have a higher antimicrobial effect on *Candida albicans* than when tested independently [46]. Numerous other examples of synergism have been reported [26, 35, 48, 70, 91, 115, 116].

On the other hand, antagonism was observed in that the activity of different combined components was less than that of the individual components. An antagonistic effect between *p*-cymene, thymol and carvacrol was reported in the oil of *Lippia chevalieri* [38]. It was demonstrated [117] that the physical properties of an aqueous tea tree oil dispersion significantly influenced the actions of the individual components, increasing or reducing antimicrobial efficacy. Thus, non-oxygenated monoterpene hydrocarbons such as *γ*-terpinene and *p*-cymene appear to create an antagonistic effect with the most active component (terpinen-4-ol) by lowering its aqueous solubility.

It was also reported that there were slight differences in the activity of enantiomers. (*R*)-(+)-Limonene and (*R*)-(+)-carvone were more biologically active than their isomers (*S*)-(-)-limonene and (*S*)-(-)-carvone [115].

The antimicrobial activities and toxicity of terpenes have been documented, but their modes of action are complex and still in some cases unknown. Considering the large number of different groups of chemical compounds present in EOs, it is most likely that their antimicrobial properties are not attributable to one specific mechanism, because of other targets in the cell [118]. Terpenoids are lipophilic agents and consequently disrupt membrane integrity and permeability [14, 119]. Leakage of K^+ ions [99, 119] is usually a sign of damage [120] and is often followed by efflux of cytoplasmic constituents [8, 14, 15, 119]. Terpinen-4-ol inhibited oxidative respiration and induced membrane swelling, increasing its permeability [119]. The antibacterial activity of oregano EO was due to the disruption of membrane integrity, which further affected pH homeostasis and equilibrium of inorganic ions [15]. It has been hypothesized that carvacrol destabilizes the cytoplasmic membrane and, in addition, acts as a proton exchanger, thereby reducing the pH gradient across the cytoplasmic membrane. The resulting collapse of the proton motive force and depletion of the ATP pool eventually leads to cell death [14]. A change in the fatty acid composition of the yeast membrane in *Saccharomyces cerevisiae* with more saturated and fewer unsaturated fatty acids in the membrane was reported after exposure to palmarosa oil [76].

Ergosterol, the predominant sterol in yeast cells, plays an important role in membrane fluidity, permeability and the activity of many membrane-bound enzymes. In terpene-treated cells, ergosterol synthesis was strongly inhibited, and a global upregulation of genes associated with the ergosterol biosynthesis pathway was described in response to terpene toxicity [80, 121].

Different methods to measure the EO activity have been described [10, 122, 123]; however, the diversity of ways of reporting the antibacterial activity of EOs limits comparison between the studies and could lead to duplications [111, 122, 123]. Also, different solvents have been used to facilitate the dispersion of antimicrobial agents in the test media [70, 74, 120], and consequently careful attention should be paid to possible interactive effects of solvents on bactericidal viability [15].

5.3 Antiviral Activity

The development of viral resistance towards antiviral agents enhances the need for new compounds active against viral infections, and therefore natural products may offer a new source of antiviral agents [124].

EO of *Melaleuca alternifolia* and eucalyptus exhibited a high level of antiviral activity against *Herpes simplex virus* type 1 (HSV-1) and *Herpes simplex virus* type 2 (HSV-2) in a viral suspension test [125]. Also, *Santolina insularis* EO

had direct antiviral effects on both HSV-1 and HSV-2 and inhibited cell-to-cell transmission of both herpes types [126]. Moreover, it was demonstrated that the incorporation of EOs in multilamellar liposomes greatly improved the antiviral activity against intracellular HSV-1 [127, 128]. EOs from Argentinean aromatic plants exhibited virucidal activity against HSV-1 and Junin virus, and the activity was time- and temperature-dependent [129, 130]. However, the authors were not able to elucidate the nature of the active components of the oils responsible for the inhibitory effect on virions. EOs from *Mentha piperita* [131] and lemon grass [132] had direct virucidal effect against HVS-1. Antiviral activity of EOs against several viruses has been described, such as poliovirus-1 [133], molluscum contagiosum [134], adenoviruses [135] and influenza virus [136].

Isoborneol has been found to be an interesting compound for inhibiting HSV life cycle, on the basis of the specificity of the inhibition of the glycosilation of viral polyptides [137]. Also linalool exhibited the strongest activity against adenoviruses; however, carvone, cineole, β-caryophyllene, farnesol, fenchone, geraniol, β-myrcene and α-thujone did not exhibit activity [135].

A study conducted on EOs from different *Melaleuca* species showed that the EO containing 1,8-cineole and terpinen-4ol exhibited stronger antiviral activity than those with high methyleugenol or 1,8-cineole contents [138].

5.4 Antioxidant Activity

Lipid peroxidation involves the oxidative deterioration of unsaturated fatty acids and the changes resulting from this process. Detrimental events include membrane fragmentation, disruption of membrane-bound enzyme activity, disintegration and swelling of mitochondria and lysosomal lysis. Reactive oxygen species (ROS) may be the causative factor involved in many human degenerative diseases, and antioxidants have been found to have some degree of preventive and therapeutic effects on these disorders. Hydrogen peroxide, one of the main ROS, causes lipid peroxidation and DNA oxidative damage in cells. Vitamins, phenolic compounds and EOs are naturally occurring antioxidants [139, 140]; thus, the commercial development of plants as new sources of antioxidants to enhance health and food preservation is of current interest [141, 142].

The antioxidant activity that some EOs possess is not surprising in view of the presence of phenol groups. It is well known that almost all phenols can function as antioxidants of lipid peroxidation because they trap the chain-carrying lipid peroxyl radicals [143]. Plant phenolics are multifunctional and can act as reducing agents, hydrogen-donating antioxidants and singlet-oxygen quenchers [141, 144]; therefore, dietary antioxidants are needed for diminishing the cumulative effects of oxidative damage [143].

There are numerous antioxidant methods and modifications for the evaluation of antioxidant activity [139, 145–151]. Multiple assays in screening work are highly advisable, considering the chemical complexity of EOs [152].

Many EOs also exhibit antioxidant activity and therefore several studies have been carried out in order to elucidate the activity of the components [139, 153]. For instance, γ-terpinene retarded the peroxidation of linoleic acid [139, 154–156], sabinene showed strong radical-scavenging capacity [139, 157], α-pinene [158] and limonene [146] showed low antioxidant activity in the 2,2-diphenyl-1-picrylhydrazyl (DPPH) test, while terpinene and terpinolene showed high hydrogen-donating capacity against the DPPH radical [146, 150, 155, 158].

The radical-scavenging effect of citronellal showed a strong protective activity in lipid peroxidation processes in a dose-dependent manner [139, 146, 159]. Also, scavenging effects have been described for neral and geranial [146, 152, 160].

Among the oxigenated terpenes, geraniol had a high hydrogen-donating capacity towards the DPPH radical [146] and terpinen-4-ol is a weak antioxidant [146, 149, 158]. Eugenol has been shown to be effective for its scavenging activities against free radicals [160, 162–165], and is more effective than terpinolene [149]. 1,8-Cineole showed scavenger activity [42, 166, 167] and inhibited malonaldehyde formation [168]. However, pro-oxidant activity of linalool and nerolidol has been reported [139].

The monoterpene ketones menthone and isomenthone [159, 166] exhibited OH· radical scavenging activity. Depending on the method employed, different activities for anethole have been reported [153, 169].

At higher concentrations, the antioxidant activities of thymol and carvacrol were close to that of α-tocopherol and were in fact responsible for the antioxidant activity of many EOs which contain them [12, 17, 139, 153, 163, 164, 168, 170–174]. The high potential of phenolic components to scavenge radicals might be explained by their ability to donate a hydrogen atom from their phenolic hydroxyl groups [175].

Germacrene-D, a ten-membered-ring system with three double bonds acting as electron-rich centers, and pinenes and menthadiene of *Xylopia aethiopica* EO showed a significant ability to scavenge superoxide anion radical [176]. EOs with β-caryophyllene as the major compound showed radical-scavenging activity [177].

In many cases, the antioxidant activity of the EOs could not be attributed to the major compounds, and minor compounds might play a significant role in the antioxidant activity, and synergistic effects were reported [158, 171, 176]. For instance, in *Melaleuca* species, EO containing 1,8-cineole (34%) and terpinen-4ol (19%) exhibited stronger antioxidant activity than those with high methyleugenol (97%) or 1,8-cineole (64.30%) contents [138].

The relative effectiveness of antioxidants depends on their antioxidant properties, their concentration, the test system, the emulsion system, the oxidation time and the test method used [155].

5.5 Analgesic Activity

Menthol is a naturally occurring compound of plant origin, and gives plants of the *Mentha* species the typical minty smell and flavour. Menthol is present in the EO of several species of mint plants, such as peppermint and corn mint oil, and it is classified by the US Food and Drug Administration as a topical analgesic [178]. Menthol is a cyclic terpene alcohol with three asymmetric carbon atoms; therefore, it occurs as four pairs of optical isomers named (+)-menthol and (-)-menthol, (+)-neomenthol and (-)-neomenthol, (+)-isomenthol and (-)-isomenthol, and (+)-neoisomenthol and (-)-neoisomenthol. Among the optical isomers, (-)-menthol occurs most widely in nature. It was able to increase the pain threshold, whereas (+)-menthol was completely devoid of any analgesic effect [179]. In contrast to what was observed for the analgesic effect, (+)-menthol and (-)-menthol were able to induce an equiactive anesthetic effect [180]. Applied topically, menthol caused a tingling sensation and a feeling of coolness owing to stimulation of 'cold' receptors by inhibiting Ca^{2+} currents of neuronal membranes [179, 181]. Menthol was able to block voltage-gated Ca^{2+} channels in human neuroblastoma cells [182]. Most research has focused on menthol's effect on cold fibres, where it appeared to accelerate inactivation of L-type Ca^{2}+ currents [183–185]. The integrity of the central κ-opioid system was fundamental for (-)-menthol antinociception [179]. The ability of a painful stimulus to suppress perception of another one (counterirritation) was assessed for menthol together with other potential analgesics [186, 187]; however, menthol was capable of producing counterirritation when applied in concentrations high enough to cause substantial sensory irritation [188, 189]. Methyl salicylate has been shown to produce significant counterirritation and had a synergic effect with menthol [190]. Menthol, as a topical irritant, may also cause analgesia by reducing the sensitivity of cutaneous apin fibres [191–193]. Earlier psychophysical work on the effects of menthol on thermal perception and heat pain had led to the conclusion that menthol did not desensitize nociceptors [194]. Studies on its supposed antipruritic activity have yielded contradictory results [195–197]. Menthol has shown antitussive activity that might be attributable to its effects on capsaicin-sensitive fibres [198, 199].

Higher analgesic efficacy was exhibited by *Lavandula hybrida* when administration was through the inhalatory route, the noniceptive responses to chemical (writhing test) and thermal (hot plate test) stimuli being significantly reduced [200]. However, linalool and linalyl acetate produced only a scarce or no analgesic effect in the pain models (writhing test and hot-plate test) [201–205]. Although opioidergic neurotransmission seemed to be primarily involved in orally induced analgesia, the cholinergic system appeared to play a significant role in lavender oil analgesia [200]. Another terpene with anticholinesterase activity and an antinocicptive effect was 1,8-cineole [206, 207]. Lavender oil and its principal components, linalool and linalyl acetate [200], and 1,8-cineole

[208] showed antiulcer activities that led to alleviation of pain. The ability of lavender oil to prevent experimental thrombus has been described [209]. The amelioration of gastric microcirculation could be the mechanism underlying the lavender gastroprotection against ethanol injury, which was known to be dependent on microvasculature engulfment in the gastric mucosa [200].

EO of *Lavandula angustifolia* containing 1,8-cineole and borneol as the main components inhibited both phases of the formalin test, reduced the number of abdominal constrictions (writhing test) and suppressed carrageenan-induced paw oedema [211]. EO of *Salvia africana-lutea* and *Dodonaea angustifolia* also showed analgesic activity [211]. The volatile oil of *Cedrus deodara* produced significant inhibition in thewrithing test and the hot-plate reaction in mice [212].

Eucalyptus citriodora, *E. tereticornis*, and *E. globulus* induced analgesic effects in acetic acid induced writhes in mice and hot-plate thermal stimulation in rats [213]. This observation indicated that EOs have both peripheral (writhe reduction) and central (thermal reaction time prolongated) effects. *E. citriodora* contains citronellal as the main component, whereas *E. tereticornis*, and *E. globulus* contain 60–90% of 1,8-cineole; thus, *E. citriodora* EO showed the highest peripheral antinoniceptive effect, whereas *E. tereticornis* EO was the most potent central antinoniceptive substance [214]. Turpentine exudes from *Pinus nigra* subsp. *pallsiana* had a strong analgesic effect when compared with metamizol as a standard analgesic compound [214]. The main components of *Lippia multiflora* EOs (*p*-cymene, thymolacetate and thymol) showed a significant and dose dependent analgesic effect on acetic acid induced writhing in mice [215].

5.6 Digestive Activity

One of the most important uses of many native aromatic plants in popular medicine is for digestive complaints [216]. Some studies suggest that EOs are responsible, at least in part, for the digestive activities of this group of plants, although it is also possible that other components (e.g. caffeic acid esters) also contribute to this activity [217, 218].

Many reports have shown that EOs regulate the digestive process before food reaches the stomach. Lavender and ginger EOs as well as perfumes and strong odours were found to affect gastrointestinal function through activation of the vagus nerve [219, 220] and gastric secretion [221]. The olfactory stimulation generated by lavender oil scent and its main component linalool activated gastric nerves that enhanced food intake and body weight in rodents [222], while grapefruit oil fragrance and its main component limonene showed the opposite effect [223].

Aromatic plants are commonly administered as an infusion or tea, and thus are delivered directly to the site of action, i.e. the gastrointestinal system [216, 224]. Basically, aromatic plants and their EOs exert their digestive action by inhibiting gastric motility (antispasmodics), releasing of bile from the gall bladder (choler-

etics), inducing the expulsion of gases from the stomach and intestine (carminatives), and more indirectly protecting liver function (hepatoprotectives).

The depressant effect of EOs on smooth muscle in the small intestine is consistent with the therapeutic uses of these aromatic plants as gastrointestinal antispasmodics and carminatives [224]. *In vitro* studies showed that EOs produced the inhibition of gastric motility, and are thus the basis of the treatment of some gastrointestinal disorders [225, 226].

The EOs of *Satureja obovata* (37% camphor, 18% linalool/linlyl acetate) [227], cardamom seed [228], *Acalypha phleoides* (thymol, camphor and γ-terpinene) [229], *Satureja hortensis* (γ-terpinene, carvacrol) [225], *Croton zehnerii* (estragol, anethole) [224], *Croton nepetafolius* (methyleugenol, α-terpineol, 1,8-cineole) [230], *Melissa officinalis* (citral, 60%) [231], *Pelargonium* sp. (citronellol, geraniol, linalool) [232], lavender (linalool/linalyl acetate) [233], *Plectantrus barbatus* (α-pinene, caryophyllene, myrcene) [234], *Pycnocycla spinosa* (14.4% geranyl isopantanoate, 10.6% caryophyllene oxide) [235], *Ferula gummosa* (α-pinene and β-pinene) [226] and peppermint [236] were reported to inhibit gastric motility in isolated segments of rodent intestine.

The EOs reduced the contraction induced by acetylcholine, histamine [226–228, 210, 225, 232, 233], carbachol (muscarinic receptor activator) [237] and 5-hydroxytryptamine [229]. The EOs were found to relax intestinal smooth muscle by reducing the influx of Ca^{2+} [227, 234], K^{+} [210, 224–226, 229, 230] and Ba^{2+} [229, 237]. However, other reports have shown that lavender and geranium EOs were unlikely to act as cationic channel blockers [232]. The activities of the EOs resembled those of dicyclomine and atropine (muscarinic receptor antagonists) and dihydropyridine (calcium antagonist) by producing smooth-muscle relaxation [225, 236].

All these experiments suggested that EOs and their components inhibit muscarinic receptors that block cationic influx and produce smooth-muscle relaxation [238], while *in vivo* studies showed that a commercial peppermint–caraway oil combination had blocking effects on gastroduodenal motility, decreasing the number and amplitude of contractions, thus acting locally to cause smooth-muscle relaxation. All these activities produced symptom-relieving effects in patients suffering from functional dyspepsia [239]. The physiological significance of the inhibition of duodenum mobility was to provide more time to process chyme [240]. The expulsion of gases from stomach and intestine (carminative effect), that was associated with smooth-muscle relaxation, provided additional relief to abdominal complaints (feeling of pressure, heaviness and fullness) [239, 241].

Chemical structure–activity relationships suggested that phenolic monoterpenes (thymol, methyleugenol) seemed to be the most active, followed by alcohols (terpineol) and other oxigenated monoterpenes (1,8-cineole) [225, 229, 230]. Within the monoterpenes, β-pinene was more active than α-pinene [226], and α-pinene was more active than caryophyllene and myrcene [234].

The inhibitory effect of a mixture of α-pinene and β-pinene was reported to be less than the sum of the separate effects [226]. α-Pinene and caryophyllene

showed additive effects but did not achieve the maximum effect obtained with the crude oil. The final therapeutic activity was due to the combine effect of several minor constituents of the oil [234].

The choleretic effect induced by EOs that involves the release of bile from the gall bladder is also important for digestion of fats, but this activity of EOs has been less studied in the last decade. The EO of *Salvia desoleana* (1,8-cineole, linalool/linalylacetate and a terpenylacetate), the purified components (linalool and α-terpineol), different chemotypes of the EOs of *Thapsia* sp. (limonene, geranylacetate and methyleugenol), menthol, peppermint oil and a commercial preparation (containing pinenes, camphene, cineole, menthone, menthol and borneol) produced a significant increase in bile secretion [242–244, 252]. *In vitro* studies also showed that *Croton zhenerii* EO increased contractile activity of the bladder in a concentration-dependent manner [224] that could also affect bile release.

Many studies have related the antioxidant activity with liver protection against free radicals [245–247], although other mechanisms also contribute to the hepatoprotective action of EOs and their components [248].

The EO of *Santolina canescens*, its main component santolinediacetylene [249], thymol [250] and *Foeniculum vulgare* (fennel) [251] showed significant hepatoprotective effects against carbon tetrachloride induced hepatotoxicity in rodents. These studies suggested that the protective effect might be mediated through inhibition of lipid peroxidation [249, 250]. Myristicin (the major components of nutmeg EO) exhibited a potent hepatoprotective activity in rats as assessed by marker enzymes of liver injury [248]. The hepatoprotective activity of myristicin might be, at least in part, due to the inhibition of tumour necrosis factor released from macrophages [248]. In *Rosmarinus officinalis*, the hepatoprotective and antimutagenic activities of ethanolic extracts and EO were attributed to the presence of phenolic compounds with high antioxidant activity [253].

Other activities on the gastrointestinal system included antidiarrhoeal and gastroprotective effects. *Satureja hortensis* and *Aloysia triphylla* EOs inhibited castor oil induced diarrhoea in rodents [225, 255]. The EO of lavender and its components (linalool, linalyl acetate) and the EO of *Cryptomeria japonica* (terpin-4-ol and elemol) showed protective activities against acute ethanol/aspirin-induced gastric ulcers in rodents [200, 254].

5.7 Anticarcinogenic Activity

Tumorigenesis is a multistep process that begins with cellular transformation, progresses to hyperproliferation and culminates with the acquisition of invasive potential, angiogenic properties and establishment of metastatic lesions [256].

The major factors for human carcinogenesis are cigarette smoking, industrial emissions, gasoline vapours, infection and inflammation, nutrition and dietary

carcinogens. Studies of nutrition and dietary condition will eventually lead to cancer prevention [257–264].

Non-nutrient compounds in the diet have been found to exert inhibitory effects in experimental carcinogenesis [259, 260, 265–269]. Monoterpenes are non-nutritive dietary components found in the EOs of aromatic plants. Several experimental and population-based studies indicate that isoprenoids in the diet play an important role in the ability to avoid cancers [263, 266, 270–276].

Among monoterpenes, perillyl alcohol and *d*-limonene are isoprenoids of great clinical interest. The monocyclic monoterpene limonene, a major component in many citrus EOs, has been used for many years as a flavouring agent, food additive and fragrance [277, 278]. *R*-(+)-limonene exhibited chemopreventive and therapeutic effects against chemically induced mammary tumours in rats [279–281] and metastasis of human gastric cancer [282]. The EO of *Citrus limonum* modulated the apoptosis through the activation of the interleukin-1β-converting enzyme-like caspases [283].

Mechanistic studies revealed that the effects of limonene on cell proliferation and cell cycle progression were preceded by a decrease in cyclin D1 messenger RNA levels [284] and inhibition of posttranslational isoprenylation, rather than through the suppression of cholesterol biosynthesis [271; 279, 285–293]. Limonene and perillyl alcohol and their active serum metabolites inhibit protein isoprenylation [287, 289–291, 294].

Although farnesol did not affect the prenylation of small G-proteins [295], the derivatized forms of farnesol inhibited methyltransferase activity [296–299] and suppressed the prenylation of G-proteins [300].

Limonene was extensively metabolized by a variety of mammalian species [279, 290, 292, 301]. Its principal circulating metabolites identified in the rat were perillic acid and dihydroperillic acid. These components were effective inhibitors of isoprenylation and cellular proliferation *in vitro* [271].

Limonene and perillic acid remarkably reduced the lung metatastatic tumour nodule formation by 65 and 67%, respectively; however, perillyl alcohol was considerably more potent than limonene against breast cancer [284, 302], rat mammary cancer and pancreatic tumours [288]. Phase I studies of *d*-limonene [303, 304] and phase I and phase II [305–311] studies of perillyl alcohol revealed dose-limiting toxicities: nausea, vomiting, anorexia, unpleasant taste and eructation, and thus a maximum tolerated dose for perillyl alcohol was determined [305].

Perillyl alcohol induced apoptosis and was more effective than perillaldehyde at inhibiting the proliferation of human carcinoma cell lines cultured *in vitro* [319]. Perillyl alcohol treatments suppressed cell growth [313–315], reduced cyclin D1 RNA and protein levels and prevented the formation of active cyclin D1 associated with kinase complexes in synchronous cells during the exit of G0 and entry into the cell cycle [284, 316, 317]. In addition, perillyl alcohol treatment induced an increased association of p21 [316–318] with cyclin E-Cdk2 complexes, inhibited the activating phosphorylation of Cdk2 [312, 316, 318–320], initiated apoptosis [321–324] and suppressed small G-protein isoprenylation

[289, 290, 325–328]. All these effects of perillyl alcohol may contribute to the inhibition of the transition out of gap phase (G1) of the cell cycle [271, 284, 317, 329].

Perillyl alcohol represents a novel small molecule that might be effective for treating leukaemia by inducing growth arrest and apoptosis in transformed cells [313]. Blends of isoprenoids suppressed growth of murine melanoma and human leukaemic cells [265, 271].

A phase I clinical trial with limonene indicated its toxic effects in humans; thus, perillyl alcohol is more effective at lower doses [279].

The hydroxylation of limonene affected its chemopreventive potential. The hydroxylated forms carveol, uroterpenol and sobrerol decreased tumour yield, sobrerol being the most potent. These monoterpenes were reported as cancer chemopreventive agents with little or no toxicity [292]. Also, carveol showed chemoprentive activity against carcinogens [293].

The EO of *Syzigium aromaticum* (Myrtaceae), which contains high levels of eugenol, exhibited anticarcinogenic activities and antimutagenic properties [330–336]. Although a single mechanism may not account for chemoprotection exerted by eugenol, it is an effective inducer of detoxifying enzymes [332, 337, 338]. Eugenol is known to inhibit lipid peroxidation by acting as a chain-breaking antioxidant [339, 340], and lipid peroxidation may play a very important role in cell proliferation, especially in tumours [341, 342]; thus, lipid peroxidation control could be a mechanism of action of eugenol as an antitumoral agent. Other reports showed that eugenol is involved in cytotoxic process and can cause apoptotic cell death [343]. Eugenol inhibited the mutagenicity of aflatoxin B1 and *N*-methyl-*N′*-nitro-*N*-nitrosoguanidine [344] and the genotoxicity of cyclophosphamide, procarbazine, *N*-methyl-*N′*-nitro-*N*-nitrosoguanidine and urethane [345].

Carvone prevented chemically induced lung and forestomach carcinoma [346], but had no effect on the lung metatastic tumour growth [347]. Geraniol showed *in vivo* antitumour activity against murine leukaemia, hepatoma and melanoma cells [348, 349]. Geraniol caused 70% inhibition of human colon cancer cell growth, with cells accumulating in the S transition phase of the cell cycle, and concomitant inhibition of DNA synthesis. No signs of cytotoxicity or apoptosis were detected. Geraniol reduced cancer growth by inhibiting polyamine metabolism, which is a process involved in cancer proliferation [350]. Geraniol induced membrane depolarisation with a decrease of membrane resistance owing to local perforation of the cell membrane, caused a 60% reduction of protein kinase C activity and decreased by 50% the amount of active forms of p44/p42 extracellular signal-regulated protein kinases [351]. The combined administration of 5-fluorouracil (20 mg kg^{-1}) and geraniol (150 mg kg^{-1}) caused a 53% reduction of the tumour volume [352]. 3-Hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase catalyses the formation of mevalonate, a precursor of cholesterol that is also required for cell proliferation. Inhibition of mevalonate synthesis could be a useful strategy to impair the growth of malignant cells. Geraniol inhibited HMG-CoA reductase activity in human breast cancer cells, and

this effect was closely correlated with the inhibition of cell proliferation [353]. HMG-CoA reductase activity [271] was also inhibited by farnesol and its derivatives [354], as well as by limonene and menthol [355].

The EO of *Matricaria chamomilla* and its main component, the sesquiterpene alcohol α-bisabolol, is considered to be the main component contributing to the mild anti-inflammatory effect of chamomile. Owing to its non-toxic effect in animals, it is widely used in cosmetic preparations [356]. α-Bisabolol was found to have a strong time- and dose-dependent cytotoxic effect on human and rat glioma cells. α-Bisabolol rapidly induced apoptosis through the mitochondrial pathway with no toxic effect on normal glial cells. Glioma is among the most invasive tumours, against which no efficient and non-toxic treatments have so far been reported; thus, α-bisabolol is very promising for the clinical treatment of this highly malignant tumour [357]. The EO of chamomile also inhibited the mutagenic effects induced by daunorubicin and methanesulfonate [358].

Anethole is known to block the nuclear factor kappa B activation process [359] that is linked with cancer proliferation [272, 360]. *trans*-Anethole was also found to inhibit the *in vivo* genotoxicity of xenobionts [345].

Cadalene reduced the incidence of adenomas and inhibited the development of induced lung tumorigenesis in mice [361], while carvacrol inhibited growth of myoblast cells [362]. Menthol exhibited chemopreventive activity against induced rat mammary cancer [363].

Cinnamaldehyde (*Cinnamomum cassia*) is a potent inducer of apoptosis via ROS generation, thereby inducing mitochondrial permeability, depletion of intracellular thiols, activation of caspase-3 and DNA fragmentation [364]. Farnesol was also found to initiate apoptotic cell death [312, 318, 365], while other studies showed that dietary administration of cinnamaldehyde significantly inhibited pulmonary tumorigenesis in mice [366].

The possibility of moderating the response of cells to a particular mutagen by natural substances opens new horizons in cancer control. On this basis, the research for antimutagens could bring about surprises in the discovery of new anticarciongenic substances.

The antimutagenic effect of EOs of *Helichrysum italicum*, *Ledum groenlandicum* and *Ravensara aromatica* could be explained by the interaction of their constituents with cytochrome P450 activation involving in the detoxification system [367].

Linalool showed no toxic or mutagenic effects on erythrocytes and micronucleus [368], or in numerical chromosome aberrations tests [369], indicating that linalool has no potential for carcinogenicity when used as a fragrance ingredient [370]. Linalyl acetate showed neither mutagenic effects in the *Ames* assay nor genotoxic potential [203], nor did it show carcinogenic activity [202, 371]. Coriander oil, dominated by linalool, did not show any significant potential for immunotoxic or neurotoxic effects [370].

Estragole is a natural constituent of a number of plants and their EOs have been widely used in foodstuffs as flavouring agents. Several studies have shown the hepatocarcinogenicity of EOs with estragole and its metabolites [372].

Methyleugenol, a substituted alkenylbenzene found in a variety of food products, caused neoplastic lesions in mice liver. Safrole caused cytotoxicity and genotoxicity in rodents [373]. However, the no-observed-effect level of methyleugenol for rodents was estimated at 10 mg kg^{-1} [374]. The concentrations (1–10 mg kg^{-1}) are approximately 100–1,000 times the anticipated human exposure to these substances. For these reasons it was concluded that the present exposure to methyleugenol and estragole resulting from consumption of food (e.g. spices) does not pose a significant cancer risk. Nevertheless, further studies are needed to define both the nature and the implications of the dose–response curve in rats at low levels of exposure to methyleugenol and estragole [375].

Tumour cells use multiple cell survival pathways to prevail, and thus the terpenes that can suppress multiple pathways have great potential for the treatment of cancer. This review presents evidence that terpenes can be used not only for cancer prevention but also for its treatment.

5.8 Semiochemical Activity

Insect control is becoming difficult because of the development of strains resistant against insecticides, and transgenic varieties [376]. Leaves, flowers, bark and ripe fruits are important for human use and are usually hosts for a wide range of herbivorous insects, and evidence is accumulating that host finding is largely guided by volatile phytochemicals [377–379]. Behaviour-modifying chemicals also have significant potential for commercial application in pest management. In fact, a major impetus for the development of the field of chemical ecology has been generated by the expectation that identified semiochemicals could be used operationally in pest management programmes [380]. Semiochemicals are molecules that carry signals from one organism to another, while pheromones are substances secreted by an individual that induce a specific reaction in another individual of the same species [381].

Gas chromatography linked to electroantennography (EAG) is a technique developed for the identification of a wide range of semiochemicals that could lead to alternative strategies to control economically important insects [376–379].

Male attraction to the female sex pheromone has been studied for the development of environmentally safe control methods. One important drawback of the mating disruption technique is that only male behaviour is affected, so the efficacy of pheromonal methods can be greatly enhanced by compounds that affect also female behaviour [378].

Nine compounds from branches with leaves and green fruit from apple consistently elicited an antennal response in codling female moths (*Cydia pomonella*, Lepidoptera), including methyl salicylate, (*E*)-β-farnesene, β-caryophyllene, 4,8-dimethyl-1,3(*E*)-7-nonatriene, (3*Z*)-hexenol, (*Z*,*E*)-α-farnesene, (*E*,*E*)-α-farnesene, linalool and germacrene D [378].

Straight-chain aliphatic alcohols elicited higher significant EAG responses in *Helicoverpa armigera* (Lepidoptera) female antennae. Hexan-1-ol and hexan-2-ol showed higher responses (hexan-1-ol being dose-dependent) than hexanal, (2*E*)-hexenal and (2*E*)-hexenyl acetate. The responses to ocimene and *β*-phellandrene were significantly larger than those elicited by the other monoterpenoids. Phenylacetaldehyde and benzaldehyde elicited EAG responses that were significantly larger than those of acetophenone and methyl salicylate, while the corresponding alcohols did not elicit a significant response [376].

Female antennae detected small amounts of (*E*)-*β*-farnesene, (*Z*,*E*)-*α*-farnesene, methyl salicylate and germacrene D, while other more abundant compounds, such as (3*Z*)-hexenyl acetate and (*E*)-*β*-ocimene, gave no significant antennal response [378].

In the weevil *Pissodes notatus* (Coleoptera), single olfactory receptor neurones on the antennae were screened for sensitivity to naturally produced plant volatiles The two most abundant types responded to α-pinene, β-pinene and 3-carene and to isopinocamphone and pinocamphone, respectively. Major as well as minor constituents of plant volatile blends were employed for host and non-host detection, mainly including monoterpenes (bicyclic and monocyclic) [382].

In female *Heliothis* sp. (Lepidoptera) moths, four colocated receptor neurone types were identified, of which three types responded most strongly to the inducible compounds (*E*)-*β*-ocimene and (*E*,*E*)-*α*-farnesene. The fourth type responded most strongly to geraniol, which is a common floral volatile [383].

Single receptor neurons on the antennae of tobacco budworm moth responded with high sensitivity and selectivity to germacrene D, suggesting that this component is an important signal for insects in the interaction with plants [384]. Experimental data demonstrated that plants containing germacrene D dispensers had great attractiveness and showed greater ovoposition than plants without them [385].

Single receptor neurons were tuned to a few structurally related components [383–384], while neurons in the antennae of individual insects were more responsive to specific enantiomers, e.g. (+)-linalool [377, 386].

Conifer monoterpenes (mainly *α*-pinene, *β*-pinene, myrcene, limonene/phellandrene) elicited antennal responses in tree-killing bark beetles. These components have potential behavioural roles in host location and discrimination [379].

Semiochemicals are being used in commercial products in mass trapping programmes. Only traps baited with ipsenol and/or ipsdienol together with the host volatiles ethanol and *α*-pinene caught significantly more male and female *Monochamus scutellatus* and *Monochamus clamator* than traps baited with host volatiles alone. Semiochemicals and pheromones thus exhibited synergistic/adding effects [387] and both could be used as the basis of more integrated control strategies [376].

5.9 Other Activities

EOs and their monoterpenes affected bone metabolism when added to the food of rats. It was demonstrated that these lipophilic compounds inhibited bone resorption [388]. It was reported that (2*E*,6*R*)-8-hydroxy-2,6-dimethyl-2-octenoic acid, a novel monoterpene, from *Cistanche salsa* had antiosteoporotic properties [389].

Pine EOs prevented bone loss in an osteoporosis model (ovariectomized rats). The monoterpenes borneol, thymol and camphor directly inhibited osteoclast resorption [388]. It was observed that inactive monoterpenes can be metabolized to their active forms *in vivo*; thus, *cis*-verbenol, a metabolite of *α*-pinene, inhibited osteoclastic resorption activity, in contrast to the parent compound *α*-pinene.

Potential activities for the treatment of Alzheimer's disease were demonstrated in a pilot open-label study involving oral administration of the EO of *Salvia lavandulaefolia* Vahl. known as Spanish sage [390].

Chinese angelica (*Angelica sinensis*) is the most important female tonic remedy in Chinese medicine. The effects of angelica EO in three assays in mice (elevated plus maze, light/dark and stress-induced hyperthermia test) suggested that angelica EO exhibited an anxiolytic-like effect [391]. A link to emotion and cognitive performance with the olfactory system was reported [392]. Moreover, the EOs could affect mood, concentration and sleep [393], while other studies had shown that EOs were potentially important to boost the immune system [394, 395].

EOs from different *Lippia alba* chemotypes showed behavioural effects. Greater effects were presented by chemotype 2 (with citral and limonene), while chemotype 1, containing citral, myrcene and limonene, decreased only the number of rearings in the open-field test [396]. The EO of lemon was found to modulate the behavioural and neuronal responses related to nociception, pain and anxiety [397, 398]. Thus, there is widespread and increasing interest in complementary and alternative medicines using EOs [399].

Aloe vera gel enhanced the antiacne properties of *Ocimum gratissimum* L. oil; the oil or its combination with *Aloe vera* gel was more effective than 1% clindamycin in the treatment of *Acne vulgaris* [399]. Linalool-rich EO was potent against promastigotes and amastigotes of *Leishmania amazonensis* [400].

5.10 Conclusions

The present review demonstrates that EOs and their components have many functional properties and exert their action in mammals as well as in other organisms (insects, fungi, bacteria and viruses). The synergistic effect of EO components is a promising field that could lead to the optimisation of a given bioac-

tivity. This phenomenon has been observed in many activities, such as those of antimicrobials, antioxidants, analgesics and semiochemicals. EOs are complex mixtures of components that show higher activities than their isolated components; their final activities are due to the combine effects of several minor components. Thus, EOs contain multifunctional components that exert their activities through different mechanisms. EOs and their components may have new applications against various diseases of different origins (cancer, fungal, bacterial or viral), because some of these complex diseases require multiple components and multifunctional therapies.

The natural product industry is actively seeking natural therapeutics, preservatives, repellents and other agents that can replace synthetic compounds. The scientific literature has identified new applications and uses of both traditional and exotic EOs. These applications can ultimately assist growers and rural communities in the developing world to increase interest in their products.

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