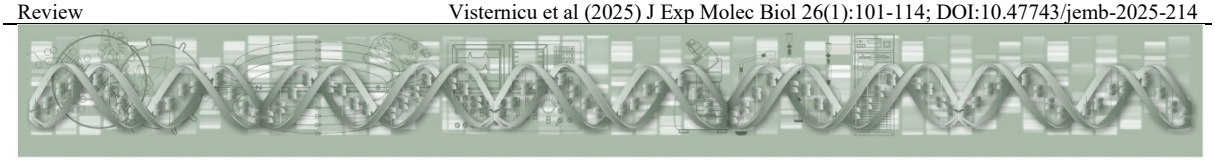

EVALUATION OF THE THERAPEUTIC EFFECTS OF *SALVIA ROSMARINUS* ON NERVOUS SYSTEM DISORDERS

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Abstract

Rosemary (*Salvia rosmarinus* Spenn) is an aromatic plant that has been used for centuries in traditional medicine for its remarkable therapeutic properties. Rosemary contains bioactive compounds with antioxidant, anti-inflammatory, and neuroprotective actions, and it is recognized for its beneficial effects on mental and cognitive health. This review explores the therapeutic potential of rosemary in alleviating nervous system disorders such as Alzheimer's disease (AD), major depressive disorder (MDD), epilepsy, Parkinson's disease (PD), addiction, and attention-deficit hyperactivity disorder (ADHD). Preclinical and clinical research suggests that rosemary extracts, through their active compounds, may enhance cognitive function, protect neurons from oxidative stress, and modulate neurotransmitters involved in cognitive and emotional processes. The findings indicate that rosemary could be a promising complementary therapy in managing nervous system disorders, offering significant benefits for mental and neurological health. However, further studies are needed to fully understand the efficacy and safety of long-term use.

Keywords: *Salvia rosmarinus*, nervous system disorders, neuroprotective effect, memory, ADHD, Alzheimer, Parkinson, epilepsy MDD

Introduction

Nervous system disorders, which involve abnormalities in the functioning or structure of the central or peripheral nervous system (Rahbardar and Hosseinzadeh 2020), have become a major public health issue, contributing to increased morbidity and mortality rates (Teixeira 2024). In recent years, researchers have increasingly focused on medicinal plants, recognized as natural sources for treating various conditions. These plants provide a renewable source of compounds, offering an almost unlimited array of new and complex chemical structures (Andrade et al. 2018). In this context, rosemary, a well-known medicinal plant, is widely used for improving memory deficits and neurodegenerative disorders (Oresanya and Orhan 2024).

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Salvia rosmarinus, an aromatic plant with thin, needle-like leaves, belongs to the Lamiaceae family (de Macedo et al. 2020), known for its multiple therapeutic properties (De Oliveira et al. 2019). Although originally from the Mediterranean region (Rahbardar and Hosseinzadeh 2020), rosemary is found worldwide (De Oliveira et al. 2019). Rosemary leaves are commonly used as a culinary spice, but the plant also has a long history of medicinal use. In traditional medicine, it has been valued for its stimulating and mild analgesic effects, being used to alleviate headaches, improve circulation, reduce inflammation, and combat physical and mental fatigue (Rašković et al. 2014). In folk medicine, it was used as an analgesic, antispasmodic, and treatment for migraines, emotional disorders, depression, and insomnia (Rahbardar and Hosseinzadeh 2020). Due to its antimicrobial (Andrade et al. 2018), anti-inflammatory, antioxidant, anticancer (Li Pomi et al. 2023), and neuroprotective (Faridzadeh et al. 2022) properties, rosemary has become the subject of extensive research, with numerous studies confirming its benefits (Singleman and Holtzman 2014; Rahbardar and Hosseinzadeh 2020).
This study aims to evaluate the therapeutic effects of *Salvia rosmarinus* on nervous system disorders, focusing particularly on AD, MDD, epilepsy, PD, addiction, and ADHD. The study will identify the mechanisms through which the active compounds in rosemary influence cognitive function, reduce oxidative stress at the neuronal level, and regulate neurotransmitters involved in order to evaluate the effectiveness of the plant as a complementary therapy in managing these disorders.

Materials and Methods

This review is based on scientific articles accessed from recognized online databases. Articles written in English were included, using relevant keywords to facilitate the searches. The papers used for this analysis come from the period between 2009 and 2024, and the databases used were: PubMed, Google Scholar, and ScienceDirect. To select and correlate information from the numerous articles found, keywords related to the health benefits of rosemary were used, with a special focus on its positive effects on nervous system disorders. Following the bibliographic analysis, we found that scientific literature uses several names for rosemary, including *'Salvia rosmarinus*,' *'Rosmarinus officinalis*,' and 'rosemary.' These terms are commonly found in scientific studies, peer-reviewed papers, and research, reflecting both linguistic variations and the historical and cultural context of studies on rosemary, highlighting its importance in botany, pharmacology, and gastronomy.
The term (rosemary [Title/Abstract] is the most frequently used and recognized in the scientific literature, with significant results in PUBMED (n=2876), GOOGLE SCHOLAR (n=19800), and SCIENCE DIRECT (n=18638), due to its versatility. Searches using (*Salvia rosmarinus* [Title/Abstract]) in PUBMED (n=1606), GOOGLE SCHOLAR (n=8320), and SCIENCE DIRECT (n=2155), and (*Rosmarinus officinalis* [Title/Abstract]) in PUBMED (n=1606), GOOGLE SCHOLAR (n=3840), and SCIENCE DIRECT (n=5646) generated relevant results (see Figure 1). This terminological diversity can influence how research and interpretations are conducted in studies, emphasizing the importance of considering all names when investigating specialized literature.

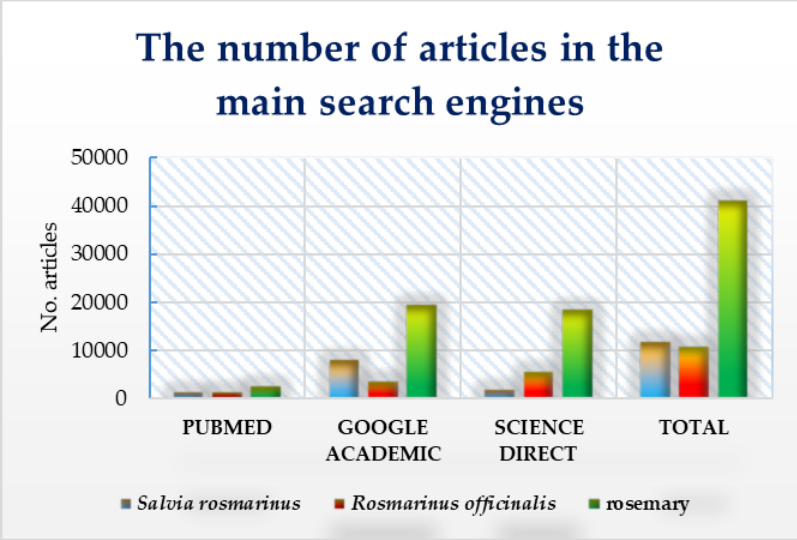

Figure 1. Graphical presentation of the total number of articles found using the main search engines

Results and discussions

To conduct a comprehensive and systematic search, we used the following keywords: ((*Salvia rosmarinus* [Title/Abstract]) AND (memory [Title/Abstract])) AND ((*Salvia rosmarinus* [Title/Abstract]) AND (nervous system disorders [Title/Abstract])) AND ((*Salvia rosmarinus*) [Title/Abstract]) AND (neuroprotective effect [Title/Abstract])) AND ((*Salvia rosmarinus* [Title/Abstract]) AND (ADHD [Title/Abstract])) and combinations thereof.
Inclusion criteria focused on studies published up to September 2024 in English that evaluate the health benefits of rosemary and its therapeutic effects on nervous system disorders, particularly Alzheimer's disease, major depressive disorder, epilepsy, Parkinson's disease, addiction, and attention-deficit hyperactivity disorder. The following exclusion criteria were applied: case reports, letters, abstracts, expert opinions and comments, conference abstracts, books, book chapters, unpublished results, and non-English papers.
Out of the 5.180 initial reports collected through electronic search, 54 articles were included. Due to the heterogeneity of the studies, narrative synthesis was deemed the most appropriate approach. The benefits of rosemary and its therapeutic effects on nervous system disorders were extensively addressed in numerous scientific articles accessed through specific searches. The results of these searches relate to the benefits of rosemary in various fields, particularly highlighting its impact on neurological health.

Medicinal properties of rosemary

Numerous phytochemical studies have demonstrated that the essential oils extracted from rosemary contain terpenoids, flavonoids, and alkaloids, which confer medicinal properties. The most active components identified include diterpenes, triterpenes, and phenolic acids, among which are rosmarinic acid, carnosic acid, rosmanol, carnosol, ursolic acid, and betulinic acid (De Oliveira et al. 2019; Rahbardar and Hosseinzadeh 2020). Triterpenic acids, such as ursolic, oleanolic, and micromeric acids have been shown to be the most effective in reducing inflammation. In addition to crude extracts, rosemary essential oil, which contains compounds such as β-pinene, 1,8-cineole, borneol, camphor, limonene, and verbenone, can be used for topical applications (Micić et al. 2021). The main compounds of rosemary essential oil are α-pinene (14.2–21.4%), 1,8-cineole (3.3–28.3%), and camphor (1.6–25.3%). Variations in the chemical composition of essential oil in different studies have been attributed to differences in

varieties, geographic origins, harvest seasons, environmental conditions, and sampling and extraction methods (de Macedo et al. 2020, Hashemi et al. 2023).

The pharmacological effects of rosemary include reducing inflammation, controlling high blood pressure, managing diabetes, alleviating bronchial asthma, treating peptic ulcers, preventing atherosclerosis, controlling hypercholesterolemia and oxidative stress, exhibiting antiviral action, reducing lipid peroxidation in the heart and brain, as well as combating physical and mental fatigue, in addition to lowering blood sugar levels (De Oliveira et al. 2019). Table 1 presents a detailed analysis of the general therapeutic effects of rosemary extracts and essential oils, including their specific compounds, highlighting their impact on health in various therapeutic contexts, and the neuroprotective power of rosemary will be included in Table 2. Rosemary essential oil is also recognized for its antibacterial activity, having the ability to inhibit the growth of pathogenic bacteria. According to research conducted by Saleh et al. (2022) and Hashemi et al. (2023), essential oil can be effectively used in health product formulations, playing a significant role in combating bacterial infections (Saleh et al. 2022; Hashemi et al. 2023). Additionally, rosemary essential oil exhibits antifungal activity, demonstrating increased sensitivity to fungal infections. This aspect extends its applicability in antifungal treatments (Neves et al. 2018).

Table 1. Pharmacological effects of phytocompounds from *Salvia rosmarinus* reported in the literature

Phytocompounds	***Pharmacological effect***	***Results***	***References***
Rosemary essential oil	Antibacterial activity	Inhibits the growth of bacteria	(Saleh et al. 2022, Hashemi et al. 2023)
	Antifungal activity	Inhibits the growth of fungi	(Neves et al. 2018)
	Wound healing	Accelerated wound healing in both diabetic and non-diabetic animals	(Umasankar et al. 2012)
Rosemary extract	Alopecia	A positive effect in hair growth	(Murata et al. 2013)
Caffeic acid	Antibacterial	Inhibits the growth of gram-negative and gram-positive bacteria	(Kim et al. 2018)
	Antioxidants	Reduces oxidative stress	(Liu et al. 2018)
Carnosic acid	Antitumor	Inhibits the growth of melanoma cells and significantly arrests the cell cycle.	(Lin et al. 2018)
Rosmarinic acid	Anti-inflammatory activity	Reduces biomarkers	(Patil et al. 2019)
		Significant reduction of skin lesions	(Lee et al. 2017)

Carnosic acid and carnosol	Antioxidant activity	Reduces cytochrome c and scavenge hydroxyl radicals	(Murata et al. 2013)
Rosmarinic acid	Anticarcinogenic (skin cancer) activity	Oral administration completely prevented the formation of skin tumors	(Khwaza et al. 2018)
Oleanolic acid	Antivirals	Prevented the entry of the virus by inhibiting the binding of the influenza virus hemagglutinin protein to host cells.	(Khwaza et al. 2018)
α-pinene	Antimicrobial	Antimicrobial capacity against tested species	(Ložienė et al. 2018)

Another remarkable benefit of rosemary essential oil is its ability to accelerate the wound healing process. A study has shown that this oil can improve wound healing in both diabetic animals, which are prone to complications, and non-diabetic animals (Umasankar et al. 2012). This property makes it valuable in regenerative medicine and dermatology. Rosemary extract has also been studied for its effects on hair growth, showing promising results in treatments for alopecia (Murata et al. 2013). This aspect makes rosemary an interesting choice in cosmetic and dermatological products. The extract used in these studies is a hydroalcoholic extract, which is known for its bioactive compounds beneficial in various cosmetic formulations. Caffeic acid also has strong antibacterial effects, inhibiting the growth of both gram-negative and gram-positive bacteria, according to research conducted by Kim et al. (2018). Additionally, caffeic acid is suitable for use in dietary supplements and health care products because it is an effective antioxidant that reduces oxidative stress (Kim et al. 2018, Liu et al. 2018).

Carnosic acid stands out for its antitumor properties, particularly its ability to inhibit the growth of melanoma cells, as highlighted by Lin et al. (2018). This activity positions it as a potential therapeutic agent in cancer treatments. Meanwhile, rosmarinic acid has been found to exhibit anti-inflammatory effects properties, reducing inflammatory biomarkers, suggesting its applicability in managing inflammatory conditions (Patil et al. 2019). Carnosol, another bioactive compound, aids in reducing of skin lesions, positively impacting skin health (Lee et al. 2017). Moreover, both carnosic acid and carnosol have demonstrated antioxidant activity, capable of reducing cytochrome c and capturing hydroxyl radicals, indicating a significant role in cellular protection (Aruoma et al. 1992).

According to Sharmila and Manoharan (2012), rosmarinic acid has anticancer effects, preventing the formation of skin tumors through oral administration. This suggests that rosmarinic acid could be a viable option in cancer prevention.

Finally, oleanolic acid exhibits antiviral properties, demonstrating the ability to prevent the influenza virus into host cells by inhibiting the binding of the hemagglutinin protein, according to the study by Khwaza et al. (2018). Furthermore, α-pinene exhibits significant antimicrobial properties against various species, suggesting its use in hygiene product formulations and natural preservatives (Ložienė et al. 2018). These findings underline the therapeutic potential of rosemary and its compounds, highlighting the need for further studies to explore its applications in medicine and cosmetology.

Moreover, rosemary has been traditionally used as an infusion in the treatment of several diseases, especially against neuropsychiatric disorders, including anxiety, depression, and cognitive disorders. Compounds in rosemary have been associated with reduced anxiety levels and alleviation of depressive symptoms, thus contributing to an overall sense of well-being. Additionally, the consumption of rosemary may improve memory and attention, potentially being useful in cases of dementia or AD. Its pleasant aroma may also help alleviate stress and headaches, such as migraines (Achour et al. 2022). Numerous studies confirm that rosemary has beneficial effects on memory, anxiety, depression, and insomnia. Memory can be improved through its inhibitory effect on acetylcholinesterase in the brain (Nematolahi et al. 2018).

Therapeutic effects of rosemary on nervous system disorders

Mental health issues are becoming increasingly prevalent worldwide, representing a significant challenge for society. In this context, various strategies have been developed to improve mental health, including a growing interest in scientific studies investigating the use of aromatic and medicinal plants as complementary and alternative treatment methods (Sasaki et al. 2013).

Alzheimer's disease is a complex condition characterized by interactions between genetic and environmental risk factors. The most common symptoms include memory loss, deterioration of speech function, and decline in intellectual abilities (Al-Tawarah et al. 2023). The main pathological characteristic of this disease consists of the progressive accumulation of beta-amyloid plaques (Aβ) and neurofibrillary tangles (Malik et al. 2022). The progression of cognitive decline in AD can also be influenced by other factors, such as neuroinflammation and oxidative stress, with the primary source of reactive oxygen species (ROS) being the electron transport chain in the inner mitochondrial membrane (Fernandes et al. 2022).

Although there is no effective remedy for this condition (Capatina et al. 2020), antidepressants used for AD patients fail to significantly alleviate symptoms (Malik et al. 2022). The most used medication for cognitive improvement is methylphenidate (Wenthur 2016). In recent years, natural compounds of plant origin have begun to be considered a promising alternative in the treatment of AD. The pharmacological properties of these compounds are due to their unique structures, allowing them to interact with key enzymes, receptors, antioxidant systems, transcription factors, and cytokines (Malik et al. 2022).

Recent studies suggest that rosemary has beneficial effects on AD, being rich in phenolic compounds and terpenoids that confer antioxidant, antidepressant, and anti-inflammatory activity (Ayaz et al. 2017, Malik et al. 2022). The efficacy of rosemary in the context of dementia and AD has been supported by in vivo research, such as that conducted by Ozarowski et al. (2013), which demonstrated that rosemary extract had a significant impact on long-term memory and cognitive responses in rats. This improvement was associated with the inhibition of acetylcholinesterase activity, an enzyme involved in the degradation of the neurotransmitter acetylcholine, and the stimulation of butyrylcholinesterase (BuChE) in the brains of the rats. These findings suggest that rosemary may play a crucial role in modulating cognitive function, with the potential to support treatments for neurodegenerative conditions (Ozarowski et al. 2013).

Major depressive disorder represents a severe mental health condition characterized by sleep disturbances, suicidal tendencies, lack of energy (Guo et al., 2018), depressed mood, and anxiety (Azizi et al. 2022). This multifactorial disorder is associated with changes in serum cytokine levels, and animal studies have highlighted a link between MDD and various inflammatory pathways, including the activation of tumor necrosis factor (Pferschy-Wenzig et al. 2022). Only one-third of patients with depression respond favorably to antidepressant treatments. This variability in clinical response, along with the risks of side effects and the slow onset of action, poses significant challenges in medical practice, prompting researchers to seek new alternatives for the treatment of depression (Azizi et al. 2022).

Carnosol, a principal active compound found in rosemary, is recognized for its strong antioxidant and anti-inflammatory properties. Due to these characteristics, carnosol has become a subject of interest in neuroprotective research (Faridzadeh et al. 2022). A study conducted by Kim et al. (2006) examined the protective effects of carnosol against rotenone-induced neurotoxicity, a chemical used to model PD. This neurotoxicity affects dopaminergic neurons, which are essential for the normal functioning of the nervous system (Kim et al. 2006).

Epilepsy is a neurological disorder characterized by chronic and persistent neuronal activity resulting from a reduced seizure threshold in the central nervous system (Ayaz et al. 2017). Overactivation of glutamate receptors causes seizures, which can lead to neuronal death. Glutamate plays an essential role in cognitive functions, including learning, memory, and synaptic plasticity; however, increased concentration and overactivation of its receptors contribute to neurodegeneration in the central nervous system (Rahbardar and Hosseinzadeh 2020). Approximately 20-30% of patients with epilepsy experience seizures that cannot be controlled by currently available medications (Schmidt 2009). Assorted studies have demonstrated the effectiveness of rosemary extract in treating induced seizures, highlighting that rosmarinic acid counteracts the effects of hypoxia and ischemia, improving mobility, spatial memory, and cognitive functions (Li et al. 2020, Faridzadeh et al. 2022).

Parkinson's disease is a neurological condition that causes difficulties in maintaining balance, walking, and coordination (Faridzadeh et al. 2022). This idiopathic degenerative disorder of the central nervous system primarily affects the elderly and is characterized by the degeneration of dopaminergic neurons in the substantia nigra of the brain, leading to motor symptoms such as tremors, rigidity, and bradykinesia. In advanced stages, cognitive problems often occur, frequently associated with dementia. The initial treatment for PD includes levodopa (L-DOPA) and dopamine agonists; however, their effectiveness decreases as the disease progresses, and long-term use can lead to motor complications, dyskinesia, and drug-induced toxicity (Stoker and Barker 2020).

The benefits of rosemary in the context of PD are underscored by the neuroprotective action of its bioactive compounds, such as carnosol, eugenol, and luteolin. Carnosol has demonstrated the ability to activate cellular signaling pathways, increase glutathione synthesis (a crucial antioxidant), and improve cellular viability by inhibiting apoptosis. Eugenol has had positive effects on neuronal viability and dopamine release, thus contributing to the alleviation of symptoms associated with PD (Kosmopoulou et al. 2024). Luteolin is associated with reducing oxidative stress and neurotoxicity, protecting neurons from damage. Additionally, compounds like 1,8-cineole and α-pinene have demonstrated antioxidant effects, contributing to neuronal protection by inhibiting the accumulation of ROS. Ursolic acid has also shown neuroprotective potential by improving mitochondrial function. Thus, rosemary may play a crucial role in preventing and managing PD by protecting neurons from damage and supporting brain health (Kosmopoulou et al. 2024).

Addiction is a psychological and physical condition in which a person develops a compulsive need to consume a certain substance or engage in a particular behavior, despite the negative effects it may have on their health and life in general (Heilig et al. 2021). In recent years, substance addiction, and alcohol consumption have become well-documented global issues (Krendl and Perry 2023), with recognition that vulnerability to dependence varies significantly from person to person. These individual differences can be attributed to both genetic and environmental factors, although the influence of each of these factors may vary (Nishizawa and Ikeda 2015). A study involving 81 patients demonstrated that rosemary (8-16 capsules per day, containing 300 mg of dried rosemary leaves) could be used as an herbal remedy to alleviate withdrawal symptoms in the treatment of opioid addiction, and in the case of other opioids as well (Solhi et al. 2013). Additionally, aromatherapy with rosemary oil may offer certain benefits in managing addiction, but it does not represent a complete solution for treating it.

Rosemary essential oil is recognized for its stimulating properties on the brain, its ability to enhance concentration, and its potential to improve well-being, which can indirectly help manage some symptoms associated with addiction (Skipper and Birkmayer 2018).

Attention-deficit/hyperactivity disorder is a commonly encountered neuropsychiatric condition that generates significant difficulties and dysfunctions throughout life. Recent research has provided new insights into the evolution of this disorder, identifying childhood risk factors that may influence the remission or persistence of ADHD in adulthood (López-Martín et al. 2024). However, despite advances in understanding the biological mechanisms of the disorder, the diagnosis of ADHD remains clinical, based on behavioral symptoms such as inattention, impulsivity, and hyperactivity (Zalsman and Shilton 2016; Leffa et al. 2022). One study assessed the effects of administering 75 mg/kg/day of rosemary for 4 weeks to young rats with rotenone-induced ADHD. Rotenone increased impulsivity, oxidative stress, inflammation, and apoptosis; however, rosemary mitigated these effects, improving locomotor activity, recognition index, and reducing oxidative stress and inflammation (Abdelrazik et al. 2023). Rosemary has been shown to improve cognitive performance in both healthy animals and those with cognitive deficiencies. This suggests a positive effect on memory and cognition, although results may vary depending on species, type of extract, and treatment duration.

Recent studies underscore the potential of rosemary in supporting cognitive and emotional health, also highlighting the importance of administering the correct dose to prevent adverse effects (Table 2). Nematolahi et al. (2018) analyzed the impact of administering rosemary extract to 68 students, with an average age of 22.9 years. Participants received a dose of 500 mg twice daily for one month. Rosemary powder, made from dried aerial parts that were encapsulated in 500 mg doses. The rosemary used had a total phenolic content of 20.1 ± 0.12 mg gallic acid/g dry weight. The results showed significant improvements in memory as well as a reduction in anxiety and depression, contributing to better sleep quality. These findings highlight the benefits of rosemary on cognitive and emotional health, particularly among young people (Nematolahi et al. 2018).

Additionally, Achour et al. (2021) investigated the effects of consuming rosemary tea by administering 5 g of dried rosemary infused in 100 ml of hot water daily for 10 days. The results showed promising anxiolytic and antidepressant effects, including an increase in BDNF levels, an important biomarker associated with depression (Achour et al. 2022). Furthermore, Filiptsova et al. (2017) conducted a study on the effects of sprayed rosemary essential oil, involving 53 adolescents aged 13 to 15 years. The results clearly demonstrated that aromatherapy with rosemary essential oil led to improvements in short-term memory (Filiptsova et al. 2017).

Table 2. Efficacy of rosemary in improving cognitive function and emotional state

Administration	*Participant*	*Age*	*Administration*	*Time*	*Results*	*References*
Rosemary	68	22.9 ± 1.7 years	500 mg 2 times/day	1 month	Stimulates memory	(Nematolahi et al. 2018)
Rosemary tea	22	20 - 50 years	5 g of dried rosemary in 100 ml of boiled water once/day	10 days	Reduces anxiety and depression and improves sleep quality	(Achour et al. 2022)
Rosemary essential oil was sprayed	53	13-15 years	-	-	Promising anxiolytic and/or antidepressa nt effects as	(Filiptsova et al. 2017)

					it increases BDNF levels	
Rosemary essential oil aromatherapy	28	86,1 ± 6,9 years	0.08 ml in the morning	28 days	Positive effect on short-term human memory	(Jimbo et al. 2009)
In the form of dried leaf powder	28	Mean age, 75 years	750 mg	7 days	Aromatherapy may have some potential to improve cognitive function, particularly in AD	(Pengelly et al. 2012)
			6000 mg	7 days	Statistically significant beneficial effect compared to placebo	
Rosemary leaves	81	20-50 years	8-16 capsules/day (300 g dry leaves)	14 days	Significant impact effect	(Solhi et al. 2013)

AD- Alzheimer's disease; BDNF - brain-derived neurotrophic factor

Another study conducted by Jimbo et al. (2010) examined the effects of aromatherapy with rosemary essential oil on cognitive function among 28 elderly participants. A dose of 0.08 ml of oil was administered daily in the morning for 28 days. The results indicated that aromatherapy could improve cognitive function, especially in patients with AD (Jimbo et al. 2009). Additionally, research conducted by Pengelly et al. (2012) investigated the effects of rosemary in the form of dried leaf powder on 28 elderly individuals with an average age of 75 years. Participants received 750 mg of rosemary in 7 days, and the results showed a significant beneficial effect on cognitive functions compared to a placebo group. In contrast, the administration of a higher dose of 6000 mg had a significantly negative impact on cognitive function, suggesting that excessive use of rosemary can be harmful (Pengelly et al. 2012).

Conclusions

Due to its remarkable properties, rosemary can be used in the treatment of the nervous system, including anxiety and depression. After analyzing the literature, it is concluded that rosemary has a significant potential to improve cognitive functions, demonstrating efficacy in healthy animals' models as well as those with cognitive impairments. Research suggests a positive impact of rosemary on memory and cognition, thus supporting its use as an adjunct in treatments for cognitive disorders, including AD. However, the available studies show considerable variability, indicating the need for further research to identify the specific factors influencing the efficacy of rosemary, considering the various doses, treatment durations, and species analyzed.

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