

AUSTRALIAN NATURAL THERAPEUTICS GROUP

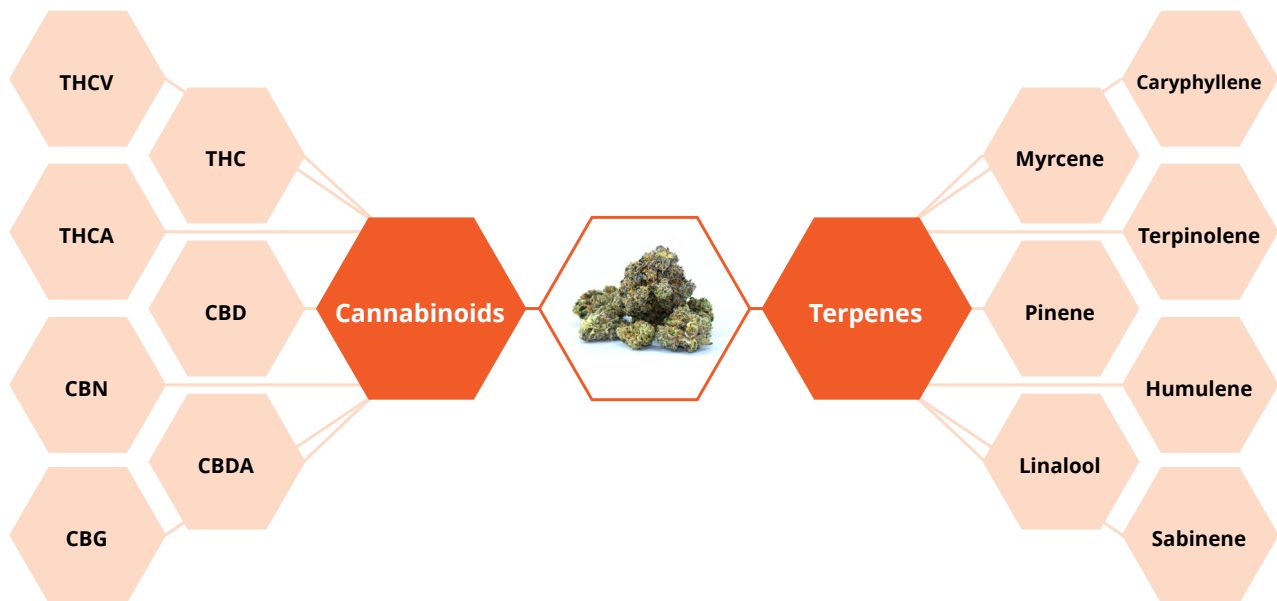


TERPENES

Terpenes are aromatic compounds found in many plants, although many people commonly associate them with cannabis because cannabis plants contain relatively high concentrations of them.

ANTG

ENTOURAGE EFFECT



These aromatic constituents create the characteristic scent of many plants, such as pine, lavender, and the smell of fresh orange peel. Not surprisingly, essential oils from various plants are full of terpenes, with the unique fragrance of most plants being due to a combination of different terpenes. In nature, these terpenes protect the plants from animals grazing on them, as well as from other pathogenic microbes.

However, terpenes may also offer some health benefits to the human body. Researchers have found nearly 200 distinct terpenes in Cannabis plants. They are important because they affect the human body in a myriad of ways that are only now being fully understood.

The cannabis plant contains many phytochemical compounds, each with their own effect and benefit. In fact, over 700 different phytochemical constituents have been characterised across various Cannabis chemovars. (1) It has been posited that the activity of these compounds may change when others are present. The entourage effect is a term commonly used to describe the synergistic effects of the various chemical compounds found in cannabis.

Examples of the entourage effect:

In a randomised controlled trial of oromucosal cannabis-based extracts in patients with intractable pain despite optimized opioid treatment, (2) a tetrahydrocannabinol (THC) predominant extract failed to demarcate favourably from placebo, whereas a whole plant extract (i.e. nabiximols) with both THC and

cannabidiol (CBD) demonstrated effectiveness with statistical significance, (2) the only significant difference being the presence of CBD in the latter.

Further, a recent study (3) of several human breast cancer cell lines in culture and implanted tumours demonstrated the superiority in anti-tumour activity of a botanical cannabis preparation compared to pure THC; the former containing small concentrations of cannabigerol (CBG) and tetrahydrocannabinolic acid (THCA). The authors concluded that such multi-target approaches could conceivably be more effective in diseases as complex as cancer. (3)

The entourage effects between cannabinoids and terpenes is currently in early stages of research, however one example of this is proposed in the paper *Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects*, (4) where Dr Russo suggests that “data would support the hypothesis that myrcene is a prominent sedative terpenoid in cannabis, and combined with THC, may produce the ‘couchlock’ phenomenon of certain chemotypes.”

There has been a shift in the way cannabis is being described to the public. Instead of classifying cannabis varieties by physical characteristics (i.e. Sativa vs Indica), the discussion is centred around their chemotype (phytochemical profile) – which is a much more accurate predictor of potential pharmacological effects.

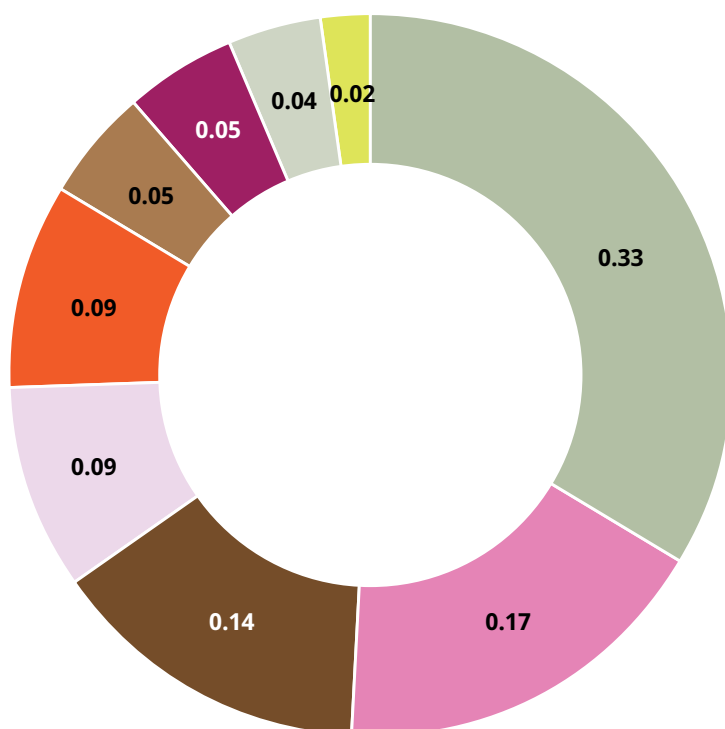
TERPENES FOUND IN ANTG PRODUCTS

TERPENE	AROMA	EFFECTS
β -Myrcene	Earthy, fruity, clove like	<ul style="list-style-type: none"> • Analgesic (5, 6) • Antioxidant (7, 8) • Antibacterial (7) • Anti-inflammatory (6, 9) • Sedative, muscle relaxant, hypnotic (10)
β -Caryophyllene	Spicy	<ul style="list-style-type: none"> • Analgesic (11) • Antidepressant (12) • Anti-inflammatory (13) • Anti-proliferative (14) • Antioxidant (14) • Anxiolytic (15) • Neuroprotective (16) • Gastric cytoprotective (17)
Terpinolene	Smoky, woody	<ul style="list-style-type: none"> • Antibacterial (18) • Anti-inflammatory (19) • anti-fungal (20) • Sedative (21) • anti-proliferative (22) • antioxidant effects (22)
Limonene	Citrus, lemon, orange	<ul style="list-style-type: none"> • Antidepressant (23, 24) • Antifungal (25, 26) • Anti-inflammatory (27, 28) • Anti-proliferative, Apoptosis of breast cancer cells (4, 29) • Anxiolytic via 5-HT1A (30, 31) • Gastro-oesophageal reflux (reduces acid reflux) (32) • Immunostimulant via inhalation (24)
3-Carene	Sweet, earthy, piney undertones	<ul style="list-style-type: none"> • Anti-inflammatory (33) • Antifungal (34) • Bone-healing properties (Increased bone metabolism) (35)
α -Pinene	Pine, fresh mountain air, slightly woody	<ul style="list-style-type: none"> • Antibiotic resistance modulation (36) • Antimicrobial (37) • Antioxidant (38) • Antiallergic (39) • Anti-inflammatory (40, 41) • Bronchodilatory (42) • Acetylcholinesterase inhibitor, aiding memory (4, 43)

TERPENE	AROMA	EFFECTS
Linalool	Spicy	<ul style="list-style-type: none"> • Analgesic via adenosine A2A (44) • Antidepressant (45) • Anti-convulsant / anti-glutamate (46) • Anti-inflammatory (47) • Anxiolytic (48) • Sedative (inhaled) (49)
gamma-Ter-pinene	Smoky, woody	<ul style="list-style-type: none"> • Anti-inflammatory (50)
Selina	Herbal, woody	<ul style="list-style-type: none"> • Potential antimicrobial effects are currently being studied
Humulene	"hoppy"	<ul style="list-style-type: none"> • Analgesic (51) • Antibacterial (52) • Anti-inflammatory (51) • Anti-proliferative (53)
β -Selinene	Herbal	<ul style="list-style-type: none"> • Antioxidant (54)

EVE TERPENE PROFILE

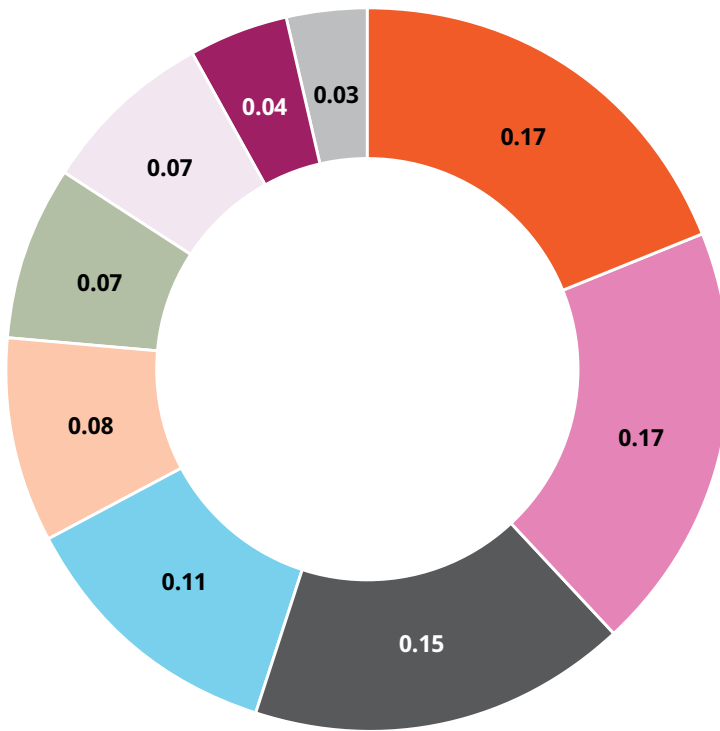
% W/W



- Myrcene
- Caryophyllene
- Terpinolene
- β -Pinene
- Limonene
- 3-Carene
- α -Pinene
- Linalool
- gamma-Terpinene

MARIPOSA TERPENE PROFILE

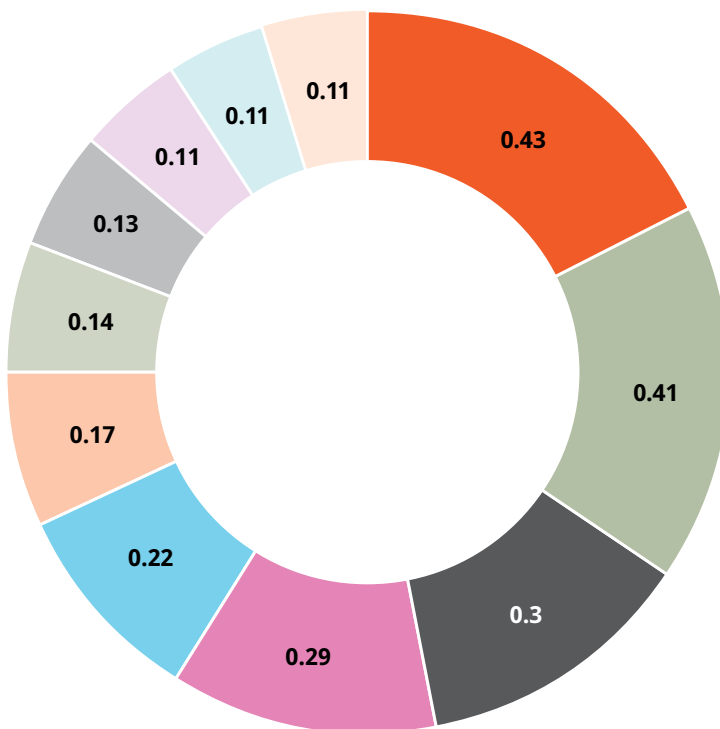
% W/W



- Limonene
- Caryophyllene
- Selina-3,7(11)-diene
- Selina-4(15),7(11)-diene
- Humulene
- Myrcene
- β-Pinene
- α-Pinene
- Germacrene B

SOLACE PROFILE

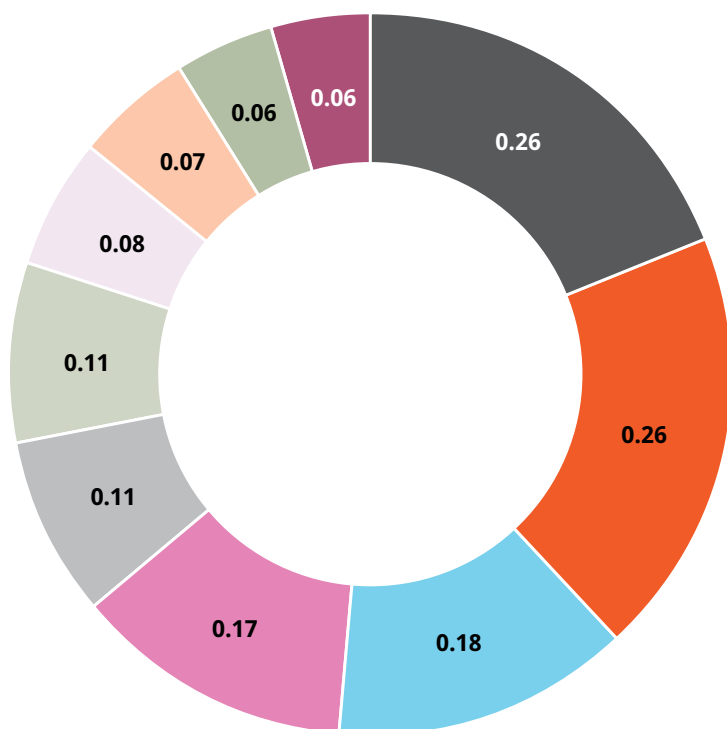
% W/W



- Limonene
- Myrcene
- Selina-3,7(11)-diene
- Caryophyllene
- Selina-4(15),7(11)-diene
- Humulene
- Linalool
- Germacrene B
- β-Pinene
- α-Bulnesene (δ-Guaiene)
- Guaia-6,9-diene

ROCKY TERPENE PROFILE

% W/W



- Selina-3,7(11)-diene
- D-Limonene
- Selina-4(15),7(11)-diene
- Caryophyllene
- Germacrene B
- Linalool
- (-)-β-Pinene
- α-Humulene
- Myrcene
- β-Selinene

REFERENCES

- Upton R, ElSohly, M., Romm, A., Russo, E., Sexton, M, editor. Cannabis inflorescence. Scotts Valley, California: American Herbal Pharmacopoeia; 2013.
- Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. *J Pain Symptom Manage*. 2010;39(2):167-79.
- Blasco-Benito S, Seijo-Vila M, Caro-Villalobos M, Tundidor I, Andradas C, Garcia-Taboada E, et al. Appraising the "entourage effect": Antitumor action of a pure cannabinoid versus a botanical drug preparation in preclinical models of breast cancer. *Biochem Pharmacol*. 2018.
- Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Br J Pharmacol*. 2011;163(7):1344-64.
- Rao VS, Menezes AM, Viana GS. Effect of myrcene on nociception in mice. *J Pharm Pharmacol*. 1990;42(12):877-8.
- Lorenzetti BB, Souza GE, Sarti SJ, Santos Filho D, Ferreira SH. Myrcene mimics the peripheral analgesic activity of lemongrass tea. *Journal of ethnopharmacology*. 1991;34(1):43-8.
- Wang C, Chen, YW., Hou, CY. Antioxidant and antibacterial activity of seven predominant terpenoids. *International Journal of Food Properties*. 2019;22(1).
- Ciftci O, Oztanir MN, Cetin A. Neuroprotective effects of beta-myrcene following global cerebral ischemia/reperfusion-mediated oxidative and neuronal damage in a C57BL/6 mouse. *Neurochem Res*. 2014;39(9):1717-
- Souza MC, Siani AC, Ramos MF, Menezes-de-Lima OJ, Henriques MG. Evaluation of anti-inflammatory activity of essential oils from two Asteraceae species. *Pharmazie*. 2003;58(8):582-6.
- do Vale TG, Furtado EC, Santos JG, Jr., Viana GS. Central effects of citral, myrcene and limonene, constituents of essential oil chemotypes from *Lippia alba* (Mill.) n.e. Brown. *Phytomedicine*. 2002;9(8):709-14.
- Klauke AL, Racz I, Pradier B, Markert A, Zimmer AM, Gertsch J, et al. The cannabinoid CB(2) receptor-selective phytocannabinoid beta-caryophyllene exerts analgesic effects in mouse models of inflammatory and neuropathic pain. *Eur Neuropsychopharmacol*. 2014;24(4):608-20.
- Hwang ES, Kim HB, Lee S, Kim MJ, Kim KJ, Han G, et al. Antidepressant-like effects of beta-caryophyllene on restraint plus stress-induced depression. *Behav Brain Res*. 2020;380:112439.
- Vijayalaxmi Aea. Anti-Arthritic and Anti Inflammatory Activity of Beta Caryophyllene against Freund's Complete Adjuvant Induced Arthritis in Wistar Rats. *Journal of Bone Reports and Recommendations*. 2015;1(2:9):1-10.
- Dahham SS, Tabana YM, Iqbal MA, Ahamed MB, Ezzat MO, Majid AS, et al. The Anticancer, Antioxidant and Antimicrobial Properties of the Sesquiterpene beta-Caryophyllene from the Essential Oil of *Aquilaria crassna*. *Molecules*. 2015;20(7):11808-29.
- Bahi A, Al Mansouri S, Al Memari E, Al Ameri M, Nurulain SM, Ojha S. beta-Caryophyllene, a CB2 receptor agonist produces multiple behavioral changes relevant to anxiety and depression in mice. *Physiol Behav*. 2014;135:119-24.
- Yang M, Lv Y, Tian X, Lou J, An R, Zhang Q, et al. Neuroprotective Effect of beta-Caryophyllene on Cerebral Ischemia-Reperfusion Injury via Regulation of Necroptotic Neuronal Death and Inflammation: In Vivo and in Vitro. *Front Neurosci*. 2017;11:583.
- Tambe Y, Tsujiuchi H, Honda G, Ikeshiro Y, Tanaka S. Gastric cytoprotection of the non-steroidal anti-inflammatory sesquiterpene, beta-caryophyllene. *Planta Med*. 1996;62(5):469-70.

18. Lee C-J, et. al. Correlations of the components of tea tree oil with its antibacterial effects and skin irritation. *Journal of Food and Drug Analysis*. 2013;21(2):169-76.
19. Macedo EM, Santos WC, Sousa BPN, Lopes EM, Piauilino CA, Cunha FV, et al. Association of terpinolene and diclofenac presents antinociceptive and anti-inflammatory synergistic effects in a model of chronic inflammation. *Braz J Med Biol Res*. 2016;49(7).
20. Yu D, Wang J, Shao X, Xu F, Wang H. Antifungal modes of action of tea tree oil and its two characteristic components against *Botrytis cinerea*. *J Appl Microbiol*. 2015;119(5):1253-62.
21. Ito K, Ito M. The sedative effect of inhaled terpinolene in mice and its structure-activity relationships. *J Nat Med*. 2013;67(4):833-7.
22. Aydin E, Turkez H, Tasdemir S. Anticancer and antioxidant properties of terpinolene in rat brain cells. *Arh Hig Rada Toksikol*. 2013;64(3):415-24.
23. Komiya M, Takeuchi T, Harada E. Lemon oil vapor causes an anti-stress effect via modulating the 5-HT and DA activities in mice. *Behav Brain Res*. 2006;172(2):240-9.
24. Komori T, Fujiwara R, Tanida M, Nomura J, Yokoyama MM. Effects of citrus fragrance on immune function and depressive states. *Neuroimmunomodulation*. 1995;2(3):174-80.
25. Chee HY, Kim H, Lee MH. In vitro Antifungal Activity of Limonene against *Trichophyton rubrum*. *Mycobiology*. 2009;37(3):243-6.
26. Thakre A, Zore G, Kodgire S, Kazi R, Mulange S, Patil R, et al. Limonene inhibits *Candida albicans* growth by inducing apoptosis. *Med Mycol*. 2018;56(5):565-78.
27. Rufino AT, Ribeiro M, Sousa C, Judas F, Salgueiro L, Cavaleiro C, et al. Evaluation of the anti-inflammatory, anti-catabolic and pro-anabolic effects of E-caryophyllene, myrcene and limonene in a cell model of osteoarthritis. *Eur J Pharmacol*. 2015;750:141-50.
28. Hirota R, Roger NN, Nakamura H, Song HS, Sawamura M, Suganuma N. Anti-inflammatory effects of limonene from yuzu (*Citrus junos* Tanaka) essential oil on eosinophils. *J Food Sci*. 2010;75(3):H87-92.
29. Vigushin DM, Poon GK, Boddy A, English J, Halbert GW, Pagonis C, et al. Phase I and pharmacokinetic study of D-limonene in patients with advanced cancer. *Cancer Research Campaign Phase I/II Clinical Trials Committee*. *Cancer Chemother Pharmacol*. 1998;42(2):111-7.
30. Carvalho-Freitas MI, Costa M. Anxiolytic and sedative effects of extracts and essential oil from *Citrus aurantium* L. *Biol Pharm Bull*. 2002;25(12):1629-33.
31. Lima NG, De Sousa DP, Pimenta FC, Alves MF, De Souza FS, Macedo RO, et al. Anxiolytic-like activity and GC-MS analysis of (R)-(+)-limonene fragrance, a natural compound found in foods and plants. *Pharmacol Biochem Behav*. 2013;103(3):450-4.
32. Harris B. Phytotherapeutic uses of essential oils. In: Baser K, Buchbauer, G, editor. *Handbook of Essential Oils: Science, Technology, and Applications*. Boca Raton, FL: CRC Press; 2010. p. 315-52.
33. Ocete MA, Risco S, Zarzuelo A, Jimenez J. Pharmacological activity of the essential oil of *Bupleurum gibraltaricum*: anti-inflammatory activity and effects on isolated rat uteri. *Journal of ethnopharmacology*. 1989;25(3):305-13.
34. Kang GQ, Duan WG, Lin GS, Yu YP, Wang XY, Lu SZ. Synthesis of Bioactive Compounds from 3-Carene (II): Synthesis, Antifungal Activity and 3D-QSAR Study of (Z)- and (E)-3-Carene-5-One Oxime Sulfonates. *Molecules*. 2019;24(3).
35. Jeong J-G, et. al. Low concentration of 3-carene stimulates the differentiation of mouse osteoblastic MC3T3-E1 subclone 4 cells. *Phytotherapy Research*. 2007;22(1):18-22.
36. Kovac J, Simunovic K, Wu Z, Klancnik A, Bucar F, Zhang Q, et al. Antibiotic resistance modulation and modes of action of (-)-alpha-pinene in *Campylobacter jejuni*. *PLoS One*. 2015;10(4):e0122871.
37. Lee JH, Yang HY, Lee HS, Hong SK. Chemical composition and antimicrobial activity of essential oil from cones of *Pinus koraiensis*. *J Microbiol Biotechnol*. 2008;18(3):497-502.
38. Turkez H, Aydin E. In vitro assessment of cytogenetic and oxidative effects of alpha-pinene. *Toxicol Ind Health*. 2016;32(1):168-76.
39. Nam SY, Chung CK, Seo JH, Rah SY, Kim HM, Jeong HJ. The therapeutic efficacy of alpha-pinene in an experimental mouse model of allergic rhinitis. *Int Immunopharmacol*. 2014;23(1):273-82.
40. Li XJ, Yang YJ, Li YS, Zhang WK, Tang HB. alpha-Pinene, linalool, and 1-octanol contribute to the topical anti-inflammatory and analgesic activities of frankincense by inhibiting COX-2. *Journal of ethnopharmacology*. 2016;179:22-6.
41. Gil ML, Jimenez J, Ocete MA, Zarzuelo A, Cabo MM. Comparative study of different essential oils of *Bupleurum gibraltaricum* Lamarck. *Pharmazie*. 1989;44(4):284-7.
42. Falk AA, Hagberg MT, Lof AE, Wigaeus-Hjelm EM, Wang ZP. Uptake, distribution and elimination of alpha-pinene in man after exposure by inhalation. *Scand J Work Environ Health*. 1990;16(5):372-8.
43. Perry NS, Houghton PJ, Theobald A, Jenner P, Perry EK. In-vitro inhibition of human erythrocyte acetylcholinesterase by *salvia lavandulaefolia* essential oil and constituent terpenes. *J Pharm Pharmacol*. 2000;52(7):895-902.
44. Peana AT, Rubattu P, Piga GG, Fumagalli S, Boatto G, Pippia P, et al. Involvement of adenosine A1 and A2A receptors in (-)-linalool-induced antinociception. *Life Sci*. 2006;78(21):2471-4.
45. Guzman-Gutierrez SL, Bonilla-Jaime H, Gomez-Cansino R, Reyes-Chilpa R. Linalool and beta-pinene exert their antidepressant-like activity through the monoaminergic pathway. *Life Sci*. 2015;128:24-9.
46. Elisabetsky E, Marschner J, Souza DO. Effects of Linalool on glutamatergic system in the rat cerebral cortex. *Neurochem Res*. 1995;20(4):461-5.
47. Huo M, Cui X, Xue J, Chi G, Gao R, Deng X, et al. Anti-inflammatory effects of linalool in RAW 264.7 macrophages and lipopolysaccharide-induced lung injury model. *J Surg Res*. 2013;180(1):e47-54.
48. Russo E. *Handbook of Psychotropic Herbs: A Scientific Analysis of Herbal Remedies for Psychiatric Conditions*. Binghamton, NY.: Haworth Press; 2001.
49. Buchbauer G. Biological activities of essential oils. In: Baser K, Buchbauer, G., editor. *Handbook of Essential Oils: Science, Technology, and Applications*. Boca Raton, FL.: CRC Press; 2010.
50. Ramalho TR, Oliveira MT, Lima AL, Bezerra-Santos CR, Piuvezam MR. Gamma-Terpinene Modulates Acute Inflammatory Response in Mice. *Planta Med*. 2015;81(14):1248-54.
51. Chaves JS, Leal PC, Pianowsky L, Calixto JB. Pharmacokinetics and tissue distribution of the sesquiterpene alpha-humulene in mice. *Planta Med*. 2008;74(14):1678-83.
52. Jang HI, Rhee KJ, Eom YB. Antibacterial and antibiofilm effects of alpha-humulene against *Bacteroides fragilis*. *Can J Microbiol*. 2020;66(6):389-99.
53. Legault J, Pichette A. Potentiating effect of beta-caryophyllene on anticancer activity of alpha-humulene, isocaryophyllene and paclitaxel. *J Pharm Pharmacol*. 2007;59(12):1643-7.
54. Chandra M, Prakash O, Kumar R, Bachheti RK, Bhushan B, Kumar M, et al. beta-Selinene-Rich Essential Oils from the Parts of *Callicarpa macrophylla* and Their Antioxidant and Pharmacological Activities. *Medicines (Basel)*. 2017;4(3).