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An Overview of the Pharmacological Properties and Potential Applications of Natural Monoterpenes

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Abstract: Monoterpenes, the major components of essential oils, belong to the group of isoprenoids containing ten carbon atoms. Being widely distributed in the plant kingdom they are extensively used in cuisine and human health care products. Studies have shown that both natural monoterpenes and their synthetic derivatives are endowed with various pharmacological properties including antifungal, antibacterial, antioxidant, anticancer, antiarrhythmic, anti-aggregating, local anesthetic, antinociceptive, anti-inflammatory, antihistaminic and anti-spasmodic activities. Monoterpenes act also as regulators of growth, heat, transpiration, tumor inhibitors, inhibitors of oxidative phosphorylation, insect repellants, feline and canine attractants and antidiabetics. These interesting activities which might be potentially used not only in pharmaceutical, but also food and cosmetic industries are discussed below.

Keywords: Acyclic, antibacterial, anticancer, antifungal, anti-inflammatory, antioxidant, antiviral, essential oils, hypotensive and vasorelaxant, local anesthetic, monocyclic and bicyclic monoterpenes, monoterpene activity, stereochemistry.

INTRODUCTION

Terpenes are a structurally diverse and widely distributed family of natural products containing over 25,000 well-defined compounds isolated from all biological kingdoms [1-3]. Terpenes possess acyclic or cyclic structures, resulting from changes within the isoprenoid chain through reactions including reductions, oxidations, cyclizations, ring cleavages or rearrangements. This wealth of terpene diversity can be attributed to enzymes known as terpene synthases, which convert acyclic prenyl diphosphates and squalene into acyclic and cyclic forms [4]. The numerous terpene synthases in plants are primarily responsible for terpene diversity. Additionally, some terpene synthases produce multiple products from a single substrate [4]. The nomenclature of terpenes is based on the number of isoprene structures that they contain. Accordingly, these compounds are classified as monoterpenes, sesquiterpenes, diterpenes, triterpenes, tetraterpenes, and polyterpenes [2, 4, 5].

Monoterpenes, sesquiterpenes, and diterpenes are considered secondary metabolites because they are not essential for viability; however, these compounds mediate important interactions between plants and their environment [2, 3]. Studies have shown that both natural monoterpenes [5-10] and their synthetic derivatives [11-15] possess various pharmacological properties, including antifungal, antibacterial, antiviral, antioxidant, anticancer, antiarrhythmic, anti-aggregating, local anesthetic, antinociceptive, anti-inflammatory, antihistaminic and antispasmodic activities. Monoterpenes also act as regulators of growth, heat, and transpiration; tumor inhibitors; inhibitors of oxidative phosphorylation; insect repellants; feline and canine attractants; and antidiabetic agents [3, 16]. These interesting properties, which may potentially be used in pharmaceuticals and the food and cosmetic industries, are discussed below.

ACYCLIC MONOTERPENES

Acyclic monoterpenes (Fig. **1**), such as β-myrcene (**1**) and configurational isomers of β-ocimene (**2**), are found in the oils of basil (*Ocimum basilicum*, Labiatae), bay (*Pimenta acris*, Myrtaceae), and hops (strobiles of *Humulus lupulus*, Cannabaceae) as well as several other essential oils. β-Myrcene (**1**), which is an acyclic unsubstituted monoterpene, is reported to exhibit estrogenic activity. This compound also exhibits cardiotonic and diuretic properties and can be orally, parenterally or rectally administered [17]. Pure β-myrcene (**1**) and β-myrcene-containing essential oils are used as intermediates for the production of terpene alcohols (geraniol, nerol, and linalool), which subsequently serve as

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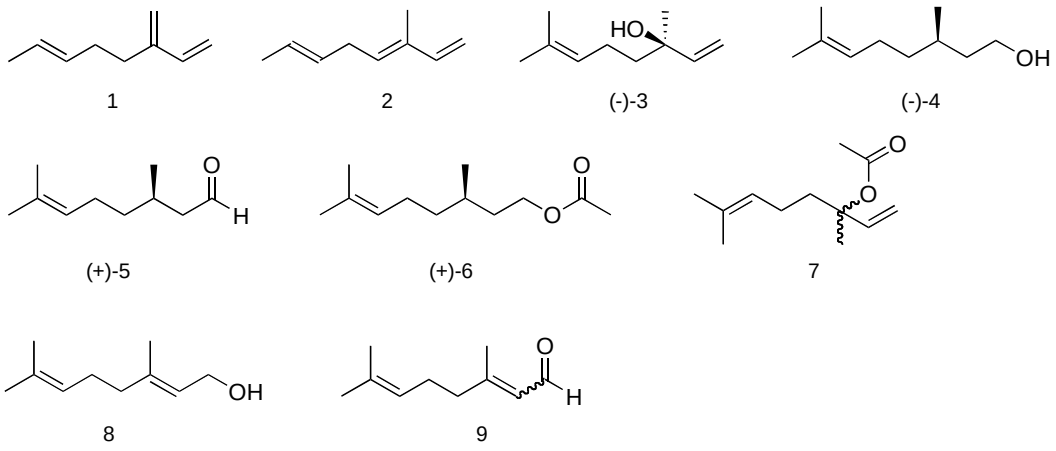


Fig. (1). Acyclic monoterpenes: β-myrcene (**1**), β-ocimene (**2**), (–)-linalool (**3**), (–)-citronellol (**4**), (+)-citronellal (**5**), (+)-citronellyl acetate (**6**), linalyl acetate (**7**), geraniol (**8**) and citral (**9**).

intermediates for the production of aroma and flavor chemicals. Thus, β-myrcene (**1**) is widely used in cosmetics, soaps and detergents and as a flavoring additive in food and beverages. For example, β-myrcene (**1**) is the primary constituent of hops and bay oils used in the production of alcoholic beverages [3, 18, 19]. Table **1** summarizes main pharmacological properties of acyclic monoterpenes.

Antimicrobial (Antibacterial, Antiviral and Antifungal) Properties of Acyclic Monoterpenes

Strong antibacterial activity against Gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*) [20] and Gram-negative bacteria (*Porphylomonas gingivalis*, *Prevotella intermedia*, *Fusobacterium nucleatum*) has been observed for (–)-linalool (**3**) [20, 21]. The mechanism of action is based on (–)-linalool-induced disruption of the lipid membrane structure in these microorganisms. Consequently, (–)-linolool (**3**) increases the permeability of cell membranes, inducing the leakage of the intracellular materials of bacterial cells and inhibiting the basic mechanisms of microbial metabolism, leading to their death [9, 21, 22, 23]. (–)-Linolool (**3**) showed also significant antibacterial properties against periodontopathic and cariogenic bacteria [21], *Staphylococcus aureus* resistant to vancomycin, *Pseudomonas aeruginosa*, *Escherichia coli* [22] and *Mycoplasma* [23].

The antimicrobial activity of a compound often increases with the presence of an oxygen-containing functional group, indicating a correlation between the structure and the biological activity [10, 24]. (–)-Linalool (**3**), (–)-citronellol (**4**), (+)-citronellal (**5**), (+)-citronellyl acetate (**6**), linalyl acetate (**7**), geraniol (**8**) and citral (**9**) are monoterpenes that exhibit antimicrobial activity [24, 25]. Comparing the effects of these compounds confirms that the hydroxy group is important for this antibacterial activity and for inhibition of swarming in *Proteus mirabilis* [10, 24]. (–)-Citronellol (**4**) demonstrated also antioxidant properties in 2,2-diphenym-1-picrylhydrazyl (DPPH) assay [25]. Citral (**9**), which is an acyclic monoterpene, has been examined for its antiviral activity against *Herpes simplex* virus type 1 (HSV-1) *in vitro*. This agent reduced HSV-1 infectivity by >96%. The mode of this antiviral action has been determined, and only a moderate antiviral effect was found when citral (**9**) was added to host cells prior to infection or following HSV entry into cells. However, citral (**9**) exhibited significant anti-HSV-1 activity by direct inactivation of free virus particles [26]. Citral (**9**) was also found to exhibit strong fungicidal properties. This compound is able to form a charge-transfer complex with an electron donor of fungal cells, resulting in fungal death [27]. Both citral (**9**) and geraniol (**8**) exhibit antifungal activity against *Cryptococcus neoformans* [28].

Anti-Inflammatory and Antiedematous Activity of Acyclic Monoterpenes

(–)-Linalool (**3**) and linalyl acetate (**7**) are the principal components of several essential oils that exhibit significant biological activities. Both (–)-linalool (**3**) and the corresponding acetate (**7**) play a major role in the anti-inflammatory activity of the essential oils that contain them, suggesting that linalool and linalyl acetate are potential anti-inflammatory agents. Following systemic administration, both the pure enantiomer, (–)-linalool (**3**), and its racemate decreased edema in the carrageenan-induced paw edema model in rats. The pure enantiomer (25 mg/kg) elicited a delayed and more prolonged effect, whereas the racemate form induced a significant reduction of edema only 1 h following carrageenan administration.

Linalyl acetate (**7**) exhibited an effect on local edema that was less effective and more delayed than equimolar doses of the corresponding alcohol, suggesting that linalyl acetate (**7**) may be a pro-drug of (–)-linalool (**3**) [29]. Standen *et al.* [30] demonstrated dose-dependent stimulation of natural killer cells *in vitro* with trans-caryophyllene (sesquiterpene) and linalyl acetate (**7**) from extracts of essential oils of chamomile (*Matricaria recutita*), frankincense (*Boswellia carteri*), geranium (*Pelargonium graveolens*), lavender (*Lavandula angustifolia*), lemon (*Citrus limon*), tea tree (*Melaleuca alternifolia*), broad-leaved paperbark (*Melaleuca viridiflora*), sandalwood (*Santalum spicatum*), atlas cedar (*Cedrus atlantica*) and common thyme (*Thymus vulgaris*).

Table 1. Acyclic monoterpenes: main source/origin, pharmacological properties and MIC values for antimicrobial activity.

Acyclic monoterpene	Main source	Main pharmacological activities	MIC value [mg/ml]
β-myrcene	Aerial parts of *Thymus pubescens, Rosmarinus officinalis, Ocimum basilicum, Pimenta acris,* strobiles of *Humulus lupulus,* aerial parts of *Calamintha nepeta, Salvia officinalis*	Antibacterial, cardiotonic, diuretic	>2.0 (*Enterococcus faecalis*) [44]; 0.4 (*Streptococcus salivarius*) [44]; 1.5 (*Streptococcus sanguinis*) [44]
β-ocimene	Aerial parts of *Dicyclophora persica, Ocimum basilicum* and *Pimenta acris,* strobiles of *Humulus lupulus,* aerial parts of *Calamintha nepeta, Lavandula angustifolia*	Antibacterial, antifungal	1.8 (*Bacillus subtilis*); 7.2 (*Enterococcus faecalis, Staphylococcus aureus; Escherichia coli*); 3.6 (*Staphylococcus epidermidis*) [45]
Linalool	Bergamot fruit (*Citrus bergamia*), aerial parts of *Coridothymus capitatus*	Antibacterial, antimycoplasmal, antiviral, anti-inflammatory, antiedematous	0.1-0.8 (*Porphylomonas sp*.) [21]; 0.2-1.6 (*Prevotella sp.*) [21]; 0.1-0.2 (*Fusobacterium nucleatum*) [21] 5.0 (VRSA); >5.0 (*Pseudomonas aeruginosa*); 2.5 (*Escherichia coli*) [22]; 0.015 ($MIC_{90:}$ *Mycoplasma pneumoniae*) [23] 0.008-0.064 (*Klebsiella pneumoniae* strains) [46]
Citronellol	*Thymus pubescens,* aerial parts of *Dracocephalum moldavica*	Antibacterial, antioxidant	0.008-0.064 (*Klebsiella pneumoniae* strains) [46]
Citronellal	*Thymus pubescens*	Antifungal	25.0-50.0 (*Pyricularia grisea; Aspergillus sp*.) [47]
Linalyl acetate	Bergamot fruit (*Citrus bergamia*), flowers of *Matricaria recutita, Boswellia carteri, Lavandula officinalis,* leaves of *Melaleuca alternifolia,* aerial parts of *Thymus vulgaris, Lavandula angustifolia*	Antibacterial, anti-inflammatory, antiedematous	0.015 ($MIC_{90:}$ *Mycoplasma pneumoniae*) [23]
Geraniol	*Thymus pubescens, Labiatae, Umbelliferae, Cymbopogon* (lemongrass), aerial parts of *Dracocephalum moldavica*	Antibacterial, antiviral, cytotoxic, antitumor	5.0 (VRSA); 2.5 (*Pseudomonas aeruginosa*); 1.2 (*Escherichia coli*) [22] 0.008-0.064 (*Klebsiella pneumoniae* strains) [46]
Citral	*Labiatae, Umbelliferae, Cymbopogon* (lemongrass), aerial parts of *Dracocephalum moldavica*	Antibacterial, antiviral, cytotoxic, anti-inflammatory	0.008-0.064 (*Klebsiella pneumoniae* strains) [46]

Cytotoxic, Antitumor and Chemopreventive Properties of Acyclic Monoterpenes

Geraniol (**8**), which is an acyclic monoterpene alcohol found in lemongrass and aromatic herb oils, has demonstrated antitumor activity *in vivo* and *in vitro* [31] and cytotoxic properties [32]. This compound effectively inhibited the growth of leukemia, hepatoma and melanoma cells as well as pancreatic and colon cancer cells. The antiproliferative effect of geraniol (**8**) on human colon cancer cells was associated with its ability to decrease DNA synthesis [31], whereas that on hepatoma and melanoma cells resulted from the inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase. This inhibition reduced the level of mevalonate, which resulted in limited protein isoprenylation and antiproliferation [31].

Unsaturated terpenes are capable of trapping activated oxygen species *in vivo* to yield intermediate epoxides, which can alkylate DNA, proteins, and other biomolecules [33-38]. This property explains why dietary monoterpenes act effectively at the cellular level in chemoprevention of different cancer types in animal models and in human clinical trials [16, 31, 39]. As a natural acyclic monoterpene, citral (**9**) is found in a wide variety of plants [38, 40]. Previous studies have indicated that this monoterpene is prone to oxidation upon exposure to air [38, 41]. The oxidation is enhanced by heat and irradiation [31, 38, 42]. Citral (**9**), which is the primary component of lemongrass oil, was found to be a dual activator of peroxisome proliferator-activated receptors α (PPARα) and PPARγand an inhibitor of cyclooxygenase-2 (COX-2). In human macrophage-like U937 cells, citral (**9**) suppressed LPS-induced COX-2 mRNA and protein expression in a dose-dependent manner. Citral (**9**) also suppressed the LPS-induced gene expression of inducible nitric oxide synthase (iNOS) and the DNA-binding activity of NF-κB, which is involved in transcriptional regulation of the iNOS gene. In contrast, citral (**9**) activated several transient receptor

potential channels (TRPM8 and TRPA1). Some of these effects may be responsible for the anti-inflammatory activity of citral (**9**) [43].

MONOCYCLIC MONOTERPNES

Cyclic terpenes are essentially extended structural homologs of cyclohexane and are typically derived, to varying extents, from dehydrogenation of the parent molecule, methyl-isopropyl cyclohexane. In Fig. **2**, the structures of monocyclic terpenes are presented with that of the parent substance, menthane. Consequently, the three isomeric menthanes, *ortho*-, *meta*- and *para*-, theoretically afford monocyclic terpenes. Notably, alicyclic hydrocarbons are invariably found to be more stable than the corresponding acyclic hydrocarbons. When evaluating the diagnostic and therapeutic efficacies of monocyclic terpenes, the possibility of geometrical isomerism and stereoisomerism must be considered [3, 19]. Table **2** summarizes main pharmacological properties of monocyclic monoterpenes.

Antitumor, Cytotoxic and Immunomodulatory Properties of Monocyclic Monoterpenes

Limonoids represent an interesting class of terpene compounds that exhibit a wide spectrum of biological properties for other groups of monoterpenes [48]. Several monoterpenes, such as carvone (**10**), (+)-limonene (**11**), thymol (**12**), (–)-carveol (**13**) and (–)-perillyl alcohol (**14**), have been reported to possess anticancer activity [19] and demonstrate the ability to not only prevent the formation or progression of tumors but also to induce regression of existing malignant tumors [16, 49, 50]. In breast cancer tumors in which regression was induced by limonene, the levels of mannose 6-phosphate/insulin-like growth factor II receptor and TGF-β1 were significantly increased, suggesting their role in the regression of cancer that is induced by this monoterpene [50]. (+)-Limonene (**11**) and (–)-perillyl alcohol (**14**) have also exhibited chemotherapeutic properties against rat mammary tumors [16]. The cytotoxic activity of (+)-limonene (**11**) during both the initiation and promotion stages of carcinogenesis was demonstrated in chemically induced rodent skin, lung, forestomach [51, 52] and mammary tumor model systems [49, 53, 54]. The cytotoxic activity of (+)-limonene (**11**)-induced tumor regression is due to limonene-induced selective inhibition of the isoprenylation of small G proteins involved in signal transduction. Inhibition of this posttranslational modification prevents the normal subcellular localization of these proteins, thereby impairing their function [49, 50, 53]. (+)-Limonene (**11**) was also reported to exert its chemopreventive effects through the inhibition of inflammation, oxidative stress and Ras signaling, as well as induction of a pro-apoptotic state in mouse models of skin cancer [55]. (+)-Limonene (**11**) increased the survival of lymphoma-bearing mice and stimulated nitric oxide production *in vitro* in peritoneal macrophages obtained from tumor-bearing mice. Moreover, (+)-limonene (**11**) modulated the immune response [56]. Carvone (**10**) and (+)-limonene (**11**) prevented the development of chemically induced lung and forestomach carcinomas [16, 51]. (+)-Limonene (**11**) inhibited the development of spontaneous neoplasms in mice and inhibited the development of Ras pathway-related mammary carcinomas in rats [16], exhibiting therapeutic protection against carcinogens. The initiation-phase chemopreventive effects of (+)-limonene (**11**) have been attributed to the modulation of phase I [57] and phase II [58] carcinogen-metabolizing enzymes, leading to enhanced detoxification of carcinogens [16]. Chemopreventive doses of dietary limonene have also been shown to induce the activity of the cytochrome P450 isoenzymes CYP2B1 and CYP2C [16, 49]. Inhibition of tumor cell proliferation and the acceleration of tumor cell death and macrophage stimulation have also been suggested [16, 56]. In contrast, (+)-limonene (**11**) promoted preneoplastic lesions and renal tumors in male rats; however, this effect was only observed in the presence of the male rat-specific urinary protein α_{2U}-G, which is responsible for both cytotoxic and carcinogenic responses in male rats [58].

Perillyl alcohol (**14**) has been used for the treatment of lung, breast, colon, prostate, and brain cancers and has also been used in cancers that did not respond to treatment [50]. This agent was also effective against pancreatic cancer at doses that were not toxic to the host organism [16]. Therefore, biological derivatization of perillyl alcohol (**14**) and its structural analog limonene (**11**) to produce new metabolites with a variety of biological properties represents an important goal of xenobiochemistry, pharmacology and toxicology [50, 59]. Most likely acting through its metabolite perillyl alcohol (**14**), (+)-limonene (**11**) has exhibited tissue-repairing properties in murine models of dermatitis. Both compounds demonstrated significant anti-inflammatory and wound-healing effects in murine dermal inflammation. The decreased systemic cytokine production and inhibition of endothelial P-selectin expression and neovascularization induced by these terpenic compounds contributed to their healing effects in the skin [60]. The chemopreventive effect of topical application of perillyl alcohol (**14**) on skin tumorigenesis initiated by 9,10-dimethylbenz(a)anthracene and promoted by 12-*O*-tetradecanoylphorbol-13-acetate and its potential mechanisms of action were investigated in Swiss Albino mice [61]. The chemopreventive efficacy of perillyl alcohol (**14**) was most likely due to inhibition of oxidative stress responses, inhibition of the Ras cell proliferation pathway and the induction of apoptosis in murine skin tumors [62].

Antimicrobial (Antibacterial, Antifungal) Effects of Monocylic Monoterpenes

Numerous monocyclic monoterpenes exhibit antimicrobial properties [21, 63, 64], which are exploited for numerous uses, including medicinal and food applications. A mixture of monoterpenes containing terpinen-4-ol (**15**), (+)-α-terpineol (**16**) and 1,8-cineole (**17**) was active against Gram-positive and Gram-negative bacteria isolated from the skin, mouth and upper respiratory tract of humans. Furthermore, promising results were obtained in studies performed on methicillin-resistant *Staphylococcus aureus* (MRSA). These results indicated that a mixture of these monoterpenes at concentrations from 2.5 to 5 mg/ml inhibited bacterial growth, whereas higher doses exhibited a bactericidal effect [63].

In a study by Trombetta *et al*. [64] the mechanism of antimicrobial action of thymol (**12**), and menthol (**22**) was investigated. It was demonstrated that their antibacterial effect resulted from the perturbation of the lipid fraction of bacterial plasma membrane, which increased cell membrane permeability and induced a leakage of intracellular materials [64].

A study by Wang *et al.* [65] found weak antibacterial and anticancer activities for 1,8-cineole (**17**), which has also been shown to exhibit anti-inflammatory properties in bronchial asthma [66] and to attenuate inflammation in rat models [66]. 1,8-Cineole (**17**) caused a steroid-like suppression of arachidonic acid metabolism and inhibited cytokine production *in vitro*. At therapeutic plasma levels, 1,8-cineole (**17**) inhibited the production of monocyte mediators in a dose-dependent manner with a magnitude of inhibition similar to that of budesonide [66]. In controlled studies, 1,8-cineole (**17**) treatment resulted in significant improvement in lung function tests and inhibited the production of leukotriene B4 and IL-1β in stimulated monocytes *ex vivo*. In bronchial asthma, long-term therapy with 1,8-cineole (**17**) was well tolerated and exhibited an anti-inflammatory effect that was equivalent to that of prednisolone (3 mg) [66].

In a study by Carson and Riley [67], terpinen-4-ol 15 and ρ-cymene (**18**) inhibited the growth of Acinetobacter *baumannii, Aeromonas veronii biogroup sobria, Enterococcus faecalis, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella enterica subsp. enterica serotype typhimurium, Serratia marcescens* and *Staphylococcus aureus*. In this study, (+)-α-terpineol (**16**) failed to inhibit the growth of only Pseudomonas aeruginosa; however, this compound demonstrated antimicrobial activity against other bacteria that was equivalent to that of terpinen-4-ol (**15**) [67].

Carvone (**10**) also exhibits antibacterial activity. Both optical isomers of carvone were effective against a wide spectrum of human pathogenic bacteria *in vitro* [68, 69, 70]. (4*R*)-(–)-Carvone (**10**) was active against *Campylobacter jejuni*, whereas (4*S*)-(+)-carvone (**10**) was effective against *Listeria monocytogenes* [69]. Carvone (**10**) also exhibited significant antibacterial activity against *Enterococcus faecium* and *Escherichia coli*.

Eugenol (**20**) inhibited the growth of thirty *Helicobacter pylori* strains *in vitro* producing significant decrease of their viability and its antibacterial activity was observed at low pH level [71]. It was also active against MRSA and MSSA *Staphylococcus aureus* [68]. Thymol (**12**), carvacrol (**19**) and eugenol (**20**) used alone or in combinations demonstrated antibacterial activity against *Escherichia coli*. These monoterpenes used in combinations showed synergistic antimicrobial effects, and effective concentrations of these combinations were significantly lower than these of used alone. As a result, their impact on the organoleptic quality of food (i.e., unpleasant smell) could be minimized [72].

1,8-Cineole (**17**) demonstrated antibacterial and anticancer properties *in vitro* but its antimicrobial activity was lower than that of α-pinene (**24**) and (+)-β-pinene (**25**) [72]. 1,8-Cineole (**17**) and carvacrol (**19**) demonstrated a synergistic antibacterial effect against *Listeria monocytogenes, Aeromonas hydrophila* and *Pseudomonas fluorescens* showing MIC in a range 0.005-0.02 mg/ml, and 0.0006-0.0025 mg/ml, respectively [73].

The expression of *Candida albicans* virulence in the oral cavity is strongly correlated with immune system impairment, particularly in patients with human immunodeficiency virus (HIV). Several conditions, such as hyposalivation, diabetes mellitus and prolonged antibiotic and corticoid therapy, can also predispose patients to oral candidiasis. Carvacrol (**19**), which is the major component of oregano and thyme extracts, and eugenol (**20**), which is the major component of clove oil, have been evaluated in several studies. Chami *et al.* [74] used an experimental model of immunosuppressed rats to confirm the efficacy of these two substances in the treatment of oral candidiasis.

Vasorelaxant and Hypotensive Activities of Monocyclic Monoterpenes

Carvacrol (**19**), which is a monoterpenic phenol, is the major component in essential oils from numerous plants that have been used for centuries in ethnomedicine, even in the absence of detailed investigations of the effects of carvacrol (**19**) on the cardiovascular system. Recently, Aydin *et al.* [75] investigated the role of carvacrol (**19**) on cardiovascular function *in vivo* in anesthetized rats. Carvacrol (**19**) (100 μg/kg, i.p.) decreased the heart rate, mean arterial pressure and systolic and diastolic blood pressure of anesthetized rats, whereas lower doses (1, 10 and 20 μg/kg) did not show any effect. Carvacrol (**19**) induced hypotension and inhibited N_{ω}-nitro-L-arginine methyl ester-induced hypertension. The lack of the inhibitory action of carvacrol (**19**) (10^{-4} M) on the calcium chloride- and phenylephrine-induced contractions of an isolated rat aorta indicated that neither adrenergic receptors nor voltage-dependent vascular L-type calcium channels were involved. Based on previous investigations, the hypotensive actions of carvacrol (**19**) were assumed to involve the blocking of cardiac L-type calcium channels [75]. The vasorelaxant effects of carvacrol (**19**) have also been investigated in isolated rat aorta. Carvacrol (**19**) demonstrated a concentration-dependent relaxation of aortic ring preparations pre-contracted by potassium chloride or phenylephrine [76]. This vasorelaxant effect was independent of nitric oxide release from the endothelium; however, it involved a transduction pathway between calcium release from the sarcoplasmic reticulum and the regulation of calcium sensitivity in the contractile system [76].

Anti-Inflammatory, Antioxidant, Local Anesthetic, Analgesic, Antiseptic and Choleretic Properties of Monocyclic Monoterpenes

In the continuous search for new bioactive natural products against inflammation, monoterpenes are emerging as a rich source of these compounds. Some monoterpenes possess both anti-inflammatory and antioxidant properties [30, 43, 56, 76-81]. (+)-limonene (**11**), and 1,8-cineole (**17**) demonstrated strong antioxidant, anti-inflammatory and anticancer properties in assays using DPPH method, pleural cell migration, and U251, UACC-62, MCF-7, NCI-ADR/RES, OVCAR-3 human cancer cell lines, respectively [80].

Menthol (**22**) is a naturally occurring plant compound that gives plants of the *Mentha* genus their typical minty fragrance and flavor. 1,8-Cineole (**17**) and menthol (**22**) had antioxidant properties in the ABTS-radical cation scavenging assay [82]. Menthol (**22**) is present in the volatile oil of several species of mint plants, such as peppermint oil derived from *Mentha piperita* (peppermint) and cornmint oil from *M. arvensis* (wild mint). When prepared by steam distillation from the fresh flowering tips of the plant, peppermint and cornmint oils contain 50% and 70%, respectively, of (−)-menthol (**22**) [83]. Menthol (**22**) can also be extracted or synthesized from other essential oils, such as citronella oil, eucalyptus oil and Indian turpentine oil. Menthol (**22**) is a cyclic terpene alcohol with three asymmetric carbon atoms. Of the optical isomers, (−)-menthol (**22**) is the isomer that occurs most widely in nature and is endowed with the peculiar property of being both a fragrance and a flavor compound.

In pharmaceutical applications, (−)-menthol (**22**) is used in topical antipruritic, antiseptic and cooling formulations [84]. Moreover, (−)-menthol (**22**) is included in eutectic formulations of local anesthetic agents [83, 85]. Peppermint is traditionally used for the symptomatic treatment of digestive disorders; the antispastic, carminative, choleretic and cholagogic properties attributed to this plant are conferred by an essential oil that is rich in (−)-menthol (**22**) [86]. Menthol (**22**) is also utilized in external broncholytic and secretolytic preparations [85].

The so-called 'menthol receptor', TRPM8, has been discovered and cloned. TRPM8 is activated by temperatures below 18-24°C and by the compounds menthol (**22**) and icillin. The receptor is involved in the detection of innocuous cold, and its activation contributes to cold pain, cold hypersensitivity following injury, and cooling analgesia. Although numerous reports indicate a primary role for TRPM8 as the principal cold sensor *in vivo*, TRPM8 also plays an important role in cold-evoked pain. Results from studies on knockout mice indicate that TRPM8 is required for cold sensation over a broad range of innocuous and noxious cold temperatures [84]. Cooling an area of injury or using menthol (**22**) to relieve pain is a popular treatment for pain, and activation of TRPM8 was shown to inhibit the central nociceptive input. Although activation of TRPM8 is required for the analgesia induced by cooling agents, this activation is also paradoxically involved in injury-evoked hypersensitivity to cold. Compounds such as menthol (**22**) induce the activation and sensitization of TRPM8, resulting in TRPM8 activation at temperatures higher than those generally observed under physiological conditions [84].

Finally, several monocyclic monoterpenes can influence mevalonate metabolism; these properties may account for their tumor-suppressing activity [16]. (+)-Limonene (**11**) and menthol (**22**) have been shown to inhibit the activity of hepatic 3-hydroxy-3-methylglutaryl-CoA reductase and reduce serum cholesterol levels [16]. Perillyl alcohol (**14**) also inhibited ubiquinone and cholesterol biosynthesis *in vitro* [16].

BICYCLIC MONOTERPENES

Bicyclic monoterpenes (Fig. **3**) possess two cyclic rings that are condensed together. This class of compounds is more complex than monocyclic monoterpenes. The second ring system typically shares 2, 3 or 4 carbon atoms with the other ring [3, 19]. Table **3** summarizes main pharmacological properties of bicyclic monoterpenes.

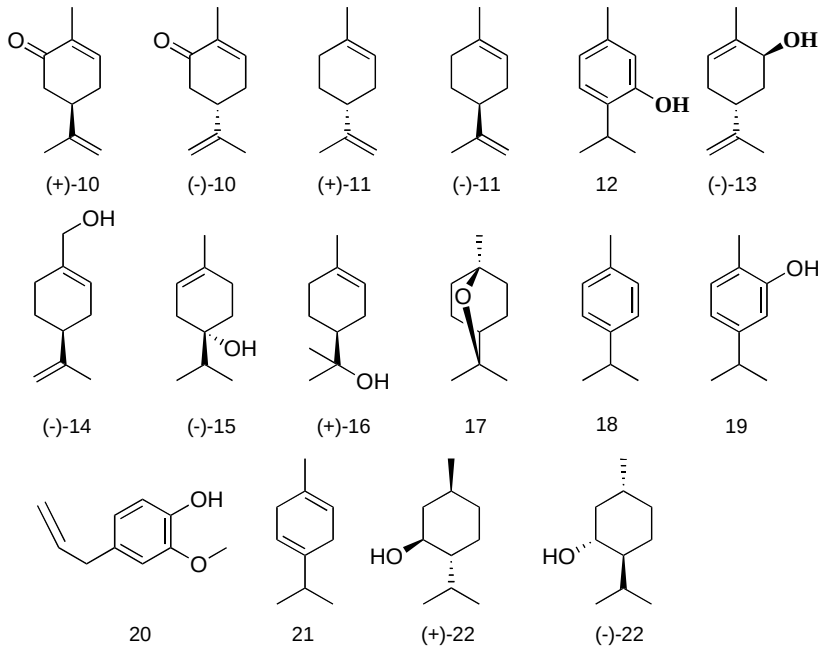


Fig. (2). Monocyclic monoterpenes: carvone (**10**), (+)-limonene (**11**), thymol (**12**), (–)-carveol (**13**), (–)-perillyl alcohol (**14**), terpinen-4-ol (**15**), (+)-α-terpineol (**16**), 1,8-cineole (**17**), ρ-cymene (**18**), carvacrol (**19**), eugenol (**20**), γ-terpinene (**21**) and menthol (**22**).

Table 2. Monocyclic monoterpenes: main source/origin, pharmacological properties and MIC values for antimicrobial activity.

Monocyclic monoterpene	Main source	Main pharmacological activities	MIC value [mg/ml]
Carvone	Leaves of *Perovskia angustifolia*	Antibacterial, anticancer	0.8 (MSSA) [68]; 0.008-0.064 (*Klebsiella pneumoniae* strains) [46]
Limonene	Citrus plants, bergamot fruit (*Citrus bergamia*), *Ocimum kilimandscharicum*, aerial parts of *Hyssopus cuspidatus*	Antibacterial, antifungal, anti-inflammatory, antioxidant, tumor-suppressing	0.03 ($MIC_{90;}$ *Mycoplasma pneumoniae*) [23]; 0.008-0.064 (*Klebsiella pneumoniae* strains) [46]
Thymol	*Thymus pubescens*	Antibacterial, anticancer	0.8 (MSSA); 3.17 (MRSA) [68]; 0.008-0.064 (*Klebsiella pneumoniae* strains) [46]
Carveol	Leaves of *Mentha spicata*, *Lavandula latifolia*	Anticancer	Not reported
Perillyl alcohol	Leaves of *Mentha spicata*	Anticancer	Not reported
Terpinen-4-ol	*Zingiber corallinum*, aerial parts of *Calamintha nepeta*, aerial parts of *Coridothymus capitatus, Salvia officinalis*	Antibacterial	*Acinetobacter baumannii* (MIC not reported) [87]
α-terpineol	Leaves of *Perovskia angustifolia*, flowers of *Salvia lavandulifolia*, aerial parts of *Salvia officinalis*, aerial parts of *Calamintha nepeta, Salvia officinalis*	Antibacterial	0.1-0.4 (*Porphylomonas sp.*); 0.4-0.8 (*Prevotella*) [21]; 0.1-0.4 (*Fusobacterium nucleatum*) [21]
1,8-cineole	Aerial parts of *Thymus pubescens*, *Rosmarinus officinalis*, aerial parts of *Coridothymus capitatus*, aerial parts of *Hyssopus cuspidatus, Salvia officinalis*	Antibacterial, anticancer, anti-inflammatory, antioxidant	>2.0 (*Enterococcus faecalis*) [44]; 0.4 (*Streptococcus salivarius*) [44]; 0.4 (*Streptococcus sanguinis*) [44]; 1.25 (*Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*); 2.5 (*Pseudomonas aeruginosa*); 5.0 (*Staphylococcus epidermidis*) [72]
ρ-cymene	Aerial parts of *Dicyclophora persica*, aerial parts of *Coridothymus capitatus*, *Lavandula latifolia*	Antibacterial; antifungal	1.8 (*Bacillus subtilis*); 7.2 (*Enterococcus faecalis*, *Staphylococcus aureus; Escherichia coli*); 3.6 (*Staphylococcus epidermidis*); 0.6 (*Aspergillus niger*) [45]
Carvacrol	*Thymus pubescens; Labiatae*, *Umbeliferae*, *Lamiaceae*	Antibacterial, antiviral, antifungal, cytotoxic, hypotensive/vasorelaxant	0.4 (MSSA); 1.6 (MRSA) [68]; 0.008-0.064 (*Klebsiella pneumoniae* strains) [46]
Eugenol	*Umbeliferae*, *Labiatae*, *Lamiaceae*	Antibacterial, antiviral, cytotoxic	0.01 (*Escherichia coli*); 0.002 (*Helicobacrter pylori*); 0.008-0.064 (*Klebsiella pneumoniae* strains) [46]
γ-terpinene	*Cinnamomum longepaniculatum* (leaves)	Antibacterial	>0.05 (*Escherichia coli*, *Staphylococcus aureus*) [88]; 0.008-0.064 (*Klebsiella pneumoniae* strains) [46]
Menthol	*Umbeliferae*, *Labiatae*, aerial parts of *Acinos rotundifolius*, *Mentha sp.* (aerial parts)	Local anesthetic, antibacterial, antiviral, cytotoxic, antioxidant, antiseptic, cooling, antipruritic, antispastic, carminative, choleretic, broncholytic, secretolytic, tumor-suppressing	0.008-0.064 (*Klebsiella pneumoniae* strains) [46]

Local Anesthetic and Antimicrobial (Antifungal, Antibacterial, Antiviral) Properties of Bicyclic Monoterpenes

Monoterpene hydrocarbon (+)-3-carene (**23**) is a popular flavoring compound that is also used in perfumery and is a major constituent of Polish turpentine, which is the essential oil from *Pinus sylvestris*. Compounds synthesized from (+)-3-carene (**23**) exhibit local anesthetic properties [14, 15, 89-91]. (+)-3-carene (**23**), an active constituent of *Asarum heterotropoides* and *Juniperus communis* inhibited growth of *Clostridium difficile, Clostridium paraputrificum, Clostridium perfringens, Staphylococcus aureus, Escherichia coli, Bacteroides fragilis* but not *Salmonella enterica* [92]. It had also antifungal properties against *Aspergillus* and Candida strains [93].

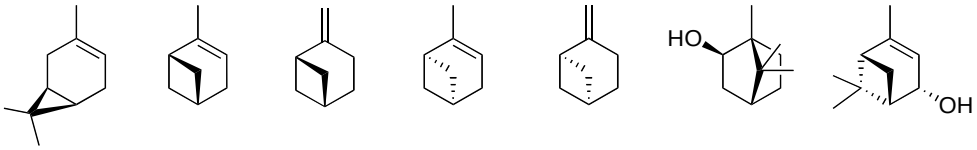
In plants, pinenes exhibit fungicidal properties. These substances are used to produce flavors and fragrances and as natural insecticides [94, 95]. The minimal inhibitory concentrations (MICs) and the minimal microbicidal concentrations of these monoterpenes have been determined. In these studies, positive enantiomers, and not negative enantiomers, exhibited microbicidal properties against fungi and bacteria, with MICs ranging from 117 to 4150 μg/ml. A mixture of (+)-α-pinene (**24**) and (+)-β-pinene (**25**) exhibited antibacterial properties against *S. aureus* [94]. In MRSA, the bactericidal effect occurred after 6 h [94]. The potential of (+)-α-pinene (**24**) and (+)-β -pinene (**25**) to inhibit phospholipase and esterase enzymes secreted by *C. neoformans* and *C. albicans* was also evaluated, and the greatest inhibition was observed for *C. neoformans*-secreted enzymes [94]. (+)-α-Pinene (**24**) and (+)-β-pinene (**25**) also inhibited a wide range of fungi *in vitro*, including *Aspergillus niger, A. flavus, Microsporum audouinii, M. canis, Trichophyton mentagrophytes* and *T. rubrum* [95, 96]. The antifungal effect of combinations of monoterpenes has been described in several studies [10, 28, 67, 74, 97-99]. Diffusion studies have been conducted to evaluate the growth inhibition of *C. albicans* by (+)-α-pinene (**24**) and (+)-β-pinene (**25**) [94]. The obtained results confirmed antifungal activity of both positive enantiomers. Additionally, these authors reported a synergistic effect with ciprofloxacin for each positive enantiomer (i.e., ciprofloxacin and (+)-α-pinene (**24**) or ciprofloxacin and (+)-β-pinene (**25**)) in MRSA [94].

Armaka *et al.* [100] demonstrated that (+)-isoborneol (**26**) potently inactivated HSV-1. The antiviral activity of (+)-isoborneol (**26**) involved the interaction of monoterpene hydroxyl groups with a viral capsid and the inhibition of glycosylation of a viral protein, which results in the loss of viral infectivity [100]. In these studies, (+)-isoborneol (**26**) did not induce cytotoxicity at concentrations ranging between 0.016% and 0.08% when evaluated in human and monkey cell lines [100]. An interesting study on the anti-IBV (infectious bronchitis virus) activities of (–)-α-pinene (**24**) and (–)-β-pinene (**25**) using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and docking and molecular dynamics simulations has also been conducted. The maximum non-cytotoxic concentrations of (–)-α-pinene (**24**) and (–)-β-pinene (**25**) were determined to be 7.88±0.06 and 6.09±0.31 mM, respectively. These two compounds were found to inhibit IBV with IC_{50} values of 0.98±0.25 and 1.32±0.11 mM, respectively. An MTT assay indicated that the anti-IBV activity of (–)-pinenes was moderate prior to viral entry into the cell; however, this activity was much stronger following viral penetration. Molecular dynamics simulations indicated that (–)-α-pinene (**24**) and (–)-β-pinene (**25**) specifically interacted with the active site of the phosphorylated nucleocapsid protein, which is located at the N-terminus. (–)-α-Pinene (**24**) exhibited more potent inhibition. These results suggest that (–)-α-pinene (**24**) and (–)-β-pinene (**25**) possess anti-IBV properties; therefore, they are a potential source of anti-IBV compounds for the pharmaceutical industry [98].

Hypotensive and Antioxidant Activity of Bicyclic Monoterpenes

The cardiovascular activities of (+)-α-pinene (**24**) and (–)-β-pinene (**25**) have also been investigated in normotensive non-anesthetized rats, and these monoterpenes were found to induce hypotension. These terpenes exhibited hypotensive effects in rats, and the pharmacological effect of terpene alcohols was more significant than that of the corresponding terpene hydrocarbons [43].

(+)-*cis*-Verbenol (**27**), which is a natural metabolite of (–)-α-pinene (**24**), derived from the pine tree, exhibits anti-ischemic activity. In a study by Choi *et al.* [79], (+)-*cis*-verbenol (**27**) reduced the cerebral ischemic injury caused by cerebral artery occlusion followed by 24-h reperfusion. Moreover, (+)-*cis*-verbenol (**27**) prevented the neuronal cell death caused by oxygen-glucose deprivation (1 h) and subsequent re-oxygenation (5 h). (+)-*cis*-Verbenol (**27**) did not inhibit NMDA-stimulated calcium influx but reduced the intracellular level of reactive oxygen species elevated by oxygen-glucose deprivation and re-oxygenation. (+)-*cis*-Verbenol (**27**) potently eliminated peroxyl radicals and reduced the expression of pro-inflammatory cytokines in ischemic brain and immunostimulated glial cells. These effects indicated that (+)-*cis*-verbenol (**27**) may represent a therapeutically useful agent with antioxidant and anti-inflammatory properties [79].



(+)-23 (+)-24 (+)-25 (-)-24 (-)-25 (+)-26 (+)-27

Fig. (3). Bicyclic monoterpenes endowed with biological activities: (+)-3-carene (**23**), (+)-α-pinene (**24**) and (+)-β-pinene (**25**), (+)-isoborneol (**26**), (+)-*cis*-verbenol (**27**).

Table 3. Bicyclic monoterpenes: main source/origin, pharmacological properties and MIC values for antimicrobial activity.

Bicyclic monoterpene	Main source	Main pharmacological activities	MIC value [mg/ml]
3-carene	*Pinus sylvestris, Asarum heterotropoides* (root); *Juniperus communis* (leaves)	Antibacterial, antifungal, local anesthetic	0.18-0.7 (*Clostridium sp., Staphylococcus aureus, Escherichia coli, Bacteroides fragilis*) [92] 0.001-0.005 (*Candida sp.*); 0.001-0.01 (*Aspergillus niger*) [93]
α-pinene	*Umbeliferae, Labiatae, Apiaceae* (aerial parts), *Ferula hermonis* (rhizome and roots), aerial parts of *Acinos rotundifolius*, aerial parts of *Hyssopus cuspidatus, Salvia officinalis*	Antibacterial, antiviral, antifungal, hypotensive	1.2 (VRSA); 2.5 (*Pseudomonas aeruginosa*); 2.5 (*Escherichia coli*) [22]; >2.0 (*Enterococcus faecalis*) [44]; 0.4 (*Streptococcus salivarius*) [44]; 0.4 (*Streptococcus sanguinis*) [44] 7.5 (*Bacillus subtilis*); >15.0 (*Staphylococcus aureus*); 15.0 (*Escherichia coli, Staphylococcus epidermidis*) [45]; 0.0625 (*Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa*); 0.0313 (*Staphylococcus aureus, Staphylococcus epidermidis*) [72] 0.117 (*Cryptococcus neoformans*); 0.004 (MRSA) [94] 0.128 (*Candida albicans*); 0.064 (*Tricophyton mentagrophytes, Aspergillus niger*) [95]; 0.008-0.064 (*Klebsiella pneumoniae* strains) [46]
β-pinene	*Umbeliferae, Labiatae,* aerial parts of *Acinos rotundifolius*, aerial parts of *Hyssopus cuspidatus, Salvia officinalis*	Antibacterial, antiviral, antifungal, hypotensive	0.0625 (*Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa, Staphylococcus epidermidis*); 0.0313 (*Staphylococcus aureus*) [72] 0.187 (*Cryptococcus neoformans*); 0.006 (MRSA) [94]; 0.008-0.064 (*Klebsiella pneumoniae* strains) [46]
Isoborneol	*Thymus pubescens*	Antibacterial, antiviral	0.008-0.064 (*Klebsiella pneumoniae* strains) [46]
Verbenol	*Ferula hermonis* (rhizome and roots)	Antifungal, neuroprotective/ anti-ischemic in the central nervous system	0.128 (*Candida albicans*); 0.032 (*Tricophyton mentagrophytes*); 0.128 (*Aspergillus niger*) [95]

STEREOCHEMISTRY OF MONOTERPENES

For millions of years, nature has utilized enantiomerically pure molecules in living organisms. In recent decades, there has been increasing interest in selectively synthesizing chiral molecules [101]. These chiral building blocks are then incorporated into target molecules such that the configuration at the stereogenic centers is not altered. Because the relative configuration of new chiral centers can be controlled, virtually any enantiomerically pure product can be constructed around the chiral starting molecule. For pheromones, chirality exhibits a similar influence on their biological activity; when one enantiomer attracts an insect species, the other enantiomer may act as a repellant [102]. Chiral recognition by receptors and enzymes has been clearly demonstrated in biochemical, pharmaceutical, and chemosensory studies [103].

The stereochemistry also affects the odor of compounds and underlies the intense odors of certain compounds and the absence of odors for other compounds. Monoterpene enantiomers, which are common in several plant species, are used in cosmetic, non-cosmetic, and pharmaceutical preparations, as well as in the food industry [5-8]. The pharmacochemical industry is currently quite interested in developing natural chiral chemicals from plant materials. Numerous industrial "naturally identical" compounds are either racemates or optically impure. In several cases, this results in differences in the organoleptic properties and biological activities between the natural and "naturally identical" compounds.

To date, little attention has been given to the stereochemical features of the resulting monoterpenes. Individual enzyme systems present in a particular organism will control binding of the substrate molecule and thus

define the stereochemistry of the final product. Most monoterpenes are optically active, and several examples have been found in which enantiomeric forms of identical compounds can be isolated from different sources, e.g., (+)-carvone (**10**) in caraway (*Carum carvi*; Umbelliferae/ Apiaceae) and (–)-carvone (**10**) in spearmint (*M. spicata*; Labiatae/Lamiaceae). Additional examples include (+)-limonene (**11**) and (–)-limonene (**11**) in peppermint (*M. piperita*; Labiatae/Lamiaceae) and (+)-α-pinene (**24**) and (–)-α-pinene (**24**) in pine (*Pinus* species; Pinaceae). The individual enantiomers can induce different biological responses, particularly toward olfactory receptors in the nose. Thus, the characteristic odor of caraway results from (+)-carvone (**10**), whereas (–)-carvone (**10**) exhibits a mint odor. (+)-Limonene (**11**) exhibits an odor of oranges, whereas the odor of (–)-limonene (**11**) resembles that of lemons.

The pharmacological activity of monoterpenes depends on their structure and on the organisms they affect. Studies have investigated the differences in bioactivities between the enantiomers of monoterpenes, such as (+)- and (–)-α-pinene (**24**) and (+)- and (–)-limonene (**11**) [101, 102]. Studies on the α-pinene enantiomers have found that (–)-α-pinene (**24**) has a greater antibacterial effect [103]. Moreover, pharmacological investigations have found that (–)-α-pinene (**24**) exhibits stronger spasmodic effects on smooth muscle than (+)-α-pinene (**24**) [105]. Because biological systems are primarily composed of chiral compounds, the observation that some drugs with stereogenic centers exhibit a large degree of stereoselectivity in their interactions with macromolecules is not surprising given such a highly chiral environment [106]. These results indicate that drugs derived from plants that contain optically active compounds should be standardized, and analyses of the biological activities of monoterpene stereoisomers are necessary.

CONCLUSION

Monoterpenes are best known as constituents of essential oils and defensive resins of aromatic plants. Numerous monoterpenes are non-nutritive dietary components found in the essential oils of citrus fruits, cherries and herbs. Monoterpenes exert several beneficial effects in humans and have been shown to penetrate into the bloodstream and act as medicinal substances. Some monoterpenes can control brain functions. Components of essential oils are also used in the treatment of upper respiratory tract diseases as expectorants and antibacterial and antiviral agents. In some gastric disorders, monoterpenes exhibit cholagogic and spasmolytic properties. Due to their hydrophobic properties, monoterpenes are used to dissolve gallstones and reduce cholesterol in humans. The antitumor, antibacterial, antifungal, antiviral, immunomodulating, local anesthetic and anti-inflammatory properties of monoterpenes are promising and necessitate further research.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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