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Anti-inflammatory Potential of Terpenes Present in *Cannabis sativa* L.

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ABSTRACT: *Cannabis sativa* L. (*C. sativa*) contains an array of plant-derived (phyto) cannabinoids and terpenes that are predominantly located in the trichome cavity of the plant. Terpenes, aromatic organic hydrocarbons characterized for their role in plant protection/pollination, are gaining attention for their potential as novel therapeutics in many areas of biomedicine. This Viewpoint will explore the exciting recent evidence that terpenes have anti-inflammatory/antioxidant propensity by targeting inflammatory signaling mechanisms relevant to human disease. Given their anti-inflammatory properties, terpenes may contribute to the effects of current cannabinoid-based therapies.

KEYWORDS: *Terpenes, inflammation, cannabis, biomedicine, therapeutics*

INTRODUCTION

Research regarding components of the cannabis plant, *Cannabis sativa* L. (*C. sativa*), continues to investigate the complex pharmacology of an increasing number (over 120) of phytocannabinoids (pCBs), with focus on cannabidiol (CBD) and Δ^9-tetrahydrocannabinol (THC). pCBs are found in the trichome cavity of the flowers, leaves, and stem of *C. sativa* and are sequestered there with terpenes, the fragrance components of *C. sativa*. Over 200 terpenes are known, consisting of monoterpenes (limonene, α-pinene, linalool) and sesquiterpenes (β-caryophyllene, (−)-α-bisabolol), which share the same biological precursor with pCBs.[1] While studies have focused on the medicinal properties of pCBs, the terpenes have remained relatively understudied in terms of their potential therapeutic value. From a pharmaceutical standpoint, terpenes are considered safe by the U.S. Food and Drug Administration (FDA) and are common fragrance/flavor components in our diets. This Viewpoint summarizes evidence from *in vitro* and *in vivo* models indicating the anti-inflammatory and antioxidant propensity of terpenes, and aims to broaden the therapeutic consideration of components of the cannabis plant.

CANNABIS PLANT

Approximately 500 constituents of *C. sativa* are known, including pCBs, terpenes, amides, fatty acids, and carbohydrates. It is important to note that the compound geranyl diphosphate is the start material for both pCBs and monoterpenes, and hence, terpenes share a biological precursor with pCBs.[1]

Both terpenes and pCBs are lipophilic, and some pCBs act via G protein-coupled cannabinoid receptors (CB_1 and CB_2) localized on cells of the nervous/immune systems.[2] Specifically, THC demonstrates affinity for CB_1/CB_2, while several receptor targets independent of $CB_{1/2}$ have been demonstrated for pCBs such as CBD. Importantly, recent evidence suggests that the sesquiterpene β-caryophyllene acts via CB_2,[3] indicating that classic cannabinoid receptors may mediate some functional effects of terpenes. It is proposed that the combination of terpenes and pCBs can result in synergistic or complementary outcomes, with this commonly termed "entourage effect" gaining weight[4] in terms of the therapeutic relevance of terpenes.

TERPENES

C. sativa contains over 200 terpenes, consisting of monoterpenes (limonene, α-pinene, linalool) and sesquiterpenes (β-caryophyllene, (−)-α-bisabolol). The composition of terpenes varies in strains of cannabis; however, α-pinene and limonene are some of the most common. Terpenes have many functions in the plant, and in particular given their aroma they act as insect/herbivore repellents while protecting the plant from pathogens and competition from vegetation. In addition, terpenes are common flavor/fragrance food additives in the diets of humans and in cosmetic products (soaps/perfumes), and many are considered safe by the FDA. As examples, limonene is common to lemon and other citrus (orange/mandarin/lime); α-pinene is present in essential rosemary and eucalyptus oil; linalool is common to lavender; (−)-α-bisabolol is found in the oils of chamomile; while β-caryophyllene is common to black pepper and clove (Figure 1).

TERPENES TARGETING INFLAMMATION

Overall the effects of cannabis-derived terpenes in humans is unclear, with the cannabis terpenes still remaining relatively

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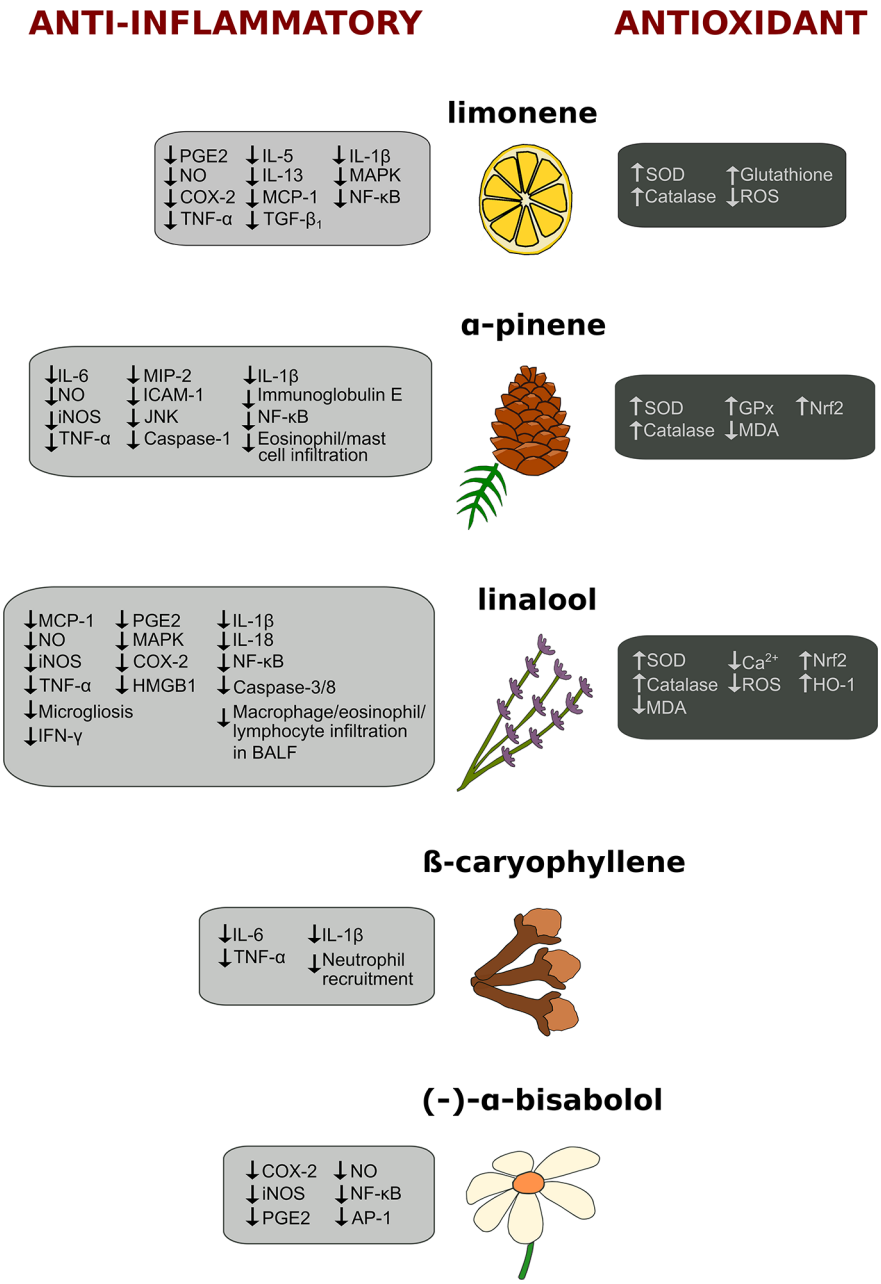

Figure 1. Summary of the effect of terpenes on inflammatory and oxidative markers.

understudied. Terpenes regulate several second messenger and neurotransmitter systems, and some evidence, albeit limited, indicates that terpenes have specific receptor targets. Due to their lipophilicity, their cellular effect(s) may be attributed to their direct partitioning into cellular membranes. The pCBs, in particular THC and CBD, have been the primary focus of many research groups in terms of targeting neuroinflammatory and neurodegenerative disorders. However, there is renewed interest in the therapeutic potential of terpenes, and a body of data, particularly from *in vitro* and *in vivo* models, indicates anti-inflammatory activity and radical scavenging potential of terpenes.[5] This Viewpont summarizes the recent data in this area for key terpenes, including limonene, α-pinene, linalool, β-caryophyllene and (−)-α-bisabolol (Figure 1).

Limonene. The monoterpene limonene demonstrates significant anti-inflammatory and antioxidant activity both *in vitro* and *in vivo*. *In vitro*, limonene has been shown to inhibit lipopolysaccharide (LPS)-induced prostaglandin E2 (PGE2), nitric oxide (NO), and TNF-α/IL-1β in macrophages, in addition to inhibiting IL-1β-induced NO production in human chondrocytes. *In vivo*, D-limonene has also been shown to reduce intestinal inflammation in animal models of colitis. This monoterpene also exhibits a protective role against renal damage by targeting cylooxygenase-2 (COX-2) and NO. In support of its antioxidant capacity, D-limonene can increase the activity of superoxide dismutase (SOD), catalase, and glutathione in the CNS in models of cerebral ischemia while reducing IL-1β and reactive oxygen species (ROS) production. In a mouse model of asthma, limonene reduced IL-5, IL-13, MCP-1, and TGF-β_1 in bronchoalveolar lavage fluid (BALF) while reducing leukocyte numbers in the BALF. In support of this, limonene protects against LPS-induced acute lung injury in mice, reducing proinflammatory cytokine production by targeting the inhibition of both nuclear factor (NF)-κB and

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mitogen-activated protein kinase (MAPK) signaling. Importantly, data indicate that this terpene is readily absorbed from the digestive tract when given orally, and that administration of D-limonene-containing orange peel extract to healthy elderly individuals can alter peripheral IL-6 expression.

α-Pinene. Antioxidant and anti-inflammatory effects of α-pinene, a monoterpene present in species of coniferous trees and *C. sativa*, have been reported in several studies. Indeed, α-pinene reduced NO/IL-6 and malondialdehyde (MDA) production in several brain regions following ischemic stroke in the rat, further restoring SOD, catalase, and glutathione peroxidase (GPx) in this model. α-Pinene also reduced pancreatic IL-1β/TNF-α/IL-6 in a model of pancreatitis, and it has shown particular promise as an antiallergic compound, targeting nasal immunoglobulin E and eosinophil/mast cell infiltration of nasal mucosa while reducing macrophage inflammatory protein-2 (MIP-2), intercellular adhesion molecule-1 (ICAM-1), and TNF-α in nasal mucosa in an allergic rhinitis model. *In vitro*, (+)-α-pinene has also been reported to blunt IL-1β-induced NO production and inducible NO synthase (iNOS) expression, in addition to both NF-κB and JNK signaling, in human chondrocytes. This terpene inhibits NF-κB signaling and caspase-1 activation in mast cells and also targets LPS-induced nuclear translocation of NF-κB/p65 in human monocyte cultures. Importantly, α-pinene also promotes antioxidant capacity in human astrocytoma cells, regulating nuclear factor erythroid 2-related factor 2 (Nrf2) transcription factor and further promoting antioxidant enzymes including GPx.

Linalool. A body of data indicates anti-ischemic, antioxidant and anti-inflammatory propensity of the monoterpene linalool. Indeed, *in vitro* (−)-linalool inhibits LPS-induced MCP-1 in airway epithelia, scavenges ROS following oxygen-glucose deprivation/reoxygenation in neurons, promotes the activities of SOD and catalase antioxidant enzymes, and reduces MCP-1-induced migration of microglia. Linalool also has neuroprotective capacity, and it can protect neurons against glutamate-induced oxidative stress by abrogating mitochondrial ROS and calcium production. This monoterpene also inhibits LPS-induced NF-κB/TNF-α expression in macrophages/microglia, with proclivity to also inhibit LPS-induced PGE2 production.

In vivo, linalool reduced complete Freud's adjuvant and carrageenan-induced paw edema. Furthermore, it inhibited eosinophil/macrophage/lymphocyte number and MCP-1 expression in BALF, in addition to iNOS and NF-κB/MAPK in lung tissue, in models of airway inflammation. Oral administration of linalool improves learning/memory in a mouse model of Alzheimer's disease (3xTg-AD), with associated reductions in astrogliosis/microgliosis, IL-1β and COX2 in the hippocampus/amygdala. *In vivo* administration of linalool, prior to injection of endotoxin, reduced the levels of nitrate/nitrite, IL-1β, IFN-γ and TNF-α in blood, spleen and mesenteric lymph nodes (MLNs). In addition, linalool ameliorated endotoxin-induced High-mobility group box 1 protein, a damage associated molecular pattern, in blood, while also reducing signaling associated with the pattern recognition receptors, toll-like receptor (TLR)4 and Nod-like receptors, in spleen and MLNs.

In terms of oxidative stress, linalool is a regulator of Nrf2 *in vitro* and *in vivo*, and can induce antioxidant enzymes regulated by Nrf2, including heme oxygenase-1 (HO-1). Indeed, intranasal administration of linalool demonstrates protection against ischemia in rodents, with an associated reduction in inflammatory markers (microgliosis, COX2) in the hippocampus. Linalool is also protective against liver injury, ameliorating LPS/D-galactosamine-induced liver injury in mice, inhibiting hepatic NF-κB, iNOS, COX2, MDA, and caspase-3/8, in addition to promoting Nrf2 and HO-1.

β-Caryophyllene. The sesquiterpene β-caryophyllene has efficacy as an anti-inflammatory, particularly in animal models of inflammation. Indeed, β-caryophyllene has been shown to ameliorate the expression of proinflammatory cytokines (IL-1β/TNF-α/IL-6) in the midbrain in an animal model of Parkinson's disease, and has also been shown to target neutrophil recruitment in a pulmonary inflammation model. β-Caryophyllene can bind to CB_2, and importantly, this sesquiterpene has been shown to inhibit LPS-induced cytokine expression in whole blood in a CB_2-dependent manner.[3]

(−)-α-Bisabolol. Data, particularly from *in vitro* studies, indicates that the sesquiterpene (−)-α-bisabolol can inhibit LPS-induced expression of PGE2, COX-2, iNOS, and NO in macrophages. Mechanistically, (−)-α-bisabolol has the proclivity to target LPS-induced activation of NF-κB and activator protein-1.

CONCLUSION

The medicinal use of cannabis dates back to ancient Chinese medicine, and currently cannabinoid-based therapies are approved in certain countries as medicinal products, including as antiemetics during cancer treatment (Marinol, synthetic THC; and Cesamet, a synthetic derivative of THC), for spasticity in multiple sclerosis (Sativex, a 1:1 mixture of THC and CBD), and for the treatment of seizures associated with Lennox-Gastaut or Dravet syndromes (Epidiolex, plant-derived purified CBD solution). Importantly, several reports have proposed entourage effects of terpenes acting synergistically with pCBs, and given that the anti-inflammatory and antioxidant propensity of terpenes outlined herein continue to be elucidated, it is important to consider that certain terpenes present in *C. sativa* may contribute to the therapeutic effects of current cannabinoid-based therapies. Indeed, the sesquiterpene β-caryophyllene can bind to CB_2 receptors, and terpenes can modulate an array of cell signaling mechanisms regulated by pCBs. Overall, particular consideration must be given to terpene/pCBs interactions that could produce synergy as therapeutics, as such interactions may further open up the development of therapeutic options from the *C. sativa* plant.

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Notes

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