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Toxicological aspects and pharmaco-therapeutic properties of linalool, a natural terpene derivative of essential oils: *Literature studies*

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Abstract

Essential oils are bioactive ingredients extracted from aromatic plants by distillation. The terpene derivatives present or extracted from these essential oils are considered in a double way, on the one hand as a support for pharmacological activities demonstrated from essential oils, on the other hand as natural biomolecules with high therapeutic potential. These are therefore natural substances or molecules, which have an important reservoir for preventing or treating many organic and functional disorders. We looked at one of these terpene derivatives, linalool, to identify and analyze the bibliographic data available and establish a balance sheet on the therapeutic, nutritional, cosmetic and environmental interests and benefit of this natural biomolecule.

Keywords: VOCs, (FOCs), linalool, pharmacology, toxicology, terpenes, risk/benefit

1. Introduction

From the beginning of human civilizations to the present day, plants have always been part of the regular and well-adjusted use of humans, which were based on observations of their harmful and beneficial effects and the adaptation of their use for care or to improve their well-being. The essences of the plants are natural aromatic substances resulting from the metabolism of the plant and which constitute a whole chemical group of various structures and multiple and varied biological effects. These are secondary metabolites produced by the plant and emitted into the environment in the form of terpene derivatives. Their role is above all to contribute to the functioning of the plant in its defense but also in its communication with the environment of the surrounding ecosystem. Their uses in humans are very old, dating back to the time of ancient Egypt, the Persian Empire, the Arab-Muslim civilization (Avicenna) before becoming very popular and used in the West (Paracelsus). Among the terpene derivatives of these essential oils, mention may be made of linalool which is very well known. These derivatives, which seem to be the supports of the activities observed, continue to challenge the scientific community on the report of their beneficial effects and their harmful effects. Within the framework of this article, we had established a state of the art on the existing bibliographic data to try to draw some open conclusions on this terpene derivative quite frequent and known in the field of aromas, food and care by the aromatherapy.

2. Physico-chemical properties

Linalool belongs to the family of monoterpene alcohols of general gross formula: $C_{10}H_{18}O$. It is also called linalyl alcohol and its INN is 3,7-dimethylocta-1,6-dien-3-ol. It has a molar mass of 154.25 g / mol. Its boiling temperature is around 198 °C and its flash point is 75 °C. [1]

Linalool has already been studied and examined; it is a plant metabolite resulting from biosynthesis in several aromatic and essential plants. It is the main source of production of linalool. At the industrial level, the production of synthetic linalool is estimated at around 12,000 tonnes / year, more than 95% of which is used for its qualities in perfumery and odorants in cosmetics, soaps, perfumes, household cleaners, etc. Linalool (3,7-dimethyl-1,6-octadiene-3-ol), which is an acyclic monoterpene tertiary alcohol, constitutes one of the main floral aromas of nature [2]. In terms of its structure and due to the chiral properties, two enantiomers of linalool are synthesized in plants:

(3*S*) - (+) -linalool (coriandrol) and (3*R*) - (–) - linalool (licareol). In olfactory terms, the intensity of the odor of the (*S*) -linalool form is approximately nine times stronger than that of

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the (*R*) – form (. In certain plant products (passion fruit, apricots), linalool is present in form of racemate [3]. The racemate is also a product resulting from the fermentation processes during the manufacture of food products and during the isolation of essential oils according to the extraction technique [4].

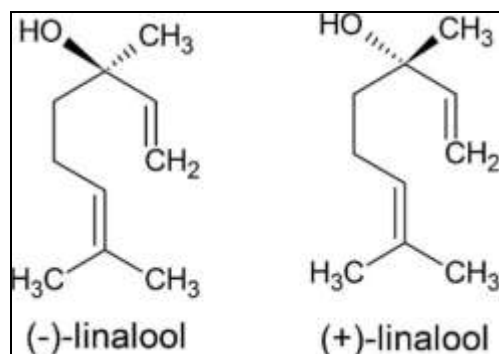


Fig 1: The enantiomers of linalool

In the perfume sector, linalool, mainly of synthetic origin, is an important fragrant ingredient widely used. It is found in 60 to 90% of cosmetic products (body lotions, shampoos, shower gels, soaps, hair spray, creams, deodorant [5]. It is also added to household detergents, furniture care products, waxes, as well as processed foods and beverages, as a fragrance and flavoring agent.

3. Linalool in nature

Linalool is found in the essential oils of more than 200 species of monocotyledonous and dicotyledonous plants, belonging to different families (more than 50% of plant families) widely distributed from tropical to boreal regions (see Table 1). In particular, many plants of the families Lamiaceae, Lauraceae and Rutaceae produce (*R*) - (-)- or (*S*)-(+)-linalool in significant quantities. Rosewood oil is the main source of (*R*) - (-)-linalool (90% and more) [6] while coriander oil contains significant levels of (*S*) - (+) -linalool [7]. In addition, certain groups of fungi produce this monoterpene alcohol. (*R*) - (-) - Linalool is most common in nature

Table 1: Main natural sources of essential oils from linalool plants [8]

Essential oil	Botanical Source	Linalool content (%), characteristic enantiomer
Rosewood, rosewood	<i>Aniba rosaedora</i> Ducke wood, Lauraceae	about 100; (<i>R</i>) - (-)
Ho leaf	<i>Cinnamomum camphora</i> Nees & Eberm var. <i>linaloolifera</i> , Lauraceae	66-95; (<i>R</i>) - (-)
Ho (China) = Shiu (Japan, Taiwan)	Wood of <i>Cinnamomum camphora</i> Nees & Eberm var. <i>linaloolifera</i> , Lauraceae	90; <i>R</i> - (-)
Orthodon oil	Aerial parts of <i>Orthodon linalooliferum</i> Fujita, Lamiaceae	82; <i>S</i> - (+)
Coriander	Fruits of <i>Coriandrum sativum</i> L., Apiaceae	45-85; <i>S</i> - (+)
Lavender	The flowering peaks of <i>Lavandula officinalis</i> Chaix sin. <i>L. angustifolia</i> Mill., Lamiaceae	25-38; (<i>R</i>) - (-)
Lavender spike	The flowering tops of <i>Lavandula latifolia</i> (DC) Vill., Lamiaceae	19-48; (<i>R</i>) - (-)
Linaloe (Mexican lavender, or Indian lavender)	Wood of <i>Bursera delpechiana</i> Poiss e.g. Angl, <i>Bursera</i> spp., Burseraceae	30; (<i>R</i>) - (-)
Bushy lippia	Leaves of <i>Lippia alba</i> (Mill.) NEBr. ex Britton and P. Wilson, Verbenaceae	65; <i>S</i> - (+)
Winged thorn ash	<i>Zanthoxylum alatum</i> Roxb., Rutaceae seeds	71; ND
Sweet basil	<i>Ocimum basilicum</i> L., Lamiaceae leaves	26-50; (<i>R</i>) - (-)
Sacred basil (tulsi)	<i>Ocimum sanctum</i> L., Lamiaceae leaves	26; <i>S</i> - (+)
Ash basil	<i>Ocimum canum</i> Sims leaves, Lamiaceae	25; <i>S</i> - (+)
Ylang ylang	Flowers of <i>Cananga odorata</i> (Lam.) Crochet f. & Thomson forma genuina, Annonaceae	15-24; (<i>R</i>) - (-)
Neroli	<i>Citrus aurantium</i> L. flower, Rutaceae, bitter orange	28-40; (<i>R</i>) - (-)
Sweet orange	Flowers of <i>Citrus sinensis</i> Osbeck, Rutaceae	15-32; <i>S</i> - (+)
Sweet marjoram	Aerial parts of <i>Origanum majorana</i> L., Lamiaceae	30-40; <i>S</i> - (+)
Petitgrain oils with bitter orange	Leaves and twigs of <i>Citrus aurantium</i> L., Rutaceae	>27; <i>S</i> - (+)
Clary sage	Aerial parts of <i>Salvia sclarea</i> L., Lamiaceae	10-21; racemate
Laurel	Leaves of <i>Laurus nobilis</i> L., Lamiaceae	16; (<i>R</i>) - (-)

4. Biosynthesis

Linalool is biosynthesized in floral and non-floral tissues from isopentenyl pyrophosphate (IPP) and its isomer, dimethylallyl diphosphate (DMAPP). The two units IPP and DMAPP are generated by the 2-methylerythritol-4-phosphate (MEP) pathway in plants, from pyruvate and glyceraldehyde 3-phosphate (GA-3P), via deoxy-d-xylulose 5-phosphate (DOXP). The condensation of one molecule of each compound, IPP and DMAPP, leads to the formation of a

geranyl diphosphate (GPP), the universal precursor of monoterpenes. GPP is a substrate for linalool synthases (LIS and R-LIS), monoterpenes synthases. At the same time, linalool, like many other terpenoids, can be produced in minor biosynthetic pathways as byproducts of other processes such as the biosynthesis of geraniol and nerol. In plants, linalool accumulates in the compartmentalized secretory structures of glandular trichomes.

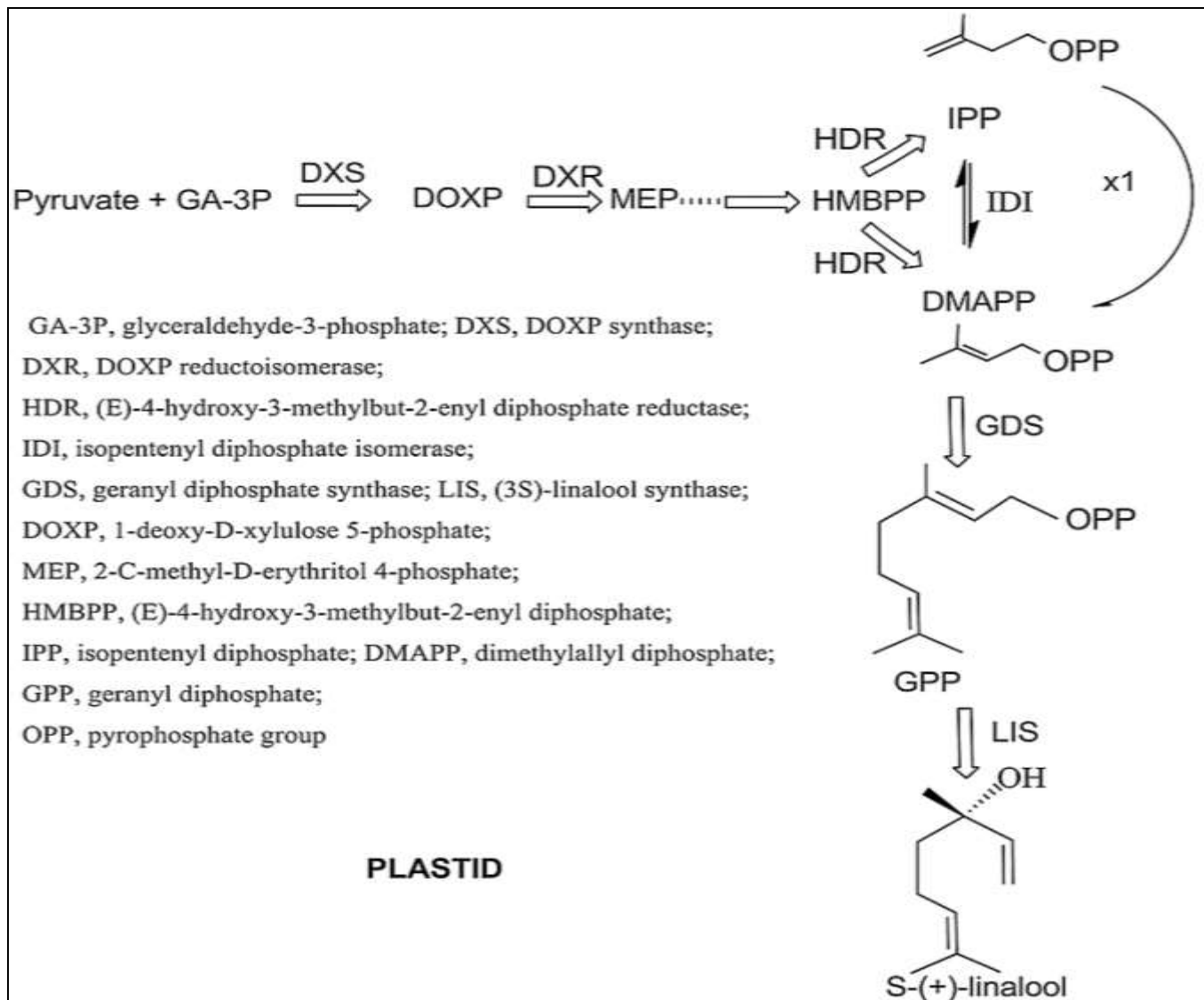


Fig 2: Aprotosoiae AC *et al.*, [8a]

Linalool is therefore synthesized naturally by the plant as follows: [8b]

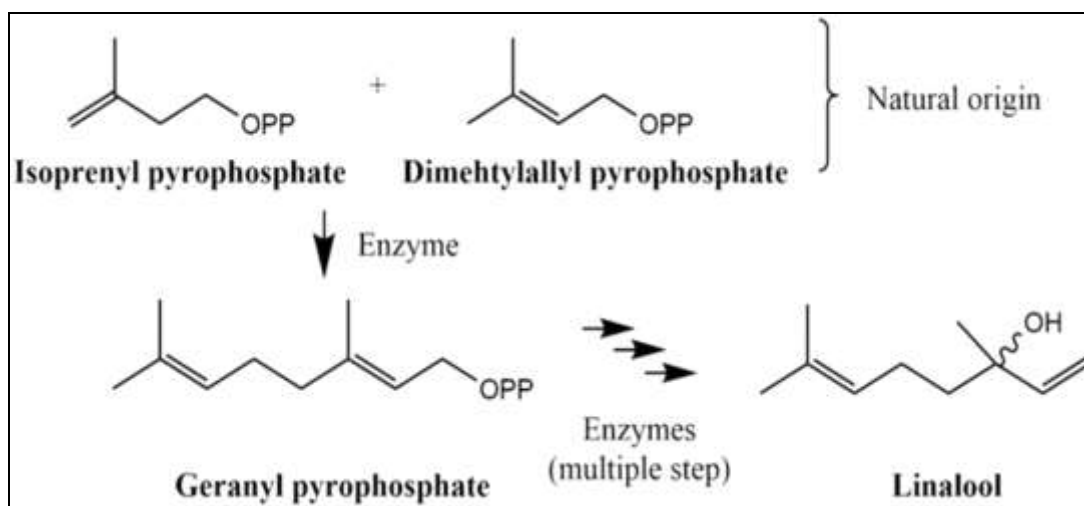


Fig 3: Biosynthetic pathway for linalool

Linalool can be produced by several laboratory methods. One of these methods uses camphene (which is generally produced by pinenes, isolated from essential oils or turpentine) [19].

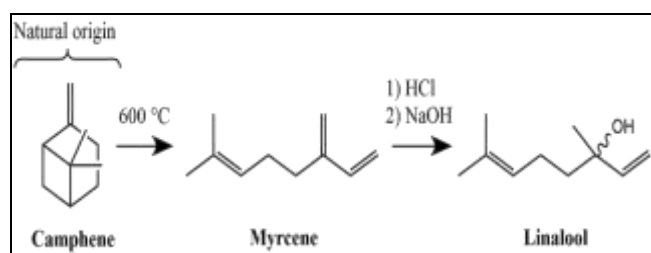


Fig 4: Synthesis of linalool from camphene

5. Synthetic linalool

In addition to natural sources, linalool is obtained by semi-synthesis from α -, β -pinene or other terpenes (geraniol, nerol, myrcene) and also by organic synthesis via 2-methyl-2-heptene-6-one [10].

Synthetic linalool contains traces of dihydrolinalool and dehydrolinalool) [11, 12]. In addition, there may be chlorine impurities present, which give a metallic character to the smell of linalool [13].

Another method uses compounds produced strictly from petroleum products [14].

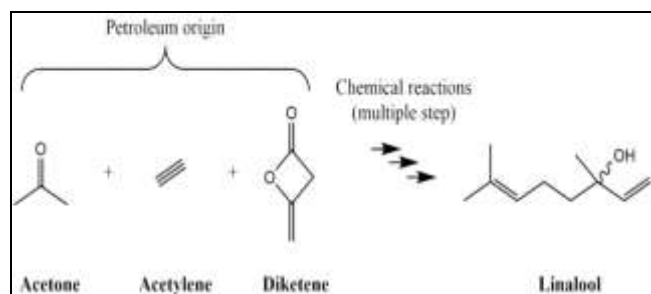


Fig 5: Synthesis of linalool from petroleum

5.1 Metabolism

Studies in rodents using carbon-14 labeled linalool (500 mg / kg bw) have shown that it is rapidly absorbed from the intestinal tract after oral or gavage administration [15]. In humans and animals, after absorption, linalool is rapidly metabolized in the liver to polar compounds, which are mainly excreted in the urine in free or conjugated form and in the majority under metabolites excreted in the feces. The main metabolic pathway of linalool involves conjugation with glucuronic acid. In the case of repeated administration, allylic oxidation becomes an important metabolic pathway, mediated by the cytochrome P-450. 8-hydroxy- and 8-carboxy-linalool, α -terpineol, geraniol and nerol have been detected as major metabolites after 20 days of administration of 800 mg linalool / kg bw / day. These metabolites are also excreted in the urine in free or conjugated form. Linalool reduction products (dihydro-, tetrahydrolinalole) have also been identified in the urine of rodents. A significant proportion of oral linalool follows intermediate metabolic pathways and is eliminated in the expired air in the form of CO₂ [16].

5.2 Toxicological data

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) have established an Acceptable Daily Intake (ADI) of 0-0.5 mg/kg bodyweight/day for linalool. Repeat dose dermal toxicity studies have been conducted to determine a NOAEL (No Observable Adverse Effect Level:

Highest dose at which there was not an observed toxic or adverse effect.) value of 250 mg/kg bw/day for linalool, while the LOAEL (Lowest dose at which there was an observed toxic or adverse effect) is 1000 mg/kg bw/day. After oral exposure, the NOAEL value is 50 mg/kg bw/day [17/18]. Toxicity and dermo-toxicity studies have been carried out by a panel of experts who have shown and achieved the non-toxicity of linalool at doses of its use in cosmetic preparations [19].

In *in vitro* tests, linalool showed no mutagenicity or genotoxicity. There are no long-term studies related to the carcinogenicity of linalool. Given the absence of genotoxic effect, the absence of chemical structural elements conferring a carcinogenic risk, as well as high NOAEL values in toxicity studies, linalool presents no risk of carcinogenicity under the conditions of current use. Data on reproductive toxicity and developmental toxicity give no indication of possible reprotoxic effects [8, 17].

According to the OECD report (CAS Number 78-70-6 2002) [20] and the reports on the evaluation of the use of linalool as an ingredient, carried out by the resource center for the evaluation of safety of perfumery materials (2015):

- Linalool has an LD₅₀; following an acute oral administration of the order of 3000 mg / kg of body weight and of 2000 mg / kg following a cutaneous administration.
- Linalool is not mutagenic and does not have immunotoxicity or genotoxicity. Dermatological studies in humans show that linalool and linalyl esters are not phototoxic [18].

In humans, linalool, at concentrations up to 20%, has not been shown to be a sensitizer. It is not phototoxic or photo-allergenic in human tests. Natural linalool can rarely cause allergic contact dermatitis and is not genotoxic [19].

In a multicenter clinical study [21], 2,900 consecutive dermatitis patients in nine test centers were tested with purified oxidized linalool. The positive reaction rate for oxidized linalool was 6.9%, of which 34% were men, and 66% were women. The patch tests were recently used in a multicenter study in the United Kingdom, which showed that 5.9 % of the patients tested had a positive patch with oxidized purified linalool (linalool hydroperoxides 1.0 %) [22]. These multicenter studies, as well as previous studies on patch tests, show that purified oxidized linalool is the cause of contact allergy in patients with dermatitis. Other studies have also used patches with oxidized lavender oil and have found no contact allergy reactions in patients [23].

In animals: purified linalool can cause irritating effects on rabbit skin. Repeated application to sheep skin has also produced signs comparable to acanthosis. According to FAO / WHO, no safety concerns at current levels of exposure when used as a flavoring agent and at recommended doses. The ADI, between 0-0.5 mg / kg bw for citral, geranyl acetate, citronellol, linalol and linalyl acetate, expressed in citral, was maintained at the fifty-first (TRS 891/90, 1998) and sixty-first (SRT for JECFA 61).

A distinction should be made between synthetic linalool chemically designed by industry for the manufacture of products such as washing powder or deodorants, and that which is naturally found in aromatic plants. Linalool, in particular synthetic, is considered as potentially allergenic by European legislators in the context of the harmonization of the European Cosmetics Directive [22]. It should be emphasized that it is not linalool itself which is involved in these allergy

phenomena but rather its metabolites after their oxidation in contact with the ambient air ^[23-24]. In a study of 1,511 dermatitis patients who came into contact with a patch containing oxidized linalool, 1.3% of dermatitis patients triggered an allergic response ^[25]. More recently, a study on patients also suffering from dermatitis has shown that concentrations greater than 6% of oxidized linalool have caused allergic reactions in 5 to 7% of test subjects ^[21, 25].

6. Environment

Linalool is a colorless liquid with a spicy herbal smell. It is used, in purified or synthetic form, as a component in perfumes, cosmetics, soaps and detergents and as a flavoring agent in food. It is also used as a synthetic intermediate. It is registered for use as a pesticide in the United States, but uses approved for pesticides may change from time to time, so federal, state, and local authorities in the United States should be consulted for uses that are approved for specific use.

6.1 Environment air

Most of the linalool, both natural and synthetic, is released into the atmosphere, where it is rapidly degraded. Linalool has a half-life of less than 30 minutes ^[27]. Purified linalool is an alcohol containing an unsaturated allylic fraction which predisposes to auto-oxidation, favored by atmospheric exposure. The concentration of linalool, the test system, the initiator of oxidative reactions and the auto-oxidation potential of linalool are some of the variables that influence the final result. Air-oxidized linalool mainly transforms into linalool hydroperoxides ^[28]. Natural linalool is found in the essential oils of many aromatic plants in a mixture, and is found in many other fruits such as apples, citrus fruits, grapes and others. The emission into the air of this natural form of linalool by plants, at a vapor pressure of 0.159 mm Hg at 23.5 °C, indicates that linalool has always existed naturally in the form of vapor in the atmosphere. Linalool in the vapor phase will be degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals ^[29]. Linalool is also degraded in the atmosphere by reaction with the ozone and nitrates radicals ^[30]. The nitrate radical is the dominant atmospheric oxidant at night in most atmospheric environments; therefore, nighttime degradation appears to be a major fate in linalool. Linalool does not absorb at wavelengths > 290 nm and therefore should not be sensitive to direct photolysis by sunlight. If released into the soil, linalool should have high mobility based on an estimated. ^[31].

6.2 Aquatic environment

The production and industrial use of purified linalool as an ingredient in perfumes, cosmetics, soaps and detergents and as a flavoring agent in food and a synthetic intermediate can lead to its release into the environment by various waste streams. In the aquatic compartment, linalool is easily biodegraded and not bioaccumulative. Its use as a pesticide also results in its direct release into the environment. In acute aquatic ecotoxicity tests, Linalool has very low toxicity to fish, algae and daphnia.

7. Biological and pharmacological activity

Linalool is one of the most studied odor molecules. Many works have been published reporting different biological activities for linalool (see Table 2). Most research has been carried out *in vitro* or *in vivo* using various routes of administration, clinical studies on linalool are fewer but demonstrate its effectiveness in humans. The chirality of

linalool determines not only the sensory character, but also the biological and pharmacokinetic properties ^[8], ^[32] and above all the notable and significant effects on the functioning of the system nervous ^[33]. The census of most of the studies shows a fairly broad bioactivity profile and fairly reliable data on efficacy.

7.1 Bioactivity on the CNS

7.1.1 Sedative activity

Lavender, a plant rich in linalool, is one of the oldest remedies that man has used in various forms (massage, aromatherapy, medicinal baths) for the soothing and relaxing effect with the reduction of nervous tension and sleep induction. The sedative activity of lavender essential oil seems to be based on linalool, (linalool (*R*)-, (*S*)-enantiomers, racemate) and has been evaluated in various experimental models and clinical trials ^[34]. In animals pretreated with caffeine administered intraperitoneally (ip), the sedation produced by inhalation of lavender essential oil was even more pronounced than that of the controls. The sedative activity of linalool depends on the dose, with an increase in sleep time and a reduction in spontaneous locomotion, without affecting motor skills. In addition, linalool and lavender essential oil exhibit behavioral effects similar to those of sedative substances by decreasing sympathetic nerve activity and increasing parasympathetic nervous activity ^[35]. Gaston and his collaborators have highlighted the sedative effects of *Coriandrum sativum* essential oil and Linalool in chicks ^[36]. In humans, inhalation of lavender essential oil and (*R*) - - linalool causes sedation, relaxation and improves sleep ^[37-38]. It has also been shown in animals that inhaling linalool improves social interaction behavior and reduces aggressive behavior ^[39-42]. Work by Kuroda *et al.* have highlighted the sedative effects of (*R*)-linalool via an effect on the autonomic nervous system and mood states ^[43, 44].

7.1.2 Anxiolytic activity

Anxiety disorders are the most widespread and frequently encountered mental problems in modern societies. They affect more than 20% of the world population and 14% of that of Europe ^[45]. In folk medicine, lavender and its essential oil are among the most popular anxiolytic phytotherapies ^[46]. Various preclinical studies in mice, rats, and Mongolian gerbils have demonstrated anxiolytic effects induced by lavender oil. The activity profile of lavender oil, particularly in chronic administration, is similar to that of diazepam or close to that of chlordiazepoxide, well-known anxiolytic reference molecules. The anxiolytic effects depend on the dose and also depend on the exposure time (in case of inhalation). Very high doses of lavender essential oil and a fairly long exposure time can cause sedative activity and possible alteration in locomotor activity. In mice, inhaling 3% linalool for one hour increases social interaction and decreases aggressive behavior ^[39-42, 47].

Little is known about the molecular mechanisms underlying these psychotropic activities of linalool, but some studies have shown that these effects are linked to an inhibitory action on glutamate receptors ^[22-23] and a potentiation of Gamma Amino-Butyric Acid, GABA_A receptors ^[48-49]. It has been shown that processes such as sedation and anxiety are mediated by different configurations of GABA ^[50-51]. Some authors have indicated that the anxiolytic effects observed are linked more to the action of linalool essential oils on serotonergic receptors than on those of GABA ^[52, 35]. Researchers have shown that lavender oil (rich in linalool)

exerts its anxiolytic effects via the modulation of voltage-dependent calcium channels [53, 54].

Linalool, one of the main bioactive constituents of *Lavandula* essential oil, is said to support antimicrobial, anticholinesterase and antioxidant activities [55-58]. *Lavandula* oil thus promotes the healing symptoms of stress, exhaustion, migraines, anxiety, insomnia and depression [33, 59-61].

Neuroprotective effects have been demonstrated with a decrease in lipid peroxidation and oxidative damage, an anti-inflammatory effect and an antidepressant and anxiolytic effect interacting with the GABA_A receptor complex by increasing its release, an inhibitory effect on the release of glutamate (antagonism with N-Methyl-D-aspartic acid « NMDA») and modulation of monoamine neuromediators [34, 62].

7.1.3 Anticonvulsant activity

Epileptic disorders are recurrent chronic conditions resulting from excessive neuronal activity. The potential for inhibition of neuronal excitability by linalool or lavender oil has been demonstrated in the context of research into their anticonvulsant activity [63]. Lavender acts in the control of crises: by inhibiting their appearance, by reducing their duration and by decreasing the intensity of the convulsive crisis. In addition, from an ethnomedical point of view, the epileptic crisis being assimilated to a diabolical crisis, lavender is considered as an "anti-diabolic" plant since it alleviates the crisis and frees the patient from his crisis. On the experimental level, linalool, tested mainly in the form of a racemate, has proved effective in various experimental models of seizures induced in animals [64]. Administration of linalool protects against attacks induced by picrotoxin, quinolinic acid, pentylentetrazol and delays the onset of NMDA-induced seizures. In mice, lavender essential oil increases the latency of pentylentetrazol-induced seizures as well as the percentage of survival [65]. The mechanism of action, demonstrated *in vitro* and *in vivo*, mainly involves a dose-dependent antagonistic interaction with the glutamatergic NMDA receptors, which play an important role in the genesis and propagation of convulsions. Other mechanisms that could be involved in the anticonvulsant effect of linalool are changes in the kinetics of the ion channel of the nicotinic receptor, blockage of calcium channels and inhibition of the release of acetylcholine. For anxiolytic effects, other studies have shown that the (*R*)-(-)-linalool form is more active than the (*S*)-(+)-enantiomer [65]. The effects observed appeared to be comparable to those of known anticonvulsants (diazepam, phenytoin) [66]. Studies have also demonstrated the involvement of GABA_A receptors in therapy for anticonvulsant and sedative agents [67-68] and as GABA_A receptors are modulated allosterically by monoterpenes, such as linalool, these binders could explain the anticonvulsant effects observed [69].

7.1.4 Local anesthetic activity

Linalool and lavender essential oil have local anesthetic activity *in vivo* and *in vitro* [70]. Linalool reversibly and dependently blocks the concentration, excitability and conductivity of all types of myelinated fibers of the sciatic nerve. The local anesthetic properties of linalool are linked to its effects on nicotinic receptors, mainly to its ability to modify their kinetics, to inhibit the release of acetylcholine but also to block the action potential [71]. Linalool inhibits nervous excitability by affecting the conductance of sodium. Inhibition of the Na⁺ current is probably the mechanism of

action by which linalool blocks the action potential. Furthermore, Jirovetz *et al.* [72] suggested that a modification of the properties of the membrane of nerve cells by certain volatile constituents could be due to their membrane accumulation and to the steric blockage of ion channels.

7.1.5 Analgesic activity

(*R*)-(-)-Linalool is one of the most studied monoterpenoids in terms of analgesic activity. The inhibitory effect on neuronal activity and the calming effect of stress facilitate the expression of analgesic properties. In addition, linalool develops anti-allodynic effects. Most of the data on the analgesic properties of linalool have been obtained from various experimental nociceptive models using the (*R*)-form. According to the literature, few clinical trials have been carried out to assess this effect [73], recent work has demonstrated the alleviation of migraine pain in humans during a randomized study [74]. Different routes of administration (systemic, oral, intraplant, intrathecal) and different doses of (*R*)-(-)-linalool (25-200 mg / kg) in rats or mice, reduce the pain response to various nociceptive stimuli (acetic acid, high temperatures, formaldehyde), inhibit carrageenan-induced edema; and also relieve hyperalgesia induced by l-glutamate, PGE 2, carrageenan and pro-inflammatory cytokines [75]. (*R*)-(-)-Linalool (50-200 mg / kg, ip) decreases the mechanical hypersensitivity induced in a model of neuropathic pain, as well as the mechanical hypersensitivity at low temperature in a model of chronic inflammation without cause tolerance [76]. Anti-allodynic activity has also been demonstrated for the linalool racemate (intraplant, 10 µg / paw) in the management of neuropathic pain induced mechanically by partial ligation of the sciatic nerve. In addition, linalool improves the anti-allodynic activity of morphine, which is an encouraging fact since neuropathic pain is often resistant to opioids. [77].

7.1.6 Anti-inflammatory activity

In various experimental models of inflammation, linalool acts anti-edematously, limiting the inflammatory response and its related histological changes [76]. *In vitro*, (*R*)-(-)-linalool significantly and dose-dependent inhibits the production induced by the lipopolysaccharides of the cytokines TNF-α and IL-6 [78]. In addition, in animal studies, it has been shown that (*R*)-(-)-linalool and racemate cause significant inhibition of carrageenan-induced edema, but the kinetics of the effect are different depending on dose and enantiomer. The mechanisms suggested by *in-vitro* and *in-vivo* studies show that (*R*)-(-)-linalool can act by inhibiting the production of inflammatory cytokines by blocking the NF-κB and MAPK pathways, by antagonizing the NMDA effects and reducing synthesis or release of NO [79].

7.1.7 Antitumor activity

Linalool exhibits high cytotoxicity on circulating tumor cells as well as antiproliferative activity against a broad spectrum of carcinoma cells including human mammary adenocarcinoma cells with multiple drug resistance [80]. In hematopoietic tumors, linalool does not affect the development of normal hematopoietic cells when exposed to cytotoxic concentrations (130 µm), and even to higher concentrations (650 µm) [81]. As an anti-tumor agent, linalool activates the tumor suppressor protein p53 and certain inhibitors of cyclin-dependent kinase (CDKI) [82]. Another possible target for linalool is mitochondria [83]. In addition, linalool can increase the anti-tumor activity of doxorubicin,

possibly by promoting the influx of doxorubicin into cells. However, the anti-tumor potential of linalool is limited due to the high doses required *in vivo* [84-85].

Coriander oil very rich in linalool, seems to be at the origin of anticancer activities with an increase in the level of toxic H₂O₂ (via an improvement in SOD activity), leading to an induction of the arrest of the cell cycle, DNA strand breakage and inhibition of cancer metastases, and increased expression of the p53 tumor suppressor, improving cell cycle arrest [62, 86].

7.1.8 Cholesterol-lowering activity

Oral administration of linalool in mice reduces plasma levels of total cholesterol, LDL-cholesterol and triglycerides [87]. In HepG2 cells of the human hepatoma, linalool decreases, the concentration of cellular cholesterol and triglycerides. The molecular mechanisms of cholesterol-lowering effects involve both the suppression of the transcription of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) by reducing the expression of proteins binding the regulatory elements of sterol and the acceleration of ubiquitin-dependent degradation [53].

7.1.9 Antibacterial, antifungal, and acaricidal activity [89]

At concentrations of 0.1% (v / v), linalool exhibits antimicrobial activity against various microorganisms (*Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pasteurella multocida*, *Saccharomyces cerevisiae*) more effective against Gram-positive bacteria than Gram-negative bacteria [90]. Its antibacterial activity has been attributed to the functional destabilization of the bacterial membrane and to an increase in the sensitivity of the bacterial strains to conventional antimicrobial agents. Remarkable activity has been demonstrated for linalool against periodontopathic and cariogenic bacteria, the minimum inhibitory concentration and the minimum bactericidal concentration values ranging from 0.1 to 1.6 mg / ml. However, due to the cytotoxic effects on the oral epithelial carcinoma (KB cells) cell line, the incorporation of linalool in oral hygiene products should be carried out at concentrations below 0.4 mg / ml. [91]. The work of de Kim *et al.*, 2003 [92] highlighted the acaricidal effects of monoterpenes in essential oils including linalool on mites (*Thyrophagus putrescentiae*)

7.1.10 Antioxidant activity

Linalool mainly acts as an anti-lipoperoxidizing agent. The antioxidant activity is greater in the case of essential oils

containing linalool, most probably due to a synergy between the active compounds. Thus, lavender essential oil has a powerful antioxidant activity expressed in particular in the trapping capacities of free radicals. Linalool protects the guinea pig brain tissue against oxidative stress induced by hydrogen peroxide, its effects are similar to those presented by lipoic acid and vitamin E [72, 93-95].

7.1.11 Broncho-spasmolytic and anti-asthmatic effect

Linalool acts as a spasmolytic agent on the intestinal and tracheal smooth muscles. The mechanism, probably induced by an increase in cAMP, is the result of the stimulation of the enzyme adenylate cyclase. The intestinal muscles are more sensitive to linalool [96-99].

7.1.12 Environmental use

According to Kırarak S. *et al.*, 2018 [100], linalool constitutes one of the main compounds of essential oils of the *Lavandula* species which are used in the food industry as a flavoring agent, preservative additives for cosmetics and in the industry of perfumery, including soaps, eau de toilette, perfumes, skin lotions [43,101-103]. Lavandin essential oil is commonly used in hygiene products, industrial and household cleaners, detergents and insecticides due to its high content of linalool and linalyl acetate and camphor [57, 104]. In addition, lavender essential oil is produced with higher yields than lavender essential oil (120 kg / ha, 40 kg / ha, respectively) [104-106].

7.1.13 Use in Galenic

Improved percutaneous penetration of drugs

Linalool promotes percutaneous penetration of other therapeutic agents by increasing the permeability of the skin and mucous membranes, so it can be used as an absorption promoter in topical preparations [107]. It appears that the absorption of linalool in the stratum corneum is higher from hydrogel formulations than from emulsions or oily solutions. [108] The assessment of the state of the art of the data from the scientific literature drawn up within the framework of this article highlights the interest and the good benefit / risk ratio of the use of linalool in its natural chemical environment to take into account preventive or curative burden of many organic and functional disorders. The control of the doses used and the use based on scientific and clinical validations are the elements that determine the great interest of a natural molecule with high functional potential.

Table 2: Summary of the main pharmacological effects of essential oils rich in linalool and natural linalool

Pharmacological effect of linalool	Description	Sources	Test models	References
	Sedative effect with an increase in sleep time and a reduction in spontaneous locomotion, without affecting motor skills	Lavander essential oil, natural linalool	Animal models	[34]
	decreasing sympathetic nerve activity and increasing parasympathetic nervous activity	Lavander, essential oil, natural linalool	Animal models	[35]
Effect on CNS	Sedative effect	<i>Coriandrum sativum</i> essential oil, natural linalool	Animal models	[36]
	Sedation, relaxation and improves sleep	Inhalation : lavender essential oil and (R) - (-) - linalool	Clinical trials	[37a, 37b, 38]
	Improvement of interaction behavior and reduction of aggressive behavior	Inhalation of natural linalool	Animal models	[39, 40, 41, 42]
	Sedative effects of linalool (R-) via an effect on the autonomic nervous system and mood states	Natural linalool	Animal models	[43, 44]

8. Conclusions

The use of essential oils and their natural derivatives, such as linalool, as well as all scientific validation work on their functional effects and their safety, have shown real effectiveness in the context of an adjuvant but also environmental medicinal use. Beyond these beneficial effects, it is important to supervise and control their uses in order to avoid the risks of improper misuse. It is also important to remember that accidental cases of misuse, which remain limited and rare according to the data in the scientific literature, should not lead to an extreme and exaggerated consideration of a risk whose danger is mainly related to a misuse and lack of recommendations for these uses whose beneficial effects are confirmed.

Furthermore, during this literature review, it appears that the numerous studies consulted and cited, mention that the beneficial effects are far more important than the harmful effects, often linked to misuse and that the doses necessary for the appearance of 'possible toxicity are very high; and that the real risk lies essentially in voluntary ingestion for the purpose of autolysis, or the accidental reception of young children whose vulnerability is explained by the immaturity of their organs (liver, nervous system, etc.). If the use of these essential oils is established on the basis of recommendations with rigor and precautions, this greatly helps to eliminate the danger and avoid the risk. The exploitation of essential oils as a derivative like linalol, for their beneficial effects, must be based on a recommendation approach, guided with the warning of their user so that users make reasonable and useful use of it. Objectives sought

From the moment when the recommendations are based on reliable scientific data, the use of oils as a derivative is part of a controlled approach with a benefit / risk ratio largely profitable in the use of these oils and their derivatives. Which are also regularly found in the environment independently of human activities.

Linalool is a molecule found naturally in the essential oils of more than 200 species of plants and herbs and represents more than 10% of the molecules in 54 essential oils. Some essential oils like that of lavender, the best known, are composed of 25% to 45% of linalool. Thyme essential oil contains 73% -79% linalool. Rosewood essential oil is very rich in natural linalool at 82%-90%. Linalool is also present in large quantities in Ho wood, Ho leaf, coriander seed, neroli, and basil.

9. References

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