

Lavandulae aetheroleum Oil: A Review on Phytochemical Screening, Medicinal Applications, and Pharmacological Effects

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Abstract: *Lavandulae aetheroleum*, the oil, was obtained by vapor condensation from the flower of *Lavandula angustifolia* Mill. or *Lavandula intermedia* Loisel (Lamiaceae) plant. Other names of *Lavandulae aetheroleum* oil are Al birri, common or English lavender. The *Lavandula angustifolia* Mill. or *Lavandula intermedia* Loisel plant is spreading in the Mediterranean, southern Europe, Bulgaria, Russia, and USA. The *Lavandula angustifolia* Mill. or *Lavandula intermedia* Loisel plant, is an odor shrub with 1-2 m in height. The oil is a clear, colorless, or pale yellow. The gas chromatography studies reported the following percentage of the major chemical constituents in the oil: linalyl acetate (25-46%), linalool (20-45%), terpinen-4-ol (1.2-6.0%), lavendulyl acetate (> 1.0%), 1,8-cineole (1,8-cineol, cineol, cineole, eucalyptol) (< 2.5%), 3-octanone (< 2.5%), camphor (< 1.2%), limonene (< 1.0%), and α -terpineol (< 2.0%). Medicinal applications of the oil include the treatment of restlessness, anxiety, cardiovascular disorders, insomnia, and gastrointestinal disorders, burns, diarrhea, headache, sore throats, and wounds. Pharmacological effects include experimental and clinical pharmacology. Experimental pharmacology includes anesthetic, anticonvulsant, sedative, anti-inflammatory, antimicrobial, antispasmodic, antispasmodic, central nervous system depressant effects. Clinical pharmacology includes anxiolytic, analgesic, and cardiovascular effects. The oil dose by inhalation = 0.06-0.2 ml/ 3 times/day while oil dose internally = 1-4 drops approximately 20-80 mg on a sugar cube per day. In conclusion, *Lavandulae aetheroleum* oil had an anesthetic, anticonvulsant, sedative, anti-inflammatory, antimicrobial, antispasmodic, antispasmodic, central nervous system depressant, anxiolytic, analgesic, and cardiovascular effects.

Keywords: *Lavandulae aetheroleum*; *Lamiaceae*; Constituents; Pharmacology; Dose.

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1. Introduction

Lavandulae aetheroleum was obtained by vapor condensation from the flower of *Lavandula angustifolia* Mill. or *Lavandula intermedia* Loisel (Lamiaceae) plant [1-4]. Other names of *Lavandulae aetheroleum* oil were Al birri, alhucema, arvaneh, aspic, broad-leaved lavenda, common lavender, Echter Lavendel, English lavender, espi, espic, espliego comun, firigla, frigous, garden lavender, grando, hanan, hanene, hzama, khazama, khirii, khouzamaa, khouzami, khuzama, khuzama fassiya, khuzama zerqua, Kleiner Speik, Lavanda, lavande, lavande femelle, lavande veritable, lavando, lavandula vraie, Lavendel, lavender, lawanda, lofinda, ostoghodous, postokhodous, spigandos, true lavender [5-10]. The *Lavandula angustifolia* Mill. or *Lavandula intermedia* Loisel plant extended through north regions of the

Mediterranean. It also occurred in southern Europe and in Bulgaria, Russia, the USA, and the former Yugoslavia regions [6, 11]. The *Lavandula angustifolia* Mill. or *Lavandula intermedia* Loisel plant is defined as a shrub with 1-2 m in height. The leaves varied from grey-brown to dark brown. The plant had a long flower. Leaves arranged on leafy shoots with widely spaced shoots. The plant had very short petiole while the blade ranged from lanceolate to linear with 17 mm long, 2 mm wide, 2-6 cm long. The plant had grey stellate, base attenuate, margin entire, revolute, apex obtuse. Inflorescence defined as crowded with 2-8 cm long and 6-10 flowers [6]. The *Lavandula angustifolia* Mill. plant extended in Kırklareli and Edirne provinces in Turkey [12]. The *Lavandula angustifolia* Mill. plant had a huge and significant influence in the world economy due to its incorporation in perfumes, cosmetics, food industrialized, aromatherapy, and pharmaceutical industries [13]. The smell of *Lavandulae aetheroleum* oil obtained from *Lavandula angustifolia* Mill. plant enhanced sleep quality and quantity, quality of life, and mood in diabetic patients with restlessness states without any effect on metabolic status [14]. The *Lavandula angustifolia* Mill plant had a similar effect to fluoxetine (antidepressant drug) to treat mild to moderate depression [15]. In another in-vitro and in-vivo research, the *Lavandula intermedia* Loisel plant caused a prospective defense product on different nematodes [16]. The *Lavandula intermedia* Loisel plant had been applied to be natural herbicide, which totally stops the seed growth of *Raphanus sativus* [17].

2. Characteristics of the oil

The oil had clear, colorless, or pale yellow fluid, miscible with 90% alcohol, ether, and fatty oils [1-4]. The oil odor had specific, perfumed, and aromatic, while the oil with a slightly bitter taste [1, 3].

3. Chemical properties of the oil

The oil relative density = 0.878-0.892. The refractive index = 1.455-1.466. The acid content in the oil does not exceed 1.0 [4].

4. Chemical constituents of the oil

The gas chromatography application proved the following 10 constituents in the oil: (1) limonene, (2) cineole, (3) 3-octanone, (4) camphor, (5) linalool, (6) linalyl acetate, (7) terpinen-4-ol, (8) lavandulyl acetate, (9) lavandulol and (10) α -terpineol [4]. The chromatography analysis revealed that the chemical composition of the oil contains carvacrol (65.27%) as the most major constituent in *Lavandula* species distributed widely in the Dead Sea Valley, Palestine [18].

5. Percentage of oil major chemical constituents

The gas chromatography studies reported the following percentage of the major chemical constituents in the oil: linalyl acetate (25-46%), linalool (20-45%), terpinen-4-ol (1.2-6.0%), lavandulyl acetate (> 1.0%), 1,8-cineole (1,8-cineol, cineol, cineole, eucalyptol) (< 2.5%), 3-octanone (< 2.5%), camphor (< 1.2%), limonene (< 1.0%), and α -terpineol (< 2.0%) [4].

6. Medicinal applications

Lavandulae aetheroleum oil used in the treatment of restlessness, anxiety and the oil caused relaxation [19-23]. It is also used for the treatment of cardiovascular disorders [24, 25]. The oil is applied in the treatment of insomnia and in the treatment of gastrointestinal disorders [26, 27]. In folklore medicine, it is used as a cholagogue, diuretic, and emmenagogue agents, and the oil also used in the treatment of burns, diarrhea, headaches, sore throats, and wounds [26]. The oil declined the restless legs syndrome in hemodialysis patients, where the oil was effective in decreasing the restless legs syndrome by the application of oil massage [28]. The oil declined the quail's liver weights. The oil also ameliorated the pH, water content, and fat content of the quail's meat. The oil decreased the endogenous intestinal population of *Lactobacillus*, and the bacteria (such as *Escherichia coli* and *Staphylococcus aureus*). Consequently, the supplementing of quail with *Lavandulae aetheroleum* oil has a beneficial effect on quail growth and antimicrobial effects [29].

7. Pharmacology of the oil

7.1. Experimental pharmacology.

7.1.1. Anesthetic effect.

The oil or its major constituents (linalyl acetate or linalool) in the *in-vitro* study at a dose of 0.01-10.0 $\mu\text{g/ml}$ declined animal diaphragm. Also, the oil or its major constituents (linalyl acetate or linalool) in an *in-vivo* study at a dose ranged from 30.0-2500.0 $\mu\text{g/ml}$ increased the number of stimuli needed to inflame the reflex [30]. The oil declined senses buried numbers. The oil also amplified time spent and entries number ratios into the open arms compared with control. No effect was seen in closed arm entries or beam interruptions ratios [31]. In Germany, the oil is approved for restlessness therapy in an anxious mood where the oil has a benzodiazepine-like effect [32]. The oil decreased the levels of pain severity in post-operative pain after inguinal hernia surgery. This study includes 90 participants in 4 stages of measurements. So, the oil decreased post-operative pain after inguinal hernia surgery [33]. The *Lavandulae aetheroleum* oil massage was effective in the control of painful temporomandibular disorders situations and narrow mouth opening [34].

7.1.2. Anticonvulsant and sedative effects.

Injection with 2.5 g/kg body weight (bw) of linalool protected against convulsions caused by pentylentetrazole, picrotoxin, and electroshock [35, 36]. The injection of 2.5 g/kg bw of linalool obstructed glutamate function and postponed *N*-methyl-d-aspartate-induced convulsions [37]. Linalool counteracts [3H]-glutamate and [3H]-dizocilpine in animal membranes and consequently counteract glutamatergic transmission. Linalool also declined potassium-stimulated glutamate discharge. In conclusion, linalool counteracts with components of the excitatory glutamatergic transmission system [38]. Linalool caused sedation at a dose of 25 mg/L and anesthesia with a dose of 50-100 mg/L, but linalool did not change acetylcholinesterase level in the muscle and brain, so linalool did not effect in gamma-aminobutyric acid antagonist (GABAA) receptors in both muscle and brain [39]. Linalool possessed an obvious antidepressant effect where the standard concentration equal to 97.0% [40]. Linalool (at a dose of 0.8 ml/kg) completely stopped pentylentetrazol-caused

convulsions with sedative effect [41]. Linalool declined squares crossed, escapes, defecation, and distress call numbers while jumped sleeping position, and this related to the sedative effect of linalool [42]. In a clinical study, the oil declined the tooth pain levels in children by inhalation with the oil. This study was done on 126 children age (6-12 years). At the same time, the oil declined the anxiety level in those children [43]. The *Lavandulae aetheroleum* oil declined the daytime sleeping, and this result was shown by decreasing the daytime sleeping scores on the scales applied, and this observation refers to decline sleepiness [44]. The oil declined the pain level in the group, which had an oil massage protocol. The oil massage decreased post-operative pain after gynecologic surgery. The oil had a longer effect in decreasing post-operative pain. Consequently, the oil had an inexpensive and easy-to-apply method was done by nurses on post-operative patients [45]. The oil declined the extubation time, surgical site pain severity, and anxiety in patients experiencing open-heart surgery [46]. The smell of the *Lavandulae aetheroleum* oil increased sleep quality and quality of life in women with sleep deficiency problems during menopause [47].

7.1.3. Anti-inflammatory effect.

Aqueous solutions of *Lavandulae aetheroleum* oil (1:500, 1:100, 1:10, 1:1, and 1:0) decreased mast cell-dependent ear edema. These doses of *Lavandulae aetheroleum* oil aqueous solutions declined cutaneous anaphylaxis caused by antidinitrophenyl IgE compound (which caused histamine secretion) and anti-antidinitrophenyl IgE compound (which caused tumor necrosis factor- α secretion) from peritoneal mast cells [48]. In other research, 0.3 ml of *Lavandulae aetheroleum* decreased thromboxane B2 secretion stimulated by arachidonic acid, so the oil has an anti-inflammatory effect [49]. *Lavandulae aetheroleum* oil improved the depression-like behavior. The oil possessed a neurogenic effect where the oil enhanced neurogenesis and dendritic complexity. The oil also improved serum oxytocin levels [50]. The inflammatory response was declined by animal treatment with oil. However, the oil possessed an anti-edematogenic effect, and it inhibited spontaneous nociception [51]. The oil also declined allergic inflammation and mucous cell hyperplasia and decreased T-helper-2 cell cytokines and RNA expression of cytokines and mucin in lung tissue in asthma. So, *Lavandulae aetheroleum* oil is a good alternative medicine for bronchial asthma [52]. The anti-inflammatory effect of oil is similar to the anti-inflammatory effect of *Oleum azadirachti* oil [53]. The oil stopped Phytohemagglutinin-caused tryptophan break and kynurenine creation. So, the oil declined neopterin and interferon- γ synthesis [54]. The oil exhibited 73.67% recovery in the psoriasis area severity index and 87% in Thymus-17 cytokines. The 2 major constituents of the oil (linalool and linalyl acetate) showed 64% and 47.61% recovery in psoriasis area severity index scores. The linalool and linalyl acetate recovered Thymus-1 tumor necrosis factor- α and interleukin-1 β . The linalool recovered Thymus-17 cytokines (interleukin-17 and interleukin-22) [55].

7.1.4. Antimicrobial effect.

Lavandulae aetheroleum oil in *in-vitro* research declined *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Streptococcus pneumoniae* growth [56, 57]. The oil at a dose of 10.0 μ l decreased *Mycobacterium chelonae*, *M. fortuitum*, *M. kansasii*, *M. marinum*, and *M. scrofulaceum* growth [58]. In another *in-vitro* study, the oil declined filamentous fungi growth [59]. The oil, besides its major constituents (linalool, linalyl

acetate, and camphor), possessed a miticidal effect against *Psoroptes cuniculi* [60]. The oil showed a higher effect on both bacilli types (Gram-positive and Gram-negative), but the oil did not inhibit the growth of Gram-positive cocci. The oil declined the mixed microbiota cell number from facial skin [61]. The oil possessed an antimicrobial effect [62]. The oil improved an anxiety state in patients, and also the oil has an obvious effect in the Pittsburgh Quality Sleep Index measurements [63]. The oil at a dose of 100 mg/kg recovers the cognitive performance of animal behavior scopolamine. The oil declined the acetylcholinesterase and malondialdehyde levels while increases superoxide dismutase and glutathione levels. The oil declined lactate dehydrogenase and nitric oxide secretion, intracellular reactive oxygen species production, and mitochondrial membrane potential activities [64]. The oil reduced donkey louse (*Bovicola ocellatus*) parasites intensity, and the reduction rate was equal to 78% [65]. In a clinical study, about 300 patients treated with the oil exhibited major symptom scores in acute viral rhinosinusitis and showed an increase in the quality of life. Consequently, oil treatment declined all the signs of acute viral rhinosinusitis in adult patients [66]. In other clinical trials, about 260 patients with acute bronchitis, the oil ameliorates the viral symptoms and improve life safety. So, oil is effective in treating severe viral symptoms in adult patients [67]. The oil possessed strong antioxidant, antiacetylcholinesterase, antibutyrylcholinesterase, and antilipase activities. The oil also had a strong antidermatophyte effect against *Trichophyton rubrum*, *Microsporum canis*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum*. The high antioxidant, enzyme inhibitory, and antimicrobial effects of the oil-related to its high monoterpenes content (carvacrol) [14].

7.1.5. Antispasmodic effect.

The aqueous doses (0.02 mg/ml and 0.2 mg/ml) of *Lavandulae aetheroleum* oil declined the animal contracting response and relaxed the animal muscle tone in *in-vitro* research [68]. The antispasmodic effect of the oil and its major constituent (linalool) was controlled by cyclic adenosine monophosphate signal transduction system in animal ileum smooth muscle preparation [69]. The oil declined phyto-hemagglutinin-caused tryptophan break and kynurenine creation. Also, the oil decreased neopterin and interferon- γ levels [70]. The oil inhalation improved brainwaves in the electroencephalogram instrument, and this effect was stable for the oil, and the oil amended the patients' questionnaire results [71]. The oil showed antioxidant and antimicrobial effects [72]. The oil revealed a cytotoxic effect against *Ichthyophthirius multifiliis* group compared to control in the *in-vitro* study [73]. The oil served as antibiotic resistance modifying agent and consequently declined antibiotics application and so declined the antibiotics adverse effects and counteracted the beta-lactam antibiotic resistance [74]. In a clinical study, 7 adult males with an age range from 20-40 years old. The oil smell declined depression score. In the same study, the *in-vivo* study showed that the oil administration increased intracellular Ca^{2+} levels in the hypothalamic oxytocin neurons. Consequently, oil is a useful treatment in stress relief. The oil mechanism includes stimulation of the central oxytocin neurons [75].

7.1.6. Central nervous system depressant effect.

Lavandulae aetheroleum oil declined caffeine-caused hyperactivity, and this effect was associated with linalool serum levels [70]. The oil caused anxiolytic effects and continued pentobarbital sleeping time [76]. The dose of 1.6 g/kg bw of the oil jumped the animal lever-

pressing response rate during the alarm phase, which related to the anti-conflict effect of the oil, which the same as diazepam [77]. In another research, the oil at a dose of 25.0 ml/kg bw increased pentobarbital sleeping times [78]. The oil at a dose of 0.3 ml declined strychnine-caused animal convulsions [48]. The oil at daily doses of 80 or 160 mg possessed an improved action on anxiety disorders such as diminished sleep, somatic illnesses, prolonged depression, or decreased life ability [79, 80].

7.2. Clinical pharmacology.

7.2.1. Anxiolytic effect.

In clinical research where 40 patients received *Lavandulae aetheroleum* oil, the electroencephalogram caused a jump in beta power, so the oil possessed drowsiness. The patients taken *Lavandulae aetheroleum* oil revealed lower depression and higher relaxation and accomplished the mathematical processes more perfectly [20]. In another clinical study, *Lavandulae aetheroleum* oil declined serum alpha-1 (8-10 Hertz), and the patients feel “pleased” [22].

In clinical research, patients are exposed to either massage or *Lavandulae aetheroleum* oil (1-3 treatments through a 5-day period) or a period of rest to evaluate different factors on the stress response and anxiety. In the stress response, no difference was found between the three above mentioned factors. The patients taken *Lavandulae aetheroleum* oil found an improvement in mood and a decline of anxiety [81]. In other clinical studies, patients with chronic hemodialysis, *Lavandulae aetheroleum* oil through a one-week period, declined the mean score in the Hamilton anxiety rating scale [21]. The oil has a good effect on anxiety and its physiological indices [82], although, in another clinical trial, 1 hour of inhalation of 0.1-mL and 0.3-mL of the oil in 120 mL of water did not have an anxiolytic effect on patients experiencing orthognathic surgery [83]. In another clinical study, the oil applies a secondary sleep improving effect by its anxiolytic action rather than by sedation [84]. In a clinical study, the oil declined the anxiety after the inhalation with the oil. The oil declined respiration and increased oxygen saturation. Consequently, the oil declined anxiety and its major symptoms in benign prostate hyperplasia patients [85]. The oil decreased the mean scores of the nurse's anxiety by 37.82%. On the other hand, the combination of music therapy and oil therapy delined the mean scores of the nurse's anxiety by 40.03%.

Consequently, music therapy and *Lavandulae aetheroleum* oil declined the anxiety of nurses in the clinical setting, which affect their professional performance [86]. In another clinical study, the bone marrow biopsy is correlated with anxiety. The oil inhalation is effective in declining the anxiety in these patients. This oil is used for the treatment of the hematology and oncology symptoms in this disease to decline anxiety induced by bone marrow biopsy [87]. The smell of the *Lavandulae aetheroleum* oil declined pain and anxiety. The oil amended patient relaxation without affecting the saliva cortisol level in myofascial pain syndrome patients [88]. The oil improved preoperative anxiety. The oil was applied by (1) inhalation, (2) oil massage, and (3) oral administration were effective. The oil showed a better effect on preoperative anxiety. So, The oil was effective in reducing preoperative anxiety in adults. The oil inhalation was to be more effective in clinical trials [89].

7.2.2. Analgesic effect.

In a clinical study, *Lavandulae aetheroleum* oil in baby bathwater daily for 10 days after childbirth did not decline the perineal discomfort rate [90]. In another clinical research, *Lavandulae aetheroleum* oil or synthetic lavender oil in a baby water bath for 10 days after childbirth revealed no change between these 2 oil treatments in the declined of perineal discomfort [91]. The oil possessed an analgesic effect besides its antioxidant and anti-inflammatory effects [51, 92]. The oil showed an obvious decline in daily acetaminophen usage in post-operative days in pediatric patients but had not any effect on pain strength and night arousal [93]. The analgesic effect of oil is very similar to the sedative effect of *Anisi aetheroleum* oil [94]. In a clinical study on palliative care patients, the oil had no effect on the major symptoms of the patients. At the same time, the oil caused a deeper sleep on the 2nd day after oil administration. The oil enabled patients to fall asleep and sleeping again when they were aroused. The oil improved sleep quality. The oil declined the arousal regularity on the 1st and 2nd days-the oil improved overall sleep quality after oil administration [95]. In a clinical study, 90 patients participated in the study, and the results found that the oil was decreased pain and anxiety levels of the patients while patients' oxygen saturation levels were increased [96]. In another study, 59 elderly individuals were applied in this study procedure. The oil administration amended the sleep quality and decreased fatigue severity in the elderly [97].

7.2.3. Cardiovascular effect.

In a clinical study, *Lavandulae aetheroleum* oil in a foot water bath for 10 minutes increased parasympathetic nerve action and improved blood circulation but without any effect on cardiac or respiratory rates [24]. The oil prompts olfactory in stroke patients with anxiety, which inflated diastolic blood pressure with higher levels of characteristic anxiety symptoms [98]. The *Lavandulae aetheroleum* oil was declined systolic and diastolic blood pressure. The oil ameliorated the pulse rate of the heart, systolic and diastolic blood pressure [75, 96]

8. Side Effect of the oil

The allergy is the obvious side effect of the oil observed in patients previously exposed to *Lavandulae aetheroleum* oil [99-101]. Owing to allergy side effect of the oil, *Lavandulae aetheroleum* oil should not be applied during pregnancy [102, 103] and must keep away from children and must be used under the supervision of a specialist physician.

9. Dosage of the oil

The dose of *Lavandulae aetheroleum* oil by inhalation is equal to 0.06-0.2 ml/ 3 times/day [104], while *Lavandulae aetheroleum* oil dose internally is equal to 1-4 drops approximately 20-80 mg on a sugar cube per day [27].

10. Conclusion

Lavandulae aetheroleum, the oil, was obtained by vapor concentration from the flower of *Lavandula angustifolia* Mill. or *Lavandula intermedia* Loisel (*Lamiaceae*) plant. The oil is a clear, colorless, or pale yellow. The gas chromatography studies reported the following major chemical constituents in the oil: linalyl acetate (25-46%), linalool (20-45%), terpinen-4-ol (1.2-

6.0%), lavendulyl acetate (> 1.0%), 1,8-cineole (1,8-cineol, cineol, cineole, eucalyptol) (< 2.5%), 3-octanone (< 2.5%), camphor (< 1.2%), limonene (< 1.0%), and α -terpineol (< 2.0%). Medicinal applications of the oil include the treatment of restlessness, anxiety, cardiovascular disorders, insomnia, and gastrointestinal disorders, burns, diarrhea, headaches, sore throats, and wounds. Pharmacological effects include experimental and clinical pharmacology. Experimental pharmacology includes anesthetic, anticonvulsant, sedative, anti-inflammatory, antimicrobial, antispasmodic, antispasmodic, central nervous system depressant effects. Clinical pharmacology includes anxiolytic, analgesic, and cardiovascular effects. The oil dose by inhalation is equal to 0.06-0.2 ml/ 3 times/day, while the oil dose internally is equal to 1-4 drops approximately 20-80 mg on a sugar cube per day.

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Conflicts of Interest

The authors declare no conflict of interest.

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