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Rosemary (*Rosmarinus officinalis* L.) and nervous system disorders: New findings on its neuroprotective properties

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ABSTRACT

Rosemary (*Rosmarinus officinalis* L.) has gained recognition for its neuroprotective potential, offering therapeutic benefits for various nervous system disorders. Its main components, including rosmarinic acid, carnosic acid, and ursolic acid, exhibit anti-oxidant, anti-inflammatory, neurotransmitter-modulating, and mitochondrial-stabilizing effects. This updated narrative review explores recent advancements in the mechanisms of action of rosemary and its therapeutic applications in various neurodegenerative diseases. Peer-reviewed studies published between 2020 and 2025 were analyzed using electronic databases, including Scopus, Google Scholar, and PubMed. Research assessing the pharmacological properties of rosemary and its main components, molecular pathways, and clinical implications was reviewed to provide a comprehensive evaluation of its neuroprotective potential. Findings reinforce the neuroprotective potential of rosemary and its main components in Alzheimer's disease, anxiety, depression, epilepsy, pain, and Parkinson's disease. They modulate key molecular pathways, including NF-κB, Nrf2, BDNF, NO/cGMP/KATP, and autophagic clearance, leading to reduced oxidative stress, neuro-inflammation, and apoptosis. They also affect neurotransmitter balance and protein aggregation. The ability of these compounds to enhance cholinergic activity, stabilize mitochondrial integrity, and regulate neuro-immune signaling supports cognitive resilience and neuronal protection. Rosemary also exhibits synergistic potential when combined with conventional treatments, such as analgesics and neuroprotective agents, improving therapeutic efficacy while minimizing adverse effects. This updated review consolidates current findings on the neuroprotective effects of rosemary and its active components, offering insights into its therapeutic applications for nervous system disorders. Future research should focus on clinical trials to validate its efficacy and optimize its use in neurological health management.

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Introduction

Neurological disorders are widespread health conditions that impact billions of individuals globally. These conditions arise due to irregularities in the functioning of both the central and peripheral nervous systems. Some neurological disorders, such as Alzheimer's disease and Parkinson's disease, pose significant challenges for those affected, profoundly affecting their quality of life and causing considerable distress (1). Neurological disorders can stem from a variety of causes, including disruptions in metabolic processes, genetic factors, infections, or trauma. Researchers around the world are actively conducting studies and making discoveries to alleviate the impact and prevalence of these conditions, alongside mental health disorders and challenges related to substance abuse (2).

Herbal medicine is increasingly regarded as a crucial resource in managing a variety of illnesses, including those affecting the nervous system (3-5).

Rosmarinus officinalis L. (syn. *Salvia rosmarinus* Spenn.), commonly known as rosemary, belongs to the genus *Rosmarinus* in the family *Lamiaceae*. Native to Europe and the Mediterranean coast of North Africa, this beneficial herb has been valued for its preservative, culinary, and medicinal properties. It has been traditionally used to alleviate conditions like depression, both mental and physical exhaustion, dysmenorrhea, epilepsy, headaches, hysteria, memory enhancement, nervous agitation, rheumatic pain, spasms, and stomach aches (6). Rosemary is rich in bioactive compounds such as terpenoids, essential oils, alkaloids, and flavonoids. Among its most potent active ingredients are triterpenes, phenolic diterpenes, and phenolic acids.

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Key examples include rosmarinic acid, carnosic acid, rosmanol, carnosol, ursolic acid, and betulinic acid, all of which contribute to its diverse therapeutic and preservative potentials (7).

Several studies disclosed that rosemary and its main components have various properties such as anti-inflammatory (8), anti-oxidant (9), anti-apoptotic (10), neuroprotective (7, 11), antinociceptive (12, 13), antidote (14), nephroprotective (15), hepatoprotective (16), cardioprotective (17, 18), antirheumatic (19), antidepressant (20), hypnotic (21), respiratory-supportive (22), and anti-obesity (23). Rosemary is widely recognized as safe for preserving food, but it is essential to consume it in moderation. Overconsumption can lead to risks such as damage to the liver, kidneys, and reproductive system, as well as potential teratogenic effects. Additionally, it is essential to consider its possible interactions with medications (24).

This narrative review aims to present a comprehensive update on the neuroprotective properties of rosemary by analyzing studies published from 2020 to 2025. The primary objective of this work is to bridge the gap between traditional herbal medicine and the progression from preclinical studies to clinical trials. While preclinical research has shed significant light on the potential therapeutic effects of rosemary, particularly in managing neurological disorders, the translation of these findings into effective clinical treatments remains underexplored.

By critically assessing recent advancements in the field, this review seeks to encourage researchers to design innovative formulations that can serve as effective medicinal options. This includes encouraging interdisciplinary integration between academic researchers and healthcare professionals to facilitate the transition of preclinical insights into practical, patient-centric solutions. Furthermore, the study emphasizes the importance of developing cost-effective therapies to improve accessibility, thereby enhancing the quality of life for individuals affected by neurological conditions.

Through its analysis, this review highlights the significance of rosemary as a promising natural resource in advancing the management of nervous system disorders, addressing both its therapeutic potential and practical application in clinical settings.

Methods

A variety of databases were utilized for this study, including Scopus, Google Scholar, and PubMed, focusing on research published between 2020 and 2025. Articles incorporating *in vitro*, *in vivo*, and clinical trials were examined to provide a comprehensive overview. The search was conducted using specific terms such as "rosemary", "*Rosmarinus officinalis* L.", "*Salvia rosmarinus* Spenn.", "rosmarinic acid", "carnosic acid", "ursolic acid", and other keywords related to the nervous system and associated conditions. These included "depression", "learning and memory deficit", "Alzheimer's disease", "Parkinson's disease", "anxiety", "anxiolytic", "learning and memory" "pain", "epilepsy", "seizure", "anticonvulsant," "antinociceptive", "neuropathic pain," "antinociceptive," and "analgesic".

Articles were evaluated for their relevance, with particular emphasis on studies exploring the mechanisms and efficacy of rosemary and its primary components in ameliorating nervous system disorders. Only original articles were included. Exclusion criteria were applied to eliminate non-English publications, non-peer-reviewed sources, and studies not directly related to the therapeutic effects of rosemary on nervous system disorders.

Effects of rosemary and its main components on nervous system disorders

Alzheimer's disease: Learning and memory deficits

Alzheimer's disease is a progressive neurodegenerative condition and the leading cause of dementia worldwide. It is commonly associated with short-term memory loss, cognitive decline, mood disturbances, and behavioral changes, which worsen over time. As the disease advances, affected individuals often experience social withdrawal and reduced engagement with family and their surroundings. While the exact mechanisms driving Alzheimer's disease remain unclear, most current drug treatments are based on the cholinergic hypothesis, which suggests that the disorder stems from a decline in acetylcholine (ACh) production, a neurotransmitter essential for memory and cognitive function. Acetylcholinesterase (AChE) inhibitors are widely used to prevent the breakdown of ACh, thereby aiming to alleviate symptoms. However, alternative theories—such as the amyloid and tau hypotheses—propose that abnormal protein accumulation contributes significantly to disease progression. Additionally, research has highlighted the roles of oxidative stress and inflammation as key factors in cognitive decline (2).

In the following section, studies examining the effects of rosemary and its main components on Alzheimer's disease and learning and memory deficits will be discussed.

In vitro

Rosemary extract

Evaluating rosemary's various extraction methods for their impact on total phenolic content, anti-oxidant activity, and AChE inhibition indicated that Soxhlet extraction with methanol yielded the highest total phenols, the greatest anti-oxidant capacity, and the lowest half-maximal inhibitory concentration (IC_{50}) value for 2,2-Diphenyl-1-Picrylhydrazyl (DPPH) scavenging activity. Furthermore, this method demonstrated considerable AChE inhibition (25).

A research focused on the development and optimization of rosemary extract-loaded polyethylene glycol (PEG) ylated nanoliposomes for potential Alzheimer's disease treatment. Optimized nanoliposomes exhibited a negative zeta potential, high drug encapsulation efficiency, and sustained drug release over 24 hr. The anti-oxidant capacity of nanoliposomes was significantly higher than that of rosemary extract. Protein adsorption studies revealed that nanoliposomes lacking PEG adsorbed the highest amount of plasma proteins in both healthy volunteers and Alzheimer's disease patients. At the same time, infrared attenuated total reflectance (IR-ATR) spectrophotometric analysis indicated stronger hydrogen bonding between PEG and bovine serum albumin in formulations with higher PEG content. Additionally, *in vitro* stability studies confirmed protein corona formation (26).

Another study examined the potential of rosemary extracts as AChE inhibitors. Among the tested extracts, the ethyl-acetate fraction demonstrated the highest inhibitory effect, comparable to the reference inhibitor, galanthamine. Kinetic analysis indicated that the extracts induced a mixed-type inhibition, modifying enzyme activity similarly to galanthamine. Also, the anti-oxidant potential followed the

order: ethyl-acetate > ethanol > aqueous, with ethyl-acetate showing the lowest IC_{50} value, highlighting its superior effectiveness. Further, the total phenolic content was highest in the ethyl-acetate extract, potentially correlating with its potent bioactivity. Molecular docking (*in silico* study) revealed robust interactions between rosmarinic acid and carnosic acid with human AChE, particularly noting strong hydrogen bonding between rosmarinic acid and enzyme residues Ser-293 and Arg-296 (27).

It has been shown that rosemary enhances cell viability and reduces apoptosis in amyloid β (Aβ)25-35-damaged hippocampal neuron HT22 cells, protecting against Alzheimer's disease-associated neurotoxicity by stabilizing mitochondrial membrane potential. By utilizing pharmacological network analysis, researchers identified eight key bioactive compounds in rosemary that interact with genes implicated in Alzheimer's disease, modulating critical pathways such as phosphoinositide 3-kinase (PI3K)-protein kinase B (Akt), Ras-proximate-1 or Ras-related protein 1 (Rap1), mitogen-activated protein kinase (MAPK), and estrogen signaling. Quantitative gene expression analysis confirmed the effect of rosemary on regulating insulin-like growth factor 1 (IGF1), matrix metallopeptidase (MMP)9, SRC, and MAPK14 (28).

Carnosic acid

The inhibitory properties of carnosic acid and its natural derivatives were assessed through *in vitro* enzymatic assays targeting key enzymes associated with neurodegenerative and metabolic disorders. Among the tested compounds, rosmanol exhibited the most vigorous anticholinesterase activity, surpassing standard treatments in efficacy. Additionally, it demonstrated significant inhibition of carbonic anhydrase I while exerting moderate effects on carbonic anhydrase II. Other derivatives also showed notable inhibitory potential, suggesting their relevance as therapeutic candidates (29).

The therapeutic potential of carnosic acid in Alzheimer's disease is underscored by its ability to suppress the CCAAT-enhancer-binding protein (CEBP)β/nuclear factor-kappa B (NF-κB) signaling pathway, effectively reducing inflammation and amyloid-associated processes. The study demonstrated that carnosic acid significantly lowered the production and secretion of key inflammatory cytokines—including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, and IL-6—while also decreasing nuclear accumulation of CEBPβ and NF-κB. Furthermore, carnosic acid inhibited cyclooxygenase-2 (COX-2) expression, alleviated mitochondrial damage, and mitigated apoptosis, contributing to enhanced cellular integrity. Beyond its anti-inflammatory effects, carnosic acid also reduced Aβ40 and Aβ42 secretion in Alzheimer's disease model cells, indicating its role in modulating amyloidogenic processes. Additionally, carnosic acid blocked NF-κB-driven beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) expression, a crucial enzyme in amyloid precursor protein cleavage, by targeting CEBPβ/NF-κB interactions. Experimental findings confirmed that carnosic suppressed NF-κB transcriptional activity, diminished NF-κB deoxyribonucleic acid (DNA) binding, and lowered NF-κB p65 and CEBPβ levels. Co-immunoprecipitation assays verified the disruption of CEBPβ-NF-κB interactions, further contributing to decreased BACE1 expression (30).

Evaluating the neuroprotective effects of carnosic acid against Aβ oligomer-induced toxicity in Alzheimer's disease with SH-SY5Y cells demonstrated that carnosic acid enhanced neuronal survival by inhibiting apoptosis and restoring synaptic integrity. Carnosic acid increased expression levels of synaptophysin, postsynaptic density protein 95 (PSD95), and brain-derived neurotrophic factor (BDNF) proteins essential for synaptic function. Further analysis revealed that the effects of carnosic acid were mediated through the inhibition of N-methyl-D-aspartate receptor subunit 2B (NMDAR2B) phosphorylation, which suppressed calcium overload and activated the extracellular signal-regulated kinase (ERK)-cAMP response element-binding protein (CREB) signaling pathway, crucial for neuroprotection. However, administration of N-methyl-D-aspartic acid (NMDA), an NMDAR agonist, contradicted the effects of carnosic acid (31).

Treating HT22 cells exposed to Aβ25-35 with carnosic acid increased cell viability and reduced apoptosis of injured cells (6).

Rosmarinic acid

Exploring the therapeutic potential of rosmarinic acid in mitigating copper (II)-induced neurotoxicity, a key factor in Alzheimer's disease pathology, demonstrated that rosmarinic acid forms a ternary complex with copper (II) and Aβ, potentially reducing neurotoxic effects (32).

The role of rosmarinic acid in regulating microglial polarization—a key factor in neuro-inflammation linked to sepsis-associated cognitive impairment—was assessed. Using a lipopolysaccharide (LPS)-induced microglial polarization model in BV-2 cells, researchers found that rosmarinic acid inhibited microglial M1 polarization, a pro-inflammatory state, by modulating the receptor for activated C kinase 1 (RACK1)/hypoxia-inducible factor-1 alpha (HIF-1α) signaling pathway. It effectively restored RACK1 levels while suppressing the LPS-induced increase in HIF-1α expression (33).

Treating SH-SY5Y cells exposed to LPS with rosmarinic acid attenuated the up-regulation of glucose-regulated protein 78 (GRP78 and protein kinase RNA-like endoplasmic reticulum kinase (PERK) expression. It also decreased the amounts of mesencephalic astrocyte-derived neurotrophic factor (MANF) (34).

Ursolic acid

To enhance ursolic acid efficacy, a study developed Pullulan-encapsulated ursolic acid nanoparticles for improved drug delivery and AChE inhibition. The nanoparticles, synthesized via solvent evaporation, exhibited an optimal size for cellular uptake and a zeta potential ensuring colloidal stability. The nanoparticles demonstrated a controlled and sustained release over 48 hr, prolonging therapeutic action. Additionally, AChE inhibition was significantly improved compared to free ursolic acid (35).

In vivo

Rosemary extract

Rosemary dried leaves' ethanolic extract could improve spatial and recognition memory in mice with Alzheimer's disease by augmenting the expression of doublecortin and PSD95 (36).

The effects of rosemary leaves' ethanolic extract and methylphenidate were examined on memory in an aluminum chloride-induced Alzheimer's disease mouse

model, comparing them with the conventional treatment, donepezil. Behavioral assessments demonstrated that both rosemary and methylphenidate improved memory function. Although Aβ plaques were detected in the hippocampus of affected mice, none of the treatments significantly reduced amyloid burden (37) (Table 1).

In another investigation, rats were administered oral doses of the rosemary oil or donepezil (positive control) in a scopolamine-induced amnesia-like Alzheimer's disease model. Behavioral assessments revealed significant improvements in long-term, reference, and working memory compared to the normal group. In the therapeutic

Table 1. Effect of rosemary and its main components on Alzheimer's disease, learning, and memory deficit

Compound	Study design	Doses/Duration	Results	Ref.
Alzheimer's disease: Learning and memory deficits				
		In vitro		
Rosemary	HT22 cells	0.01875, 0.0375, 0.075, 0.15, 0.3, 0.6, and 0.8 µg/ml, 24 hr	↑ Cell viability, expression of IGF1, MMP9 ↓Apoptosis, mRNA levels of SRC and MAPK14	(28)
Carnosic acid	SH-SY5Y, human glioblastoma A172, and hCMEC/D3 cells	0.1–10 µM	↓CEBPβ/NF-κB signaling pathway, inflammation and amyloid-associated processes, COX-2 expression, mitochondrial damage, apoptosis, Aβ40 and Aβ42 secretion, BACE1 expression, NF-κB DNA binding	(30)
Carnosic acid	SH-SY5Y cells	-	↑ Neuronal survival, expression of synaptophysin, PSD95, BDNF ↓ Apoptosis, NMDAR2B phosphorylation	(31)
Carnosic acid	HT22 cells	0.5 µg/ml	↑ Cell viability, ↓Apoptosis of injured cells	(6)
Rosmarinic acid	BV-2 cells	-	↑ RACK1 levels ↓ Microglial M1 polarization, HIF-1α expression	(33)
Rosmarinic acid	SH-SY5Y cells	40-160 µM, 24-28 hr	↓ GRP78 and PERK expression, MANF	(34)
		In vivo		
Rosemary dried leaves' ethanolic extract	Male BALB/c mice	100 mg/kg, 15 days, PO	↑ Spatial and recognition memory, expression of doublecortin, PSD95	(36)
Rosemary leaves' ethanolic extract	Male BALB/c mice	100 mg/kg, 5 days, IP	↑ Memory function	(37)
Rosemary oil	Male Wister albino rats	50 and 100 mg/kg, PO	↑ Long-term, reference, and working memory, BDNF level in the hippocampus, neurogenesis within the sub-granular zone	(38)
Rosemary ethanolic extract	Male SAMP8 and SAMR1 mice	20 and 50 mg/kg, 30 days, gavage	↑ Spatial learning and memory, BDNF, Sirt1, neurotransmitter levels, Olig1 and Olig2 expression ↓ Aβ42, inflammatory cytokines	(39)
Rosemary extract	Male Wistar rats	100 mg/kg, 12 weeks, IG	↑ White matter, myelin basic protein intensity, neuronal count, GPx activity ↓ Oxidative stress markers	(40)
Carnosic acid	*Caenorhabditis elegans*	-	↑ cha-1, unc-17, cholinergic function, drp-1, eat-3, phb-1, and phb-2 gene expression ↓ Aβ deposition, age-related paralysis, ace-1 and ace-2 gene expression, AChE, mitochondrial dysfunction, oxidative stress	(41)
Carnosic acid	Male C57BL/6 mice and APP/PS1 (B6C3-Tg [APPswe, PSEN1dE9] 85Dbo/Mmjax) double Tg mice	10 and 30 mg/kg, 5 months, gavage	↑ Cognitive function ↓ Microglial and astrocyte activation, IL-1β, IL-6, TNF-α, interaction between CEBPβ and NF-κB p65, inflammatory gene transcription, neuronal damage	(30)
Di-acetylated carnosic acid	Male 5xFAD mice	10, 20, and 50 mg/kg, three times a week, 3 months PO	↑ Learning and memory ↓ Astrocytic and amyloid plaque formation, phospho-tau aggregates, microglial inflammation	(42)
Rosmarinic acid nano-emulsions	Male Wistar rats	100 µl per nostril, twice a day, 6 day	↑ Cognitive function, brain thiol levels, and rosmarinic acid bioavailability in the brain ↓ Neuro-inflammation, oxidative markers, TBARS, CD11b expression, $GFAP^+$ cell count	(43)
Rosmarinic acid	Sprague-dawley rats	20 mg/kg, 5 days, IP	↑ Motor function, spatial memory, learning, oligodendrocyte progenitor cell proliferation in the sub-ventricular zone, myelin sheaths in the corpus callosum	(44)
Rosmarinic acid	Male Wistar rats	25 and 50 mg/kg, 7 days, IP	↑ SOD activity in the hippocampus and prefrontal cortex	(45)

Continued Table 1.

		mg/kg, 7 days, IP	↓ Working memory deficits, neuronal damage in hippocampal subfields, IL-1β, IL-6, TNF-α, NO, MDA	
Rosmarinic acid	Male BALB/c mice	16 mg/kg, 15 days, PO	↑ Spatial and recognition memory, expression of NeuN, doublecortin, synaptophysin	(36)
Rosmarinic acid	Male Swiss albino mice	0.5 and 1 mg/kg, 28 days, IP	↑ Memory retention, SOD activity, GSH ↓ Cognitive decline, lipid peroxidation, AChE activity, TNF-α, IL-6, c-Jun, caspase-3	(46)
Rosmarinic acid	Male 3 × Tg-AD mice	0.5% of diet, 7 weeks, PO	↑ Cognitive function ↓ Aβ aggregation, phosphorylated tau accumulation, hippocampal inflammation, activation of the JNK signaling pathway	(47)
Rosmarinic acid	Male BALB/c mice,	16 mg/kg, 15 days, PO	↑ Social interaction, expression of doublecortin and Ki-67 ↓ Aβ plaques	(48)
Rosmarinic acid	Male sprague dawley rats	1 ml, 21 days, PO	↑ Cognitive and motor performances ↓Oxidative damage, impaired cell integrity in serum and hippocampus, and cellular damage	(122)
Rosmarinic acid	C57Bl/6 male	500 mg/kg, 52 days, PO	↑ Learning and memory in aged mice ↓ BDNF levels in young females	(49)
Rosmarinic acid	APP/PS1 transgenic mice	-	↑ Cognitive function, Ach levels in the hippocampus ↓ Aβ oligomer expression, Aβ deposition, AChE activity	(50)
Rosmarinic acid	C57Bl/6N mice	500 mg/kg, 42 days, PO	↑ Glp1r expression in both sexes, NF-κB, GR, and STAT3, and Lhb expression in females ↓ Memory impairment, insulin resistance in males, oxidative stress pathways in the hippocampus in males, Lhcgr expression in females	(51)
Rosmarinic acid	Mice	-	↑ Whole-brain glucose uptake ↓ Hippocampal neuron loss, microglial M1 polarization	(33)
Rosmarinic acid	Male C57BL/6 mice	20 and 40 mg/kg, 14 days, IP	↑ Cognitive function, MANF expression in CA1 and dentate gyrus ↓ PERK protein levels	(34)
Ursolic acid	Male BALB/c mice	40 mg/kg, 15 days, PO	↑ Spatial and recognition memory, Ki67, expression of NeuN, doublecortin, synapsin I	(36)
Ursolic acid	Male BALB/c mice	40 mg/kg, 15 days, PO	↑ Social interaction, expression of doublecortin and Ki-67 ↓ Aβ plaques	(48)
Ursolic acid	*Caenorhabditis elegans*	-	↑ Proteasome activity ↓ Aβ deposits, monomers, and oligomers, paralysis, hypersensitivity to serotonin in transgenic nematodes	(52)
Ursolic acid	Male Wistar rats	250 mg/kg, 8 weeks	↑ Spatial memory, Nrf2 expression, SOD	(53)
Ursolic acid	Male Wistar rats	500 mg/kg, 8 weeks, PO	↑ IRS2 levels ↓ IL-1β, TNF-α, c-Jun, tau,	(54)
		Clinical trials		
Rosemary aerial parts powder	50 healthy participants	1000 mg, 30 days, PO	↑ Antioxidant defense, total antioxidant capacity ↓AChE activity, protein carbonylation	(55)

Ach: acetylcholine; AChE: acetylcholinesterase; Aβ: amyloid beta; BACE1: beta-site amyloid precursor protein cleaving enzyme 1; BDNF: brain-derived neurotrophic factor; CA1: cornu ammonis 1; CD11b: cluster of differentiation molecule 11b; CEBPβ: CCAAT-enhancer-binding protein beta; COX-2: cyclooxygenase-2; DNA: deoxyribonucleic acid; GFAP: glial fibrillary acidic protein; Glp1r: glucagon-like peptide 1 receptor; GPx : glutathione peroxidase; GR: glutathione reductase; GRP78 : glucose-regulated protein 78; GSH: glutathione; HIF-1α: hypoxia-inducible factor-1 alpha; IGF1: insulin-like growth factor 1; IL: interleukin; IRS2: insulin receptor substrate 2; Lhb: luteinizing hormone beta subunit; Lhcgr: luteinizing hormone/choriogonadotropin receptor; MANF: mesencephalic astrocyte-derived neurotrophic factor; MAPK: mitogen-activated protein kinase; MDA: malondialdehyde; MMP: matrix metalloproteinase; mRNA: messenger ribonucleic acid; NeuN: neuronal nuclei; NF-κB: nuclear factor kappa B; NMDAR2B: N-methyl-D-aspartate receptor subunit 2B; NO: nitric oxide; Nrf2: nuclear factor erythroid 2-related factor 2; Olig: oligodendrocyte transcription factor; PERK: protein kinase RNA-like endoplasmic reticulum kinase; PSD95: postsynaptic density protein 95; RACK1: receptor for activated C kinase 1; SOD: superoxide dismutase; STAT3: signal transducer and activator of transcription 3;TBARS: thiobarbituric acid reactive substances; TNFα: tumor necrosis factor alpha.

phase, memory processing enhancements were observed relative to the positive control group. Furthermore, hippocampal analysis indicated dose-dependent increases in BDNF levels, alongside enhanced neurogenesis within the sub-granular zone, reversing scopolamine-induced suppression (38).

The administration of the ethanolic extract of rosemary to mice in an animal model of Alzheimer's disease improved spatial learning and memory in the Morris water maze test, reduced levels of Aβ42 and inflammatory cytokines (TNF-α, IL-6), and increased BDNF, sirtuin (Sirt)1, and neurotransmitter (serotonin, noradrenaline, and dopamine) levels. Also, the extract up-regulated genes associated with oligodendrocyte differentiation, myelination, and adenosine triphosphate (ATP) production while down-regulating stress, neuro-inflammation, and apoptosis-related genes. Notably, rosemary extract increased oligodendrocyte transcription factor (Olig)1 and Olig2 expression (39).

It has been reported that aging led to decreased neuronal markers and increased malondialdehyde (MDA) levels in the prefrontal cortex of rats, while rosemary extract supplementation significantly improved white matter, myelin basic protein intensity, neuronal count, and glutathione peroxidase (GPx) activity, alongside reducing oxidative stress markers. However, comparisons between young untreated and old rosemary extract-treated groups showed no significant differences (40).

Carnosic acid

Using *Caenorhabditis elegans* Alzheimer's disease models, researchers examined the ability of carnosic acid to counteract Aβ toxicity. The findings revealed that carnosic acid protected neurons from Aβ-induced damage, reduced Aβ deposition, and delayed age-related paralysis. Carnosic acid down-regulated ace-1 and ace-2 gene expression, while up-regulating cha-1 and unc-17, leading to AChE inhibition and improved cholinergic function. In addition, carnosic acid mitigated Aβ-related mitochondrial dysfunction and oxidative stress by enhancing drp-1, eat-3, phb-1, and phb-2 gene expression (41).

The findings of a study revealed that nuclear CEBPβ interacts with NF-κB p65, enhancing the transcription of pro-inflammatory cytokines in an Alzheimer's disease mouse model. Administration of carnosic acid via a nano-carrier delivery system demonstrated its ability to reduce microglial and astrocyte activation, lower inflammatory cytokine levels (IL-1β, IL-6, and TNF-α), and improve cognitive function. Carnosic acid specifically inhibited the interaction between CEBPβ and NF-κB p65, suppressing inflammatory gene transcription and protecting against Aβ-induced neuronal damage. To further enhance its efficacy, researchers utilized sulfobutyl ether-beta-cyclodextrin (SBEβCD) as a delivery system, which improved the solubility and bioavailability of carnosic acid without inducing toxicity (30).

A study explored the therapeutic potential of carnosic acid for Alzheimer's disease. To address the instability of carnosic acid, a pro-drug derivative, di-acetylated carnosic acid (diAcCA), was developed, disclosing enhanced bioavailability, efficacy, and stability comparable to carnosic acid. In Alzheimer's disease transgenic mice, diAcCA treatment rescued synaptic integrity, improved learning and memory in the water maze test, and reduced amyloid plaque formation, phospho-tau aggregates, and astrocytic and microglial inflammation. Toxicity studies confirmed that diAcCA is as safe or safer than carnosic acid (42).

Rosmarinic acid

Researchers evaluated the protective effects of chitosan-coated rosmarinic acid nano-emulsions against LPS-induced memory deficits in rats. Rosmarinic acid nano-emulsions significantly enhanced cognitive function and reduced neuro-inflammation and oxidative markers compared to LPS-only groups, including an increase in recognition index, brain thiol levels, thiobarbituric acid reactive substances (TBARS), cluster of differentiation molecule 11b (CD11b) expression, and reductions in glial fibrillary acidic protein $(GFAP)^+$ cell count. Additionally, rosmarinic acid nano-emulsions improved rosmarinic acid bioavailability in the brain, unlike the free rosmarinic acid group, which showed limited neuroprotection and no brain rosmarinic acid quantification (43) (Table 1).

In a study using perinatal hypoxia/ischemia rat models, researchers induced injury by temporarily ligating the right common carotid artery of 3-day-old rats, followed by controlled exposure to low oxygen conditions. The rats were then treated with rosmarinic acid. At 22 days post-birth, improvements were observed in motor function, learning, and spatial memory impairments caused by the injury. Rosmarinic acid also enhanced oligodendrocyte progenitor cell proliferation in the sub-ventricular zone and counteracted the reduction of myelin basic protein and myelin sheath loss in the corpus callosum. Besides, rosmarinic acid exerted a partial inhibitory effect on the expression of the oligodendrocyte marker Olig2 and myelin basic protein, while also limiting the rise in the oligodendrocyte apoptosis marker inhibitors of DNA binding 2 (44).

Moreover, in a rat model of LPS-induced neuroinflammation, rosmarinic acid was administered to animals. Cognitive assessments revealed that rosmarinic acid alleviated LPS-induced working memory deficits and reduced neuronal damage in hippocampal subfields. Rosmarinic acid treatment also inhibited the overproduction of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) and improved oxidative balance by lowering nitric oxide (NO) and MDA levels while enhancing superoxide dismutase (SOD) activity in the hippocampus and prefrontal cortex (45).

Considering the association between impaired neurogenesis and Alzheimer's disease pathology, researchers aimed to assess whether rosmarinic acid could enhance synaptic plasticity and cognitive function compared to Donepezil. The results demonstrated a neuroprotective role for rosmarinic, effectively reversing deficits in spatial and recognition memory. Additionally, treatment restored neuronal density and normalized the expression of neurogenic (neuronal nuclei (NeuN), doublecortin) and synaptic (Synaptophysin) markers (36).

Likewise, another study investigated the prophylactic neuroprotective effects of rosmarinic acid on memory impairment and cognitive decline induced by LPS in mice. LPS impaired memory retention and heightened cognitive decline, as assessed by Morris water maze and Y maze tests, while elevating oxidative stress markers, including reduced SOD activity, decreased glutathione (GSH) levels, and increased lipid peroxidation. Additionally, cholinergic imbalance was observed via increased AChE activity. Rosmarinic acid pre-treatment alleviated these effects, improving memory and behavioral disturbances while suppressing oxidative stress, pro-inflammatory cytokines (TNF-α, IL-6), apoptotic proteins (c-Jun, caspase-3), and AChE activity (46).

Rosmarinic acid intake effectively mitigated key pathological markers of Alzheimer's disease, including Aβ aggregation and phosphorylated tau accumulation, while also enhancing cognitive function in a mouse model. Moreover, rosmarinic acid demonstrated anti-inflammatory properties, reducing hippocampal inflammation and suppressing activation of the Jun N-terminal kinase (JNK) signaling pathway, which plays a role in tau phosphorylation. Interestingly, this anti-inflammatory effect extended beyond the central nervous system to peripheral regions (47).

Exploring the effects of rosmarinic acid in a model of Alzheimer's disease induced by amyloid Aβ1-42 in mice indicated improvements in social interaction, while histological analyses showed a reduction in Aβ plaques and increased expression of neurogenesis markers, such as

doublecortin and Ki-67, compared to controls. Additionally, molecular docking studies confirmed that rosmarinic acid binds similarly to neurogenesis markers as donepezil (48).

Rosmarinic acid administration improved learning and memory in aged mice, which may be linked to enhanced glucose regulation. However, young adults exhibited lipid profile disruptions, with males showing impaired glycemic control and females displaying reduced BDNF levels (49).

A group of researchers explored the potential of rosmarinic acid to alleviate the hepatotoxicity associated with tacrine while enhancing its therapeutic efficacy against Alzheimer's disease in mice. The results demonstrated that rosmarinic acid combined with tacrine improved cognitive function, reduced Aβ oligomer expression, inhibited Aβ deposition, suppressed AChE activity, and enhanced Ach levels in the hippocampus. Furthermore, rosmarinic acid alleviated tacrine-induced hepatotoxicity, likely by inhibiting apoptosis-related pathways (B-cell lymphoma protein 2 (Bcl-2)/Bcl-2-associated X (Bax), caspase-3) and reducing JNK phosphorylation, thereby preventing liver damage (50).

Investigating the impact of rosmarinic acid supplementation in mitigating cognitive decline and metabolic dysfunction driven by a Western diet in aging mice revealed that rosmarinic acid supplementation protected against Western diet-induced memory impairment in both sexes and prevented insulin resistance in males. Transcriptomic analysis of the hippocampus revealed that rosmarinic acid modulated oxidative stress pathways in males and immune and sex hormone signaling pathways in females, including the luteinizing hormone beta subunit (Lhb) and luteinizing hormone/choriogonadotropin receptor (Lhcgr) genes. Moreover, rosmarinic acid up-regulated glucagon-like peptide 1 receptor (GLP-1R) expression, associated with preventing metabolic disorders, and enriched transcription factors (NF-κB, glutathione reductase (GR), and signal transducer and activator of transcription (STAT)3) linked to inflammation regulation and cell survival (51).

The ameliorative effects of rosmarinic acid on cognitive impairment associated with sepsis were investigated using a cecal ligation and puncture-induced mouse model. Researchers evaluated the impact of rosmarinic acid on neuronal damage and inflammation. Behavioral tests and positron emission tomography (PET)–computed tomography (CT) imaging demonstrated that rosmarinic acid enhanced brain glucose metabolism. Additionally, rosmarinic acid promoted hippocampal neuron preservation and suppressed microglial M1 polarization, a critical factor in neuro-inflammation (33).

Another study was carried out to explore the neuroprotective effects of rosmarinic acid against endoplasmic reticulum stress-related cognitive dysfunction induced by endotoxins in mice. Researchers found that rosmarinic acid significantly improved cognitive function, with no dose-dependent differences. While no substantial changes were observed in hippocampal and amygdala neuron morphology, the higher dose of rosmarinic acid reduced PERK protein levels and increased MANF expression in the cornu ammonis (CA)1 and dentate gyrus regions (34).

Ursolic acid

The administration of ursolic acid to mice with Alzheimer's disease effectively reversed deficits in spatial and recognition memory. Moreover, treatment restored neuronal density and normalized the expression of neurogenic (Ki67, NeuN, doublecortin) and synaptic (synapsin I) markers (36).

Supplementation of ursolic acid to mice with Alzheimer's disease induced by Aβ1-42 caused a substantial reduction in hippocampal Aβ plaque burden in the ursolic acid-treated group compared to both the Aβ1-42 and donepezil-treated groups. Neurogenesis was significantly restored, as reflected in enhanced doublecortin and Ki-67 immunoreactivity within ursolic acid-treated groups relative to Aβ1-42-induced pathology. Additionally, social affiliation deficits observed in Aβ1-42-treated mice were reversed upon administration of ursolic acid. Molecular docking studies further corroborated these findings, revealing comparable binding affinities of ursolic acid to neurogenesis-associated proteins (Ki-67 and doublecortin) relative to donepezil (48).

Examining the protective effects of ursolic acid against Aβ-induced neurotoxicity demonstrated that ursolic acid reduced Aβ deposits, monomers, and oligomers, alleviating Aβ-induced paralysis and hypersensitivity to serotonin in transgenic nematodes. Notably, ursolic acid enhanced proteasome activity through transcriptional regulation of the ubiquitin-proteasome system, contributing to Aβ homeostasis. However, inhibiting proteasomal activity with MG132 neutralized its therapeutic effects. Additionally, Parkinson's disease-related-1 was required for its efficacy (52).

The combined effects of ursolic acid supplementation and exercise training were tested on anti-oxidant defenses and the nuclear factor erythroid 2-related factor 2 (Nrf2)/Kelch-like ECH-associated protein 1 (Keap1)/anti-oxidant response element (ARE) pathway in aged diabetic rats. Rats with diabetes were divided into groups receiving ursolic acid alongside resistance or endurance training. Results indicated that resistance training significantly increased Nrf2 expression, while endurance training with ursolic acid supplementation influenced Keap1 levels. A notable interaction effect was observed for SOD, though no substantial impact on catalase (CAT), GPx, or GSH was detected. Spatial memory improvements were observed in the ursolic acid and exercise groups (53).

Similarly, another study examined the impact of exercise and ursolic acid on brain protein levels in aged rats with diet-induced Type 2 diabetes, a condition linked to increased inflammation and a heightened risk of Alzheimer's disease. The findings revealed that diabetes elevated levels of tau, IL-1β, TNF-α, and c-Jun, while reducing insulin receptor substrate 2 (IRS2) protein levels. Endurance training helped improve tau, Jun, and IRS2 levels, whereas ursolic acid intake mitigated the increases in tau, IL-1β, TNF-α, and c-Jun while enhancing IRS2 levels. Notably, the combined effects of ursolic acid and training caused even greater improvements (54).

Clinical trials

Rosemary

The impact of rosemary on AChE activity and oxidative stress markers in young, healthy individuals was assessed. Participants were divided into two groups: one receiving rosemary supplements and the other a placebo. Analysis of blood samples before and after supplementation revealed that rosemary significantly inhibited AChE activity and improved anti-oxidant defense, as evidenced by

increased total anti-oxidant capacity and reduced protein carbonylation. However, lipid peroxidation levels remained unaffected (55).

In general, rosemary and its bioactive compounds—including carnosic acid, rosmarinic acid, and ursolic acid—exhibit multi-target neuroprotective properties that position them as promising candidates for Alzheimer's disease intervention and memory enhancement (Figure 1). These compounds function through anti-oxidant, anti-inflammatory, anti-apoptotic, and AChE inhibitory pathways, effectively reducing Aβ toxicity, preserving synaptic integrity, and supporting cognitive performance.

One of the core therapeutic actions of rosemary and its derivatives is modulation of the cholinergic system, achieved via AChE inhibition, which preserves ACh levels essential for learning and memory. Additionally, these bioactive compounds stabilize mitochondrial function, preventing oxidative stress-induced neurotoxicity and reinforcing neuronal survival through anti-apoptotic and synaptic protective mechanisms. Neuro-inflammatory control is another hallmark, particularly through NF-κB and RACK1/HIF-1α pathway modulation, thereby reducing microglial and astrocyte activation and limiting inflammatory damage linked to neurodegeneration. Beyond direct neuroprotective actions, rosemary-derived compounds also influence metabolic pathways, modulating glucose metabolism, insulin sensitivity, and oxidative stress defense (Nrf2/Keap1/ARE signaling).

The integration of nanotechnology in delivering these compounds enhances bioavailability, improving brain penetration and sustained therapeutic effects. Furthermore, combining rosemary compounds with exercise interventions has shown synergistic benefits, reinforcing neurogenesis, synaptic repair, and cognitive resilience.

It is also essential to note that rosemary-derived compounds may exert sex-dependent effects, influencing metabolic responses, glycemic control, and neuroprotection differently in males and females. While rosmarinic acid has shown significant cognitive benefits, caution should be exercised in its administration to young healthy adults, as its metabolic impact varies based on age and sex-specific hormonal and inflammatory pathways. Future studies should focus on refining dosing strategies to account for individual biological differences.

Despite these promising findings, some limitations remain, including inconsistent reductions in amyloid burden, poor bioavailability, and a lack of extensive human trials to confirm long-term efficacy. While animal and *in vitro* studies strongly support cognitive improvements, further clinical validation is necessary. Additionally, variability in extraction methods and formulations influences therapeutic potency, highlighting the need for standardized preparations.

Future research should explore synergistic applications with existing Alzheimer's disease treatments, refine nano-based delivery systems, and conduct large-scale human trials to establish clinical effectiveness. Given its multi-target neuroprotective potential, rosemary and its components represent a promising foundation for alternative Alzheimer's disease therapies, offering potential benefits not only in neurodegeneration, but also in age-related cognitive decline and metabolic dysfunction.

Anxiety

Anxiety disorders are highly prevalent among individuals and are characterized by intense fear and avoidance behaviors. These responses often occur in relation to specific circumstances or objects, even when there is no actual threat present (11). Excessive activation of the hypothalamic-pituitary-adrenal axis and autonomic nervous system in response to environmental stimuli can lead to physical manifestations of anxiety, including excessive sweating, elevated blood pressure, difficulty breathing, nausea, and rapid heart rate (2).

In the next section, studies investigating the impact of rosemary and its main components on anxiety and stress-related disorders will be reported.

In vivo

Rosemary

Rosemary essential oil was tested for its ability to counteract cognitive and behavioral impairments in

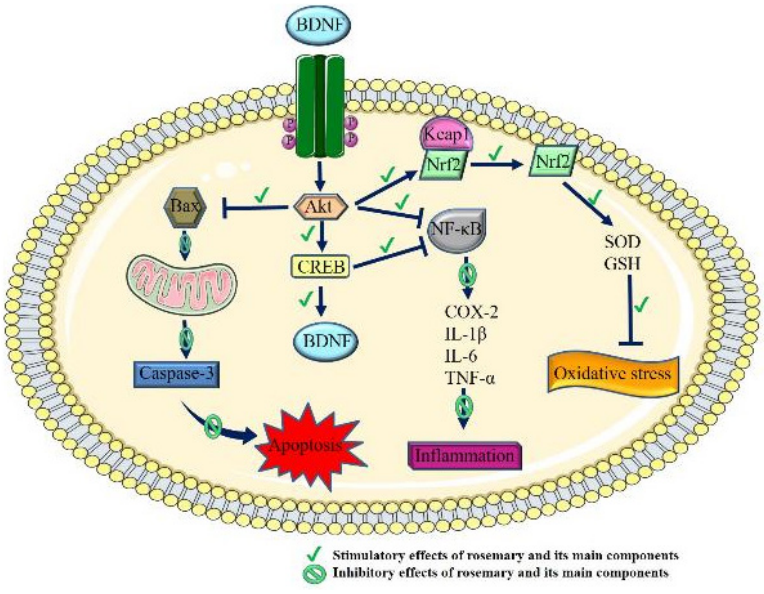

Figure 1. Ameliorative effects of rosemary and its main components on Alzheimer's disease by targeting Akt/CREB/BDNF signaling pathway (Images from https://smart.servier.com)

zebrafish. The obtained data showed that rosemary essential oil effectively reversed scopolamine-induced memory deficits, anxiety, and oxidative stress, while also reducing AChE activity in the brain (56).

Using mouse models, researchers investigated the effects of oral rosemary extract administration on central oxytocin levels, stress biomarkers, and neurotransmitters. Behavioral assessments through elevated plus maze tests and tail suspension revealed significant improvements following oxytocin pretreatment. Whole-genome microarray analysis indicated that oxytocin reversed stress-induced gene expression alterations linked to oxytocinergic, neurotransmitter, and inflammatory pathways. Additionally, rosemary extract increased oxytocin and oxytocin receptor expressions, enhanced oxytocin protein levels, BDNF, neurotransmitter (brain adrenaline, dopamine, noradrenaline, serotonin) levels, and attenuated serum corticosterone (57).

Rosmarinic acid

Researchers investigated the anxiolytic properties of rosmarinic acid using an animal model of acute stress. Results showed that rosmarinic acid improved social interaction behaviors, increased time in open arms, and reduced time in closed arms (58).

Ursolic acid

The administration of ursolic acid to *C. elegans* reduced reactive oxygen species (ROS) and prolonged the lifespan of *C. elegans*. The data confirmed that ursolic acid interacts with serotonin receptors, enhancing stress resilience (59).

It has also been observed that ursolic acid lessened anxiety-like symptoms caused by maternal separation in mice (60).

Clinical trials

Rosemary extract and oil

To evaluate the effectiveness of continuous rosemary hot-water extract intake in individuals with significant mood disturbances, researchers selected participants whose total mood disturbance scores were above the baseline median. The study focused on healthy Japanese men with Beck Depression Inventory-II scores below 21. The findings revealed significant reductions in total mood disturbance and confusion-bewilderment scores and notable increases in vigor-activity in the rosemary group compared to the control. Additionally, significant improvements were observed in daytime sleepiness, fatigue on awakening, psychomotor speed, tension-anxiety, and vigor-activity within the rosemary group (61).

Investigating the effectiveness of progressive muscle relaxation and aromatherapy with rosemary oil in patients undergoing general surgery illustrated that both progressive muscle relaxation and aromatherapy significantly reduced anxiety scores compared to baseline levels, but neither method demonstrated superiority over the other. Despite this, both approaches proved beneficial in lowering preoperative anxiety (62).

Drinking rosemary tea in volunteers aged 20–50 caused an increase in plasma BDNF and TNF-α levels, suggesting potential anxiolytic and antidepressant properties. However, other measured biomarkers, including cortisol and interleukins, showed only slight, non-significant variations (63).

It has been observed that aromatherapy with rosemary in individuals with diabetes aged 65 and older caused significant improvements in cognitive function, reduced anxiety, and improved sleep quality compared to baseline scores (64).

In the same way, the effect of inhalation aromatherapy using rosemary essential oil and music therapy in reducing preoperative anxiety in general surgery patients was examined. Participants were divided into four groups: control, music therapy, aromatherapy, and combined therapy group. Results showed substantial anxiety reduction in all intervention groups, with aromatherapy demonstrating the highest effect and combined therapy the lowest (65).

Rosmarinic acid

A pilot study explored the therapeutic potential of balneotherapy with peloids for managing osteoarthritis. Researchers investigated whether supplementing matured peloids with rosmarinic acid could enhance clinical outcomes and functional status. Elderly subjects with osteoarthritis participated in a treatment cycle using either rosmarinic acid-fortified or non-fortified peloids. Both treatments led to significant pain reduction, improved functionality, and better quality of life. However, the rosmarinic acid-enhanced peloid demonstrated greater benefits, especially in alleviating anxiety and depression symptoms (66) (Table 2).

In summary, Rosemary and its main components, including rosmarinic acid and ursolic acid, demonstrate significant anxiolytic properties through multiple neuroprotective mechanisms. These compounds exert their effects by modulating neurotransmitter systems, reducing oxidative stress, and influencing neuro-inflammatory pathways, all of which are crucial for maintaining emotional balance. One particularly important pathway involves BDNF, which typically declines in individuals with anxiety and depression. Rosemary interventions have been shown to enhance BDNF levels, thereby promoting neuroplasticity and cognitive resilience.

A key paradox in the study findings is the observed increase in TNF-α following rosemary treatment, despite TNF-α typically needing to decrease for effective anxiety relief. This unexpected result may stem from the immunomodulatory properties of rosemary, where an initial spike in TNF-α represents a transient inflammatory response that subsequently contributes to long-term neuroprotective effects. Rosemary compounds may stimulate immune signaling temporarily, priming the system for more balanced inflammatory control over time. Alternatively, the study population's baseline inflammatory status might have influenced the response, suggesting that the effects of rosemary on TNF-α could vary depending on individual health conditions or underlying etiological factors.

The strengths of this research lie in its integration of clinical and preclinical studies, offering a comprehensive perspective on the anxiolytic effects of rosemary. Its ability to influence multiple biological pathways highlights rosemary as a potential non-pharmacological strategy for anxiety management. However, limitations include the relatively short study durations, variable participant health conditions, and the need for mechanistic investigations to clarify the precise immunological effects of rosemary. Future research should explore long-term immune responses and optimize dosing strategies to ensure consistent therapeutic

Table 2. Effect of rosemary and its main components on anxiety and depression

Compound	Study design	Doses/Duration	Results	Ref.
		Anxiety		
		In vivo		
Rosemary essential oil	*Danio rerio*	25, 150, and 300 µl/l, 8 days, immersion	↓ Anxiety, brain oxidative stress, memory impairment, brain AChE activity	(56)
Rosemary ethanolic extrac	Male ICR mice	10 and 100 mg/kg, 7 days, PO	↑ Behavioral assessments, oxytocin and oxytocin receptor expressions, BDNF, brain adrenaline, dopamine, noradrenaline, serotonin ↓ Stress-induced gene expression alterations linked to oxytocinergic, neurotransmitter, and inflammatory pathways, serum corticosterone	(57)
Rosmarinic acid	Male Wistar rats	15 mg/kg, 14 days, gavage	↑ Social interaction behaviors, time in open arms ↓ Time in closed arms	(58)
Rosmarinic acid	CD1 male mice	5 mg/kg, 28 days, PO	↓ Anxiety	(93)
Ursolic acid	Mice	-	↓ Anxiety-like symptoms	(60)
		Clinical trial		
Rosemary hot-water extract	42 healthy Japanese men with a Beck Depression Inventory-II score less than 21 points	1 g, 4 weeks, PO	↑ Vigor-activity ↓ Total mood disturbance, and Confusion-Bewilderment scores, daytime sleepiness, fatigue on awakening, tension-anxiety	(61)
Rosemary oil	90 participants undergoing general surgery	3 drops of 10% rosemary essential oil 1 hr before surgery	↓ Anxiety scores compared to baseline levels	(62)
Rosemary oil	Candidates for general surgery	-	↓ Anxiety	(123)
Rosemary tea	22 healthy participants aged 20 50	5 g, 10 days, PO	↑ Plasma BDNF and TNF-α levels	(63)
Rosemary	Patients with major depressive disorder	8 weeks, PO	↓Anxiety score	(124)
Rosemary	63 diabetic individuals aged 65 and over	4 weeks	↑ Cognitive function, sleep quality ↓ Anxiety	(64)
Rosemary essential oil	236 general surgery patients	30 min an hour before surgery	↓ Anxiety	(65)
Rosmarinic acid	42 elderly with osteoarthritis	10 days	↑ Functionality, quality of life ↓ Anxiety and depression symptoms	(66)
		Depression		
		In vitro		
Rosmarinic acid	HT22 cells	12.5, 25, 50, and 75 µM	↑ Cell viability, BDNF, expression of PSD95, synaptophysin, doublecortin, neuronal nuclear protein, BDNF/TrkB/PI3K signaling axis ↓ Apoptosis	(68)
		In vivo		
Rosemary extract	Male ICR mice	10 and 100 mg/kg, 7 days, PO	↑ Behavioral assessments, oxytocin and oxytocin receptor expressions, BDNF, brain adrenaline, dopamine, noradrenaline, serotonin ↓ Gene expression alterations linked to oxytocinergic, neurotransmitter, and inflammatory pathways, serum corticosterone	(57)
Rosemary essential oil	Male heterogeneous Wistar rats	300- 600 mg/kg, IP	↑ Muscle relaxation, excitability, convulsive episodes, and electrocorticographic activity ↓ GABAergic activity	(69)
Carnosic acid	Male ICR mice and adipo ′ mice	25, 50, and 100 mg/kg, 21 days, PO	↑ Serum and hippocampus tissue adiponectin levels, adiponectin receptor 2 expression in hippocampus, PPAR-γ in adipose tissue ↓ Depressive-like behaviors, FGF9, hippocampal damage	(70)
Carnosic acid	Male pathogen-free Sprague Dawley rats	20 and 40 mg/kg, 2 weeks, PO	↑ Mood-related behaviors, locomotion, FGFR-3/actin levels ↓ Immobility time, hippocampal FGF9 expression	(71)
Carnosic acid	Female Balb/c mice	20 mg/kg, 3 weeks, gavage	↑ Nrf2 expression, HO-1, thioredoxin-1, BDNF, serotonin levels ↓ IL-1β, TNF-α, iNOS mRNA in the hippocampus and prefrontal cortex, oxidative stress, and histopathological changes	(72)
Rosmarinic acid	Male Swiss mice	5, 25, 50, and 100 mg/kg, single administration or 7 days, gavage	↑ Grooming activity ↓ Depressive behaviors, immobility time	(73)
Rosmarinic acid	Male Sprague-Dawley rats	1, 2, 4, 8, 16, 32 mg/kg, up to 7 days, IP	↑ Neurological function, CAT, GSH, SOD, expression of Nrf2 ↓ Infarct volume, depression-related behaviors	(74)
Rosmarinic acid	Mice	-	↑ Expression of Nrf2 and BDNF, HO-1, NQO1, GCLC, Beclin1, LC3-II, ME1, IDH1, 6-PGDH ↓ Sickness-related symptoms, histological brain damage, CD44, iNOS, TNF-α, IL-1β	(75)
Rosmarinic acid	Wistar rats	25 and 50 mg/kg, 40 days, PO	↑ Brain serotonin levels, sucrose consumption, cardiac function ↓ Immobility period, corticosterone, adrenal hyperplasia, oxidative stress markers, MMP2, cardiac troponin-I, TNF-α, IL-6	(76)
Rosmarinic acid	Rats	25 and 50 mg/kg, 20 days, PO	↑ IL-10, BDNF, GSH, SOD activity ↓ Physiological and behavioral effects of maternal separation, anhedonia, immobility, corticosterone levels, LDH, CK-MB, and ST-segment elevation	(77)
Rosmarinic acid	Male C57BL/6 J mice	10 and 20 mg/kg, 21 days, PO	↑ Serum BDNF, doublecortin expression in dentate gyrus, density of dendritic spines, synaptic vesicles, synaptophysin, and PSD95 ↓ Anxiety, depression, and sleep quality	(68)
Rosmarinic acid essential oil	60 depressed patients admitted to the hospital	8 weeks	↑ Quality of life, sleep quality ↓ Depression severity, anxiety levels	(83)

Continued Table 2.

Rosmarinic acid	Male Swiss mice	5, 25, 50, and 100 mg/kg, single administration or 7 days, gavage	↑ Grooming activity ↓ Depressive behaviors, immobility time	(73)
Rosmarinic acid	Male Sprague-Dawley rats	1, 2, 4, 8, 16, 32 mg/kg, up to 7 days, IP	↑ Neurological function, CAT, GSH, SOD, expression of Nrf2 ↓ Infarct volume, depression-related behaviors	(74)
Rosmarinic acid	Mice	-	↑ Expression of Nrf2 and BDNF, HO-1, NQO1, GCLC, Beclin1, LC3-II, ME1, IDH1, 6-PGDH ↓ Sickness-related symptoms, histological brain damage, CD44, iNOS, TNF-α, IL-1β	(75)
Rosmarinic acid	Wistar rats	25 and 50 mg/kg, 40 days, PO	↑ Brain serotonin levels, sucrose consumption, cardiac function ↓ Immobility period, corticosterone, adrenal hyperplasia, oxidative stress markers, MMP2, cardiac troponin I, TNF-α, IL-6	(76)
Rosmarinic acid	Rats	25 and 50 mg/kg, 20 days, PO	↑ IL-10, BDNF, GSH, SOD activity ↓ Physiological and behavioral effects of maternal separation, anhedonia, immobility, corticosterone levels, LDH, CK-MB, and ST-segment elevation	(77)
Rosmarinic acid	Male C57BL/6 J mice	10 and 20 mg/kg, 21 days, PO	↑ Serum BDNF, doublecortin expression in dentate gyrus, density of dendritic spines, synaptic vesicles, synaptophysin, and PSD95 relative expression ↓ Depression-like behavior, feeding latency, serum ACTH, CRH, SGK-1, HSP90, p-glucocorticoid receptor, hippocampus BDNF, p-CREB/CREB, p-PI3K/PI3K, p-Akt/Akt, p-mTOR/mTOR	(68)
Ursolic acid	*Caenorhabditis elegans*	100 μM, 14 hr	↑ Dopamine receptor gene expression, life span ↓ ROS levels	(59)
Ursolic acid	Male Swiss mice	0.1 mg/kg, 7 days, PO	↓ Immobility time, delayed grooming responses, hippocampal Bax expression	(78)
Ursolic acid	*Caenorhabditis elegans*	0.1 and 200 μM	↑ Skn-1 and PRDX2 gene expression, lifespan	(79)
Ursolic acid	Mice	0.01 and 0.1 mg/kg	↑ Antidepressant effect, hippocampal HO-1 levels	(80)
		Clinical trials		
Rosemary essential oil	88 pre-hospital emergency technicians	1 ml, 2 hr, 3 shifts/week, a month	↓ Depression	(81)
Rosemary essential oil	81 undergraduate students	two drops, 30 min, 4 weeks	↑ Sleep quality ↓ Anxiety, depression, and sleep quality	(82)
Rosmarinic acid essential oil	60 depressed patients admitted to the hospital	8 weeks	↑ Quality of life, sleep quality ↓ Depression severity, anxiety levels	(83)

6-PGDH: 6-phosphogluconate dehydrogenase; AChE: acetylcholinesterase; ACTH: adrenocorticotropic hormone; Akt: protein kinase B; BDNF: brain-derived neurotrophic factor; CAT: catalase; CD44: cluster of differentiation 44; CK-MB: creatine kinase-muscle/brain;CREB: cAMP response element-binding protein; CRH: corticotropin-releasing hormone; FGF9: fibroblast growth factor 9; FGFR-3: fibroblast growth factor receptor 3; GABA: gamma-aminobutyric acid; GCLC: glutamate-cysteine ligase catalytic subunit; GSH: glutathione; HO-1: heme oxygenase 1; HSP90: heat shock protein 90; IDH1: isocitrate dehydrogenase 1; IL: interleukin; iNOS: inducible nitric oxide synthase; LC3-II: microtubule-associated protein 1 light chain 3-II; LDH: lactate dehydrogenase; ME1: malic enzyme 1; MMP2: matrix metalloproteinase 2; mRNA: messenger ribonucleic acid; mTOR: mechanistic target of rapamycin; NQO1: NAD(P)H quinone dehydrogenase 1; Nrf2: nuclear factor erythroid 2-related factor 2; PI3K: phosphoinositide 3-kinase; PPAR-γ: peroxisome proliferator-activated receptor-gamma; PRDX2: peroxiredoxin 2; PSD95: postsynaptic density protein 95; ROS: reactive oxygen species; SGK-1: serum and glucocorticoid-regulated kinase-1; SOD: superoxide dismutase; TNF-α: tumor necrosis factor alpha; TrkB: tropomyosin receptor kinase B.

benefits, ultimately reinforcing the role of rosemary in anxiety treatment.

Depression

Depression ranks among the most widespread mental health conditions, impacting millions across the globe. Based on epidemiological research from the World Health Organization, approximately 4.4% of the world's population experiences this disorder (20, 67). The understanding of biological mechanisms of depression has evolved from focusing on monoamine dysfunction to exploring neuroendocrine disturbances, including cortisol elevation, BDNF reduction, and neurotransmitter imbalances. Unfortunately, conventional antidepressants have limited effectiveness, delayed therapeutic onset, and adverse effects, highlighting the urgent need for faster-acting treatments (20).

The following section will explore research focused on the antidepressant effects of rosemary and its main components in alleviating depression symptoms.

In vitro

Rosmarinic acid

Treating HT22 cells exposed to corticosterone with rosmarinic acid enhanced cell viability, BDNF levels, increased the expression of PSD95, synaptophysin, doublecortin, neuronal nuclear protein, and activated BDNF/tyrosine kinase receptor B (TrkB)/PI3K signaling axis. It also reduced apoptosis (68) (Table 2).

In vivo

Rosemary extract

The impact of orally administered rosemary extract,

obtained from the distillation residue of rosemary essential oil, was assessed for its effects on central oxytocin levels, stress biomarkers, and neurotransmitter activity in mouse models. Pretreatment with rosemary extract led to notable behavioral improvements in the tail suspension test and elevated plus maze test. Whole-genome microarray analysis demonstrated that rosemary extract effectively counteracted tail suspension test-induced gene expression changes associated with oxytocinergic signaling, neurotransmitter pathways, and inflammatory responses. In experimental models, rosemary extract significantly enhanced the expression of oxytocin and its receptor, and increased oxytocin protein concentrations. Furthermore, it mitigated stress-related alterations in serum corticosterone, brain and serum levels of BDNF, and neurotransmitter concentrations (57).

An *in vivo* study was carried out to test the effects of high doses of rosemary essential oil on neurological activity in rats. The experiments assessed behavioral responses, electrocorticographic activity, and interactions with anticonvulsant medications. Findings revealed a biphasic response to rosemary essential oil administration. The first phase was marked by muscle relaxation and decreased power of low-frequency brain oscillations. In contrast, the second phase showed heightened excitability, including convulsive episodes and increased electrocorticographic activity up to 40 Hz. Beta oscillations dominated this phase and were most effectively managed by diazepam, suggesting that rosemary essential oil-induced excitatory effects may be linked to diminished gamma-aminobutyric acid (GABA) ergic activity (69).

Carnosic acid

An *in vivo* experiment showed that carnosic acid treatment pointedly alleviated depressive-like behaviors and restored adiponectin levels in both serum and hippocampus tissue while suppressing fibroblast growth factor 9 (FGF9) levels. Carnosic acid also up-regulated adiponectin receptor 2 expression in the hippocampus and proliferator-activated receptor (PPAR)-γ in adipose tissue, reducing hippocampal damage. These antidepressant effects were diminished in chronic unpredictable mild stress-treated adipo$^{-/-}$ mice (70).

In another research, carnosic acid was administered to rats after inducing stroke through middle carotid artery occlusion and a subsequent recovery period. Behavioral tests showed that carnosic acid significantly improved mood-related behaviors, increasing sucrose preference and locomotion while reducing immobility time. Molecular analysis revealed that carnosic acid lowered hippocampal fibroblast growth factor 9 (FGF9) expression while enhancing fibroblast growth factor receptor (FGFR-3)/actin levels (71).

Using a mouse model, researchers found that ovariectomized mice displayed depressive behaviors, which were accompanied by suppressed Nrf2-related signaling and elevated pro-inflammatory markers in the hippocampus and prefrontal cortex. Administration of carnosic acid effectively reversed these depressive behaviors, enhancing the expression of Nrf2, Heme oxygenase-1 (HO-1), thioredoxin-1, and BDNF, while also increasing serotonin levels. Furthermore, carnosic acid alleviated oxidative stress, reduced pro-inflammatory markers—including IL-1β, TNF-α, and inducible nitric oxide synthase (iNOS) messenger ribonucleic acid (mRNA)—and improved the histopathological changes induced by ovariectomy. In contrast, treatment with tin protoporphyrin IX, an HO-1 inhibitor, worsened neurobehavioral and biochemical impairments, diminishing the protective effects of carnosic acid (72).

Rosmarinic acid

It has been demonstrated that acute, repeated, and therapeutic administration of rosmarinic acid remarkably reduced depressive behaviors, such as immobility time and increased grooming activity in the LPS-induced depression model in mice. Furthermore, blocking cannabinoid receptor 1 (CB)1, CB2, and PPAR-γ receptors prevented the antidepressant-like effects of rosmarinic acid (73).

Besides, rosmarinic acid administration following cerebral ischemia significantly improved neurological function, reducing infarct volume and moderating oxidative stress markers, including CAT, GSH, and SOD. Behavioral assessments demonstrated an antidepressant-like effect, as rosmarinic acid treatment alleviated depression-related behaviors. Molecular analysis revealed that rosmarinic acid enhanced the expression of Nrf2, while Nrf2 down-regulation through short-hairpin ribonucleic acid (RNA) sequences contradicted the protective effects of rosmarinic acid (74).

Behavioral assessments demonstrated that rosmarinic acid significantly reduced sickness-related symptoms and histological brain damage in mice with sickness behavior induced by LPS. Further molecular analysis revealed that rosmarinic acid enhanced the expression of Nrf2 and BDNF, along with its regulatory proteins p21 and p62. Additionally, rosmarinic acid boosted anti-oxidant enzymes (HO-1, NAD(P)H quinone dehydrogenase 1 (NQO1), GCLC), autophagy markers (Beclin1 and LC3-phosphatidylethanolamine conjugate (LC3-II)), and mitochondrial respiratory enzyme genes (malic enzyme 1 (ME1), isocitrate dehydrogenase 1 (IDH1), 6-phosphogluconate dehydrogenase (6-PGDH)), while suppressing pro-inflammatory mediators (cluster of differentiation (CD44), iNOS, TNF-α, IL-1β) (75).

The role of rosmarinic acid was tested against depression-related cardiac abnormalities induced by chronic unpredictable stress in rats. Findings demonstrated that rosmarinic acid treatment alleviated the immobility period, reduced corticosterone level, adrenal hyperplasia, oxidative stress markers, MMP2, cardiac troponin-I, TNF-α, IL-6, and improved serotonin levels, sucrose consumption, and cardiac function (76).

Examining the protective effects of rosmarinic acid against myocardial infarction in a comorbid depression model induced by maternal separation in rats demonstrated that rosmarinic acid and fluoxetine lessened physiological and behavioral effects of maternal separation, reducing anhedonia, immobility, elevated corticosterone levels, cardiac markers (lactate dehydrogenase (LDH), creatine kinase-MB (CK-MB)), and ST-segment elevation, while increasing IL-10, BDNF, GSH, and SOD activity (77).

A study explored the antidepressant potential of rosmarinic acid by evaluating its effects on chronic corticosterone-induced depression-like behavior in mice. Findings revealed that rosmarinic acid reduced depression-like behavior, feeding latency, serum adreno-cortico-tropic-hormone (ACTH), corticotropin-releasing hormone (CRH), serum/glucocorticoid regulated kinase-1 (SGK-1), heat shock protein 90 (HSP90), p-glucocorticoid receptor,

hippocampus BDNF, p-CREB/CREB, p-PI3K/PI3K, p-Akt/Akt, p-mammalian target of rapamycin (mTOR)/mTOR. It also increased serum BDNF, doublecortin expression in dentate gyrus, density of dendritic spines, synaptic vesicles, synaptophysin, and PSD95 relative expression (68).

Ursolic acid

The supplementation of ursolic acid to mice exposed to chronic unpredictable stress effectively prevented depressive-like behaviors, including increased immobility time and delayed grooming responses. Further analysis revealed that stress significantly elevated hippocampal Bax expression but did not alter Bcl-2. Ursolic acid specifically counteracted the increase in Bax expression, while both ursolic acid and fluoxetine helped maintain the Bcl-2/Bax ratio. Interestingly, serum corticosterone levels remained unchanged across all groups, implying that the antidepressant-like effects of ursolic acid might be independent of stress-related hormonal alterations (78).

Since Nrf2 and peroxiredoxin 2 (PRDX2) are promising molecular targets for combating oxidative stress-related depression, a study was designed to assess the effects of ursolic acid on depression in *C. elegans*. Outcomes showed that ursolic acid exhibited strong anti-oxidant properties, improved stress resistance, and up-regulated Skn-1 and PRDX2 gene expression. Ursolic acid demonstrated superior effectiveness compared to fluoxetine across many tests (79).

Another study examined the role of HO-1 in the antidepressant-like effects of ursolic acid in a mouse model. Researchers administered intra-cerebroventricular injections of zinc protoporphyrin IX to inhibit HO-1 and cobalt protoporphyrin IX to induce it, alongside effective and sub-effective doses of ursolic acid or fluoxetine. Results showed that zinc protoporphyrin IX blocked the antidepressant-like effects of ursolic acid and fluoxetine. In contrast, cobalt protoporphyrin IX combined with a sub-effective dose of ursolic acid produced a synergistic antidepressant effect. Ursolic acid and cobalt protoporphyrin IX increased hippocampal HO-1 levels, suggesting their involvement in the mechanism of action (80).

Clinical trials

Rosemary

The effect of rosemary essential oil was assessed on occupational fatigue and depression in pre-hospital emergency technicians. Conducted in eight emergency stations, the study assigned four stations to an intervention group using badges infused with rosemary oil and four to a placebo group using badges with refined almond oil. Technicians exposed to rosemary essential oil experienced a meaningful reduction in depression compared to the placebo group (81).

Similarly, another study evaluated the therapeutic effects of rosemary essential oil on mental health indicators such as anxiety, depression, and sleep quality. Participants were assigned either to a control group or an experimental group receiving the essential oil intervention. Psychological assessments indicated a significant reduction in anxiety, with moderate improvements in depression and sleep quality among treated participants (82).

Rosmarinic acid

The probable effects of rosmarinic acid essential oil were studied on sleep quality and daily care in depressed patients. Over eight weeks, depression severity, sleep quality, and quality of life were assessed. Results indicated that rosmarinic acid essential oil-treated patients had significantly greater reductions in depression symptoms, higher quality of life scores, and improved sleep quality compared to controls. Anxiety levels also progressively decreased, with more pronounced improvements observed in the rosmarinic acid essential oil group (83).

Briefly, rosemary and its bioactive components, including rosmarinic acid, carnosic acid, and ursolic acid, exhibit significant antidepressant effects through a complex interaction of protective mechanisms. These compounds regulate neurotransmitter systems—particularly serotonin, dopamine, and oxytocin—while activating neurotrophic factors like BDNF and key anti-oxidant pathways such as Nrf2 and HO-1. Their ability to mitigate oxidative stress, neuro-inflammation, and apoptosis positions them as promising agents for improving synaptic plasticity, cellular resilience, and mood regulation.

A novel perspective emerging from these findings is the synergy between neurotransmitter modulation and cellular defense mechanisms, suggesting rosemary-based interventions may offer broader therapeutic applications beyond traditional monoaminergic antidepressants. Notably, their interactions with adiponectin and fibroblast growth factor signaling introduce new opportunities for exploring stress-induced neuropsychiatric and cardiovascular dysfunctions. Considering these effects, rosemary-derived compounds appear to be promising candidates for personalized treatment strategies in depression management.

However, inconsistencies arise regarding the neural excitability effects of rosemary essential oil. Some studies highlight its anxiolytic and neuroprotective potential, while others report excitatory responses, including seizure-like activity at high doses. This biphasic action underscores the need for precise dose standardization to ensure therapeutic safety. Another limitation is the reliance on preclinical studies, emphasizing the necessity for large-scale human trials to validate their efficacy and optimize dosing strategies.

Epilepsy and seizures

Epilepsy is a prevalent neurological disorder that impacts millions of people worldwide. Treatment often involves pharmaceutical interventions that primarily target neurotransmitter receptors and ion channels. However, despite the availability of antiepileptic drugs, approximately 30% of individuals with epilepsy continue to experience seizures that do not respond to conventional pharmacological treatments. Seizures disrupt the balance between oxidative and anti-oxidant systems in the brain, leading to the oxidation of lipids, proteins, and DNA, which contributes to neurodegeneration (67).

The following section will highlight studies analyzing the anticonvulsant effects of rosemary and its main components in mitigating epilepsy symptoms.

In vitro

Rosmarinic acid

A study investigated the effects of rosmarinic acid on epileptiform activity using tissue from the entorhinal cortex and hippocampus of rats. Results indicated that rosmarinic acid reduced stimulated lactate release. However, rosmarinic acid did not alter 2-NBDG uptake (84).

Ursolic acid

An experiment was conducted on rat cortical nerve terminals (synaptosomes) to assess the effects of ursolic acid on glutamate regulation. Ursolic acid demonstrated a concentration-dependent inhibition of evoked glutamate release. This inhibition was prevented when synaptosomes were placed in a calcium-free medium or when P/Q-type calcium channels were blocked using ω-agatoxin IVA. However, blocking N-type calcium channels with ω-conotoxin GVIA did not affect the impact of ursolic acid. A molecular docking analysis revealed direct interactions between ursolic acid and P/Q-type calcium channels. Additionally, ursolic acid suppressed the activation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and reduced synapsin I phosphorylation, which were essential for regulating neurotransmitter release. The inhibition of CaMKII with KN 62 blocked the effects of ursolic acid on glutamate release (85) (Table 3).

An *in vitro* study aimed to check the effects of ursolic acid on epilepsy-related gene expression using a primary neuron model of epilepsy. Ursolic acid treatment increased the expression levels of Gng4 and calcium/calmodulin-dependent protein kinase II alpha (Camk2a) while decreasing Gnas expression in neurons. Immunofluorescence and Western blot analyses demonstrated that, compared with the epileptic group, ursolic acid-treated neurons exhibited an increased expression level of the GABAA receptor γ2 subunit (GABRG2) (86).

In vivo

Rosemary

The neuroprotective effects of rosemary leaves' methanolic extract were assessed in rats experiencing epilepsy induced by pentylenetetrazol. Behavioral tests showed that pentylenetetrazol impaired spatial learning and memory, as indicated by increased time and distance to locate the platform in the Morris water maze test. Rosemary extract supplementation improved cognitive performance in pentylenetetrazol-treated rats, reducing their swimming time and distance. Moreover, rosemary extract notably reduced seizure severity, decreased myoclonic jerks, and prolonged the onset of the first seizure episode. Passive avoidance learning, which was negatively affected by pentylenetetrazol, was restored with rosemary extract administration. Biochemical assessments indicated heightened oxidative stress in pentylenetetrazol-treated rats, whereas rosemary extract increased anti-oxidant levels and preserved normal brain histology (87).

Rosmarinic acid

Rosmarinic acid was administered to rats prior to kainic acid injection to evaluate its effects. The results showed that rosmarinic acid significantly reduced neuronal apoptosis and the number of neuronal nitric oxide synthase $(nNOS)^+$ neurons compared to the kainic acid group. But, rosmarinic acid did not alter MAPK and COX-2 immunoreactivity relative to kainic acid-treated animals (88).

Likewise, the potential neuroprotective effects of rosmarinic acid were investigated in a pilocarpine-induced *in vivo* model of epileptiform activity. Rosmarinic acid alleviated neuro-motor impairments and decreased protein carbonyl levels in the cerebral cortex (84) (Table 3).

Ursolic acid

It has been indicated that the administration of ursolic acid to rats with temporal lobe epilepsy lessened cognitive impairments and seizure behavior induced by epilepsy. In addition, ursolic acid helped restore hippocampal neuronal integrity, regulated neurogenesis, and corrected aberrant cell migration—factors commonly linked to epilepsy progression. The study further revealed that ursolic acid significantly reduced status epilepticus-induced neuro-inflammation by suppressing activated microglial cells and lowering pro-inflammatory markers such as TNF-α and IL-1β. Moreover, ursolic acid treatment decreased oxidative stress damage markers and down-regulated mitochondrial oxidative phosphorylation enzyme complexes. Ursolic acid also preserved GABAergic interneurons (89).

An *in vivo* experiment assessed the neuroprotective properties of ursolic acid in a kainic acid-induced excitotoxicity model in rats. Pretreatment with ursolic acid significantly mitigated kainic acid-induced cortical neuronal degeneration. This neuroprotection was associated with reduced glutamate levels in the cortex, characterized by a decrease in glutamate and glutaminase and an increase in glutamate-aspartate transporter, glutamate dehydrogenase, glutamine synthetase, and glutamate transporter 1 levels (85).

Another research focused on analyzing hippocampal tissues from rats in the control, epilepsy, and ursolic acid-treated epilepsy groups through full-length transcriptome sequencing. Differential gene expression analysis identified 220 differential genes, with 143 genes up-regulated and 77 down-regulated in the ursolic acid group compared to the epilepsy group. Gene ontology classification indicated involvement in biological processes, cellular components, and molecular functions, while the Kyoto Encyclopedia of Genes and Genomes pathway analysis highlighted 36 biological pathways, including cyclic adenosine monophosphate (cAMP) and calcium signaling pathways. Protein-protein interaction analysis showed that differential genes were closely linked to GABA regulation and inflammation. Also, ursolic acid treatment increased the expression of Gng4 and GABA synthesis-associated genes (Camk2a, Vgf, and Npy), while reducing Nptx2 (GABA synthesis) and Gnas (cAMP pathway) expression in hippocampal tissue (86).

The administration of ursolic acid to zebrafish that received pentylenetetrazol reduced the mean seizure duration and mean seizure score. The protective effect of the lower dose of ursolic acid was comparable to that of the standard drug diazepam (90).

To sum up, rosemary and its main components, rosmarinic acid and ursolic acid, exhibit substantial neuroprotective effects against epilepsy and seizure-related brain damage through various mechanisms, including anti-oxidant, anti-inflammatory, and neurotransmitter-regulating actions (Figure 2). These compounds modulate excitotoxicity by regulating glutamate and GABAergic neurotransmission, mitigating oxidative stress, and stabilizing neuro-inflammatory pathways. Their therapeutic potential lies in their ability to preserve neuronal integrity and improve cognitive performance following epileptiform activity.

A major protective mechanism of rosemary components is their regulation of excitotoxicity, particularly through the suppression of excessive glutamate release. Ursolic acid achieves this by inhibiting P/Q-type Ca^{2+} channels and CaMKII signaling, thereby reducing glutamate-mediated neuronal hyper-excitability. Additionally, ursolic

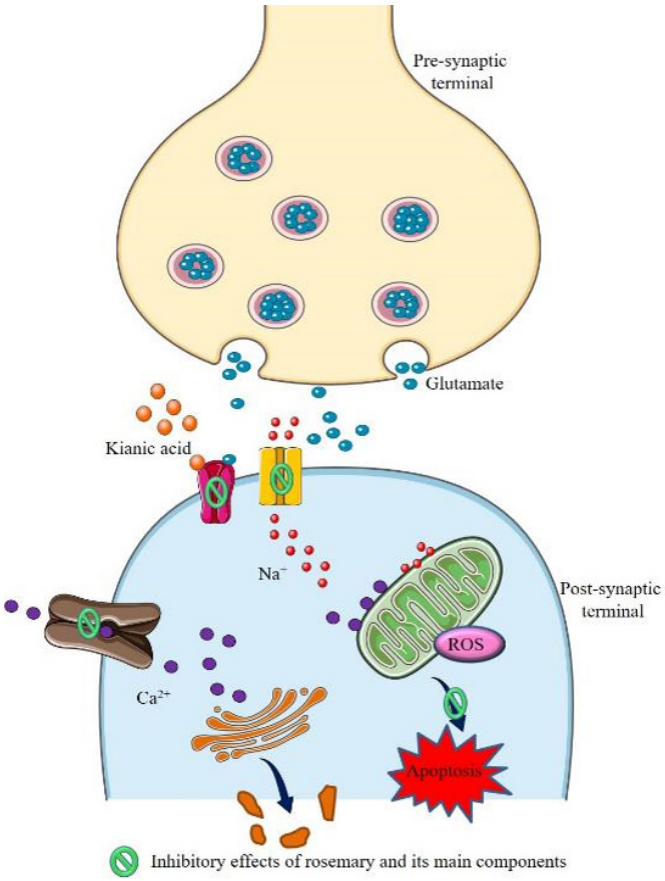

Figure 2. Therapeutic effects of rosemary and its main components on epilepsy (Images from https://smart.servier.com)

acid enhances GABAergic transmission, increasing the expression of GABAA receptor-related genes, which helps restore neuronal balance in epileptic conditions. The antioxidant capacity of rosemary and its main components also plays a critical role, as these compounds reduce oxidative stress markers.

The strength of the existing research lies in its multidimensional approach, spanning *in vitro* and *in vivo* analyses, allowing for a comprehensive understanding of the neuroprotective potential of rosemary. Nonetheless, limitations include inconsistent methodologies, a lack of long-term studies, and the need for clinical validation. Future research should explore combination therapies, optimal dosing strategies, and standardization of experimental models to enhance the translational potential of rosemary-derived compounds for epilepsy treatment.

Pain

Pain is commonly defined as a distressing sensory or emotional experience linked to actual or potential damage to body tissues (91). Neuropathic pain, as defined by the International Association for the Study of Pain (IASP), arises from damage or dysfunction within the somatosensory system. This chronic and debilitating condition is characterized by heightened pain responses (hyperalgesia), pain triggered by normally non-painful stimuli (allodynia), and abnormal sensations (dysesthesia). It is commonly associated with various medical conditions, including nerve compression, infections such as herpes zoster, cancer, autoimmune diseases, diabetes, and post-surgical complications. The prevalence of neuropathic pain continues to rise due to the increasing number of individuals affected by these disorders (92).

Studies assessing the potential analgesic properties of rosemary and its main components in pain management will be reviewed in the following section.

In vitro

Rosmarinic acid

Researchers explored the senolytic effects of rosmarinic acid on microglial cells exposed to LPS. BV2 cells stimulated with LPS showed increased inflammation and signs of senescence. Rosmarinic acid treatment enhanced cell viability and significantly reduced the release of IL-1β. Further tests on prolonged LPS stimulation revealed that rosmarinic acid effectively minimized nuclear foci of senescence (senescence-associated heterochromatin foci (SAHF)), reduced the release of senescence-associated secretory phenotype (SASP) factors, and decreased the expression of β-galactosidase (93) (Table 3).

In vivo

Rosemary extract and oil

A study examined the antinociceptive and anti-inflammatory effects of rosemary ethanolic extract in rats using formalin and carrageenan assays. The extract exhibited significant concentration-dependent pain-relieving and anti-inflammatory properties (94).

The antinociceptive properties of rosemary essential oil were inspected in mice using the formalin test. Several receptor antagonists and enzyme inhibitors were administered to evaluate the involvement of serotonergic, adrenergic, cholinergic, dopaminergic, opioid receptors, and

Table 3. Effect of rosemary and its main components on epilepsy and pain

Compound	Study design	Doses/Duration	Results	Ref.
Epilepsy and seizures				
In vitro				
Rosmarinic acid	Entorhinal cortex and hippocampus of Wistar rats	1-100 µg/ml, 1-4 hr	↓ Lactate release	(84)
Ursolic acid	Rat cortical nerve terminals	-	↓ Glutamate release, activation of CaMKII, synapsin I phosphorylation	(85)
Ursolic acid	Primary neurons	-	↑ Expression of Gng4, Camk2a, GABRG2 ↓ Expression of Gnas in neurons	(86)
In vivo				
Rosemary leaves' methanolic extract	Male Wistar rats	)0 mg/kg, 24 days, gavage	↑ Cognitive performance, onset of the first seizure episode, and antioxidant levels ↓ Swimming time and distance, seizure severity, myoclonic jerks, oxidative stress	(87)
Rosmarinic acid	Male Wistar rats	10 mg/kg, 7 days, gavage	↓ Neuronal apoptosis, nNOS-positive	(88)
Rosmarinic acid	Male C57BL/6 mice	30 mg/kg, 48 hr, VO	↓ Neuro-motor impairments, protein carbonyl levels in the cerebral cortex	(84)
Ursolic acid	Male sprague dawley rats	20 and 100 mg kg, 77 days, IG	↑ GABAergic interneurons ↓ Cognitive impairments, seizure behavior induced by epilepsy, activated microglial cells, TNF-α, IL-1β, oxidative stress damage markers, mitochondrial oxidative phosphorylation enzyme complexes	(89)
Ursolic acid	Male sprague dawley rats	-	↑ Glutamate-aspartate transporter, glutamate dehydrogenase, glutamine synthetase, glutamate transporter 1 levels ↓ Cortical neuronal degeneration, glutamate levels in the cortex, glutamate glutaminase	(85)
Ursolic acid	Rats	-	↑ Expression of Gng4, Camk2a, Npy, Vgf ↓ Expression of Nptx2, Gnas	(86)
Ursolic acid	Zebrafish	50 and 150 mg/kg	↓ Mean seizure duration, mean seizure score	(90)
Pain				
In vitro				
Rosmarinic acid	BV2 cells	1 µM	↑ Cell viability ↓ IL-1β, SAIIF, release of SASP factors, expression of β-galactosidase	(93)
In vivo				
Rosemary aerial parts ethanolic extract	Female Wistar rats	0.1, 1, 10, 30, and 100 µg/paw, SC or intraplantarly	↓ Pain, inflammation	(94)
Rosemary oil	Male swiss mice	150, 300, and 450 µl/kg	- Sulpiride reversed its effect in the early phase - Methylene blue, L-NAME, and glibenclamide reduced its analgesic effects in both phases	(95)
Carnosic acid	Male sprague dawley rats	-	↑ Antioxidant defense system ↓ Joint inflammation, paw swelling, expression of COX-2, iNOS, mPGES-1, gastrointestinal side effects, weight loss, gastric ulcers, bone degradation	(96)
Rosmarinic acid	Wistar rats	30 and 60 mg/kg, 21 days, PO	↑ Joint movement, locomotor activity, muscle rigidity ↓ Inflammation, paw volume	(97)
Rosmarinic acid	Mice	5 mg/kg, PO	↓ Hyperalgesia, anxiety, depression, senescence markers of hippocampal and spinal tissues	(93)
Rosmarinic acid	Male NMRI mice	5, 10, 20, 50, and 100 mg/kg, IP	↓ Pain	(98)
Rosmarinic acid	-	10, 20, and 40 mg/kg	↑ Opioid and adrenergic receptor stimulation ↓ Pain, allodynia	(99)

Continued Table 3.

Ursolic acid	Rats	-	↑ Plantar withdrawal latency, paw withdrawal threshold, and NeuN expression ↓Pain sensitivity, IBA1, and GFAP in the spinal cord	(100)
Clinical trials				
Rosemary leaves' alcoholic extract	82 students with primary dysmenorrhea	250 mg, three times a day, first three days of menstruation, two cycles, PO	↓ Pain intensity scores, nausea, boredom	(101)
Rosemary oil	75 elderly patients with knee osteoarthritis	4 cm of ointment, twice a day, 10 days	↓ Pain and overall WOMAC scores	(102)

Camk2a: calcium/calmodulin-dependent protein kinase II alpha; CaMKII: Ca^{2+}/calmodulin-dependent protein kinase II; COX-2: cyclooxygenase-2; GABA: gamma-aminobutyric acid; GABRG2: gamma-aminobutyric acid type A receptor subunit gamma 2; GFAP: glial fibrillary acidic protein; IBA1: ionized calcium-binding adaptor molecule 1; IL-1β: interleukin-1 beta; iNOS: inducible nitric oxide synthase; L-NAME: L-NG-nitro arginine methyl ester; mPGES-1: microsomal prostaglandin E synthase-1; nNOS: neuronal nitric oxide synthase; SAHF: senescence-associated heterochromatin foci; SASP: senescence-associated secretory phenotype; TNF-α: tumor necrosis factor-alpha; WOMAC: western Ontario and McMaster universities osteoarthritis index.

the NO/cyclic guanosine monophosphate (cGMP)/ATP-sensitive potassium channel (K_{ATP}) pathway. Most receptor antagonists did not reverse the antinociceptive effect of rosemary essential oil, except sulpiride, which showed limited activity in the early phase. However, methylene blue, L-N^G-nitro arginine methyl ester (L-NAME), and glibenclamide significantly reduced the analgesic effects of rosemary essential oil in both phases, suggesting a role of the NO/cGMP/K_{ATP} pathway (95).

Carnosic acid

In an adjuvant-induced arthritis model, carnosic acid significantly reduced joint inflammation and paw swelling while enhancing the anti-oxidant defense system. It inhibited the expression of pro-inflammatory markers, including COX-2, iNOS, and microsomal prostaglandin E synthase-1 (mPGES-1), leading to symptom relief without severe gastrointestinal side effects. Moreover, carnosic acid prevented weight loss, bone degradation, and gastric ulcers commonly associated with traditional rheumatoid arthritis treatments such as corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) (96).

Rosmarinic acid

Examining the anti-inflammatory and anti-arthritic effects of rosmarinic acid in a rat model of arthritis revealed that rosmarinic acid significantly controlled inflammation, increased joint movement, locomotor activity, and muscle rigidity. It also decreased inflammation and paw volume, demonstrating potential therapeutic benefits in managing arthritis-related pain (97).

The efficacy of rosmarinic acid in managing neuropathic pain symptoms was assessed in the spared nerve injury model. Mice with neuropathic pain received repeated doses of rosmarinic acid, which resulted in a significant reduction in hyperalgesia and neuropathic pain-associated comorbidities such as anxiety and depression. Additionally, analysis of hippocampal and spinal tissues revealed a decrease in senescence markers (93).

The analgesic potential of rosmarinic acid in comparison to piroxicam was examined using hot plate and tail-flick tests. Results showed that doses of 10 mg/kg and above significantly alleviated pain within 30 min of injection. Notably, combining rosmarinic acid with piroxicam enhanced analgesic effects compared to piroxicam alone (98).

Likewise, another study examined the anti-allodynic effects of rosmarinic acid in a chronic constriction injury-induced neuropathic pain model. The highest dose of rosmarinic acid demonstrated significant pain reduction comparable to pregabalin. Mechanistic analysis using receptor antagonists indicated that the anti-allodynic activity was mediated by opioid and adrenergic receptor stimulation, with α2-adrenergic receptors playing a primary role (99).

Ursolic acid

In a rat model with spinal nerve ligation, researchers administered varying concentrations of ursolic acid to study MAPK1 expression. The treatment improved pain sensitivity, as shown by increased paw withdrawal threshold and plantar withdrawal latency. Gut microbiota analysis revealed notable shifts in bacterial composition between treated and control groups. Network pharmacology identified MAPK1 and intercellular adhesion molecule-1 (ICAM1) as key molecular targets of Ursolic acid in neuropathic pain. Molecular docking confirmed binding interactions between ursolic acid and these targets. Ursolic acid reduced neuro-inflammation markers ionized calcium-binding adapter molecule 1 (IBA1) and GFAP in the spinal cord, alongside increased NeuN expression. Overexpression of MAPK1 reversed the analgesic effects of ursolic acid, leading to higher inflammatory factor levels and decreased plantar withdrawal latency and paw withdrawal threshold (100).

Clinical trials

Rosemary extracts and oil

The effectiveness of the alcoholic extract of rosemary leaves was compared to mefenamic acid in alleviating symptoms of primary dysmenorrhea. Participants were assigned to receive either rosemary or mefenamic acid capsules over two menstrual cycles. Pain intensity scores significantly decreased in both groups compared to baseline measurements, though no significant differences were observed between the two treatments. However, rosemary demonstrated a greater effect in reducing nausea and boredom during both cycles (101).

Assessing the effects of rosemary ointment on osteoarthritis symptoms in elderly patients with knee osteoarthritis indicated significant reductions in pain

and overall Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores in both the rosemary and placebo groups, with the rosemary group showing greater improvement post-intervention compared to the placebo and control groups. However, joint stiffness and function did not show significant differences (102).

In summary, rosemary and its main components, including rosmarinic acid, carnosic acid, and ursolic acid, exhibit significant analgesic and anti-inflammatory properties through multiple protective mechanisms. These compounds modulate pain by reducing inflammation, enhancing anti-oxidant defenses, and influencing key signaling pathways. Studies suggest that rosemary exerts its effects via the NO/cGMP/KATP pathway, adrenergic and opioidergic receptor stimulation, and the inhibition of pro-inflammatory mediators such as COX-2, iNOS, and mPGES-1. Additionally, its neuroprotective effects extend to reducing senescence markers, improving gut microbiota homeostasis, and mitigating neuropathic pain-related comorbidities such as anxiety and depression.

A particularly novel insight from these findings is the potential of rosemary to work synergistically with conventional analgesics, possibly reducing the required dosage and minimizing side effects. For instance, the combination of rosmarinic acid with piroxicam enhanced pain relief, highlighting its potential as an adjunct therapy in clinical applications. Furthermore, the comparable efficacy of rosemary to mefenamic acid in managing dysmenorrhea symptoms suggests it may serve as a viable natural alternative with fewer gastrointestinal risks.

However, while *in vitro* and animal studies strongly support the pain-relieving properties of rosemary, clinical trials remain limited. The absence of long-term human studies assessing its effectiveness and safety across diverse patient populations is a key limitation. Additionally, variability in rosemary extract formulations, dosages, and administration methods may impact therapeutic consistency. Future research should focus on standardized clinical protocols, optimal dosing strategies, and mechanistic studies to further validate the role of rosemary in pain management.

Parkinson's disease

Parkinson's disease is a prevalent neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta. It manifests through motor impairments, including speech difficulties, bradykinesia, and tremors, as well as nonmotor symptoms such as cognitive decline and sleep disturbances. Various pathological mechanisms contribute to disease progression, including oxidative stress, neuroinflammation, α-synuclein accumulation, and apoptotic signaling. Both genetic predisposition and environmental toxins—such as pesticides, herbicides, and heavy metals—are implicated in its onset (103).

In the next section, research on the effects of rosemary and its main components on Parkinson's disease and its symptoms will be discussed.

In vitro

Carnosic acid

Exposure of SH-SY5Y cells to the neurotoxin 6-hydroxydopamine (6-OHDA) disrupted mitochondrial balance by reducing fusion proteins optic atrophy 1 (OPA1) and mitofusin 2 while increasing fission-related proteins fission 1 and dynamin related protein 1 (DRP1). Immunofluorescence analysis confirmed cytochrome c release into the cytoplasm, marking heightened apoptosis. Carnosic acid pretreatment counteracted these effects, restoring fusion protein levels and preventing cytochrome c release, though DRP1 remained unchanged. Additionally, carnosic acid promoted inhibitor of nuclear factor kappa-B kinase subunit gamma (IKKγ) ubiquitination, increased nuclear p65 activity, enhanced OPA1-p65 DNA binding, and elevated OPA1 protein expression. Notably, silencing parkin impaired the ability of carnosic acid to reverse these effects. Furthermore, knocking down OPA1 eliminated the ability of carnosic acid to mitigate apoptosis and cytochrome c release (104).

Exposing SH-SY5Y cells to 6-OHDA disrupts mitochondrial function by increasing parkin-interacting substrate (PARIS) levels while lowering peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) expression and mitochondrial biogenesis-related genes. Carnosic acid pretreatment counteracts these disruptions, restoring mitochondrial integrity. Protein interaction assays confirm that carnosic acid enhances PARIS ubiquitination, leading to its degradation. Notably, knocking down parkin diminishes the protective effects of carnosic acid, reinforcing its role in mitochondrial regulation. Moreover, silencing PGC-1α prevents carnosic acid from mitigating mitochondrial dysfunction and apoptosis induced by 6-OHDA (105) (Table 4).

An investigation was carried out to explore how carnosic acid may offer neuroprotection by protecting mitochondrial integrity in a Parkinson's disease model. The research focused on the role of Mic60, a protein essential for mitochondrial structure and function, and assessed whether carnosic acid could counteract the neurotoxic effects of 6-OHDA in SH-SY5Y cells. The results indicate that carnosic acid pretreatment restores Mic60 and citrate synthase levels while countering the protein kinase A (PKA) protein activation induced by 6-OHDA. Furthermore, the protective effects of carnosic acid were inhibited when Mic60 and PTEN-induced kinase 1 (PINK1) were silenced using small interfering RNAs (siRNAs), leading to enhanced cytochrome c release. Immunoprecipitation analyses revealed shifts in Mic60 phosphorylation interactions under 6-OHDA exposure, which were reversed by PINK1 siRNA and forskolin, a PKA activator. Notably, forskolin treatment disrupted the ability of carnosic acid to rescue PINK1-Mic60 interaction and mitigate cytochrome c release and mitophagy impairments (106).

Rosmarinic acid

An *in vitro* study explored the neuroprotective potential of rosmarinic acid against rotenone-induced toxicity in SH-SY5Y cells, a Parkinson's disease model. The findings revealed that rosmarinic acid effectively lessened apoptotic cell death and preserved normal cellular morphology in a dose-dependent manner. Additionally, rosmarinic acid reduced α-synuclein and Tau phosphorylation while promoting adenosine monophosphate-activated protein kinase (AMPK), Akt, and PGC-1α activation, crucial for cellular energy regulation and survival. The compound further improves mitochondrial function by restoring ATP levels and suppressing excessive ROS production. The neuroprotective effects of rosmarinic acid were partly

Table 4. Effect of rosemary and its main components on Parkinson's disease

Compound	Study design	Doses/Duration	Results	Ref.
Parkinson's disease				
In vitro				
Carnosic acid	SH-SY5Y cells	-	↑ IKKγ ubiquitination, nuclear p65 activity, OPA1-p65 DNA binding, OPA1 protein expression ↓ Cytochrome c release	(104)
Carnosic acid	SH-SY5Y cells	-	↑ Mitochondrial integrity, PARIS ubiquitination	(105)
Carnosic acid	SH-SY5Y cells	-	↑ Synthase levels of Mic60 and citrate, mitochondrial integrity ↓ PKA protein activation	(106)
Rosmarinic acid	SH-SY5Y cells	0, 1, 10, or 100 μM, 24 hr	↑ Normal cellular morphology, AMPK, Akt, and PGC-1α activation, mitochondrial function, ATP levels ↓ Apoptotic cell death, α-synuclein and Tau phosphorylation, ROS production, Abl tyrosine kinase, hyper-phosphorylation of Abl Y412, and CrkII Y221	(107)
Rosmarinic acid	SH-SY5Y cells	20 200 μM	↑ Cell viability ↓ Oxidative stress, morphological alterations, mtUPR activation, CLPP, HSPA9, SIRT4, HSPE1, LONP1	(108)
Rosmarinic acid	Raw 264.7 cells	-	↑ Tubulin cytoskeleton stability ↓ Cytoskeletal disruption, α-synuclein aggregation	(125)
Ursolic acid	SH-SY5Y cells	5 μM	↑ Autophagic flux, JNK phosphorylation, beclin 1 activation	(126)
Ursolic acid	SH-SY5Y cells	0-100 μM	↑ Cell viability ↓ Expression of IL-1β, TNF-α, IL-6, phosphorylation of p44/42 MAPK, cleaved-caspase-3, cleaved-caspase-8	(109)
Ursolic acid	PC12 cells and primary neurons	-	↑ Autophagy ↓ Oxidative stress, AMPK activation, p62 accumulation	(110)
In vivo				
Rosemary hydro-alcoholic extract	Mice	50, 100, and 200 mg/kg, IP	↑ Movement and coordination ↓ Parkinson's symptoms	(111)
Rosemary	Male Wistar rats	50 mg/kg, 10 weeks, gavage	↑ Memory retention, neuronal density ↓ Latency in spatial navigation tasks, $GFAP^+$ astrocytes	(112)
Rosemary leaves' aqueous extract	Male mice	100, 150, and 200 mg/kg, 14 days, IP	↓ Lipid peroxidation, muscle rigidity, rotation/h	(113)
Rosemary extract	Male Wistar rats	50 mg/kg, 10 weeks, gavage	↑ Cognitive performance, expression of BDNF, NGF, neurotrophin 3, neurotrophin 4, activity of SOD, GPx, ↓ MDA, $GFAP^+$ cell density	(114)
Rosmarinic acid	Zebrafish	0-100 μM	↑ GSH, expression of p-Akt, DJ-1, HO-1, nuclear Nrf2, ↓ Motor impairments, ROS MDA, PTEN expression	(115)
Rosmarinic acid	Male C57BL/6 mice	16 mg/kg, 8 days, IP	↓ Motor deficits, microglial activation, and inflammatory markers	(116)
Rosmarinic acid	Male C57BL/6 mice	40, 60, and 80 mg/kg, IP	↑ Motor function ↓ Dopaminergic neuron loss in substantia nigra, abnormal mitochondrial ultrastructure	(108)
Rosmarinic acid	Mice	20 mg/kg, 14 days, gavage	↑ Dopaminergic signaling, MAO-A expression ↓ Hyper-locomotion behavior	(117)
Rosmarinic acid	Male C57BL/6 mice	100 mg/kg, 15 days, PO	- Regulated proteins associated with oxidative phosphorylation, glutamatergic synapse, vesicular cycle signaling pathway - Cellular targets mGluR2/mGluR3/EAAT-proteins from the glutamatergic system, and proteins from the Complex I of the electron transport chain	(118)
Ursolic acid	Mice	-	↓ Motor deficits, oxidative stress, neuro-inflammation, NF-κB, TNF-α	(119)
Ursolic acid	Male sprague dawley rats	5 and 10 mg/kg, 30 days, PO	↑ Mitochondrial function ↓ Oxidative stress, inflammation	(120)
Ursolic acid	Male Swiss albino mice	25 mg/kg, 42 days, PO	↑ Calcium homeostasis ↓ Oxidative stress, inflammation, α-synuclein overexpression, mitochondrial dysfunction, GSK-3β activity	(121)
Ursolic acid	Male C57BL/6 mice	10 mg/kg, 1-2 weeks, IP	↑ Neuronal health ↓ Motor impairments, dopaminergic neuron loss, excessive accumulation of p62, and ubiquitin	(126)
Ursolic acid	Male SPF C57BL/6 mice	50 mg/kg, 14 days, PO	↑ Distance, center duration time, mean speed, TH^+ dopamine neuron	(109)

Abl Y412: Abelson tyrosine kinase at tyrosine 412; Akt: protein kinase B; AMPK: adenosine monophosphate-activated protein kinase; ATP: adenosine triphosphate levels; BDNF: brain-derived neurotrophic factor; CLPP: caseinolytic mitochondrial matrix peptidase proteolytic subunit; CrkII Y221: Crk-like protein at tyrosine 221; DJ-1: Parkinson disease protein 7; DNA: deoxyribonucleic acid; EAAT: excitatory amino acid transporter; GFAP: glial fibrillary acidic protein; GPx: glutathione peroxidase; GSH: glutathione; GSK-3β: glycogen synthase kinase-3 beta; HO-1: heme oxygenase-1; HSPA9: heat shock protein family A member 9; HSPE1: heat shock protein family E member 1; IKKγ: inhibitor of nuclear factor kappa-B kinase subunit gamma; IL: interleukin; JNK: Jun N-terminal kinase; LONP1: lon peptidase 1, mitochondrial; MAO-A: monoamine oxidase A; MAPK: mitogen-activated protein kinase; MDA: malondialdehyde; mGluR: metabotropic glutamate receptor; mtUPR: mitochondrial unfolded protein response; NF-κB: nuclear factor-kappa B; NGF: nerve growth factor; Nrf2: nuclear factor erythroid 2-related factor 2; OPA1: optic atrophy 1 protein; PARIS: parkin-interacting substrate; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PKA: protein kinase A; PTEN: phosphatase and tensin homolog; ROS: reactive oxygen species; SIRT4: sirtuin 4; SOD: superoxide dismutase; TH+:tyrosine hydroxylase-positive neurons; TNF-α: tumor necrosis factor-alpha.

attributed to its ability to inhibit Abelson (Abl) tyrosine kinase, as it prevented hyperphosphorylation of Abelson tyrosine kinase at tyrosine 412 (Abl Y412) and Crk-like protein at tyrosine 221 (CrkII Y221). This was reinforced by the similar protective effects observed with nilotinib, an Abl inhibitor (107) (Table 4).

It has been reported that rosmarinic acid protected SH-SY5Y cells exposed to 1-Methyl-4-phenylpyridinium (MPP+) from oxidative stress, morphological alterations, and cell viability reduction caused by mitochondrial damage. The findings indicate that rosmarinic acid prevented mitochondrial unfolded protein response (mtUPR) activation triggered by methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) by down-regulating proteins such as heat shock protein family A member 9 (HSPA9), heat shock protein family E member 1 (HSPE1), caseinolytic mitochondrial matrix peptidase proteolytic subunit (CLPP), lon peptidase 1, mitochondrial (LONP1), and Sirt4 (108).

Ursolic acid

Treating SH-SY5Y cells exposed to N-Methyl-4-phenyl-pyridinium iodide (MPP^+) with ursolic acid increased cell viability by reducing the expression of IL-1β, TNF-α, IL-6, phosphorylation of p44/42 MAPK, cleaved-caspase-3, and cleaved-caspase-8 (109).

Correspondingly, another study investigated the potential neuroprotective effects of ursolic acid in a Parkinson's disease model using PC12 cells and primary neurons, particularly its role in regulating autophagy-dependent apoptosis by mitigating oxidative stress. The findings demonstrate that rotenone disrupts autophagy by reducing autophagy-related protein 5 (ATG5)/LC3-II expression and autophagosome formation while increasing p62 accumulation, ultimately accelerating neuronal apoptosis. The suppression of autophagy is further intensified when ATG5 is silenced, emphasizing its critical role. Additionally, the study highlights that rotenone induces oxidative stress, activating AMPK, which further inhibits autophagic processes and promotes apoptosis. Conversely, ursolic acid counteracts these detrimental effects by reducing oxidative stress, suppressing AMPK activation, enhancing autophagy, and decreasing p62 accumulation, thereby protecting neurons. Furthermore, inhibiting AMPK activity alleviates rotenone-induced impairments in autophagy and apoptosis (110).

In vivo

Rosemary extracts

Researchers administered varying doses of hydro-alcoholic rosemary extract to Parkinson's model mice alongside a Selegiline treatment group. Findings demonstrated that the highest dose of rosemary extract significantly enhanced movement and coordination, suggesting its potential therapeutic role in reducing Parkinson's symptoms in a dose-dependent manner (111).

A study investigated whether adipose tissue-derived stem cells or rosemary extract could enhance hippocampal neurogenesis and memory function in rats with Parkinsonian lesions. Rats were exposed to neurotoxic damage via bilateral intra-nigral injections of 6-OHDA and assigned to different intervention groups, receiving either rosemary extract, adipose tissue-derived stem cells, or control treatments. Behavioral assessment using the Morris Water Maze revealed that rats treated with adipose tissue-derived stem cells or rosemary extract demonstrated improved memory retention and reduced latency in spatial navigation tasks. Histopathological examination showed greater neuronal density and Bromo-deoxyuridine $(BrdU)^+$ cell proliferation at lesion sites in treated animals, along with diminished levels of $GFAP^+$ astrocytes (112).

It has been observed that rosemary leaves' aqueous extract, particularly at higher doses, significantly improved motor functions and reduced oxidative stress markers when compared to the Parkinson's group. The highest dose notably lowered lipid peroxidation, though it remained higher than in the control group (113).

A study investigated the combined effects of rosemary extract and adipose-derived stem cells on Parkinson's disease-related cognitive impairment. Researchers examined their influence on anti-oxidant enzyme activity, neurotrophin levels, and spatial memory in a rat model. Experimental groups underwent neurotoxin administration and subsequent treatments, with behavioral assessments showing improved cognitive performance in cell-transplanted and rosemary-treated rats. The cell transplant plus rosemary group exhibited significant neuroprotective effects, including enhanced expression of BDNF, nerve growth factor (NGF), neurotrophin 3, and neurotrophin 4, increased anti-oxidant enzyme activity (SOD, GPx), and reduced oxidative stress markers like MDA. Additionally, hippocampal immunohistochemical analysis revealed decreased $GFAP^+$ cell density, supporting the role of adipose-derived stem cells and rosemary extract in neuroprotection and memory enhancement (114).

Rosmarinic acid

The evaluation of the neuroprotective potential of rosmarinic acid against MPTP-induced dopaminergic damage in a zebrafish model of Parkinson's disease indicated that rosmarinic acid effectively preserves dopaminergic neurons and mitigates motor impairments caused by MPTP exposure. Furthermore, rosmarinic acid reduces oxidative stress markers such as ROS and MDA while enhancing GSH levels and promoting the expression of neuroprotective proteins, including Parkinson's disease protein 7 (DJ-1), p-Akt, HO-1, and nuclear Nrf2. In addition, rosmarinic acid inhibits phosphatase and tensin homolog (PTEN) expression. The Nrf2 inhibitor brusatol weakened the effects of rosmarinic acid (115).

Exploring the impact of microRNA-155-5p (miR-155-5p) on Parkinson's disease and its modulation by rosmarinic acid revealed that up-regulating miR-155-5p counteracted the protective effects of rosmarinic acid, worsening motor impairments and intensifying neurodegenerative markers. Further validation confirmed the involvement of miR-155-5p in regulatory pathways linked to Parkinson's disease progression (116).

The therapeutic effects of rosmarinic acid were explored in a Parkinson's disease model using MPTP-induced neurodegeneration in mice. The results demonstrate that rosmarinic acid effectively counteracts the hyper-locomotion behavior caused by MPTP treatment. Additionally, rosmarinic acid strengthens dopaminergic signaling in Parkinson's disease-affected mice and positively influences the monoaminergic system in healthy ones. Molecular analysis showed an increase in monoamine oxidase A (MAO-A) expression in the MPTP plus rosmarinic acid group, suggesting a regulatory role in neurotransmission (117).

Similarly, it has been shown that rosmarinic acid exerts neuroprotective effects in Parkinson's disease by regulating molecular pathways in the substantia nigra. The results showed that rosmarinic acid significantly alters the expression of 371 proteins, influencing pathways related to oxidative phosphorylation (OXPHOS), glutamatergic synapse activity, and vesicular cycle signaling. Rosmarinic

acid notably modulates targets such as metabotropic glutamate receptor (mGluR)2, mGluR3, excitatory amino acid transporter (EAAT) proteins, and Complex I proteins from the electron transport chain (118).

Ursolic acid

Behavioral tests and biochemical analyses revealed that ursolic acid alleviated motor deficits, reduced oxidative stress, and suppressed neuroinflammation in a rotenone-induced mouse model of Parkinson's disease. Furthermore, ursolic acid preserved tyrosine hydroxylase (TH) levels, modulated phosphorylation of survival-related kinases (Akt and ERK), and decreased inflammatory markers such as NF-κB and TNF-α (119).

Assessing the neuroprotective effects of ursolic acid against rotenone-induced Parkinson's disease revealed that ursolic acid efficiently reduced oxidative stress by increasing the activity of reduced GSH, CAT, and SOD and reducing MDA amounts. It also attenuated TNF-α levels and $GFAP^+$ astrocytes. Moreover, ursolic acid preserved TH^+ neurons, restored mitochondrial function, and enhanced mitochondrial biogenesis (120).

The supplementation of ursolic acid to mice with Parkinson's disease induced by rotenone exposure exhibited protective effects by mitigating oxidative stress and inflammation. Moreover, ursolic acid down-regulated glycogen synthase kinase-3 beta (GSK-3β) activity and restored calcium homeostasis, reducing mitochondrial dysfunction and α-synuclein overexpression (121).

Generally, rosemary and its bioactive compounds—carnosic acid, rosmarinic acid, and ursolic acid—have demonstrated considerable neuroprotective potential in Parkinson's disease by targeting multiple pathological mechanisms (Figure 3). Their beneficial effects converge on key cellular pathways that regulate mitochondrial function, oxidative stress responses, autophagic clearance, neurotransmission, and protein aggregation, making them promising candidates for disease modification.

One of the central mechanisms of rosemary compounds in neuroprotection is mitochondrial stabilization. Mitochondrial dysfunction is a primary contributor to neurodegeneration in Parkinson's disease, leading to impaired oxidative phosphorylation, excessive ROS generation, and neuronal apoptosis. These compounds restore mitochondrial balance by enhancing fusion proteins, mitigating cytochrome c release, and preventing oxidative stress-induced damage. Carnosic acid regulates mitochondrial integrity through parkin-mediated pathways, while rosmarinic acid influences mitochondrial biogenesis via AMPK and PGC-1α activation. Moreover, ursolic acid promotes autophagic flux, clearing harmful protein aggregates and reducing the burden on mitochondrial health.

Beyond mitochondrial protection, rosemary components exhibit potent anti-oxidant and anti-inflammatory effects. By increasing anti-oxidant enzyme activity—including glutathione GSH, SOD, and CAT—they neutralize oxidative stress and reduce damage caused by mitochondrial instability. Moreover, their inhibitory effects on inflammatory mediators, such as NF-κB, TNF-α, and PTEN, suggest that they may slow neuro-inflammation-driven degeneration. Interestingly, the interaction of rosmarinic acid with microRNA networks, particularly miR-155-5p, points to an epigenetic regulatory role that could further modulate Parkinson's disease progression.

Another significant aspect of the neuroprotective effects of rosemary is its role in neurotransmission and protein aggregation. Rosmarinic acid modulates excitatory-inhibitory balance in Parkinson's disease-related neural circuits through its regulation of metabotropic glutamate receptors (mGluR2 and mGluR3) and EAATs. Meanwhile, ursolic acid inhibits α-synuclein aggregation, restoring calcium homeostasis and down-regulating GSK-3β, which is implicated in protein misfolding and neurodegeneration. Additionally, rosemary compounds prevent the formation of cytotoxic aggregates, stabilizing remaining proteins in a non-toxic state, a dual action that highlights their therapeutic relevance.

Despite these promising findings, some limitations must be considered. Many studies have been conducted *in vitro* or in animal models, requiring further validation in human trials to confirm their efficacy and applicability in the clinical field. Moreover, while individual compounds exhibit protective properties, their synergistic interactions within full rosemary extracts remain underexplored. Investigating optimized formulations and combination therapies could enhance their neuroprotective potential and bioavailability.

Future research should focus on translating these molecular insights into viable therapeutic approaches. Examining how rosemary compounds integrate with emerging neuroprotective strategies—including stem cell therapy, immune modulation, and multi-target drug formulations—could provide new opportunities for Parkinson's disease treatment. Finally, rosemary and its components provide a robust base for intervention in Parkinson's disease, addressing multiple disease mechanisms simultaneously to slow neurodegeneration and improve

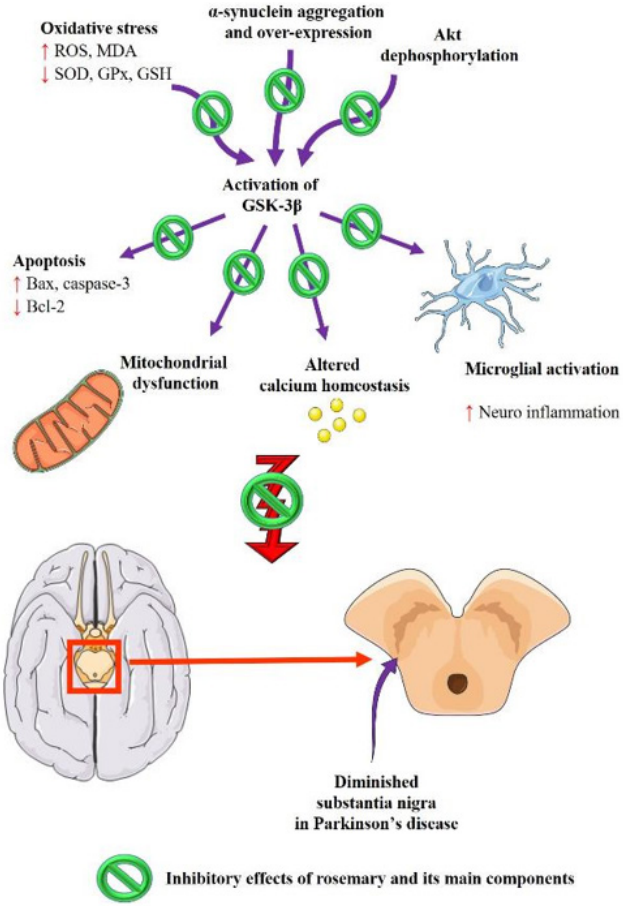

Figure 3. Effects of rosemary and its main components on Parkinson's (Images from https://smart.servier.com)

neuronal resilience.

Future perspectives

Rosemary has appeared as an advantageous neuroprotective agent, demonstrating various benefits for several nervous system disorders. While preclinical and mechanistic studies strongly support its efficacy, several key areas warrant further investigation to enhance its clinical applicability and therapeutic potential.

Future research should prioritize large-scale clinical trials to validate the effects of rosemary and its main components in human populations, particularly in Alzheimer's and Parkinson's disease, epilepsy, mood disorders, and pain management. Standardizing extraction methods, formulations, and dosing strategies will be essential in optimizing efficacy and minimizing variability in therapeutic outcomes. Additionally, exploring sex-dependent metabolic differences will allow for the development of personalized treatment approaches, improving safety and effectiveness across different patient groups.

Advancements in drug delivery systems, such as nanotechnology and bioengineered formulations, offer opportunities to improve the bioavailability and brain penetration of rosemary-derived compounds. Developing targeted delivery mechanisms will enhance therapeutic precision, reducing systemic side effects while maximizing neuroprotective benefits.

Beyond pharmacological applications, synergistic strategies combining rosemary with exercise, dietary interventions, and conventional neurotherapeutics could intensify its effects. Investigating its role in integrative medicine may uncover novel therapeutic pathways for cognitive enhancement and neuroprotection.

Finally, expanding research into epigenetic and immunomodulatory effects of rosemary could reveal new dimensions in its therapeutic applications, particularly in neuro-immune regulation and age-related cognitive decline. By bridging traditional medicinal knowledge with innovative scientific advancements, rosemary holds immense potential for shaping future neuroprotective strategies.

Conclusion

Rosemary and its bioactive compounds demonstrate remarkable neuroprotective potential across a diverse range of nervous system disorders. Their anti-oxidant, anti-inflammatory, neurotransmitter-modulating, mitochondrial-stabilizing, and metabolic-regulating properties highlight their usefulness as therapeutic agents for conditions such as Alzheimer's disease, anxiety, depression, epilepsy, pain, and Parkinson's disease. By influencing key molecular pathways—including NF-κB, Nrf2, BDNF, NO/cGMP/KATP, and autophagic clearance—rosemary compounds help preserve neuronal function, control oxidative stress, and mitigate neuro-inflammatory damage.

One of the most promising aspects of the therapeutic profile of rosemary is its potential for integration with existing treatment strategies, offering synergistic benefits while reducing the adverse effects associated with conventional medicines. Whether enhancing cognitive resilience, stabilizing mitochondrial function, or modulating neurotransmission, rosemary presents an opportunity for both pharmacological and non-pharmacological interventions in neuropsychiatric and neurodegenerative disorders. Furthermore, its interaction with metabolic and immune regulatory systems highlights additional opportunities for personalized medicine, emphasizing the importance of individualized dosing strategies.

Despite substantial preclinical evidence, challenges remain in optimizing bioavailability, refining standardized formulations, and validating long-term efficacy through large-scale human trials. The incorporation of advanced delivery systems, such as nanotechnology, alongside adjunctive therapies like exercise interventions, could enhance its therapeutic potential and clinical applicability. Addressing sex-dependent metabolic variations and refining treatment protocols are essential to ensuring safety and maximizing effectiveness.

Looking ahead, rosemary represents a promising and innovative tool for neurological health, bridging traditional medicinal approaches with modern scientific advancements. Continued research will be critical in translating its diverse neuroprotective mechanisms into practical, clinically useful interventions, ultimately facilitating more effective and accessible therapies in nervous system disorder management.

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Availability of data and Materials

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Authors' Contributions

E VM, B RK, and Z Y co-authored the manuscript. M GR supervised and reviewed the document. J J contributed to the concept and assisted in data collection. All authors approved the final version.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Declaration

During the preparation of this work, the author(s) used ChatGPT to rephrase and reduce plagiarism, and improve the language and grammar. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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