

# Rosemary

## Species (Family)

*Rosmarinus officinalis* L. (Labiatae)

## Synonym(s)

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## Part(s) Used

Leaf, twig

## Pharmacopoeial and Other Monographs

BP 2001<sup>(G15)</sup>

BHP 1996<sup>(G9)</sup>

Complete German Commission E<sup>(G3)</sup>

ESCOP 1997<sup>(G52)</sup>

Martindale 32nd edition<sup>(G43)</sup>

PDR for Herbal Medicines 2nd edition<sup>(G36)</sup>

Ph Eur 2002<sup>(G28)</sup>

## Legal Category (Licensed Products)

GSL<sup>(G37)</sup>

## Constituents<sup>(G2,G41,G52,G58)</sup>

**Flavonoids** Include diosmetin, diosmin, genkwanin and derivatives, luteolin and derivatives, hispidulin, nepetin, nepitrin and apigenin.

**Phenols** Caffeic, chlorogenic, labiatic, neochlorogenic and rosmarinic acids.

**Volatile oil** 1–25%. Components vary according to chemotype. Composed mainly of monoterpene hydrocarbons including  $\alpha$ - and  $\beta$ -pinenes, camphene and limonene, together with 1,8-cineole, borneol, camphor (20–50% of the oil), linalool, verbinol, terpineol, 3-octanone and isobornyl acetate.

**Terpenoids** Carnosol, carnosolic acid, rosmanol (diterpenes);<sup>(1)</sup> oleanolic and ursolic acids (triterpenes).

## Food Use

Rosemary herb and oil are commonly used as flavouring agents in foods. Rosemary is listed by the

Council of Europe as a source of natural food flavouring (category N2). This category indicates that rosemary can be added to foodstuffs in small quantities, with a possible limitation of an active principle (as yet unspecified) in the final product.<sup>(G16)</sup> In the USA, rosemary is listed as GRAS (Generally Recognised As Safe).<sup>(G65)</sup>

## Herbal Use<sup>(G2,G4,G7,G32,G52)</sup>

Rosemary is stated to act as a carminative, spasmolytic, thymoleptic, sedative, diuretic and antimicrobial.<sup>(G7)</sup> Topically, rubefacient, mild analgesic and parasiticide properties are documented.<sup>(G7)</sup> Traditionally rosemary is indicated for flatulent dyspepsia, headache, and topically for myalgia, sciatica, and intercostal neuralgia. The German Commission E approved internal use for dyspeptic complaints and external use as supporting therapy for rheumatic diseases and circulatory problems.<sup>(G3)</sup>

## Dosage

**Dried leaf/twig** 2–4 g or by infusion three times daily;<sup>(G7)</sup> 4–6 g daily; external use 50 g for one bath.<sup>(G3)</sup>

**Liquid extract** 2–4 mL (1:1 in 45% alcohol) three times daily.<sup>(G7)</sup>

## Pharmacological Actions

### *In vitro* and animal studies

**Antimicrobial activity** Antibacterial and antifungal activities *in vitro* have been reported for rosemary oil.<sup>(2,G41,G52)</sup> Rosemary herb is an effective antimicrobial agent against *Staphylococcus aureus* in meat and against a wide range of bacteria in laboratory media.<sup>(1)</sup> Antimicrobial activity has been documented for the oil towards moulds, and Gram-positive and Gram-negative bacteria<sup>(1)</sup> including *S. aureus*, *S. albus*, *Vibrio cholerae*, *Escherichia coli* and corynebacteria.<sup>(3)</sup> Carnosol and ursolic acid have inhibited a range of food spoilage microbes (*S. aureus*, *E. coli*, *Lactobacillus brevis*, *Pseudomonas fluorescens*, *Rhodotorula glutinis* and *Kluyveromyces bulgaricus*). Activity was comparable to

that of known antioxidants butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT), and correlated with the respective antioxidant properties of the two compounds (carnosol > ursolic acid).<sup>(11)</sup>

**Antiviral activity** A dried 95% ethanol extract of rosemary (2–100 µg/mL) inhibited *in vitro* formation of herpes simplex virus type 2 plaques from 2 to 100% in a concentration-dependent manner. Carnosolic acid had activity against human immunodeficiency virus type 1 (HIV-1) protease (IC<sub>50</sub> value 0.08 µg/mL) when assayed against HIV-1 virus replication (IC<sub>90</sub> value 0.32 µg/mL).<sup>(4,5)</sup> Carnosolic acid was cytotoxic to lymphocytes with a TC<sub>90</sub> on H9 lymphocytes of 0.36 µg/mL.

**Antitumour activity** An extract of rosemary (precipitate from aqueous phase of 70% alcohol extract) inhibited KB cells by 87% when applied at a concentration of 50 µg/mL.<sup>(G52)</sup> The volatile oil (1.2–300 µg/mL) was reported to be toxic to L-1210 leukaemia cells.<sup>(6)</sup> Topical administration of a methanol extract 5 minutes prior to application of carcinogens to the dorsal surface of CD-1 mice reduced the irritation and promotion of tumours. Application of rosemary extract (1.2 mg and 3.6 mg) prior to [<sup>3</sup>H]-benzo(a)pyrene reduced the formation of metabolite-DNA adducts by 30% and 54%, respectively.<sup>(7)</sup> In rats, dietary supplementation with 1% rosemary extract for 21 weeks reduced the development of dimethylbenz(a)anthracene mammary carcinoma in the treated group, compared with the control group (40% versus 75%, respectively).<sup>(8)</sup>

**Antispasmodic and anticonvulsant activities** Rosemary oil, 1,8-cineole, and bornyl acetate have exerted a spasmolytic action in both smooth muscle (guinea-pig ileum) and cardiac muscle (guinea-pig atria) preparations, with the latter more sensitive.<sup>(9)</sup> In smooth muscle this spasmolytic effect has been attributed to antagonism of acetylcholine,<sup>(10)</sup> with borneol considered the most active component of the oil.<sup>(10)</sup> The spasmolytic action of rosemary oil is preceded by a contractile action, which is attributed to the pinene components.<sup>(10)</sup> α-Pinenes and β-pinenes have exhibited a spasmogenic activity towards smooth muscle, with no effect on cardiac muscle.<sup>(9)</sup>

Spasmolytic action *in vivo* (guinea-pigs) has been demonstrated by rosemary oil (administered intravenously) via a relaxant action on Oddi's sphincter contracted by morphine. Activity increased with incremental doses of oil until an optimum dose was reached (25 mg/kg) at which the unblocking effect

was immediate.<sup>(11)</sup> Further increases in dose reintroduced a delayed response time.<sup>(11)</sup> Smooth muscle-stimulant and analgesic actions have been documented for a rosmarinic derivative.<sup>(G41)</sup>

The volatile oil of rosemary inhibited contractions of rabbit tracheal smooth muscle induced by acetylcholine, and inhibited contraction of guinea-pig tracheal smooth muscle induced by histamine.<sup>(12)</sup> The oil also inhibited contractions in both preparations induced by high potassium concentrations. Contractions of rabbit and guinea-pig tracheal smooth muscle induced by acetylcholine and histamine, respectively, were inhibited by rosemary oil in calcium ion-free solution. It was suggested that the oil has calcium antagonist activity.<sup>(12)</sup> A 30% ethanol extract of rosemary produced a spasmolytic effect on guinea-pig ileum, as demonstrated by measuring the increase in the ED<sub>50</sub> of acetylcholine (4.9 µg/L after addition of 2.5 mL extract and 25.1 µg/L after addition of 10 mL extract).<sup>(G52)</sup> An increase in the ED<sub>50</sub> for histamine from 8.1 µg/L to 44.6 µg/L, respectively, was noted for the same doses of extract.

Noradrenaline (norepinephrine)- and potassium ion-induced contractions of rabbit aortic rings were significantly reduced by rosemary oil 0.48 mg/mL and 0.64 mg/mL, respectively. It was proposed that action was by a direct vascular smooth muscle effect.<sup>(13)</sup>

**Anti-inflammatory activity** Complement activation and subsequent triggering of the arachidonic acid cascade are thought to play an important role in the early phase of shock. An intact complement system is required for the formation of vasoactive prostanooids (prostacyclin, thromboxane A<sub>2</sub>), arterial hypotension and thrombocytopenia.<sup>(14)</sup> The effect of rosmarinic acid on endotoxin-induced haemodynamic and haematological changes has been studied in a rabbit model of circulatory shock.<sup>(14,15)</sup> Rosmarinic acid (20 mg/kg, intravenous) was found to suppress the endotoxin-induced activation of complement, formation of prostacyclin, hypotension, thrombocytopenia, and the release of thromboxane A<sub>2</sub>.<sup>(14)</sup> Unlike non-steroidal anti-inflammatory drugs (NSAIDs), the mode of action by which rosmarinic acid suppresses prostaglandin formation does not involve interference with cyclooxygenase activity or prostacyclin synthetase.<sup>(15)</sup> Activity has been attributed to inhibition of complement factor C3 conversion to activated complement components, which mediate the inflammatory process.<sup>(15)</sup> Rosmarinic acid has inhibited carrageenan-induced rat paw oedema, and passive cutaneous anaphylaxis, also in rats (ID<sub>50</sub> 1 mg/kg, intravenously; 10 mg/kg, intramuscularly).<sup>(16)</sup>

Topical application of rosmarinic acid (5%) to rhesus monkeys reduced gingival plaque indices when compared with placebo.<sup>(G52)</sup> A methanol extract of herb (3.6 mg) applied topically to CD-1 mice twice daily for four days inhibited skin inflammation and hyperplasia caused by 12-O-tetradecanoylphorbol-13-acetate (TPA).<sup>(G52)</sup> A similar extract inhibited both TPA- and arachidonic acid-induced inflammation as well as TPA-induced hyperplasia.<sup>(7)</sup>

**Anti-hepatotoxic activity** A lyophilised aqueous extract of rosemary significantly reduced hepatotoxicity of *t*-butylperoxide to rat hepatocytes *in vitro*, significantly decreasing malonaldehyde formation, release of lactic acid dehydrogenase and aspartate aminotransferase.<sup>(17)</sup> Pretreatment of rats with an aqueous extract (1 mg of lyophilisate equivalent to 7 mg young shoots) 30 minutes prior to exposure to carbon tetrachloride, resulted in a 72% decrease in plasma glutamic-pyruvic transaminase.<sup>(18)</sup> Rosemary extract supplementation in the diet of rats enhanced the activity of GSH-transferase and NAD(P)H-quinone reductase.<sup>(G52)</sup>

**Cholagogic activity** A lyophilised ethanolic extract (1 mg) of young shoots at doses of 0.1, 1.0 and 2.0 g/kg was injected into the jugular vein of common bile duct-cannulated Sprague-Dawley rats infused with sodium taurocholate.<sup>(18)</sup> A significant, rapid increase in bile flow (114%) was achieved with maximum effect in 30 minutes. The extract of young shoots was significantly more active in stimulating bile flow than a similar extract of whole plant. A rapid increase in bile secretion was observed (138% in 40 minutes) in cannulated guinea-pigs given an aqueous-ethanol extract (15%).<sup>(G52)</sup>

**Antioxidant activity** A number of extracts and constituents of rosemary have been shown to have antioxidant activity.<sup>(G52)</sup> An antioxidant action, demonstrated by inhibition of chemiluminescence and hydrogen peroxide generation from human granulocytes, has been reported for rosmarinic acid.<sup>(15)</sup>

Lipophilic and hydrophobic fractions of rosemary showed activity which was attributed to the diterpenes carnosol, carnosolic acid and rosmanol inhibiting superoxide anion production in the xanthine/xanthine oxidase system.<sup>(19)</sup> These diterpenes at concentrations of 3–30  $\mu\text{mol/L}$  also completely inhibit mitochondrial and microsomal lipid peroxidation induced by NADPH or NADPH oxidation.<sup>(19)</sup>

The complement-inhibiting and antioxidant properties of rosmarinic acid are not thought to adversely

affect the chemotactic, phagocytic and enzymatic properties of polymorphonuclear leukocytes.<sup>(20)</sup>

**Other activities** A hyperglycaemic effect was observed in glucose-loaded rats treated with a solution of rosemary oil (925 mg/kg, intramuscular).<sup>(23)</sup> In rabbits with alloxan-induced diabetes given rosemary oil (25 mg/kg, intramuscular) 6 hours after fasting, plasma glucose concentrations increased by 17% 6 hours later.

Pretreatment with rosmarinic acid (20 mg/kg and 10 mg/kg, intravenously) has been reported to inhibit the development of adult respiratory distress syndrome (ARDS) in a rabbit model.<sup>(20)</sup> This action can be attributed to both the antioxidant and anticomplement activities of rosmarinic acid.<sup>(20)</sup>

The ability to reduce capillary permeability has been described for diosmin.<sup>(G41)</sup> Activity reportedly exceeds that exhibited by rutin.<sup>(G41)</sup>

An increase in locomotor activity has been observed in mice following either inhalation or oral administration of rosemary oil.<sup>(21)</sup> The increase in activity paralleled a dose-related increase in serum 1,8-cineole level. Biphasic elimination of 1,8-cineole from the blood was observed ( $t_{1/2} = 6$  minutes,  $t_{1/2} = 45$  minutes).<sup>(21)</sup>

In rats, antigonadotrophic activity has been documented for oxidation products of rosmarinic acid administered intramuscularly.<sup>(22)</sup> Activity was determined by suppression of pregnant mares' serum-induced increase in ovarian and uterine weights. Concentrations of  $10^{-7}$  mol/L of the flavonoids nepitrin and nepetin inhibited aldose-reductase activity in homogenised rat eye lenses by 31%.<sup>(G52)</sup>

### Side-Effects, Toxicity<sup>(G58)</sup>

Rosemary oil is stated to be non-irritating and non-sensitising when applied to human skin,<sup>(G58)</sup> but moderately irritating when applied undiluted to rabbit skin.<sup>(G41)</sup> Bath preparations, cosmetics and toiletries containing rosemary oil may cause erythema and dermatitis in hypersensitive individuals.<sup>(G51)</sup> Photosensitivity has been associated with the oil.<sup>(G51)</sup>

Rosmarinic acid exhibits low toxicity (an LD<sub>50</sub> in mice is stated as 561 mg/kg for intravenous administration) and is rapidly eliminated from the circulation ( $t_{1/2} = 9$  minutes following intravenous administration).<sup>(16)</sup> Transient cardiovascular actions become pronounced at intravenous doses exceeding 50 mg/kg.<sup>(16)</sup> Acute LD<sub>50</sub> values quoted include 5 mL/kg (rat, oral) and >10 mL/kg (rabbit, dermal).<sup>(3)</sup>

Diosmin is reportedly less toxic than rutin.<sup>(G41)</sup> No mortality was seen in Wistar rats and Swiss mice

given single intraperitoneal doses of 2g/kg of aqueous alcoholic rosemary extract (15%).<sup>(G52)</sup>

### Contra-indications, Warnings

Topical preparations containing rosemary oil should be used with caution by hypersensitive individuals. Rosemary oil contains 20–50% camphor; orally, camphor readily causes epileptiform convulsions if taken in sufficient quantity.<sup>(G58)</sup>

**Pregnancy and lactation** Rosemary is reputed to be an abortifacient<sup>(G30)</sup> and to affect the menstrual cycle (emmenagogue).<sup>(G48)</sup> In view of its common culinary use, rosemary should not be ingested in amounts greatly exceeding those normally encountered in foods.

### Pharmaceutical Comment

In addition to the well-known culinary uses of rosemary, various medicinal properties are also associated with the herb. Documented antibacterial, anti-inflammatory and spasmolytic actions, which support the traditional uses of the herb, are attributable to the essential oil. Anticomplement and antioxidant activities documented for rosmarinic acid have generated considerable interest in a potential preventative use against endotoxin shock and adult respiratory distress syndrome. A method for the isolation (TLC, thin-layer chromatography) and subsequent identification (HPLC, high-performance liquid chromatography) of rosmarinic acid has been proposed.<sup>(24)</sup> Rosemary should not be used by epileptic patients in doses greatly exceeding amounts used in food.

### References

See also General References G2, G3, G9, G12, G16, G22, G29, G31, G32, G36, G37, G41, G43, G48, G51, G52 and G58.

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