Folium Rosmarini

Definition
Folium Rosmarini consists of the whole dried leaves of *Rosmarinus officinalis* L. (Lamiaceae) (*1*).

Synonyms
No information was found.

Selected vernacular names
Alecrim, azir, biberine, biberye, boithran, common rosemary, echter Rosmarin, encensier, garden rosemary, gusmarino, hasalban, hatsa louban, hhassâ lubân, iklil, iklil el jabal, iklil kuhi, kusdilli, mannenrou, old man, romani, romarin, romero, romero blanco, rosmariin, Rosmarin, rosmarina, rosmarini, rosmarino, rosemary, tresmarino (*2–4*).

Geographical distribution
Native to the Mediterranean region of Europe, and cultivated worldwide (*4–7*).

Description
A bushy, low, much branched, perennial sub-shrub attaining a height of about 1 m. Leaves leathery with fringed margin, 1.0–2.5 cm long, aromatic, evergreen, opposite, sessile, linear and coriaceous. Old branches brown in colour. Spiciform inflorescences of pale blue or light lilac flowers spotted with purple, with the two stamens projecting far beyond the corolla (*4*, *5*, *7*, *8*).

Plant material of interest: dried leaves
General appearance
Leaves linear to linear-lanceolate, curved, 1–4 cm long, 2–4 mm wide; coriaceous, greyish-green or occasionally brownish; margins entire and strongly revolute, apex obtuse, base tapering and non-petiolate; upper

surface dark green, reticulately pitted, lower surface tomentose. Occasional pieces of stems up to 4 cm long, 1–2 mm wide, dark brown to greenish, tomentose or woody with numerous opposite and decussate leaf scars (*1*).

Organoleptic properties

Odour: strongly aromatic; taste: pungently aromatic, camphoraceous and bitter (*1*).

Microscopic characteristics

Leaf dorsiventral; upper epidermal cells polygonal with slightly thickened walls and occasional pits; lower epidermal cells sinuous; numerous diacytic stomata on the lower surface only; very abundant uniseriate, multicellular, much-branched covering trichomes on the lower epidermis, also glandular trichomes with a unicellular stalk and unicellular, bicellular or multicellular head occurring on both epidermises; hypodermis underlying the upper epidermis composed of large, ovoid cells with thickened and beaded anticlinal walls; these cells extending across the lamina at intervals, separating the two-layered palisade into large, crescent-shaped areas, each with a group of spongy mesophyll (*9*).

Powdered plant material

Greyish-green to yellowish-green. Shows fragments of lower epidermis with straight to sinuous-walled cells and numerous diacytic stomata; fragments of the upper epidermis with straight-walled cells, slightly thickened and pitted, and an underlying hypodermis composed of large, irregular cells with thickened and beaded anticlinal walls; fragments in sectional view showing the hypodermal cells extending across the lamina at intervals, separating the one or two-layered palisade into large, crescent-shaped areas; numerous multicellular, extensively branched, covering trichomes of the lower epidermis and rare conical covering trichomes of the upper epidermis; glandular trichomes of 2 types, the majority with a short, unicellular stalk and a radiate head composed of 8 cells, others, less abundant, with a unicellular stalk and a spherical, unicellular or bicellular head. Occasional cork fragments, fibres, vascular tissue and lignified parenchyma from the stems (*1*).

General identity tests

Macroscopic and microscopic examinations (*1*), thin-layer chromatography (*1*), and high-performance liquid chromatography for phenolic acids (*10*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines for assessing quality of herbal medicines with reference to contaminants and residues (*11*).

Foreign organic matter

Not more than 5% of stem, and not more than 2.0% other foreign matter (*1*).

Total ash

Not more than 9.0% (*1*).

Acid-insoluble ash

Not more than 1.5% (*9*).

Water-soluble extractive

Not less than 15.0% (*9*).

Water content

Not more than 10% (*1*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*1*). For other pesticides, see the *European pharmacopoeia* (*1*) and the WHO guidelines for assessing quality of herbal medicines with reference to contaminants and residues (*11*) and pesticide residues (*12*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines for assessing quality of herbal medicines with reference to contaminants and residues (*11*).

Radioactive residues

Where applicable, consult the WHO guidelines for assessing quality of herbal medicines with reference to contaminants and residues (*11*).

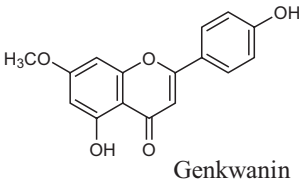
Chemical assays

Not less than 1.2% (v/w) of essential oil and not less than 3% total hydroxycinnamic acid derivatives expressed as rosmarinic acid (*1*).

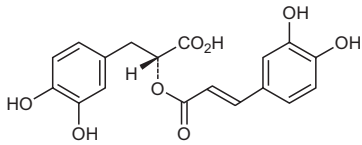
Major chemical constituents

Contains up to 2.5% of essential oil, the chief constituents of which are camphor (5–21%), 1,8-cineole (15–55%), α-pinene (9–26%), borneol (1.5–5.0%),

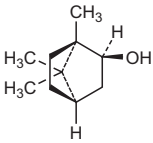
camphene (2.5–12.0%), β-pinene (2.0–9.0%) and limonene (1.5–5.0%). Phenolic compounds are represented by flavonoids with a methylated aglycone (e.g. genkwanin) and by phenolic acids (> 3%), particularly by rosmarinic, chlorogenic and caffeic acids. Also present are tricyclic diterpenes such as rosmaridiphenol, carnosol, carnosic acid and rosmanol, and diterpenes, including seco-hinokiol (*1*, 3, 5, *7*, *13*, *14*). The structures of rosmarinic acid, 1,8-cineole, borneol, camphor, genkwanin and carnosol are presented below.



Genkwanin

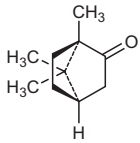


Rosmarinic acid



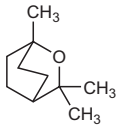
and enantiomer

Borneol

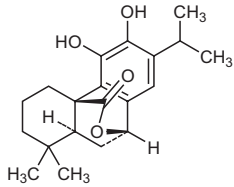


and enantiomer

Camphor



1,8-Cineole



Carnosol

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and well established documents

Orally as a carminative and spasmolytic to treat dyspepsia (*9*). Externally for supportive therapy of rheumatism and circulatory disorders (*13*).

Uses described in traditional medicine

Orally as a cholagogue, diaphoretic, diuretic, emmenagogue and as a tonic (*3*, *6*, *7*). Also used in the management of headache, menstrual disorders, nervous menstrual complaints, tiredness and defective memory. Used externally for treatment of spraining and bruising (*15*).

Pharmacology

Experimental pharmacology

Antihepatotoxic activity

Intragastric administration of 200.0 mg/kg body weight (bw) of a standardized methanol extract of the leaves (corresponding to 6.04 mg/kg bw

of carnosol) to rats, 1 hour after treatment of the animals with carbon tetrachloride (CCl_4), fully prevented CCl_4-induced lipid peroxidation in the liver. The CCl_4-induced increase in plasma bilirubin concentrations and alanine aminotransferase activity was completely normalized after treatment with the extract. The treatment also resulted in a significant recovery from CCl_4-induced decrease in liver glycogen content. The extract also increased liver cytosolic reduced glutathione activity and produced an additional increase in plasma glutathione activity in rats treated with CCl_4. Histological evaluation showed that the extract partially prevented CCl_4-induced inflammation, necrosis and vacuolation (*16*).

The hepatoprotective and antimutagenic effects of an ethanol extract of the leaves were investigated using CCl_4 and cyclophosphamide as the hepatotoxic and mutagenic compounds. The results indicated that intragastric administration of the ethanol extract (1.5 g/kg bw) to rats for 3 weeks produced a pronounced hepatoprotective effect as compared with silymarin (reference compound) due to the amelioration of most of the serum and liver parameters studied and confirmed by histopathological examination of the liver tissue. Pretreatment of mice for 7 days with the essential oil (1.1 mg/g bw) followed by intraperitoneal administration of cyclophosphamide significantly reduced the induced mitodepression in the bone marrow cells of the animals (*17*).

Anti-inflammatory activity

Treatment of mouse macrophage RAW 264.7 cells with carnosol markedly reduced lipopolysaccharide-stimulated nitric oxide production in a concentration-related manner with an IC_{50} of 9.4 µM. Western blot, reverse transcription–polymerase chain reaction, and northern blot analyses demonstrated that carnosol decreased lipopolysaccharide-induced inducible nitric oxide synthase mRNA and protein expression. Carnosol treatment reduced the translocation of nuclear factor-kappa B subunits and the binding activity of nuclear factor-B DNA in activated macrophages. Carnosol also inhibited inducible nitric oxide synthase and nuclear factor-B promoter activity in a transient transfection assay. These activities were due to down-regulation of inhibitor B kinase activity by carnosol (5 µM), which in turn inhibited lipopolysaccharide-induced phosphorylation as well as degradation of inhibitor B. Carnosol also inhibited lipopolysaccharide-induced p38 and p44/42 mitogen-activated protein kinase activation at a higher concentration (20 µM). These results suggest that carnosol suppresses production of nitric oxide and inducible nitric oxide synthase gene expression by inhibiting activation of nuclear factor-B, and provide possible mechanisms for its anti-inflammatory activity (*18*).

Antioxidant activity

Oxidative damage to DNA, RNA, proteins and cell membranes occurs when the cellular concentration of reactive oxygen species exceeds the capacity of the cell to eliminate them. The crude drug and its constituents have been shown to have both antioxidant and pro-oxidant properties both in vitro and in vivo (*19–21*). The antioxidant activity of six extracts of the leaves, with different compositions of six polyphenolic compounds (carnosic acid, carnosol, 12-*O*-methylcarnosic acid, rosmarinic acid, isoscutellarein 7-*O*-glucoside and genkwanin), were tested in aqueous (malonyldialdehyde formation) and lipid systems (Rancimat method). The results demonstrate that the extracts were excellent antioxidants in both systems at a concentration of 500 ppm (*22*). The ability of the phenolic diterpenes, carnosol, rosmanol and epirosmanol, to prevent oxidization of low-density lipoprotein in human blood and their ability to scavenge free radicals and superoxide anions was assessed in vitro. The antioxidant activities were evaluated by the thiobarbituric acid reactive substances (TBARS) assay and electron spin resonance method. The inhibition of the $Cu2^{+}$-mediated oxidization of apo B formation in low-density lipoprotein was investigated by fluorescence spectroscopy. The results demonstrated that carnosol, rosmanol and epirosmanol inhibited lipid peroxidation and oxidized apo B formation in low-density lipoprotein in human blood. The median inhibitory concentration range was 7–10 µM (*23*). Supplementation of the diet of mice with a dried hexane extract of the leaves (1% w/w of diet) for 1 week reduced the level of phospholipid hydroperoxides in the plasma, red blood cells (65–74% of the levels of non-supplemented control mice) and liver of the animals (*24*).

The antioxidant activities of carnosol and other compounds extracted from rosemary were compared. Carnosol showed potent antioxidative activity, and scavenged 1,1-diphenyl-2-picrylhydrazyl free radicals, as well as protecting DNA in the Fenton reaction (*18*).

An alcohol extract of the crude drug was assessed in vitro and in vivo for its ability to protect against free radical-induced skin damage. The extract inhibited oxidative alterations to skin surface lipids (*25*). The protective effect of a 96% ethanol extract of the crude drug against oxidative DNA damage induced by hydrogen peroxide and visible light-excited methylene blue in colon cancer cells (CaCo-2) and hamster lung cells (V79) was investigated. The level of DNA damage (DNA strand-breaks) was measured using the comet assay. The extract reduced the genotoxic activity of both agents after long-term (24 h; 0.3 µg/ml) or short-term (2 h; 30.0 µg/ml) pre-incubation of cells, demonstrating that the extract

has a protective effect against oxidative damage to DNA as a consequence of scavenging of both hydroxyl radicals and singlet oxygen (*26*).

Antimicrobial activity

A commercial extract of the leaves (no further details of extract given), dissolved in ethanol (100.0 mg/ml) was tested against foodborne microorganisms. In the Gram-positive bacteria, the minimum inhibitory concentration of the ethanolic solution was 1% for *Leuconostoc mesenteroides,* 0.5% for *Listeria monocytogenes,* 0.5% for *Staphylococcus aureus*, 0.13% for *Streptococcus mutans* and 0.06% for *Bacillus cereus*. It was fungistatic in *Penicillium roquefortii* and *Botrytis cinerea*. Up to 1% of the ethanolic solution had no activity against the Gram-negative bacteria *Escherichia coli*, *Salmonella enteritidis* and *Erwinia carotovora* and on the yeasts *Rhodotorula glutinis* and *Cryptococcus laurentii*. The antibacterial activity was associated with phenolic diterpenoids in the hexane extract of the leaves (*27*).

An extract of the leaves inhibited the growth of *Shigella flexneri* and *S. sonnei* with a minimum inhibitory concentration ranging from 0.5 to 1% (w/v) depending on the *Shigella* strain used (*28*).

Antinephrotoxic activity

The effects of rosmarinic acid on the suppression of mesangioproliferative glomerulonephritis, induced by intravenous injection of rabbit anti-rat thymocyte serum to rats was assessed. Intragastric administration of rosmarinic acid to the rats at a dose of 100.0 mg/kg bw per day for 8 days decreased the quantity of proliferating cell nuclear antigen, fibronectin, type IV collagen and fibrin in the glomerulus. Superoxide dismutase activity of renal cortex homogenate was also significantly augmented in animals treated with rosmarinic acid (*29*).

Antitrypanosomal activity

A methanol extract of the leaves at a concentration of 2.0 mg/ml inhibited the motility of cultured epimastigotes of *Trypanosoma cruzi* after 2 h of incubation. Two triterpene acids, oleanolic and ursolic acids, isolated from the extract were responsible for the activity. Ursolic acid stopped the movement of all *T. cruzi* epimastigotes at the minimum inhibitory concentration of 40.0 µg/ml (88.0 µM) after 48 h of incubation. Oleanolic acid was less active, with a minimum inhibitory concentration of 250.0 µg/ml (550.0 µM) (*30*).

Antitumour activity

The effect of dietary intake of an extract of the leaves on 7,12-dimethylbenz[a]anthracene-induced mammary tumorigenesis and on the

in vivo formation of mammary 7,12-dimethylbenz[a]anthracene-DNA adducts was evaluated. Supplementation of a semi-purified diet with 1.0% by weight of the rosemary extract resulted in a significant (47%, $p < 0.01$) decrease in incidence of mammary tumours compared to controls. In subsequent studies, dietary supplementation with 0.5% and 1.0% rosemary extract inhibited total in vivo binding of 7,12-dimethylbenz[a]anthracene to mammary epithelial cell DNA by an average of 42%. This decrease in total binding was not due to a uniform decrease in the formation of all mammary 7,12-dimethylbenz[a]anthracene-DNA adducts (*31*).

Antiulcer activity

An ethanol (70%) extract was evaluated for antiulcerogenic activity in vivo. Intragastric administration of 100.0 mg/kg bw per day to 1.0 g/kg bw per day of the extract decreased the ulcerative lesion index produced by ethanol and reserpine in rats. No antisecretory activity was observed in the pyloric ligation model. Prior administration of L-NAME (N[G]-nitro L-arginine methyl ester), a nitric oxide-synthase inhibitor, did not reduce the antiulcerogenic activity of the extract in the ethanol-induced ulcer model, suggesting that the pharmacological mechanism has no relationship with nitric oxide. When the animal groups were treated with indomethacin using the same experimental model, the extract did not reduce the antiulcerogenic activity, suggesting that the pharmacological mechanism has no relationship with prostaglandins. The previous treatment with N-ethylmaleimide, a thiol blocker, including mucosal nonprotein sulfhydryl groups, reduced the antiulcerogenic activity of the extract in the ethanol-induced ulcer model. This result suggests that the ethanol extract has active substances that increase the content of mucosal nonprotein sulfhydryl groups (*32*).

Diuretic effects

The effects of aqueous extracts of the crude drug on the treatment of kidney function and diuresis in rats were determined. Outcomes assessed included urinary volume and the excretion of sodium, potassium and chloride. The concentration of electrolytes and urea in plasma and creatinine clearance were also measured. Daily intragastric administration of the aqueous extracts of the leaves, at a dose of 10 ml/kg bw of an 8% or 16% extract in distilled water for 1 week, significantly enhanced diuresis in rats compared to the control group from the fifth day of treatment ($p < 0.001$). At a dose of 8%, the peak of urinary excretion of sodium, potassium and chloride was reached after 6 days of treatment ($p < 0.001$). A dose of 16% did not significantly affect the excretion of water and electrolytes over a similar period but significantly increased the urinary ex-

cretion of sodium and chloride on the seventh day and of potassium on the sixth day ($p < 0.05$). No change was observed in plasma electrolytes and urea in any group, except for a decrease in sodium and chloride concentration in the group treated with the 16% extract of the crude drug. A decrease in creatinine clearance was observed after treatment with a daily dose of the 8% extract (*33*).

Enzyme induction

The effects of an aqueous extract of the leaves and of rosmarinic acid were investigated on xenobiotic metabolizing enzymes in rat liver after dietary administration (0.5% daily rations) for 2 weeks. The modulation of phase I enzymes such as cytochrome P450 1A, 2B, 2E1, 3A and phase II enzymes such as glutathione S-transferase, quinone reductase and uridine diphosphate (UDP)-glucuronosyltransferase was evaluated by measuring enzyme activities with specific substrates. The aqueous extract enhanced cytochrome P450 1A1, 2B1/2, 2E1 and glutathione S-transferase (especially recombinant glutathione S-transferase A3/A5, M1 and M2), quinone reductase and UDP-glucuronosyltransferase. No modification of xenobiotic metabolizing enzymes was observed in response to treatment with rosmarinic acid, indicating that other constituents of the leaves are responsible for this activity (*34*).

The ability of the leaves to modulate cytochrome P450 and detoxification enzymes in rat liver was evaluated by comparing the effects of dried leaves and leaf extracts with those of the essential oil. Rats received the powdered leaves or extracts of the leaves in their diet at 0.5% (w/w) for 2 weeks. The effects of such treatments were evaluated for cytochrome P450 isozymes 1A, 2B, 2E1, glutathione S-transferase, NAD(P)H, quinone reductase and UDP-glucuronosyltransferase activities and on protein levels (immunoblot analyses). The results demonstrated that essential oil selectively induced cytochrome P450, particularly cytochrome P450 2B. The leaf extract enhanced both cytochrome P450 and detoxification enzymes. A dichloromethane extract of the leaves acted as a monofunctional inducer, inducing glutathione S-transferase, quinone reductase and UDP-glucuronosyltransferase, in particular UDP-glucuronosyltransferase 1A6 (*35*).

An extract of the crude drug was fed to female mice at concentrations of 0.3% and 0.6% (by weight) for 4 weeks prior to determination of the activities of the detoxification enzymes glutathione-S-transferase and NAD(P)H, and quinone reductase in lung, liver and stomach. Liver activities of glutathione S-transferase and quinone reductase, and stomach glutathione S-transferase activity, were significantly increased in animals fed diets containing the extract. However, diets supplemented with the

extract did not affect lung glutathione S-transferase and quinone reductase activities (*36*).

Estrogenic effects

The effects of a methanol extract of the leaves on the metabolism and action of estradiol and estrone were assessed in vivo. Treatment of female mice with 2% rosemary in an American Institute of Nutrition (AIN)-76A diet for 3 weeks increased the liver microsomal 2-hydroxylation of estradiol and estrone by approximately 150%, increased their 6-hydroxylation by approximately 30% and inhibited the 16α-hydroxylation of estradiol by approximately 50%. Treatment of female CD-1 mice with 2% rosemary in the diet for 3 weeks also stimulated the liver microsomal glucuronidation of estradiol and estrone by 54–67% and 37–56%, respectively. In further studies, feeding 2% rosemary in the diet to ovariectomized CD-1 mice for 3 weeks inhibited the uterotropic action of estradiol and estrone by 35–50% compared with animals fed a control diet (*37*).

Immune stimulant activity

The effect of an ethanol extract of the leaves on splenic mononuclear cell proliferation was determined in vivo. Rats were fed diets containing 0, 100, 200 or 400 ppm leaf extract or 400 ppm butylated hydroxytoluene in combination with 10 or 20% casein-enriched diets for 8 weeks. Splenic mononuclear cells were isolated from these animals and the mitogenic response to concanavalin A, phytohaemagglutinin and lipopolysaccharide was determined. Concanavalin A- and phytohaemagglutinin-stimulated proliferation of spleen cells in rats fed 10% casein and 200 ppm leaf extract was significantly higher than that of cells from the corresponding control animals. Other concentrations of the extract were not active, suggesting that the leaf extract does not have a generalized immune-enhancing effect (*38*).

Rosmarinic acid induced apoptosis in a p56(lck) (Lck)-dependent manner. Lck(+) Jurkat T cells underwent apoptosis in response to treatment with rosmarinic acid , whereas Lck(-) Jurkat subclone J.CaM1.6 cells did not. J.CaM1.6 cells with various Lck mutants indicated that Lck SH2 domain, but not Lck kinase activity, was required for rosmarinic acid-induced apoptosis. Rosmarinic acid-mediated apoptosis involved a mitochondrial pathway as indicated by cytochrome c release and the complete blockage of apoptosis by an inhibitor of mitochondrial membrane depolarization. Both caspase-3 and caspase-8 were involved in rosmarinic acid-induced apoptosis and work downstream of mitochondria and caspase-9 in the order of caspase-9/caspase-3/caspase-8. In freshly isolated human peripheral blood mononuclear cells, rosmarinic acid

specifically induced apoptosis of Lck(+) subsets such as T and NK cells, but not Lck-deficient cells, including B cells and monocytes. Moreover, the ability of rosmarinic acid to kill T and NK cells was restricted to actively proliferating cells, and was not seen in resting cells (*39*).

Toxicology

To find out whether the crude drug induces abortion and/or interferes with the normal development of the concepts, doses of 26 mg of a 30% (w/v) aqueous extract (13 mg solids/ml) made with leaves, flowers and stem, were administered daily to rats by gavage during two different periods of pregnancy. One group of animals (n = 12) received the extract from days 1 to 6 of pregnancy (pre-implantation period) and another group (n = 14) received the same extract from days 6 to 15 of pregnancy (organogenic period). Control groups (n = 12) received saline solution at the same volume and during the same periods as the comparable experimental groups. The animals were killed at term. The treatment of the dams during either the pre-implantation or the organogenic period did not cause significant changes in the post-implantation loss or in the number of anomalies or malformations of the term fetuses, which also showed a similar degree of development to that of the control animals. The percentage of pre-implantation loss in the group treated before embryo implantation increased compared to the control group, although the difference was not statistically significant. This result suggests that rosemary extract may have an anti-implantation effect without interfering with the normal development of the concept after implantation (*40*).

Clinical pharmacology

One of the postulated mechanisms of action of phenolic compounds as antioxidants is chelation of pro-oxidant metals, such as iron. Although the antioxidant activity is viewed as a positive effect, this activity may impair the utilization of dietary iron. A small clinical study assessed the effect of phenolic-rich extracts obtained from green tea or the crude drug on nonhaem-iron absorption. Twenty-four female volunteers consumed test meals on four separate occasions. The meals were identical except for the absence (meal A) or presence (meal B) of a phenolic-rich extract from green tea (study 1; n = 10) or rosemary (study 2; n = 14). The extracts (0.1 mM) were added to the meat component of the test meals. The meals were labelled with either ^{55}Fe or ^{59}Fe and were consumed on four consecutive days in the order ABBA or BAAB. Iron absorption was determined by measuring whole-body retention of ^{59}Fe and the ratio of ^{55}Fe or ^{59}Fe activity in blood samples. The results demonstrated that the presence of phenolic-rich extracts resulted in decreased non-haem-iron absorption.

Mean (± standard deviation) iron absorption decreased from 12.1 ± 4.5% to 8.9 ± 5.2% ($p < 0.01$) in the presence of green tea extract and from 7.5 ± 4.0% to 6.4 ± 4.7% ($p < 0.05$) in the presence of the rosemary extract (*41*).

Adverse reactions

There is a single case-report of photoaggravated allergic contact dermatitis, in which a patient developed contact dermatitis after handling the leaves of the plant on a sunny day (*42–44*). One case of cheilitis has been reported (*45*). A 56-year-old man developed occupational contact dermatitis of his hands, forearms, and face after coming into contact with an extract of the leaves. He reacted to carnosol, the main constituent of the extract (*44*).

Contraindications

Folium Rosmarini is contraindicated in cases of hypersensitivity or allergy to the plant material.

Warnings

No information was found.

Precautions

Drug interactions

While no drug interactions have been reported, an aqueous extract of the crude drug enhanced the activity of cytochrome P450 1A1, 2B1/2, 2E1 and glutathione S-transferase (especially recombinant glutathione S-transferase A3/A5, M1 and M2), quinone reductase and UDP-glucuronosyltransferase (*34*). Thus, drugs metabolized through these cytochrome P450 isozymes may be affected.

Carcinogenesis, mutagenesis, impairment of fertility

An ethanol extract of the leaves was not mutagenic in the Hist revertant *Salmonella typhimurium* TA 1530 strain at a concentration of 5 µg/ml (*46*). See also the study by Lemonica (*40*) under Toxicology.

Pregnancy: non-teratogenic effects

See Toxicology.

Other precautions

No information was found.

Dosage forms

Crude drug for infusions, dry extracts, fluidextract and other Galenical preparations for internal and external use (*47*).

Posology

(Unless otherwise specified)
Daily dosage: for oral use 4–6 g of herb. Infusion: 2–4 g in 150 ml water three times daily. Fluidextract (1:1, 45% ethanol w/w) 1.5–3.0 ml daily. Tincture (1:5, 70% ethanol) 3–8.5 ml daily. Dry extract (4.5–5.5:1 w/w) 0.36–0.44 g, three times daily. External use: boil 50 g of herb in 1 l of water, add to one full bath (*47*).

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