

Rosemary (*Rosmarinus officinalis* L.) and its extract for neurodegenerative disease

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Abstract: Rosemary (*Rosmarinus officinalis* L.) is an aromatic evergreen shrub traditionally used for the management of neurological and psychological ailments. Growing evidence highlights its broad pharmacological potential, including antibacterial, anti-inflammatory, antioxidant, antinociceptive, and neuroprotective activities. Rosemary is rich in bioactive secondary metabolites that enhance memory and cognitive performance and exert anxiolytic and antidepressant effects. Mechanistically, its neuroprotective actions involve cholinesterase inhibition, modulation of dopaminergic and oxytocinergic signaling, regulation of oxidative stress and neuroinflammation, and attenuation of neuropathic pain pathways. Preclinical studies demonstrate significant efficacy of rosemary extracts and constituents in animal models of neurodegeneration, including amyloid β - and toxin-induced neurotoxicity, oxidative stress-associated neuronal damage, and chemically induced cognitive impairment. Although preliminary clinical evidence supports these findings, comprehensive clinical validation remains limited. This review highlights the therapeutic potential of rosemary in neurodegenerative diseases and underscores the importance of integrating modern neuroscience with herbal medicine to develop novel, safer neuroprotective strategies.

Keywords: Rosemary, Neurodegenerative diseases, Phytoconstituents, Rosmarinic acid, Alzheimer's disease, Parkinson's disease.

1. Introduction

Neurological disorders (NDs) are a group of conditions that cause structural and functional impairments in sensory and motor neurons, ultimately leading to dysfunction of the nervous system [1]. NDs can be broadly classified into neurodegenerative, neuroinflammatory, and neuroplastic disorders. Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, prion diseases, motor neuron diseases, spinal muscular atrophy, and other cognitive disorders have become increasingly prevalent, largely due to the aging global population [2]. These disorders significantly reduce quality of life and represent the second leading cause of death worldwide, as well as the primary cause of long-term disability [3]. According to a 2019 report by the Pan American Health Organization (PAHO), approximately 500,000 deaths were attributed to neurological disorders in that year, with men accounting for 40% and women for 60% of the total mortality. Among these, the United States of America reported the highest mortality rate, with 47.4 deaths per 100,000 people, followed by Canada and Uruguay [4]. Given the high morbidity and mortality associated with NDs, the development of effective preventive and curative strategies is essential. To date, several classes of drugs have shown therapeutic potential in the management of NDs. These include N-methyl-D-aspartate (NMDA) receptor antagonists such as memantine, and acetylcholinesterase (AChE) inhibitors such as amantadine, baclofen, rivastigmine, tacrine, and donepezil [5]. While these therapies can alleviate symptoms and delay disease progression in the early stages, their long-term use is often associated with adverse effects. These range from mild effects such as dizziness and hormonal imbalance to severe complications, including carcinogenic risks in some cases [6].

Owing to these limitations, natural products have gained considerable attention as safer and more promising alternatives for the treatment of neurological disorders [7]. Plants belonging to the Lamiaceae (mint) family have long been recognized for their medicinal significance. Many members of this family are capable of withstanding the high temperatures characteristic of Mediterranean regions due to their ability to synthesize essential oils [8]. Among them, rosemary (*Rosmarinus officinalis* L.), now botanically recognized as *Salvia rosmarinus*, is a perennial aromatic plant native to the Mediterranean region and widely distributed across the globe [9]. Rosemary is valued not only for its aesthetic, cosmetic, and nutritional properties but also for its extensive therapeutic potential. Numerous studies have reported that rosemary exhibits a wide range of pharmacological activities, including analgesic, antidepressant, antifungal, antiviral, antibacterial, anti-inflammatory, anticancer, antithrombotic, antinociceptive, and antiulcerogenic effects. Additionally, it has demonstrated hepatoprotective properties and therapeutic efficacy in improving symptoms associated with Alzheimer's disease [10-11]. Due to its rich phytochemical profile, various parts of *R. officinalis* L. are used either fresh or dried to prepare extracts and essential oils, which appear as colorless to pale-yellow liquids [12-13].

Rosemary essential oil (REO) is metabolically synthesized and extracted from almost all parts of the plant. It is characterized by its volatility and pleasant aroma. Given its widespread applications in the food, pharmaceutical, and cosmetic industries, REO holds substantial economic value [14-16]. The pharmacological activities of rosemary extracts and essential oils are primarily attributed to their diverse primary and secondary metabolites. These include carnosol, α -pinene, camphor, carnosic acid (CA), chlorogenic acid, oleanolic acid, ursolic acid, eucalyptol, rosmanol, 1,8-cineole, and rosmarinic acid, predominantly polyphenolic diterpenes [17-21]. The synergistic combination of various phytochemicals in rosemary extracts (RE) leads to the formation of unique phenolic compounds, terpenes, essential oils, and aromatic constituents. Water-soluble REs are particularly rich in rosmarinic acid (RA) and are suitable for aqueous formulations, whereas oil-soluble REs contain higher concentrations of diterpenes and are commonly used in lipid-based formulations [22]. The phytochemical composition of rosemary extracts largely depends on the extraction method and solvent employed. In recent years, due to the notable therapeutic potential of REO and its bioactive metabolites, increasing attention has been directed toward their role in neurological health. Consequently, it is proposed that rosemary essential oil and its active constituents may serve as effective alternatives or complementary agents to conventional therapeutic strategies for neurological disorders. This chapter aims to comprehensively explore the chemistry, pharmacology, and secondary metabolites of *R. officinalis* L., with particular emphasis on their therapeutic efficacy against neurological disorders. The mechanisms discussed include modulation of neuroinflammation, inhibition of neuronal cell death, suppression of β -secretase (BACE-1) activity, acetylcholinesterase inhibition, prevention of amyloid- β aggregation, and regulation of mitochondrial redox homeostasis [23].

2. Historical Use and Traditional Knowledge

Throughout history, rosemary (*Rosmarinus officinalis* L.) has attracted considerable interest not only for its culinary and aromatic qualities but also for its remarkable therapeutic potential. Various species of *Rosmarinus* have been traditionally employed in folk medicine for their antioxidant, anti-inflammatory, antispasmodic, diuretic, carminative, expectorant, antiepileptic, and antidiabetic properties, as well as in the management of renal colic, dysmenorrhea, cardiovascular ailments, and respiratory disorders. However, among its many medicinal applications, rosemary has emerged as a particularly valuable agent in the treatment of neurodegenerative disorders. Over the centuries, its use has evolved from traditional folklore and ancient remedies to the subject of rigorous scientific investigation, especially in the context of neurological disorders [24]. Archaeological evidence suggests that rosemary was present in Egyptian tombs dating back to 3000 B.C. By around 500 B.C., civilizations such as the Greeks, Egyptians, and Romans extensively used rosemary not only as a culinary herb but also for its medicinal properties. It was widely believed to enhance memory and cognitive function [25]. Greek students often wore braided garlands of rosemary in their hair—earning it the name “herb of crowns”—to improve memory and mental alertness. Renowned physicians of antiquity, including Hippocrates, Avicenna, and Galen, incorporated rosemary leaves and flowers into ointments and oils prepared by maceration to treat joint pain and promote wound healing [26]. One of the earliest English herbal texts, Banckes' Herbal, also praised rosemary for its health-promoting properties, stating that its fragrance “shall preserve youth,” and recommending its consumption as an herbal tea for protection against various bodily ailments. The text further suggested preparing rosemary in wine or as a decoction for therapeutic baths—referred to as the “bath of life”—believed to strengthen the heart, brain, and entire body, as well as

improve skin health. In the 13th century, Queen Elizabeth I of Hungary reportedly used rosemary water to alleviate symptoms of gout and rheumatism, which was believed to restore vitality and strength [27]. The historical significance of rosemary is further highlighted by its use during the London plague of 1665, when its vapors were inhaled to prevent infection [28]. During World War II, mixtures of rosemary leaves and juniper berries were burned in French hospitals as a disinfectant to eliminate pathogens. In recent decades, scientific research has increasingly focused on the neuroprotective potential of rosemary, driven by the discovery of its bioactive phytoconstituents. These compounds have demonstrated significant therapeutic benefits in neurological conditions such as Alzheimer's disease, Parkinson's disease, migraine, and cognitive disorders, thereby reinforcing rosemary's enduring relevance in modern neurodegenerative disease research [29].

3. Phytochemistry and Pharmacology

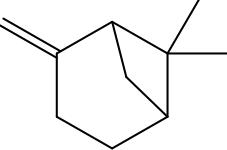
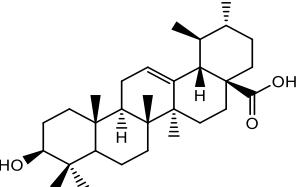
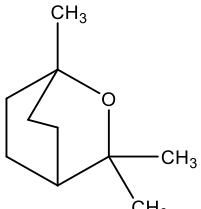
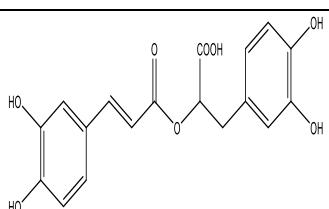
The composition of rosemary essential oil (REO) varies considerably depending on the vegetative stage of the plant and prevailing bioclimatic conditions. The major constituents typically include camphor (5.0–21%), 1,8-cineole (15–55%), α -pinene (9.0–26%), borneol (1.5–5.0%), camphene (2.5–12%), β -pinene (2.0–9.0%), and limonene (1.5–5.0%). In addition to these volatile compounds, a wide range of phytochemicals has been identified in *R. officinalis* extracts. These include betulinic acid, rosmarinic acid, oleanolic acid, carnosol [30], carnosic acid, chlorogenic acid, camphor, camphene, hesperidin, β -myrcene, luteolin-7-O-glucuronide, p-cymene, linalool, isopulegol, terpinen-4-ol, verbenone, caffeic acid, α -pinene, isorosmanol, rosmanol, 1,8-cineole, ursolic acid, apigenin-7-O-rutinoside, eucalyptol, methyl rosmarinate, and rosmarinic acid [31].

Supercritical fluid extraction performed at low temperatures is particularly advantageous, as it preserves the physicochemical integrity of thermolabile and photolabile compounds such as carnosic acid, which is otherwise readily oxidized to carnosol. Polyphenols represent a major class of antioxidant compounds responsible for fruit coloration and play a crucial role in protecting plants against pathogens, herbivores, and environmental stressors. In humans, these compounds are especially effective in controlling infectious agents and mitigating oxidative stress. Common polyphenols present in *R. officinalis* include carnosol [32], diosmin, luteolin, genkwanin, and rosmarinic acid. Collectively, rosemary essential oils, terpenes, and phenolic compounds constitute the principal bioactive components of *R. officinalis*. These phytochemicals comprise more than 10,000 identified molecules and are broadly classified as mono-, di-, tri-, and sesquiterpenes based on the number of carbon atoms and isoprene units. The major secondary metabolites of rosemary, along with their proposed mechanisms of action, are summarized in **Table 1**.

Table 1: Major secondary metabolites along with their possible mechanism of action.

Sr. No.	Phytoconstituents	Structure	Proposed mechanism of action for ND	Ref.
1.	Betulinic acid		Decreased amount of brain damage and cell death, halting the onset of working memory and motor impairments.	[33]
2.	Oleanolic acid		Linked to a decrease in the blood-brain barrier's leakage as well as a decrease in the CNS's inflammatory cell infiltration.	[34]
3.	Carnosol		Reduced demyelination in the myelin oligodendrocyte glycoprotein (MOG35-55) peptide-induced EAE model and reduced inflammatory cell infiltration into the central nervous system, which improved clinical progression.	[35]

4.	Carnosic acid		Prevention of neurodegeneration caused by amyloid- β (A β), autophagy induction, reduction of oxidative stress, and anti-apoptotic effects.	[36]
5.	Chlorogenic acid		Protects against oxidative stress through AMPA receptors, free radical scavenging, Ca $^{2+}$ handling, and antioxidant enzyme modulation, associated with protein kinase A signalling pathways transduction.	[37]
6.	Camphor		Stimulates vasodilatation and constriction after improving the sense of heat and cold through the use of TRPM8 and TRPV3.	[38]
7.	Hesperidin		Hesperidin activates the Nrf2/ Glo-1/ARE pathway, reduces 5-HT/IL- β /TNF- α in hippocampal, and ameliorates anxiety-like behaviors through the PKA/BDNF/CREB pathway.	[39]
8.	Luteolin-7-O-glucuronide		Effectively prevents OGD-induced intracellular Ca $^{2+}$ overload, ATP depletion, and a decrease in mitochondrial membrane potential.	[40]
9.	Linalool		Reduces oxidative stress markers brought on by long-term D-galactose and aluminium trichloride injection, improving the symptoms that are typical of AD.	[41]
10.	Isopulegol		Demonstrated that it effectively reduced the increase in lipid peroxidation induced by PTZ, maintained normal catalase activity, and prevented the loss of GSH.	[42]
11.	Caffeic acid		Activates the PI3/Akt signaling pathway, phosphorylates GSK-3 β , reduces Tau protein hyperphosphorylation, and activates Nrf2, regulating protein translation, oxidative stress imbalance, and eNOS activation, preventing neuronal death in Alzheimer's disease.	[43]

12.	α -pinene		Preserves human dopaminergic SH-SY5Y cells against 6-hydroxydopamine (6-OHDA)-induced damage in PD.	[44]
13.	Ursolic acid		Help prevent mood and cognitive dysfunctions linked to neurodegenerative and psychiatric conditions by modulating the monoaminergic system.	[45]
14.	Eucalyptol		Effectively regulates the development of seizures by demonstrating antioxidant benefits that may be achieved through oxidative stress reduction, muscarinic cholinergic antagonistic antagonism, and monoaminergic system modulation.	[46]
15.	Rosmarinic acid		Alleviate PD by regulating miR-155-5p.	[47]

4. Rosemary and the Active Constituents: Clinical Studies

According to clinical research, the anti-inflammatory and antioxidant properties of rosemary may contribute to its potential neurological benefits. Studies suggest that the plant's bioactive constituents and various extracts may be effective in managing a range of neurological conditions through multiple mechanisms of action. **Table 2** summarizes selected clinical investigations supporting these effects.

Table 2: Clinical investigations on rosemary and its active ingredients on various neurological disorders.

Depression, cognition and learning				
Animal subject	Type of extract/constituent	Dose	Result of the study	Ref.
Mice	Hydroalcoholic extract	10 to 300 mg/kg	The hydroalcoholic extract increased anhedonic and exploratory behaviour and reduced the hyperactivity brought on by olfactory bulbectomy. In animals with bulbectomies, it reduced hippocampus AChE activity and raised serum glucose levels.	[48]
Mice	Ursolic acid	0.01 and 0.1 mg/kg	In both the forced swimming test (10 mg/kg) and the tail suspension test (0.01 and 0.1 mg/kg), ursolic acid shortened the immobility duration. The pretreatment of SCH23390 (0.05 mg/kg, a dopamine D1 receptor antagonist) and sulpiride (50 mg/kg, a dopamine D2 receptor antagonist)	[49]

			inhibited the effect of ursolic acid (0.1 mg/kg) in the tail suspension test.	
Wistar rats	extract with 40% carnosic acid content	50,100 and 200 mg/kg/day	The extract (100 mg/kg) improved the score for retrieving spatial memory. There was a discernible increase in SOD, GPx, and CAT enzyme levels compared to the normal group.	[50]
(hAPP)-J20 mice and (3xTg AD) mice	Carnosic acid		In the Morris water maze test, carnosic acid administration improved memory and learning in hAPP-J20 mice. It also boosted dendritic and synaptic markers and decreased phospho-tau staining, A β plaque count, and astrocytes in the hippocampus.	[51]
Epilepsy and Addiction				
Rats	extract with 40% carnosic acid content	100 mg/kg	Significant reduction in neuronal death in CA1 was observed in the rats in the Kainic Acid (9.5 mg/kg) plus extract group. Decrease in the rats' impairment of spatial memory in the Kainic Acid (9.5 mg/kg) plus extract group. The animals in the aforementioned group showed higher passive avoidance learning deficit, according to the results of the shuttle box test.	[52]
HEK-293T cells	Methanolic and essential oil extracts		The concentration-dependent inhibition of Cav3.2 current is exhibited by both the methanolic extract and the essential oil of rosemary. - These extracts force a negative shift in the balanced inactivation of CaV3.2 current while maintaining the activating properties.	[53]
Mice	Aqueous and ethanol extracts	1.68, 2.4 g/kg and 0.96 g/kg resp.	The quantity of leaps following naloxone administration was reduced by both extracts.	[54]
Mice	Aqueous, methanolic-aqueous, and chlorformic fractions	0.96 g/kg and 1.68 g/kg	On delivering the fractions one hour before the final dose of morphine, the number of jumps decreased.	[55]
Neuropathic pain, Stress and Anxiety				
Rats	Alcoholic extract	100, 200, and 400 mg/kg	Comparing the CCI mice given the vehicle to the three doses of rosemary extract indicated below, the latter two lessened neuropathic behavioural alterations. When compared to CCI mice treated with a vehicle, the levels of Bax, cleaved caspases 3 and 9, Iba1, TNF- α , iNOS, and TLR4 were significantly reduced by 400 mg/kg of rosemary extract.	[56]

Mice	Rosmanol, cirsimarinin and salvigenin	50 to 200 mg/kg	These compounds had anxiolytic, antinociceptive, and antidepressant effects. Additionally, they were found to exhibit biphasic regulation of GABA _A receptors.	[13]
Mice	essential oil		Mice's serum corticosterone level and immobility duration were significantly reduced while inhaling rosemary essential oil, and their brain dopamine levels were also elevated.	[57]
Mice	Rosemary tea	2% w/w	The brain activity of cholinesterase isoforms was reduced in the group that received rosemary therapy.	[58]

5. Mechanism of Action of Rosemary and Its Extract on Various Neurological Conditions

Experimental studies have demonstrated that rosemary extract exhibits potent antioxidant, anti-inflammatory, and anti-acetylcholinesterase activities. It has also been shown to enhance cognitive function, regulate mood disorders by increasing brain-derived neurotrophic factor (BDNF) levels, and reduce acute mental stress, particularly in elderly populations. In Parkinson's disease models, rosemary inhibits neuronal cell death and upregulates ERK1/2 signaling, while also reducing agitation in patients with dementia. The pharmacological effects of rosemary and its extracts on various neurological conditions are discussed below.

5.1 Depression

Depression is a severe and chronic psychological disorder. Clinical and experimental evidence suggests that alterations in central nervous system noradrenergic and serotonergic neurotransmission contribute significantly to its pathophysiology [59]. Another major hypothesis involves dysfunction of brain-derived neurotrophic factor (BDNF) signaling. Additionally, endogenous metabolites and inflammatory cytokines have been implicated in the induction and progression of depressive disorders [49]. The antidepressant-like effects of hydroalcoholic extracts of rosemary leaves and stems were observed in mice following 14 days of behavioral testing. These effects were found to be mediated through interactions with dopaminergic (D1 and D2), serotonergic (5-HT1A, 5-HT2A, and 5-HT3), and noradrenergic (α 1) receptor systems [60]. Chronic oral administration of rosemary hydroalcoholic extract (10–300 mg/kg) for 14 days significantly reduced hyperactivity and anhedonia-like behavior, which correlated with decreased hippocampal acetylcholinesterase (AChE) activity [61]. Ursolic acid, a pentacyclic triterpenoid derived from rosemary, also exhibits antidepressant effects through modulation of dopaminergic pathways and activation of D1 and D2 receptors [62]. Additional studies have identified antidepressant properties in other rosemary constituents, including carnosol, 1,8-cineole, and betulinic acid, all of which are major components of rosemary essential oil.

5.2 Alzheimer's disease (AD)

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive memory loss and cognitive decline resulting from cholinergic dysfunction. Restoration of acetylcholine balance in the brain has therefore been proposed as a therapeutic strategy for alleviating AD symptoms [63]. Rosemary has demonstrated significant efficacy in enhancing memory and reducing oxidative stress, a major contributor to AD pathology. The plant contains natural cyclooxygenase-2 (COX-2) inhibitors, including apigenin, carvacrol, eugenol, oleanolic acid, thymol, and ursolic acid [64]. Rosemary also contains approximately twenty antioxidant and twelve anti-inflammatory compounds. Among these, carnosic acid and ferulic acid exhibit stronger antioxidant activity than commonly used synthetic antioxidants such as butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA). Administration of rosmarinic acid (1, 2, 4, or 8 mg/kg, PO) in mice for acute (4 days) or sub-chronic (2–3 weeks) periods significantly inhibited prolyl oligopeptidase (POP) activity and enhanced cognitive performance [65-66]. Additionally, rosemary extract standardized to 20% carnosic acid improved cognitive deficits in rats by reducing oxidative stress, neuroinflammation, and hippocampal levels of amyloid- β (A β), TNF- α , IL-6, and IL-1 β [67].

5.3 Epilepsy

Epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures resulting from neuronal hyperexcitability and excessive free radical production [68]. This leads to glutamate-mediated excitotoxicity, neuronal apoptosis, hippocampal neuron loss, and cognitive impairment [52]. Rosemary extract (250, 500, and 750 mg/kg) significantly reduced lipid peroxidation by neutralizing free radicals and interrupting oxidative chain reactions. A study demonstrated that rosemary extract containing 40% carnosic acid improved memory, reduced neuronal degeneration, and decreased seizure severity and onset in rats due to its antioxidant properties [69]. Furthermore, rosemary extract inhibited Cav3.2 calcium currents in HEK 293T cells, suggesting neuroprotective and anxiolytic effects.

5.4 Stress and Anxiety

Chronic stress leads to neuronal loss, structural atrophy, and reduced brain volume due to elevated glucocorticoid levels and hyperactivation of the hypothalamic–pituitary–adrenal axis [70]. Stress-induced acetylcholine release further contributes to anxiety and impaired cognitive function. Clinical and experimental studies indicate that rosemary improves mood and cognitive performance in healthy individuals. Inhalation of rosemary essential oil has been shown to exert anxiolytic effects with minimal adverse outcomes. Rosemary tea (2% w/w) demonstrated anxiolytic and antidepressant effects in mice by inhibiting cholinesterase activity [71]. In vivo studies further revealed that rosmarinic acid reduced immobility time in forced swim tests, while caffeic acid also exhibited antidepressant activity. Rosemary essential oil modulates neurotransmitter activity, enhances acetylcholine synthesis, and promotes neuronal differentiation via ERK1/2 phosphorylation in PC12 cells [58].

5.5 Parkinson's disease (PD)

Parkinson's disease is characterized by bradykinesia, resting tremor, rigidity, and postural instability [72], resulting from the progressive loss of dopaminergic neurons in the substantia nigra [73]. These neurons are particularly vulnerable to oxidative stress due to high oxygen consumption and polyunsaturated fatty acid content. Neurotoxicity induced by 6-hydroxydopamine (6-OHDA) involves oxidative stress, mitochondrial dysfunction, and apoptosis [74]. Carnosol has been shown to increase tyrosine hydroxylase expression, an enzyme downregulated in PD. Carnosic acid protects against 6-OHDA-induced neurotoxicity in rat models through its antioxidant and anti-apoptotic effects [75], highlighting its potential as a neuroprotective agent in PD.

5.6 Neuropathic Pain

Neuropathic pain is a chronic condition characterized by dysesthesia, hyperalgesia, and allodynia arising from damage to the central or peripheral nervous system [76]. Pro-inflammatory cytokines such as IL-1 β , produced by immune cells, microglia, and astrocytes, play a central role in pain initiation and maintenance [77]. Hydroalcoholic rosemary extract (10–50 mg/kg, IP) and carnosol (0.5–2 mg/kg, IP) significantly inhibited formalin-induced pain and inflammation in mice [78]. Histological analysis further revealed that terpenoid-rich rosemary extract prevented edema, tissue degeneration, and inflammatory infiltration in the lumbar spinal cord [79], supporting its traditional use in inflammatory and neuropathic pain management.

6. Conclusion

Compelling preclinical evidence suggests that *Rosmarinus officinalis* possesses significant therapeutic potential in the management of neurodegenerative diseases. This chapter highlights the neuroprotective effects of rosemary extracts, primarily attributed to bioactive compounds such as rosmarinic acid and carnosic acid, which exhibit strong antioxidant and anti-inflammatory properties. These compounds reduce oxidative stress, attenuate neuroinflammation, and restore signaling pathways involved in neuronal survival and plasticity. Multiple studies have demonstrated the efficacy of rosemary extracts in improving cognition and memory, suggesting their potential as future therapeutic agents for neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. Despite encouraging preclinical outcomes, further clinical investigations are required to validate efficacy in humans, optimize dosage, and establish standardized formulations. Addressing challenges related to bioavailability and extract standardization will be essential for successful clinical translation.

Overall, rosemary represents a promising natural therapeutic strategy with substantial neuroprotective potential against progressive neurological decline.

7. References

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