



DOSSIER · SUBSTANCE

Rosmarinic Acid

Rosmarinic acid is a plant-derived **polyphenol metabolite** with a broad preclinical evidence base, but only a limited number of studies have been conducted in humans. The most notable findings come from controlled trials focusing on **cognition** and **safety**, while other potential applications—such as inflammation or immune modulation—remain scarcely explored in clinical settings.

302

STUDIES IN
TOTAL

23

IN HUMANS

11

OF WHICH
CONTROLLED

16

IN ANIMALS

94

IN THE LAB

Figures from the IHR study database · Last updated 2026-10-15

How to Read This Dossier

ESTABLISHED

measured in humans, with a comparison group

PLAUSIBLE

supported by mechanism, animal studies or observation

HYPOTHESIS

a likely connection that still needs to be tested

Rosemary acid at a glance

ORIGIN:

Rosemary acid is a plant-derived polyphenol metabolite from the group of hydroxycinnamic acid derivatives and an ester of caffeic acid.

STUDY EVIDENCE:

302 evaluated works · 11 controlled human studies · 12 observational studies · 26 review articles · 16 animal experiments · 77 cell culture studies

STRONGEST EVIDENCE:

- **Safety and tolerability: Plausible:** Extracts containing rosmarinic acid (e.g., from *Melissa officinalis*, 500 mg/dose) showed no severe adverse effects or changes in laboratory parameters in controlled studies. A 90-day study with *Mentha spicata* extract (600–900 mg/day) confirmed tolerability during long-term intake.
- **Cognition and psychology Plausible:** *Melissa officinalis* extract (500 mg/day) showed stabilisation of neuropsychiatric symptoms (NPI-Q) in mild Alzheimer's dementia. In a subgroup of older adults without hypertension, cognitive measures (CDR-SB) were stabilised.
- **Sleep and mood Plausible:** Extracts containing rosmarinic acid improved sleep quality (ISI score ↓ 2.9 points) and prolonged deep sleep by 15%. As adjunctive therapy in major depression, they reduced anxiety and depression scores (HADS-A, BDI-II).
- **Oxidative stress Plausible:** In cancer patients with chemotherapy-induced fatigue, a rosmarinic acid-rich extract (1000 mg, 3× daily) reduced fatigue scores (BFI) and showed a trend toward lower urinary F2-isoprostanes, a biomarker for oxidative stress.
- **Inflammatory processes: Plausible:** *Prunella vulgaris* extract containing rosmarinic acid reduced thyroid hormones (FT3, FT4) and TRAb levels significantly in Graves' disease, indicating immunomodulatory effects of the extract.

LIMITATIONS:

- Long-term safety studies of rosmarinic acid over several years are still pending, particularly in vulnerable groups such as pregnant women or chronically ill patients.
- Cognitive effects in healthy older adults remain to be clarified; studies on structural joint parameters (e.g., cartilage biomarkers) in osteoarthritis have not yet been conducted.
- The transferability of preclinical findings (e.g., antiviral or neuroprotective mechanisms) to humans is not yet established and requires clinical validation.

ASSESSMENT:

Rosmarinic acid is a promising plant-derived polyphenol metabolite with plausible effects on cognition, sleep, mood, and oxidative stress. Its clinical potential requires targeted long-term and mechanism studies to confirm these findings.

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1. What Rosemary Acid Is

Rosemary acid (chemical name: *O*-caffeoyl-3,4-dihydroxyphenyllactic acid) is an **ester of caffeic acid** and a secondary plant compound from the group of **hydroxycinnamic acid derivatives**. It occurs in numerous **Lamiaceae** species, including rosemary (*Rosmarinus officinalis*), lemon balm (*Melissa officinalis*), sage and mint. In plants, it serves as an **antioxidant** and **defence compound** against pathogens. For research, it is relevant as a **marker compound** in extracts, as it can be measured in a standardised way and correlates with other polyphenols. Industrially, it is extracted from plant raw materials, with *Melissa officinalis* being the most common source for controlled studies.

Crucial for the study evidence is the **bioavailability** and **metabolism** of rosemary acid: After oral intake, it is partially hydrolysed in the intestine, with **caffeic acid** and **3,4-dihydroxyphenyllactic acid** emerging as main metabolites. These metabolites reach higher plasma concentrations than the parent compound and are presumably responsible for systemic effects. Most human studies use **standardised extracts** with a defined rosemary acid content, as the pure substance is poorly water-soluble. **Pharmacokinetics** show rapid absorption (peak values after 1–2 hours) and a half-life of 4–6 hours, which supports daily intake.

2. What the Studies Show in Detail

The key human studies and most important reviews — grouped by application area, with population, duration, preparation, measurement parameters and results as reported in the original works. Numbers are included only where the study provides them.

Distribution of **controlled human studies** by application area — the numbers are not additive, as one study may be assigned to multiple areas:

APPLICATION AREA	CONTROLLED STUDIES
Cognition and psychology	7
Safety and tolerability	6
Fatigue and stress	4
Oxidative stress	2

APPLICATION AREA	CONTROLLED STUDIES
Absorption and availability	2
Inflammatory processes	1
Immune system	1
Oncology	1

Safety and Tolerability

PROVEN Rosmarinic acid in the form of a *Melissa officinalis* extract (500 mg rosmarinic acid per dose) was tested for safety and pharmacokinetics in a randomised, controlled study involving 11 healthy volunteers ¹. In the fasting state, serum rosmarinic acid concentration reached a maximum of 162.20 nmol/L after 1 hour, with an area under the curve (AUC) of 832.13 nmol·h/L. Food intake delayed absorption and increased AUC without affecting tolerability. Laboratory parameters (liver, kidney function, blood count) remained unchanged, and no adverse events occurred. The study confirms the safety of a single dose of 500 mg rosmarinic acid from *Melissa officinalis* in healthy adults.

PROVEN A 90-day, placebo-controlled study with an aqueous *Mentha spicata* extract (standardised to rosmarinic acid) at 600 and 900 mg/day showed no impact on hormone levels (FSH, LH, TSH), vital signs or haematological/biochemical markers in healthy adults with age-related memory impairment ¹⁹. No serious adverse events were reported, and observed side effects were not attributable to the extract. The results support the tolerability of long-term intake of rosmarinic acid-containing extracts at these doses.

Missing: Long-term studies on the safety of rosmarinic acid over several years, particularly in vulnerable groups such as pregnant women or patients with chronic diseases.

Cognition and Psyche

Evidence: A 24-week, randomised, placebo-controlled double-blind study in 23 patients with mild Alzheimer's dementia investigated the effects of *Melissa officinalis* extract (500 mg rosmarinic acid/day) ². The primary endpoint was safety, which was confirmed: no differences in vital signs or physical examinations between the verum and placebo groups. Secondary outcomes showed a significant improvement in the *Neuropsychiatric Inventory Questionnaire* (NPI-Q) by 0.5 points in the verum group, while the placebo group worsened by 0.7 points ($p = 0.012$). Cognitive measures (e.g., MMSE) remained unchanged, as did biomarkers. The study suggests that rosmarinic acid may stabilise neuropsychiatric symptoms in mild Alzheimer's dementia.

Evidence: In a 96-week, randomised, placebo-controlled study involving 323 older adults without dementia (subjective or mild cognitive impairment), *Melissa officinalis* extract (500 mg rosmarinic acid/day) was tested ⁴. The primary endpoint was the *Alzheimer's Disease Assessment Scale-cognitive subscale* (ADAS-cog), which showed no significant differences between groups. However, a subgroup analysis in participants without hypertension revealed stabilisation of the *Clinical Dementia Rating Sum of Boxes* (CDR-SB) in the verum group (-0.085 points) compared to deterioration in the placebo group (+0.006 points). The results suggest potential cognitive benefits in specific populations but require further confirmation.

Evidence: An 8-week, randomised, placebo-controlled study in patients with major depression examined the effects of rosemary capsules (containing rosmarinic acid among other compounds) as adjunctive therapy. After 8 weeks, the verum group showed a significant reduction in anxiety scores (*Hospital Anxiety and Depression Scale*, HADS-A) and depression scores (*Beck Depression Inventory-II*) compared to the placebo group. A positive side effect was an improvement in memory. The study suggests that *rosemary extracts* may contribute to alleviating depressive and anxiety symptoms, though the specific role of rosmarinic acid remains to be clarified.

Evidence: A 30-day, randomised, placebo-controlled study of a polyphenol-rich plant extract (including rosmarinic acid among other compounds) in 89 participants with subclinical sleep disorders showed significant improvements in subjective sleep quality ($p = 0.008$) and a reduction in insomnia severity (*Insomnia Severity Index*, ISI; $p = 0.044$) in the verum group ²⁰. No impairments in neurocognitive functions were observed; instead, improvements were seen in vigilance, working memory, and risk assessment. The study supports the assumption that *polyphenol-rich extracts* may positively influence sleep quality and cognitive functions, though the contribution of individual compounds, including rosmarinic acid, is not isolated.

Evidence: A prospective, placebo-controlled cross-over study with a highly standardised *Melissa officinalis* phytosome (containing 500 mg rosmarinic acid/day) in participants with sleep disorders showed a significant reduction in ISI scores by 2.9 points ($p = 0.003$) in the verum group after 30 days ⁵. The duration of the *slow-wave sleep* phase (deep sleep) increased by 15%, while the REM phase decreased by 10%. 87% of participants reported improved sleep quality (vs. 30% in the placebo group). The results indicate that *Melissa officinalis* extracts may influence sleep architecture and quality, though the specific role of rosmarinic acid remains to be determined.

HYPOTHESIS The observed effects on neuropsychiatric symptoms, sleep, and mood may be due to rosmarinic acid's modulation of neurotransmitter systems such as GABA, serotonin, and acetylcholine. Additionally, its antioxidant and anti-inflammatory properties may mediate neuroprotective effects, particularly in neurodegenerative processes.

Missing: Long-term studies on the cognitive effects of rosmarinic acid in healthy older adults, as well as targeted investigations into underlying neurobiological mechanisms (e.g., modulation of neurotransmitters or inflammatory markers).

Bones and Joints

Primary endpoints were pain, stiffness, and physical function (measured using the *Western Ontario and McMaster Universities Osteoarthritis Index*, WOMAC). In the verum group, WOMAC pain scores decreased significantly, while the placebo group showed no change. Both groups experienced a reduction in WOMAC stiffness and physical impairment scores. Quality of life (*SF-36*, Bodily Pain Index) improved only in the verum group, though without a significant difference compared to the placebo group. The study provides preliminary evidence that rosmarinic acid-containing extracts may influence surrogate endpoints related to symptoms in knee osteoarthritis, though clinical relevance remains to be confirmed.

Missing: Studies on the effects of rosmarinic acid on structural joint changes (e.g., cartilage degradation) and investigations into potential synergistic effects with established therapies such as NSAIDs or physiotherapy.

Oxidative Stress

Evidence: A 9-week, randomised, placebo-controlled phase II study in 110 cancer patients (stage II–IV) with chemotherapy-induced fatigue examined the effects of *Nuvastatic* (1000 mg, 3× daily; standardised rosmarinic acid-rich extract) ⁷. Primary endpoints were fatigue scores (*Brief Fatigue Inventory*, BFI; *Visual Analog Scale for Fatigue*, VAS-F). The verum group showed a significant reduction in BFI scores ($F(1.4; 147) = 16.554$; $p < 0.001$; partial $\eta^2 = 0.333$) compared to the placebo group. Secondary outcomes included a decrease in urinary F2-isoprostanes (a biomarker for oxidative stress), indicating a potential antioxidant effect of rosmarinic acid. The study showed that rosmarinic acid may influence fatigue and oxidative stress biomarkers in cancer patients.

Preclinical evidence: An *in-vitro* study in prostate cancer cells (PC3, LNCaP) and healthy fibroblasts (HFF-1) investigated the effects of a nanocomplex composed of rosmarinic acid, selenium-doped titanium oxide, and graphene oxide ⁹. The complex exhibited significantly higher cytotoxicity against cancer cells (IC50 values after 24/48 h were markedly lower than for pure rosmarinic acid) and induced apoptosis by increasing reactive oxygen species (ROS) and modulating gene expression (Bcl-2↓, Bax↑). The results suggest potential oncological applications for rosmarinic acid in nanotechnologically optimised formulations, though these preclinical findings require clinical validation.

Missing: Clinical studies on the antioxidant effects of rosmarinic acid in other conditions involving oxidative stress (e.g., cardiovascular diseases, diabetes) and investigations into optimal dosing and formulations for maximum bioavailability.

Inflammatory Processes

Evidence: A systematic review and meta-analysis of 9 randomised controlled trials ($n = 966$) examined the effects of *Prunella Oral Liquid* (an extract of *Prunella vulgaris* containing rosmarinic acid) *in combination with standard Western therapy* in patients with Graves' disease ¹⁸. The combination therapy led to a significant reduction in free thyroid hormones FT3 (SMD = -0.94; 95% CI: -1.63 to -0.26) and FT4 (SMD = -0.87; 95% CI: -1.55 to -0.19), as well as an increase in TSH (SMD = 0.79; 95% CI: 0.31 to 1.27) compared to standard therapy alone. Additionally, TRAb levels (thyroid-stimulating hormone receptor antibodies) decreased significantly. The study provides evidence for the potential anti-inflammatory and immunomodulatory effects of the *Prunella vulgaris* extract *in combination with standard therapy* in autoimmune thyroid diseases.

Preclinical evidence: An *in-vitro* study in BV2 microglial cells investigated the effects of a *Melissa officinalis* phytocomplex (high in rosmarinic acid) on neuroinflammation induced by high glucose concentrations ¹¹. After 48 hours of exposure to high glucose levels, microglial activation (CD11b↑ by 187%), NF-κB pathway activation (↑ 179%), increased expression of iNOS (↑ 225%) and IL-6 (↑ 173%), and enhanced phosphorylation of ERK1/2 (↑ 180%) were observed. Pretreatment with the phytocomplex prevented these inflammatory changes. The study suggests a *preclinical* modulatory effect of the phytocomplex on neuroinflammatory processes, though human relevance remains to be investigated.

HYPOTHESIS The anti-inflammatory effects of rosmarinic acid may involve multiple mechanisms, including inhibition of the NF-κB pathway and modulation of cytokines (e.g., IL-6, TNF-α). These effects could be relevant not only in autoimmune diseases but also in chronic inflammatory conditions such as rheumatoid arthritis or inflammatory bowel disease.

Missing: Clinical studies on the anti-inflammatory effects of rosmarinic acid in chronic inflammatory diseases and investigations into potential synergistic effects with established anti-inflammatory therapies.

Viral Infections

Preclinical evidence: An *in-vitro* study identified rosmarinic acid as an inhibitor of the interaction between the ε-RNA element of the hepatitis B virus (HBV) and the viral polymerase, a critical step in the replication cycle ⁸. Rosmarinic acid reduced HBV DNA levels in primary human hepatocytes from a humanised mouse liver without cytotoxic effects. Combination with lamivudine (a nucleoside analogue) showed additive effects, suggesting different mechanisms of action. Structural analyses of 25 rosmarinic acid derivatives indicated that the "two phenolic hydroxyl groups at both ends" and the "caffeic acid-lactic acid structure" are crucial for antiviral activity. These *preclinical* findings require clinical validation.

Preclinical evidence: A network pharmacology analysis and *in-vitro* validation examined the antiviral effects of rosmarinic acid against Chikungunya virus (CHIKV) ¹⁰. The analysis identified the IL-17 signalling pathway as a central mechanism in CHIKV pathogenesis. Rosmarinic acid (60 μM) significantly improved the survival rate of infected 293T cells and modulated 30 target proteins, nearly half of which were associated with the IL-17 pathway. Molecular docking studies confirmed stable binding to 10 of these target proteins. The results suggest a *preclinical* antiviral potential of rosmarinic acid through modulation of host immune responses.

HYPOTHESIS The antiviral effects of rosmarinic acid may result from a combination of direct inhibition of viral enzymes (e.g., polymerases) and indirect modulation of host immune responses (e.g., IL-17 pathway). This could make rosmarinic acid a promising candidate for the development of broad-spectrum antiviral therapies, particularly against viruses with limited treatment options.

What is missing: Clinical studies on the antiviral effect of rosmarinic acid in human infections (e.g., HBV, CHIKV), as well as investigations into optimal dosages and formulations for therapeutic application.

Oncology

Preclinically demonstrated: An *in-vitro* and *in-vivo* study examined the effect of *Echium amoenum* extract (EAEC) and rosmarinic acid on gastric cancer cells (AGS cell line) ¹². EAEC and rosmarinic acid inhibited cell growth by inducing apoptosis (mediated via caspases) and suppressed metastasis by modulating biomarkers of epithelial-mesenchymal transition (EMT). Additionally, the STAT3, AKT, and ERK1/2 signaling pathways were inactivated. In a *preclinical* model, rosmarinic acid significantly reduced tumour growth. The results suggest that rosmarinic acid may exert *preclinical* antiproliferative and antimetastatic effects in gastric cancer.

HYPOTHESIS

The oncological effects of rosmarinic acid may be based on a combination of antioxidant activity, inhibition of inflammatory pathways (e.g., NF-κB), and direct modulation of signal transduction pathways (e.g., STAT3, AKT) ²¹. These mechanisms could also be relevant in other cancer types, particularly those with high metastatic potential or therapy resistance.

What is missing: Clinical studies on the oncological effect of rosmarinic acid in cancer patients, particularly in combination with established therapies such as chemotherapy or immunotherapy, as well as investigations into possible resistance mechanisms.

Overall Picture

Rosmarinic acid demonstrates broad therapeutic potential, with preclinical and early clinical investigations across multiple indication areas. Its anti-inflammatory, antioxidant, and neuroprotective properties are particularly well studied in preclinical models, while human trials showed effects on cognition, sleep, mood, and oxidative stress markers. The safety and tolerability of rosmarinic acid-containing extracts are documented in short- to mid-term studies, with dosages of 500–1000 mg/day causing no serious adverse effects.

While some applications, such as knee osteoarthritis, have been investigated in clinical studies, other areas (e.g., antiviral or oncological effects) still require further clinical research. Preclinical data on fatigue in cancer models suggest promising mechanisms, but human studies are needed to confirm these effects. Systematic gaps remain, particularly in long-term use, optimal formulation for maximum bioavailability, and the study of synergistic effects with established therapies.

Methodology of the evidence base

Studies on rosmarinic acid encompass a wide range of designs, from randomised, placebo-controlled double-blind trials (RCTs) to preclinical *in-vitro* and *in-vivo* models. Among the clinical studies, durations range from 4 weeks (e.g., sleep studies) to 96 weeks (cognitive studies) and examine endpoints such as symptom scores (e.g., WOMAC), biomarkers (e.g., F2-isoprostanes, TRAb), or neurocognitive tests (e.g., ADAS-cog, CDR-SB). Preclinical data on fatigue in cancer models suggest mechanisms, but human studies are needed to confirm these effects. Common preparations include standardised extracts from *Melissa officinalis* or *Mentha spicata* with defined rosmarinic acid content (e.g., 500 mg/day).

Rosmarinic acid in cognition research: Mechanism or placebo?

MOST CONTROLLED STUDIES

on rosmarinic acid and cognition report **positive effects** on **attention**, **working memory**, and **executive function**, yet the **mechanistic explanation** remains unclear. The **most common hypothesis**—modulation of the cholinergic system or **inhibition of acetylcholinesterase**—is based on **preclinical data**, while human studies lack **direct neurotransmitter measurements**. Instead, **cognitive tests** are used, whose results may be strongly influenced by **placebo effects** and **learning curves**. A recent study in older adults showed **significant improvements** in test batteries, though **effect sizes** were small. Moreover, **comparisons with established nootropics** are lacking, which limits the **clinical relevance** of the findings.

A FURTHER ISSUE

is the **lack of specificity** in the extracts: most studies use *Melissa officinalis* extracts, which contain **additional polyphenols** alongside rosmarinic acid. A study on Alzheimer's prevention showed **slowed progression** on the scale, yet the **contribution of rosmarinic acid** to the effect remains unclear. Even a recent study using a **standardised rosmarinic acid extract** failed to demonstrate a **dose-response relationship**. It is therefore **plausible** that rosmarinic acid is **one of several active constituents**—but whether it is **effective on its own** remains unproven. The **next critical study** should test **pure substance vs. placebo** in a **homogeneous population** and include **biochemical markers**.

3. How Robust Is the Research?

Research on rosmarinic acid encompasses a substantial body of preclinical work alongside a smaller set of human studies. **Controlled human studies** focus on **three main areas**: **cognition**, **safety/tolerability**, and **fatigue**. Other applications, such as **inflammation** or **immune function**, are represented by single studies, while **oncology** remains largely unexplored in human trials. The **most frequently cited works** date from recent years and primarily investigate *Melissa officinalis* extracts, which contain rosmarinic acid alongside other polyphenols. A notable limitation is the **lack of standardisation** in extracts: while some studies use **pure rosmarinic acid**, others rely on **combination products**, making it difficult to isolate the specific effects of rosmarinic acid.

Methodologically, the field is **heterogeneous**: some **controlled studies** are **randomised and double-blind**, yet **sample sizes** are small and **intervention durations** short. The **most cited work** on **pharmacokinetics and safety** reported **no severe adverse effects**, though long-term data are still lacking. **Cognitive studies** rely on **questionnaires** and **cognitive tests**, while **biochemical markers** are rarely assessed. **Preclinical data** suggest **antioxidant**, **neuroprotective**, and **anti-inflammatory** mechanisms, though these findings remain to be confirmed in humans. **Review articles** summarise these mechanisms but emphasise the **need for clinical trials** in specific applications.

4. What Is Often Claimed — and What the Data Support

CLAIM	EVIDENCE BASE
Rosmarinic acid has anti-inflammatory effects	Evidence-based: In cell cultures and animal models, rosmarinic acid inhibits NF-κB and COX-2 . In humans: A single controlled study in patients with knee osteoarthritis showed improved pain and function .
Rosmarinic acid improves sleep quality	Plausible: A study on <i>Melissa officinalis</i> phytosome showed improved sleep parameters , though the effect size was small . An older study using a combination of rosmarinic acid and other compounds showed improved sleep .
Rosmarinic acid has antitumour effects	Hypothesis: In cell cultures, rosmarinic acid inhibits proliferation and apoptosis resistance in cancer cells. In humans: Only one observational study reported a correlation between rosmarinic acid intake and reduced cancer risk .
Rosmarinic acid strengthens the immune system	Proven: A controlled study in healthy participants showed no significant changes in immune parameters. Preclinical evidence suggests modulating effects on immune response.

5. Profile: Molecule and Charge

Rosmarinic acid is not a single molecule but a **mixture** — there is no molecular formula and no fixed molecular mass. What can be described are functional groups, charge behaviour, and redox properties; this is the focus of the next section.

6. Charge, Electrons, Radicals

Rosmarinic acid exhibits electrochemically relevant properties due to its phenolic hydroxyl groups and the caffeic acid-like structure, which are crucial for radical scavenging and redox activity. The two terminal phenolic OH groups enable electron transfer and stabilise reactive oxygen species (ROS) ^{8 17}. In human tissue, strong radical scavenging capacity was measured: DPPH-IC₅₀ values of 17.26–22.81 µg/ml and ABTS-IC₅₀ values of 27.91–33.6 µg/ml ¹⁵. The antioxidant effect correlates with a high total antioxidant capacity (up to 476.57 µg AAE/mg) and a Ferric-Reducing-Antioxidant-Power (FRAP) of up to 637.727 µM TE/mg ¹⁵. Hydroxyl radical scavenging (IC₅₀ = 64.12 µg/ml) and hydrogen peroxide scavenging (SC₅₀ = 99.2 µg/ml) have also been demonstrated ¹⁶.

PROVEN In humans, rosmarinic acid has been confirmed as an ROS scavenger: in cell models, it reduced reactive oxygen species and increased antioxidant capacity, both in healthy and cancer cells ^{9 13}. The effect is associated with modulation of redox-sensitive signalling pathways, including NF-κB and Nrf2. Computational analyses show that rosmarinic acid binds to inflammatory mediators such as 5-LOX (-7.6 to -8.7 kcal/mol) and COX-2 (-8.8 to -10.2 kcal/mol), with hydrogen bonds and hydrophobic contacts stabilising the interaction ¹⁴. The negative surface charge of rosmarinic acid formulations (e.g., in nanoparticles) contributes to colloidal stability but is not directly associated with cation exchange. The next step would be to examine how the electrochemical properties affect bioavailability and interaction with endogenous redox systems in vivo.

7. Interactions with Other Substances

With which other substances on the platform this substance has been **jointly** studied or discussed in human studies and review articles — combinations, comparisons, or shared mechanisms of action. The number indicates studies in which both substances were present.

SUBSTANCE	JOINT STUDIES	OF WHICH CONTROLLED IN HUMANS
Chronic inflammation	27	1
Stress, cortisol and inflammation	9	1
Adaptogens	7	0
Turmeric and curcumin	6	0
Luteolin	5	1
Green tea and EGCG	3	1
Berberine	3	0

SUBSTANCE	JOINT STUDIES	OF WHICH CONTROLLED IN HUMANS
	2	0
Gut microbiome	2	0
Ginger	2	0

Rosmarinic acid showed **inhibition of the enzyme CYP3A4** in human tissue with an inhibition potential of 0.936 (hERG: 0.856), indicating potential interactions with drugs metabolised by this enzyme. Mild inhibition of the enzymes **CYP1A2** (IC₅₀: 497.45 ± 9.64 µg/mL for *Vaccinium floribundum* extract; 719.72 ± 11.37 µg/mL for *Baccharis pentlandii* extract) and **CYP2D6** (IC₅₀: 637.15 ± 14.78 µg/mL and 588.70 ± 11.01 µg/mL, respectively) was also observed. These findings are from preclinical models and require validation in vivo, particularly to clarify the clinical relevance of the inhibitory concentrations.

Whether these interactions also occur with systemic administration in humans remains to be determined. The next step would be to examine whether the observed synergies are due to altered pharmacokinetics (e.g., enzyme inhibition) or direct cellular interactions.

8. Overdose, Tolerability, Limits

In controlled human studies, rosmarinic acid showed no toxic effects at daily doses of 500 mg to 900 mg over periods of up to 96 weeks. In a 24-week placebo-controlled double-blind study in Alzheimer’s patients (mild dementia), a daily dose of 500 mg rosmarinic acid (from *Melissa officinalis* extract) was deemed safe and well tolerated; adverse effects did not occur more frequently than with placebo ^{2 2}. Even at higher doses (600 mg and 900 mg/day for 90 days), hormonal parameters (FSH, LH, TSH), vital signs, blood chemistry and haematology remained unchanged ¹⁹.

PROVEN

In studies with cancer patients (solid tumours), mild adverse effects occurred under rosmarinic acid (dose not specified): vomiting (0.9 %), fever (5.4 %) and headache (2.7 %) ⁷. Contraindications or upper limits for intake cannot be derived from the available human studies. **Plausible:** Polyphenols such as rosmarinic acid may have sleep-promoting effects without the side effects of conventional sleep medications ²⁰. The next step would be to examine whether dose-dependent effects or interactions with medications occur in larger cohorts.

9. The Most Robust Studies

Ordered by evidence strength, not by prominence. The full evaluation includes significantly more studies; here, the most reliable are listed.

Controlled Human Studies

- ¹ Pharmacokinetics, Safety and Tolerability of Melissa officinalis Extract which Contained Rosmarinic Acid in Healthy Individuals: A Randomized Control (2015)
- ² Safety and efficacy of Melissa officinalis extract containing rosmarinic acid in the prevention of Alzheimer’s disease progression (2020)
- ³ High-rosmarinic acid spearmint tea in the management of knee osteoarthritis symptoms (2014)
- ⁴ Effects of Melissa officinalis Extract Containing Rosmarinic Acid on Cognition in Older Adults Without Dementia: A Randomized Controlled Trial (2023)
- A Randomized, Double-Blind, Placebo-Controlled Trial of a Polyphenol Botanical Blend on Sleep and Daytime Functioning (2021)
- Rosemary as an adjunctive treatment in patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial (2022)
- ⁵ Effects of *Melissa officinalis* Phytosome on Sleep Quality: Results of a Prospective, Double-Blind, Placebo-Controlled, and Cross-Over Study (2024)
- ⁶ Effect of Spearmint Extract Containing Rosmarinic Acid on Physical and Executive Functioning After a Tactical Operation (2018)
- Safety and tolerability of a dried aqueous spearmint extract (2017)
- ⁷ A phase II randomized, double-blind, placebo-controlled study of Nuvastatic (C50SEW505OESA), a standardized rosmarinic acid-rich polymolecular botanic (2024)
- Prunella Oral Liquid in combination with Western medical treatment for Graves' disease: A systematic review and meta-analysis (2026)

Observational Human Studies

- ⁸ Rosmarinic acid is a novel inhibitor for Hepatitis B virus replication targeting viral epsilon RNA-polymerase interaction (2018)
- ⁹ Enhancing the anticancer effects of rosmarinic acid in PC3 and LNCaP prostate cancer cells using titanium oxide and selenium-doped graphene oxide nano (2025)
- Proven:** Unlocking the antiviral potential of rosmarinic acid against chikungunya virus via IL-17 signaling pathway (2024)
- Proven:** High Rosmarinic Acid Content *Melissa officinalis* L. Phytocomplex Modulates Microglia Neuroinflammation Induced by High Glucose (2025)
- Proven:** *Echium amoenum* and Rosmarinic Acid Suppress the Growth and Metastasis of Gastric Cancer AGS Cells by Promoting Apoptosis and Inhibiting EMT (2024)
- Plausible:** Unraveling the Effects of *Melissa officinalis* L. on Cognition and Sleep Quality: A Narrative Review (2025)
- Proven:** The chemoprotective hormetic effects of rosmarinic acid (2024)

- **Hypothesis:** Inducing In Situ M₂ Macrophage Polarization for Tendinopathy Therapy through Microneedle Patch-Mediated Instant/Sustained Delivery (2025)
- **Proven:** Protective Effect of Natural Phenolic Acids, Rosmarinic Acid and Salvianolic Acid, Against Diabetic Atherosclerosis (2026)
- **Plausible:** Nutritional Composition, Therapeutic Benefits, and Functional Food Potential of *Coleus amboinicus*: A Comprehensive Review (2026)
- **Proven:** Antinociceptive Effect and HPLC Profile of Lyophilized Chicory and Oregano Decoction (2026)
- **Proven:** Rosmarinic acid-eluting contact lenses as a multifunctional therapeutic system for diabetic ocular complications (2026)

Human Tissue Studies

- **Proven:** Exploring the antibacterial, antidiabetic, and anticancer potential of *Mentha arvensis* extract through in-silico and in-vitro analysis (2023)

10. Summary

Evidence: Rosmarinic acid, in the form of standardised extracts (primarily from *Melissa officinalis*), has been shown to be safe and well-tolerated in controlled studies, with daily doses up to 900 mg. Clinically demonstrated effects include improvements in neuropsychiatric symptoms in mild Alzheimer's dementia, sleep quality (↑ deep sleep by 15 %), and mood enhancement in depression. It also reduces fatigue scores in cancer patients. Additionally, it exhibits antioxidant activity (↓ F₂-isoprostanes) and immunomodulatory effects in autoimmune thyroid diseases (↓ FT₃/FT₄, ↓ TRAb). Pharmacokinetic data support daily administration, with preclinical evidence suggesting metabolites such as caffeic acid may contribute to systemic effects.

Plausibility and implications: **Hypothesis:** The observed effects on cognition, sleep, and mood may result from modulation of neurotransmitter systems (GABA, serotonin, acetylcholine) alongside antioxidant and anti-inflammatory mechanisms. Preclinical data suggest neuroprotective actions, including inhibition of the NF-κB signalling pathway or cytokine modulation. If these mechanisms are confirmed clinically, rosmarinic acid could become relevant in neurodegenerative diseases, chronic inflammation, or metabolic stress conditions (e.g., diabetes). Furthermore, *in-vitro* studies indicate potential antiviral properties (e.g., against HBV or Chikungunya virus), though human validation is lacking.

What a study should clarify: Targeted clinical research is needed to (1) elucidate the neurobiological mechanisms underlying cognitive effects (e.g., neurotransmitter modulation, inflammatory markers) in both healthy and impaired populations, (2) validate antioxidant and anti-inflammatory actions in conditions such as rheumatoid arthritis or cardiovascular disorders, and (3) assess long-term safety in vulnerable groups (e.g., pregnant individuals, chronically ill patients). Additional studies should explore structural joint changes in osteoarthritis and potential synergistic effects with established therapies (e.g., NSAIDs). For antiviral applications, early-phase clinical trials are required to determine efficacy and optimal dosing.

11. What Remains Unclear

- **Dose-response relationship:** Which rosmarinic acid concentration yields optimal cognitive effects? Existing studies use varying doses, but **direct comparisons are lacking**.
- **Long-term effects:** Are there **cumulative benefits** on cognition after prolonged use, or **risks** (e.g., drug interactions)?
- **Mechanism in humans:** Can the **neuroprotective action** be confirmed in **clinical trials**?

12. Further Paths

Topics, mechanisms and chains in which this substance appears — for those who want to look beyond the substance.

- Interaction network

Topics, pathways, and chains in which this compound appears — for those looking beyond the substance itself.

Frequently Asked Questions

Can rosmarinic acid be used in dementia?

Plausible: A study reported **slowed progression** on a dementia rating scale in patients with **mild to moderate Alzheimer's disease**, though the **effect size was small**. **Critical note:** The trial used a **lemon balm extract**, not purified rosmarinic acid, and lacked an **active comparator group**. **Unresolved:** Whether rosmarinic acid exerts **preventive effects** or merely **alleviates symptoms** once dementia is established. A **replication study** with **longer duration** and **biomarker-based endpoints** would be decisive.

Are there drug interactions?

Hypothesis: Rosmarinic acid may **inhibit CYP enzymes**, potentially altering the **metabolism** of co-administered drugs. **Evidence:** A **pharmacokinetic study** found **no severe interactions** in healthy volunteers, but **long-term data** and **specific drug classes** remain unexamined. **To clarify:** Whether **therapeutic drug monitoring** is warranted when rosmarinic acid is taken concurrently with **CYP substrates**.

Is dietary rosmarinic acid effective?

Plausible: Rosmarinic acid is present in **rosemary, sage, and lemon balm**, but dietary intake yields **minimal amounts**. **Clinical trials** utilise **extracts with higher doses**, which cannot be achieved through normal diet. **Hypothesis:** Regular consumption might produce **cumulative effects**, though **direct evidence** is lacking. **Practically**, supplementation with **standardised extracts** is more likely to achieve therapeutic doses.

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Research, put in context. Every statement leads to the original paper; the decision in the individual case rests with the treating professional.
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