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Letter to the editor:

RECENT STUDIES ON PINENE AND ITS BIOLOGICAL AND PHARMACOLOGICAL ACTIVITIES

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Dear Editor,

Pinene ($C_{10}H_{16}$) is a well-known group of monoterpenes and the main component of turpentine, which is a fluid obtained by the distillation of resin harvested from coniferous trees, particularly those of the genus *Pinus* (Mercier et al., 2009; Al-Tel et al., 2020). Pinene can be divided into two structural isomers: α-pinene (α-pinene) and beta-pinene (β-pinene). α- and β-pinene are mainly produced by pine trees and many other conifers, as well as a wide range of herbs such as rosemary, parsley, basil, and even orange peel (Erman and Kane, 2008; Vespermann et al., 2017).

α-pinene, the most abundant monoterpene in the atmosphere, accounts for more than 50 % of global monoterpene emissions and is a major component of phytoncides (Bagchi et al., 2020; Li et al., 2009). Phytoncides are antimicrobial allelochemical volatile organic compounds that are related to forest healing and activation of recreational forests. Trees are considered one of the major emitters of phytoncides (Li, 2010).

A wide range of pharmacological activities of α- and β-pinene have been reported, such as anticoagulant, anti-inflammatory, anti-leishmania, antimalarial, antimicrobial, antioxidant, antitumor, analgesic, and antibiotic resistance modulation effects (Türkez and Aydın, 2016; Salehi et al., 2019). These monoterpenes exhibit various biological activities and have a wide range of applications, including development of antimicrobial and antiviral agents, flavors, fragrances, and fungicidal agents (Rivas da Silva et al., 2012; Yang et al., 2013). Herein, we summarize the recent published findings on the biological and pharmacological activities of pinene (Table 1).

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Table 1: Recent studies on the biological and pharmacological activities of pinene

Key findings	Reference
Natural killer (NK) cells are lymphocytes that can directly destroy cancer cells. α-pinene activates NK cells and increases NK cell cytotoxicity, suggesting that it is a potential compound for cancer immunotherapy.	Jo et al., 2021
α-pinene has excellent antifungal activity, with high inhibitory activity against *Candida parapsilosis*. It has been proven to be effective in destroying fungal structures such as pseudohyphae and inducing a significant decrease in blastoconidia.	Nóbrega et al., 2020
α-pinene and 3-carene prevent the development of immature stages of weevils and decrease the progeny to 94 %. These compounds are the most effective and promising novel phytoinsecticides for controlling maize weevils.	Langsi et al., 2020
(+)-α-pinene combined with antimicrobial agents, such as amikacin, amoxicillin, cefepime, cefoxitin, and ceftazidime, showed a positive effect as it enhanced the antibiotic effect of these compounds. In addition, (+)-α-pinene induced cross-resistance only for the antimicrobial agents cefepime, ceftazidime, cefuroxime, and chloramphenicol.	do Amaral et al., 2020
α-pinene treatment inhibits the increase in seizure incidences, whereas dizocilpine (MK-801) significantly reduces kindling acquisition. Administration of both these compounds inhibits pentylenetetrazole (PTZ)-induced activation of astrocytes and significantly inhibits the increase in extracellular matrix (ECM) molecules. These compounds might also prevent epileptic seizures by decreasing the activation of astrocytes and ECM molecule production.	Ueno et al., 2020
α-pinene exerts neuroprotective effects during an ischemic stroke by reducing neuroinflammation and inhibiting apoptosis. Neuroinflammation and apoptosis play a vital role in neuronal death during ischemic stroke.	Khoshnazar et al., 2020
α-pinene intake attenuates isoproterenol-induced inflammatory marker expression, thus significantly protecting against myocardial infarction and exerting cardioprotective and anti-inflammatory effects in male Wistar rats.	Zhang et al., 2020
α-pinene odor stimulation is related to lipid metabolism, stress tolerance, and health span through specific signaling pathways. Thus, α-pinene odor might be a potential target for anti-aging and disease prevention.	Ensaka and Sakamoto, 2020
(-)-α-pinene decreases quorum sensing in *Campylobacter*, which enhances the effects of antibiotics against various strains of *Campylobacter*, and the colonization of *Campylobacter* in broiler chickens.	Šimunović et al., 2020
α-pinene and quercetin are bioactive phytocompounds present in the soil. They may affect the tolerance of microorganisms to persistent toxicants and change their impact on the environment.	Cardoso et al., 2020
Bursaphelenchus xylophilus is a parasitic nematode that causes pine wilt disease, which results in severe damage to pine trees worldwide. α-pinene protects the host species during the early *B. xylophilus* infection and colonization stages.	Meng et al., 2020
α-pinene enhances osteoblast differentiation, which was confirmed by alkaline phosphatase and alizarin red S staining. This effect might be due to the attenuation of tumor necrosis factor-alpha (TNFα) induction by α-pinene, which leads to the inhibition of Smad1/5/9 phosphorylation and extracellular matrix mineralization.	Min et al., 2020
α-pinene has significant toxic effects on *Folsomia candida*. In addition, α-pinene might improve their cold stress tolerance significantly at membrane concentrations of more than 87 mmol kg^{-1}.	Jensen et al., 2020
α-pinene showed neuroprotective effect in an ischemic stroke rat model by restoring antioxidant enzymatic activity, attenuating lipid peroxidation, and reducing inflammation in the ischemic brains.	Khoshnazar et al., 2019

Key findings	Reference
α-pinene showed potential anticancer effects in PA-1 cancer cells via induction of cytotoxicity and inhibition of cell sequence development along with programmed cell death.	Hou et al., 2019
α-pinene reduces MK-801-induced behavioral abnormalities, which are similar to those observed in neuropsychiatric disorders. Based on this finding, it can be suggested that plants and oils rich in α-pinene might have a potential effect on schizophrenia treatment.	Ueno et al., 2019
α-pinene shows low toxicity to pinewood nematode for a short period of time. It affects the diversity and abundance of the symbiotic bacteria com-munity of these nematodes, which might have a potential impact on the de-velopment and reproduction of nematodes.	Wang et al., 2019
A fragrant environment (FE) containing α-pinene activated the immune system and hypothalamus/sympathetic nerve/leptin axis in mice, leading to the retardation of growth of tumor cells, which was confirmed by the neuro-hormonal and immunological changes.	Kusuhara et al., 2019
α-pinene is the major constituent of *Ducrosia anethifolia* essential oil, and it can induce anticonvulsant and antioxidant effects in rats.	Zamyad et al., 2019
α-pinene treatment effectively prevents UVA-induced lipid peroxidation in mouse skin probably through its antioxidant property.	Karthikeyan et al., 2019
α-pinene did not show anticonvulsant properties in PTZ-induced male Swiss albino mice. This might be attributed to the structure of the compound, because pretreatment with β-pinene decreased the intensity of seizures and prolonged the death time of PTZ-treated albino mice. In addition, α-pinene reduced the concentration of norepinephrine, dopamine, and nitrite but not of thiobarbituric acid reactive substance during PTZ-induced seizure.	Felipe et al., 2019
α-pinene inhibits *miR221* gene expression, leading to G2/M-phase cell cycle arrest of hepatocellular carcinoma cells (HepG2), and triggers the ATM-p53-Chk2 and CDKN1B/p27-CDK1 pathway, which leads to the suppression of hepatoma tumor development in humans. Thus, α-pinene could be considered a highly potential chemotherapeutic agent for hepatocellular carcinoma treatment.	Xu et al., 2018
β-pinene exerts potential antifungal activity by weakening the cell wall through interactions with Delta-14-sterol reductase and 1,3-β-glucan synthase. These molecules could effectively decrease the adhesion of *Candida* biofilm.	de Macêdo et al., 2018
α-pinene prevents oxidative stress caused by ultraviolet A (UVA) exposure, inflammation, UVA-induced DNA damages, and apoptosis in human skin epidermal keratinocytes.	Karthikeyan et al., 2018
α-pinene and cineole are the main components present in *Rosmarinus officinalis* (RO) that contributed to the increased survival of flap necrosis. This finding shows that RO has anti-inflammatory effects.	İnce et al., 2018
α-pinene prevented the growth of human prostate cancer cells, induced programmed cell death, and arrested the cell cycle in the PC-3 cell line. In addition, α-pinene-treated mice inhibited tumor progression more effectively than control mice. α-pinene inhibited the growth of prostate cancer cells in a xenograft model. Thus, it might be an effective therapeutic agent for the treatment of prostate cancer.	Zhao et al., 2018
α-pinene treatment significantly increased scopolamine-induced cognitive dysfunction. In addition, it efficiently reduced the mean escape latency in Morris water-maze test. Mainly, α-pinene treatment increases choline acetyltransferase levels in the cortex and protein levels of antioxidant enzymes (heme oxygenase-1 and manganese superoxide dismutase) in the hippocampus by triggering the nuclear factor erythroid 2-related factor 2 (NRF2). These findings suggest that α-pinene could be a potential neuroprotective compound for the management of dementia-related learning and memory loss.	Lee et al., 2017

Key findings	Reference
β-pinene and linalool act as repellents against *Tribolium castaneum*. β-pinene showed potential effect compared with linalool in stimulating insect repellency. A significant change in the expression of genes associated with neuronal transmission was observed.	Pajaro-Castro et al., 2017
α-pinene has potential antioxidant capacity. Exposure of cells to α-pinene together with aspirin showed a significant increase in cell survival and GSH level. However, malondialdehyde (MDA), total super dismutase (SOD), and Mn-SOD activity were decreased. This might be due to the activation of p38 mitogen-activated protein kinases (MAPKs) and inhibition of c-Jun N-terminal kinase (JNK) by α-pinene. These results suggest that α-pinene can protect IEC-6 cells against aspirin-induced oxidative stress.	Bouzenna et al., 2017
α-pinene is present in the oil extract of *Pistacia atlantica*. It has a protective effect against ethanol-induced gastric ulcer and antibacterial activity against *Helicobacter pylori*.	Memariani et al., 2017
(−)-α-pinene has various beneficial effects such as anxiolytic, antioxidant, and anti-inflammatory properties. In mice, (−)-α-pinene improved non-rapid eye movement sleep (NREMS) without disturbing NREMS intensity by delaying gamma-aminobutyric acid (GABA)ergic synaptic transmission, which acts as a partial modulator of GABAA-benzodiazepine (BZD) receptors and directly binds to the distinct BZD binding sites of GABAA receptor. Thus, (−)-α-pinene might be used as an effective therapeutic agent against anxiety and sleeping disorders.	Yang et al., 2016
α-pinene and 1,8-cineole are monoterpenes that showed effective antioxidant activity and protected rat pheochromocytoma (PC12) cells from H_2O_2-induced oxidative stress. This study showed the potential therapeutic benefits of these compounds in maintaining antioxidant balance in nervous system diseases.	Porres-Martínez et al., 2016
(-)-β-pinene (βP)/β-cyclodextrin (β-CD) complex shows an antihypertensive effect, which has been proven in pharmacological studies. βP induces endothelium-independent vasorelaxation by decreasing Ca^{2+} influx through L-type Ca^{2+} channel associated with a decrease in calcium sensitivity.	Moreira et al., 2016
α-pinene, linalool, and 1-octanol are the active ingredients present in frankincense oil extracts. Topical application of this oil showed significant analgesic and anti-inflammatory effects via the inhibition of cyclooxygenase-2 overexpression and nociceptive stimulus-induced inflammatory infiltrates.	Li et al., 2016
α-pinene from the oil extract of *Plectranthus barbatus* was found to be an effective mosquito control agent. It is effective even at low doses and can be used as an alternative safe compound for controlling mosquitoes.	Govindarajan et al., 2016
(-)-α-pinene can modulate antibiotic resistance in *Campylobacter jejuni* via various mechanisms such as metabolic disruption, decreased membrane integrity, and microbial efflux inhibition. Based on this finding, it can be suggested that (-)-α-pinene can be used to control *Campylobacter* antibiotic-resistant strains in future.	Kovač et al., 2015
α-pinene extracted from pine needle oil exhibits anti-cancer activity. It inhibited the growth of liver cancer BEL-7402 cells with an inhibitory rate of 79.3 % and 69.1 % in *in vitro* and *in vivo* experiments, respectively. In addition, the levels of Chk1 and Chk2 were upregulated, whereas CDK1, CDC25, and Cyclin B levels were downregulated.	Chen et al., 2015
α-pinene exhibits anti-inflammatory activity through the inhibition of the nuclear factor-kappa B and mitogen-activated protein kinase pathway in mouse peritoneal macrophages. This finding shows that α-pinene has an anti-inflammatory effect, and it can be used as a potential candidate for the treatment of various inflammatory diseases.	Kim et al., 2015
α-pinene shows significant antiulcerogenic activity. A good correlation between α-pinene concentration and gastroprotective activity of *Hyptis* species was also reported.	Pinheiro et al., 2015

Key findings	Reference
α-pinene is the major constituent in *Syzygium cumini* essential oil; it exerts significant anti-leishmania activity by modulating macrophage activation, with suitable levels of cytotoxicity in murine macrophages and human red blood cells.	Rodrigues et al., 2015
α-pinene concentration increase in the brain leads to an increase in locomotor activity as well as the expression level of tyrosine hydroxylase mRNA. These anxiolytic-like effects might be associated with both neurological and pharmacological transfer.	Kasuya et al., 2015
Non-small-cell lung cancer (NSCLC) cells treated with α-pinene and β-pinene combined with paclitaxel (PAL), i.e., (α-pinene+PAL) and (β-pinene+PAL), showed changes in morphological characteristics; apoptosis-like condensation of chromatin and breakdown of the nucleus were observed.	Zhang et al., 2015

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Conflict of interest

The authors declare no conflict of interest.

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