Lavender as treatment of Alzheimer's disease: literature review

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Abstract

Neurodegenerative diseases affect the grey matter of the brain and secondarily the functions related to the white matter, with aging being one of the main responsible for their development. Among neurodegenerative diseases, dementia stands out, which has been considered by the World Health Organization (WHO) as a public health priority since 2012 due to its high prevalence. It is believed that degeneration of the cholinergic system in the hippocampus and cortex is closely related to cognitive deficits in dementia. Among the forms of treatment for dementia, aromatherapy stands out, which is part of phytotherapy and uses extracts and essential oils extracted from different organs of aromatic plants, and frequently administered via inhalation or topical application. Lavender is one of these plants and has traditionally been used to treat memory dysfunction. Thus, the present study sought to verify in the literature research using Lavandula as a form of treatment for neurodegenerative diseases, especially Alzheimer's disease. The search for the studies took place in January 2020, in the electronic database Web of Science. 42 articles were found, of which 13 adequately met the inclusion criteria. It can be concluded with this review, that both the extract and the essential oil of different lavender species have positive influences on memory formation, as well as on the improvement of cognitive function, especially in patients with Alzheimer's disease.

Keywords: *Dementia; Alzheimer's disease; Phytotherapy; Lavandula.*

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1. Introduction

Neurodegenerative diseases are a group of conditions characterized by the gradual and progressive loss of cells in the brain and spinal cord, caused by the accumulation of pathological proteins.[1] Thus, they affect the grey matter of the brain and secondarily the functions related to the white matter.[2] Aging is considered one of the main responsible for the development of neurodegenerative diseases,[3] where inflammatory mediators,[4] defects in cholinergic transmission,[5] glutamate-induced neurotoxicity[6] and oxidative stress[7] involved in the pathogenesis of these diseases.[8]

Among neurodegenerative diseases, dementia stands out, which has been considered by the World Health Organization (WHO) as a public health priority since 2012 due to its high prevalence.[9] WHO data confirm the aforementioned information and highlight that as the world population ages, the number of people with dementia is expected to triple from 50 million to 152 million by 2050, with about 10 million

people developing dementia each year, and 6 million of them are in low and middle income countries.[10]

Based on the cholinergic hypothesis, the degeneration of the cholinergic system in the hippocampus and cortex is closely related to cognitive deficits in dementia. [11,12] Acetylcholinesterase (AChE) is an enzyme responsible for the hydrolysis of acetylcholine (Ach), and its high activity promotes the formation of beta-amyloid (Aβ) that can contribute to the loss of spatial memory.[13-15] Ach is vital for cognitive functions, but it is a neurotransmitter with low amounts in patients with Alzheimer's disease (AD).[17] Thus, increasing the level of Ach in the brain can be an effective therapy for the treatment of AD.[8]

There are different forms of treatment for dementia, which can be through the use of medications or through non-pharmacological therapy. However, the effects of drugs are limited to the delay in the natural evolution of the disease, allowing only stabilization or temporary improvement of the patient[17] without the ability to cure dementia or change its progressive course,[9] in addition to having significant adverse effects, thus hampering patient compliance.[18]

In this context, another form of treatment for dementia that is growing worldwide is aromatherapy, which is part of phytotherapy and uses essential oils and extracts extracted from different organs of aromatic plants, and frequently administered via inhalation or topical application.[19] The genus *Lavandula*, belonging to *Lamiaceae* family, is one of these plants, has small purple flowers that are used to produce aromatic extracts,[20] which have been traditionally used in the treatment of memory dysfunction.[21] Lavender is composed of more than 100 constituents, whose major components are linalool, linalyl acetate, 1,8-cineole and camphor.[22] Several pharmacological properties are attributed to its extract, including anti-inflammatory and antimicrobial activity,[23] as well as in cancer treatment.[20] The ethanolic extract of *Lavandula officinalis* also demonstrated an improvement in spatial learning and memory, as well as in motor coordination and passive avoidance learning in an animal model.[24] Inhibitory effects of different concentrations of *Lavandula* extract on the AChE enzyme have been proven through various tests on cell lines.[14,22,25]

In addition to the extract, *Lavandula angustifolia* essential oil has shown sedative,[26] anxiolytic[27,28] analgesic effects,[29] and melatonin production.[30] A decrease in neurological deficit, infarct size, carbonyl and reactive oxygen species was also observed in rats submitted to ischemia and reperfusion, demonstrating a strong neuroprotective effect.[31]

Considering the high prevalence, the economic and social importance of neurodegenerative diseases, the difficulty of effective treatments and the potential of products of natural origin, such as essential oils and extracts, the objective of present study was to investigate in the literature research that uses *lavender* as a form of treatment for neurodegenerative diseases, especially Alzheimer's disease.

2. Materials and Methods

This study is characterized as exploratory, of the literature review type. The search for the studies took place in January 2020, in the electronic database Web of Science. The descriptors and keywords used were: lavender, lavandula, neurodegenerative diseases, central nervous system, dementia, Alzheimer, followed by the Boolean operators AND; OR.

Complete articles were included in this literature review, which addressed the use of lavender as a

treatment for neurodegenerative diseases of the central nervous system, especially Alzheimer's disease. Literature review studies and pilot studies were excluded from the sample, as well as studies that approached the use of lavender with another therapeutic approach. All stages of the methodological quality analysis of the articles were carried out by two independent and blind evaluators.

After searching the database, titles and abstracts were evaluated and studies that met the inclusion criteria were selected for full reading. The following characteristics of the publications were recorded: year of publication, name of the author (s), species and form used, as well as the purpose of the study.

3. Results and Discussion

The search in the Web of Science database resulted in the collection of 42 articles, where 13 adequately answered the inclusion criteria, 12 were literature reviews and 17 were outside the proposed theme. The publications that comprised the sample of the present study were published between the years 2009 to 2019 as shown in Table 1.

Table 1 - Studies that used Lavender to treat dementia.

Author (Publication Year)	**Study model**	**Species used**	**Objective of the study**
Jimbo *et al.* (2009)[32]	*In vivo* (human)	Essential oils of rosemary, lemon, lavender and orange (species not reported)	To investigate the healing effects of aromatherapy on dementia in elderly people with Alzheimer's disease (AD)
Kashani *et al.* (2011)[8]	*In vivo* (Wistar rats)	Aqueous extract of *Lavandula angustifolia*	To evaluate the effects of aqueous lavender extract on the spatial performance of rats with AD
Hritcu; Cioanca; Hancianu, (2012)[33]	*In vivo* (Wistar rats)	Essential oils of *Lavandula angustifolia* and *Lavandula hybrida*	Investigate the effects of two types of lavender essential oils on neurological capacity in a model of dementia
Costa *et al.* (2013)[34]	*In vitro*	*Lavandula viridis* extracts	To evaluate the neuroprotective effect of extracts against oxidative damage
Hancianu *et al.* (2013)[34]	*In vivo* (Wistar rats)	Essential oils of *Lavandula angustifolia ssp. Mill angustifolia.* and *Lavandula hybrida* (lavandin)	Investigate the relationship between the antioxidant and anti-apoptotic action of lavender essential oils and their neuroprotective properties in a dementia model

Videira *et al.* (2013)[36]	*In vitro*	*Lavandula luisieri* essential oil	To evaluate lavender essential oil as a possible inhibitor of the enzyme beta-secretase 1 (BACE 1).
Soheili; Tavirani; Salami (2015)[37]	*In vivo* (Wistar rats)	Aqueous extract of *Lavandula angustifolia*	To evaluate the effect of aqueous lavender extract on induction of LTP (long-term potentiation) in the CA1 area of the hippocampus
Zali *et al.* (2015)[38]	*In vivo* (Wistar rats)	Aqueous extract of *Lavandula angustifolia*	To evaluate the protective effect of lavender on the hippocampus of rats in an AD model, studied by proteomic techniques
Xu *et al.* (2017)[39]	*In vivo* (mice)	*Lavandula angustifolia* essential oil	To investigate the effects of lavender essential oil and its active component, linalool (LI), against cognitive impairment in an AD model
Mushtaq Anwar; Ahmad (2018)[40]	*In vivo* (mice)	Methanolic extract of *Lavandula stoechas*	Explore the pharmacotherapeutic role of lavender in the management of dementia
Oskouie *et al.* (2018)[16]	*In vivo* (Wistar rats)	Aqueous extract of *Lavandula angustifolia*	Investigate the therapeutic effects of aqueous lavender extract on Alzheimer's models of rats
Soheili *et al.* (2018)[41]	*In vitro*	*Lavandula angustifolia* essential oil	Assess whether lavender essential oil influences aggregations of beta amyloid (Aβ) plaques
Qneibi et al. (2019)[42]	*In vitro*	Essential oils of *Lavandula dentata* and *Origanum syriacum L.*	Investigate the depressive properties of these oils in AMPA receptors

Source: Elaborated by the authors.

Jimbo et al.[32] examined the effects of aromatherapy on dementia in 28 elderly people, 17 of whom had Alzheimer's disease (AD). The therapy took place for 28 days, where the participants were exposed to the aroma of lemon essential oil (0.04 mL) and that of rosemary essential oil (0.08 mL) in the morning, from 9:00 am to 11:00 am, as well as lavender essential oil (0.08 mL) and orange essential oil (0.04 mL) at night, from 7:30 pm to 9:00 pm. The oils were placed on a piece of gauze in diffusers with an electric fan. Two

diffusers were installed in each room where the patients were transferred. To determine the effects of aromatherapy, patients were assessed using the Gottfries, Brane, Steen scale (GBSS-J), Functional assessment of Alzheimer's disease staging (FAST), Hasegawa's Dementia Scale (HDS-R) and the Scale evaluation of Touch Panel dementia (TDAS).

The study authors observed that all patients showed significant improvement in personal orientation related to cognitive function in GBSS-J and in TDAS after therapy. In particular, patients with AD showed a significant improvement in total TDAS scores. The results of routine laboratory tests did not show significant changes, suggesting that there were no side effects associated with the use of aromatherapy. Thus, they concluded that aromatherapy, through the use of essential oils of lemon, rosemary, lavender and orange, is an effective non-pharmacological therapy for the treatment of dementia and can be a strong potential to improve cognitive function, especially in patients with AD.[32]

In the study by Kashani et al.[8] the effects of *Lavandula angustifolia* aqueous extract on the spatial performance of 80 male Wistar rats with AD were observed. Animal model of AD was established by intracerebroventricular, 20 day prior to the administration of the lavender extract. All animals received lavender intraperitoneally at a volume of 0.4 mL/kg of body weight and were divided into a control group (distilled water) and an experimental group (aqueous extract of *L. angustifolia*), in doses of 50, 100, and 200 mg/kg. The treatment was carried out once a day for 20 consecutive days. The authors observed an improvement in the performance of animals with AD at doses of 100 and 200 mg/kg and believe that the protective effect of lavender extract can be attributed to its anti-inflammatory property, as well as, they believe that the suppression of glutamatergic neurotoxicity may also be responsible for the relief of cognitive deficits in AD.

Researchers Hritcu, Cioanca and Hancianu[33] conducted a survey of 50 male Wistar rats with scopolamine-induced dementia and investigated behavioral recovery after chronic exposure to *Lavandula angustifolia Mill*. and *Lavandula hybrida* essential oils. The animals were exposed to oil vapor (4 drops of oil = 200 μL) for a period of 60 min before conducting behavioral tests, daily, for 7 consecutive days. A significant reduction in anxiety-like behavior and inhibition of depression was observed, suggesting that lavender essential oils have anxiolytic and antidepressant activity. In addition, the performance of spatial memory has also been improved, suggesting positive effects on memory formation. Thus, lavender essential oils can effectively reverse deficits in spatial memory induced by dysfunction of the cholinergic system in the brain of rats and can be considered an opportunity to treat neurological abnormalities in dementia conditions. [33]

The neuroprotective effect of *L. viridis*, an important aromatic plant, as well as its main component, rosmarinic acid, was evaluated in the study by Costa et al.,[34] in relation to the neurotoxic effect, intracellular production of reactive oxygen species (ROS) and activity of the antioxidant enzyme catalase (CAT). The authors carried out an in vitro study on the human astrocyte cell line (A172) and observed that the *L. viridis* extract protected the astrocytes (A172) against oxidative damage. In addition, the protective effect was not caused by CAT modulation, suggesting that other intracellular mechanisms are involved in the neuroprotective effect. Thus, the researchers point out that *L. viridis* extracts, as well as their main

component, rosmarinic acid, have beneficial effects against oxidative damage associated with neurodegenerative diseases, however, they suggest new investigations to fully understand the mechanisms behind the neuroprotective effect of *L. viridis*.[34]

In the study by Hancianu et al.[35] the antioxidant and anti-apoptotic activities of the essential oils of *Lavandula angustifolia ssp. Mill.* and *Lavandula hybrida* were investigated, through the specific activities of superoxide dismutase (SOD), glutathione peroxidase (GPX) and catalase (CAT). The total content of reduced glutathione (GSH), level of malondialdehyde (MDA) (lipid peroxidation) and DNA fragmentation assays were also evaluated in 50 male Wistar rats, submitted to scopolamine-induced dementia model. The animals were exposed to lavender oil vapors for a period of 60 minutes, daily, for 7 continuous days. The authors observed that treatment with lavender oils significantly increased the activities of antioxidant enzymes (SOD, GPX and CAT), reduced the total GSH content and reduced lipid peroxidation (MDA level) was also observed in the temporal lobe of the animals rats, suggesting strong antioxidant potential. In addition, it was noted that DNA cleavage patterns were absent in the lavender groups, suggesting anti-apoptotic activity. Following, the authors suggest that the antioxidant and anti-apoptotic activities of lavender essential oils are the main mechanisms for their neuroprotective effects against oxidative stress induced by scopolamine in the brain of rats. [35]

According to Videira et al.[36] one of the most important characteristics in AD is the generation and deposition of neurotoxic β-amyloid (Aβ) peptide. Inhibition of BACE-1, a key enzyme in the formation of Aβ, is considered a promising therapeutic alternative for this disease. Thus, the authors screened several essential oils for their inhibitory activity in BACE-1 and chose to evaluate *Lavandula luisieri* essential oil as a possible enzyme inhibitor. The essential oil was characterized and demonstrated high levels of monoterpenes containing oxygen, mainly derived from necrodane. According to the study's authors, the main inhibitory activity was attributed to monoterpenic ketone 2,3,4,4-tetramethyl-5-methylene-cyclopent-2-enone, one of the distinguishing components of the essential oil of *L. luisieri*. These results showed that this essential oil and its components inhibited BACE-1 activity, both in enzymatic and cellular assays, presenting the ability to permeate cell membranes, which can be considered a possible treatment for AD.[36]

In the study by Soheili, Tavirani and Salami[37] the effect of the aqueous extract of *Lavandula angustifolia* on LTP (long-term potentiation) of synaptic transmission in the CA1 area of the hippocampus in an Alzheimer's model was evaluated. For the development of this model, the animals received an intracerebroventricular injection of 1 micrograms Aβ1 - 42. Thirty-two male Wistar rats participated in the study, who received intraperitoneally, distilled water or 200 mg/kg of *L. angustifolia* extract. The administrations were carried out for 20 days and the volume of injections was adjusted to 0.4 ml / kg of body weight for all groups of animals. The authors noted that the herbal extract was ineffective in basic synaptic activity in the hippocampus circuits; however, it had a positive impact on the synaptic transmission mediated by the tetanized NMDA receptor, both in normal animals and, mainly, in animals with AD.

The aqueous extract of *L. angustifolia* (200 mg) was also used in the study by Zali et al.[38] in which 30 Wistar rats received treatment administered intraperitoneally once a day, for 20 consecutive days. The animals were divided into two groups, the control group that received distilled water and the experimental

group, which received the treatment with *L. angustifolia* extract. The authors investigated the hippocampus of mice injected with beta-amyloid (Aβ) and treated with *L. angustifolia* by proteomics techniques. The study showed that the lavender extract improves the spatial performance in an animal model of AD, decreasing the production of Aβ, proven through histopathology of the hippocampus.

In addition to the extract, *L. angustifolia* essential oil was also of interest to researchers Soheili, Tavirani and Salami[41] who developed a study to verify whether the oil has an influence on the aggregations of beta amyloid plaques (Aβ) through the measurement technique thioflavin T and atomic force microscopy (AFM). Different doses of *L. angustifolia* essential oil (1, 10 and 100 µg/mL) were used and the results demonstrated that the effectiveness of essential oil in reducing the formation of Aβ aggregates is dose dependent. The dose of 1 µg/mL did not indicate a significant difference, however when the concentration of the herbal medicine increased to 10 µg/mL, the formation of Aβ fibrils occurred, however, the changes were not statistically significant. An additional increase of *L. angustifolia* oil to 100 µg/mL gave rise to real polymerization and induced considerable Aβ aggregates, thus demonstrating that lavender essential oil influences Aβ fibrillation at a dose of 100 µg/mL.

In a previous study, the same researchers observed that the aqueous extract of *L. angustifolia* has an important potential in removing Aβ plaques from the brain of animals with Alzheimer's disease.[43,8] Contrary to the histological evidence of the aqueous extract, the essential oil of *L. angustifolia* polymerized the Aβ peptides in the study by Soheili, Tavirani and Salami.[41] The authors believe that the discrepancy between the two forms of lavender may be due to the different composition of extracts and essential oil. While the essential oil of *L. angustifolia* has linalool and linalyl acetate as its main component, the aqueous extract has rosmarinic acid as its main component[41-37] which according to Ono et al.[45] inhibits Aβ polymerization, confirming the anti-aggregative effect of aqueous lavender extract.[41]

Another recent study was developed to investigate the effects of *L. angustifolia* essential oil and its main component, linalool, on cognitive impairment induced by D-galactose (D-gal) and AlCl3 in male mice. Ninety animals received treatment via intraperitoneal for 8 weeks. The authors observed that *L. angustifolia* oil and linalool significantly improved the cognitive impairment induced by D-gal and AlCl3 in the mice. The results indicated that these effects were related to the relief of oxidative stress, reversing AChE activity and increasing weakened synaptic plasticity. The authors suggest that *L. angustifolia* oil, especially its main linalool component, may have a strong potential to be developed to prevent or improve cognitive deficits in AD.[39]

Oskouie et al.[16] evaluated the effects of aqueous extracts of *L. angustifolia* on the improvement of memory and cognition in an animal model of Alzheimer's, for this, the disease was induced in rats using Aβ, and the serum metabolic investigations were performed using spectroscopy Nuclear Magnetic Resonance (NMR). Forty male Wistar rats were treated with aqueous extract of *L. angustifolia*, at a dosage of 200 mg/kg, intracerebroventricularly, once daily, for 20 days at a volume of 0.4 mL/kg of body weight. Ten metabolic markers, including alanine, glutamine, serine, isoleucine, valine, carnitine, isobutyrate, pantothenate, glucose and asparagine were reversed to control values after treatment with lavender extract. The results revealed that the pathways most affected during the treatment with *L. angustifolia* extract

belonged to the metabolism of carbohydrates and amino acids. As the lavender extract reversed the direction of changes in some metabolites involved in the pathogenesis of AD, the authors concluded that *L. angustifolia* extract may play a role in improving the disease and serve as a potential therapeutic option for the treatment of AD. In addition, the metabolites found in AD mice can serve as a potential panel of markers for the disease; however, more research is needed to validate the results.[16]

It is noticed that medicinal plants, especially those of the *Lamiaceae* family, specifically the genus *Lavandula*, have been widely used as memory enhancers and in the treatment of dementia. Among the forms of use, we highlight the aqueous extracts and essential oils, which due to their low molecular weight and the high hydrophobicity of the terpenoids have a high probability of crossing the cell membranes and the blood-brain barrier.[36] However, some studies have used the extract of *L. angustifolia*, as they believe that due to its components being different from oils, such as rosmarinic acid, it may have some effects not found in essential oil.[44,41]

In the present literature review, it was observed that of the 13 studies included in this research, 7 used lavender essential oil and 6 opted for lavender extract. Since most studies used lavender of the species *L. angustifólia*, two used *L. hybrida*, and only one study used *L. viridis*, as well as *L. luisieri*, *L. stoechas* and *L. dentata*. Of the 13 studies, only one did not report the type of lavender used. Most of the research was carried out in an animal model, four were in vitro studies and one study was carried out in a human model.

Regarding the main effects promoted by lavender essential oil, studies highlight its antioxidant and anti-apoptotic activities, reversing AChE activity and increasing synaptic plasticity. The authors believe that lavender can effectively reverse deficits in spatial memory induced by dysfunction of the cholinergic system, as well as being a strong potential to improve cognitive function, especially in patients with AD, due to its positive effects on memory formation.

Studies using lavender extract have also found positive effects against oxidative damage associated with neurodegenerative diseases, and believe that the aqueous extract of *L. angustifolia* has an important potential in removing Aβ plaques from the brain of animals with Alzheimer's and that suppression glutamatergic neurotoxicity may also be responsible for alleviating cognitive deficits in AD.

5. Conclusion

It can be concluded with this review that there is scientific evidence about the use of lavender essential oil in the formation of memory and in the improvement of cognitive function in an Alzheimer's animal model. Evidence is also found in relation to the antioxidant and anti-apoptotic activities of lavender essential oil, with the ability to reverse AChE activity and increase synaptic plasticity. Regarding lavender extract, it can be concluded that it has positive effects against oxidative damage, as well as in the removal of Aβ plaques from the brain in an Alzheimer's animal model. Thus, it is believed that lavender has a promising activity both in the prevention and in the treatment of cognitive deficits in neurodegenerative diseases, especially Alzheimer's disease.

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