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Application of Lavender in Integrative Medicine: From Aromatherapy to Potential Anticancer Treatment

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Abstract

The aromatic and medicinal properties of lavender have been used since ancient times. Essential Oils (OE) have shown analgesic, pesticide, antispasmodic and antimicrobial effects. Anxiolytic effect EO of the species *Lavandula angustifolia* has been demonstrated in preclinical studies in animal models of anxiety. Among the isolated components from lavender, the most studied is linalool, a terpene, which seems to be the responsible for the major beneficial effects, such as antiallergenic, anti-inflammatory, nociceptive and antitumor growth. Linalool has also been described to be antioxidant, anxiolytic, analgesic, and to possess anesthetic activity. It also largely prevented microbial activity against *Staphylococcus epidermidis*, *Pseudomonas aeruginosa* and *Candida albicans*. Other lavender EO such as silexan is effective in controlling generalized anxiety. Lavender has been increasingly used as an integrative medicine for patients in different situations, mainly those associated with pain, such as gynecological examination, dysmenorrhea, arthritis and cancer. This review points out to the recent therapeutic action of lavender essential oils on cancer. Indeed, several research groups have been focusing on elucidating the mechanism underlying the action of essential oils in cancer cells, especially those related to antioxidant and antiproliferative aspects.

Keywords: Anxiety; Cancer; Clinical trials; Essential oils; Linalool

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Lavender as a Multipurpose Plant

Lavender is widely used in folk and traditional medicine due to its anxiolytic, antimicrobial, antiseptic, relaxing and skin healing among other effects.

As an aromatic plant, lavender exhibits active ingredients used to treat both the causes and undesirable symptoms of a wide range of diseases [1-6], as depicted in Figure 1.

The efficiency of the active principles of plants and substances with pharmacological activities depends directly on the form of cultivation as well as internal and external factors [7]. The internal factors refer to the specific physiology and genetics of each plant, while the external factors include temperature, photoperiod, altitude, latitude, soil, humidity, availability of water and nutrients [8].

Lavender derives from the Latin "lavare" which means washing and belongs to the *Lavandula* genus of the *Lamiaceae* family (*Labiatae*). Among the most common species of lavender are *L. angustifolia* (also known as *L. Frances* and *L. officinalis*), *L. latifolia*, *L. stoechas* and *L. dentata* [1-10].

Lavender has about 300 genera and 7,500 species, which consists of a shrub with an average height of 20 cm to 60 cm, small, with narrow and elongated leaves and flowers of a violet color. For example, in Brazil 28 genera with about 350 species of lavender were found, whereby *L. dentata* is the most common species and named alfazema [10].

The substantial use of lavender is due to its Essential Oils (EO), which are natural complex compounds endowed with great pharmacological and therapeutic potential [11-15]. EO characteristics are closer to alcohol than to oil, and their low molecular weight and high volatility make them ideal for use in nebulization or inhalations, which allows their rapid elimination from the organism [12]. Generally, EO are obtained by steam distillation method from natural raw materials of vegetable origin [8,9,13].

As a multipurpose plant, lavender exerts its effects as a raw vegetable, through its essential oils, as well as in combination with allopathic drugs-integrative medicine. Linalool and linalyl acetate are

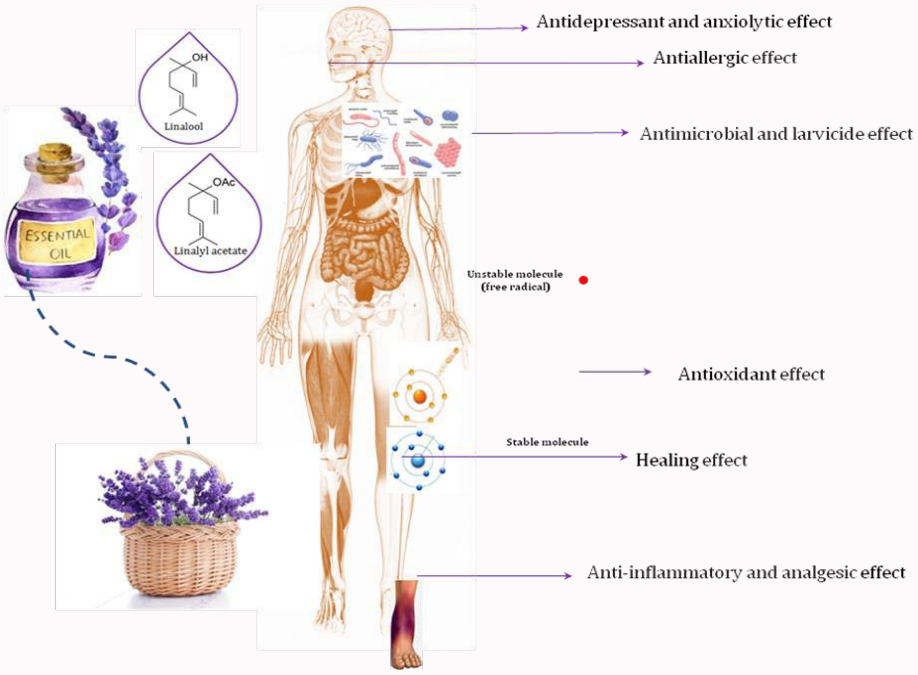

Figure 1: Applications of lavender and its essential oils in humans.

the most active and frequently used compounds as shown on the left side of the figure. In addition, the high level of antioxidant compounds in lavender makes its good scavenger of harmful free radicals, as indicated on the right side. Many properties of linalool, one of the principal lavender components, are well established, among them as anti-inflammatory [16,17], nociceptive [18], and antiproliferative of tumor cells [16,19]. Moreover, patients undergoing intense pain in situations such as gynecological examination [14], cancer treatments [16,19-21], dysmenorrhea arthritis [22,23] and neurasthenic or somaticized disorders have benefited from the calming effect of lavender when this was applied as a component of integrative therapy [23-27].

Several examples of studies of lavender properties *in vitro* or pre-clinical experiments, as well as in clinical trials are described on references [2,3,16,20,22-29].

Since 19th century the studies of lavender were motivated not only by its fragrance, but also for the high value of its EO [30]. Other previous uses of lavender have been in perfumery, culinary, and ornamental landscaping.

Composition and Activities of Essential Oils: Relevance of Anxiolytic Effect

The main constituents of *Lavandula* species are essential oils acetates, alcohols, terpenes, esters and aldehydes [31-34].

The main compounds found in *Lavandula angustifolia* EO are tannins, coumarins, flavonoid and ursolic acids, including linalool, 1,8-cineole, camphor and endo-borneol. Other components such as linalyl acetate, α-pinene, camphene, β-pinene, limonene, α-camphonelal, terpinen-4-ol and krypton can also be found [28,32,33]. The type of EO yields, as well as their biomass, can vary according to the conditions of the method of extraction, processing, genotype and environment [8,9,34,35]. For example, in *Lavandula angustifolia*, Gas Chromatographic Mass Spectrometry studies (GC-MS) identified the predominance of the compound 1,8-cineol (39.8%), followed by endo-borneol (22.6%) and camphor (22.1%) [31].

The anxiolytic effect of *Lavandula angustifolia* EO has been demonstrated in preclinical studies in animal models of anxiety [8,22,23,30], for example Mongolian squirrels and mice in elevated plus maze tests as well as rats submitted to hyperthermia [22,30,35] or open field behavior tests [35]. In mice, this anxiolytic action of linalool is potentiated in the presence of the linalyl acetate component, thus suggesting that synergies between the compounds may also be responsible for the beneficial effects classically mentioned in the literature [22-28].

Studies with the isolated compounds also demonstrated positive anxiolytic effects in anxiety tests, such as linalool inhalation in both light/dark box and social interaction tests as well as in Vogel and Geller-Seifter tests [17,34,36]. When used topically, *Lavandula angustifolia* EO inhibits allergic reactions by reducing TNFα secretion [36].

Other studies described analgesic, pesticide, antispasmodic and antimicrobial EO effects, which include antibacterial and antifungal activity on Methicillin-Resistant *Staphylococcus aureus* (MRSA) strains [18,37-40]. Further research has suggested possible oil suppressive action on histamine release and cytokine production [14-16,28,29]. Linalool also largely prevented microbial activity against *Staphylococcus epidermidis*, *Pseudomonas aeruginosa* and *Candida albicans* [39].

Linalool demonstrated an anti-inflammatory effect by inhibiting the expression of Cycloxygenase (COX-2) and research who carried out tests on humans suggested analgesic action of the oil. They observed that linalool treatment minimized the use of opioid medications in the postoperative process of patients undergoing intra-abdominal laparoscopy surgery [17].

Controlled clinical studies (randomized, comparative and double-blind) in patients diagnosed with generalized anxiety disorder also point to the anxiolytic effect of lavender essential oil. These studies used a preparation of essential oil extracted from flowers of the *Lavandula angustifolia* species, authorized for sale and consumption in Germany. This EO, called silexan [4,6,39] or commercially Lasea. Woelk and Schläfke [6] studied silexan in 36 patients and noted that it was as effective in controlling generalized anxiety as the benzodiazepine drug lorazepam, in 33 patients, after 6 weeks of treatment. The assessment was performed using the Hamilton anxiety scale. In addition, the authors also observed that silexan did not cause sedation, which is one of the main side effects of benzodiazepine drugs [6].

Kasper et al. [4] conducted research with 221 in patients with unspecified anxiety disorder. The patients were separated into 2 groups (placebo and silexan users), and after 10 weeks of treatment there was an improvement in the sleep and anxiety disorders of the patients in the silexan group, compared to the placebo group, without complaints of sedation or other side effects.

Similar good result was observed by Uehleke et al. [23], who observed that after 6 weeks of treatment, 50 patients diagnosed with post-traumatic stress reported improvement in the symptoms of insomnia, anxiety and restlessness [24], reporting gastrointestinal discomfort as the only unwanted effect. For these studies, the lavender EO in capsules (80 mg/day) was used orally and not by the inhalation method, as observed in other studies. Thus, it has been demonstrated that lavender EO has a beneficial effect on humans regardless of the route of administration [24-27].

Lehrner et al. [15] demonstrated lavender's calming effect in clinical studies (inhaling lavender EO by patients prior to dental care reduced their anxiety levels). This kind of beneficial lavender effect has been increasingly used as an integrative medicine for patients in different situations, mainly those associated with pain, such as gynecological examination [14], dysmenorrhea [22], arthritis [33] and cancer [19,21,28].

Lavender as an Integrative Component in Anticancer Therapy

The process of cancer treatment is delicate in several aspects, generating high levels of stress and anxiety in patients due to the lack of procedures for an immediate treatment that yields positive and significant results immediately [16,19,20,21,41-45]. Unfortunately, the current drugs for the treatment of inflammatory and cancer conditions often show undesirable side effects. Thus, researchers are seeking for more natural or mixed therapy, which include the use of ancient aromatherapy.

Recently, Boukhatem et al. [16] studied the anticancer activity of Algerian *L. stoechas* essential oil against different cancer cell lines, as well as its *in vitro* and *in vivo* topical and acute anti-inflammatory properties; cineole was the major active component that exhibits anti-inflammatory and anticancer properties, besides being a promising candidate for use in skin care.

In 2009, the lavender EO associated with mandarin, sweet orange, sandalwood and geranium showed anxiolytic and antidepressant activity when used by the aromatherapy technique associated with massage [21]. In that study, an open semi-comparative trial with 12 breast cancer patients, the researchers observed that one 30 min aromatherapy massage reduced anxiety as measured by the State-Trait Anxiety Inventory (STAI) test; moreover anxiety decreased in eight sequential aromatherapy massage sessions in the Hospital Anxiety and Depression Scale (HADS). Such results suggested that aromatherapy massage ameliorates the immunologic state.

Physician Anne-Marie Giraud, a general practitioner specializing in aromatherapy, homeopathy and herbal medicine, authored the book "Essential oils and cancer." (2016). The book addresses the great potential of chemicals as an integrative therapy in supporting cancer patients, explaining biochemical and physiological aspects of oils, as well as their energetic and emotional properties. The author emphasizes the usefulness of EO in all stages of the disease, by means of reducing the effects caused by nausea, fatigue and burns [20].

The integrative therapy results in improvement of the quality of life of the patients because essential oils can stimulate immune defenses and preserve healthy cells from the harmful effects of allopathic treatments. To this effect, important studies have addressed the wide understanding of the mechanisms of action of the EO on cancer cells [16], reporting an increase in the survival rate of patients treated with an allopathic-aromatic combined approach. In this sense, an alliance between conventional treatments combined with aromatherapy could stimulate scientific researches directed at EO as a complementary therapy to cancer treatment [20].

Interestingly, researchers at the Ruhr University Bochum (Germany), under the guidance of Professor Hatt, have discovered "fragrance receptors" in cancer cells [42]. Their research has indicated that some EO when in contact with, for example, cancerous hepatocytes, act by preventing their development.

Several essential oils have a specific molecular group, the terpenes, which are of great value in terms of fighting cancer [19,28,29,40,46,47]. This molecular group predominates in the oils of citrus such as lemon. There are specific molecular mechanisms that hinder and may also inhibit the growth and development of cancer cells through the application of terpenes. In fact, the OR1A2 odor receptor is responsible for this process and is present in the cell membrane of cancer cells, which has its growth inhibited when they react with terpenic molecules. The linalool, abundant in lavender essential oil and other oils, is considered a terpene of great antioxidant, anxiolytic, analgesic, anesthetic activity, among others [19,40]. There is also pinene, present in EO conifers, such as wild pine; mircene, found in lemongrass oil; limonene, present in citrus oils and karyophylene present in clove oil.

Lavender angustifolia has linalool (26% to 49%) and linalyl acetate (17.6% to 53%) which showed anti-inflammatory activity in rats with edema induced by carrageenan. It has been demonstrated elsewhere that the mechanism controlling carcinogenesis is associated with oxidative stress [19,45] and apoptosis that ultimately result in cleavage of nuclear DNA [28,45,47] and cell death.

Lavender essential oils have also been effective in inhibiting prostate cancer tumor growth in cell culture *in vitro* and *in vivo* [19,40]. The evidences suggest that suppression tumor by lavender is ultimately given by inhibition of cell proliferation [19,28,29,33,40,46,47].

Final Considerations

Recently the number of studies examining the effects of lavender and of its main bioactive compound, linalool, as a potential herbal medicine for many diseases, has grown dramatically.

Besides the well- known aromatherapy property of lavender to treat anxiety, neurological disorders or muscular pains, lavender could be used to alleviate many side effects of allopathic drugs. The capability of lavender to counterattack oxidant and inflammatory molecules, which tend to increase with age and comorbidities, is already expanding the spectrum of use of lavender. Several studies have demonstrated recently that the natural product lavender is potentially efficient both as primary agent and as co-adjuvant in integrative medicine.

As this review indicates, a large body of research is focused on the therapeutic effect of essential oils on cancer. Moreover, several research groups are now focused on elucidating the molecular mechanism underlying essential oils properties.

It is expected, therefore, that in the future the application of lavender in oncology will further increase.

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