Pharmacological, medicinal and toxicological properties of lavender essential oil: A review

Propriedades farmacológicas, medicinais e toxicológicas do óleo essencial de lavanda: Uma revisão

Propiedades farmacológicas, medicinales y toxicológicas del aceite esencial de lavanda: Una revisión

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Abstract
The natural products extracted from plants are part of traditional medicine and are also therapeutic possibilities for treating many diseases. Recently, its use in the development of new drugs has shown much visibility for its efficiency and few adverse effects. Essential oils extracted from medicinal plants are indicated to treat numerous diseases due to their antimicrobial, antiviral, antimutagenic, anticancer, antioxidant, anti-inflammatory, immunomodulatory, and antiprotozoal properties. Among essential oils, lavender essential oil stands out for having several important pharmacological properties. This review detailed the main studies on essential oils from different species of lavender and obtained a valuable collection on all their pharmacological, medicinal and toxicological potential. In this context, we evaluated lavender essential oil as a promising substance that can help treat several diseases. We provide some evidence and an overview of the potential therapeutic effect of lavender essential oil to guide new research.

Keywords: Lavenders; Essential oils; Therapeutic potentials; Biological properties.

Resumo
Os produtos naturais extraídos das plantas fazem parte da medicina tradicional e também são possibilidades terapêuticas para o tratamento de muitas doenças. Recentemente, seu uso no desenvolvimento de novos medicamentos...
tem mostrado muita visibilidade por sua eficácia e poucos efeitos adversos. Os óleos essenciais extraídos de plantas medicinais são indicados para o tratamento de inúmeras doenças devido às suas propriedades antimicrobiana, antiviral, antimitagênica, anticâncer, antioxidante, antimetamórfica, imunomoduladora e antiprotozoária. Dentro os óleos essenciais, o óleo essencial de lavanda se destaca por possuir diversas propriedades farmacológicas importantes. Esta revisão detalhou os principais estudos sobre os óleos essenciais de diferentes espécies de lavanda e obteve um valioso acervo sobre todo o seu potencial farmacológico, medicinal e toxológico. Nesse contexto, avaliamos o óleo essencial de lavanda como uma substância promissora que pode auxiliar no tratamento de diversas doenças. Fornecemos algumas evidências e uma visão geral do potencial efeito terapêutico do óleo essencial de lavanda para orientar novas pesquisas.

Palavras-chave: Lavandas; Óleos essenciais; Potencial terapêutico; Propriedades biológicas.

1. Introduction

The natural products extracted from plants are part of traditional medicine and are therapeutic possibilities for treating various diseases (Thomford et al., 2018). Recently, its use in the production of new drugs has shown much visibility for its efficiency (Es-Safi et al., 2020; Newman & Cragg, 2012).

In this context, the active compounds extracted from medicinal plants in the form of essential oil have several pharmacological activities (Bakkali et al., 2008). Essential oils are secondary metabolites found in natural products consisting mainly of terpenoids, such as monoterpenes and sesquiterpenes (Bakkali et al., 2008).

Essential oils are recommended to treat numerous diseases due to their antimicrobial, antiviral, antimitagenic, anticancer, antioxidant, anti-inflammatory, immunomodulatory, and antiprotozoal properties (Dhifi et al., 2016; Sharifi-Rad et al., 2017). Thus, new treatment methods using natural products are being developed for human health, considering its low cost and few adverse effects (Carson & Riley, 2003).

Among essential oils, lavender essential oil stands out for having several important pharmacological properties to treat many health problems (Wells et al., 2018). Therefore, in the next section, we provide some evidence and an overview of the potential therapeutic effect of lavender essential oil to guide new research.

2. Methods

We adopted the narrative review methodology, a qualitative study suitable for discussing a given subject and a comprehensive analysis of the literature. This analysis and interpretation of works in the literature facilitate identifying existing problems and gaps to assist in the development of new research (Sant’Anna Ramos Vosgerau & Paulin Romanowski, 2014). A literature review was performed using the following search terms: Essential oil and Lavender or Essential oil and Lavandula. The research included literature until March 2021 in four electronic databases (PubMed, Scopus, Web of Science and Google Scholar). No restrictions were placed in the year of publication for the articles included. The research included articles on humans and animals, in the English language and that contained abstract. The titles and abstracts of the publications were reviewed and after an initial screening of the abstract, the publications that were potentially eligible were reviewed in their entirety and included in the review.
3. Results and Discussion

Lavender essential oil

The Lamiaceae family can be found in practically all-natural ecosystems and comprises more than 200 genera with approximately 6000 species (Salehi et al., 2018). Several species of the Lamiaceae family have valuable essential oils for use in medicinal purposes with several pharmacological properties such as antibacterial, anti-inflammatory, antioxidants and, antivirals, in addition to being widely used in the cosmetics and perfumery industries (Mamadalieva et al., 2017; Raja, 2012). Plants of the Lavandula genus are native to the Mediterranean. However, nowadays, they are grown worldwide due to the constituents of their essential oils that have aromatic and medicinal properties highly valued in the pharmaceutical and cosmetic industry and, currently, in aromatherapy products (Lis-Balchin, 2002; Salehi et al., 2018). Besides, the lavender plants are widely used for decorating environments (Touati et al., 2011). However, its importance is predominantly related to the characteristics of its essential oils, which have internationally regulated standards and have been used for centuries (Cavanagh & Wilkinson, 2002; Woronuk et al., 2011).

The first registers of the use of lavender as an alternative treatment can be found in ancient Greece, and currently, the interest in using it as an alternative treatment for various diseases has been increasing, making lavender and its essential oils very popular (Woronuk et al., 2011). Lavender was widely used in Italy as an antiseptic used after bathing. Besides, it was considered an aphrodisiac plant. On the other hand, oriental medicine uses lavender essential oil for its anxiolytic activity (Samuelson et al., 2020). Currently, many researchers are dedicated to investigating the historical use of lavender and, in this way, several important pharmacological properties such as antioxidants, antibacterial, anxiolytics, analgesics, and anti-inflammatories have been found. These activities may be related to the activity of their terpenoid constituents (Cardia et al., 2018; Generoso et al., 2017; Miladinović et al., 2012; Silva et al., 2015).

The use of essential oils in aromatherapy is widely practiced for the numerous benefits that are found (Cavanagh & Wilkinson, 2002). Several studies have proven that lavender oil can stimulate and improve sleep, reducing stress and anxiety (Bradley et al., 2007; Dobetsberger & Buchbauer, 2011; Gonçalves & Romano, 2013; Hallschmid et al., 2004). Besides, evidence suggests the use of lavender for the treatment of dementia (Smallwood et al., 2001). Other studies suggest using lavender essential oil to treat several health problems due to the important pharmacological activities presented as antimicrobial, anti-inflammatory, antioxidant and, agent anticholinesterase (Cardia et al., 2018; Costa et al., 2012; Hanamanthagouda et al., 2010). A large part of these pharmacological activities found in lavender are their active metabolites, such as flavonoids and phenolic acids, that present several important activities (Costa et al., 2011; Spiridon et al., 2011). Besides, lavender oils are widely used by the food industry, cosmetics, and cleaning products, as in soaps, shampoos, detergents, perfumes, beverages, and food flavorings, due to their pleasant aroma (Bakkali et al., 2008). In this way, all these properties make lavender essential oil stand out in the market.

As explained earlier, essential oils extracted from plants are complex mixtures composed of terpenes, monoterpene, and aromatic compounds, usually with some main constituents (Bakkali et al., 2008; Isman et al., 2011). However, essential oils' characteristics vary due to different factors, such as plant species, climatic conditions, time of harvest, and extraction method. These conditions can modify the amount of main constituents present in the oil (Cheng et al., 2009; Rahimzadeh et al., 2016).

In this way, essential oils' pharmacological and therapeutic properties may be due to an isolated or synergistic effect of the constituents present in the essential oil (Lesage-Meessen et al., 2015). Several studies have shown that the main constituents identified in most lavender essential oils are 1,8-cineole, borneol, camphor, linalool, thymol, α-pinene, β-pinene, and ρ-cymene (Ebadollahi et al., 2020; Woronuk et al., 2011).

Several studies with isolated compounds present in lavender essential oil, such as linalool and linalyl acetate, have shown sedative, anesthetic, and antispasmodic actions. Antimicrobial, antioxidant, and anti-inflammatory activities have been found in constituents such as linalool, 1,8-cineole, camphor, and terpineol (Angioni et al., 2006; Blažeković et al., 2010;
Cavanagh & Wilkinson, 2002; Lis-Balchin & Hart, 1999; Lis-Balchin, 2002; Moon et al., 2007). In addition, Linalool, linalyl acetate, and 1,8-cineole have antispasmodic action. Some insecticidal activities have been determined for linalool, and narcotic activities have been found in linalyl acetate (Lesage-Meessen et al., 2015).

Lavender essential oil in Wound healing

Over the years, several studies have been produced to evaluate the healing activity of many products. Among them, the lavender essential oil stands out with several evidences of its healing effect. Historically the use of lavender essential oil as a healing agent was discovered in France by chance after a chemist applied the oil over a burn on his hand and described a complete recovery process. Besides, oil was widely used during World War II to heal soldiers' wounds (Samuelson et al., 2020).

Studies recommend the topical use of lavender essential oil as a healing agent for speeding up the process of contracting skin lesions and also presenting antimicrobial activity (Altaei, 2012; Ben Djemaa et al., 2016; Mori et al., 2016; Predoi et al., 2018; Vasireddy et al., 2018). Several mechanisms of action are suggested to determine the effect of lavender oil on wound healing. Research has shown that lavender essential oil increases levels of transforming growth factor (TGF)-β, thereby induces an increase in the production of fibroblasts and type I collagen that would assist in improving the injury (Mori et al., 2016). In addition, treatment with lavender essential oil has been shown to increase the amount of fibroblast growth factor-2 (FGF-2) and epidermal growth factor (EGF) (Koca Kutlu et al., 2013). This scarring effect of lavender essential oil may be due to an isolated or synergistic effect of the oil's constituents, such as linalyl acetate and linalool, which also have healing activity (Li et al., 2016).

Lavender essential oil in Aromatherapy

Aromatherapy is a resource used in alternative medicine to treat various disorders using massages, inhalation, or baths (Buckle, 1999; Cooke & Ernst, 2000). The use of lavender essential oil in aromatherapy is widespread. Studies indicate that the aroma exhaled by the wash is effective in reducing anxiety and pain, being a procedure used by many women during childbirth, is considered a safe technique capable of decreasing cortisol and anxiety levels (Ezzo, 2007; Mirzaei, Keshtgar, Kaviani, 2015).

Besides, several clinical trials have determined the ability of lavender essential oil to treat patients with some degree of dementia. It has been shown that the use of aromatherapy with lavender essential oil can reduce body agitation, and when combined with massage therapy, excessive motor behaviour has also been reduced (Holmes et al., 2002; Smallwood et al., 2001). The dermal application of creams containing lavender essential oil was also able to reduce the cognitive impairment of patients with dementia (Joy Bowles, 2002). Although many researches indicate the use of aromatherapy for the treatment of psychological disorders, the studies present several methodological restrictions that can interfere in the interpretation of the results, mainly due to the lack of standardization of the dosage used, however, the published results are quite promising and other studies must be developed (Woronuk et al., 2011).

The use of lavender oil to improve sleep is a practice used for many years. Several studies have proven its effectiveness, increasing the duration of deep sleep in both babies and the elderly (Field et al., 2008; Goel et al., 2005; Hudson, 1996). Besides, lavender essential oil decreased the anxiety levels of intensive care unit patients treated with lavender aromatherapy (Dunn et al., 1995).

Anxiolytic effects of lavender essential oils

There are many reports of the medicinal use of lavender due to its anxiolytic and soothing activity. Anxiety is a disease that affects many people worldwide. Although it is simple, it can get worse and be debilitating, requiring treatment with drugs. Thus, the use of lavender can be an alternative for a lighter treatment than the conventional ones since it does not present many allergic reactions or gastrointestinal complaints (Cavanagh & Wilkinson, 2002; Coulson & Khan, 1999; Leung & Foster, 1996;
Wittchen et al., 2011).

A study with the essential oil of lavender in animals suggested an anxiolytic activity with the treatment with essential oil of lavender. However, depending on the dose, the treatment can reduce the animals' mobility presenting a sedative effect (Shaw et al., 2007). On the other hand, another study showed the activity of lavender essential oil in animals submitted to the test in the open field and concluded that the treatment with lavender inhalation had an anxiolytic effect without reducing the animals' mobility. The authors concluded that the anxiolytic activity of Lavender oil could be mediated by a different mechanism of action than benzodiazepines (Shaw et al., 2011). Besides, the inhalation of lavender essential oil demonstrated an anxiolytic effect, both in stressed animals and in non-stressed animals (Takahashi et al., 2012).

Clinical research has assessed the anxiolytic effect of lavender essential oil. It has shown that patients who have been exposed to aromatherapy have experienced a significant decrease in anxiety conditions due to an effect on the central nervous system, suggesting that lavender essential oil may have a similar action. With benzodiazepines, the use of lavender can therefore be indicated for complementary treatments in patients with anticipatory anxiety (Kritsidima et al., 2010; Tasev et al., 1969; Tisserand, 1988).

The anxiolytic effect of lavender essential oil has proven its effectiveness. There is already a medicine called Silexan, produced with lavender essential oil and indicated for patients with anxiety disorder (Kasper et al., 2010). Experimental animal studies using the elevated plus-maze model showed that treatment with Silexan had an anxiolytic effect, increasing animal exploitation in the environment and social interaction. However, the treatment also showed changes in the animals' motor activity (Kumar, 2013). Another study also using Silexan demonstrated that the animals that were treated had an anxiolytic effect by increasing the exploration of open arms in the elevated plus-maze model, and the authors concluded that the anxiolytic effect of Silexan could be related to the inhibition of kennels of calcium, showing similarities with pregabalin (Schuwald et al., 2013).

**Lavender essential oil alleviates pain and inflammation**

Lavender is an alternative therapy for treating pain and inflammation used in several countries (Djenane et al., 2012). In this sense, many clinical researchers have reported that treatment with aromatherapy or inhalation of lavender essential oil provides a reduction in the pain and inflammation of patients with different types of diseases, such as pediatric, postoperative pain, labor, and various chronic inflammatory diseases (Cardia et al., 2018; Nasiri et al., 2016; Olapour et al., 2013; Ou et al., 2012; Soltani et al., 2013; Yazdkhasti & Pirak, 2016). Besides, the topical application of lavender essential oil effectively reduces pain perception in patients with carpal tunnel syndrome, showing the possible effect of lavender oil on neuropathic pain (Eftekharasadat et al., 2018).

The essential oils of several different lavender plants are being used to treat wounds and burns due to their anti-inflammatory activities (Cavanagh & Wilkinson, 2002; Ez zoubi et al., 2020). Other studies show that lavender essential oil is an important inflammatory agent in preventing liver and kidney damage, reducing the inflammatory process, and inhibiting oxidative stress, proving to be an excellent alternative for treating liver diseases (Aboutaleb et al., 2019; Cardia et al., 2021; Kozics et al., 2017).

Several works were produced to find the possible anti-inflammatory mechanisms of lavender essential oil. Lavender oil treatment has been shown to reduce nitric oxide and various pro-inflammatory cytokines and reduce the inflammatory process in different experimental models (Cardia et al., 2018, 2021; Neves et al., 2010; Zuzarte et al., 2013). In this sense, some studies have determined the anti-inflammatory activity isolated from the main constituents of lavender essential oil, such as 1.8 cineol, camphor, linalool, and linalyl acetate, and have evidenced the significant anti-inflammatory and antiedematogenic effect present in these constituents (Hajhashemi et al., 2003; Peana et al., 2006; Silva-Filho et al., 2015). Another study also demonstrated the anti-inflammatory and cardioprotective activity of lavender essential oil, and the proposed mechanism was due to the antioxidant
activity of its main constituents (Ziaee et al., 2015). Thus, the use of constituents of lavender essential oil in the clinical treatment of different diseases is very promising due to the great anti-inflammatory potential. However, more research is important to deepen the mechanisms of action of these constituents (Peana et al., 2006).

Antioxidant Properties of Lavender essential oil

The antioxidant activity of several natural products, mainly essential oils and compounds isolated from medicinal plants, has gained much interest due to its enormous potential. Several studies have highlighted the antioxidant potential of lavender (Cardia et al., 2021; Dif et al., 2017; Matos et al., 2009). Lavender extracts have antioxidant activity due to their numerous constituents, especially flavonoids and isoprenoids (Tsai et al., 2008). The essential oil of Lavandula officinalis demonstrated hepatoprotective activity due to its ability to inhibit oxidative stress and increase levels of antioxidant enzymes (Cardia et al., 2021). Likewise, Lavandula angustifolia also showed antioxidant activity against lipid peroxidation in a myocardial infarction model in rats (Hui et al., 2010; Ziaee et al., 2015). In addition, another study compared the antioxidant activity of different species of lavender, and Lavandula dentata showed the greatest ability to scavenge free radicals (Dif et al., 2017).

Lavender essential oil in Cosmetics

Lavender essential oils are well known and valued by the cosmetic industry, and their constituents are often used in beauty products mainly for their pleasant aroma (Cavanagh & Wilkinson, 2002; Dreger & Wielgus, 2013). The various species of lavender have different characteristics. Lavandula angustifolia oil has been used in fragrances, cosmetics, and medicines. Besides, the essential oils of Lavandula hybrids are indicated for the anti-louse treatment (Sarkic & Stappen, 2018). Several studies have demonstrated the potential use of essential oil as a natural preservative in cosmetics and beauty products as a substitute for synthetic preservatives that can cause allergic reactions in some consumers (Carvalho et al., 2016; Ghica et al., 2016; Herman et al., n.d.). However, the use of lavender oil in cosmetics must be correctly labeled in products, as we will report in the next topic, some consumers may suffer from contact dermatitis and allergies to some constituents present in the oil.

Toxicity of Lavender essential oil

The oral use of several essential oils without dilution is not indicated as a result of some irritating or cytotoxic effects. Thus, the dilution of the oils is necessary for administration. However, toxicity from the use of lavender is uncommon (Jenner et al., 1964). Lavender essential oil did not demonstrate cytotoxicity in vitro, and in mice, oral administration was considered safe, with an LD50 of 13.5 g/kg (Cardia et al., 2018; Jenner et al., 1964) However, one study evaluated the in vitro genotoxicity of lavender essential oil and its main constituents in the proliferation of lymphocytes. Lavender essential oil and linalool, its main constituent, was considered safe. However, linalyl acetate may have aneugenic activity (Di Sotto et al., 2011). Another in vitro study determined that lavender essential oil damages the cell membrane of human skin (Prashar et al., 2004). Also, some previous work has shown that lavender extract and some of its constituents, such as linalool and linalyl acetate, can cause contact dermatitis in patients with cosmetic dermatitis (Sugiura et al., 2000; Thomson & Wilkinson, 2000). Anyway, several clinical studies present in this review used lavender essential oil in high concentrations and did not show irritability in contact with the skin.

4. Conclusion

Nowadays, the demand for natural products has been increasing more and more, and in this way, the interest in the pharmacological activities of essential lavender oils is being detached. This review detailed the main studies on the different essential oils of lavender and obtained a valuable collection on all their pharmacological potential. In this context, the current
body of literature suggests the lavender essential oil as a very promising substance that has several pharmacological activities such as anti-inflammatory (Cardia et al., 2018), hepatoprotective (Cardia et al., 2021), antidepressant and anxiolytic (Woelk & Schläfke, 2010), cardioprotective (Ziae et al., 2015), analgesic (Silva et al., 2015), wound healing (Mori et al., 2016), antimicrobial and antioxidant (Cardia et al., 2021; Niksic et al., 2017). Thus, with all these properties found in lavender essential oils, new research is important to expand knowledge and use in clinical conditions to determine the therapeutic efficacy of lavender oils.

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