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Review

TRADITIONAL USE OF POLAR EXTRACTS FROM LAVENDER FLOWERS – SYSTEMATIC REVIEW OF LITERATURE DATA

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ABSTRACT

Lavender is one of the most popular herbal medicines used to treat mild mood disorders like anxiety and depression. The most cultivated species is *Lavandula officinalis*, which has a diverse traditional use. This plant is valued for antibacterial, antifungal, hypolipidemic, antioxidant, neuroprotective, anti-aging, diuretic, sedative, hypnotic, anxiolytic and antidepressant properties. However, most often it is used as a water extract for treatment of mild mood disorders (restlessness, insomnia) as additional therapy. Most of the studies were dedicated to the volatile compounds contained in lavender flowers, but few of them were focused on water extract, which contains fewer essential oils, but more polar natural products (polyphenols and other non-volatile compounds). This medicinal plant species is rich in phytochemicals belonging to different chemical groups, including phenolic acids, phenolic aldehydes and flavonoids. Pharmacotherapy of mild mood disorders with infusion of lavender can improve quality of life, so that's why it needs to be investigated more.

KEYWORDS: *Lavandula officinalis*, water extract, gut microbiota, infusion of lavender, non-volatile compounds.

1. Introduction

In the last years, there has been a huge interest in natural products of medical plants and their implementation to treat mental disorders has become widespread. The earliest known records of the genus *Lavandula* come from over 2500 years ago. Early Indian and Tibetan medicine used lavender to treatment of psychiatric disorders. Evidence of lavender use can be found in ancient Egyptian mummification [1]. But nowadays lavender is not less popular than in ancient times.

Various species of the genus *Lavandula* have hypoglycemic, analgesic, tranquillizer, antiseptic, antibacterial activity and have positive effects on wounds, urinal infections, cardiac diseases, and eczema [2]. Moreover, the genus *Lavandula* includes species which have been used traditionally for treatment diseases of the central nervous system (CNS) as epilepsy and migraine, also as sedative remedy. It is being used as an antispasmodic in colic pain and an anticonvulsant [3-5]. Some experiments proved the immunomodulatory activity of lavender *in vitro* as well as intestinal anti-inflammatory effect [6].

In recent years, more and more new activities of *Lavandula officinalis* have appeared. For example, *Lavandula officinalis* was shown to express antihistaminic, anti-tumor properties and modulate the CNS [3]. Moreover, *L. officinalis* is rich in flavonoid luteolin-7-*O*-glucoside that has antiproliferative and antioxidant effects reduces oxidative stress and decreases inflammatory response in different physiological systems [7].

Consequently, pharmacotherapy of mild mood disorders by infusion of lavender (LOI) can improve quality of life [8]. The concern of mild mood disorders continues to increase, and it needs professional psychotherapeutic and psychiatric help. Nevertheless, in the case of mild mood disorders such as anxiety and mild depression, self-care is recommended as sufficient and effective [9].

Among all species of *Lavandula*, only *Lavandula angustifolia* is a source of pharmacopoeial raw material *Lavandulae flos* [10] and one of the most often cultivated plants [11].

2. Materials and Methods

For systematic review, a literature search was conducted using scientific databases such as PubMed, Web of Science Core Collection and Scopus with the keywords "*Lavandula officinalis*", "*Lavandula* *angustifolia*", "gut microbiota", "water extract", "HPLC". Studies written in English or Arabic languages were considered.

3. Results

3.1. Traditional use of LOI

Lavandula angustifolia Mill. (*Lavandula officinalis*), also known as true lavender, is a source of important medicinal plant material - lavender flower (*Lavandulae flos*) belonging to the Lamiaceae family. The genus *Lavandula* consists of 47 species [12] and some of them, including *L. angustifolia*, are used to treat headaches, diabetes, and depression [13]. In ancient Rome, lavender was used as a laxative and as a food additive. The most valuable use was as an additive for baths. Thanks to essential oils, lavender was used to make perfumes and soaps [14]. Therefore, LOI treats restlessness, insomnia, nervous disorders of the stomach and intestines [15]. Generally, *Lavandula angustifolia* as an herbal remedy is linked to anxiolytic properties [16]. LOI was proven to help postpartum women, who have a problem with physical and mental health [17]. In folk medicine it is used as good antioxidant, sedative, antitumor, anti-inflammatory, antihistaminic, antidiabetic, antimicrobial, analgesic and anticonvulsive agent. It is also used for alopecia [18].

Lavender is traditionally used as dried flower arrangements, placed among stored clothing to give a fresh fragrance and as a deterrent to moths [19].

The German Standard license and European guidelines for medicinal tea recommend *L. angustifolia* for a mild tranquilizer, lack of appetite and treatment of sleep disorders. The *Ayurvedic Pharmacopoeia* includes *L. officinalis* indicating its use for digestive (carminative effect) and depressive (sedative effect) disorders [1].

3.2. Chemical composition of *Lavandula officinalis* flowers

Lavender is famous not only for essential oils, but also for containing many other compounds such as polyphenols, coumarins, triterpenes, sterols and tannins [20].

In most studies focused on the effects of lavender, the activity of the essential oil was investigated [12,21,22]. However, this review is focused on herbal preparations, which contain fewer essential oils, but more polar natural products (polyphenols and other non-volatile compounds).

One of the main components contained in the LOI is polyphenols, which are powerful antioxidants and help protect the organism from oxidative stress and inflammation [23]. Polyphenols are plant metabolites, which are commonly presented as flavonoids, characterized by a 15-carbon C6-C3-C6 structure, and non-flavonoids. Flavonoids are categorized as anthocyanins, flavonols, flavan-3-ols, flavones, isoflavones and flavanones [24]. Non-flavonoids are classified into phenolic acids, lignans and stilbenes [25]. Phenolic acids are bioactive compounds, divided into three groups: hydroxybenzoic, phenylacetic and hydroxycinnamic acids [26]. They are classified according to the number of carbons in the chain which is bound to the phenolic ring. Hydroxybenzoic acids belong to C6-C1 type, so, one carbon chain attached to the phenolic ring. Phenylacetic acids are C6-C2 type, with two carbon chains attached to the phenolic ring. C6-C3 type phenolics belong to hydroxycinnamic acids - three carbon chains attached to the phenolic ring [27]. These compounds scavenge free radicals, chelate metal ions and inhibit the activity of pro-oxidative enzymes, for this reason, they have antioxidant activity. Flowers of lavender contain hydroxybenzoic acids (4-hydroxybenzoic acid, 3,4-dihydroxybenzoic acid, protocatechuic acid, vanillic acid, syringic acid, gallic acid), hydroxycinnamic acids (rosmarinic acid, caffeic acid, *p*-coumaric acid, ferulic acid, chlorogenic acid, sinapic acid, cinnamic acid) and flavonoids (luteolin glycosides, apigenin, myricetin, vanillin) [20]. Their chemical structures are presented in Fig. 1. The phenolic compounds found in *Lavandula officinalis* flowers are presented in Table 1.

Table 1. Chemical composition of flowers of *Lavandula officinalis*

Group	Subgroup	Chemical composition	References
Phenolic acids	Hydroxycinnamic acids	Rosmarinic acid	[28], [10]
		Caffeic acid	[28], [10], [29]
		Cinnamic acid	[28], [10]
		Chlorogenic acid	[28], [29]
		p-Coumaric acid	[28]
		Ferulic acid	[28], [10], [29]
		Sinapic acid	[10]
	Hydroxybenzoic acids	Gallic acid	[28], [10]
		Vanillic acid	[28], [10]
		3,4-dihydroxybenzoic acid	[28]
		4-hydroxybenzoic acid	[28], [10]
		Protocatechuic acid	[10]
		Syringic acid	[10]
Flavonoids		Apigenin	[28], [10], [29]
		Luteolin-7-O-glucoside	[10], [29]
		Myricetin	[10], [29]
Phenolic aldehyde		Vanillin	[10]

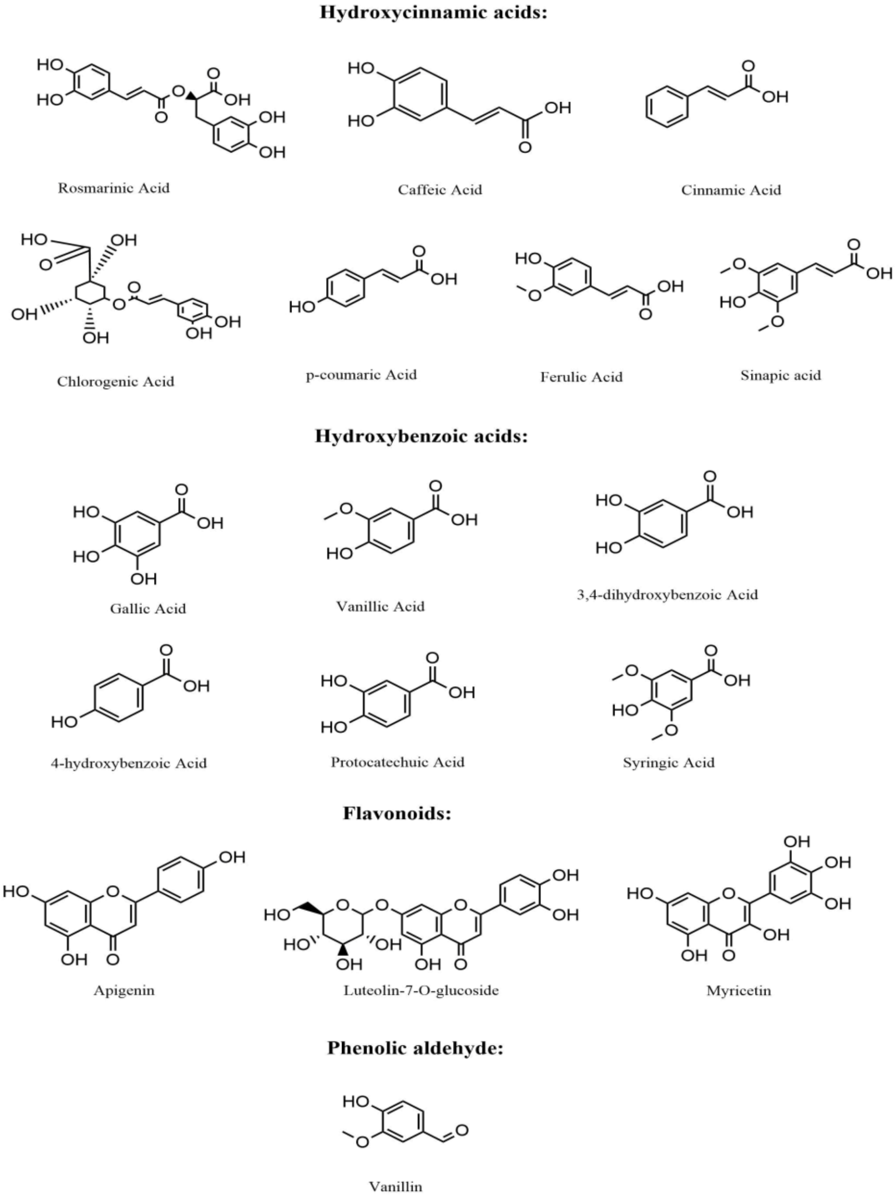

Fig 1. Chemical structures compounds of flowers of *Lavandula officinalis*

The research on the elemental composition of *L. officinalis* flower buds (Table 2) indicated the highest content of Mg and Fe [30].

Table 2. Chemical composition of flowers of *Lavandula officinalis*

Element	Concentration (μg/g)
Cu	0.1141
Pb	0.0077
Mg	4.2063
Fe	4.1350
Cd	not detected
Co	not detected

3.3. The role of gut microbiota in anxiety

Anxiety represents a prevalent minor illness within the spectrum of CNS disorders [31]. The multifaceted nature of anxiety underscores its significance as a subject of ongoing investigation within the neuroscientific community. Numerous etiological mechanisms have been implicated in the pathogenesis of this disease, with emerging attention directed toward the potential involvement of the gut microbiota (GM). The investigation of the interplay between GM and anxiety has become a prominent and burgeoning domain within the scientific community. A mounting body of research endeavors to elucidate the intricate relationship between these factors, contributing to the heightened interest in this scientific paradigm. Nowadays, epidemiological studies about the relationship between GM and anxiety showed changes in microbiota such as augmenting the abundance of *Fusobacteria*, *Bacteroidetes* spp., *Lactobacillales*, *Sellimonas*, and *Streptococcus* and reducing the abundance of *Firmicutes* spp., *Lachnospira*, *Butyricicoccus*, *Prevotella_9*, *Lachnospira*, *Firmicutes*/*Bacteroidetes* and *Faecalibacterium* spp. [32]. The study of Simpson et al. revealed that variations in bacterial taxa suggest that disorders may be defined by an increased prevalence of proinflammatory species (such as *Enterobacteriaceae* and *Desulfovibrio*) and a decreased presence of bacteria that produce short-chain fatty acids (such as *Faecalibacterium*) [33].

The GM residing in the gastrointestinal tract creates a sophisticated, bidirectional network with the brain, the gut-brain axis [34]. This system involves neural, endocrine, and immune pathways [35]. Moreover, GM is a producer of neurotransmitters, including gamma-aminobutyric acid (GABA) and serotonin, which play a crucial role in mood regulation [36]. It is equally important to note that the intestinal microbiota produces metabolites such as short-chain fatty acids (SCFAs) obtained from the diet macronutrients. They are essential in anti-inflammatory effects, controlling the pro-inflammatory cytokines production and neuroprotective effects that play a part in anxiety regulation [37-38]. The GM contributes to hormonal regulation, influencing stress hormones, such as cortisol which is linked to anxiety disorders [39].

The utilization of herbal interventions in addressing mood disorders encompasses a multifaceted array of mechanisms [40]. Because of the rich chemical composition of herbs, they can engage with different pathways, offering a wide spectrum of potential effects, with their interplay with the GM community standing out as a noteworthy aspect [41].

Research on the interaction between *Lavandula* (lavender) and GM is still evolving, but there is growing interest in understanding how lavender and its components may influence gut microbial communities and vice versa. A few studies in the literature have focused on essential oils and their components derived from lavender, notably linalool and linalyl acetate, which exhibit antimicrobial properties capable of influencing the gut microbiota's composition and function [42-43]. Given lavender's frequent consumption as a tea for mild mood disorders, there is a compelling curiosity regarding the potential interactions between water extracts and GM.

Following an extensive examination of the literature, it has been determined that there is a lack of information regarding the LOI interaction with intestinal microbiota. However, Bilan et al. established that feeding rats with *Lavandula angustifolia* dry leaves as part of their combined feed resulted in a decrease in the population of typical *Escherichia coli*. Similarly, the population of *Candida* fungi significantly increased by up to 9%. Additionally, the consumption of *Lavandula angustifolia* by rats notably reduced the number of *Enterococcus* spp., *Proteus* spp., and *Pseudomonas* spp., while increasing the number of *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Candida albicans* [44]. Moreover, several studies have examined isolated compounds, including chlorogenic acid, rosmarinic acid, and apigenin, which are the main constituents found in lavender. Li et al. determined the alteration of rosmarinic acid on mouse intestinal microbiota. They confirmed that rosmarinic acid increases the abundance of *Lactobacillus johnsonii* and *Candidatus Arthromitus* sp *SFB-mouse-NL* and decreases the abundance of *Bifidobacterium pseudolongum*, *Escherichia coli*, and *Romboutsia ilealis* [45]. Mills et al. established that chlorogenic acid selectively changes human faecal microbiota growth increasing *Bifidobacterium* spp. and *Clostridium coccoides - Eubacterium rectale* group, which could be beneficial to host health [46]. Wang et al. described apigenin enhancement in the growth of the genus *Enterococcus* [47].

Additionally, certain studies have outlined the microbial transformations of these single compounds. It is important to know because natural products' metabolites can also modify the structure and function of GM. For example, it is known that dietary apigenin and its glycosides are transformed by GM to 3-(4-hydroxyphenyl)-propionic acid and 3-(3-hydroxyphenyl)-propionic acid [47]. *In vitro* intestinal metabolism of chlorogenic acid showed the production of dihydrocaffeic acid, dihydroferulic acid [46], 3-(3-hydroxyphenyl)-propanoic acid, and phenyl-acetic acid [48]. However, due to the current absence of data on how the human GM transforms LOI, further research is necessary to fully understand both the potential applications and limitations of lavender water extract as an antimicrobial agent or microbiota modulator. Gaining insight into the metabolism of lavender by the intestinal microbiota will contribute to understanding its broader health impacts and potential mechanisms of action in therapeutic interventions for anxiety.

3.4. *In vitro* and *in vivo* studies with *Lavandula officinalis* polar extracts

Existing literature predominantly examines the biological activity of lavender in both *in vivo* and *in vitro* studies, with a primary focus on essential oil. However, there is notably less knowledge regarding research on polar extracts. The available reports primarily emphasize alcoholic and hydroalcoholic extracts, with limited information on aqueous extracts.

In the literature, 4 studies were found describing the sedative and antidepressant effects of LOI in animal models.

In the study conducted by Alnamer, the sedative and hypnotic effects of the aqueous extract derived from the stems and flowers of *Lavandula officinalis* L. were investigated through various behavioral models in male Swiss mice. These models included the traction test, fireplace test, hole-board test, and thiopental-induced sleep test. The findings revealed that the LOI displayed sedative properties, particularly at doses of 200 and 400 mg/kg in the traction test and 200, 400, and 600 mg/kg in the subsequent two tests (methanolic extract showed activity at all doses). Additionally, the aqueous extract did not induce hypnotic effects, in contrast to the methanolic extract, which exhibited activity comparable to diazepam. Moreover, the study underscored the favorable safety profile of the extracts. This was evident from the LD_{50} values, with an LD_{50} exceeding 5000 mg/kg, indicating a remote risk of acute toxicity and demonstrating good tolerance [3].

The next study by Kageyama presented the antidepressant efficacy of aqueous and hydroalcoholic extracts derived from *Lavandula officinalis* in male mice subjected to forced swim tests (FST) and tail suspension tests (TST). The results revealed that LOI, administered at doses of 200 and 400 mg/kg in FST, as well as 100, 200, and 400 mg/kg in TST, exhibited significant and dose-dependent reductions in the duration of immobility time in both tests (hydroethanolic extract showed activity at all doses). Notably, these extracts concurrently increased swimming time without eliciting a significant alteration in climbing time. Furthermore, the observed antidepressant effects were found to be comparable to those induced by fluoxetine [15].

The following research by Abbasi investigated the antidepressant-like effects of lavender aqueous extract in male Wistar rats. LOI, administered orally, significantly reduced immobility time in the FST in doses (100, 200 and 400 mg/kg body weight), comparable to imipramine (30 mg/kg). The effect was not related to motor stimulation, as confirmed by the open field test. Linalool, a major lavender aroma constituent, was absent in LOI, suggesting that non-volatile compounds contributed to the antidepressant-like effects. Rosmarinic acid was identified as a potential active ingredient [49].

The research by Ghadim examined LOI for anxiolytic and antidepressant effects in a chronic mild stress (CMS) in a male Sprague Dawley rats. Using tests like sucrose preference, open field, and elevated plus maze after lavender extract administration, they found CMS-induced anhedonia was alleviated by LOI at 200 and 400 mg/kg doses. LOI, especially at 400 mg/kg, reversed CMS-induced reduction in exploration and anxiety-related behaviors [12].

Studies on the activity of LOI in the treatment of Alzheimer's disease using animal models were also found in the literature.

For example, the study by Soheili explored the impact of LOI on protein expression in male Wistar rats with Alzheimer's (after injection of beta-amyloid (Aß)). Rats were administered lavender extract, and their spatial learning and memory were evaluated through the Morris water maze. The findings revealed significant alterations in protein expression in Alzheimer's rats treated with lavender extract compared to the control group. The comparison between the control and lavender-treated groups revealed 80 new proteins expressed and 104 proteins suppressed in the lavender-treated group. These results suggest a promising potential for enhancing memory and learning [50].

The other study by Afsaneh Arefi Oskouie investigated the therapeutic effects of LOI on memory improvement in Alzheimer's disease. The serum metabolic fingerprint of Aß-induced rat AD models was analyzed using nuclear magnetic resonance (NMR) spectrometry. Lavender extract treatment reversed the direction of changes in 10 metabolite markers, including alanine, glutamine, serine, isoleucine, valine, carnitine, isobutyrate, pantothenate, glucose, and asparagine. These metabolites are associated with altered pathways in carbohydrate and amino acid metabolism [51].

LOI exhibited moderate acetylcholinesterase (AChE) inhibitory activity in microtiter plate assay based on Ellman's method and a thin layer chromatography bioautographic assay conducted by Adsersen. The AChE inhibitory activity was defined as more than 15% at a concentration of 0.1 mg/mL. However, aqueous extracts exhibit lower activity compared to methanolic [52].

There are also reports in the literature about the neuroprotective effect of lavender extract.

The experiment by Büyükokuroglu examined the neuroprotective effects of LOI on glutamate-induced neurotoxicity in rat pups cerebellar granular cell culture. Lavender extract, particularly at doses of 100 µg/mL and 1 mg/mL, significantly protected against glutamate-induced neurotoxicity, with 1 mg/mL being the most effective dose. However, the highest dose (10 mg/mL) showed increased cell death, though statistically insignificant [53].

In a similar study involving a rat model with Aß, conducted by Zali, it was demonstrated that LOI exhibited improvements in spatial performance. Additionally, LOI was found to reduce Aß production and elevate the expression of neuroprotective proteins, including Snca, NF-L, Hspa5, Prdx2, Apoa1, and Atp5a1 [54].

In the literature, the evaluation of the aqueous extract of *Lavandula officinalis* extended beyond its impact on the CNS to explore additional biological activities.

The study by Yaghoobi concludes that the transplantation of human umbilical mesenchymal stem cells provides benefits for spinal cord injury (SCI) in rats. Additionally, the application of LOI enhances these positive effects. Notable findings include improvements in locomotor and sensory functions, increased electro-physiological activity, reduced spinal cord cavities, and diminished astrogliosis with *Lavandula* treatment [55].

Research by Simsek explored the synthesis of silver nanoparticles (AgNPs) using LOI and investigated their impact on U87MG glioblastoma cancer cells (human brain tumor cells). LOI, in a dose-dependent manner, decreased cell proliferation, increased cytotoxicity (IC_{50} value of 7.536 µg/mL), and induction of apoptosis in U87MG cells through the p53-mediated intrinsic apoptotic pathway [56].

The antioxidant activity of plants belonging to the genus *Lavandula* has been demonstrated in a lot of studies and can play a crucial role in neutralizing free radicals, quenching singlet and triplet states by oxygen or decomposing peroxides [10,20,29,57-60].

For example, an experiment by Kemal demonstrated that *Lavandula angustifolia* (lavender) demonstrates strong antioxidant activity, especially before gastric digestion in a simulated gastrointestinal digestion assay. However, its effectiveness declines in the intestinal and colon phases, pointing to variations in the bioaccessibility of phenolic compounds. Additionally, lavender exhibits limited antiproliferative effects against human cancer cell lines (MCF-7, T47D, and Caco-2) compared to certain other plant extracts [61].

The study by Yassine Ez Zoubi showed an antioxidant effect of *Lavandula officinalis* [62]. The stronger antioxidant activity in lavender flowers is determined by the presence of derivatives of rosmarinic and caffeic acids [59]. It depends on the presence of hydroxyl group at position C3 in the flavonoids. What is more, the antiradical properties increase depending on the number of methoxy groups: the greater the number of groups, the greater the antioxidant effects. For example, sinapic acid (2 methoxy groups) compared to ferulic acid (1 methoxy group) will have higher antioxidant activity [10].

A lot of experiments, connected with designing tyrosinase inhibitors, have become a main purpose lately. Some of them showed an impact in preventing melanin-related disorders. Study by Sariri presented screening lavender species (including *Lavandula angustifolia*) for antioxidant and anti-tyrosinase activity. For the experiment a water extracts of LOI were taken and their efficiency as tyrosinase inhibitors was explored. Polyphenols are good scavengers of free radicals. DPPH is a stable free radical and accepts hydrogen atom to become a 2,2-diphenyl-1-picrylhydrazine. In the presented study, a water extract of lavender was checked for its antioxidant activity, and its capacity to neutralize a DPPH free radical. A free radical scavenging activity (SC_{50} - the concentration that scavenges 50% of the DPPH radical) for *Lavandula angustifolia* was 29.2 ± 1.2 µg/mL. It means that extract of lavender has an antioxidant effect, but not high. This study also showed that the extract of lavender inhibited tyrosinase activity but was not potent [19].

Research Mona Zamanian-Azodi concluded that LOI exhibits significant anticancer activity against the MKN45 gastric cancer cell line. Various methods, including MTT assay, microscopic analysis, flow cytometry, and proteomics, were employed to assess its impact. The extract inhibited cell proliferation, induced morphological changes, and predominantly triggered necrosis. Proteomics analysis revealed substantial alterations in protein expression, suppressing three cancer biomarkers (Annexin1, Anolase1, and HSP70) [63].

In a 15-day administration study, Torabzadeh investigated the impact of LOI on liver tissue and blood fat in Balb/C adult female mice. High doses of the lavender extract showed substantial preventive effects on liver cell fat accumulation. Specifically, Group A (500 mg/kg/day) exhibited no fat accumulation in liver cells and notable reductions in triglyceride, LDL, and cholesterol levels compared to other groups. Group B (300 mg/kg/day) displayed a marked reduction in liver fat, while Group C (100 mg/kg/day) exhibited significant fat accumulation, though less than the control groups [64].

The study by Hosseini demonstrated that LOI exerts a hypolipidemic effect by reducing cholesterol, triglyceride, and other lipid metabolites in the experimental groups of mature female BALB/c mice. The hypolipidemic effect is evidenced by a significant decrease in serum cholesterol and LDL levels, particularly in the groups treated with 300 and 500 mg/kg/day of lavender extract. This reduction in lipid levels is notable, even in the group that was treated with high-fat foods and received high doses of the lavender extract [65].

Elhajili showed that administering lavender flower infusion orally to Wistar rats significantly increased urine production (diuresis) and induced moderate sodium excretion (natriuresis). The diuretic effect, originating from tubular activity, was associated with an increase in free water clearance, facilitating the elimination of excess water. Importantly, the study highlighted the stability of aldosteronemia (aldosterone concentrations in the plasma), showing no correlation with plasma sodium levels. This suggests that lavender's diuretic effect is not directly influenced by aldosterone. Additionally, a marked decrease in urinary osmolarity during the peak diuretic response indicated efficient elimination of water overload [66].

The literature also includes an assessment of the toxicity of extracts from *Lavandula officinalis* leaves and flowers, employing a Brine Shrimp (*Artemia Salina*) model, presented by Braguini. The EC50 (36 h) for the hatching success of *A. salina* cysts and LD50 (24h) for aqueous extracts were found to be higher than those for the corresponding hydroethanolic extracts. Additionally, these values were also higher for flower extracts when compared to their leaf counterparts [67].

Among the other applications, the potential anti-aging effects of LOI were explored by assessing the activity of enzymes such as tyrosinase, elastase, and collagenase. However, the extract exhibited no inhibitory effect on these enzymes and showed no antioxidant capacity, as reported by Salem [68].

Interestingly, LOI was tested for antifungal activity against gray mold in Moroccan tomatoes. Lavender extract demonstrated a significant inhibition of sporulation, contributing to the pursuit of safer solutions compared to conventional fungicides. This finding was highlighted by Kasmi [69].

3.5. Clinical studies in anxiety with LOI

Available studies indicated limited information about clinical research of lavender water extract. However, they confirm the impact of LOI on the treatment of mild mood disorders.

For the study of Nikfarjam 120 patients were selected for comparison of effects of *Lavandula officinalis* and Venlafaxine in treating depression. There were three groups: venlafaxine (control group), venlafaxine with *L. officinalis* (*L. officinalis* group) and venlafaxine with *placebo* (*placebo* group). This study showed that the depression scores were significantly different between the control and *L. officinalis* groups and no significant difference in decreased depression scores compared with *placebo* group [70].

A similar experiment was done with methanolic extract combined with another antidepressant medication by Akhondzadeh. The methanolic extract of lavender and imipramine (tricyclic antidepressant) were compared. This study showed that a combination of both is more effective than imipramine alone and is accompanied by less pronounced side effects related to anticholinergic activity and their inducing higher rate of noncompliance in a high dose. So, *Lavandula angustifolia* was shown to reinforce the nervous system and help in cases of nervous exhaustion [71].

However, some research shows that the application of boiling water extract of lavender is also effective. The results of different studies showed a reduction in depression and anxiety after treatment with LOI. As stated in research by Mohammad-Rafi Bazrafshan, after two weeks of treatment of LOI of mild mood disorders the impact of LOI on reducing anxiety and depression was indicated. This effect was connected with the influence on the neurotransmitter pathways, generally blocking the process of the serotonin transporter [72].

The study by Sanei presented investigation of the effect of *Lavandula angustifolia* therapeutic effect in periods of 3 and 20 days before the exam on students. This study showed that LOI is very efficacious in reducing anxiety, but results are not dependent on the duration of consumption (3- or 20-day intervals) [73].

Lavandula angustifolia has a low toxicity profile, so, it has been found safe [71].

3.6. Missing data

GM is very important for human health and influences pathophysiological conditions and drug metabolism [74]. Of course, GM plays an important role in obesity, metabolic syndrome, non-alcoholic fatty liver disease, diabetes, intestinal inflammation, autism spectrum and immune system disorders [75-77]. GM plays a huge role in the metabolism of drugs, so, we can suppose that it works on the other side and plant extracts influence the composition of microorganisms inhabiting the intestine. Intestinal microbiota is considered to be connected with the neuro-endocrine-immune pathways, generating the concept of the gut-brain axis. A lot of people with anxiety and depression suffer from intestinal function disturbances [78]. But until nowadays there is no scientific evidence on the interaction of LOI with GM in the context of the treatment and prevention of anxiety disorders in humans. So, no information on how GM biotransforms LOI to postbiotic metabolites produced in the gut is available as well as the influence on the maintenance of intestinal barrier remains not explored.

The natural products and their gut metabolites were shown to cross the intestinal barrier and improve its functions [79]. One of the most frequently used models for investigating the bioavailability of xenobiotics is the human colon adenocarcinoma cell line - Caco-2 cell model. The analysis of the permeability of compounds contained in analyzed samples through Caco-2 monolayers, cultivated on inserts, provides information about what kind of compounds can cross the epithelium. Some research on the metabolism of xenobiotics shows compounds can be modified while passing through Caco-2 monolayers [80]. That is, with the help of CACO-2 cells it is possible to establish which compounds are bioavailable. But there is no information in the reports about the condition of Caco-2 monolayers after the treatment with LOI, GM, or postbiotic metabolites.

Nowadays comprehensive data on the safety and mechanism of action of plant extracts and raw plant materials is still lacking in many cases. On the other side, the efficacy of LOI was confirmed clinically [71], but without any information on the mechanism of action or compounds responsible for the observed effects and their pharmacokinetics [70].

4. Discussion

Lavandula officinalis is a source of essential oils, but also, the flowers are often used in the form of self-prepared infusions to treat mild symptoms of anxiety [9], [20]. The investigations of essential oil from *Lavandula angustifolia* and its constituents have been done in different variations (linalool, linalyl acetate, cineole, ß-ocimene, p-lavender acetate, lavender alcohol, terpene-4-alcohol and camphor) [81]. The effects of lavender oil on the CNS were established [12], [21,22]. The most attention was dedicated to the volatile compounds contained in lavender flowers [82]. Many studies of lavender's essential oil demonstrated the therapeutic benefits of *L. officinalis* in massage and aromatherapy. For example, a study [83] showed that aromatherapy massage significantly reduces anxiety in breast cancer patients. Hudson described the improvement in the quality of daytime and sleep in the night after aromatherapy of *Lavandula angustifolia* [84]. The next study [85] evaluated pain perception and sleep quality in a participant with rheumatoid arthritis after receiving massage and inhalation of *L. angustifolia*. Aromatherapy with essential lavender oil was used in [86] on a home care hospice patient, demonstrating positive scoring for pulse, blood pressure, pain, anxiety, depression, and well-being. Studies conducted for water extracts of lavender flowers don't have the same volume of information as on aromatherapy. The form of an infusion usually contains small amounts of essential oil while being rich in polar natural products, which can provide a more favorable impact *in vivo* [72].

Reviewing the literature shows that there are no studies about the role of LOI and its postbiotic metabolites produced in the gut in the maintenance of intestinal barrier and interactions of LOI with GM and intestinal barrier. Nowadays interactions with GM and bioavailability of natural products contained in lavender flowers are not clear. The available literature has no information about studies of LOI and its postbiotic metabolites with Caco-2 cells. So, future research should include an exploration of the role of LOI and its postbiotic metabolites produced in the gut.

5. Conclusions

The review explored available scientific literature on water extract of lavender flowers, focusing on *Lavandula officinalis (Lavandula angustifolia)* as the most representative species. In the clinical and preclinical studies, the effect of reducing anxiety, stress and other psychiatric disorders of *Lavandula angustifolia* has been studied. They proved that LOI can be used for mild mood disorders and depression as additional therapy, but still lack information on the mechanism of action or indication of compounds responsible for the observed effects as well as their pharmacokinetics. Nevertheless, there are premises from basic research for the use of lavender in mild mood disorders, but there is still a lack of sufficient research to fully confirm its effectiveness.

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