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Linalool: A mechanistic treatise

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Abstract

Researchers have been mainly emphasized on nutritional and functional bioactive moieties which have enormous health endorsing perspectives. Linalool is a bioactive component and utilized as a functional and nutraceutical tool in different foodstuffs. Linalool (3, 7-dimethyl-1,6-octadien-3-ol) is a volatile compound present in diverse plant tissues such as leaves, fruits and flowers, respectively. Linalool and its esters are the mostly used in perfumery substances, and the odour of (R)- and (S)-linalool known as lavender-like and petitgrain. Owing to their phytochemical profile, it prevents from the lipid oxidation and enhances the shelf life of the food. Linalool, a monoterpene alcohol is also present in essential oils of various medicinal plants along with diverse health promoting activities such as prevention from cancer insurgence, preventive role in diabetes complications, protection from microbial growth and inflammations. Besides, Linalool possesses several depressant effects on the central nervous system and literature elucidated the potential perspectives of linalool. Furthermore, health promoting potentials of linalool agaist various physiological threats like coronary atherosclerosis, alzheimer's disease, carcinogenesis, and aging processes are also the limelight of the article.

Keywords: Phytochemical, coriander, linalool, diet-based therapy, functional aspects

Brief overview

Phytochemicals were isolated from the plants which are prevalent in the human diet from the ancient times to curtail various human disorders. People are adopting the natural materials as diet-based therapy to cure various maladies. Researchers and scientists are diverting towards herbs and spices owing to their health promoting attributes used as natural food preservatives in many food-based products. Herbal medicines are becoming popular not only in developed but also in developing countries for health caring due to their extensive biological activities and safe status.[1]

Among different herbs, coriander (*coriandrum sativum* L.) has unique significance due to presence of essential bioactive compounds. It is fully enriched with diversified food constituents for instance; protein, fat, minerals, fibre, carbohydrates, and water.[2] Moreover, coriander seeds are promising source of beneficial phytonnutrients including geraniol, borneol, carvone, elemol, limonene, camphor, and linalool. The essential fatty oil contents were present as 0.03% to 2.6% and whilst fatty oil content ranged from 9.9% to 27.7%, respectively.[3,4] The coriander seeds are comprised of linalool which varied from 50% to 70%, as well as used in creams, perfumes, detergents, surfactants, emulsifiers, and lotions.[5] It also enriched with linalool (60-80%), terpinen-4-ol (trace-3%), γ-terpinene (1-8%), hydrocarbons; ketones (7-9%), and ρ-cymene (trace-3.5%), respectively.[6]

Linalool

Linalool is a volatile flavor compound which found in numerous plant tissues i.e. leaves, fruits, and more commonly in flowers (Figure 1). Linalool is isolated from the flowers, leaves, herbs, and wood and present in the oils of rosewood, petitgrain, jasmine, linaloe seed, rose, coriander, lavender, and bergamot. Linalool has two imperative forms generally known as R (-)-linalool (licareol)and S (π)-linalool (coriandrol) and these two forms varied in different plants depending upon nature and agro-climatic conditions. Linalool oil is extracted from the coriander seeds through steam distillation and further also quantified by gas chromatography-mass spectrometry. The coriander seeds properly smashed and soaked by using the ratio of two different solvent such as volume of deionized water (mL)) and the extractant (ethyl acetate and ether) as 1:7, respectively. After 4 hours distillation, the extractant was obtained which was pourly natural linalool.[7] Diederichsen and Hammer[8] determined that out of 1% essential oil, the major component of which is S-(+)-linalool (60-70%) whereas other minor active constituents are monoterpenes hydrocarbons viz. limpnene, α-pinene, γ- terpinene, camphor, citronellol, p-cymene, geraniol, borneol, and geraniol acetate, heterocyclic components like pyridine, pyrazine, furan, thiazole, and tetrahudrofuran derivatives, dihydrocoriandrin, coriandrin, coriandrons A-E, isocoumarins, neochidilide, pthlides, digustilide phenolic acids and sterols. It also passes the cytoplasmic membrane and cell wall, dislocates the structure of polysaccharides, fatty acids & phospholipids and permeabilizes them due to lipophilic nature.[9] In bacteria, the permeabilization of the membranes is associated reduction of membrane potential and loss of ions, depletion of the ATP pool and collapse of the proton pump.[9,10] Essential oils coagulate the cytoplasm and damage proteins and lipids. The damage to the cell wall and membrane can lead to the leakage of macromolecules and to lysis.[11] It is also used in preparation of perfumed hygiene products, cleaning agents i.e. detergents, soaps, shampoos, lotions, insecticides, and mosquito repellent.[7,12]

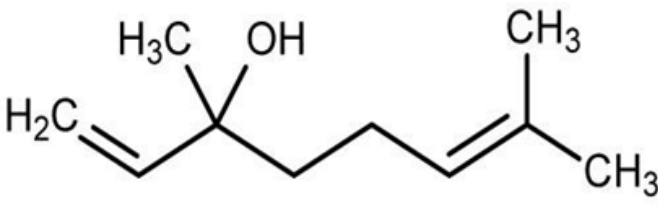

Figure 1 Chemical structure of linalool

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Health Perspectives

A summary of the health perspective of linalool can be see in Table 1.

Table 1 Health perspectives of linalool

Disorders	Mechanism	References
Cancer insurgence	Showed anticancer activity against human breast adenocarcinoma cells, amelanotic melanoma cells, HepG2, MCF-7 cells and renal cell adenocarcinoma cells-	17
	Induced rapid apoptosis via activating the p53 and cyclin-dependent kinase inhibitors.	18, 15
	Induced GADD45μ/JNK signaling pathway	19,20
	Exhibited anticancer activity against Burkitt lym-phoma cells P3HR1 and histiocytic lymphoma cells U937	16
Oxidative stress	Protected the cell membrane from the oxidative stress Enhanced the concentration of superoxide dismutase, and glutation peroxidase Stimulated the glucose utilization	21,22
Anti-diabetic	Suppressed the glucosidase and amylase activity Decreased the atherosclerotic index, and enhanced the cardio-protective index	24, 25
Hypercholesterolemia	Suppressed the low density liporpotein (LDL) oxidation Enhanced high density lipoprotein Incraesed the expression of HMGCR.	30
Antimicrobial	Showed antifungal activity against Mucor dimorphosphorus, Rhizopus azigosporum, Fusarium solani, Penicillium commune and Helicobacter pylori	33
	Exhibited the antibacterial activity against *Streptococcus haemolyticus*, *Staphylococcus aureus*, *B. subtilis* (gram-positive), *E. coli*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, and *Klebsiella species*.	35

Antitumor activity

Leukemia is associated with the prevalence of serious hematological malignancies.[13] There are multiplechemical therapies which have been used to cure the tumor incidences but on the other side long term survival after these therapies is very poor.[14,15] In this context, administration of bioactive polyphenols from medicinal plants are widely using to cure these malignancies. Among these compounds linalool is a significant source of coriander and has strong antileukematic activity against Burkitt lym-phoma cells P3HR1 and histiocytic lymphoma cells U937.[16] Multiple studies reported by different researchers, they investigated that linalool being anticancer agent has been found effective against different cancer lines such as human breast adenocarcinoma cells, amelanotic melanoma cells, HepG2, MCF-7 cells and renal cell adenocarcinoma cells by reversing doxorubicin resistance.[17] In human leukemia cells including including lymphoblastic leukemia (Molt-4, H- 9), myeloid leukemia (Kasumi-1, HL-60), and lymphoma (Raji), linalool administration (130μM) markedly induced rapid apoptosis via activating the p53 and cyclin-dependent kinase inhibitors.[15,18] Mechanistically, the activation of p53 tumor suppressor and cyclin-dependent kinase inhibitors (p27Kip1, p21Waf1, P57Kip2) that led to induce GADD45μ/JNK signaling pathway after linalool treatment. p53 has potential role to prevent from the inappropriate cell proliferation and maintain the genome integrity.[19,20]

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Oxidative Stress

It is imbalance between oxidation and antioxidants that produce the nitric oxide synthase activity, hydrogen peroxide in fasted rats due via reducing the concentrations of glutathione, mitochondrial GSH. Testes which are the source of fertility and heredity in male mammals are particularly sensitive feeding. Secretion of testosterone is impaired due to excessive oxidative stress and the degeneration of leydig cells.[21] The data from other studies also revealed that administration of linalool @ 120 mg/kg protected the cell membrane from the oxidative stress and enhanced the biochemical damage of reproductive organ such as testis via increasing the concentration of superoxide dismutase, and glutation Peroxidase (GSH-Px).[21,22]

Antidiabetic role

Being strong antidiabetic agent, linalool supplementation exhibited hypoglycemic activity in streptozotocin induced diabetic mice through multiple processes such as reduction of blood sugar, enhancement of glucose uptake and metabolism, and increment of insulin secretion by muscle**.** Linalool also lowered the concentrations of insulin resistance, triglycerides, low density lipoprotein and enhanced the high density lipoprotein and insulin. It also provides protection against cardiovascular, hyperlipidemia and other metabolic syndromes.[23] Linalool also stimulates the glucose utilization by peripheral tissues including muscle and adipose tissue, enhancing insulin signaling, decreasing hepatic glucose production, enhancing the glucose uptake, lowering the glucokinase activity and gluconeogenesis, enhancing increase glucose-6-phosphataseact, and suppressing the glucosidase and amylase activity in the gastrointestinal tract and inhibition of intestinal nutrient transporters such as intestinal Na-dependent glucose transporter 1 (SGLT1). Linalool also decreases the atherosclerotic index, and enhanced the cardioprotective index in rats.[24,25]

Hypercholesterolemia

Hypercholesterolemia is associated with the formation of atheromas after cholesterol buildup in the coronary arteries.[26] The earlier finings of Anum and Adera,[27] they determined that 10 mg/dl reduction in plasma cholesterol level lower the mortality rate of coronary heart disease up to 9%. The diet enriched with phytochemicals and fibers but free from the saturated fats can be reduced the concentration of cholesterol. The small aromatic terpenes from herbs and spices reduce the plasma cholesterol level by regulating 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) expression.[28,29]

Linalool suppresses the low density liporpotein (LDL) oxidation that increases the cholesterol uptake through macrophage scavenger receptors. The treatment of linalool to high fructose diet-HFD lowered the total plasma and LDL cholesterol level in hepatic lipid levels whereas enhanced the high density lipoprotein (HDL). The linalool in higher concentrations have been proven effective in reduction of plasma cholesterol levels in mice which was achieved via enhancing the expression of HMGCR.[30]

Antimicrobial activity

Scientists has focused the research regarding the utilization of phytochemicals which have antimicrobial characters instead of conventional food preservatives. More than 1340 plants exhibit the antimicrobial activity. Spices are promising source of essential oils and exhibited antimicrobial activity. The antmicrobial potential is mainly depend on the type of spice, composition and concentration, substrate composition, processing and food storage conditions.[31] Earlier, Hulin et al.[32] determined the antimicrobial character of purified essentials oils from spices variety of microorganism such as shigella. Linalool shows the antimicrobial potential against various microorganism outbreaks due to the interaction between phenolic compounds and the food matrix.

O'Mahony et al.[33] implicated that linalool showed antifungal activity against Mucor dimorphosphorus, Rhizopus azigosporum, Fusarium solani, Penicillium commune and Helicobacter pylori. The studies of different scientists[34] determined that linalool treatment exhibited the antimicrobial activity against *Escherichia coli, Candida albicans*, and *Staphylococcus aureus*. Similarly, Pattnaik et al.[35] investigated the antibacterial role of linalool against gram-positive bacteria and fungi. It also showed the antibacterial activity against eight different human pathogens gram-positive and gram-negative bacteria such as *Streptococcus haemolyticus*, *Staphylococcus aureus*, *B. subtilis* (gram-positive), *E. coli*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, and *Klebsiella species*. A study conducted by Lis-Balchin et al.[36] determined the effectiveness of linalool (500 ppm) against *Saccharomyces ludwigii, Salmonella enteriditis, Zygosaccharomyces bailii,* and *Listeria innocua*. The concentrations of coriander oil (less than 0.5% (vol/vol) observed the minimum inhibitory concentration (MIC) for *E. coli*, 0.23%; *S. aureus,* 0.4%, *Listeria monocytogenes,* 0.47%; and *S. cerevisiae* 0.13%.[37]

Antinociceptive effects

In experimental volunteers, linalool has been found to exert strong anti-inflammatory and antinociceptive activity. The supplementation of linalool in rats suppresses the carrageenan-induced oedema and lowers pain responses by different stimulus such as hot plate, l-glutamate, hyperalgesia, formalin injection, acetic acid-induced, and prostaglandin E2 (PGE2). Linalool antinociceptive activity is related to the positive interference with opioid, muscarinic, and dopaminergic transmission as well as also exhibited local anaesthetic activity and antioxidant perspectives.[38] The intraplantar injection of carrageenan and formalin cause the production and release of nitric oxide (NO) at the injured side.[39,40]

Linalool suppresses voltage-gated currents

Linalool affects the human brain beta wave and shows an inhibitory effect on glutamatergic neurons in the rat cerebral cortex.[41] Olfactory receptor cells (ORCs) convey chemosensory information to the olfactory bulb, and express various types of ionic channels such as voltage-gated Na^{+}, Ca^{+2} and K^{+} channels on their somatic membrane. The deodorants including amyl acetate, acetophenone, and limonene have lower lipid solubility than linalool. The ionic channels are affected by interacting with the lipids of somatic membranes. Indeed, those odorants block not only voltage-gated channels but also ligand-gated channels such as glutamate-gated channels and cyclic nucleotide-gated channels. Linalool suppresses various types of voltage-gated currents in retinal neurons. These observations are similar to the action of odorants on the ligand-gated currents in ORCs and retinal neurons.[42]

Miscellaneous properties

Being a potent anitinflammatory agent, linalool has been found to cure acute and chronic variety of ailments due to the presence of content of alcohols and its corresponding ester (linalyl acetate). Likewise, linalool, terpenes and terpenoids markedly increased the permeability of number of drugs through biological tissues like mucus membranes or skin. Many authors reported the data on anti-inflammatory role of linalool against several human disoerders.[43]

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In developing countries, massive population is suffering from anxiety disorders and preventing herself from these stress by consuming high cost medicines. Moreover, Furthermore, anxiolytic drugs are using to cure the anxiety as well as also creating problems. To resolve these problems, researchers are diverting their attention to use alternative therapies to cure chronic pain, depression and anxiety. Linalool as essential oils has been shown as effectual agent in humans and animals to lower the anxiety-related behavior.[44] It also induces hypothermia, reduces ambulation and increases pentobarbital-induced sleep time in mice.[45]

In vivo, linalool blockade of intracerebroventricular quinolinic acid-induced convulsions and *in vitro* (competitive antagonism of L-[3H] glutamate binding) through modulating the glutamate activation expression.[46] Linalool also showed the anesthetic activity and spasmolytic effect on the nicotinic receptor-ion channel. Additionally, it markedly impaired the behavioural expression of PTZ-kindling, although not modifying the associated increase in L-[3H] glutamate binding in cortical membranes.[47]

Conclusion

Interference in the territory of nutraceutical and functional foods mainly focused on detection and isolation of bioactive moities from plant origin that hold therapeutic prospectives. Recently, linalool has been highlighted in assorted systematic researches, probing its therauptic potential to authorize its remedial significance. Scientific investigations in the era of sustenance led to the detection of phenomena accredited for occurrence and pathogenesis of numerous health disparities. Importance of natural products revitalized currently to alleviate such maladies. Linalool holds a promising place as it possesses valuable health-promoting benefits due to antioxidant, anticarcinogenic, antiinflammatory, antibacterial, and antidiabetic properties. Nevertheless, there are adequate evidences in favor of medicinal significance of linalool, but needs further interest from scientists to explore its health endorsing aspects for strengthening the claims as natural theraupatic stimulant.

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