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## Carnosic acid

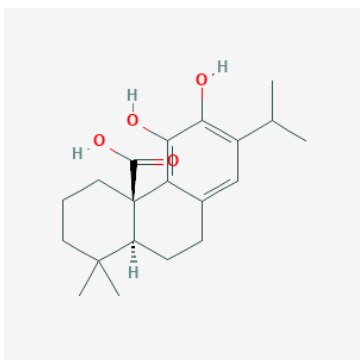
### Evidence Summary

Preclinical studies have shown that carnosic acid has antioxidant, neuroprotective, and mitoprotective effects. No clinical trials have tested carnosic acid specifically, but a few have tested rosemary products with mixed results.

**Neuroprotective Benefit:** Treatment with rosemary failed to reliably improve cognition in healthy older adults. Preclinical studies suggest carnosic acid improves cognitive function and mitochondrial health while increasing BDNF and synapses.

**Aging and related health concerns:** No evidence exists for humans, but preclinical studies suggest carnosic acid may protect against cancer, brain injury, inflammation, metabolic syndrome, arthritis, and neuropathic pain. It also extended lifespan in *C. elegans*.

**Safety:** No studies have specifically examined the long-term safety of carnosic acid in humans. Rosemary is GRAS, but doses above what is found in food may have toxic effects, though the toxic effects may not be due to carnosic acid.

<p><b>Availability:</b> Rosemary extract is available OTC. Some products list the % of carnolic acid.</p>	<p><b>Dose:</b> Not established in humans. No clinical studies have tested carnolic acid alone.</p>	<p><b>Chemical formula:</b> C<sub>20</sub>H<sub>28</sub>O<sub>4</sub> <b>MW:</b> 332.4</p>
<p><b>Half life:</b> Not documented; likely depends on route of administration.</p>	<p><b>BBB:</b> Penetrant in rodents</p>	 <p>Source: <a href="#">PubChem</a></p>
<p><b>Clinical trials:</b> No clinical trials have tested carnolic acid alone. Small trials have examined the effects of rosemary powder and extract (n=28 and 44, respectively).</p>	<p><b>Observational studies:</b> No observational studies have examined carnolic acid intake.</p>	

**What is it?** Carnolic acid is a phenolic diterpene found in rosemary (*Rosmarinus officinalis*) and common sage (*Salvia officinalis*) (Loussouarn et al., 2017). Carnolic acid is best known as an antioxidant. Carnolic acid induces the antioxidant defense system through its di-phenolic catechol moiety, which can scavenge free radicals, making it an electron-donating antioxidant. Also, the catechol of carnolic acid is metabolically converted to a quinone which is responsible for activating the transcription factor Nrf2, which regulates the expression of antioxidant proteins. Thus, carnolic acid is a dual mechanism antioxidant with combined electron-donating properties as well as Nrf2-activating activity (Hall et al., 2019).

**Neuroprotective Benefit:** Treatment with rosemary failed to reliably improve cognition in healthy older adults. Preclinical studies suggest carnolic acid improves cognitive function and mitochondrial health while increasing BDNF and synapses.

*Types of evidence:*

- No clinical trials that specifically tested carnolic acid
- 1 double-blind randomized controlled crossover trial of rosemary powder in elderly people
- 1 double-blind randomized controlled trial of herbal extracts including rosemary in healthy older adults



- 1 open-label clinical study testing the effects of aromatherapy that included rosemary in dementia patients
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

No studies have specifically tested carnosic acid for prevention of dementia or cognitive decline.

One randomized double-blind controlled cross-over trial of 28 elderly people (mean age, 75 years old) reported that a single treatment of rosemary dried leaf powder (4 different doses, 750, 150, 3000, and 6000 mg) had mixed effects on cognitive functions ([Pengelly et al., 2012](#)). The lowest dose (750 mg) of rosemary had a statistically significant beneficial effect compared with placebo ( $p=0.01$ ), whereas the highest dose (6,000 mg) had a significant impairing effect ( $p<0.01$ ). All treatments including placebo showed a significant impairment compared with baseline except the 750 mg dose, which showed negligible difference from baseline. There were significant deleterious effects on other measures of cognitive performance; “continuity of attention” was significantly impaired at 1,500 mg ( $p<.001$ ), 3,000 mg ( $p=0.04$ ), and 6,000 mg ( $p<0.001$ ) doses, and “quality of working memory” was significantly impaired at 750 mg ( $p=0.02$ ), 1,500 mg ( $p=0.01$ ), and 6,000 mg ( $p=0.01$ ), in both cases compared with placebo. There were no effects for the “power of attention” and “quality of episodic secondary memory” scores. For the self-ratings of mood and alertness, all scores including placebo were reduced from baseline as the testing day progressed. There was a significant improvement at 750 mg in alertness ( $p=0.01$ ) compared with placebo, whereas the 6,000 mg dose was associated with decreased alertness compared with placebo ( $p=0.02$ ). This study did not statistically control for multiple comparisons, and therefore some of these significant p-values could be due to chance.

One randomized double-blind controlled trial of 44 healthy older adults (mean age 61) reported that treatment with an ethanol extract of sage, rosemary, and melissa (*Salvia officinalis*, *Rosmarinus officinalis*, and *Melissa officinalis*; equal proportions, equivalent to daily dose of 5 g original plant material) for 2 weeks did not show any significant differences in immediate delayed word recall when compared to 2 weeks of placebo (50% fresh sweet cicely, *Myrrhis odorata*) ([Perry et al., 2018](#)). However, a subgroup analysis showed significant improvements to delayed word recall in people under 63 years old ( $p < 0.0123$ ) with Cohen's effect size of 0.92. Because of the many different bioactive compounds present in these 3 herbs, it is not possible to attribute the benefit, if any, to carnosic acid.



Human research to suggest benefits to patients with dementia:

No studies have tested whether carnosic acid is beneficial for patients with dementia.

One small open-label study of dementia patients (17 Alzheimer's, 3 vascular dementia, 8 other diagnoses) reported that aromatherapy consisting of rosemary and lemon essential oils in the morning and lavender and orange in the evening for 28 days was associated with improvement in orientation and dementia assessment scale (measured by the Touch Panel-type Dementia Assessment Scale)([Jimbo et al., 2009](#)). However, this was an open-label trial that cannot rule out a placebo or practice effect. Also, it is not clear what the mechanism of actions are, and whether the aromatherapy components are penetrating the blood-brain barrier. The study is not able to tease apart benefits of any specific ingredient of aromatherapy.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Numerous preclinical studies suggest neuroprotective benefits of carnosic acid. Carnosic acid crosses the blood-brain barrier and accumulates in the mammalian brain ([de Oliveira et al., 2018](#)).

**Alzheimer's models:** In a mouse model of Alzheimer's disease (hAPP-J20 mice), carnosic treatment (10 mg/kg, transnasal) for 3 months improved learning and memory as measured by the Morris water maze test ([Lipton et al., 2016](#)). Carnosic acid also increased dendritic and synaptic markers, and decreased astrogliosis, A $\beta$  plaque number, and phospho-tau staining in the hippocampus. In rat primary neurons exposed to oligomeric A $\beta$ , carnosic acid reduced dendritic spine loss. In rats injected with A $\beta$ 40 into the hippocampus, carnosic acid treatment (3 mg/kg, i.p.) before surgery and once daily after surgery for up to 12 days restored passive avoidance learning and spontaneous alternation behavior scores when compared to controls ([Rasoolijazi et al., 2013](#)).

**Traumatic brain injury models:** In a mouse model of traumatic brain injury, carnosic acid treatment (a single 1 mg/kg, i.p.) 15 min after controlled cortical impact injury significantly preserved respiratory function and reduced mitochondrial damage in the injured cortex after 24 h ([Hall et al., 2019](#)). Furthermore, carnosic acid's antioxidant effects were still apparent at 48 h post-injury as measured by attenuation of 4-HNE and 3-NT in the injured cortical tissue and a decrease in Ca<sup>2+</sup>-activated, calpain-mediated, neuronal cytoskeletal degradation. Ongoing studies are evaluating the behavioral recovery and tissue protective effects of carnosic acid to determine whether these benefits are also seen with a more clinically practical 8-hour therapeutic window ([Hall et al., 2019](#)). In a mouse model of repetitive mild traumatic brain injury, carnosic acid treatment (1 mg/kg, i.p., 30 minutes after each injury)



significantly improved motor and cognitive function, and decreased Gfap and Iba1 immunoreactivities within white matter tracks to levels comparable to sham-operated mice ([Maynard et al., 2019](#)).

**Other rodent models:** In rats, intranasal carnosic acid treatment (4 mg/kg with 0.25% w/v chitosan dissolved in hydroxypropyl- $\beta$ -cyclodextrin) for 4 days significantly increased levels of neurotrophins NGF and BDNF by 3.2-fold and 2.7-fold, respectively, compared with the control group ([Vaka et al., 2011](#)). This study used hydroxypropyl- $\beta$ -cyclodextrin to enhance the aqueous solubility of carnosic acid and the intranasal delivery strategy to circumvent the limitations associated with parenteral delivery.

Other rodent studies have examined the effects of rosemary extract treatments. In rats with memory dysfunction (induced by scopolamine), rosemary extract treatment (200 mg/kg, orally) for 28 days significantly improved long-term memory ([Ozarowskii et al., 2013](#)). The extract inhibited acetylcholinesterase activity in the rat brain. No effects were seen for short-term memory.

In a mouse model of accelerated aging ([SAMP8 mice](#)), rosemary extract containing 60% carnosic acid improved acquisition and retention in T-maze foot shock, object recognition and lever press ([Farr et al., 2016](#)). Rosemary extract with 10% carnosic acid improved retention in T-maze foot shock avoidance and lever press. Lipid peroxidation (measured by 4-hydroxynonenal; HNE) was reduced in the brain cortex after treatment with rosemary extracts ( $P < 0.001$ ) compared to the vehicle-treated SAMP8 mice. Protein carbonyls were reduced in the hippocampus after administration of rosemary with 10% carnosic acid ( $P < 0.05$ ).

**In vitro models:** Several studies have examined the effects of carnosic acid on cell culture systems. In human neuroblastoma SH-SY5Y cells, carnosic acid pretreatment alleviated the A $\beta$ 25-35-induced loss of cell viability, inhibited both A $\beta$ 42 accumulation and tau hyperphosphorylation, reduced reactive oxygen species generation, and maintained the mitochondrial membrane potential ([Meng et al., 2015](#); [Liu et al., 2016](#)). Carnosic acid increased the microtubule-associated protein light chain 3 (LC3)-II/I ratio and decreased SQSTM1(p62), suggesting that carnosic acid may induce autophagy. Autophagy inhibitor (3-methyladenine) attenuated the neuroprotective effect of carnosic acid, suggesting that autophagy was involved in the neuroprotection of carnosic acid. Carnosic acid also activated AMP-activated protein kinase (AMPK) but inhibited mammalian target of rapamycin (mTOR). Thus, carnosic acid appears to induce autophagy by activating AMPK.

In human neuroblastoma SH-SY5Y cells exposed to the neurotoxin 6-hydroxydomapine ([6-OHDA](#)), treatment with carnosic acid prevented the disruption of the mitochondrial membrane potential,



inhibition of the voltage-dependent anion channel 1 (VDAC1) protein, and induction of cytosolic cytochrome c ([Lin and Tsai, 2019](#)). Carnosic acid also promoted the translocation of parkin into mitochondria. Thus, carnosic acid appears to counteract the neurotoxicity of 6-OHDA by activating PINK1/parkin-mediated mitophagy and preventing the apoptotic pathway.

**Mitochondria effects:** A review on the effects of carnosic acid on mitochondria discusses wide ranging mechanisms ([de Oliveira et al., 2018](#)). Carnosic acid promotes mitochondrial health by activating the PI3K/Akt/Nrf2 signaling pathway, reducing the impact of pro-oxidant agents on the mitochondrial membranes, decreasing production of reactive oxygen species (ROS) by mitochondria, increasing the levels of the endogenous antioxidant glutathione (GSH) in the mitochondria, upregulating the antioxidant enzyme Mn-SOD, and restoring the function of the mitochondria oxidative phosphorylation system.

**APOE4 interactions:** No studies have examined whether carnosic acid has different effects depending on people's ApoE genotype. But one study in PC12 cells showed that carnosic acid increases cell surface expression of apolipoprotein E receptor 2 (ApoER2) by enhancing the interaction of ApoER2 with sorting nexin 17 (SNX17), activating the reelin signaling pathway to promote neurite growth, and reversing the inhibitory effects of ApoE4 on these functions ([Feng et al., 2020](#)).

**Aging and related health concerns:** No evidence exists for humans, but preclinical studies suggest carnosic acid may protect against cancer, brain injury, inflammation, metabolic syndrome, arthritis, and neuropathic pain. It also extended lifespan in *C. elegans*.

*Types of evidence:*

- 0 clinical trials that have tested carnosic acid alone
- Numerous laboratory studies

**Lifespan:** ENHANCEMENT IN WORMS.

In *C. elegans*, carnosic acid treatment increased lifespan from a mean of 20.17±0.16 days to 23.35±0.05 days at 180 uM (at 20°C)([Lin et al., 2019](#)). Carnosic acid was absorbed by the worms and improved their mobility, reduced the accumulation of age pigment, delayed Aβ-induced and polyQ-dependent paralysis and increased the resistance to heat and oxidative stress. In terms of the mechanism underlying the lifespan extension, the beneficial effects were associated with the increased expression of SOD-3 but



not with ROS scavenging activity. Mitogen-activated protein kinase (MAPK) and heat-shock transcription factor-1 (HSF-1) pathways were associated with the lifespan-extending properties in *C. elegans*.

**Cancer:** POTENTIAL BENEFIT IN RODENT AND CELL CULTURE MODELS.

**Breast cancer:** In a mouse model of breast cancer (xenograft), carnosic acid treatment (30 mg/kg) combined with tamoxifen (10 mg/kg) inhibited breast cancer growth more significantly than each therapy alone ([Han et al., 2017](#)). Anti-apoptotic molecules Bcl-2 and Bcl-xl were down-regulated, while pro-apoptotic signals Bax and Bad were up-regulated. In a cell culture model of breast cancer (ERBB2+ breast cancer cells), carnosic acid enhances trastuzumab (chemotherapy) inhibition of cell survival, inhibits cell migration, and induces cell cycle arrest in G0/G1 ([D'Alesio et al., 2017](#)). Carnosic acid impairs late autophagy and causes derangement of the lysosomal compartment as shown by up-regulation of SQSTM1/p62 and ultrastructural analysis.

**Colon cancer:** In a mouse model of colon cancer (xenograft), carnosic acid-rich rosemary extracts (1 mg extract/mL drinking water) for 5 weeks inhibited tumor growth ([Gonzalez-Vallinas et al., 2014](#)). The mechanism of protection may be due in part to significant downregulation of an epigenetic modulator, miR-15b and upregulation of a metabolic-related gene GCNT3.

**Lung cancer:** Carnosic acid inhibited the growth of A-549 human non-small cell lung carcinoma cells dose-dependently while also inhibiting cell migration and invasion ([Zhao et al., 2019](#)). This growth inhibition was mediated via apoptotic cell death. The expression of matrix metalloproteinase-9, which plays a critical role in cell migration, was significantly decreased with carnosic acid.

**Arthritis:** POTENTIAL BENEFIT IN RODENTS.

In a rat model of arthritis, carnosic acid treatment suppressed expression of pro-inflammatory cytokines including TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-8, IL-17 and MMP-3, and downregulated the production of RANKL, an apoptosis regulator gene ([Liu et al., 2018](#)). Carnosic acid also inhibited osteoclastogenesis and bone resorption *in vitro* and exerted therapeutic protection against joint destruction *in vivo*.

In a mouse model of arthritis induced by collagen, carnosic acid treatment (30 or 60 mg/kg/day, i.p.) for 4 weeks significantly ameliorated bone loss, and reduced pro-inflammatory cytokines and reactive oxygen species ([Xia et al., 2017](#)). Additionally, carnosic acid inactivated the p38 mitogen activated protein kinases (MAPK), inhibited NF- $\kappa$ B phosphorylation, resulting in downregulation of pro-inflammatory cytokines.



**Neuropathic pain:** POTENTIAL BENEFIT IN RODENTS.

In a rat model of neuropathic pain (chronic constriction injury of the sciatic nerve), carnosic acid treatment (25-100 µg once daily, intrathecal) from 3 days after injury to 6 days after injury attenuated mechanical allodynia (pain from non-painful stimuli) and thermal hyperalgesia (increased sensitivity to pain)([Chen et al., 2016](#)). The authors speculated that spinal Sirt1 activation could mediate the antinociceptive effect of carnosic acid through a mechanism involving the down-regulation of p66shc expression. P66shc is an isoform of the mammalian adapter protein ShcA and is thought to contribute to physiological and pathophysiological processes.

In a mouse model of chronic neuropathic pain (chronic constriction injury of the sciatic nerve), Noxiall treatment (including carnosic acid, phenylethylamine, myrrh, beta-caryophyllene, etc.) for 14 days starting 24 hours after nerve ligation significantly attenuated mechanical allodynia (pain from non-painful stimuli) and thermal hyperalgesia (increased sensitivity to pain)([Fotio et al., 2019](#)). When Noxiall was combined with a non-effective dose of pregabalin (nerve pain medication), there was a significant decrease in neuropathic pain, suggesting an additive efficacy.

**Brain injury:** POTENTIAL PROTECTION IN RODENTS.

In rats after subarachnoid hemorrhage, carnosic acid treatment (3 mg/kg, i.v. immediately after hemorrhage) decreased oxidative stress (ROS) levels, alleviated brain edema and blood-brain barrier permeability, reduced neuronal cell death, and promoted neurologic function improvement ([Teng et al., 2019](#)). Carnosic acid increased SIRT1, MnSOD, and Bcl-2 expression, as well as decreased p66shc, Bax, and cleaved caspase-3 expression. A selective inhibitor of SIRT1 (sirtinol) abolished the anti-apoptotic effects of carnosic acid. Thus, the potential mechanism may involve suppression of neuronal apoptosis through the SIRT1/p66shc signaling pathway. Carnosic acid-induced SIRT1 upregulation may play a protective role in early brain injury secondary to subarachnoid hemorrhage.

In a mouse model of cerebral ischemia-reperfusion injury, carnosic acid treatment (10 mg/kg immediately after injury and 3 mg/kg daily for 10 days, i.p.) significantly increased the number of healthy cells and decreased the expression of Caspase-3 and Bax, while increasing the expression of the anti-apoptotic Bcl-2 ([Babahajian et al., 2019](#)). However, carnosic acid did not improve the latency time for passive avoidance test.

In a mouse model of type 2 diabetes (high fat diet-induced) with ischemia-reperfusion injury, carnosic acid treatment (50 mg/kg, oral gavage) for 5 days decreased oxidative stress and inflammatory responses ([Hu et al., 2019](#)). The generation of superoxide and malondialdehyde (fatty acid peroxidation)



was inhibited by carnosic acid treatment and oxidized GSSG was reduced to glutathione GSH, the endogenous antioxidant. Carnosic acid inhibited cytokine production and enhanced autophagy in cardiomyocytes via regulation of the AMPK and mTOR signaling pathway.

***Inflammation, metabolism, and lipid profiles:*** POTENTIAL BENEFIT IN RODENTS.

In mice fed a high fat diet, carnosic acid treatment (10 or 20 mg/kg, oral gavage) for 9 weeks significantly decreased the metabolic syndrome by decreasing serum levels of triglycerides, total cholesterol, insulin and glucose ([Liu et al., 2019](#)). Carnosic acid also significantly decreased the protein expression levels of various pro-inflammatory cytokines in serum and brain tissues, including IL-1 $\beta$ , IL-6 and tumor necrosis factor- $\alpha$ , regulated by the NF- $\kappa$ B signaling pathway. Carnosic acid also promoted the expression levels of anti-apoptotic Bcl-2, and decreased the expression of pro-apoptotic Bax and matrix metalloproteinase 9. In a rat model of diabetes (induced by high fat diet plus streptozotocin), carnosic acid treatment (30 mg/kg, intragastric) for 15 weeks decreased the levels of fasting plasma glucose by 15.6%, total cholesterol by 14.1% and triglyceride 47.8% ([Ou et al., 2018](#)). Carnosic acid also exhibited an antioxidative and anti-glycative effect by lowering the formation of malondialdehyde and advanced glycation end products. Prebiotic effects of carnosic acid on gut microbiota were demonstrated by increasing the population of diabetes-resistant bacteria and decreasing the amounts of diabetes-sensitive bacteria.

In a mouse model of arthritis induced by collagen, carnosic acid treatment (30 or 60 mg/kg/day, i.p.) for 4 weeks significantly down-regulated fasting blood glucose, glucose level in oral glucose tolerance test and insulin tolerance test ([Xia et al., 2017](#)).

**Safety:** No studies have specifically examined the long-term safety of carnosic acid in humans. Rosemary is GRAS, but doses above what is found in food may have toxic effects, though the toxic effects may not be due to carnosic acid.

*Types of evidence:*

- No clinical trials that specifically tested carnosic acid
- 1 double-blind randomized controlled crossover trial of rosemary powder in elderly people
- 1 double-blind randomized controlled trial of herbal extracts including rosemary in healthy older adults
- 1 open-label clinical study testing the effects of aromatherapy that included rosemary in dementia patients

No clinical trials have tested the safety of carnosic acid specifically. Rosemary is generally recognized as safe (GRAS) when used in food ([Drugs.com](#)). Safety is unproven for dosages above those found in food. In excess levels, rosemary may increase menstrual flow or cause miscarriages. Ingestion of large amounts of rosemary essential oils can be toxic and have antigonadotrophic activity, based on a study in mice. Dermatitis and allergy to rosemary have also been reported.

Clinical trials testing the efficacy of an herbal extract including rosemary ([Perry et al., 2018](#)), rosemary oil aromatherapy ([Jimbo et al., 2009](#)), and rosemary dried leaf powder ([Pengelly et al., 2012](#)) have reported no adverse events.

**Drug interactions:** Drug interactions with carnosic acid have not been well studied ([Drugs.com](#)).

**Sources and dosing:** Carnosic acid is a phenolic diterpene found in rosemary (*Rosmarinus officinalis*) and common sage (*Salvia officinalis*) ([Loussouarn et al., 2017](#)). Rosemary extract containing carnosic acid is available over-the-counter. Some products list the percentage of carnosic acid. Rosemary is also widely used as a culinary spice. Dried leaves of rosemary or sage contain 1.5-2.5% of carnosic acid. Dosage is not established for carnosic acid as no clinical studies have specifically tested carnosic acid for prevention or treatment of any diseases. Traditional uses include 2 g of chopped leaf infused in water, or 2 to 4 g of the shoot ([Drugs.com](#)).

**Research underway:** No ongoing clinical trials are testing the efficacy of carnosic acid specifically. There are 7 ongoing clinical trials testing different formulations of rosemary for various indications, such as allergic rhinitis, chemotherapy-induced peripheral neuropathy, white spot lesions, and acne ([ClinicalTrials.gov](#)).

**Search terms:**

Pubmed, Google: carnosic acid

- + Alzheimer, + dementia, + cognitive, + apolipoprotein, + clinical trial, + mortality, + lifespan



Websites visited for carnosic acid:

- [Clinicaltrials.gov](https://clinicaltrials.gov) (0 for carnosic acid, 6 with some formulation of rosemary)
- Examine.com (0)
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com ([Rosemary](#))
- WebMD.com (0)
- [PubChem](#)
- DrugBank.ca (0)
- Labdoor.com (0)
- ConsumerLab.com (0)
- Cafepharma (0)
- Pharmapro.com (0)

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