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REVIEW ARTICLE

The potential therapeutic value of terpenes

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Abstract

Terpenes form part of a huge and diverse class of naturally occurring and volatile secondary metabolites produced by many plants, fruits, animals, insects, and other organisms. They are the largest group of naturally occurring metabolites, with over 55,000 types of terpenes produced by plants alone, primarily as essential oils. In humans, they contain significant biological properties such as antifungal, antiviral, antimicrobial, anti-inflammatory, antiparasitic, antihyperglycemic, anti-cancer, and analgesic agents. In plants, terpenes also play significant roles in defensive mechanisms against herbivores and invasive plants, disease resistance, chemical signaling and communication between plants, protection against photo-oxidation, plant-environment mediation, thermo-protection, and the attraction of pollinators. In addition, terpenes are responsible for a plant's scent, taste, flavor, and pigmentation, leading to their commercial use as fragrances and food dyes. Terpenes are also used in the production of synthetic polymers, natural rubbers (polyisoprene), organic solvents, varnishes, inks, adhesives, cleaning products, biofuels, pesticides, and food and drink products. For these reasons, terpenes have significant value in modern medicine, pharmacy, nutraceuticals, cosmetics, and other industries.

Keywords: Terpenes; Terpenoids; Metabolites; *Cannabis sativa*; Essential oils; Sterol; Squalene; Phytotherapeutics

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1. Introduction

1.1. History and general overview

The term terpene was first coined in 1866 by the German chemist August Kekule to classify camphene and all other hydrocarbons with the empirical formula $C_{10}H_{16}$.[1,2] The term has expanded to include other secondary metabolites such as limonene, myrcene, caryophyllene, linalool, ocimene, and many others, making terpenes the largest class of secondary metabolites. Notably, pinene is the most common terpene produced across plant species.[3,4]

Terpenes are found in many living organisms, most notably plants and animals, and have significant biological functions (Table 1). Owing to their chemical properties, terpenes have been used in the industrial production of fragrances (cosmetics, perfumes, etc.), inks, varnishes, adhesives, biofuels, rosin, solvents, flavorings, pesticides, insecticides, herbicides, aromatherapy, lubricants, biofuels, and agricultural chemicals.[5]

1.2. Classification of terpenes

While the terms terpenes and terpenoids (also known as isoprenoids) are often used interchangeably, terpenoids refer to an oxidized and denatured form of terpenes that contain an additional functional group with oxygen.[1,48] This oxidation occurs during drying and curing processes when the plant is exposed to open air.[49]

The building block of all terpene structures is an isoprene unit – a gaseous hydrocarbon (Figure 1). All terpenes and terpenoids are made up of varying combinations of these isoprene building blocks and can be further modified with a wide variety of functional groups, such as ketones, alcohols, and other substituents (e.g., fatty acids and sugars), to form a wide range of linear and cyclized hydrocarbon structures.[50]

Table 1. Functions of terpenes in plants

Function of terpenes in plants	Reference (s)
Host protection (i.e., the strong aroma may be a repellent to herbivores and may even detract invasive plant species)	5-8,9,10
Attraction of pollinators	5,11-16
Disease resistance	17-24
Combating oxidative stress	25
Combating abiotic and biotic stress, such as drought, temperature fluctuations, high light intensity, mechanical damage, and air and soil pollution	26
Inter-plant communication (chemical signaling)	16,27
Communication with the surrounding environment (e.g., beneficial species, such as pollinators, herbivores, predators, seed dispersers, and parasitoids)	16
Plant protection against ozone damage	28
Photoprotection	25,29-31
Light harvesting	31
Cloud-seeding	32-41
Modulation of cell growth	31
Plant elongation	31
Membrane permeability and fluidity control	31,42-47

The classification of terpenes is dependent on the number and organization of these isoprene units and the number of carbon atoms thereof. For example, monoterpenes have 10 carbon atoms (C_{10}), sesquiterpenes have 15 carbon atoms (C_{15}), and diterpenes have 20 carbon atoms (C_{20}). Figure 2 depicts the chemical structures of several popular terpenoids produced by *Cannabis sativa*. In a 2020 study, Jin *et al.* profiled secondary metabolites in cannabis inflorescences, leaves, stem bars, and roots for medicinal purposes, and the list of monoterpenoids and sesquiterpenoids is listed in Table 2.[51]

2. Production and extraction of terpenes

2.1. Terpene biosynthesis

Terpenes are synthesized from an isoprenoid precursor, isopentenyl pyrophosphate (IPP), and dimethylallyl pyrophosphate (DMAPP) through the plastidial deoxyxylulose phosphate/methyl-erythritol phosphate (DOXP/MEP) pathway (monoterpenoids) in plastids of plant cells[5,52] and the cytoplasmic mevalonate (MVA) pathway (sesquiterpenoids, triterpenoids, and sterols) in the cytosol of plant cells (Figure 3).[5,51,52]

2.2. *C. sativa* as a source of terpenes

C. sativa is well known for its agricultural and medicinal values in East Asian, African, and Indian cultures dating as far back as 6,000 years ago.[53-60] The medicinal properties

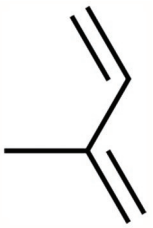


Figure 1. Chemical structure of an isoprene unit (C_5H_8), a five-carbon cyclic compound

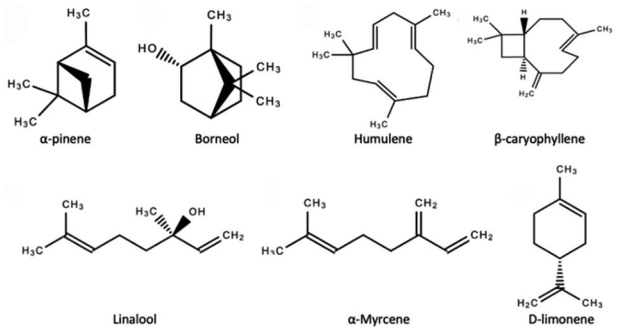


Figure 2. The chemical structures of some terpenoids produced by Cannabis sativa: α-pinene, borneol, humulene, β-caryophyllene, linalool, α-myrcene, and D-limonene

Table 2. Examples of monoterpenoids and sesquiterpenoids profiled in cannabis inflorescences, leaves, stem bars, and roots for medicinal purposes

Terpenoids	Examples
Mono-terpenoids	α-Pinene; eucalyptol; borneol; camphene; ocimene; terpinen-4-ol; sabinene; γ-terpinene; terpineol; (-)-β-pinene; sabinene hydrate; (+)-dihydrocarvone; β-myrcene; terpinolene; nerol; α-phellandrene; frenchone; pulegone; Δ^3-carene; linalool; carvone; α-terpinene; frenchol; geraniol; p-cymene; (-)-isopulegol; geranyl acetate; limonene; camphor.
Sesqui-terpenoids	(-)-β-Elemene; viridiflorol; β-caryophyllene; (-)-guaiol; aromadendrene; (+)-cedrol; trans-β-farnesene; β-eudesmol; α-humulene; α-bisabolol; valencene; ledene; trans-nerolidol; caryophyllene oxide; globulol.

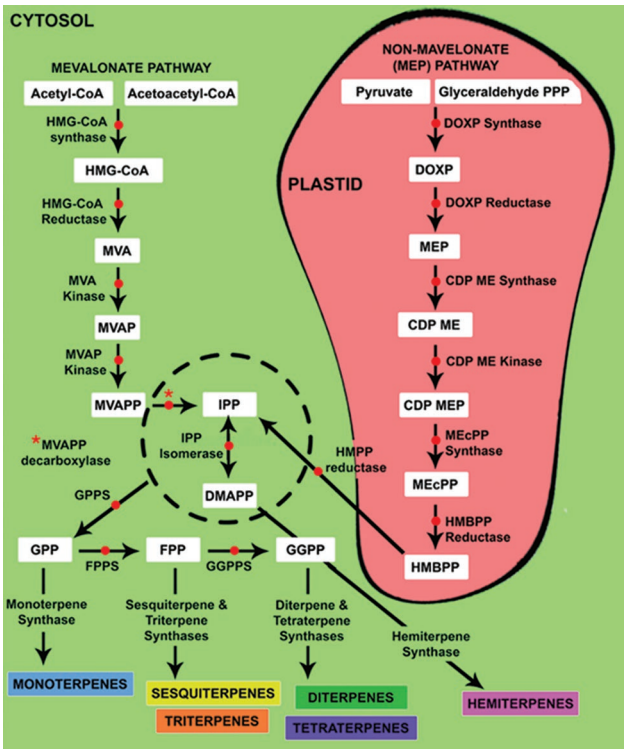


Figure 3. The mevalonate (MVA) pathways that occur in the cytosol of plant cells, the methyl-erythritol phosphate (MEP) pathway that takes place in plastids of plant cells and the Apicomplexa phylum of protozoa and bacteria, and the subsequent biosynthesis of terpenes from isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) Abbreviations: CDP MEP: Diphosphocytidyl-2-C-methyl-D-erythritol 2-phosphate; DOXP: 1-Deoxy-d-xylulose 5-phosphate; HMG-CoA: 3-hydroxy-3-methyl-glutaryl-coenzyme A; FPP: Farnesyl pyrophosphate; FPPS: Farnesyl pyrophosphate synthase; GPP: Geranyl pyrophosphate; GGPP: Geranylgeranyl pyrophosphate; GPPS: Geranyl diphosphate synthase; HMBPP: (E)-4-hydroxy-3-methyl-but-2-enyl diphosphate; MEcPP: 2-C-methyl-d-erythritol cyclodiphosphate; MEP: 2-C-methyl-d-erythritol-4-phosphate; MVAPP: Mevalonate 5-diphosphate; PPP: PPP:3-phosphate.

of *C. sativa* primarily stem from its secondary metabolites, such as cannabinoids and terpenoids, the profiles of which vary across cannabis strains. Hence, it is suggested that these secondary metabolites work synergistically in a phenomenon known as the entourage effect to produce an enhanced pharmacological effect in humans.[61,62] This phytocannabinoid-terpenoid synergy could also be beneficial in the treatments of microbial infections, mental disorders, pain, inflammation, nociception, insulin resistance, diabetes, and comorbidities.[61,63-66] In this review, we will focus on the medicinal value of terpenoids instead of cannabinoids and their synergistic effects. Nonetheless, the terpenes of the cannabis plant have been well studied, and they shall be used as a reference in this review when discussing terpenes.

Over 150 different terpenes and 100 cannabinoids (e.g., tetrahydrocannabinol, cannabidiol, and cannabigerol) are produced in a resin that forms within glandular trichomes located on the surfaces of pistillate inflorescences as well as the foliage of a cannabis plant.[67,68] Specifically, the isoprenoid biosynthetic system of the cannabis plant produces the terpenes using the MVA and MEP pathways (Figure 3). Studies have indicated that the number of terpenes in cannabis plants from different origins can vary from 12 to 66.[67] The diversity of the hydrocarbon terpenes is mostly attributed to (i) the diversity of terpene synthase enzymes that are present and (ii) genetic and environmental differences. The terpenes that are most often found in cannabis plants include myrcene, β-caryophyllene, α-humulene, α-pinene, limonene, linalool, bisabolol, and (E)-β-farnesene.[67]

2.3. Extraction of terpenes

Terpenes are traditionally extracted through maceration, hydrodistillation, and soxhlet extraction. Other modern extraction methods have since been developed that are faster, use less solvent, and are environmentally safer, such as ultrasound,[69] microwave,[70] pressurized liquid, and supercritical fluid. Peres *et al.* reported that pressurized liquid extraction was easier and significantly more efficient to extract terpenes than both soxhlet and ultrasound-assisted extraction methods.[71] Similarly, Reddy *et al.* evaluated the comparison between supercritical fluid and conventional solvent extractions and reported that the use of butane or propane extracted more significant amounts of terpenes than supercritical CO_2 because of the mild nature of the solvents and the properties of the molecules (e.g., polarity).[72,73] In addition, terpenes can also be extracted through chemical-free methods, such as using heat, pressure, water, and mechanical approaches. For example, terpenes located in the glandular trichomes of the cannabis plant are extracted by mechanical sieving or centrifugation, where the separated glandular trichomes,

known as kief, are inserted in between hot metal plates to produce rosin containing both terpenes and cannabinoids.[74]

3. Biological and medicinal benefits of terpenes

3.1. Medicinal properties of terpenes

Terpenes were recognized for hundreds of years as essential oils from various plants and used in ancient ceremonies and for medicinal purposes in ancient civilizations. The primary constituents of essential oils are a combination of hydrophobic and volatile monoterpenes, sesquiterpenes, and phenylpropanoids. Plant families, such as *Asteraceae*, *Myrtaceae*, *Alliaceae*, *Apiaceae*, *Lamiaceae* (e.g., lavender and rosemary), *Poaceae*, and *Rutaceae*, produce a variety of essential oils of significant medicinal and industrial value.[75-77] In ancient times, the Arabs, Chinese, and Egyptians applied camphor as a topical medication for insect bites, itches, joint pain, swellings, sprains, and inflammation, as a decongestant, and as a therapeutic agent in the treatment of diarrhea, depression, fever, and dental cavities.[52,78-92] Terpenes are also traditionally used in exotic perfumes, incense, embalming fluid (e.g., in burial rituals, mummification, and religious ceremonies), as a fumigant and repellent against pests, and in cooking.[52,78-92] In modern days, terpenes and their derivates are widely used in industries, such as food (flavoring), toiletries, pharmaceutical, nutraceutical, and cosmeceutical industries (fragrances).

By various mechanisms of action, terpenes and their derivates demonstrate anti-cancer, antioxidant, neuroprotective, anti-inflammatory, cardioprotective, digestive, antitumor, antibacterial, anti-plasmodial, antiviral, antiseptic, antimalarial, immunoregulatory, antiaging, diuretic, antidiabetic, hypoglycemic properties, and more.[93-98] Limonene (from *Citrus limon/Citrus reticulata/Juniperus communis*) is among the most common terpenes used in folk medicine, particularly in Indian Ayurvedic medicine and traditional Chinese medicine (TCM) to treat oral cavities, digestive problems, abdominal colic pain, cough, cold, swelling, and urinary problems.[99-101]

Humulene (*Panax* sp./Ginseng) is also widely used in Ayurvedic medicine and TCM to boost energy and memory, reduce fatigue, and treat symptoms of menopause and muscular skeletal conditions (such as arthritis and rheumatism).[102-104] Garlic (*Allium sativum*) contains nerolidol, alpha-pinene, and terpinolene and is also widely used in folk medicine to treat wounds, headaches, heart disease, ulcers, and gastric/digestive problems.[105,106] Zingiberene (ginger/*Zingiber officinale*) is also a mainstay in folk medicine, and it is used to treat digestive problems, colds, coughs, asthma, wheezing, and joint pain.[107,108] Likewise, cinnamon (*Cinnamomum verum*) contains many medicinal terpenes, such as α-pinene, caryophyllene, cymene, linalool, humulene, α-phellandrene, and cymene. It is used to treat respiratory issues (e.g., cold, sinus, congestion, and bronchitis), digestive problems, diabetes, and chest pain.[109]

3.2. Biological properties of terpenes

The secondary metabolites of cannabis have a wide range of biological characteristics, such as anticancer, anti-inflammatory, analgesic, antimicrobial, neuroprotective, and antioxidant properties.[51,110-112] These characteristics of terpenes have enabled the treatment of various conditions, such as stress, anxiety, depression, decongestion, inflammation, pain, cancer, digestive disorders, bacterial infections, viral infections, fungal infections, metabolic diseases, and cardiovascular diseases (CVDs) (Table 3).[75,110,113-115]

The antioxidant properties of terpenes are of significance to counteract the effects of reactive oxygen species (ROS) involved in the aging process and the pathology of many conditions (e.g., diabetes, CVDs, liver disease, renal disease, cancer, and neurodegenerative diseases).[116-119] Other proposed mechanisms of antioxidant action of terpenes are through free radical scavenging mechanisms and by enhancing the activity of antioxidant molecules.[116] Notably, a patented combination of cannabis terpenes has demonstrated clinical significance in the treatment and prevention of COVID-19.[120,121]

Cannabis terpenes, such as ocimene, terpinolene, and β-myrcene, have exhibited anti-cancer effects in a taxol-resistant model of breast cancer.[122] Similarly, other cannabis terpenes, such as myrcene, linalool humulene, β-caryophyllene, limonene, pinene, eucalyptol, and borneol, have all demonstrated anti-cancer effects by various mechanisms of action such as induction of apoptosis, induction of cell cycle arrest.[61,122-138]

The pharmacological effects of *C. sativa* are primarily induced by the interaction of secondary metabolites with the endocannabinoid system (ECS). The ECS is primarily responsible for maintaining homeostasis.[162] In addition to regulating physiological processes, the ECS directly influences other biological aspects of a human being (e.g., physical, mental, and psychological),[163,164] and the multifaceted role of ECS has been implicated in several pathophysiological diseases, such as cancer, CVDs, and neurodegenerative diseases. In this regard, the genetic and pharmacological modulations of the ECS

Table 3. Biological properties of common terpenes in cannabis and other plants

Terpene (or its derivative)	Biological property	Other sources	Reference (s)
Myrcene	Potent analgesic	Ginger	139-141
	Antioxidant; neuroprotective; anti-inflammatory	Mango, guava, and hops	95
	Anticonvulsant	N/A	96
1,8-Cineole	Increases cerebral blood flow and enhances cortical activity	*Eucalyptus obliqua* L'Hér.	142
Limonene	Inhibits many species of bacteria and fungi; repellent	N/A	98
	Anti-inflammatory; antioxidant; antiviral; antidiabetic; anticancer; anti-hyperglycemic	Grapefruit, lemon, orange peel, and vitex	95,119,140,141, 143,144
	Antidepressant; anticonvulsant	N/A	95,98
α-Pinene	Antimicrobial; repellent	N/A	96
	Bronchodilator; anti-inflammatory	Basel	140,141
	Memory improvement/enhancement; acetylcholinesterase inhibitor, antiseptic, antibacterial, anti-inflammatory, bronchodilator, gastroprotective	Pine needle and rosemary	145
β-Pinene	Antimicrobial; antiseptic; anti-tumor	Mint, pepper, nutmeg, and pine needle	140,141,145
Linalool	Anxiolytic; anti-inflammatory; antimicrobial; anticancer; neuroprotective; antidepressant	Lavender	4,95,140
	Anti-influenza	N/A	146
	Sedative; induces apoptosis in cancer cells	N/A	95
α-Terpineol	Antimicrobial; repellent; anti-ischemic	N/A	98
	Anti-inflammatory	Cardamom and mugwort	141,147-149
	Analgesic	Pine and bitter orange tree (*Citrus aurantium* L.) essential oils	150
	Nociception inhibition	N/A	150,151
	Anticonvulsant	N/A	152
	Antimicrobial	N/A	96,97
	Gastroprotective	N/A	97
Borneol	Antimicrobial; repellent	Rosemary (*Rosmarinus officinalis*) and mugwort (*Artemisia absinthium* L.)	98
β-caryophyllene	Anti-inflammatory; analgesic	N/A	95
	Antispasmodic in gut muscles	Parsley	96
	Anti-inflammatory; gastroprotective; analgesic; anticancerogenic; antifungal; antibacterial; antihyperglycemic; antidepressant; anti-inflammatory; antiproliferative; antioxidant; anxiolytic; analgesic; neuroprotective	Clove, angelica, pennywort, and black pepper	61,63,140,141,143, 153-156
Caryophyllene oxide	Antifungal	Clove, rosemary, and hops	63
Humulene	Antiallergy; anticancer	Basil	95,141
Ocimene	Antifungal; antibacterial; antioxidant; antiviral; anti-inflammatory	Alfalfa and thyme	141,157-161
Eucalyptus oil	Expectorant (stimulates mucus); diuretic	N/A	52
Clover leaf oil	Analgesic	N/A	52
Menthol	Reduces flatulence and combats indigestion	N/A	52

Abbreviation: N/A: Not available.

have gained significant interest in medicine, research, and drug discovery and development (e.g., cannabinergic, cannabimimetic, and cannabinoid-based therapeutic drugs) to inhibit the metabolic pathways and/or agonism or antagonism of the ECS receptors.[165,166] Consequently, ECS regulation enables the treatment of a wide range of diseases, including (but not limited to) general pain, headache, migraine, glaucoma, mood and anxiety disorders, obesity/metabolic syndrome, osteoporosis, neuromotor, neuropsychological and neurodegenerative diseases, respiratory diseases (i.e., asthma), and vascular diseases such as stroke, atherosclerosis, myocardial infarction, arrhythmias, and hypertension.[49,165-170]

3.3. Antimicrobial properties of terpenes

The antimicrobial properties of essential oils are well established and are primarily attributed to the presence of a complex mixture of terpenes and other secondary metabolites.[18,19,24,77,171-180] In a 2019 study, Guimarães *et al.* investigated that the antibacterial activities of terpenes and terpenoids present in essential oils against bacteria such as *Salmonella enterica* and *Staphylococcus aureus*.[77] Terpenes (i.e., eugenol and terpineol) demonstrated rapid bactericidal action against *S. enterica* serovar Typhimurium and *S. aureus*, respectively, while other terpenes (i.e., carveol, citronella, and geraniol) exhibited significant bactericidal activity against *Escherichia coli*.[77] Therefore, terpenes may serve as a suitable alternative to current antibiotics when antibiotic resistance becomes a critical issue.

3.4. Analgesic and anti-nociceptive properties of terpenes

The demand for analgesic drugs continues to increase due to the increasing prevalence of pain (of all sorts) affecting people worldwide, leading to a growing interest in novel therapeutic options.[181] The analgesic potential of terpenes is also well studied and documented,[75,182] particularly in animals subjected to pain and nociceptive tests, such as hot-plate, formalin, tail-flick, and acetic acid-induced writhing tests.

Plant species, such as *Hyptis fruticosa* Salzm. ex Benth. (Lamiaceae), *Hyptis pectinata* Poit. (Lamiaceae), *Illicium lanceolatum* A.C. Smith (Illiciaceae), *Lippia gracilis* Schauer (Verbenaceae), *Matricaria recutita* L. (Asteraceae), *Mentha x villosa* Huds (Labiatae), *Pimenta pseudocaryophyllus* (Gomes) L.R. Landrum (Myrtaceae), and *Erythrina velutina* Willd. (Fabaceae), are known for their therapeutic essential oils and are widely used in folk medicine as analgesics and antinociceptives.[183-187] These properties are primarily due to the presence of terpenoids (monoterpenes and sesquiterpenes) and phenylpropanoids. Monoterpenes, such as linalool, myrcene, limonene, and 1,8-cineole in particular, are strong candidates for the treatment of chronic pain (e.g., chronic muscle pain, cancer-related pain, chronic inflammatory pain, and neuropathic pain).[139,182,188-191] Likewise, the combination of cannabinoids and flavonoids may be used to treat headaches and migraines.[64]

The analgesic activity of terpenes involves stimulating the release of anti-inflammatory cytokines,[182] regulating ion channels (e.g., transient receptor potential cation channels),[192] and directly acting on nociceptive afferent fibers[75] through multiple receptors (e.g., opioid, adenosine A1 and A2, and capsaicin).[151,191,193-196] The possible mechanisms of analgesic and antinociceptive actions of terpenes and their derivatives are displayed in Table 4.

Furthermore, terpenes can also enhance skin permeability and drug permeation by promoting interactions with the lipid bilayer of the stratum corneum of the human skin. Therefore, terpenes are good candidates for transdermal and transmucosal drug delivery systems, particularly for pain relief and management.[197]

3.5. Anti-inflammatory properties of terpenes

The pathological development of inflammatory diseases is regulated by NF-κB and is characterized by an overproduction of inflammatory cytokines (e.g., interleukin-6 [IL-6, IL-1β, IL-4, IL-8, IL-17, and tumor necrosis factor-alpha [TNF-α]). Nonetheless, terpenes have demonstrated the ability to inhibit the inflammation-associated signaling pathways by downregulating the expression of specific inflammatory cytokines.[208-213]

D-Limonene reportedly inhibited several pro-inflammatory cytokines, i.e., IL-1β, IL-4, IL-8, and IL-17,[197,214-218] thereby suggesting a protective role against various inflammatory disorders, such as asthma, rheumatoid arthritis, inflammatory bowel disease, skin inflammation, and psoriasis.[219-223] Artemisinin has reportedly treated inflammation-associated pain that is regulated by NF-κB signaling, promoted TNF-α-induced apoptosis, inhibited ROS production, and blocked the phosphorylation of p38 and ERK, both of which are pro-inflammatory processes.[208,221,224-226] In contrast, pinene, linalool, and 1-octanol-inhibited COX-2 overexpression, inducible nitric oxide synthase (iNOS), and nociceptive stimulus-induced inflammatory infiltrate.[182,197,208,221,227] Similarly, citral (geranial) and carvacrol activate the peroxisome proliferator-activated receptors (PPAR) α and γ.[197] α-Terpineol reportedly inhibited the intracellular formation of IL-6,[147] while borneol, linalool, catalpol, carvacrol, citronellol, geniposide, paeoniflorin, and 1,8-cineole (eucalyptol) inhibited the expression of

Table 4. Analgesic and anti-nociceptive mechanisms of action of terpenes and terpene derivatives

Terpene (and its derivative)	Plant species	Mechanism of action	Reference (s)
p-Cymene	*Hyptis pectinata* (L.) Poit. (Lamiaceae); *Protium heptaphyllum* (Aubl.) Marchand (Burseraceae)	Protective effects with a reduction of pro-inflammatory cytokines; inhibition of NF-κB and MAPK signaling	
(-)-Linalool	*Aniba rosaeodora* (Lauraceae)	Acts on several receptors, including opioids, adenosine A1 and A2, and cholinergic M2; regulation of changes in K^+channels	196,198-201
(-)-Menthol	*Mentha* species (including *M. piperita* and *M. arvensis*)	Acts on opioid receptors	202
Eugenol	*Abutilon indicum; Eugenia caryophyllata*	Acts on capsaicin, opioid, and α-adrenergic receptors; inhibition of high-voltage-activated calcium channels	151,193-195
Thymol	*Hofmeisteria schaffneri*	Inhibition of prostaglandin synthesis; inhibition of voltage-operated $Na^+$and K^+channels; activation of aminobutyric acid GABAA receptors	203-207
β-Pinene	*Hyptis fruticosa; Hyptis pectinata* (L.) Poit	Partial agonism of opioid μ receptors	191

Abbreviations: NF-κB: Nuclear factor kappa B; MAPK: Mitogen-activated protein kinase.

Table 5. Mechanisms of action of terpenes and terpenoids against inflammatory diseases

Terpene/ terpenoid	Origin	Inflammatory disease or experimental model	Mechanism of action	Reference (s)
Ginkgolide C	*Ginkgo biloba* leaves	I/R- related inflammation	Suppression of CD40-NF-κB signal pathway; inhibition of downstream inflammatory cytokines, IKK-β, and IκB-α phosphorylation	229,230
α-Pinene	Oils of coniferous trees and rosemary	LPS-induced macrophages	Inhibition of MAPK, NF-κB, and pro-inflammatory cytokines, such as IL-6 and TNF-α	231,232
Linalool	Essential oils of aromatic plants	Cigarette smoke-induced acute lung inflammation; LPS-induced inflammation in microglial cells	Inhibition of NF-κB activation; inhibition of pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-1β, IL-8, and MCP-1)	231,226,233,234
p-Cymene	N/A	Elastase-induced lung emphysema and inflammation	Inhibition of proinflammatory cytokines, such as IL-1β, IL-6, IL-8, and IL-17, in BALF	231,235
Malloconspur A and malloconspur B (diterpenoids)	*Mallotus conspurcatus* croizat (Euphorbiaceae) (Native to China)	Pelvic inflammatory disease and possibly other inflammatory diseases	N/A	236
α-Pinene	Essential oils of coniferous trees	Skin inflammation	Photoprotective effect against inflammatory signaling in human skin cells; inhibition of UVA-induced expression of inflammatory protein, such as TNF-α and IL-6; suppression of MAPKs pathway through inhibition of ERK and JNK phosphorylation	232,237
β-Pinene	*Boswellia serrata* Linn.	RA	Inhibition of inflammatory biomarkers (NF-κB, COX-2, and LOX-5) involved in the pathogenesis of RA	222
D-Limonene	Essential oils of citrus plants	Neuroinflammation	Inhibition of inflammatory cytokines, such as IL-1, IL-6, and TNF-α	219,234,238

Abbreviations: BLAF: Bronchoalveolar lavage fluid; I/R: Ischemia/reperfusion; LPS: Lipopolysaccharide; MAPK: mitogen-activated protein kinase; MCP-1: Monocyte chemoattractant protein-1; N/A: Not available; RA: Rheumatoid arthritis.

TNF-α.[197,228] Moreover, linalool, myrcene, carvacrol, α-phellandrene, paeoniflorin, and citronellal reportedly downregulated GluN2B receptors and, subsequently, glutamate, a pro-inflammatory amino acid.[182,197] Table 5 displays the mechanisms of action of several common terpenes (and terpenoids) as anti-inflammatory agents.

3.6. Anxiolytic and anti-depressant properties of terpenes

According to the World Health Organization (WHO), it is estimated that one billion people are affected by mental illness globally, and depression and anxiety-related disorders are reportedly the most prevalent mental conditions.[239-242]

Studies have suggested that terpenes may have anxiolytic and anti-depressant properties, but the molecular mechanism(s) of action remains unclear. It was hypothesized that anxiolytic and anti-depressant properties might be mediated through interaction with serotonergic 5-hydroxytryptamine receptors, noradrenergic, dopaminergic systems, or glutamate receptors.[243] In a study on *C. sativa*, it was suggested that the combination of terpenes, phytocannabinoids, and flavonoids synergistically induced the entourage effect to generate enhanced anxiolytic and anti-depressant activities,[244-246] warranting further studies to validate the anxiolytic and anti-depressant effects.

The aromatherapeutic and medicinal value of essential oils containing terpenes has been recognized in traditional medicine for hundreds of years based on their anxiolytic and anti-depressant properties.[52,78-92,247,248] Several common terpenes (i.e., linalool, geraniol, citronellol, citronellal, myrcene, β-caryophyllene, and limonene) have reported sedative, anxiolytic, anti-depressant, sedative, and anticonvulsant proprieties in both humans and murine models.[61,247,249-254,63,247,255-259] In particular, hydroxycitronellal (HC) exhibited anxiolytic and anti-depressant properties through regulating the GABAergic system ($GABA_A$ receptors).[260] Linalool and linalyl acetate reportedly inhibited voltage-gated calcium channels[252] and, subsequently, $5HT1_A$ receptor activity.[252,258] In murine models, D-limonene has demonstrated anti-depressant properties by downregulating IL-1, IL-6, and TNF-α.[234,238]

3.7. Cardioprotective properties of terpenes

CVDs collectively refer to conditions affecting the cardiac (i.e., heart failure, cardiac arrest, coronary heart disease, angina pectoris, myocardial infarction, hyperlipidemia, and cardiomyopathy) and vascular (i.e., atherosclerosis, peripheral artery disease, ischemic stroke, and pulmonary embolism) systems.[76,230] In 2021, CVDs were the leading cause of death globally with 17.9 million deaths.[261]

Ongoing research efforts have investigated terpenes as prospective novel therapeutics drug candidates for CVDs.[76] Limonene, carveol, linalool, and several diterpenes (and their derivatives) have demonstrated therapeutic potential against CVDs.[262-267]

Table 6 features several terpenoids that have reported cardioprotective effects against CVDs. Although the mechanisms of action of terpenes in the cardiovascular system have not yet been fully elucidated, it is suggested that they work by regulating heart rate and vasorelaxation.[263] Diterpenes such as dehydrocrotonin, 14-deoxyandrographolide, ent-18-hydroxytrachyloban-3β-ol, ent-18-hydroxyisopimara-7,15-diene-3β-ol, and neoorthosiphols A and B are used in folk medicine to treat hypertension.[266,268-270] Stevioside, a diterpenoid glycoside extracted from the plant *Stevia rebaudiana* Bertoni, also demonstrated vasodilatory effects and the ability to regulate mean arterial pressure.[76,266,267,271,272]

Another possibility is that terpenes, in synergy with phytocannabinoids and endocannabinoid-like molecules, regulate ECS and, subsequently, the cardiac and vascular systems.[264] In addition, terpenes may also ameliorate CVD through scavenging free radicals and enhancing the activity of antioxidant molecules.[116] The other more commonly proposed cardioprotective mechanisms include (i) inhibiting NF-κB and subsequently disrupting the NF-κB signaling pathway[116,208,236,269,209,236,269] and (ii) inhibiting NLRP3 inflammasome formation and subsequently disrupting the NLRP3 inflammatory pathway.[273]

Besides that, several terpenes (i.e., forskolin and marrubiin) have also displayed anticoagulant and anti-platelet properties.[274,275] Similarly, α-bulnesene, a sesquiterpene, exhibited anti-platelet-activating factor (PAF) properties,[276] while (+)-linalool and (-)-linalool could stimulate the cardiovascular system.[76,277,278] Citronellol has demonstrated antihypertensive and vasorelaxant properties that may be beneficial in the treatment of hypertension.[76] Thymol, a monoterpenoid, has vasorelaxant properties,[279] while limonene demonstrated cardioprotective and anti-hypertensive properties.[76]

Camphene, a plant-derived monoterpene, demonstrated hypolipidemic, hypocholesterolemic, and hypotriglyceridemic effects in rats, thereby reducing and preventing the accumulation of lipids, cholesterol, and triglycerides in arterial blood vessels.[280] In another study, Jiang *et al.* demonstrated that terpenoids from different polar extracts of *Cyclocarya paliurus* leaves had cholesterol-lowering effects in hyperlipidemic mice by converting cholesterol into bile acids.[281] These findings suggested that terpenes can regulate hyperlipidemia as well.

3.8. Anticancer properties of terpenes

Cancer is a major health burden that affected an estimated 19.3 million people globally in 2020 with an estimated 10 million deaths in the same year.[294-296] According to GLOBOCAN2020, global cancer cases are expected to

Table 6. Terpene derivatives (terpenoids, triterpenoids, and triterpenic acids) used to treat cardiovascular diseases

Terpene derivatives	Plant species	Mechanism(s) of action	Reference(s)
Rubiarbonone C	Roots of *Rubia yunnanensis* Diels	N/A	230,282
Platycodin D	Roots of *Platycodon grandiflorum*	Promotes atherosclerotic activity in HUVECs by increasing NO concentration, reducing the oxLDL-induced cell adhesion molecule expression, and regulating endothelial cell adhesion to monocytes	230,283
3,4-Seco-olean-18-ene-3,2,8-dioic acid	*Phoradendron reichenbachianum* (Viscaceae)	Not fully elucidated – possibly through inhibition of the NF-κB signaling pathway, DNA binding, or p65 translocation	230,284
Rubiarbonol C	Roots of *Rubia yunnanensis* Diels	Not fully elucidated – possibly through inhibition of the NF-κB signaling pathway, DNA binding, or p65 translocation	230,284
Triterpenic acid	Several plant taxa but primarily in plants of the mint family (*Mentha spicata* L.)	Not fully elucidated – possibly through inhibition of the NF-κB signaling pathway, DNA binding, or p65 translocation	230
Ursolic acid	Plants, such as elderflower, peppermint, oregano, and lavender	Not fully elucidated – possibly through inhibition of the NF-κB signaling pathway, DNA binding, or p65 translocation	230
β-Sitosterol glycoside	Saw palmetto (*Serenoa repens* [Bartram] J.K. Small); pygeum extract from the bark of the African cherry tree (*Prunus Africana* [Hook. f.] Kalkman)	Not fully elucidated – possibly through inhibition of the NF-κB signaling pathway, DNA binding, or p65 translocation	230
Astragaloside IV	*Astragalus membranaceus*	Not fully elucidated – possibly through inhibition of the NF-κB signaling pathway, DNA binding, or p65 translocation	230,285
Betulinic acid	White birch (*Betula pubescens*); Ber tree (*Ziziphus mauritiana*); self-heal (*Prunella vulgaris*)	Not fully elucidated – possibly through inhibition of the NF-κB signaling pathway, DNA binding, or p65 translocation	230,284
6β-OH-Betulinic acid	*Licania cruegeriana*	Not fully elucidated – possibly through inhibition of the NF-κB signaling pathway, DNA binding, or p65 translocation	230,286
Boswellic acid	*Boswellia* plant genus (such as *Boswellia serrata* Roxb.)	Not fully elucidated – possibly through inhibition of the NF-κB signaling pathway, DNA binding, or p65 translocation	230,287
Elatoside C	Longya *Aralia chinensis* L.	Increases cell viability, mitochondrial membrane potential, Bcl-2/Bax ratio, and pSTAT3/STAT3 ratio; decreases mitochondrial ROS, and the expression levels of CHOP, cleaved caspase-12, GRP78, and p-JNK	230,288
Ginkgolide C	*Ginkgo biloba* leaves	Enhances the survivability of H/R-induced ventricular myocytes; reduces inflammatory damage by reducing NF-κB p65 subunit translocation, phosphorylation of IκBα, and the activity of IκB kinase	230,231, 289-291
Forskolin	N/A	Promotes vasorelaxation	292
Kaurane	Roots of *Viguiera robusta*	Blocks extracellular Ca^{2+} influx to promote vasorelaxation and inhibit vasoconstriction	114,293
Pimarane-type diterpenes	Roots of *Viguiera arenaria*	Blocks extracellular Ca^{2+} influx to promote vasorelaxation and inhibit vasoconstriction	114,293
Marrubenol	*Marrubium vulgare* (Horehound, Lamiaceae)	Blocks L-type Ca^{2+} channels to inhibit smooth muscle contraction	114

Abbreviations: H/R: Hypoxia/reoxygenation; HUVECs: Human umbilical vein endothelial cells; N/A: Not available; NO: Nitric oxide; oxLDL: Oxidized low-density lipoprotein; ROS: Reactive oxygen species.

rise to 28.4 – 30.2 million.[294,297] Breast, lung, prostate, and nonmelanoma skin cancers are among the most prevalent cancers.[294,296] In addition, cancer occurs more often in males than in females, though this figure varied significantly in other parts of the world.[294]

The anti-cancer properties of terpenes are well established. Terpenoids modulate various intracellular pathways to (i) activate apoptosis, (ii) initiate cell-cycle arrest and subsequently suppress tumorigenesis, (iii) counteract oxidative stress (i.e., ROS scavenging and enhancement of antioxidant activity), (iv) inhibit

angiogenesis and metastasis, and (v) induce autophagy (e.g., through MAPK/ERK/JNK, PI3K/AKT/mTOR, AMPK, and NF-κB signaling pathways).[298-302]

Taxol (paclitaxel), a diterpenoid-based chemotherapy drug, is widely used to treat solid-tumor cancers (e.g., lung, prostate, breast, ovarian, esophageal, and melanoma)[303] and is considered one of the most effective terpenoid-based chemotherapeutic drugs. Taxol exhibits its anticancer effect by destabilizing microtubules, resulting in mitotic arrest, inhibition of cancer cell division, and ultimately cancer cell death.[304] Taxol also indirectly promotes apoptosis by binding to and inhibiting B-cell lymphoma 2 (Bcl-2) which prevents cell death.[304]

Terpenoids have demonstrated anticancer effects in several liver cancer cell lines through different mechanisms.[305] For example, geraniol reduced the expression of HMG-CoA reductase to inhibit HepG2 cell growth,[306] while asiatic acid-induced apoptosis through increased intracellular Ca^{2+} release and expression of p53.[307,308]

Oleanolic acid,[309] ursolic acid,[309] echinocystic acid,[310] lupeol,[311] and betulinic acid[312] reportedly promoted apoptosis of cancer cells, while the anticancer property of β-carotene is attributed to an antioxidant mechanism.[313] Various terpenes and their derivatives (e.g., geraniol and neral) are natural inhibitors of the NF-κB signaling pathway that plays a significant role in the pathological development

Table 7. Mechanisms of action of terpenes and terpenoids for treating various cancers

Terpene/ terpenoid	Origin	Type of cancer (cell line)	Mechanism(s) of action	Reference(s)
Taxol	N/A	Female breast cancer	Destabilizes microtubules to arrest cancer cell division and induce cancer cell death; promotes apoptosis through binding to Bcl-2	304,316
Geraniol (monoterpene)	N/A	HCC	Inhibits HepG2 cell growth through reducing HMG-CoA reductase production	305,306
Geraniol	N/A	Colon Cancer	Inhibits polyamine biosynthesis and metabolism (i.e., increased in cancer growth); apoptosis; DNA damage; cell cycle arrest; disruption of cell membrane	317-321
Andrographolide (diterpene)	*Andrographis paniculata*	HCC	Inhibits Hep3B cell growth (increase apoptosis, MAP kinases, ERK1/2, and pJNK); inhibits MMP-7 expression	305,306,322
Limonene	Lemon, orange, grapefruit, caraway, bergamot, peppermint, spearmint, dill, and tomato	Human bladder cancer cell (T24 cell line)	Inhibits human bladder cancer cell growth through apoptosis, caspase activation, and G2/M-phase cell cycle arrest	124
		Colon, mammary, pancreatic, and prostate cancers	Induces apoptosis; inhibits the post-translational isoprenylation of cell growth-regulating proteins	299,323,324
		Bladder cancer	Induces cellular apoptosis; caspase activation; G2/M-phase cell cycle arrest; inhibits cancer metastasis	124
Retinol	Carrot, spinach, pumpkin, broccoli, mango, papaya, cherry, tomato, corn, orange, cabbage, watermelon, and lettuce	Prostate cancer	Induces apoptosis; inhibits premalignant cell growth; suppresses carcinogens through retinoid nuclear receptors, retinoic acid receptors (RARs), and retinoid X receptors (RXRs)	325-331
Lycopene	Tomato, orange, carrot, pea, sprout, green, bean, and corn	Colon cancer	Suppresses Akt signaling and non-phosphorylated β-catenin protein levels; G-phase cell cycle arrest	299,332,333
		Prostate cancer	N/A	334,335
Latilagascenes C and D; 3β-acetoxy-helioscopinolide B and E	Extract from the *Euphorbia* species	Gastric (EPG85-257), pancreatic (EPP85-181), and colon (HT-29) carcinomas	N/A	336
Geraniol and neral (in combination)	*Zingiber officinale* (ginger)	Endometrial cancer cells	Promoted apoptosis by p53 activation	337
β-Caryophyllene	*Cannabis Sativa and Pamburus missionis* (SV1)	Taxol-resistant model of breast cancer	Activates apoptotic cascade; reduces cellular invasion	338

Abbreviations: HCC: Hepatocellular carcinoma; N/A: Not available.

of many cancers.[209,225,314,315] Other terpenes (e.g., menthol, β-caryophyllene, d-limonene, eugenol, and menthol) may be used independently or with chemotherapeutic drugs to promote anticancer activity by inducing apoptosis or necrosis and inhibiting cell proliferation.[5] Table 7 features several terpenes and terpenoids, as well as their mechanisms of action against various cancers.

3.9. Neuroprotective properties of terpenes

Neurological disorders are those characterized by the dysregulation of the neurons (nerve cells) in the brain or of the central and peripheral nervous systems. Neurodegenerative diseases (Alzheimer's disease, amyotrophic lateral sclerosis, and Parkinson's disease) are a subgroup of neurological disorders characterized by progressive and inexorable damage to the nervous system and accompanied by loss of neurological function. In 2019, it was estimated that 10 million global deaths were attributed to neurological disorders.[339] Nonetheless, the increasing prevalence of neurological disorders with the aging of the global population has prompted the search for novel therapeutics.

Alzheimer's disease is the most prevalent neurological disorder, with an estimated 10 million global cases diagnosed annually.[340,341] The WHO has estimated that 55 million people are currently suffering from dementia. It has also been predicted that the number of Alzheimer's cases will reach 75 million by 2030 and up to 135 million by 2050.[341,342] Dementia (of which 80% are due to Alzheimer's disease) alone accounted for US$1.3 trillion worldwide in 2019 and is projected to exceed US$2.8 trillion by 2030.[342] In the United States alone, this amount is estimated to surpass $800 billion annually.[343] In addition, the increasing prevalence of Parkinson's disease and other neurological disorders (e.g., stroke and epilepsy) suggests that neurological diseases will be a substantial health burden, and their management may not be affordable or accessible to the less developed regions of the world.

Neuroprotective agents may increase the recovery and regeneration or slow the rate of deterioration of nerve tissues due to neurodegenerative diseases or other insults (e.g., ischemia or toxic injury). In one study, both monoterpenes and sesquiterpenes extracted from *Citrus sinensis* (orange) by-products demonstrated the ability to cross the blood–brain barrier, suggesting their potential as neuroprotective agents.[117] Sesquiterpenes (e.g., δ-cadinene and nootkatone) and other more common terpenes (e.g., limonene, pulegone, carvone, and γ-terpinene) have demonstrated the capacity to inhibit acetylcholinesterase (AChE) and butylcholinesterase (BChE), both of which are involved in the formation of amyloid β plaques in Alzheimer's disease.[117,344-347] The terpenoids of the orange extract also demonstrated the ability to inhibit IL-6, a pro-inflammatory mediator.[117] In addition, limonene reportedly inhibited the activation/phosphorylation of extracellular receptor kinase (ERK) that is linked to oxidative stress and pro-inflammatory immune responses in the pathogenesis of Alzheimer's disease.[348,349]

The aforementioned sesquiterpenes have also displayed the inhibition of lipoxygenase (LOX), the overactivity of which leads to synaptic dysfunction and neuroinflammation.[117,344] In another study, 1,8-cineole, bornyl acetate, terpinen-4-ol, and camphor (extracted from essential oils of *Rosmarinus officinalis* L.) reportedly inhibited LOX, while 1,8-cineole and 3-carene (also from the same extract) reportedly inhibited AChE.[350] The inhibition of AChE and BChE increases acetylcholine levels to promote neural activity and regulate Alzheimer's disease, respectively. Similarly, the inhibition of LOX also ameliorated the inflammatory and immune responses in the brain tissue of patients with Alzheimer's disease.[344] In a drosophila model of Aβ42-induced neurotoxicity in Alzheimer's disease, ρ-cymene, (+)-limonene, (-)-limonene, linalool, (+)-α-pinene, and (-)-β-pinene demonstrated partial suppression of amyloid β42 (Aβ42) expression and accumulation in the flies.[144]

Oxidative stress and the accumulation of ROS and reactive nitrogen species (RNS) are also characteristics of Alzheimer's disease due to the decline in the antioxidant activities of superoxide dismutase (SOD) and glutathione peroxidase (GPx).[351] In this context, monoterpenes, such as limonene and nerol, with strong antioxidant properties can also be considered neuroprotective agents.[117-119] Besides that, the regulation of inflammation may play an important role in ameliorating neurological disorders.

Likewise, non-degenerative neurological disorders can be managed by terpenes in isolation or combination with other agents. For example, caryophyllene and β-caryophyllene have been studied for treating somatic pain and migraine, respectively. In contrast, linalool may directly target GABAergic neurotransmission in epilepsy and enhance the effects of other agents, similar to the entourage effect with cannabinoids.

3.10. Antidiabetic properties of terpenes

Diabetes is another major health burden that affects over 500 million people worldwide[252-354] with an estimated 6.7 million deaths annually. It is estimated that approximately 578 million people will be affected by diabetes by 2030 and up to 700 million people by 2045.[354] Notably, the global health expenditure for diabetes is estimated at US$966 billion.[352]

Diabetes mellitus is a chronic disease characterized by impairment in the regulation of glucose in the blood (blood

Table 8. List of terpene-related patents

Title of invention	Patent number	Treatment	References
Injectable formulation of paclitaxel for coronary artery disease treatment	EP1618879B1	Coronary artery disease	375
Anti-tumor terpene compounds	(i) WO2005049001A1 (ii) CA2545717A1	Cancer	376
Use of monoterpenes, sesquiterpenes and diterpenes for the treatment of cancer	WO1994020080A9	Prostate cancer, colon cancer, astrocytoma, and sarcoma	377
Monoterpenoid derivatives for treatment of cancer	WO1999045912A1	Cancer	378
Terpene and cannabinoid formulations	WO2015068052A2	Pain, allergies, inflammation, infection, epilepsy, depression, migraine, bipolar disorders, anxiety disorder, and drug dependency and withdrawal syndromes	379
Penetrating topical pain relief compositions and methods of use	WO2020243352A1	Topical pain	380
Device with compositions for delivery to the lungs, the oral mucosa, and the brain	AU2021201949A1	Pain, anxiety, depression, and plaque-related diseases.	381
Terpene-enriched cannabinoid composition	US20220323371A1	Treating acute and/or chronic pain, including chronic pain from multiple sclerosis, fibromyalgia, cancer, and peripheral neuropathy	382
Composition for preventing or treating neurodegenerative diseases, containing diterpene-based compound	EP3701946A1	Neurodegenerative diseases	383
Compositions comprising terpene compounds for treating negative sensory phenomena	US9415023B2	Negative sensory phenomena	384
Novel medicines based on sesquiterpene mixtures	WO2001080868A1	Cancer and treatment of epithelial and connective tissues	385
Compositions for improving skin conditions comprising alpha-bisabolol as an active ingredient	WO2000062744A2	Acne, aging, and skin inflammation	386

sugar). There are two types of diabetes: type 1 diabetes is characterized by the pancreas's inability to produce insulin, whereas type 2 diabetes is characterized by the body's inability to use insulin, often caused by a lack of physical exercise or obesity. Both types of diabetes are characterized by an increase in blood sugar (hyperglycemia) and ROS in the body.[143] In addition, diabetes is a significant risk factor for CVD, such as stroke, coronary artery disease, and blood vessel disease.[355-357]

Insulin is a hormone produced by the pancreas, and it regulates blood sugar by facilitating its uptake into cells and subsequent conversion into energy.[358] Insulin also regulates glucose storage in the liver, muscles, and fat cells of the body and plays a role in the metabolism of fats, proteins, and carbohydrates.[358] A dysregulation of these processes may lead to widespread damage to the body's tissues and organs, such as the heart, eyes, and kidneys.

Triterpenes have demonstrated multiple antidiabetic mechanisms, as well as hypoglycemic, hypolipidemic, and anti-obesity properties.[345] In addition, triterpenes can ameliorate insulin resistance, normalize plasma glucose and insulin levels, and inhibit the formation of advanced glycation end products (AGEs), commonly implicated in diabetic nephropathy, diabetic neuropathy, diabetic embryopathy, and impaired diabetic wound healing.[345,346]

Terpenes, such as D-limonene, β-caryophyllene, trans-anethole (TA), geranic acid, citral, farnesol, farnesal, and terpinen-4-ol, have demonstrated potent antihyperglycemic, anti-α-glucosidase, antioxidant, and anti-inflammatory properties,[143,347,359-363] suggesting their potential application as anti-diabetic agents.[345] In a study on streptozotocin (STZ)-induced diabetes rats, D-limonene was evaluated against oxidative stress parameters (i.e., lipid peroxidation by-products) and enzymatic antioxidants (i.e., glutathione-S-transferase, GPx, SOD, and catalase [CAT]),[347,361,364,365] and D-limonene demonstrated the ability to alleviate oxidative stress by enhancing the bioactivity of the enzymatic antioxidants and reducing the levels of lipid peroxidation by-products.[347]

Safranal, a monoterpenoid produced by the saffron plant (*Crocus sativus* L.), also demonstrated protection against oxidative damage in STZ-induced diabetes rats through enhancement of antioxidant enzymes such as GPx, SOD, and CAT.[366,367] There was also a reduction in the levels of lipid peroxidation markers, including nitric oxide

(NO) and malondialdehyde (MDA), lipids, triglycerides, and cholesterol.[366,367] These results suggest that safranal could be used as an anti-diabetic agent.

The sodium-glucose co-transporter-1/sodium glucose-linked transporter-1 (SGLT-1) regulates the reabsorption of glucose into the small intestines (and less frequently, the kidneys), thereby reducing blood glucose levels and improving glycemic control.[368] Farnesol and farnesal, two acyclic terpenoids, reportedly inhibit SGLT-1 to produce antihyperglycemic effects.[369]

ECS overactivity, particularly cannabinoid receptor type 1 (CB_1R), has been implicated in the progression of insulin resistance and diabetes (especially type 2) and its age-related comorbidities, such as atherosclerosis, retinopathy, neuropathy, and nephropathy.[65] Terpenes, in combination with phytocannabinoids, may also interact with CB_1R to ameliorate diabetes and its complications.[65] Cannabinoid receptor type 2 (CB_2R), also of the ECS, has been implicated in glucose and lipid metabolism and may also have therapeutic benefits against diabetes and chronic inflammatory diseases.[143] β-caryophyllene is reported to interact with CB_2R[143] and exhibit antiglycemic properties through interaction with PPAR-α and PPAR-γ.[143]

AMP-activated protein kinase (AMPK) is a stress kinase that increases fatty acid oxidation, inhibits lipid synthesis, improves insulin action, and facilitates GLUT4 translocation of glucose entry into adipocytes and muscle cells.[370] Two cucurbitane triterpenoids from *M. charantia*, karaviloside XI, and momordicoside, have demonstrated the ability to mediate the phosphorylation and activation of AMPK.[370-372] In the same study, momordicoside reportedly enhanced fatty acid oxidation and glucose disposal in both insulin-resistant and insulin-sensitive mice.[370]

4. Economic value of terpenes

Besides their medicinal value, terpenes and their derivatives also have high economic value as they are used widely in many industries, such as the food, toiletries, pharmaceutical, nutraceutical, and cosmeceutical industries. Notably, the COVID-19 pandemic has also greatly influenced the growth of the terpene market.

Terpenes are an important industrial raw material and play a significant role in the production of synthetic polymers, natural rubbers (polyisoprene), organic solvents, varnishes, inks, adhesives, cleaning products, and biofuels. For example, (-)-menthol (1-menthol) is widely used in the manufacturing of many beverages, cigarettes, and other products with a wild mint flavor or fragrance. Likewise, linalool is responsible for the distinct lavender fragrance and is also widely used in many industries.

As aforementioned, taxol (paclitaxel) is widely used to treat solid-tumor cancers, and its economic value has been increasing annually, correlating to the growing incidence of many cancers globally. In 2021, the global paclitaxel injection market was valued at US$4.51 billion and is expected to exceed US$11.16 billion by 2030 at a compound annual growth rate (CAGR) of 12.5% between 2022 and 2030.[373]

According to a 2022 market growth report, the global terpenes market was estimated to value around US$693 million and is expected to reach a valuation of over US$1 billion by 2028, with a CAGR of 6.4% between 2021 and 2027.[374] It should also be noted that several terpene-based patents contribute to this growth, and Table 8 presents several existing terpene-related patents for the treatment of various diseases.

5. Conclusion

Terpenes have significant therapeutic potential and a wide range of industrial applications. Owing to their high natural abundance and chemical diversity, terpenes are suitable candidates for novel and commercially valuable products and alternatives to synthetic products.

With the increasing incidence of cancer, there is also a growing interest in the therapeutic benefits of terpenes. Based on the treatment efficacy of taxol (paclitaxel), other terpenoids may have similar potential. However, there is currently a lack of definitive terpene and terpenoid profiles, and the biosynthetic systems and metabolic processes influencing the anticancer properties of terpenes remain unclear.

Given these limitations, further research is warranted to elucidate the bioactivity and potential synergism of terpenes and terpenoids when used in combination with cannabinoids and flavonoids. Consequently, this approach would result in more advanced commercial terpene- and terpenoid-based therapeutics in the market.

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