



Monoterpenoids: A Neuropharmacological Approach

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ABSTRACT

Monoterpenoids, being a valuable component of essential oils, constitute important groups of natural compounds. They contain two isoprenoid units in their structure. Monoterpenoids are the secondary metabolites of the plants and they do not exert primary function in the plants. Owing to their higher abundance in the plant kingdom, they find wide application in the perfumery industry, food, and health care products for human beings. Monoterpenoids either in direct form or modified form exert diverse pharmacological effects. The present review reports wide pharmacological activities of monoterpenoids like learning and memory enhancer, antidepressant, anxiolytic, antinociceptive, anticonvulsant, and neuroprotective indicating the promising potential of monoterpenoids to treat a wide range of complex diseases.

Keywords: Acyclic; Bicyclic, Monocyclic, Monoterpenoids, Neuropharmacological activities

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INTRODUCTION

Terpenoids are the most abundant and structurally highly complex natural products. They are also known as isoprenoids. The term ‘terpene’ was used for the hydrocarbons present in the turpentine, with the ‘ene’ suffix suggesting the presence of double bonds (olefinic bonds) (1). The basic moiety present in the structure is the isoprenoid unit. Depending on the modifications in the isoprenoid chain due to various reactions like oxidation, reduction, rearrangements, cleavage of the rings, or cyclization, they possess cyclic or acyclic structures(2). They are named based on the number of isoprenoid units present in their structure. Based on this, they are classified as monoterpenoids, sesquiterpenoids, diterpenoids, triterpenoids, tetraterpenoids, and polyterpenoids (2–4). Monoterpenoids, sesquiterpenoids, and diterpenoids are regarded as secondary metabolites as they are not important for plant survival. Moreover, they are responsible for the mediation of essential interactions in the plant environments (3,5).

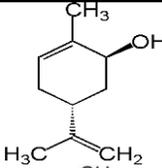
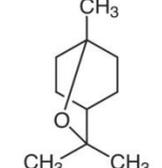
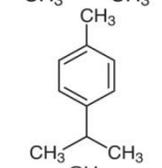
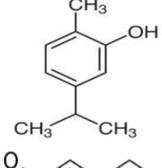
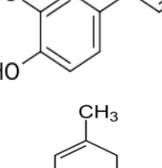
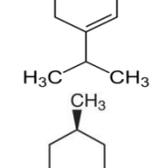
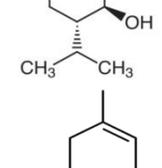
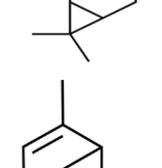
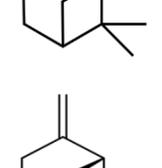
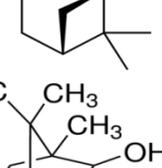
It has been well established that monoterpenoids besides having fragrance also possess diverse pharmacological activities such as antioxidant, anti-inflammatory, anticancer, local anesthetic, antiviral, antibacterial, antifungal, anti-arrhythmic, neuroprotective, anti-spasmodic, antinociceptive, etc. (6–8). They are widely used in perfumes, foods, cosmetics, drinks, etc. as a flavoring agent (9). They are also used as growth regulators, oxidative phosphorylation inhibitors, tumor inhibitors, insect repellants, antidiabetic agents, canine and feline attractants, etc.(5,10). Hence, monoterpenoids possess wide applications in various fields like agriculture, medicine, and industry.

Biosynthesis

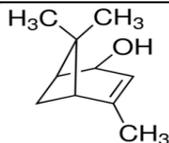
Monoterpenoids are acyclic (linear) or cyclic (ring structure). Cyclic monoterpenoids are further divided into monocyclic and bicyclic depending on the number of rings present in the structure. Some of the common examples of the monoterpenoids along with their structure and source of origin are summarized in Table 1. There are several functional groups present in their structure like aldehyde, ketone, alcohol, esters, ethers, etc. (11). The key components for the biosynthesis of monoterpenoids are isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP), an allylic isomer of IPP (12). In plants, two distinct pathways are used to form the IPP, viz. plastidialmethyl-erythritol-4-phosphate (MEP) pathway, and cytosolic acetate-mevalonate (MVA) pathway (13). Cytosolic IPP is formed by the MVA pathway in plant cells and transported to mitochondria to synthesis isoprenoids in mitochondria (14), whereas in the plastid, the MEP pathway is responsible for the synthesis of the IPP and DMAPP (15).

Table 1 Different types of monoterpenoids, their examples along with structure and main source of origin.

Type of monoterpenoid	Examples	Structure	Main source of origin
Acyclic monoterpenoid	Geraniol		Lemongrass (<i>Cymbopogon</i>), <i>Thymus pubescens</i> , <i>Umbelliferae</i> , <i>Labiatae</i> , aerial parts of <i>Dracocephalum moldavica</i>
	Linalool		<i>Citrus bergamia</i> (Bergamot fruit), aerial parts of <i>Ocimum canum</i> , <i>Coridothymus capitatus</i>
	Citral		<i>Cymbopogon</i> (lemongrass), <i>Umbelliferae</i> , <i>Labiatae</i> , aerial parts of <i>Dracocephalum moldavica</i>
	Citronellol		Aerial parts of <i>Dracocephalum Moldavica</i> , <i>Thymus pubescens</i>
	Citronellal		<i>Thymus pubescens</i>
	β -myrcene		Aerial parts of <i>Thymus pubescens</i> , <i>Calamintha nepeta</i> , <i>Ocimum basilicum</i> , <i>Pimenta acris</i> , <i>Salvia officinalis</i> , <i>Rosmarinus officinalis</i> , strobiles of <i>Humulus lupulus</i>
β -ocimene		Aerial parts of <i>Dicyclophora persica</i> , <i>Pimenta acris</i> , <i>Ocimum basilicum</i> , <i>Lavandula angustifolia</i> , <i>Calamintha nepeta</i> , strobiles of <i>Humulus lupulus</i>	
Monocyclic monoterpenoid	Carvone		<i>Perovskia angustifolia</i> (leaves)
	Limonene		<i>Ocimum kilimandscharicum</i> , Citrus plants, <i>Citrus bergamia</i> (bergamot fruit), aerial parts of <i>Hyssopus cuspidatus</i>
	Thymol		<i>Thymus pubescens</i>

Carveol		<i>Lavandula latifolia</i> , leaves of <i>Mentha spicata</i> ,
1,8-cineole		Aerial parts of <i>Coridothymuscapitatus</i> , <i>Thymus pubescens</i> , <i>Rosmarinus officinalis</i> , <i>Hyssopuscuspidatus</i> , <i>Salvia officinalis</i>
p-cymene		Aerial parts of <i>Lavandula latifolia</i> , <i>Dicyclophorapersica</i> , <i>Coridothymuscapitatus</i>
Carvacrol		<i>Labiatae</i> , <i>Umbeliferae</i> , <i>Lamiaceae</i> ; <i>Thymus pubescens</i>
Eugenol		<i>Labiatae</i> , <i>Umbeliferae</i> , <i>Lamiaceae</i>
γ -terpinene		Leaves of <i>Cinnamomum longepaniculatum</i>
Menthol		<i>Labiatae</i> , <i>Umbeliferae</i> , aerial parts of <i>Mentha sp.</i> and <i>Acinosrotundifolius</i>
Bicyclic monoterpeneoid		
3-carene		Roots of <i>Asarumheterotropoides</i> , <i>Pinus sylvestris</i> ; leaves of <i>Juniperus communis</i>
α -pinene		Aerial parts of <i>Labiatae</i> , <i>Umbeliferae</i> , <i>Apiaceae</i> , rhizome and roots of <i>Ferulahermonis</i> , aerial parts of <i>Salvia officinalis</i> , <i>Acinosrotundifolius</i> , <i>Hyssopus cuspidatus</i>
β -pinene		<i>Labiatae</i> , <i>Umbeliferae</i> , aerial parts of <i>Salvia officinalis</i> , <i>Acinosrotundifolius</i> , <i>Hyssopus cuspidatus</i>
Isoborneol		<i>Thymus pubescens</i>

Verbenol

Rhizome and roots of *Ferula hermonis*

The MVA pathway

The MVA pathway of the plant can be directly comparable to the MVA pathway taken place in animals. The synthesis of IPP in the cytosol through the MVA pathway is summarized in Fig. 1. Initially, two units of acetyl coenzyme A (acetyl CoA) undergo a Claisen condensation reaction and form acetoacetyl CoA. This reaction is catalyzed by the enzyme acetoacetyl CoA thiolase. The resultant product condensed with another unit of acetyl CoA and form 3-hydroxy-3-methylglutaryl CoA (HMG CoA) in presence of HMG coenzyme A synthase (HMG CoA synthase) through aldol condensation. HMG CoA reductase enzyme then acts upon HMG CoA to form mevalonate through the nicotinamide adenine dinucleotide phosphate (NADPH)-dependent reduction reaction. This reaction is reversible and takes place in two steps (16). The mevalonate is then converted to mevalonate-5-diphosphate via phosphorylation reaction. This phosphorylation reaction occurs in two steps and is catalyzed by the mevalonate kinase enzyme and phosphomevalonate kinase enzyme. The mevalonate-5-diphosphate is then undergone a decarboxylation reaction to form IPP in presence of a diphospho-mevalonate decarboxylase enzyme. This decarboxylation reaction is an adenosine triphosphate (ATP)-dependent reaction. In the last stage of the pathway, DMAPP has formed via isopentenyl-diphosphate isomerase enzyme (17).

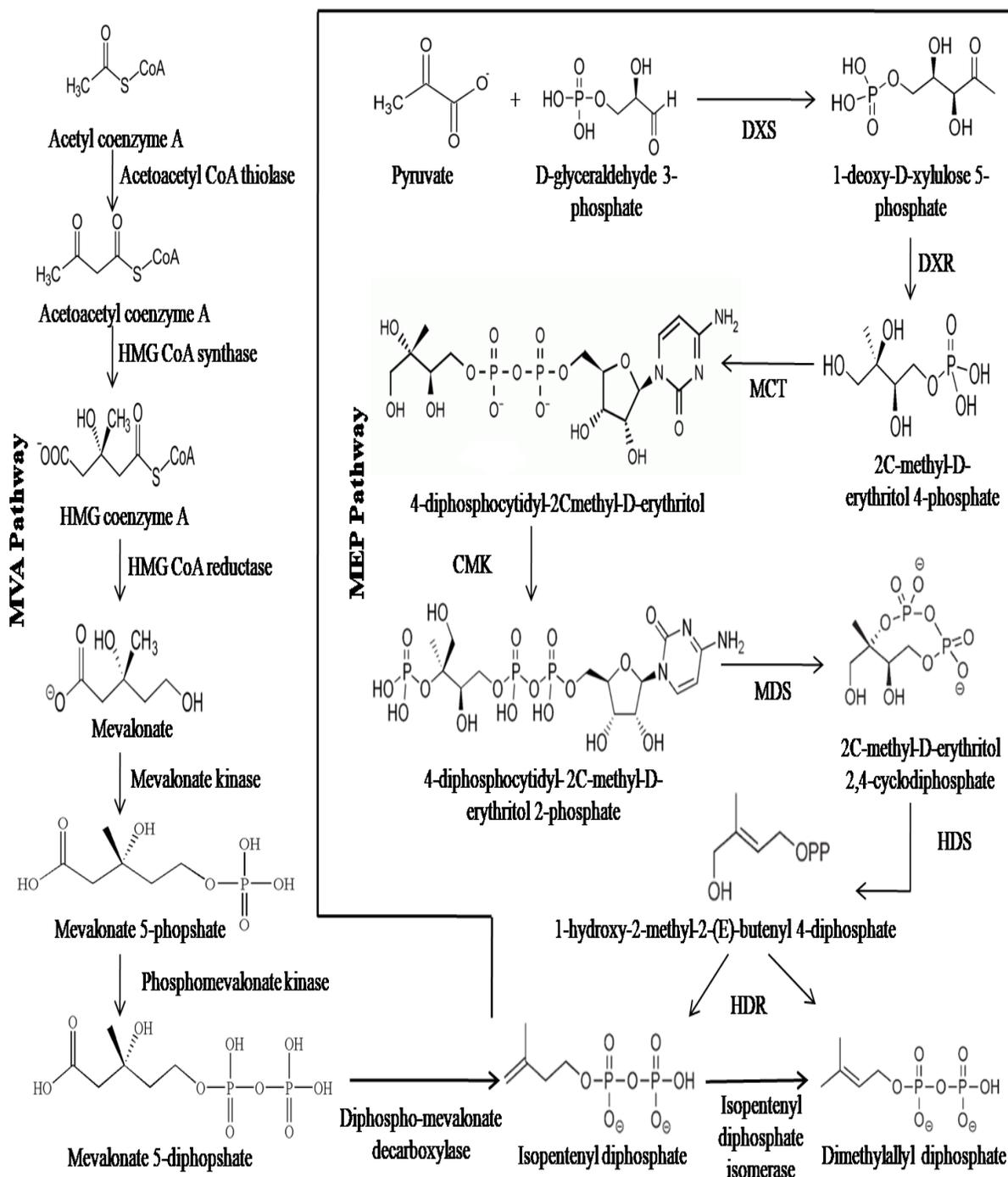


Figure 1: Isopentenyl diphosphate synthesis via the MVA or the MEP pathway

Intermediates involved in the biosynthesis are as follows: MVA pathway, Acetyl CoA; acetoacetyl CoA; HMGCoA; mevalonate; mevalonate 5-phosphate; mevalonate 5-diphosphate; isopentenyl diphosphate (IPP); dimethylallyl diphosphate (DMAPP). MEP pathway, pyruvate; D-glyceraldehyde 3-phosphate; 1-deoxy-D-xylulose 5-phosphate; 2C-methyl-D-erythritol 4-phosphate; 4-diphosphocytidyl-2C-methyl-D-erythritol; 4-diphosphocytidyl-2C-methyl-D-erythritol 2-phosphate; 2C-methyl-D-erythritol 2,4-cyclodiphosphate; 1-hydroxy-2-methyl-2-(E)-

butenyl 4-diphosphate; isopentenyl diphosphate (IPP); dimethylallyl diphosphate (DMAPP). Enzymes of the MVA pathway are as follows: AcetoacetylCoA thiolase; HMGCoA synthase; HMGCoA reductase; mevalonate kinase; phosphomevalonate kinase; diphospho-mevalonate decarboxylase. Enzymes of the MEP pathway are as follows: DXS, 1-deoxy-D-xylulose 5-phosphate synthase; DXR, 1-deoxy-D-xylulose 5-phosphate reductoisomerase; MCT, 2C-methyl-D-erythritol 4-phosphate cytidyl transferase; CMK, 4-diphosphocytidyl-2C-methyl-D-erythritol kinase; MDS, 2C-methyl-D-erythritol 2,4-cyclodiphosphate synthase; HDS, 1-hydroxy-2-methyl-2-(E)-butenyl 4-diphosphate synthase; HDR, 1-hydroxy-2-methyl-2-(E)-butenyl 4-diphosphate reductase; The interconversion of IPP into DMAPP is catalyzed by IDI, isopentenyl diphosphate isomerase.

The MEP pathway

The formation of IPP and DMAPP through the MEP pathway occurs in seven steps as shown in Figure 1. Briefly, pyruvate and glyceraldehydes-3-phosphate undergo a condensation reaction in presence of 1-deoxy-D-xylulose-5-phosphate (DXP) synthase enzyme and leads to the formation of DXP. The DXP is then converted to MEP with the help of the enzyme DXP reductoisomerase (DXR), also known as MEP synthase enzyme. The resultant product is then transformed into 1-hydroxy-2-methyl-2-(E)-butenyl-4-diphosphate (HMBPP). This is a multistep process which catalyzed by various enzymes viz., 2C-methyl-D-erythritol 4-phosphate cytidyl transferase (MCT), 4-diphosphocytidyl-2-C-methyl-D-erythritol kinase (CMK), 2-C-methyl-D-erythritol 2,4-cyclodiphosphate synthase (MDS), and 1-hydroxy-2-methyl-2-(E)-butenyl-4-diphosphate synthase (HDS). In the end, IPP and DMAPP are formed by the branching of HMBPP in presence of an enzyme 1-hydroxy-2-methyl-2-(E)-butenyl-4-diphosphate reductase (HDR)(18).

EFFECT OF MONOTERPENOIDS ON PSYCHOPHARMACOLOGICAL AND BEHAVIORAL EFFECTS

Effect of some selected acyclic monoterpenoids

Effect on memory

Lee (19) have examined the effects of linalool on rapid eye movement (REM) sleep deprivation-induced cognitive impairment and behavioral changes. They have carried out the Y maze test and passive avoidance test to assess spatial and learning memory and forced swimming test to assess the anti stress effect of linalool. They have concluded that linalool markedly improves spatial and learning memory loss and stress activity due to increased levels of serotonin. Another acyclic monoterpene, citral was tested on animals to study its effects on spatial and learning memory through the Morris water maze (MWM) test. It has been shown that citral produces a biphasic

effect i.e. in a low dose, it improved spatial memory of rats whereas, in a higher dose, an opposite effect was produced. This biphasic effect was observed because of increased and decreased levels of retinoic acid in the hippocampus due to lower and higher doses of citral respectively(20).

Effect on depression

Geraniol, chiefly found in essential oils of lemon, orange, ginger, lavender, rose, etc. was investigated for anti-depressant effect using a chronic unpredictable mild stress model of depression in mice. The results of the study showed that geraniol markedly reduced depression-like behavior possibly by regulation of chronic unpredictable mild stress model induced pro-inflammatory cytokine interleukin-1 beta (21). In another study, linalool was tested for anti-depressant activity using a forced swimming test. The study has shown that linalool produced an anti-depressant effect by affecting the serotonergic pathway (22).

Effect on convulsion

Geraniol, used as a folk medicine for the treatment of epilepsy in Brazil, was tested for anticonvulsant activity using pentylenetetrazole (PTZ)-induced convulsion model (23). Rf Lins(23) have found that geraniol remarkably increased the latency, and the percentage of animals convulsed was decreased. At last, they have concluded that geraniol possessed an anticonvulsant effect in the PTZ model in mice. Similarly, citral, a chief constituent of citrus oils, was investigated for its role in the treatment of epilepsy through the same PTZ-induced convulsion model and maximum electric shock (MES) test (24), and it was observed that citral increased latency for PTZ-induced convulsion development as well as it significantly prevented tonic convulsion in MES-induced convulsion model. Another acyclic monoterpene, linalool was also evaluated for its anticonvulsant effect using N-methyl-D-aspartate (NMDA)-induced convulsion model and quinolinic acid-induced convulsion model (25). The results of the study revealed that linalool not only delayed NMDA-induced convulsion but also block the quinolinic acid-induced convulsions.

Effect on pain and nociception

A study on the antinociceptive activity of geraniol carried out by La Rocca (26) in mice revealed that geraniol markedly reduced the acetic acid-induced number of writhes and suggested a non-opioid mechanism for this effect. Furthermore, intraperitoneal injection of geraniol significantly decreased the time of paw licking and suggesting modulation of glutaminergic neurotransmission. In conclusion, geraniol produced an antinociceptive effect particularly in pain because of inflammation and partly because of decreased nerve excitability in the periphery.

In another study, (-) linalool was investigated against chemicals viz. acetic acid and formalin and heat-induced nociception models in mice. It was found that writhings induced by acetic acid and

two phases of nociception induced by formalin were markedly inhibited by linalool in mice. These indications were suggestive of central and peripheral analgesic activity of (-) linalool (27).

Another acyclic monoterpene, citral was evaluated for its effects in acute and chronic experimental models of nociception, non-steroidal anti-inflammatory drugs (NSAIDs)-induced gastric ulcers, and inflammation. The results of the study revealed that citral when given orally remarkably inhibited responses of neurogenic as well as inflammatory pain caused by formalin intra-plantar injection. Moreover, citral possessed an anti-nociceptive effect against mechanical hyperalgesia in various models such as the sciatic nerve partial ligation model, chronic regional pain syndrome, and plantar incision surgery. In conclusion, it was found that the anti-nociceptive activity of citral was due to the activation of the 5-HT_{2A} serotonin receptor (28).

Effect on anxiety

The anxiolytic effects of linalool odor have been investigated using various tests such as the light/dark box test and elevated plus maze (EPM) test. It was found that exploratory behavior was remarkably increased by linalool odor in the light chamber which indicates the anxiolytic effect of linalool odor. Moreover, in the EPM test, linalool odor exposure has significantly increased time spent in the open arm, i.e. exploration of the open arm, the number of entries in the open arm. Besides, an accelerating rotarod test, carried out to check whether linalool odor exposure impaired motor function or not, showed that there was no difference in latency to fall time of the linalool odor exposed group and control group (29).

Intraperitoneal injection of geraniol in BALB/c mice produced an anxiolytic effect indicated by the increased distance moved in the arena center, increased percentage of open arm time, and an increased percentage of open arm entries (30).

Neuroprotective activities

Geraniol was investigated for neuroprotective activity using various models. It has shown a significant neuroprotective effect in the acrylamide (ACR)-induced nerve injury model in *Drosophila* by attenuating ACR-induced mitochondrial dysfunction, oxidative stress, and neurotoxicity. Moreover, co-administration of curcumin along with geraniol decreased acetylcholinesterase effect and produced a negative effect on cholinergic functions (31). Besides, pretreatment with geraniol produced a significant protective effect in Parkinson's disease (PD) using the MPTP-induced PD mouse model. It markedly increased the expression of tyrosine hydroxylase and decreased the expression of alpha-synuclein (32).

Similarly, linalool was investigated for neuroprotective effects against ACR-induced neurotoxicity in Wistar rats. The results showed that linalool significantly reduced severe gait abnormalities

caused by acrylamide exposure. Besides, linalool also significantly increased glutathione content and decrease malondialdehyde levels in the cerebral cortex (33). Linalool was also assessed for its protective effect against an *in vitro* model of ischemic stroke, viz. oxygen-glucose deprivation/reoxygenation (OGD/R) model. It has been shown that linalool markedly reduced cortical neuronal injury and oxidative stress caused by OGD/R (34). The study on the L-linalool effect on PD showed that linalool significantly produced a neuroprotective effect by improving behavioral changes, decreasing dopamine, homovanillic acid, and 3,4-Dihydroxy phenylacetic acid contents in the striatum, decreasing nitrite contents and lipid peroxidation (35).

Effects of some selected monocyclic monoterpenoids

Effect on memory

A natural monoterpene, limonene was investigated to study its effect on memory impairment and the results showed that in the MWM test, the distance traveled to reach the hidden platform was remarkably small and in the target quadrant, time spent was significantly higher. Similarly, in the EPM test, the percentage of open arm entries were also increased by limonene. This indicated that limonene provides spatial memory improvement(36). Similarly, intraperitoneal injection of carvacrol also improves short term memory impairments tested using passive avoidance test in rats (37). It has been shown that eugenol, a chief constituent of clove oil, improves learning and memory impairment through the olfactory pathway on vascular dementia when tested using the MWM test (38). A study carried out by Bhadania(39) showed that significant improvement in learning and memory was observed when treated with menthol in mice.

Effect on depression

Oral administration of (R)-(+)-Limonene significantly increased immobility showing an anti-depressive effect when evaluated using forced swim test in rats (40). A bioactive constituent of *Thymus vulgaris*, thymol, was investigated for anti-depressive effect using chronic unpredictable mild stress (CUMS) model of depression in mice (41). The results of the study revealed that thymol has significantly reversed the CUMS-induced decreased immobile time in various tests such as tail suspension test and forced swimming tests. It has also significantly restored altered levels of monoamine neurotransmitters due to CUMS indicating its potential as an anti-depressant. In another study, 1,8-cineole was evaluated for antidepressant effect using a forced swimming test and tail suspension test. Following this, inhalation of 1,8-cineole has significantly reduced immobility time in the mentioned tests indicating its anti-depressant activity in mice (42). In the behavior models, like tail suspension and forced swimming tests, carvacrol, a monoterpene phenol, has remarkably decreased immobility time by affecting the dopaminergic system (43). Another

fragrant compound, eugenol was evaluated for antidepressant effect and found that the eugenol leads to increased expression of brain-derived neurotrophic factor gene, inhibition of monoamine oxidase-A enzyme, and restoration of monoamines in hippocampus suggesting its beneficial role in depression (44).

Effect on convulsion

A study carried out by Joushi(45) showed that eugenol significantly decreases the epilepsy stage, duration, and mortality in rats. Besides, eugenol pretreatment preserved the neuronal numbers in convulsive animals. These all such events confirming the neuroprotective activity of eugenol. The anticonvulsant effect of a monoterpene phenol, viz. carvacrol was investigated against two models of epilepsy, i.e. the PTZ or MES test, and found that carvacrol increased latency in the PTZ model and prevented tonic convulsions in the MES test (24). The anticonvulsant and antiepileptic potential of thymol when tested on different models viz., MES, PTZ, strychnine, and 4-aminopyridine models showed that thymol blocked both tonic and clonic seizure (46).

Effect on pain and nociception

A monoterpene ketone, (-) carvone, was investigated for the anti-nociceptive effect using various experimental pain models, and it was found that carvone significantly decreased the number of writhes in the acetic acid-induced writhing test, remarkably inhibited licking response of the injected paw in the first and second phases of the formalin test, and indicated that carvone involved non-opioid system in the modulation of pain (47). In another study, (R)-(+)-limonene was tested for the anti-nociceptive activity against thermal and chemical models of nociception. The results of the study showed that it produced significant inhibitory action on chemically induced nociception but not produced a significant effect in thermally induced nociception indicating the peripheral analgesic effect of limonene (48). A monoterpene oxide, 1,8-cineole has also produced an anti-nociceptive effect against formalin and acetic acid-induced nociception model in mice (49). Evaluation of the anti-nociceptive effect of p-cymene was done using various models such as acetic acid-induced writhes, hot plate test, carrageenan-induced paw edema, and rotarod test. The results of the study revealed that it caused a significant decrease in nociception and inflammation indicating its analgesic and anti-inflammatory properties (50). A similar study was carried out to investigate the effect of carvacrol against the different models of nociception like an acetic acid-induced writhing, formalin test, hot plate test. It significantly reduced the number of writhes, inhibited formalin-induced neurogenic pain and inflammatory pain, increased latency time showing its anti-nociceptive effect (51). Eugenol was studied for the anti-nociceptive effect in the different mouse models. It was found that it remarkably inhibited nociception induced by

acetic acid, glutamate, kainic acid, substance P, and α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA). The mechanism involved behind this was thought to be the modulation of the opioid system, glutaminergic receptors, and tumor necrosis factor- α inhibition (52). The anti-nociceptive effect of γ -terpinene has been investigated by De Brito Passos(53). In this study, it was found that γ -terpinene produced an anti-nociceptive effect in various chemical-induced nociception models such as formalin, capsaicin, glutamate test. The mechanism involved in this effect suggests the involvement of cholinergic and opioid systems.

Effect on anxiety

Carvacrol was tested using different experimental models such as the EPM, open field, rotarod, and barbiturate-induced sleeping time and it was found that carvacrol significantly inhibited anxiolytic effects (54). Intraperitoneal injection of thymol, another monocyclic monoterpene, showed an anti-anxiety effect in the EPM and light/dark tests in mice at a dose of 20 mg/kg (55). A study carried out by Bigdeli and his co-authors (36) showed that limonene significantly reduces anxiety in rats when exposed to chronic immobilization stress at a dose of 10 mg/kg. Effect of intraperitoneal treatment of (R)-(-) carvone was investigated using elevated T-maze (ETM) for anxiolytic action and findings showed that it impaired ETM avoidance latencies, a measure of effect on generalized anxiety at a dose of 25 mg/kg (56).

Neuroprotective activities

Screening of neuroprotective effects of p-cymene, limonene (+), and limonene (-) using *Drosophila* Alzheimer's disease (AD) models led to the interesting findings i.e. all these partially suppressed rough eye phenotype induced by beta-amyloid 42 (A β 42). Moreover, among these, (+) limonene caused an increase in flies' survival expressing A β 42 in neurons, and a decrease in cell death, reactive oxygen species, and inflammation in brains indicating a good candidacy in the treatment of AD(57).

To evaluate the therapeutic potential of thymol for neuroprotective activity, thymol was tested in rotenone-induced neurodegeneration resembling PD in humans. The findings of the study showed that it significantly improved oxidative stress, dopaminergic neuronal loss, and inflammation caused by rotenone at a dose of 50 mg/kg (58).

Investigation of neuroprotective activity of (-)-cis-carveol against β -amyloid-peptide 1-42 (A β 1-42)-induced AD demonstrated that it significantly improved memory deficits induced by A β 1-42 and investigated using Y-maze and radial arm maze tests. Furthermore, it significantly decreased A β 1-42-induced oxidative stress indicating an important candidate to decrease symptoms of AD(59).

Pretreatment of 1,8-cineole in rat pheochromocytoma cells (PC12 cells) against oxidative stress induced by hydrogen peroxide (H₂O₂) has significantly improved cell viability loss and cell morphology changes, inhibited reactive oxygen species (ROS) production, increased the expression of various antioxidant enzymes and decreased apoptosis (60).

A study carried out by Yu (61) showed that carvacrol, a food additive, significantly reduced infarct volume and neurological deficit in a middle cerebral artery occlusion mouse model showing its neuroprotective potential. Furthermore, Wang (62) has reported that carvacrol significantly reduced ethanol-induced hippocampal neuronal impairment through antioxidant and antiapoptotic activity. Besides, it promotes significant neuroprotection in the 6-hydroxy dopamine (6-OHDA) model of PD by blockage of TRPM7 channels (63).

Spice active constituent, eugenol when tested for the neuroprotective efficacy in ACR-induced neuropathy model in rats, produced promising results such as it caused significant improvement in gait score, reduced ACR-induced oxidative markers, reduced not only cytosolic calcium levels but also acetylcholinesterase activity indicating its beneficial role (64). In another study carried out on eugenol showed its neuroprotective potential in aluminum-induced toxicity in rat brain through its antioxidant, hydrophobic, anti-apoptotic, and neurotrophic ability (65). Furthermore, it also protects neurons of the hippocampus from the global model of ischemia in gerbils through its postischemic hypothermic action (66).

Effects of some selected bicyclic monoterpenoids

Effect on memory

Lee (67) has reported that α -pinene significantly ameliorated learning and memory impairment induced by scopolamine in C57B/6 mice.

Effect on depression

Investigation of anti-depressant potential of β -pinene in mice using forced swimming test showed a marked decrease in the immobility time confirming its beneficial potential (22).

Effect on convulsion

A comparison study carried out between α - and β -pinene to investigate their anticonvulsant effect against PTZ-induced convulsion in mice showed that α -pinene did not exert an anticonvulsant effect while β -pinene produced a significant anticonvulsant effect at a dose of 400 mg/kg, i.e. it significantly increased the death time of PTZ-treated animals by reducing nitrite levels in hippocampus and dopamine and norepinephrine levels in the striatum (68).

Effect on pain and nociception

Intraperitoneal injection of α -pinene demonstrated the significant analgesic effect by reducing the threshold of nociception in the tail-flick test, a commonly employed model of pain in mice (69).

Effect on anxiety

Saeedi and Rafiei-Rad (2020) demonstrated the effect of α -pinene on anxiety behaviors in comparison with diazepam in male rats using the EPM test. The results of the study showed that it significantly reduced responses related to anxiety similarly to diazepam by binding to the GABA_A receptors (70).

Neuroprotective activities

(S)-cis-Verbenol was investigated for anti-ischemic and inflammatory activity. It was found that it significantly decreased ischemic injury caused by occlusion of the middle cerebral artery for 1.5 hr followed by 24 hr reperfusion. Besides, it remarkably hampered neuronal cell death due to oxygen-glucose deprivation for 1 hr and subsequent re-oxygenation for 5 hr. It also reduced pro-inflammatory cytokines expression in the ischemic brain (71). Similarly, isoborneol was examined for the neuroprotective activity against 6-OHDA-induced cell death in human neuroblastoma SH-SY5Y cells. The results of the study showed that it remarkably decreased ROS production and intracellular calcium levels induced by 6-OHDA. It also reversed 6-OHDA-induced apoptosis and increased the activity of caspase-3 and translocation of cytochrome c into the cytosol from mitochondria. Thus, the study indicated the therapeutic potential of isoborneol for the treatment of various neurodegenerative diseases (72).

In vitro study carried to examine the neuroprotective potential of α -pinene against H₂O₂-induced oxidative stress in PC12 cells showed that attenuation of cell viability, inhibition of ROS production, increased antioxidant enzyme expression, decreased activity of caspase-3 (60). Furthermore, α -pinene also exerts neuroprotective activity in ischemic stroke by restoring antioxidant enzymes, attenuating lipid peroxidation, decreasing inflammation in ischemic brains (73).

CONCLUSION

Monoterpenoids are important constituents of essential oils and are better recognized as protective resins of aromatic plants. They are generally present as non-nutritious food components in essential oils of herbs and citrus fruits. They are considered as one the most important natural compounds because of their increased potential as pharmacological agents. They exert a crucial role as expectorants in upper respiratory tract infections, antibacterial, antiviral, and spasmolytic in gastric disorder. Owing to their hydrophobicity, monoterpenoids are used in the treatment of gallstone and hypercholesterolemic conditions. Several monoterpenoids are used either directly or

modified to enhance their potency and selectivity. The antiviral, antifungal, antibacterial, antitumor, local anesthetic, neuroprotective, learning and memory enhancer, antidepressant, anticonvulsant, anxiolytic, anti-inflammatory, and antioxidant properties are favorable and warrant future research in translating the monoterpenoids as therapeutic agents.

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