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An Evidence-Based Systematic Review of Rosemary (*Rosmarinus officinalis*) by the Natural Standard Research Collaboration

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ABSTRACT. An evidence-based systematic review of rosemary (*Rosmarinus officinalis*), including written and statistical analysis of scientific literature, expert opinion, folkloric precedent, history, pharmacology, kinetics/dynamics, interactions, adverse effects, toxicology, and dosing.

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KEYWORDS. adverse effects, rosemary (*Rosmarinus officinalis*) dosing, evidence-based, interactions, pharmacodynamics, pharmacology, pharmacokinetics, systematic review

SYSTEMATIC AGGREGATION, ANALYSIS, AND REVIEW OF THE LITERATURE

Search Strategy

To prepare this Natural Standard review, electronic searches were conducted in several databases, including AMED, CANCERLIT, CINAHL, CISCOM, the Cochrane Library, EMBASE, HerbMed, International Pharmaceutical Abstracts, Medline, and NAPRALERT. Search terms included the common name(s), scientific name(s), and all listed synonyms. Hand searches were conducted of 20 additional journals (not indexed in common databases), and of bibliographies from 50 selected secondary references. No restrictions were placed on language or quality of publications. Researchers in the field of complementary and alternative medicine (CAM) were consulted for access to additional references or ongoing research.

Selection Criteria

All literature was collected pertaining to efficacy in humans (regardless of study design, quality, or language), dosing, precautions, adverse effects, use in pregnancy/lactation, interactions, alteration of laboratory assays, and mechanism of action (in vitro, animal research, and human data). Standardized inclusion/exclusion criteria were utilized for selection.

Data Analysis

The data extraction and analysis were performed by healthcare professionals conducting clinical work and/or research at academic centers, using standardized instruments that pertained to each review section (defining inclusion/exclusion criteria and analytic techniques, including validated measures of study quality). The data were verified by a second reviewer.

Review Process

A blinded review was conducted by multidisciplinary clinical research faculty at major academic centers with expertise in epidemiology and biostatistics, pharmacology, toxicology, complementary and alternative medicine (CAM) research, and clinical practice. In cases of editorial disagreement, a three-member panel of the editorial board addressed conflicts, and consulted experts, when applicable. Authors of studies were contacted when clarification was required.

FIGURE 1. *Rosmarinus officinalis.*

Synonyms/Common Names/Related Substances

(−)-camphene, (−)-methyljasmonate, 1,8-cineole, 3,4,5-trimethoxyphenylmethanol, 5-hydroxy-7,4′-dimethoxyflavone, 7-alpha-methoxyabieta-8,13-diene-11,12-dione-(20, 6beta)-olide, 7-beta-methoxyabieta-8,13-diene-11,12-dione-(20,6beta)-olide, 12-O-methylcarnosic acid, Albus (cultivar), alecrim (Portuguese), alpha-pinene, Arp (cultivar), Aureus (cultivar), Benenden Blue (cultivar), biberiye (Turkish), Blue Boy (cultivar), borneol, bornyl acetate, caffeic acid, camphor, carnosic acid, carnosol, *cis*-4-glucosyloxycinnamic acid, Colorlife® powdered rosemary concentrate, compass plant, compass-weed, dendrolivano (Greek), dentrolivano (Greek), dew of the sea, diosmin, diterpenes, eklil kuhi (Persian), epirosmanol, eriocitrin, eucalyptol, Fierabras, flavones, genkwanin, Golden Rain (cultivar), harilik rosmariin (Estonian), hasalban (Turkish), Herbalox® Type O oleoresin rosemary extract, Herbor 025, hesperidin, hispidulin 7-O-glucoside, honey of rosemary, Hungary water, iklil al-jabal (Arabic), Incensier (cultivar), Irene (cultivar), isoscutellarein 7-O-glucoside, Ken Taylor (cultivar), kuşdili otu (Turkish), lá hu'o'ng thao (Vietnamese), Labiatae (family), Lamiaceae (family), luteolin, luteolin 3′-O-(3′′-O-acetyl)-beta-D-glucuronide, luteolin 3′-O-(4′′-O-acetyl)-beta-D-glucuronide, luteolin 3′-O-beta-d-glucuronide, linalool,

Lockwood de Forest (cultivar), Majorca Pink (cultivar), mannenrou (Japanese), methanol (MeOH), mi die xiang (Chinese), Miss Jessop's Upright (cultivar), monoterpenes, old man, oleoresin rosemary, Oxy'less®, p-cymene, phenols, pilgrim's flower, Pinkie (cultivar), polar plant, polyphenolic compounds, Prostratus (cultivar), Pyramidalis (cultivar), Queen of Hungary water, quinate, ro ju ma ri (Korean), romaní (Catalan), romarin (French), romarin commun (French), romer (Catalan), romero (Spanish, Tagalog), romero común (Spanish), roozumari (Japanese), roozumarii (Japanese), rosemary honey (Miel de La Alcarria, Spain), Roseus (cultivar), rosmanol, Rosmanox®, rosmaquinone A, rosmaquinone B, rosmariin (Estonian), rosmariini (Finnish), rosmarin (Danish, German, Norwegian, Swedish), rósmarín (Icelandic), *Rosmarini* folium, rosmarinic acid, rosmarino (Italian), Rosmarinus acid, *Rosmarinus officinalis*, *Rosmarinus officinalis* L. var. *genuina* forma *erectus*, *Rosmarinus tomentosus*, *Rosmarinus tomentosus* Huber-Morath & Maire, rosmario (Spanish), rosumarin (Japanese), rozemarijn (Dutch), rozmari (Greek, Persian), rozmarin (Bulgarian, Hebrew, Romanian, Russian), rozmarín (Slovakian), rožmarin (Slovenian), rozmarín lekársky (Slovakian), rozmaring (Hungarian), rozmaryn (Polish, Ukranian), rozmarýn lékařský (Czech), rozmaryn spravzhnii (Ukranian), rozmarýna (Czech), rozmarýna lékařská (Czech), rozumarii (Japanese), ružmarin (Croatian, Serbian), sædögg (Icelandic), seco-hinokiol, Severn Sea (cultivar), Spanish rosemary, Suffolk Blue (cultivar), thymol, triterpenes, Tuscan blue (cultivar), verbenone.

CLINICIAL BOTTOM LINE/EFFECTIVENESS

Brief Background

- Rosemary (*Rosmarinus officinalis*) is a common aromatic evergreen shrub grown in many parts of the world. The fresh and dried leaves are frequently used as a food preservative and in traditional Mediterranean cuisine as a flavoring agent.
- Historically, rosemary has been used medicinally to treat renal colic and dysmenorrhea. It has also been used to relieve symptoms caused by respiratory disorders and to stimulate hair growth. Today, rosemary extracts are often used in aromatherapy to treat anxiety-related conditions and increase alertness.
- The most well-studied constituents of rosemary are caffeic acid and its derivative, rosmarinic acid. These compounds are thought to have antioxidant properties and are under investigation as potential therapies for cancer, hepatotoxicity, and inflammatory conditions.
- Currently, high-quality human trials investigating rosemary and its possible therapeutic applications are lacking. A small number of methodologically weak studies show some promise in the improvement of mental state (via aromatherapy) and as a treatment for alopecia.

Scientific Evidence for Common/Studied Uses

Natural Standard Evidence-based Validated Grading Rationale™

- Grades reflect the level of available scientific evidence in support of the efficacy of a given therapy for a specific indication.

Alopecia areata	C
Anxiety/stress	C
Breast cancer (adjuvant)	C
Cognitive performance enhancement	C
Constipation	C
Dermatitis	C
Rheumatic diseases (pain)	C

- Expert opinion and historic/folkloric precedent are not included in this assessment, and are reflected in a separate section of each review ("Expert Opinion and Historic/Folkloric Precedent").
- Evidence of harm is considered separately; the grades given below apply only to evidence of benefit.

Level of Evidence Grade	Criteria
A (strong scientific evidence)	Statistically significant evidence of benefit from >2 properly randomized trials (RCTs), or evidence from one properly conducted RCT and one properly conducted meta-analysis, or evidence from multiple RCTs with a clear majority of the properly conducted trials showing statistically significant evidence of benefit and with supporting evidence in basic science, animal studies, or theory.
B (good scientific evidence)	Statistically significant evidence of benefit from 1–2 properly randomized trials, or evidence of benefit from >1 properly conducted meta-analysis or evidence of benefit from >1 cohort/case-control/nonrandomized trials and with supporting evidence in basic science, animal studies, or theory.
C (unclear or conflicting scientific evidence)	Evidence of benefit from >1 small RCT(s) without adequate size, power, statistical significance, or quality of design by objective criteria,[a] or conflicting evidence from multiple RCTs without a clear majority of the properly conducted trials showing evidence of benefit or ineffectiveness, or evidence of benefit from >1 cohort/case-control/nonrandomized trials and without supporting evidence in basic science, animal studies, or theory, or evidence of efficacy only from basic science, animal studies, or theory.
D (fair negative scientific evidence)	Statistically significant negative evidence (i.e., lack of evidence of benefit) from cohort/case-control/ nonrandomized trials, and evidence in basic science, animal studies, or theory suggesting a lack of benefit.
F (strong negative scientific evidence)	Statistically significant negative evidence (i.e., lack of evidence of benefit) from >1 properly randomized adequately powered trial(s) of high-quality design by objective criteria.[a]
Lack of Evidence[b]	Unable to evaluate efficacy due to lack of adequate available human data.

[a]Objective criteria are derived from validated instruments for evaluating study quality, including the 5-point scale developed by Jadad et al. (1996), in which a score below 4 is considered to indicate lesser quality methodologically.
[b]Listed separately in reviews in the "Historical or Theoretical Uses Which Lack Sufficient Evidence" section.

Historical or Theoretical Uses, Which Lack Sufficient Evidence

- Abortifacient, acne (Weckesser et al., 2007), Alzheimer's disease (Abascal & Yarnell, 2004a, 2004b; Adams, Gmunder, & Hamburger, 2007), amyotrophic lateral sclerosis (ALS) (Shimojo, Kosaka, Noda, Shimizu, & Shirasawa, 2010), analgesic (Gedney, Glover, & Fillingim, 2004; Gonzalez-Trujano et al., 2007; Takaki et al., 2008), anthelmintic, anti-aging, and antibacterial (Ahn, Grun, & Mustapha, 2004; Bagamboula, Uyttendaele, & Debevere, 2003; Lee et al., 2007; Oluwatuyi, Kaatz, & Gibbons, 2004; Santoyo et al., 2005), anticoagulant (Yamamoto, Yamada, Naemura, Yamashita, & Arai, 2005), antifungal (Angioni et al., 2004; Boyraz & Ozcan, 2005; Daferera, Ziogas, & Polissiou, 2000; Fenner, Betti, Mentz, & Rates, 2006; Giordani et al., 2004; Hethelyi, Kaposi, Domonkos, & Kernoczi, 1987; Lopez-Munoz, Alamo, & Garcia-Garcia, 2006; Ozcan, 2005; Perrucci et al., 1994), anti-inflammatory (Gonzalez-Trujano et al., 2007; Minich et al., 2007), antimicrobial (Alippi, Ringuelet, Cerimele, Re, & Henning, 1996; Angioni et al., 2004; Lai & Roy, 2004; Larrondo, Agut, & Calvo-Torras, 1995; Lopez-Munoz et al., 2006; Mangena & Muyima, 1999; Martinez, Cilla, Beltran, & Roncales, 2006; Montes, Wilkomirsky, Valenzuela, Bello, & Osses, 1991; Moreno, Scheyer, Romano, & Vojnov, 2006; Panizzi, Flamini, Cioni, & Morelli, 1993; Ramirez et al., 2006; Rota, Carraminana, Burillo, & Herrera, 2004; Santoyo et al., 2005; Schelz, Molnar, & Hohmann, 2006), antioxidant (Aruoma, 1999; Choi, Choi, Han, Bae, & Chung, 2002a; Galobart, Barroeta, Baucells, Codony, & Ternes, 2001; Gladine, Rock, Morand, Bauchart, & Durand, 2007; Gutierrez et al., 2003, 2009; Haraguchi Saito, Okamura, & Yagi, 1995; Ho, Wang, Wei, Huang, & Huang, 2000; Ibanez et al., 2000, 2003; Kahkonen et al., 1999; Kaliora & Andrikopoulos, 2005; Kim & Kim, 2003; Leal et al., 2003; Lee et al., 2007; Lopez-Bote, Gray, Gomaa, & Flegal, 1998; Makino et al., 2002; Monino, Martinez, Sotomayor, Lafuente, & Jordan, 2008; Moreno et al., 2006; Nakatani, 2000; Okamura, Haraguchi, Hashimoto, & Yagi, 1994; Ozcan, 2003; Peng, Yuan, Liu, & Ye, 2005; Rababah, Hettiarachchy, & Horax, 2004; Ramirez et al., 2006; Saito et al., 2004; Shukla & Bhattacharya, 2003; Siurin, 1997; Smet et al., 2008; Zeng et al., 2001), antispasmodic (Aleisa, 2008; Lai & Roy, 2004; Shahidi, 2000; Takaki et al., 2008), appetite stimulation, and atherosclerosis (Yu, Lin, & Chang, 2008), bronchial asthma, and cancer (Abascal & Yarnell, 2001; Cheung & Tai, 2007; Esiyok, Otles, & Akcicek, 2004; Ho, Tsai, Tsai, & Lin, 2008; Ho et al., 2000; Huang et al., 1994; Kahkonen et al., 1999; Lee et al., 2007; Makino et al., 2000; Rau et al., 2006; Sancheti & Goyal, 2006a, 2006b; Scheckel, Degner, & Romagnolo, 2008; Shabtay et al., 2008; Sharabani et al., 2006; Singletary, MacDonald, & Wallig, 1996; Singletary & Nelshoppen, 1991; Steiner et al., 2001; Wargovich, Woods, Hollis, & Zander, 2001; Wei, Liu, Wang, Li, & Luo, 2008; Zunino & Storms, 2009), cardiovascular disease (Hsieh et al., 2007), carminative (Takaki et al., 2008), cataracts, and chemotherapy (adjunct) (Laszczyk, 2009; Nabekura, Yamaki, Hiroi, Ueno, & Kitagawa, 2009; Wang et al., 2008), cholagogue (Takaki et al., 2008), colic, and colon cancer (Scheckel et al., 2008), dandruff, and depression (Machado et al., 2009), diabetes mellitus (Bakirel, Bakirel, Keles, Ulgen, & Yardibi, 2008; Dearlove, Greenspan, Hartle, Swanson, & Hargrove, 2008; Hsieh et al., 2007; Prat, Lopez-Gonzalvez, Ruiz, & Barbas, 2009), diagnostic procedure (cell culture media for candida identification) (de Loreto et al., 2008), diaphoretic, and diuretic (Takaki et al., 2008), drug withdrawal (morphine) (Hosseinzadeh & Nourbakhsh, 2003), dry skin (Jimenez, Fresno Contreras, & Selles, 2002), dysmenorrhea, dyspepsia, and eczema (Weckesser et al., 2007), epilepsy (Abdul-Ghani,

El-Lati, Sacaan, Suleiman, & Amin, 1987; Takaki et al., 2008), expectorant (Takaki et al., 2008), food additive (animal feed) (Cross, Acamovic, & McDevitt, 2004a, 2004b; Cross, McDevitt, Hillman, & Acamovic, 2007; Hernandez, Madrid, Garcia, Orengo, & Megias, 2004), food preservative (Ayadi, Grati-Kamoun, & Attia, 2009; Soler-Rivas et al., 2010), gout, and halitosis (Frackowiak, Fiszer-Kuc, Maliszewska, Bruziewicz-Mikla-Szewska, & Gancarz, 2003), headache (Yarnell & Abascal, 2007), hepatoprotection (Amin & Hamza, 2005; Fahim, Esmat, Fadel, & Hassan, 1999; Gutierrez et al., 2009; Hoefler, Fleurentin, Mortier, Pelt, & Guillemain, 1987; Kitano et al., 2000; Sotelo-Felix et al., 2002b), herpes labialis (Reichling, Nolkemper, Stintzing, & Schnitzler, 2008), HIV infection, hypercholesterolemia, and hyperglycemia (Kwon, Vattem, & Shetty, 2006; Rau et al., 2006), hypertension (Kwon et al., 2006), hyperthyroid (Yarnell & Abascal, 2006), immunostimulation, and infections (drug-resistant) (Luqman, Dwivedi, Darokar, Kalra, & Khanuja, 2007), ischemic heart disease, joint pain, and lice (Veal, 1996), liver cirrhosis (Harach et al., 2009; Kaziulin, Petukhov, & Kucheriavyi, 2006; Vitaglione, Morisco, Caporaso, & Fogliano, 2004), memory enhancement, and metabolic disorders (bone) (Putnam, Scutt, Bicknell, Priestley, & Williamson, 2007), methicillin-resistant *Staphylococcus aureus* (MRSA) (Quave, Plano, Pantuso, & Bennett, 2008; Yarnell & Abascal, 2009), muscle relaxant (smooth muscle), and nerve regeneration (Hsieh et al., 2007), obesity (Harach et al., 2009; Lee et al., 2007; Takahashi et al., 2009), osteoporosis (Muhlbauer, Lozano, Palacio, Reinli, & Felix, 2003; Putnam et al., 2007), paralysis, and Parkinson's disease (sporadic) (Park et al., 2008), peptic ulcer (Dias, Foglio, Possenti, & de Carvalho, 2000; Mahady et al., 2005), peripheral vascular disease, and photoprotection (Hsu, 2005; Lee et al., 2007; Martin et al., 2008; Offord, Mace, Ruffieux, Malnoe, & Pfeifer, 1995), poor circulation, and psychiatric disorders (Aleisa, 2008), quality of life, renal colic, and respiratory disorders (Rakover, Ben Arye, & Goldstein, 2008), skin care (Baumann, 2007; Calabrese et al., 2000, 2001), skin conditions (excessive oil secretion and cellulite), sperm motility, and stomach ulcers caused by *Helicobacter pylori* bacteria (Matsubara et al., 2003), tonic, and toxicity (dieldrin-induced neurotoxicity) (Park et al., 2008), wound healing (Hsu, 2005), and wrinkle prevention.

Expert Opinion and Historical/Folkloric Precedent

- Germany's Commission E has approved rosemary leaf for the treatment of dyspepsia, and rosemary oil (used externally) for joint pain and poor circulation.
- In folk medicine, rosemary is used for various therapeutic effects (Aggarwal et al., 2008; Winkler, 2004), including in the alleviation of renal colic, dysmenorrhea, respiratory disorders, depression (Machado et al., 2009), and hair loss. Rosemary is an herb that has been used for its potential to prevent free radical damage (Etter, 2004; Hasani-Ranjbar, Larijani, & Abdollahi, 2009; Louli, Ragoussis, & Magoulas, 2004; Peng et al., 2005; Zandi & Ahmadi, 2000) and gastrointestinal disorders caused by various bacterial strains (Tayel & El Tras, 2009). Some alternative practitioners use rosemary extract for aromatherapy to promote well-being. Rosemary has been also used as an aromatherapy agent used in air diffusers, creams, lotions, oils, incense, and other products. Current cosmetic uses of rosemary include treating cellulite and wrinkles, and normalizing excessive oil secretion from the skin.
- Based on an ethnopharmacological survey in Morocco and Canada, use of rosemary was common for gastrointestinal disorders in Morocco but not in Canada (Haddad,

Depot, Settaf, Chabli, & Cherrah, 2003). In Morocco, rosemary is also used traditionally to treat diabetes and hypertension (Tahraoui, El Hilaly, Israili, & Lyoussi, 2006).
- According to an ethnobotanical survey of Guatemala done in 1988–1989, *Rosmarinus officinalis* found in the region is used medicinally among the Carib population (Giron, Freire, Alonzo, & Caceres, 1991).

Brief Safety Summary

- *Likely safe*: When rosemary is used orally in amounts commonly found in foods.
- *Possibly safe*: When used topically in medicinal quantity for up to 7 months (Hay, Jamieson, & Ormerod, 1998).
- *Possibly unsafe*: In patients who are pregnant or trying to become pregnant, due to evidence of hormone-altering activity (Lemonica, Damasceno, & di Stasi, 1996; Zhu et al., 1998) and embryotoxic effects (Lemonica et al., 1996; Zhu et al., 1998), as well as its traditional use as an abortifacient. In patients who are at risk for iron deficiency, as rosemary has been shown to decrease iron absorption (Samman et al., 2001). In patients with coagulation disorders or taking anticoagulation or anti-platelet agents, as rosemary has shown antithrombotic activity and may increase the risk of bleeding (Yamamoto et al., 2005). In patients with blood pressure disorders or who are using hypotensive agents, as rosemary may inhibit angiotensin I-converting enzyme (ACE) (Kwon et al., 2006). In patients with diabetes or those who are using hypoglycemic agents, as rosemary has been shown to increase and decrease glucose levels (al Hader, Hasan, & Aqel, 1994; Kwon et al., 2006; Rau et al., 2006). In patients receiving ciprofloxacin, as based on laboratory study rosemary essential oils may antagonize the effects of ciprofloxacin (van Vuuren, Suliman, & Viljoen, 2009). In patients taking cyclosporine, as rosemary may potentially interact with this agent (Beaulieu, 2001). In patients taking drugs that are metabolized by cytochrome P450 pathways, as results from in vitro and rat study suggest that rosemary may selectively induce P450 enzymes, particularly CYP 2B, CYP 1A1, CYP 2B1/2, and CYP 2E1 (Debersac et al., 2001a; Debersac, Vernevaut, Amiot, Suschetet, & Siess, 2001b; Offord, Mace, Avanti, & Pfeifer, 1997). In patients using salicylates, as based on in vitro evidence, rosemary contains high levels of salicylates (Swain, Dutton, & Truswell, 1985). In patients predisposed to seizures or epilepsy, as seizures have been associated with rosemary use in human case report (Burkhard, Burkhardt, Haenggeli, & Landis, 1999).
- *Likely unsafe*: In patients who have a known allergy or hypersensitivity to rosemary, its constituents, or other members of the Lamiaceae family. In patients taking lithium, as rosemary may precipitate lithium toxicity due to its diuretic properties (Pyevich & Bogenschutz, 2001).

DOSING/TOXICOLOGY

General

- Doses are based on those most commonly used in available trials or in historical practice. However, with natural products, it is often not clear what the optimal doses are to balance efficacy and safety. Preparation of products may vary from

manufacturer to manufacturer, and from batch to batch within one manufacturer. As it is often not clear what the active components of a product are, standardization may not be possible, and the clinical effects of different brands may not be comparable.

Standardization

- There is no widely available standard extract of rosemary.
- Active constituents are thought to be caffeic acid and its derivatives, such as rosmarinic acid.

Dosing

Adult (age ≥18 years)

Inhaled

- *Anxiety/stress*: Four drops of pure rosemary essential oil (Tisserand Aromatherapy, Newtown Road, Hove, Sussex, UK) applied to an aromatherapy diffuser pad 5 min before a single test period has been used (Moss, Cook, Wesnes, & Duckett, 2003). Three drops of rosemary (from *Rosmarinus officinalis* with a camphor phenotype) essential oil were used in an inhaler prior to the start and during the single test; a piece of cotton with the saturated oil was placed in the inhaler 3 min before usage (McCaffrey, Thomas, & Kinzelman, 2009).
- *Cognitive performance enhancement*: Four drops of pure rosemary essential oil (Tisserand Aromatherapy, Newtown Road, Hove, Sussex, UK) applied to an aromatherapy diffuser pad 5 min before a single test period has been used (Moss et al., 2003).

Oral.

- *General*: 4–6 g daily has been used (anecdotal); brand and duration were not noted.

Children (age <18 years)

- Insufficient available evidence to recommend.

PRECAUTION/CONTRAINDICATION

Allergy

- Known allergy/hypersensitivity to rosemary, its constituents, or members of the Labiatae or Lamiaceae families.
- Contact dermatitis has been reported in a small number of persons exposed to rosemary (Armisen, Rodriguez, & Vidal, 2003; Fernandez et al., 1997; Guin, 2001; Hjorther, Christophersen, Hausen, & Menne, 1997).

- According to a case report, a 56-year-old man, working in a food-processing factory, developed contact dermatitis on his hands, forearms, and face following introduction of a new herb extract (Rosmanox®) made from the leaves of rosemary (*Rosmarinus officinalis*) (Hjorther et al., 1997). He reacted to carnosol, the main constituent of Rosmanox®.
- In a case report, a 23-year-old woman using various cosmetics and a cleansing gel containing rosemary leaf extract developed an itchy erythema on her face (Inui & Katayama, 2005). She reacted positively to rosemary leaf extract (0.1% in distilled water) in patch tests.
- In a case report, an instance of occupational asthma caused by several aromatic herbs, including thyme, rosemary, bay leaf, and garlic, was described (Lemiere, Cartier, Lehrer, & Malo, 1996). The diagnosis was confirmed by inhalation challenges. Although all of the herbs had immediate skin reactivity, a radioallergosorbent test (RAST) showed that garlic was the most potent allergen by weight, with rosemary and the other constituent herbs showing less reactivity. Concomitant allergic dermatitis from rosemary and thyme has also been observed (Martinez-Gonzalez, Goday Bujan, Martinez, & Fonseca, 2007).

Adverse Effects/Post-Market Surveillance

- *General*: Based on historical usage and the available research, it appears that rosemary is well tolerated with few documented cases of adverse events. Contact dermatitis has been noted in select case reports (Armisen et al., 2003; Fernandez et al., 1997; Guin, 2001; Hjorther et al., 1997). According to secondary sources, ingestion of rosemary oil may be toxic.
- *Dermatologic*: Allergic contact dermatitis and cheilitis have been reported in response to rosemary (Armisen et al., 2003; Fernandez et al., 1997; Guin, 2001; Inui & Katayama, 2005).
- *Endocrine*: In rabbit study, the intramuscular (i.m.) administration of rosemary leaf volatile oil (25 mg/kg) produced 20% ($p < .05$), 27% ($p < .01$), and 55% ($p < .001$) increase in plasma glucose levels in normal rabbits at 60-, 90- and 120-min intervals, respectively (al Hader et al., 1994). This injection also decreased serum insulin by 30% at a 30-min interval ($p < .002$), in comparison with control rabbits. In alloxan diabetic rabbits, rosemary volatile oil increased fasting plasma glucose levels by 17% ($p < .05$) when compared with the controls (Bakirel et al., 2008).
- One animal study suggests that rosemary may increase the rate at which the liver deactivates estrogen, which may lead to estrogen-deficient conditions (Zhu et al., 1998).
- *Gastrointestinal*: Ingestion of a rosemary twig resulted in the perforation of the gastric antrum, followed by migration to the liver, complicated by hepatic abscess and *Staphylococcus aureus* sepsis, as reported in a 59-year-old male (Karamarkovic et al., 2007).
- *Hematologic*: Rosemary ingestion has been shown to decrease absorption and utilization of dietary iron (Samman et al., 2001), which may theoretically result in iron deficiency anemia.
- *Immunological*: In rat study, injection of 1,8-cineole, a rosemary constituent, produced inflammatory edema in the hind paw, which may be due to the involvement of mast cells (Santos & Rao, 1997).

- *Neurologic/CNS*: Seizures or epilepsy associated with rosemary have been reported (Burkhard et al., 1999).
- *Pulmonary/respiratory*: In a case report, occupational asthma caused by several aromatic herbs, including thyme, rosemary, bay leaf, and garlic, was observed (Lemiere et al., 1996). The diagnosis was confirmed by inhalation challenges. Although all of the herbs had immediate skin reactivity, RAST showed that garlic was the most potent allergen by weight, with rosemary and the other herbs showing less reactivity.

Precautions/Warnings/Contraindications

- Avoid in patients who have a known allergy or hypersensitivity to rosemary, its constituents, or other members of the Lamiaceae or Labiatae family.
- Avoid in patients taking lithium, as rosemary may precipitate lithium toxicity due to its diuretic properties (Pyevich & Bogenschutz, 2001).
- Use cautiously in patients who are pregnant or trying to become pregnant, due to evidence of hormone-altering activity (Lemonica et al., 1996; Zhu et al., 1998) and embryotoxic effects (Lemonica et al., 1996; Zhu et al., 1998), as well as its traditional use as an abortifacient.
- Use cautiously in patients who are at risk for iron deficiency, as rosemary has been shown to decrease iron absorption (Samman et al., 2001).
- Use cautiously in patients with coagulation disorders or taking anticoagulation or anti-platelet agents, as rosemary has shown antithrombotic activity and may increase the risk of bleeding (Yamamoto et al., 2005).
- Use cautiously in patients with blood pressure disorders or those who are using hypotensive agents, as rosemary may inhibit ACE (Kwon et al., 2006).
- Use cautiously in patients with diabetes or those who are using hypoglycemic agents, as rosemary has been shown to increase and decrease glucose levels (al Hader et al., 1994; Kwon et al., 2006; Rau et al., 2006).
- Use cautiously in patients receiving ciprofloxacin, as based on laboratory study rosemary essential oils may antagonize the effects of ciprofloxacin (van Vuuren et al., 2009).
- Use cautiously in patients taking cyclosporine, as rosemary may potentially interact with this agent (Beaulieu, 2001).
- Use cautiously in patients taking drugs that are metabolized by cytochrome P450 pathways, as results from in vitro and rat study suggest that rosemary may induce P450 enzymes, particularly CYP 2B, CYP 1A1, CYP 2B1/2, and CYP 2E1 (Debersac et al., 2001a, 2001b; Offord et al., 1997).
- Use cautiously in patients using salicylates, as based on in vitro evidence rosemary contains high levels of salicylates (Swain et al., 1985).
- Use cautiously in individuals predisposed to seizures or epilepsy, as seizures have been associated with rosemary usage in human case report (Burkhard et al., 1999).

Pregnancy and Lactation

- Based on its hormone-altering activity (Lemonica et al., 1996; Zhu et al., 1998), preliminary evidence showing embryotoxic effects and its traditional use as an

abortifacient, rosemary should be used cautiously by pregnant women or women who wish to become pregnant.

- In rats, ingestion of 500 mg/kg of rosemary for 63 days resulted in a decline in spermatogenesis and decrease in sperm motility and density in male rats (Nusier, Bataineh, & Daradkah, 2007). Following impregnation by males fed with 500 mg/kg of rosemary, there were a markedly increased number of fetal resorptions.
- Information concerning the use of rosemary during pregnancy or lactation is currently lacking in the U.S. National Library of Medicine Drugs and Lactation Database (LactMed).

INTERACTION

Rosemary/Drug Interactions

- *Aminophylline*: Based on in vitro evidence, rosemary may increase skin permeability and percutaneous absorption of aminophylline in human skin (Wang, Wang, & Kuo, 2007).
- *Analgesics*: Based on human evidence, inhalation of the essential oil of rosemary may affect subjective perception of pain, although without reducing pain sensitivity (Gedney et al., 2004).
- *Antianxiety drugs*: In clinical study, inhalation of rosemary essential oil reduced anxiety (Burnett, Solterbeck, & Strapp, 2004; Diego et al., 1998; McCaffrey et al., 2009; Moss et al., 2003; Park & Lee, 2004).
- *Antibiotics*: On the basis of laboratory study, rosemary essential oil may act antagonistically with ciprofloxacin (van Vuuren et al., 2009). Incorporation of 10 mcg/ml carnosic acid and carnosol into the growth medium caused a 32- and 16-fold potentiation of activity of erythromycin against an erythromycin-effluxing strain, respectively (Oluwatuyi et al., 2004). Rosemary and several of its constituents, including carnosic acid and carnosol, have exhibited antibacterial effects against various Gram-positive and Gram-negative bacteria in vitro, including oral planktonic bacteria (Silva, Silva, Higino, Pereira, & Carvalho, 2008), Bacillus subtilis, Escherichia coli, Enterococcus faecalis, Pseudomonas aeruginosa, MRSA, H[2]O[2]-producing lactobacilli, Bacillus brevis FMC3, Bacillus megaterium DSM32, Micrococcus luteus LA 2971, Mycobacterium smegmatis RUT, Listeria monocytogenes SCOTT A, Streptococcus thermophilus, Pseudomonas fluorescens, Yersinia enterocolitica O:3 P 41797, Propionibacterium acnes (ATCC 6919), Staphylococcus epidermidis, Propionibacterium acnes, and Staphylococcus aureus ME/GM/TC resistant (ATCC 33592) (Abdel-Fatah, El-Hawa, Samia, Rabie, & Amer, 2002; Angioni et al., 2004; Antonio et al., 2009; Bogdadi et al., 2007; Bozin, Mimica-Dukic, Samojlik, & Jovin, 2007; Cordeiro, do Sacramento, Correa, Pizzolitto, & Bauab, 2006; Elgayyar, Draughon, Golden, & Mount, 2001; Erdogrul, 2002; Fu et al., 2007b; Gutierrez, Barry-Ryan, & Bourke, 2008a; Jirovetz et al., 2005; Klancnik, Guzej, Kolar, Abramovic, & Mozina, 2009; Larrondo et al., 1995; Lopez, Sanchez, Batlle, & Nerin, 2005; Luqman et al., 2007; Oskay & Sari, 2007; Panizzi et al., 1993; Quave et al., 2008; Ramirez et al., 2006; Rasooli, Shayegh, Taghizadeh, & Astaneh, 2008b; Santoyo et al., 2005; Schwiertz, Duttke, Hild, & Muller, 2006; Scollard, Francis, & O'Beirne, 2009; Tada, Ohkanda, & Kurabe, 2010; Verluyten, Leroy, & De Vuyst, 2004; Watt, Christofi, & Young, 2007; Weckesser et al., 2007).

- *Anticoagulants/anti-platelet drugs*: Rosemary has shown significant in vitro and in vivo antithrombotic activity in mice (Naemura, Ura, Yamashita, Arai, & Yamamoto, 2008; Yamamoto et al., 2005). The antithrombotic mechanism may involve a direct inhibitory effect on platelets. In rat study, oral rosmarinic acid decreased fibronectin and fibrin in the glomerulus (Makino et al., 2002). Theoretically, concurrent use may increase the risk of bleeding.
- *Antidiabetic agents*: Based on animal study, rosemary extract may increase blood sugar levels in both diabetics and non-diabetics (al Hader et al., 1994). However, laboratory studies have indicated that rosemary extracts may theoretically lower glucose levels (Kwon et al., 2006; Rau et al., 2006), a hypothesis substantiated in animal study (Bakirel et al., 2008; Erenmemisoglu, Saraymen, & Ustun, 1997).
- *Antihypertensive drugs*: On the basis of in vitro study, water extracts of rosemary may inhibit ACE (Kwon et al., 2006).
- *Anti-inflammatory drugs*: On the basis of in vitro study, rosemary may have anti-inflammatory activity (Chan, Ho, & Huang, 1995; Englberger et al., 1988). However, in rat study, injection of 1,8-cineole, a rosemary constituent, produced inflammatory edema in the hind paw (Santos & Rao, 1997).
- *Antineoplastic agents*: On the basis of in vitro study, rosemary may increase the intracellular accumulation of commonly used chemotherapeutic agents, including doxorubicin and vinblastine, in cancer cells that express P-glycoprotein (Nabekura et al., 2009; Plouzek, Ciolino, Clarke, & Yeh, 1999). However, rosemary extract probably does not affect accumulation or efflux of doxorubicin in cells that lack P-glycoprotein. An increase in the activation of caspase-3 in high-risk pre-B acute lymphoblastic leukemia cells has been observed *in vitro* during coadministration of carnosol and chemotherapeutic agents high-risk pre-B acute lymphoblastic leukemia has been observed in vitro (Zunino & Storms, 2009). Furthermore, a lower percentage of caspase-3 positive cells progressed to an apoptotic phenotype during coadministration compared to treatment with chemotherapeutics alone.
- *Antiobesity agents*: In mice fed with a high-fat diet, rosemary leaf extract induced a significant reduction of weight and fat mass gain, an effect that may be related to the inhibition of pancreatic lipase activity, as determined in vitro (Harach et al., 2009). Carnosic acid and carnosol from rosemary inhibited the in vitro differentiation of mouse preadipocytes, 3T3-L1 cells, into adipocytes, possibly mediated by the activation of the antioxidant-response element (ARE) and induction of phase-2 enzymes (Takahashi et al., 2009).
- *Antispasmodic agents*: Rosemary oil produced spasmolytic effects in circular smooth muscle strips of the guinea pig stomach accompanied by agonistic effects on alpha(1) and alpha(2) adrenergic receptors in vitro (Sagorchev, Lukanov, & Beer, 2009). The antispasmodic effects of alcoholic extracts of *Rosmarinus officinalis* have also been evaluated in isolated guinea pig ileum using acetylcholine and histamine as spasmogens (Forster, Niklas, & Lutz, 1980).
- *Cyclosporine*: Rosemary may potentially interact with cyclosporine (Beaulieu, 2001).
- *Cytochrome P450-metabolized agents*: Results from in vitro and rat study suggest that rosemary may selectively induce P450 enzymes in the liver, particularly CYP 2B, CYP 1A1, CYP 2B1/2, and CYP 2E1 (Debersac et al., 2001, 2001b; Offord et al., 1997).
- *Diuretics*: In animal study, rosemary demonstrated diuretic effects, decreasing electrolytes (Haloui, Louedec, Michel, & Lyoussi, 2000). Rosemary has been shown to increase the permeability of furosemide in vitro (Laitinen et al., 2004).

- *Hormonal agents*: On the basis of human evidence, a combination of botanical supplements (i.e., *Curcuma longa*, *Cynara scolymus*, *Rosmarinus officinalis*, *Schisandra chinensis*, *Silybum marinum*, and *Taraxacum officinalis*) decreased dehydroepiandrosterone, dehydroepiandrosterone sulfate, androstenedione, and estrone sulfate levels in women (Greenlee, Atkinson, Stanczyk, & Lampe, 2007). On the basis of evidence from mouse study, rosemary may enhance the liver's rate of deactivating estrogen in the body (Zhu et al., 1998).
- *Iron salts*: Rosemary has been shown to decrease iron absorption (Samman et al., 2001).
- *Lithium*: According to case reports, rosemary may precipitate lithium toxicity due to its diuretic properties (Pyevich & Bogenschutz, 2001).
- *Salicylates*: On the basis of in vitro evidence, rosemary may contain high levels of salicylates (Swain et al., 1985).

Rosemary/Herb/Supplement Interactions

- *Analgesics*: Based on human evidence, inhalation of the essential oil of rosemary may affect subjective perception of pain although without reducing pain sensitivity (Gedney et al., 2004).
- *Antibacterials*: Based on laboratory study, rosemary essential oils may act antagonistically with ciprofloxacin (van Vuuren et al., 2009). Rosemary and several of its constituents, including carnosic acid and carnosol, have exhibited antibacterial effects against various Gram-positive and Gram-negative bacteria in vitro, including oral planktonic bacteria (Silva et al., 2008), Bacillus subtilis, Escherichia coli, Enterococcus faecalis, Pseudomonas aeruginosa, MRSA, H[2]O[2]-producing lactobacilli, Bacillus brevis FMC3, Bacillus megaterium DSM32, Micrococcus luteus LA 2971, Mycobacterium smegmatis RUT, Listeria monocytogenes SCOTT A, Streptococcus thermophilus, Pseudomonas fluorescens, Yersinia enterocolitica O:3 P 41797, Propionibacterium acnes (ATCC 6919), Staphylococcus epidermidis, Propionibacterium acnes, and Staphylococcus aureus ME/GM/TC Resistant (ATCC 33592) (Abdel-Fatah et al., 2002; Angioni et al., 2004; Antonio et al., 2009; Bogdadi et al., 2007; Bozin et al., 2007; Cordeiro et al., 2006; Elgayyar et al., 2001; Erdogrul, 2002; Fu et al., 2007b; Gutierrez et al., 2008a; Jirovetz et al., 2005; Klancnik et al., 2009; Larrondo et al., 1995; Lopez et al., 2005; Luqman et al., 2007; Oskay & Sari, 2007; Panizzi et al., 1993; Quave et al., 2008; Ramirez et al., 2006; Rasooli et al., 2008b; Santoyo et al., 2005; Schwiertz et al., 2006; Scollard et al., 2009; Tada et al., 2010; Verluyten et al., 2004; Watt et al., 2007; Weckesser et al., 2007).
- *Anticoagulants and anti-platelets*: Rosemary has shown significant antithrombotic activity in vitro and in vivo in mice (Naemura et al., 2008; Yamamoto et al., 2005). The antithrombotic mechanism may involve a direct inhibitory effect on platelets. In rat study, oral rosmarinic acid decreased fibronectin and fibrin in the glomerulus (Makino et al., 2002). Theoretically, concurrent use may increase the risk of bleeding.
- *Anti-inflammatory herbs*: Based on in vitro study, rosemary may have anti-inflammatory activity (Chan et al., 1995; Englberger et al., 1988). However, in rat study, injection of 1,8-cineole, a rosemary constituent, produced inflammatory edema in the hind paw (Santos & Rao, 1997).
- *Antiobesity herbs and supplements*: In mice fed with a high-fat diet, rosemary leaf extract induced a significant reduction of weight and fat mass gain, an effect that

may be related to the inhibition of pancreatic lipase activity, as determined in vitro (Harach et al., 2009). Carnosic acid and carnosol from rosemary inhibited the in vitro differentiation of mouse preadipocytes, 3T3-L1 cells, into adipocytes, possibly mediated by the activation of the ARE and induction of phase-2 enzymes (Takahashi et al., 2009).

- *Antispasmodics*: Rosemary oil produced spasmolytic effects in circular smooth muscle strips of the guinea pig stomach accompanied by agonistic effects on alpha(1) and alpha(2) adrenergic receptors in vitro (Sagorchev et al., 2009). The antispasmodic effects of alcoholic extracts of *Rosmarinus officinalis* have also been evaluated in isolated guinea pig ileum using acetylcholine and histamine as spasmogens (Forster et al., 1980).
- *Anxiolytics*: In clinical study, inhalation of essential oil of rosemary reduced anxiety (Burnett et al., 2004; Diego et al., 1998; McCaffrey et al., 2009; Moss et al., 2003; Park & Lee, 2004.
- *Cardiovascular herbs and supplements*: In laboratory study, water extracts of rosemary inhibited rabbit lung ACE by 90.5% (Kwon et al., 2006).
- *Cytochrome P450 substrates*: Results from in vitro and rat study suggest that rosemary may selectively induce P450 enzymes in liver, particularly CYP 2B, CYP 1A1, CYP 2B1/2, and CYP 2E1 (Debersac et al., 2001a, 2001b; Offord et al., 1997).
- *Diuretics*: In vitro evidence suggests that rosemary may enhance the effects of herbal agents used for diuresis (Laitinen et al., 2004; Pyevich & Bogenschutz, 2001). In animal study, rosemary demonstrated diuretic effects, decreasing electrolytes (Haloui et al., 2000). Rosemary has been shown to increase the permeability of furosemide in vitro (Laitinen et al., 2004).
- *Hormonal herbs and supplements*: On the basis of human evidence, a combination of botanical supplements (i.e., *Curcuma longa*, *Cynara scolymus*, *Rosmarinus officinalis*, *Schisandra chinensis*, *Silybum marinum*, and *Taraxacum officinalis*) decreased dehydroepiandrosterone, dehydroepiandrosterone sulfate, androstenedione, and estrone sulfate levels in women (Greenlee et al., 2007). On the basis of evidence from mouse study, rosemary may enhance the liver's rate of deactivating estrogen in the body (Zhu et al., 1998); and based on another in vitro demonstration, rosemary may decrease cortisol levels (Atsumi & Tonosaki, 2007).
- *Hypoglycemics*: On the basis of animal study, rosemary extract may increase blood sugar levels in both diabetics and non-diabetics (al Hader et al., 1994). However, laboratory study has theoretically indicated that rosemary extracts may lower glucose levels (Kwon et al., 2006; Rau et al., 2006), a hypothesis substantiated in animal study (Bakirel et al., 2008; Erenmemisoglu et al., 1997).
- *Iron*: On the basis of clinical study, rosemary may decrease iron absorption (Samman et al., 2001).
- *Lycopene*: In laboratory study, the polyphenols rosmarinic acid and carnosic acid (derived from rosemary) interacted synergistically with lycopene, inhibiting low-density lipoproteins (LDL) oxidation in a dose-dependent manner (Fuhrman, Volkova, Rosenblat, & Aviram, 2000).

Rosemary/Food Interactions

- *Iron-containing foods*: On the basis of clinical study, rosemary may decrease iron absorption (Samman et al., 2001).

- *Lycopene-containing foods*: In laboratory study, the polyphenols rosmarinic acid and carnosic acid (derived from rosemary) interacted synergistically with lycopene, thereby inhibiting LDL oxidation in a dose-dependent manner (Fuhrman et al., 2000).

Rosemary/Laboratory Interactions

- *Blood glucose*: On the basis of animal study, rosemary extract may increase blood sugar levels in both diabetics and non-diabetics (al Hader et al., 1994). However, laboratory studies have indicated that rosemary extracts theoretically may lower glucose levels (Kwon et al., 2006; Rau et al., 2006), a hypothesis substantiated in animal study (Bakirel et al., 2008; Erenmemisoglu et al., 1997).
- *Blood pressure*: In laboratory study, water extracts of rosemary inhibited rabbit lung ACE by 90.5% (Kwon et al., 2006).
- *Chloride*: In rat study, aqueous extracts of rosemary significantly increased urinary excretion of chloride (Haloui et al., 2000).
- *Coagulation panel*: Rosemary has shown significant antithrombotic activity in vitro and in vivo in mice (Naemura et al., 2008; Yamamoto et al., 2005). The antithrombotic mechanism may involve a direct inhibitory effect on platelets. In rat study, oral rosmarinic acid decreased fibronectin and fibrin in the glomerulus (Makino et al., 2002).
- *Cortisol*: On the basis of in vitro evidence, rosemary may decrease cortisol levels (Atsumi & Tonosaki, 2007).
- *Creatinine clearance*: In rat study, aqueous extracts of rosemary significantly decreased creatinine clearance (Haloui et al., 2000).
- *Electroencephalogram (EEG)*: Human study investigating the effects of rosemary aromatherapy on alertness and EEG activity found that patients showed decreased frontal alpha- and beta-power, suggesting increased alertness (Diego et al., 1998). In another research, subjects with a greater baselines relative to the right frontal EEG activation shifted left during exposure to rosemary aroma, while those with greater baselines relative to left frontal EEG activation shifted right (Sanders et al., 2002).
- *Estrogen levels*: On the basis of evidence from mouse study, rosemary may enhance the liver's rate of deactivating estrogen in the body (Zhu et al., 1998).
- *Iron*: On the basis of clinical study, rosemary may decrease iron absorption (Samman et al., 2001).
- *Lithium concentrations*: According to case reports, rosemary may result in increased lithium serum concentrations due to its diuretic properties (Pyevich & Bogenschutz, 2001).
- *Liver function tests*: In animal study, rosemary normalized the increase in bilirubin level and alanine aminotransferase activity in plasma induced by CCl_4 (Gutierrez et al., 2009).
- *Potassium*: In rat study, aqueous extracts of rosemary significantly increased urinary excretion of potassium (Haloui et al., 2000).
- *Sodium*: In rat study, aqueous extracts of rosemary significantly increased urinary excretion of sodium (Haloui et al., 2000).
- *Triglycerides*: In animal study, hepatic triglyceride levels were decreased following rosemary extract administration (Harach et al., 2009).

Rosemary/Nutrient Depletion

- *Antioxidants*: Research has shown that the antioxidant capacity of rosemary may be reduced when grilling and stir-frying or storing in cold vinegar (Chohan, Forster-Wilkins, & Opara, 2008).
- *Glucose*: On the basis of animal study, rosemary extract may increase blood sugar levels in both diabetics and non-diabetics (al Hader et al., 1994). However, laboratory studies have indicated that rosemary extracts theoretically may lower glucose levels (Kwon et al., 2006; Rau et al., 2006), a hypothesis substantiated in animal study (Bakirel et al., 2008; Erenmemisoglu et al., 1997).

MECHANISM OF ACTION

Pharmacology

- *Constituents*: The active constituents of rosemary are caffeic acid, rosmarinic acid, carnosol, and carnosic acid, which are thought to have antioxidant activity (al Sereiti, Abu-Amer, & Sen, 1999; Bassani, Casadebaig, Jacob, Menut, & Lamaty, 1990; Herrero, Plaza, Cifuentes, & Ibanez, 2009; Hsieh et al., 2007; Luis, Martin, Frias, & Valdes, 2007; Nabekura et al., 2009; Perez-Fons, Garzon, & Micol, 2010; Takahashi et al., 2009). The essential oil also contains alpha-pinene, borneol, (-)-camphene, 1,8-cineole, camphor, verbenone, and bornyl acetate (Angioni et al., 2004; Flamini, Cioni, Morelli, Macchia, & Ceccarini, 2002; Granger, Passet, Arbousset, & Girard, 1970; Martinez et al., 2009; Santoyo et al., 2005; Waliwitiya, Kennedy, & Lowenberger, 2009). Rosemary also contains phenolic diterpenes (carnosic acid, carnosol, and 12-O-methylcarnosic acid), caffeoyl derivatives (rosmarinic acid), triterpenes (lupane, oleanane, and ursane triterpenes, ursolic acid, and rofficerone), monoterpenes (e.g., myrcene and camphor), and flavones (isoscutellarein 7-O-glucoside and genkwanin) (Backleh, Leupold, & Parlar, 2003; Bassani et al., 1990; Benhabiles, Ait-Amar, boutekdjiret, & Belabbes, 2001; Brieskorn & Zweyrohn, 1970; del Bano et al., 2003; Doolaege et al., 2007; Ganeva, Tsankova, Simova, Apostolova, & Zaharieva, 1993; Grayer et al., 2003; Herrero et al., 2009; Hosny, Johnson, Ueltschy, & Rosazza, 2002; Hsieh et al., 2007; Huang, Huang, Lin-Shiau, & Lin, 2009; Jager, Trojan, Kopp, Laszczyk, & Scheffler, 2009; Karlsen & Svendsen, 1968; Kreis, Dietrich, & Mosandl, 1994; Laszczyk, 2009; Masuda, Kirikihira, & Takeda, 2005; Masuda et al., 2002; Munne-Bosch, Schwarz, & Alegre, 1999a; Munne-Bosch & Alegre, 2000, 2001; Munne-Bosch, Schwarz, & Alegre, 1999b; Nabekura et al., 2009; Ormeno, Fernandez, & Mevy, 2007a; Ormeno et al., 2007b; Ormeno, Baldy, Ballini, & Fernandez, 2008; Papageorgiou, Mallouchos, & Komaitis, 2008b; Pertino and Schmeda-Hirschmann, 2009; Rasmussen, Rasmussen, & Baerheim, 1972; Schwarz & Ternes, 1992b; Steinmetz, Vial, & Millet, 1987; Tada et al., 2010; Tamaki, Tabuchi, Takahashi, Kosaka, & Satoh, 2009; Thorsen & Hildebrandt, 2003; Yassaa & Williams, 2005). Other studies have also characterized the chemical characteristics of rosemary (Proenca da Cunha & Roque, 1986).
- P-cymene (44.02%), linalool (20.5%), gamma-terpinene (16.62%), thymol (1.81%), beta-pinene (3.61%), alpha-pinene (2.83%), eucalyptol (2.64%), linoleic acid, rosmariquinone, monoterpenic hydrocarbons, oxygenated monoterpenes, sesquiterpene hydrocarbons, and (-)-methyl jasmonate have been also isolated (Croteau &

Kolattukudy, 1974; Cuppett, Hall, Conway, Birt, & Lawson, 1995; Ozcan & Chalchat, 2008; Ruiz Del Castillo & Blanch, 2007). Isoflavonoids have been isolated from rosemary (Bajer, Adam, Galla, & Ventura, 2007; Bezanger & Guilbert, 1965), including eriocitrin, luteolin 3′-O-beta-d-glucuronide, hesperidin, diosmin, isoscutellarein 7-O-glucoside, hispidulin 7-O-glucoside, and genkwanin (del Bano et al., 2004).

- Rosemary leaves contain 5-hydroxy-7,4′-dimethoxyflavone (Brieskorn & Domling, 1967), seco-hinokiol (Cantrell, Richheimer, Nicholas, Schmidt, & Bailey, 2005), and alpha-tocopherol (Munne-Bosch et al., 1999a; Torre, Lorenzo, Martinez-Alcazar, & Barbas, 2001). Rosemary leaves also contain luteolin, luteolin 3′-O-beta-D-glucuronide, luteolin 3′-O-(4′′-O-acetyl)-beta-D-glucuronide, luteolin 3′-O-(3′′-O-acetyl)-beta-D-glucuronide, and hesperidin (Lopez-Lazaro, 2009; Okamura et al., 1994).
- 7-Beta-methoxyabieta-8,13-diene-11,12-dione-(20,6beta)-olide (rosmaquinone A) and 7-alpha-methoxyabieta-8,13-diene-11,12-dione-(20,6beta)-olide (rosmaquinone B) have been isolated from the aerial parts of *Rosmarinus officinalis* L. (Mahmoud, Al Shihry, & Son, 2005). Quinate, *cis*-4-glucosyloxycinnamic acid, and 3,4,5-trimethoxyphenylmethanol have been also isolated from rosemary (Xiao, Dai, Liu, Wang, & Tang, 2008).
- Various drying methods altered the mineral content (K, Ca, Na, Mg, and P) in samples of rosemary leaves (Arslan & Musa Ozcan, 2008). Growing conditions (i.e., sunlight vs. shaded) may affect protein and soluble sugar contents of various plants; higher soluble sugar contents were observed for rosemary, which is grown in sunlight conditions with no differences between sunlight or shade for protein content (Castrillo, Vizcaino, Moreno, & Latorraca, 2005). Irradiation of rosemary has been shown to result in a decrease in carotenoid content (Calucci et al., 2003). Drought conditions have not been shown to affect carotenoid concentrations in rosemary leaves (Nogues, Munne-Bosch, Casadesus, Lopez-Carbonell, & Alegre, 2001).
- Microencapsulation procedures of essential oils of rosemary have been developed and described (Ribeiro, Arnaud, Frazao, Venancio, & Chaumeil, 1997). Various methods, including a method based on headspace solid-phase microextraction (HS-SPME) and gas chromatography and a capillary electrophoresis-electrospray ionization-mass spectrometry method, have been proposed for the determination of volatile compounds from rosemary (Arraez-Roman, Gomez-Caravaca, Gomez-Romero, Segura-Carretero, & Fernandez-Gutierrez, 2006; Carrillo & Tena, 2005; Lemberkovics et al., 2004; Mastelic & Kustrak, 1997).
- The combination of laser-induced acoustic desorption and electrospray ionization mass spectrometry (LIAD/ESI/MS) (Cheng, Huang, & Shiea, 2009) and a method based on capillary electrophoresis-electrospray-mass spectrometry (CE-ESI-MS) (Herrero et al., 2005) have been used to detect components of rosemary essential oils. Ultrasound techniques have been used to extract carnosic acid from rosemary (Albu, Joyce, Paniwnyk, Lorimer, & Mason, 2004). Among tested isolation techniques, microwave distillation demonstrated several advantages over other approaches (i.e., traditional hydrodistillation, supercritical fluid extraction, organic solvent extraction) in the extraction of rosemary essential oil (Presti et al., 2005).
- *Analgesic effects*: On the basis of human study, rosemary aromatherapy had no analgesic effect (Gedney et al., 2004).
- *Antibacterial effects*: In vitro, rosemary and several of its constituents, including rosmarinic acid, carnosic acid, and carnosol, have exhibited antibacterial effects against various Gram-positive and Gram-negative bacteria, including oral planktonic

bacteria (Silva et al., 2008), Bacillus subtilis, Escherichia coli, Enterococcus faecalis, Pseudomonas aeruginosa, MRSA, H[2]O[2]-producing lactobacilli, Bacillus brevis FMC3, Bacillus megaterium DSM32, Micrococcus luteus LA 2971, Mycobacterium smegmatis RUT, Listeria monocytogenes SCOTT A, Streptococcus thermophilus, Pseudomonas fluorescens, and Yersinia enterocolitica O:3 P 41797, Propionibacterium acnes (ATCC 6919), Staphylococcus epidermidis, Propionibacterium acnes, Helicobacter pylori, and Staphylococcus aureus ME/GM/TC resistant (ATCC 33592) (Abdel-Fatah et al., 2002; Angioni et al., 2004; Antonio et al., 2009; Bogdadi et al., 2007; Bozin et al., 2007; Cordeiro et al., 2006; Elgayyar et al., 2001; Erdogrul, 2002; Fu et al., 2007b; Gutierrez et al., 2008a; Jirovetz et al., 2005; Klancnik et al., 2009; Larrondo et al., 1995; Lopez et al., 2005; Luqman et al., 2007; Matsubara et al., 2003; Moreno et al., 2006; Oskay & Sari, 2007; Panizzi et al., 1993; Quave et al., 2008; Ramirez et al., 2006; Rasooli et al., 2008b; Santoyo et al., 2005; Schwiertz et al., 2006; Scollard et al., 2009; Tada et al., 2010; Verluyten et al., 2004; Watt et al., 2007; Weckesser et al., 2007). In laboratory research, essential oils of rosemary with the highest quantity of camphor, borneol, and verbenone were found to exert the highest levels of antimicrobial activity (Santoyo et al., 2005). On the basis of in vitro study, the antibacterial effects of rosemary may be attributed to its ability to prevent cell adhesion (Sandasi, Leonard, & Viljoen, 2010) or biofilm production (Quave et al., 2008; Rasooli et al., 2008b). Rosemary oil exhibited potent quorum sensing inhibition, which may reduce the pathogenicity, antibiotic resistance, and biofilm formation during infection (Szabo et al., 2009). Rosemary oil significantly damaged Propionibacterium acnes bacterial bodies, as evidenced by reductions in the length, width, and height of the bacteria, loss of shape, and leakage of cytoplasm out of the bacterial body (Fu et al., 2007a).

- The major components of a chloroform extract of the aerial parts of *Rosmarinus officinalis* had minimum inhibitory concentrations ranging from 16–64 mcg/ml against strains of Staphylococcus aureus possessing efflux mechanisms of resistance (Oluwatuyi et al., 2004). A methanol extract of *Rosmarinus officinalis* leaf had a Helicobacter pylori minimal inhibitory concentration (MIC) of 25 mcg/ml (Mahady et al., 2005).
- Rosemary essential oil exhibited some inhibition against sheep and deer rumen microorganisms in vitro (Oh, Jones, & Longhurst, 1968). Oleoresin rosemary (1%) resulted in an approximately 1-log CFU/g reduction in the populations of Escherichia coli O157:H7, Salmonella typhimurium, and Listeria monocytogenes in ground beef after nine days of refrigerated storage (Ahn et al., 2004). Rosemary at 1% (weight/volume) in Mueller-Hinton (MH) agar showed antimicrobial effects on Shigella, with an MIC ranging from 0.5 to 1% (weight/volume) depending on the used Shigella strain (Bagamboula et al., 2001). In food safety tests, rosemary extracts also inhibited common pathogenic microorganisms significant in food hygiene (Bagamboula, Uyttendaele, & Debevere, 2003; Bentayeb, Rubio, Batlle, & Nerin, 2007; Brooks et al., 2008; Carraminana, Rota, Burillo, & Herrera, 2008; da Silva et al., 2008; Del Campo, Amiot, & Nguyen-The, 2000; Fabio, Corona, Forte, & Quaglio, 2003; Fan, Sommers, & Sokorai, 2004; Gutierrez et al., 2008a; Gutierrez, Rodriguez, Barry-Ryan, & Bourke, 2008b; Ismail, Dea, Abd El-Rahman, Yassien, & Beuchat, 2001; Karpinska-Tymoszczyk, 2008; Keokamnerd, Acton, Han, & Dawson, 2008; Lee, Gwon, Kim, & Moon, 2009; Lee, Williams, Sloan, & Littell, 1997; Lopez-Munoz et al., 2006; Mangena & Muyima, 1999; Martinez et al., 2006; Pozo-Insfran, Follo-Martinez, Talcott, & Brenes, 2007; Rasooli et al., 2008a; Rota et al., 2004; Ruiz,

Williams, Djeri, Hinton, & Rodrick, 2009; Sasse, Colindres, & Brewer, 2009; Scollard et al., 2009; Seyfert et al., 2005; Suhr & Nielsen, 2003; Tovar, Salafranca, Sanchez, & Nerin, 2005; Valero & Salmeron, 2003). It has been suggested that rosemary's food preservation effects may be attributed to its phenolic constituents (Schwarz & Ternes, 1992a), including carnosol and carnosic acid (Smith, Halliwell, & Aruoma, 1992). This preservative effect may be due to rosemary's antioxidant capability (Baardseth, 1989; Bhale, Xu, Prinyawiwatkul, King, & Godber, 2007; Botsoglou, Govaris, Giannenas, Botsoglou, & Papageorgiou, 2007; Campbell, Drake, & Larick, 2003; Gramza-Michalowska, Korczak, & Regula, 2007; Jaswir, Che Man, & Hassan, 2005; Martinez-Tome et al., 2001; Negroni, D'Agostina, & Arnoldi, 2001; Nissen, Mansson, Bertelsen, Huynh-Ba, & Skibsted, 2000; Pezo, Salafranca, & Nerin, 2008; Rudzinska, Korczak, Gramza, Wasowicz, & Dutta, 2004; Talcott, Brenes, Pires, & Pozo-Insfran, 2003), possibly through the maintenance of alpha-tocopherol (Beddows, Jagait, & Kelly, 2000) or the inhibition of lipid peroxidation (LPO) (Chang & Chen, 1998).

- *Anticancer effects*: Rosemary and its constituents may exert anticancer effects through a variety of mechanisms, including the induction of apoptosis and inhibition of tumor formation. Alcohol extracts of rosemary have shown strong antitumorigenic activity (Ho et al., 2000; Kahkonen et al., 1999). In mice, topical rosemary extract prolonged the latency period of 7,12-dimethylbenz[a]anthracene (DMBA)-induced tumor occurrence, and decreased tumor incidence, tumor burden, and tumor yield (Sancheti & Goyal, 2006a, 2006b), possibly due to the extract's ursolic acid content (Huang et al., 1994). Ursolic acid, a constituent of rosemary, reduced interleukin-1 beta (IL-1beta) or tumor necrosis-alpha (TNF-alpha)-induced rat C6 glioma cell invasion in vitro with no effects on cell proliferation or cell cytotoxicity (Huang et al., 2009). Activity and expression of matrix metalloproteinase-9 (MMP-9) (the target gene of the transcription factor nuclear factor-kappaB (NF-kappaB)) was also eliminated by ursolic acid, and the upregulated levels of IkappaBalpha attenuated the nuclear translocation of p65, and suppressed IL-1beta- or TNF-alpha-induced activation of protein kinase C-zeta (PKC-zeta). However, in another research, intraperitoneally injected carnosol from rosemary inhibited DMBA-induced tumors, whereas ursolic acid did not (Singletary et al., 1996). In leukemia laboratory study, carnosic acid inhibited proliferation of human myeloid leukemia without induction of apoptotic or necrotic cell death (Steiner et al., 2001). Carnosic acid decreased viability of the human promyelocytic leukemia cell line HL-60 and induced G(1) arrest and apoptosis in vitro (Wang et al., 2008). This effect was augmented by the addition of arsenic trioxide, which resulted in the upregulation of p27 and activation of caspase-9, possibly mediated by the induction of phosphatase and tensin homologue (PTEN) expression. Rosemary essential oil reduced the expression of the gene bcl-2 and increased the expression of bax in the liver cancer cell line HepG2 in vitro (Wei et al., 2008). Crude ethanolic rosemary extract exhibited antiproliferative effects on human leukemia and breast cancer cells in vitro (Cheung & Tai, 2007). Rosmarinic acid inhibited cytokine-induced mesangial cell proliferation and suppressed platelet-derived growth factor (PDGF) and c-myc mRNA expression in PDGF-stimulated mesangial cells in vitro (Makino et al., 2000).
- Rosemary extracts demonstrated tumor inhibition in vitro as well as in animal study (Arican, 2009; Singletary & Nelshoppen, 1991). When combined with 1 alpha, 25-dihydroxyvitamin D(3) (1,25D(3)), rosemary extract increased the survival of mice with acute myeloid leukemia and exhibited strong antiproliferative and differentiation effects (Shabtay et al., 2008). The results of a study conducted by Steiner et al. (2001) indicate that carnosic acid is capable of antiproliferative action in leukemic cells

and can cooperate with other natural anticancer compounds in growth-inhibitory and differentiating effects. Rosemary extracts have been shown to induce quinine reductase activity and glutathione-S-transferase in vitro and in animal study (Singletary & Rokusek, 1997; Tawfiq et al., 1994). Tumor development (secondary sources) may be reduced by decrease in the expression of the proinflammatory gene cyclooxygenase-2 (COX-2). In colon cancer, HT-29 cells in vitro, rosmarinic acid, a constituent of rosemary, reduced 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced COX-2 promoter activity ($p < .05$) and protein levels ($p < .05$), reduced TPA-induced transcription from a control activator protein-1 (AP-1) promoter-luciferase construct, and repressed binding of the AP-1 factors c-Jun ($p < .01$) and c-Fos ($p < .05$) to COX-2 promoter oligonucleotides harboring a cAMP-response element (CRE) (Scheckel et al., 2008). Furthermore, in a nonmalignant breast epithelial cell line (MCF10A), rosmarinic acid antagonized the stimulatory effects of TPA on COX-2 protein expression, the recruitment of c-Jun and c-Fos, and activation of the extracellular signal-regulated protein kinase-1/2. Supercritical fluid SF-CO2 treatment of *Rosmarinus officinalis* L. fresh leaves exhibited viability suppression and tumor necrosis factor alpha (TNF-alpha) production in Hep 3B cells (Peng et al., 2007). In a mouse model of colonic tumorigenesis, dietary administration of carnosol, a constituent of rosemary, decreased intestinal tumor multiplicity (Moran, Carothers, Weyant, Redston, & Bertagnolli, 2005). Treatment of intestinal tissue from tumorigenic mice with carnosol restored both E-cadherin and beta-catenin to these enterocyte membranes in vitro, resulting in a phenotype typical of wild-type mice. Furthermore, treatment of wild-type mouse intestine with the phosphatase inhibitor pervanadate removed E-cadherin and beta-catenin from the lateral membranes of enterocytes, resulting in tissues that resembled the tumorigenic mice.

- In a mouse model, carnosic acid and 1 alpha, 25-dihydroxyvitamin D(3), a powerful differentiation agent, resulted in a strong cooperative antitumor effect, without inducing hypercalcemia (Sharabani et al., 2006). Rosemary extract's antiproliferative effects may be due to its concentration-dependent capability of selectively activating a fusion receptor of peroxisome proliferator-activated receptor-gamma, a ligand-activated transcription factor (Rau et al., 2006).
- Carnosol phenolic compound extracted from rosemary has been reported to have anticancer activity against B-lineage leukemias, and possibly other types of cancers that express high levels of the protective protein, Bcl-2 (Dorrie, Sapala, & Zunino, 2001). On the basis of cell line research, an ethanol extract from rosemary reduced genotoxic activity and appeared to exhibit a protective effect against oxidative damage to DNA as a consequence of the scavenging of both *OH radicals and singlet oxygen (Slamenova, Kuboskova, Horvathova, & Robichova, 2002). Furthermore, rosemary extracts inhibited benzo(a)pyrene- or aflatoxin B1-induced DNA adduct formation by strongly inhibiting CYP450 activities and inducing the expression of glutathione S-transferase (Mace, Offord, Harris, & Pfeifer, 1998). These results in human cell models give some insight into the different mechanisms involved in the chemopreventive action of both natural and synthetic compounds in relation to phase-I and phase-II enzymes. Based on laboratory study, carnosic acid (2.5–10 mcM) has been shown to inhibit some myeloid lymphomas (Steiner et al., 2001).
- Potential mechanisms of rosemary's chemoprotective action include inhibition of the metabolic activation of procarcinogens catalyzed by the phase-I cytochrome P450 enzymes and induction of the detoxification pathway catalyzed by the phase-II enzymes, such as glutathione S-transferase (Offord et al., 1997). Carnosol suppresses

nitric oxide (NO) production and inducible NO synthase gene expression, possibly by inhibiting NF-kappaB activation (Lo, Liang, Lin-Shiau, Ho, & Lin, 2002). These effects may be related to the chemopreventative effects of rosemary.

- An increase in the activation of caspase-3 during coadministration of carnosol and chemotherapeutic agents in high-risk pre-B acute lymphoblastic leukemia has been observed in vitro (Zunino & Storms, 2009). It was further observed that a lower percentage of caspase-3 positive cells progressed to an apoptotic phenotype during coadministration compared to the treatment with chemotherapeutics alone. Phytochemicals found in rosemary, such as carnosic acid, carnosol, rosmarinic acid, and ursolic acid, stimulated the ATPase activity of P-glycoprotein in P-glycoprotein-overexpressing human carcinoma KB-C2 cells (Nabekura et al., 2009). In addition, KB-C2 cells were sensitized to vinblastine cytotoxicity by carnosic acid, indicating reversal of multidrug resistance by carnosic acid.
- In laboratory tests, rosemary extracts have been observed to exhibit anticancer activities (Leal et al., 2003). Specifically, carnosol from rosemary extract inhibited the invasion of highly metastatic mouse melanoma B16/F10 cells in vitro (Huang, Ho, Lin-Shiau, & Lin, 2005). Further study indicates that carnosol targets MMP-mediated cellular events in cancer cells. In rat study, oral administration of rosemary essential oil prior to the administration of mutagenic compounds significantly inhibited mutagenesis, which may be due to rosemary essential oil's relatively high percentage of highly antioxidant phenolic compounds (Fahim et al., 1999). Various constituents of rosemary, including rosmariquinone, inhibited the mutagenicity of N-methyl-N-nitrosourea (MNU) and N-Nitroso-bis-(2-hydroxy-propyl) amine (BHP) in V79 cells and inhibited ornithine decarboxylase activity in mouse skin (Cuppett et al., 1995). Antimutagenic effects of carnosic acid and carnosol have been demonstrated in Ames tester strain TA102 (Minnunni, Wolleb, Mueller, Pfeifer, & Aeschbacher, 1992). Oleoresin rosemary reduced 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine formation in fried beef patties and other foods (Awney & Sindi, 2010; Balogh et al., 2000; Persson, Graziani, Ferracane, Fogliano, & Skog, 2003; Zochling, Murkovic, & Pfannhauser, 2002).
- *Anti-diabetic effects*: In rabbit study, the i.m. administration of the rosemary leaf volatile oil (25 mg/kg) produced 20% ($p < .05$), 27% ($p < .01$), and 55% ($p < .001$) increase in plasma glucose levels in normal rabbits at 60-, 90- and 120-min intervals, respectively (al Hader et al., 1994). This injection also decreased serum insulin by 30% ($p < .002$) in comparison with that of control rabbits at the 30-min interval. In alloxan diabetic rabbits, rosemary volatile oil increased fasting plasma glucose levels by 17% ($p < .05$) when compared with controls (Bakirel et al., 2008). However, in another animal study, administration of rosemary extract significantly lowered blood glucose levels and increased serum insulin concentrations (Bakirel et al., 2008; Erenmemisoglu et al., 1997).
- In laboratory tests, water extracts of three different clonal lines of rosemary (rosemary LA (71.4%), rosemary 6 (68.4%), and rosemary K-2 (67.8%)) showed significant alpha-glucosidase inhibitory activity; rosmarinic acid had an alpha-glucosidase inhibitory activity of 85.1% (Kwon et al., 2006).
- Rosemary extract prepared with 80% aqueous ethanol is capable of selectively activating Gal4-PPARgamma fusion receptor, in a concentration-dependent manner, with an EC_{50} value of 22.8 $\pm$ 8.4 mg/L (Rau et al., 2006). The phenolic diterpene compounds, carnosol and carnosic acid, are the active principles of these extracts, showing EC_{50} values of 41.2 $\pm$ 5.9 mcM and 19.6 $\pm$ 2.0 mcM, respectively. These

findings suggest that the glucose-lowering effect of rosemary may be attributed to PPARgamma activation.

- The metabolism of essential elements in the liver, including Zn, Cu, Fe, Mg, and Mn, may play a role in the pathogenesis and progress of diabetes (secondary sources). In diabetic rats, rosemary extract decreased Mn level in the liver (Prat et al., 2009).
- Rosemary extract inhibited glycation of albumin in vitro; this effect may be related to its high phenolic content (Dearlove et al., 2008; Hsieh et al., 2007).
- *Antifungal effects*: In several in vitro studies, rosemary has shown weak antifungal activity (Angioni et al., 2004; Boyraz & Ozcan, 2005; Daferera et al., 2000; Durakovic & Durakovic, 1979; Giordani et al., 2004; Karanika, Komaitis, & Aggelis, 2001; Lopez-Munoz et al., 2006; Luqman et al., 2007; Ozcan, 2005; Ozcan & Chalchat, 2008; Pozzatti et al., 2008; Shin, 2003; Steinmetz, Moulin-Traffort, & Regli, 1988; Tantaoui-Elaraki & Beraoud, 1994). An inductive effect has been observed on fungal growth, especially toward Fusarium graminearum (Angioni et al., 2004). Rosemary essential oils had some inhibitory effect on the radial growth and conidial germination of Penicillium digitatum, though conidial production was not affected by the oil at concentrations up to 1,000 mcg/ml (Daferera et al., 2000). In contrast, other research has shown that rosemary extract can act as a substrate for mycelial growth, sporulation, and aflatoxin production (Llewellyn, Burkett, & Eadie, 1981).
- *Anti-inflammatory effects*: Various rosemary extracts have exhibited anti-inflammatory effects in animal models (Altinier et al., 2007). Rosemary has been shown to interrupt the pathway that activates nuclear transcription factor kappaB in vitro (Aggarwal & Shishodia, 2004). Carnosic acid and carnosol from rosemary have been shown to activate peroxisome proliferator-activated receptor-gamma, inhibit the formation of pro-inflammatory leukotrienes in intact human polymorphonuclear leukocytes, potently antagonize intracellular Ca(2+) mobilization induced by a chemotactic stimulus, and attenuate the formation of reactive oxygen species (ROS) and the secretion of human leukocyte elastase (Poeckel et al., 2008). Rosmanol, a phenolic constituent of rosemary, suppressed the lipopolysaccharide (LPS)-induced phosphorylation of ERK1/2, p38 mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/Akt signaling (Lai et al., 2009). As a result, it may downregulate inflammatory iNOS and COX-2 gene expression by inhibiting the activation of NF-kappaB and STAT3 through interfering with the activation of PI3K/Akt and MAPK signaling. Carnosic acid from rosemary inhibited TNF-alpha-induced migration of human aortic smooth muscle cells in vitro, accompanied by inhibition of MMP-9 activity and expression and suppression of TNF-alpha-induced production of ROS and the nuclear translocation of NF-kappaB p50 and p65 (Yu et al., 2008).
- Carnosol from rosemary inhibited LPS- and interferon-gamma (IFN-gamma)-induced nitrite production by mouse peritoneal cells by more than 50% at 2.5–10 mcM (Chan et al., 1995). Rosemary extract inhibited the enzymatic activity of human leukocyte elastase HLE in vitro (Baylac & Racine, 2004). Rosemary essential oil significantly reduced the volume of pleural exudate and slightly decreased the number of cells that had migrated during the carrageenan-induced edema testing (Takaki et al., 2008).
- Rosmarinic acid isolated from *Rosmarinus officinalis* inhibited the in vitro immunohemolysis of antibody-coated sheep erythrocytes by guinea pig serum because of the inhibition of the C3-convertase of the classical complement pathway (Englberger et al., 1988). Rosmarinic acid (0.316–3.16 mg/kg, i.m.) also reduced paw edema induced by cobra venom factor in rat, and, at 1–100 mg/kg, orally, inhibited passive cutaneous anaphylaxis in rat. In addition, at 10 mg/kg, i.m., rosmarinic acid

impaired in vivo activation by heat-killed *Corynebacterium parvum* (intraperitoneally) of mouse macrophages. Rosmarinic acid (0.1–10 mg/kg, i.m.) did not inhibit t-butyl hydroperoxide-induced paw edema in the rat, indicating selectivity for complement-dependent processes.

- In mice, intratracheal exposure to volatile constituents of rosemary inhibited the increase in the number of eosinophils, neutrophils, and mononuclear cells around airways and those in the bronchoalveolar lavage fluid, and suppressed the expression of interleukin (IL)-13 (Inoue et al., 2005).
- *Antinociceptive effects*: In animal study, rosemary produced significant antinociceptive effects on different types of induced pain through various mechanisms of action (Gonzalez-Trujano et al., 2007; Martinez et al., 2009). Rosemary oil extract administration in mice reduced the number of writhing movements induced by the intraperitoneal administration of acetic acid solution and inhibited licking and shaking behaviors in both the early (neurogenic pain) and the late (inflammatory pain) phases of the formalin test (Gonzalez-Trujano et al., 2007). These effects may be modulated by the serotonin system (i.e., 5-HT1A receptors) or the endogenous opioid system (Martinez et al., 2009).
- *Anti-obesity effects*: In mice fed with a high-fat diet, rosemary leaf extract induced a significant reduction of weight and fat mass gain, an effect that may be related to the inhibition of pancreatic lipase activity, as determined in vitro (Harach et al., 2009). Administration of the lower dose of rosemary extract (20 mg/kg of body weight) was ineffective on all the measured parameters. Carnosic acid and carnosol from rosemary inhibited the in vitro differentiation of mouse preadipocytes, 3T3-L1 cells, into adipocytes, possibly mediated by the activation of the ARE and induction of phase-2 enzymes (Takahashi et al., 2009). Using cDNA microarray analysis, it was shown that phase-2 enzymes (Gsta2, Gclc, Abcc4, and Abcc1), all of which are involved in the metabolism of glutathione (GSH), constituted four of the top five carnosic acid-induced genes.
- *Antioxidant effects*: Rosemary's oxygen radical absorbance capacity (ORAC) value was reported as 1.66 (Bentayeb, Vera, Rubio, & Nerin, 2009). Numerous laboratory tests indicate that rosemary and its extracts have antioxidant properties (Choi et al., 2002a; Dragan et al., 2007; Galobart et al., 2001; Ho et al., 2000; Ibanez et al., 2000, 2003; Kahkonen et al., 1999; Kaliora & Andrikopoulos, 2005; Kim & Kim, 2003; Kim, Han, Moon, & Rhee, 1995; Lamaison, Petitjean-Freytet, & Carnat, 1991; Leal et al., 2003; Makino et al., 2002; Mirshekar, Dastar, & Shabanpour, 2009; Moreno et al., 2006; Nakatani, 2000; Okamura et al., 1994; Ozcan, 2003; Pukalskas, van Beek, & de Waard, 2005; Rababah et al., 2004; Ramirez et al., 2006; Siurin, 1997; Stashenko, Puertas, & Martinez, 2002). In addition, a number of constituents have been noted for their high antioxidant properties, including carnosol (Aruoma, 1999; Haraguchi et al., 1995; Masuda et al., 2005; Saenz-Lopez, Fernandez-Zurbano, & Tena, 2002; Zeng et al., 2001), carnosic acid (Aruoma, 1999; Aruoma, Halliwell, Aeschbach, & Loligers, 1992; Costa et al., 2007; Geoffroy, Lambelet, & Richert, 1994; Haraguchi et al., 1995; Hosny et al., 2002; Lee & Shibamoto, 2002; Masuda, Inaba, & Takeda, 2001; Masuda et al., 2002; Munne-Bosch et al., 1999a; Perez-Fons et al., 2010; Saenz-Lopez et al., 2002; Wellwood & Cole, 2004), rosmanol (Haraguchi et al., 1995; Zeng et al., 2001), epirosmanol (Haraguchi et al., 1995; Zeng et al., 2001), hesperidin (Okamura et al., 1994), 1,8-cineole (Saito et al., 2004), and select phenolic diterpenes (Gobert et al., 2009; Munne-Bosch et al., 1999b; Schwarz, Ternes, &

Schmauderer, 1992c; Yesil-Celiktas, Nartop, Gurel, Bedir, & Vardar-Sukan, 2007). Rosemary extract decreased antioxidant enzyme activity, LPO and ROS levels (significantly in the heart and brain), nitric oxide synthase (NOS) in the heart, and LPO and ROS levels in different brain tissues in aged rats (Posadas et al., 2009). Rosemary exhibited 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical-scavenging activity in vitro (Bhale et al., 2007; Monino et al., 2008; Topal, Sasaki, Goto, & Otles, 2008), an effect that may be related to its carnosic acid, carnosol, and, in particular, rosmarinic acid content (Kuhlmann & Rohl, 2006; Papageorgiou, Gardeli, Mallouchos, Papaioannou, & Komaitis, 2008a; Papageorgiou et al., 2008b). Diterpenes and genkwanin from rosemary have shown membrane-rigidifying effects, which may contribute to their antioxidant capacity through hindering diffusion of free radicals (Perez-Fons, Aranda, Guillen, Villalain, & Micol, 2006).

- The rosemary extract (Herbor 025) inhibited peroxidation of phospholipid liposomes with 50% inhibition concentration values of 0.0009% (volume/volume, v/v) (Aruoma, 1999; Aruoma et al., 1996). Herbor 025 reacted with trichloromethylperoxyl radical with calculated rates of 2.7×10^4/s. The main active components in the herbal preparation, carnosol and carnosic acid, at 0.05% (v/v), reacted with a rate constant of $(1–3) \times 10^6$/M s. Rosemary extract showed good antioxidant activity in the Rancimat test, especially in lard. Carnosic acid and carnosol reduced membrane damage in Cac o-2 cells by 40–50% in vitro when stressed by oleic acid hydroperoxide (OAHPx) as a means to measure oxidative stress (Wijeratne & Cuppett, 2007). Furthermore, carnosic acid and carnosol inhibited lipid peroxidation by 88–100% and 38–89%, respectively, under oxidative stress conditions and significantly lowered DNA damage induced by OAHPx. Rosemary also showed DNA protective effects against H_2O_2-induced DNA damage in vitro (Aherne, Kerry, & O'Brien, 2007).
- Rosemary extracts have demonstrated NO- and iNOS expression-suppressing effects in vitro without any evidence of NO-scavenging ability (Tsai, Tsai, Yu, & Ho, 2007). The antioxidant effects of rosmarinic acid have also been noted to be partly due to its ability to chelate heavy metals, such as iron, and result in decreased nonheme-iron absorption and utilization (Samman et al., 2001).
- Rosemary's scavenging effects are stronger than vitamin C, but are weaker than vitamin E, as shown in a comparison study conducted by Zhao, Li, He, Cheng, and Xin (1989). Crude fresh rosemary extracts were found to have excellent antioxidant activity, which was almost identical to that of pure delta-tocopherol and higher than that of butylated hydroxytoluene (BHT); extracts prepared from distilled rosemary showed the lowest activity (Almela, Sanchez-Munoz, Fernandez-Lopez, Roca, & Rabe, 2006). The drying or distillation treatments used with the plant material strongly affected the content of rosmarinic acid and carnosic acid, two compounds with higher antioxidant activity. Treatment with supercritical CO_2 is proposed for deodorizing antioxidant rosemary extracts obtained by steam distillation and Soxhlet extraction (Lopez-Sebastian et al., 1998). Of a number of investigated processes, it was determined that ideal extraction (maximizing yield and antioxidant capacity) was obtained at 5000 psi and 80°C (Chang et al., 2008). Research has shown that cooking and storage can significantly affect antioxidant uptake in various culinary herbs, including rosemary (Chohan et al., 2008). Laboratory study has indicated that rosmarinic acid also has antioxidant capabilities at stomach acidity levels (pH 2) (Cervellati, Renzulli, Guerra, & Speroni, 2002).

- Rosemary extract may inhibit cholesterol oxidation product formation from the nucleus and the lateral chain of the cholesterol molecule (Valenzuela, Sanhueza, & Nieto, 2003; Valenzuela, Sanhueza, Alonso, Corbari, & Nieto, 2004).
- In rat study, a spice mixture, including rosemary, lowered phospholipid hydroperoxides in red blood cells (65–74% of the non-supplemented control mice) (Asai, Nakagawa, & Miyazawa, 1999). During a screening for toxic quinoid species, rosemary was found to produce glutathione adducts (Johnson, Bolton, & van Breemen, 2001).
- *Antiparasitic effects*: In turkey poults, an oral herbal product with extracts from cinnamon, garlic, lemon, and rosemary reduced the mortality of birds infected with the protozoan parasite Histomonas meleagridis (Hafez & Hauck, 2006). A mixture of carvacrol, cassia oil, an essential oil mixture containing thyme and rosemary, and a *Quillaja saponaria* saponin exerted antiparasitic effects in vitro (Grabensteiner, Arshad, & Hess, 2007). The methanol extract rosemary leaves completely inhibited the motility of cultured epimastigotes of *Trypanosoma cruzi* at a concentration of 2 mg/ml after 2 hr of incubation (Abe et al., 2002). The activity-guided fractionation of the MeOH extract resulted in the isolation of three triterpene acids: betulinic, oleanolic, and ursolic acids. Ursolic acid stopped the movement of all T. cruzi epimastigotes at the minimum concentration (MC_{100}) of 40 mcg/ml (88 mcM) after 48 hr of incubation. Oleanolic acid was less active (MC_{100}) at 250 mcg/ml (550 mcM), and betulinic acid was practically inactive.
- *Antispasmodic effects*: The antispasmodic effects of alcoholic extract of *Rosmarinus officinalis* on isolated guinea pig ileum using acetylcholine and histamine as spasmogens have been examined (Forster et al., 1980); however, the results were not clearly described in the abstract.
- *Antiviral activity*: A liquid, deodorized rosemary extract (Herbor 025) inhibited human immunodeficiency virus (HIV) infection in vitro at very low, though cytotoxic, concentrations (Aruoma, 1999). However, purified carnosol from rosemary extract exhibited anti-HIV activity at a concentration of 8 mcM, which was not cytotoxic. Herbor 025 promoted some DNA damage in the copper–phenanthroline and the bleomycin–iron systems. The inhibitory activity of the diterpenes carnosic acid and carnosol (isolated from rosemary), rosmanol, and semisynthetic derivatives were tested against HIV-1 protease, with carnosic acid showing the strongest inhibitory effect ($IC_{90} = 0.08$ mcg/ml) (Paris et al., 1993). The same compound was also assayed against HIV-1 virus replication ($IC_{90} = 0.32$ mcg/ml). The cytotoxic TC90 on H9 lymphocytes was 0.36 mcg/ml, which is very close to the effective antiviral dose. In addition, the tested compounds did not inhibit cellular aspartic proteases cathepsin D and pepsin at concentrations ranging up to 10 mcg/ml.
- In vitro study has indicated that aqueous rosemary extract has high and time-dependent antiviral activity against herpes simplex type 1, herpes simplex type 2, and an acyclovir-resistant strain of herpes simplex type 1 (Mancini, Torres, Pinto, & Mancini, 2009; Nolkemper, Reichling, Stintzing, Carle, & Schnitzler, 2006; Reichling et al., 2008). These results indicate that the extract affects herpes simplex before adsorption, but has no effect on intracellular virus replication. However, rosemary essential oil showed only partial antiviral activity against herpes simplex at higher concentrations (Vijayan, Raghu, Ashok, Dhanaraj, & Suresh, 2004).
- *Biliary effects*: Rosemary may exert pharmacological activity on Oddi's sphincter (Giachetti, Taddei, & Taddei, 1986); however, the details were not described in the abstract.

- *Bone effects*: Rosemary, rosemary essential oil, and their monoterpene components inhibited bone resorption when added to rat food (Muhlbauer et al., 2003).
- *Cardiovascular effects*: The water extracts of rosemary inhibited rabbit lung ACE by 90.5% in vitro (Kwon et al., 2006).
- *Coagulation effects*: Rosemary has shown significant antithrombotic activity in vitro and in vivo in mice, but was not observed to affect flow-mediated vasodilation (Yamamoto et al., 2005). The antithrombotic mechanism may involve a direct inhibitory effect on platelets. A Western diet containing 0.55% and 5% dried rosemary significantly inhibited arterial thrombus formation in mice; 5% rosemary exerted a significant antithrombotic effect and inhibited platelet reactivity (though no effect on bleeding time was observed); however, it enhanced flow-mediated vasodilation (Naemura et al., 2008). Carnosic acid significantly inhibited collagen-, arachidonic acid-, U46619- and thrombin-induced washed rabbit platelet aggregation in a concentration-dependent manner, while it failed to inhibit PMA- (a direct PKC activator) and ADP-induced platelet aggregation (Lee et al., 2007). However, carnosic acid had no effect on the formation of arachidonic acid-mediated thromboxane A2 and prostaglandin D2.
- In a study on rats injected with rabbit anti-rat thymocyte serum, oral rosmarinic acid decreased fibronectin and fibrin in the glomerulus (Makino et al., 2002).
- *Dermatologic effects*: In patients with experimentally induced contact dermatitis, rosemary extracts induced a protective effect against dermatitis (Fuchs, Schliemann-Willers, Fischer, & Elsner, 2005).
- A water-soluble extract of rosemary inhibited the ultraviolet (UV)-induced upregulation of matrix metalloproteinase-1 (MMP-1) gene transcription in vitro, a process that has been shown to be involved in the development of skin photodamage and inhibited the release of cytokines IL-1-alpha and IL-6, which participate in the upregulation of MMP-1 induced by the UV exposure (Martin et al., 2008). This effect may be modulated, at least in part, by carnosic acid, a rosemary constituent (Offord et al., 2002). At a concentration of 2 mcL/ml, rosemary extracts demonstrated high levels of absorption in the UV B region during a test of their effectiveness as potential sunscreen agents (Garcia, Dos Santos, Da Salva, Di Giacomo, & Soares, 1992).
- Treatment with a natural antioxidant from rosemary extract provided notable protection against stress-induced modifications of cellular sulfdryl and carbonyl content in human skin fibroblasts, maintaining functional levels of cytoprotective heat shock protein 70 (Calabrese et al., 2001). These results point to the possible involvement of redox mechanisms in the heat shock signal transduction pathway, which may play an important regulatory role in the genetic mechanisms of tolerance to oxidative stress. In both in vitro and in vivo experiments, an alcoholic extract of rosemary leaves, Rosm1, had a strong antioxidant activity and was capable of inhibiting oxidative alterations to skin surface lipids (Calabrese et al., 2000).
- *Diuretic effects*: In vitro evidence suggests that rosemary may enhance the effects of herbal agents used for diuresis (Laitinen et al., 2004; Pyevich & Bogenschutz, 2001).
- *Food microbiology*: Rosemary essential oil exhibited some inhibition against sheep and deer rumen microorganisms in vitro (Oh et al., 1968). Oleoresin rosemary (1%) resulted in an approximately 1-log CFU/g reduction in the populations of Escherichia coli O157:H7, Salmonella typhimurium, and Listeria monocytogenes in

ground beef after nine days of refrigerated storage (Ahn et al., 2004). Rosemary at 1% (weight/volume, w/v) in MH agar showed antimicrobial effects on Shigella, with an MIC ranging from 0.5–1% (w/v) depending on the used Shigella strain (Bagamboula et al., 2001). In food safety tests, rosemary extracts also inhibited common pathogenic microorganisms that are significant in food hygiene (Bagamboula et al., 2003; Bentayeb et al., 2007; Brooks et al., 2008; Carraminana et al., 2008; da Silva et al., 2008; Del Campo et al., 2000; Fabio et al., 2003; Fan et al., 2004; Gutierrez et al., 2008a, 2008b; Ismail et al., 2001; Karpinska-Tymoszczyk, 2008; Keokamnerd et al., 2008; Lee et al., 2009, 1997; Lopez-Munoz et al., 2006; Mangena & Muyima, 1999; Martinez et al., 2006; Pozo-Insfran et al., 2007; Rasooli et al., 2008a; Rota et al., 2004; Ruiz et al., 2009; Sasse et al., 2009; Scollard et al., 2009; Seyfert et al., 2005; Suhr & Nielsen, 2003; Tovar et al., 2005; Valero & Salmeron, 2003). It has been suggested that the food preservation effects of rosemary may be attributed to its phenolic constituents (Schwarz & Ternes, 1992a), including carnosol and carnosic acid (Smith et al., 1992). This preservative effect may be due to the antioxidant capability of rosemary (Baardseth, 1989; Bhale et al., 2007; Botsoglou et al., 2007; Campbell et al., 2003; Gramza-Michalowska et al., 2007; Jaswir et al., 2005; Martinez-Tome et al., 2001; Negroni et al., 2001; Nissen et al., 2000; Pezo et al., 2008; Rudzinska et al., 2004; Talcott et al., 2003), possibly through the maintenance of alpha-tocopherol (Beddows et al., 2000) or the inhibition of lipid peroxidation (Chang & Chen, 1998).

- In cooked ground beef, oleoresin rosemary (Herbalox®) retarded the formation of thiobarbituric acid-reactive substances (TBARS) by 92% after nine days, and significantly lowered the hexanal content throughout the storage period (Ahn, Grun, & Mustapha, 2007). Dietary supplementation of rosemary and sage in addition to alpha-tocopheryl acetate to broilers resulted in decrease in TBARS (Lopez-Bote et al., 1998; Smet et al., 2008) and smaller concentations of total cholesterol oxidation products (COPS) (Lopez-Bote et al., 1998). Rosemary has also been shown to delay the oxidation of the lipid fraction of products, such as minced meat and sausage, to prevent the onset of rancid taste due to aging (Du & Ahn, 2002; Karpinska, Borowski, & Danowska-Oziewicz, 2000).
- *Gastrointestinal effects*: In various experimental models, *Rosmarinus officinalis* L. crude hydroalcoholic (70%) extract decreased the ulcerative lesion index in rats, with a pharmacological mechanism of likely no relation to NO or prostaglandins (Dias et al., 2000). However, the activity may be due to substances that increase the mucosal non-protein sulfhydryl group's content or the activity of antioxidant compounds found in the crude hydroalcoholic extract, which can react with N-ethylmaleimide. No antisecretory activity was observed on pyloric ligation model.
- *Germination inhibitory effects*: The essential oils obtained from rosemary (*Rosmarinus officinalis* L.), thyme (*Thymus vulgaris* L.), and savory (*Satureja montana* L.) demonstrated inhibitory effects on weed germination (Angelini et al., 2003).
- *Growth-enhancement effects (in animals)*: Rosemary has been added to animal feed in order to improve digestibility of the feed and growth and intestinal flora status of broiler chicks (Cross et al., 2007). Labiatae extract from rosemary has been also found to enhance growth rates of broiler chickens (Hernandez et al., 2004).

- *Hepatic effects*: Rosemary has demonstrated hepatoprotective effects in animal study (Amin & Hamza, 2005; Fahim et al., 1999; Hoefler et al., 1987; Sotelo-Felix et al., 2002b). Animals pretreated with water extracts retained livers that, for the most part, were found to be histologically normal. In addition, rosemary blocked the induced elevated levels of alanine aminotransferase and aspartate aminotransferase in serum, likely by preventing malonaldehyde formation and lacticodehydrogenase and aspartate aminotransferase leakage. Other proposed mechanisms of action for the hepatoprotective effects of rosemary may be related to its antioxidant properties (Fahim et al., 1999). In rats, rosemary's oral administration fully prevented CCl_4 effect on hepatic lipid peroxidation after 24 hr of CCl_4 administration (Sotelo-Felix et al., 2002b). Rosemary's effects on CCl_4-induced hepatotoxicity may be a result of the prevention of free radicals during CCl_4 metabolism by carnosol (Sotelo-Felix, Martinez-Fong, & Muriel, 2002a). In a study on female mice, a 2% rosemary diet increased the liver microsomal oxidation and glucuronidation of estradiol and estrone, and inhibited their uterotropic action (Zhu et al., 1998). In rat, rosemary ethanol extracts prepared from young sprouts showed significant dose-related choleretic activity and were more active than the total plant extract (Hoefler et al., 1987). Rosemary completely normalized the increase in bilirubin level and alanine aminotransferase activity in plasma induced by CCl_4 (Gutierrez et al., 2009). The dietary intake of rosemary and its constituent carnosol in female rats significantly increased liver glutathione-S-transferase (GST) and liver NAD(P)H-quinone reductase (QR) activities (Singletary, 1996). In rat study, rosemary extract nonsignificantly decreased the number and area of GST placental form-positive foci after initiation by diethylnitrosamine (Kitano et al., 2000). In mice, an extract from rosemary leaves decreased (but did not prevent) post-irradiation increases in alkaline contents in the liver (Soyal, Jindal, Singh, & Goyal, 2007). Both sprouts and whole plant aqueous extracts have been found to have no hepatoprotective effects (Hoefler et al., 1987).
- *Hormonal effects*: Greenlee et al. (2007) conducted a placebo controlled, parallel-arm trial to examine the effects of a combination of botanical supplements containing rosemary on sex hormones and metabolic markers in healthy premenstrual women and found that the supplement decreased dehydroepiandrosterone ($p = .02$), dehydroepiandrosterone sulfate ($p = .07$), androstenedione ($p = .05$), and estrone sulfate ($p = .08$) compared with controls.
- *Immunomodulatory effects*: According to a review, rosemary has been shown to increase the production of prostaglandin E2 and reduce the production of leukotriene B4 in human polymorphonuclear leucocytes, as well as inhibit the complement system (al Sereiti et al., 1999). In rats, rosemary extract in combination with a casein-enriched diet induced spleen cell proliferation in response to concanavalin A (Con A) and phytohemagglutinin (PHA) (at 10% dietary casein and 200 ppm of rosemary) (Babu, Wiesenfeld, & Jenkins, 1999).
- *Insecticidal effects*: Rosemary essential oils alone or in combination with other essential oils have demonstrated insecticidal activity in vitro (Ariana, Ebadi, & Tahmasebi, 2002; Cloyd, Galle, Keith, Kalscheur, & Kemp, 2009a; Cloyd, Timmons, Goebel, & Kemp, 2009b; Erkr, Erdemir, Ceylan, & Toker, 2009; Katerinopoulos, Pagona, Afratis, Stratigakis, & Roditakis, 2005; Khater, Ramadan, & El Madawy, 2009; Ranger, Reding, Oliver, Moyseenko, & Youssef, 2009; Yang, Lee, Clark, & Ahn, 2004). Camphor, isolated from rosemary, was most toxic for armyworm (Isman, Wilson, & Bradbury, 2008). In a laboratory test, Hexacide® (5% rosemary oil) caused

significant mortality in red flour beetles (Akbar, Lord, Nechols, & Loughin, 2005). Rosemary has demonstrated larvicidal activity and repellant activity against *Aedes aegypti* L. as evidenced by oviposition deterrent or repellent activities (Gillij, Gleiser, & Zygadlo, 2008; Waliwitiya et al., 2009). Repellant activities of rosemary have also been determined against Culex pipiens pallens (Choi, Park, Ku, & Lee, 2002b). This effect may be related to the alpha-terpinene content in rosemary.

- *Lipid effects*: In animal study, hepatic triglyceride levels were decreased following the administration of rosemary extract (Harach et al., 2009).
- *Memory-enhancing effects*: In human study, rosemary aromatherapy improved the quality of memory recall and secondary memory factors (though speed of recall was reduced), as well as elicited significantly higher levels of contentment relative to control (Moss et al., 2003). Using the Ellman colorimetric method, rosemary, an herb used in Danish folk medicine to treat memory dysfunction, has been found to moderately inhibit acetylcholinesterase (defined as more than 15% at 0.1 mg/ml) (Adsersen, Gauguin, Gudiksen, & Jager, 2006). Rosemary also produced an environmental context-dependent memory (ECDM) effect in humans and produced a more unpleasant mood in participants compared with lemon usage (Ball, Shoker, & Miles, 2009). Rosemary's ability to promote ECDM may be related to its distinctive aroma and ability to evoke a notion of unpleasantness in participants.
- *Neurological effects*: In clinical study, inhalation of rosemary essential oil increased alertness, improved recall, and reduced anxiety (Burnett et al., 2004; McCaffrey et al., 2009; Moss et al., 2003; Park & Lee, 2004). Two studies investigating the effects of rosemary aromatherapy on alertness and the EEG activity found that patients showed decreased frontal alpha- and beta-power, suggesting increased alertness (Diego et al., 1998). Patients also had lower state anxiety scores, reported feeling more relaxed and alert, and were faster, though not more accurate, at completing the math computations after the aromatherapy session. The second study evaluated the frontal EEG symmetry shift following exposure to rosemary (Sanders et al., 2002). In the rosemary experimental group, those with a greater baselines relative to the right frontal EEG activation shifted left, while those with greater baselines relative to left frontal EEG activation shifted right during the aroma. In other human study, rosemary aromatherapy improved the quality of memory recall and secondary memory factors (though speed of recall was reduced), as well as elicited significantly higher levels of contentment relative to control (Moss et al., 2003).
- The locomotor effects of oral administration or inhalation of rosemary oil in mice (Kovar, Gropper, Friess, & Ammon, 1987) and the actions of rosemary essential oils on the cerebral cortex in rat brain (in vitro) have been examined (Steinmetz et al., 1987).
- Intraperitoneal administration of rosemary extract or rosmarinic acid from the presymptomatic stage of ALS significantly delayed motor dysfunction in paw grip endurance tests, attenuated the degeneration of motor neurons, and extended the life span of ALS model mice (Shimojo et al., 2010), although the mechanism of action is unclear.
- *Neuroprotective effects*: In in vitro study, a rosemary extract enhanced the production of nerve growth factor in T98G human glioblastoma cells (Kosaka & Yokoi, 2003). Furthermore, the results indicated that carnosic acid and carnosol, both major components of the rosemary extract, were able to promote markedly enhanced synthesis

of nerve growth factor. Rosemary extract was not found to exert a protective effect against L-glutamate-induced neurotoxicity in vitro (Mazzio, Huber, Darling, Harris, & Soliman, 2001). However, carnosic acid and carnosol from rosemary demonstrated enhancement of total glutathione levels, transcriptional activation, and neuroprotective effects in cortical neurons in vitro (Tamaki et al., 2009). Carnosic acid also demonstrated protective effects in a concentration-related manner and prevented dieldrin (10 mM)-induced caspase-3 activation, Jun N-terminal kinase phosphorylation, and caspase-12 activation in cultured dopaminergic cells (Park et al., 2008). Furthermore, the dieldrin-induced downregulation of the brain-derived neurotrophic factor production was significantly attenuated by carnosic acid. Carnosic acid has also been shown to activate the Keap1/Nrf2 transcriptional pathway by binding to specific Keap1 cysteine residues, thereby protecting neurons from oxidative stress and excitotoxicity (Satoh et al., 2008). Carnosic acid also strongly promoted neurite outgrowth of PC12h cells (Kosaka et al., 2010). Carnosic acid activated Nrf2, an effect that was suppressed following Nrf2 gene knockdown, and also activated TrkA-downstream kinase Erk1/2 independently of Nrf2. These results suggest that carnosic acid induction of p62/ZIP by Nrf2 enhances TrkA signaling, which subsequently potentiates Nrf2 pathway. In cerebrocortical cultures, carnosic acid–biotin accumulates in non-neuronal cells at low concentrations and in neurons at higher concentrations. It has been suggested that this distribution may contribute to carnosic acid's neuroprotective effects.

- *Psychiatric effects*: In animal study, rosemary produced antidepressant-like effects reducing immobility time likely mediated by the monoaminergic system (Machado et al., 2009). On the basis of human study, rosemary scent may have the potential to moderate different aspects of mood following an anxiety-provoking task (Burnett et al., 2004). In humans, free radical scavenging activity (as measured by DPPH activity) increased and cortisol levels decreased by smelling high concentrations (10 times dilution) of rosemary (Atsumi & Tonosaki, 2007).
- *Reproductive effects*: In adult rats, ingestion of rosemary (250 and 500 mg/kg of body weight for 63 days) did not affect body weight or absolute and relative teste weights but did decrease the average weights of epididymides, ventral prostates, seminal vesicles, and preputial glands (Nusier et al., 2007). In the 500-mg/kg group, significant decrease in spermatogenesis in the testes, as well as sperm motility and density, were observed. Female rats that were impregnated with sperm from affected rats experienced an increase in the number of fetal resorptions.
- *Respiratory effects*: In vivo pharmacological magnetic resonance imaging detected a secretory response in the rat trachea following rosemary essential oil inhalation (Nicolato, Boschi, Marzola, & Sbarbati, 2009).
- *Smooth muscle effects*: Rosemary oil produced spasmolytic effects accompanied by agonistic effects on alpha(1) and alpha(2) adrenergic receptors in vitro in circular smooth muscle strips of the guinea pig stomach (Sagorchev et al., 2009).
- In in vitro study, the volatile oil of rosemary leaves inhibited the contractions of rabbit tracheal smooth muscle induced by acetylcholine stimulation and the contractions of guinea pig tracheal smooth muscle induced by histamine stimulation, as well as the contractions of rabbit and guinea pig tracheal smooth muscle induced by high potassium (K+) solution (Aqel, 1991). This inhibition was dose-dependent and reversible. In addition, the volatile oil inhibited the contractions of rabbit and guinea

pig tracheal smooth muscles induced by acetylcholine and histamine stimulation, respectively, in Ca(2+)-free solution.

Pharmacodynamics/Kinetics

- *Absorption*: Rosmarinic acid is well absorbed in the gastrointestinal tract and from the skin. Upon topical administration of rosmarinic acid in the form of a w/o ointment (25 mg/kg, 50 cm^2) in rat, the absolute bioavailability was 60% (Ritschel, Starzacher, Sabouni, Hussain, & Koch, 1989).
- The supplementation of rosemary extract with sunflower oil and lecithin (37 mg/g) resulted in a 50% reduction in bioaccessibility in terms of antioxidant activity in vitro (bioavailability was 31%) (Soler-Rivas et al., 2010). This effect was not attributed to the original levels of carnosol, carnosic acid, and methyl carnosate (of which only 47% remained after digestion) but due to their derivatives and digestion products.
- *Distribution*: Distribution of rosmarinic acid following intravenous (i.v.) administration in rat has been described by a two-compartment open model: $t_{1/2} = 1.8$ hr, and $t_{1/2}$ alpha = 0.07 hr, V tau = 2.3 L/kg, V beta = 15.3 L/kg for rat (Ritschel et al., 1989). After 30 min of injection, rosmarinic acid was detected and measured in brain, heart, liver, lung, muscle, spleen, and bone tissue, showing the highest concentration in lung tissue (13 times the blood concentration), followed by spleen, heart, and liver tissue (Ritschel et al., 1989). After $4\frac{1}{2}$ hr (peak time) of topical administration of about 3 mg on the hind leg, over 20 cm^2 of rosmarinic acid was measured in blood, skin, muscle, and bone tissue.
- *Metabolism*: Rosmarinic acid is metabolized by gut microflora into caffeic acid and derivatives (secondary sources). In one study, verbenone (a component of the essential oil from rosemary) was found to be converted to 10-hydroxyverbenone by rat and human liver microsomal cytochrome P450 (CYP450) enzymes (Miyazawa, Sugie, & Shindo, 2002; Miyazawa, Sugie, & Shimada, 2003). There was a good correlation between activities of coumarin 7-hydroxylation and (-)-verbenone 10-hydroxylation catalyzed by liver microsomes in 16 human samples, indicating that CYP2A6 is a principal enzyme in (-)-verbenone 10-hydroxylation in humans.
- In a study conducted on rat, rosemary essential oil selectively induced CYP, particularly CYP2B (Debersac et al., 2001a). Rosemary water-soluble extract enhanced both CYP 1A1, 2B1/2, 2E1, and glutathione S-transferase (GST) (especially rGST A3/A5, M1, and M2), quinone reductase, and UDP-glucuronosyltransferase (UGT), whereas a dichloromethane extract acted as a monofunctional inducer, inducing glutathione S-transferase, quinone reductase, and UGT, in particular UGT1A6 (Debersac et al., 2001a, 2001b). Rosemary inhibited P-glycoprotein activity and caused reversal of multi-drug resistance (MDR) in vitro (Plouzek et al., 1999).
- Kinetic analysis showed that the Km and Vmax values for (-)-verbenone hydroxylation were 1.1 mM and 4.8 nmol/min/nmol P450, 0.6 mM and 2.1 nmol/min/nmol P450, and 2.8 mM and 4.6 nmol/min/nmol P450 (from three human samples: HG-70, HG-56, and HG-23, respectively).
- *Elimination half-life*: Following the i.v. administration of rosmarinic acid in animal study, the elimination half-life was 1.8 hr (Ritschel et al., 1989)

HISTORY

- The botanical name *Rosmarinus* is believed to be derived from old Latin for "dew of the sea," a reference to the plant's pale blue, dew-like flowers and the fact that it often grows near the sea. Rosemary has been used medicinally for centuries (Al Qura'n, 2009; Artico, Cervoni, Nucci, & Giuffre, 1996; Heinrich, Kufer, Leonti, & Pardo-de-Santayana, 2006; Lev, 2007; Parada, Carrio, Bonet, & Valles, 2009; Selmi, 1967), and has appeared in various medieval texts (Boot & Mayer, 1990; Zimmermann, 1980).
- Traditionally, rosemary has been used for improving memory, and, as such, gained notoriety as a symbol of remembrance and friendship. In Shakespeare's *Hamlet*, Ophelia refers to the herb: "There's rosemary, that's for remembrance." In Greek tradition, songs about rosemary are sung at New Year. In other European cultures, the bride or bridal couple would carry or wear rosemary as a symbol of love and fidelity.
- Examples of historical usage include a concoction of rosemary, "Queen of Hungary water," so named as it was invented as a topical cure for the paralysis of a Hungarian monarch. In a French custom, rosemary and juniper berries were burnt to purify the air and prevent disease. The ancient Greeks burned rosemary to drive away evil spirits and illnesses. In a similar tradition, a fresh twig placed beneath a pillow was thought to prevent nightmares. In *Don Quixote de la Mancha* (first volume, chapter XVII), Don Quixote claims, he knows the recipe of the miraculous balm of Fierabras, a mixture of oil, wine, salt, and rosemary, which was used on the corpse of Jesus Christ (Lopez-Munoz, Garcia-Garcia, & Alamo, 2007; Lopez-Munoz et al., 2006). Rosemary is often associated with mourning, and in some customs, mourners carry sprigs of rosemary at funerals and place them on the coffin in the grave. It is reported that the internal organs of Prince Joseph Habsburg (1776–1847) and his first wife, Alexandra Pavlovna Romanova (1783–1801), were stored in rosemary oil (Jozsa, 2008).
- According to a Spanish legend, the Virgin Mary took shelter beneath a rosemary bush during her flight to Egypt. Thus rosemary's Spanish name is *romero*, or "pilgrim's flower." In another Christian legend, rosemary is said to grow for 33 years, until it reaches the height of Jesus Christ, when he was crucified, and then perishes.
- The prayer book of Mihailo Plamenac, an orthodox priest living in Montenegro at the turn of the 18th Century, contains several medical recipes of herbs, including rosemary (Milovic, 1998).
- Rosemary wood has also been used in the construction of flutes and other musical instruments. Rosemary has also been used to make honey (de la, Martinez-Castro, & Sanz, 2005; Fernandez-Torres et al., 2005; Gonzalez-Miret, Terrab, Hernanz, Fernandez-Recamales, & Heredia, 2005; Nozal Nalda, Bernal Yague, Diego Calva, & Martin Gomez, 2005).
- Rosemary has been discussed as a solution to prevent desertification and rapid soil erosion because of its good resistance to adverse environmental conditions (Olmos, Sanchez-Blanco, Ferrandez, & Alarcon, 2007). Rosemary has also been used by researchers to gauge air quality by analyzing the amount of polycyclic aromatic hydrocarbons present in leaves (Culotta, Melati, & Orecchio, 2002).

EVIDENCE TABLE

Condition Treated	Study Type/Design	Author, Year	*N*	Statistically Significant Results?	Quality of Study: 0–2 = poor 3–4 = good 5 = excellent	Magnitude of Benefit (how strong is the effect?)	Absolute Risk Reduction	# of Patients Needed to Treat for One Outcome	Comments
Anxiety/stress	Randomized controlled trial	Burnett et al., 2004	73	Yes	1	NA	NA	NA	Rosemary aroma had no effect on physiological measures but significantly increased mood ratings related to tension–anxiety and confusion–bewilderment.
Anxiety/stress	Randomized controlled trial	Moss et al., 2003	144	Mixed	1	Mixed	NA	NA	Aromatherapy improved quality of memory recall, though decreased speed. Control group also reported significantly lower levels of contentment.
Cognitive performance enhancement	Randomized controlled trial	Moss et al., 2003	144	Yes	1	Small	NA	NA	Aromatherapy improved quality of memory recall, though decreased speed. Compared with the control (water) group, rosemary produced small improvements that were only statistically significant for two of the five tests. When compared to lavender, statistical significance was reached for three of the five tests.

Explanation of Columns in Natural Standard Evidence Table Condition

Refers to the medical condition or disease targeted by a therapy.

Study Design

Common types include the following:

- *Randomized controlled trial (RCT)*: An experimental trial in which participants are assigned randomly to receive either an intervention being tested or placebo. Note that Natural Standard defines RCTs as being placebo-controlled, while studies using active controls are classified as equivalence trials (see below). In RCTs, participants and researchers are often blinded (i.e., unaware of group assignments), although unblinded and quasi-blinded RCTs are also often performed. True random allocation to trial arms, proper blinding, and sufficient sample size are the basis for an adequate RCT.
- *Equivalence trial*: It is an RCT that compares two active agents. Equivalence trials often compare new treatments to usual (standard) care, and may not include a placebo arm.
- *Before and after comparison*: A study that reports only the change in outcome in each group of a study, and does not report between-group comparisons. This is a common error in studies that claim to be RCTs.
- *Case series*: A description of a group of patients with a condition, treatment, or outcome (e.g., 20 patients with migraine headache underwent acupuncture and 17 reported feeling better afterwards). Case series are considered weak evidence of efficacy.
- *Case-control study*: A study in which patients with a certain outcome are selected and compared to similar patients (without the outcome) to see if certain risk factors/predictors are more common in patients with that outcome. This study design is not common in the complementary and alternative medicine literature.
- *Cohort study*: It is a study that assembles a group of patients with certain baseline characteristics (e.g., use of a drug), and follows them forward in time for outcomes. This study design is not common in the complementary and alternative medicine literature.
- *Meta-analysis*: A pooling of multiple trials to increase statistical power (often used to pool data from a number of RCTs with small sample sizes, none which demonstrates significance alone, but in aggregate can achieve significance). Multiple difficulties are encountered when designing/reviewing these analyses; in particular, outcome measures or therapies may differ from study to study, hindering direct comparison.
- *Review*: An author's description of his or her opinion based on personal, non-systematic review of evidence.
- *Systematic review*: A review conducted according to pre-specified criteria in an attempt to limit bias from the investigators. Systematic reviews often include a meta-analysis of data from the included studies.
- *P*: Pending verification.

Author, Year

Identifies the study being described in a row of the table.

N

The total number of subjects included in a study (treatment plus placebo groups). Some studies initially recruit a larger number of subjects, but do not use all of them because they do not meet the study's entry criteria. In this case, it is the second, smaller number that qualifies as *N*. It includes all subjects that are part of a study at the start date, even if they drop out, are lost to follow-up, or are deemed unsuitable for analysis by the authors. Trials with a large number of dropouts that are not included in the analysis are considered to be weaker evidence for efficacy. (For systematic reviews, the number of studies included is reported. For meta-analyses, the number of total subjects included in the analysis or the number of studies may be reported.) P = pending verification.

Statistically Significant?

Results are noted as being statistically significant if a study's authors report statistical significance, or if quantitative evidence of significance is present (such as *p*-values). P = pending verification.

Quality of Study

A numerical score between 0–5 is assigned as a rough measure of study design/reporting quality (0 being the weakest and 5 being the strongest). This number is based on a well-established and validated scale developed by Jadad et al. (1996). This calculation does not account for all study elements that may be used to assess quality (other aspects of study design/reporting are addressed in the "Evidence Discussion" section of reviews).

- The Jadad score is calculated using the seven items given in the table, "Jadad Score Calculation." The first five items are indications of good quality, and each counts as one point toward an overall quality score. The final two items indicate poor quality, and a point is subtracted for each if its criteria are met. The range of possible scores is 0 to 5.

JADAD SCORE CALCULATION

Item	Score
Was the study described as randomized (this includes words, such as randomly, random, and randomization)?	0/1
Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)?	0/1
Was the study described as double-blind?	0/1
Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)?	0/1
Was there a description of withdrawals and dropouts?	0/1
Deduct one point if the method used to generate the sequence of randomization was described and was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc).	0/−1
Deduct one point if the study was described as double-blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	0/−1

Magnitude of Benefit. This summarizes how strong a benefit is: small, medium, large, or none. If results are not statistically significant "NA" for "not applicable" is entered. In order to be consistent in defining small, medium, and large benefits across different studies and reviews, Natural Standard defines the magnitude of benefit in terms of the standard deviation (SD) of the outcome measure. Specifically, the benefit is considered

- large, if >1 SD,
- medium, if 0.5 to 0.9 SD,
- small, if 0.2 to 0.4 SD,

P = pending verification.

In many cases, studies do not report the SD of change of the outcome measure. However, the change in the SD of the outcome measure (also known as effect size) can be calculated, and is derived by subtracting the mean (or mean difference) in the placebo/control group from the mean (or mean difference) in the treatment group and dividing that quantity by the pooled SD, i.e.,

Effect size = (mean treatment – mean placebo)/SDp.

Absolute Risk Reduction (ARR)

This describes the difference between the percentage of people in the control/placebo group experiencing a specific outcome (control event rate) and the percentage of people in the experimental/therapy group experiencing that same outcome (experimental event rate). Mathematically, ARR equals experimental event rate minus control event rate. ARR is better able to discriminate between large treatment effects and small treatment effects than relative risk reduction (RRR), a calculation that is often cited in studies, i.e.,

$$\frac{\text{(control event rate)} - \text{(experimental event rate)}}{\text{control event rate}}$$

Many studies do not include adequate data to calculate the ARR; in such cases, "NA" is entered into this column. P = pending verification.

Number Needed to Treat

This refers to the number of patients who would need to use the therapy under investigation for the period of time described in the study, in order for one person to experience the specified benefit. It is calculated by dividing the ARR into 1 (1/ARR). P = pending verification.

Comments

When appropriate, this brief section may comment on design flaws (inadequately described subjects, lack of blinding, brief follow-up, no intention to treat, etc.), notable study design elements (crossover etc.), dosing, and/or specifics of study group/subgroups (age, gender, etc). More detailed description of studies is found in the "Evidence Discussion" section that follows the "Evidence Table" in Natural Standard reviews.

EVIDENCE DISCUSSION

Alopecia Areata

- *Summary*: Rosemary has been reported to increase circulation in the scalp and possibly promote hair growth, based on historical use. Limited research has indicated some small benefit with the use of essential oils of rosemary, thyme, lavender, and Atlas cedar for the treatment of alopecia areata; however, additional study of higher rigor is necessary before any firm assessment can be made.
- *Select combination study* (not included in the Evidence Table): Hay et al. (1998) conducted a randomized, double-blind, controlled trial to investigate the effect of aromatherapy on alopecia areata. Subjects were 84 patients with alopecia areata. Subjects with a medical history of hypertension, epilepsy, or pregnancy were excluded. Two of the originally recruited patients were excluded because they had androgenic alopecia. Medication for alopecia was stopped before beginning the study. Subjects were randomized into two groups: the active group, which received a mixture of oils of rosemary (3 drops (114 mg) of *Rosmarinus officinalis*), *Thyme vulgaris* (2 drops (88 mg)) and *Lavandula angustifolia* (3 drops (108 mg)) mixed with carrier oil (a combination of 3 ml of jojoba and 20 ml of grapeseed oil), or control, which consisted of just the carrier oil. Each treatment was self-applied and massaged into the scalp for a minimum of 2 min followed by a warm towel, which was wrapped around the head to facilitate the absorption of the oils. Subjects performed this technique every night for 7 months. Treatment success was evaluated on sequential photographs independently by two dermatologists (blinded). Improvement was also measured using a six-point scale as well as computer analysis of affected areas. Of the subjects receiving the active treatment (N = 43), 19 (44%) showed improvement compared with six (15%) of the patients in the control group (N = 41; $p = .008$). Photographic assessment of improvement was also significant ($p = .05$). It should be noted that this study suffered from a number of methodological weaknesses. ARR of 2.6 (95% CI: 1.2–5.6) was calculated for improving on active therapy. Sample size was not adequate to detect a significant difference. In addition, the process of randomization was not described. It is also not clear if the differences in baseline characteristics were adjusted. The investigators state that results were statistically significant, although the number of participants was not adequate to detect a 20% improvement with a 5% significance level as they originally described. Furthermore, the use of a combination product precludes conclusions regarding any specific oil. Further considerations include that; although the trial design was described as double-blind, the smell of the treatment oil may have been identifiable.

Anxiety/Stress

- *Summary*: Rosemary extract is frequently used in aromatherapy for its purported benefits in mental health, such as relieving anxiety, enhancing mood, altering pain perception, and increasing alertness and improving recall. Studies have reported improvements in stress and alertness, feelings of contentment, as well as quality of memory recall and secondary memory factors. Other research has noted increases in measures of tension–anxiety and confusion–bewilderment. In general, available

studies remain limited and of generally low methodological rigor. Additional inquiry is required.

- *Evidence*: Burnett et al. (2004) conducted a randomized controlled trial to investigate the effects of water, lavender, or rosemary scent on physiology and mood state following an anxiety-provoking task. A total of 73 nonsmoking patients were included in the study, aged between 18 and 30 years (42 women and 31 men). Subjects performed an anxiety-provoking task and then completed the "Profile of Mood States" to assess mood. Temperature and heart rate were assessed before and after the task. Participants also rated the pleasantness of the received scent. When pleasantness ratings of scent were covaried, physiological changes in temperature and heart rate were found not to differ based on scent exposure, though mood ratings varied by scent condition. Participants in the rosemary condition scored higher on measures of tension–anxiety and confusion–bewilderment relative to the lavender and control conditions. The lavender and control conditions showed higher mean vigor–activity ratings relative to the rosemary group, while both rosemary and lavender scents were associated with lower mean ratings on the fatigue–inertia subscale, relative to the control group. The authors suggest that when controlling for the individual perception of scent pleasantness, aromatherapy has the potential to moderate different aspects of mood following an anxiety-provoking task.
- Moss et al. (2003) conducted a randomized controlled trial to evaluate the aromatherapeutic efficacy of the essential oils of rosemary and lavender on cognitive performance and mood swings in adults. Subjects were 144 healthy adults who performed the Cognitive Drug Research (CDR) computerized cognitive assessment battery in an experimental space containing the aroma of rosemary, lavender, or no aroma as a control. Mood questionnaires (visual analogue) were administered before and after the assessment. Subjects were misled as to the purpose of the experiment to prevent expectancy effects. Outcome measures included CDR and mood questionnaire results. Analysis of these measures indicated that rosemary aromatherapy improved the quality of memory recall and secondary memory factors (though speed of recall was reduced), as well as significantly higher levels of alertness ($F(2,141) = 5.43, p = .005$) and contentedness ($F(2,141) = 9.72, p = .0001$) in the treatment group. A significant difference between groups was reported for quality of memory ($F(2,141) = 4.80$, $p = .01$). Rosemary produced significantly higher scores than the lavender condition (mean = 326.61, $p < .05$). Statistical analysis revealed no other significant difference. A between-group analysis, however, revealed no statistically significant differences between groups in calmness scores ($F(2,141) = 0.73$, $p = .481$). Limitations of this study include a failure to describe dropouts and the method of randomization.
- *Studies of lesser methodological rigor*: McCaffrey et al. (2009) conducted a quasi-experimental study using pre- and post-test measures to examine the effects of lavender or rosemary on test-taking stress in graduate nursing students. Forty students participated in the study. During the semester each student completed four examinations, which were averaged for a final grade in the class. Primary outcome measures included the test anxiety scale (TAS), a 10-item self-report measurement, used to measure perceived stress. Blood pressure and radial pulse were used as measures of physical stress and anxiety. The first examination served as a baseline with no intervention given. During the second and third interventions, students received a lavender or rosemary essential oil inhaler, respectively, and were asked to breathe in the aroma prior to and after the test. Students were asked to record the number of times they used the inhaler during the test period. The rosemary essential oil used

was of *Rosmarinus officinalis* with a camphor phenotype; a cotton insert was used to apply 3 drops of the oil to the inhaler. The use of lavender and rosemary essential oils reduced test-taking stress in graduate nursing students, as evidenced by lower scores on test anxiety measure ($p < .003$ and $p < .01$, respectively), personal statements (significance not assessed), and pulse rates ($p < .000$ and $p < .033$, respectively), but not blood pressure. Due to the nature of the study, blinding was not possible. Each student served as his or her own control and therefore the study was not randomized.

- Park and Lee (2004) conducted a controlled, quasi-experimental trial using a nonequivalent pre- and post-design to identify the effect of aroma inhalation on stress responses (physical symptoms, levels of anxiety, and perceived stresses) of nursing students. The subjects consisted of 77 junior nursing students, who were divided into 39 experimental group members and 38 control group members. In the experimental group, lavender, peppermint, rosemary, and Clary-Sage aromas were given using an aroma lamp. In the control group, the treatment was not administered. Students receiving the experimental treatment experienced decreased physical symptoms and had lower anxiety and perceived stress scores.

Breast Cancer (Adjuvant)

- *Summary*: A limited research has indicated that a diet consisting of balsamic vinegar from apples and honey, with seabuckthorn berry, rosemary, sage, and basil extracts, whole wheat bread with 2.5% of the nutraceutical mixture VITAPAN, and grape seed extract is capable of reducing oxidative stress and improving well-being in women with breast cancer. However, the effects of rosemary alone are unclear. Additional research is required.
- *Select combination study* (not included in the Evidence Table): Drăgan et al. (2007) conducted a randomized controlled trial to examine the effects of diet consisting of balsamic vinegar from apples and honey, with seabuckthorn berry, rosemary, sage, and basil extracts, whole wheat bread with 2.5% of the nutraceutical mixture VITAPAN, and grape seed extract on oxidative stress and various well-being scales in women with stages IIIB and IV breast cancer. Thirty-four female patients with histologically confirmed stages IIIB and IV breast cancer were put on a special diet consisting of the following: 15 ml of daily balsamic vinegar from apples and honey, with seabuckthorn berry, rosemary, sage, and basil extracts, to be used in salads and vegetable soups, 150 g daily of whole wheat bread with 2.5% of the nutraceutical mixture VITAPAN, and 15 ml of daily grape seed extract ($N = 17$) or a control diet (unspecified) ($N = 17$). All the patients filled the "Quality of Life" (QOL) questionnaire, FACT-B version 4. Outcome measures at baseline and after 3 months of treatment included serum lipids and IR-HOMA insulin resistance index (measured parameters of metabolic syndrome), free oxygen radical test (FORT) as a measure of oxidative stress, and total hydro- and liposoluble antioxidants (ACW and ACL) in serum measured by chemoluminometry. Patients also completed the Physical Well-Being subscale score of the QOL, FACT-B version 4 questionnaire; the Functional Well-Being subscale; FACT-G; FACT-B; the Breast Cancer Score (Additional Concerns); the Social/Family Well-Being subscale; and the Emotional Well-Being subscale. Scores of the physical well-being subscale of the QOL, FACT-B version 4 questionnaire ($p = .001$), the functional well-being subscale ($p = .004$), FACT-G ($p = .003$), and FACT-B ($p = .002$) showed significant differences between the two groups. The breast cancer score

(additional concerns) displayed a borderline significant difference between the two groups ($p = .057$), whereas the social/family well-being subscale and emotional well-being subscale scores showed no significant difference. At baseline, radical activity >310 FORT units (indicative of increased oxidative stress) were present in 95.1% of the cases. After 3 months of treatment, radical activity >310 FORT units was present in 52.8% of the cases in the treatment group.

Cognitive Performance Enhancement

- *Summary*: Limited research has indicated that aromatherapy with essential oils from rosemary may enhance cognitive performance. More well-designed trials are needed before a definitive assessment can be made.
- *Evidence*: Moss et al. (2003) conducted a randomized controlled trial to evaluate the aromatherapeutic efficacy of the essential oils of rosemary and lavender on cognitive performance and mood in adults. Subjects were 144 healthy adults, who performed the CDR computerized cognitive assessment battery in an experimental space containing the aroma of rosemary and lavender, and no aroma as a control. Mood questionnaires (visual analogue) were administered before and after the assessment. Subjects were misled as to the purpose of the experiment to prevent expectancy effects. Outcome measures included CDR and mood questionnaire results. A significant difference between all the groups was reported for quality of memory ($F(2,141) = 4.80$, $p = .01$). Overall, rosemary produced significantly higher scores than the lavender condition (mean = 326.61, $p < .05$). In the analysis of the individual tests, rosemary was associated with small and statistically significant improvements in two of the five memory tests when compared with the control group. When compared to lavender, however, statistical significance was reached for three of the five individual tests. Limitations of this study included a failure to describe dropouts or the method of randomization.

Constipation

- *Summary*: Based on limited research, aromatherapy with essential oils from rosemary, lemon, and peppermint, combined with abdominal massage, may alleviate constipation in the elderly. More well-designed trials are needed before a definitive assessment can be made.
- *Select combination studies* (not included in the Evidence Table): Kim, Sakong, Kim, Kim, & Kim (2005a) conducted a randomized, controlled, pre- and post-test trial to examine the effects of aromatherapy massage on constipation in the elderly. Participants received abdominal massage using essential oils from rosemary, lemon, and peppermint for 10 days. Placebo consisted of massage without essential oils. The degree of constipation was measured using the constipation assessment scale (CAS) and the number of bowel movements per week. The CAS score of the experimental group was significantly lower than that of the control group. In addition, the average number of bowel movements in the experimental group was higher than that of the control group. This effect lasted for 2 weeks following the cessation of treatment, while the placebo effect lasted for 7–10 days.

Dermatitis

- *Summary*: On the basis of limited research, the combination of marigold and rosemary extracts may exert a significant protective effect in a model of experimentally induced contact dermatitis. Additional research examining the effect of rosemary alone is required.
- *Select combination studies* (not included in the Evidence Table): Fuchs et al. (2005) conducted a study to examine the effects of a cream containing seven different types of marigold and rosemary extracts on experimentally induced irritant contact dermatitis (ICD) in healthy volunteers. Twenty volunteers were included in the study. The use of detergents or emollients was not allowed during the study period, nor was sunbathing or excessive sun exposure. Inclusion criteria included the absence of any major internal or dermatological diseases. Exclusion criteria included pregnancy or lactation, immunosuppressive therapy, topical dermatological treatment within last 2 weeks, and very fair complexion. Marigold and rosemary extracts in a base cream Deutscher Arzneimittel-Codex (DAC; German Pharmaceutical Codex) were tested in a four-day repetitive irritation test using sodium lauryl sulfate. The effect was evaluated visually and quantified by noninvasive methods (i.e., chromometry and tewametry). When the test products were applied parallel to the induction period of ICD, a statistically significant protective effect of all cream preparations was observed by all methods ($p < .001$–0.05). The sequential treatment (post-irritation) once a day for five days displayed no effect. The influence of rosemary alone cannot be determined from this study.

Rheumatic Diseases (Pain)

- *Summary*: In a rat model of arthritic pain, the essential oil of rosemary exhibited antinociceptive effects, which may be modulated by the serotonin system (i.e., 5-HT1A receptors) or the endogenous opioid system (Martinez et al., 2009). Several clinical trials have attempted to examine the effects of rosemary, in combination with other essential oils, on pain associated with rheumatic diseases in humans; however, research remains limited. Additional study is required before a definitive assessment can be made.
- *Select combination studies* (not included in the Evidence Table): Minich et al. (2007) conducted a multicenter trial to examine the clinical safety and efficacy of NG440, a phytochemical-based anti-inflammatory formula consisting of a combination of rho iso-alpha acids from hops, rosemary, and oleanolic acid in patients with arthritis pain. Sixty subjects were recruited, of which 56 were included in the analysis. As early as 2 weeks following the start of the therapy, a significant improvement in visual analog scale (VAS) scores ($p < .001$) was observed. At study closeout, VAS scores were 66.2% lower compared to the baseline score ($p < .001$). A 30% reduction in clinical symptoms associated with joint distress was also observed. This study is limited by a lack of blinding and randomization, as well as the use of a combination product.
- Lukaczer et al. (2005) conducted an open-label, 8-week observational trial to investigate the efficacy of Meta050 (a proprietary, standardized combination of reduced iso-alpha acids from hops, rosemary extract, and oleanolic acid) on pain in patients with rheumatic disease. Fifty-four subjects with rheumatic disease completed the trial. Subjects were men and women aged between 18 and 65 years with ongoing

pain, who met the criteria for rheumatoid arthritis, osteoarthritis, or fibromyalgia. Exclusion criteria included abnormal complete blood count (CBC), blood glucose, or kidney or liver function markers; allergy to an ingredient in Meta050, nonsteroidal anti-inflammatory (NSAID) medications, or aspirin; a history of peptic ulcer, gastritis, esophagitis, or liver, kidney, or heart disease; current pregnancy or lactation; uncontrolled hypertension (BP $>$ 140/90); diabetes; HIV or acquired immunodeficiency syndrome (AIDS); history of or active cancer (excluding skin cancer); use of oral corticosteroids in the preceding 4 weeks; history of untreated endocrine, neurological, or infectious disorders; or a history of serious mental illness or episode of attempted suicide within the preceding 5 years. Patients were given a dose of 440 mg of Meta050 thrice a day for 4 weeks, which was increased to 880 mg twice a day for the subsequent 4 weeks (in the majority of patients). Pain and condition-specific symptoms were assessed using a standard VAS, an abridged arthritis impact measurement scale (AIMS2), and the fibromyalgia impact questionnaire. Following treatment, a statistically significant decrease in pain of 50% and 40% was observed in arthritic subjects using the VAS ($p < .0001$) and AIMS2 ($p < .0001$), respectively. Fibromyalgia subject scores did not improve significantly. A decreasing trend of C-reactive protein, a marker for inflammation, was also observed in the subjects who presented with elevated C-reactive protein. No serious side effects were observed. The effects of rosemary alone cannot be determined from this study. This study was limited by a lack of randomization and blinding.

- Kim, Nam, and Paik (2005b) conducted a quasi-experimental pre- and post-test study to examine the effect of aromatherapy on pain, depression, and feeling of satisfaction in life of arthritis patients. Forty patients were included in the trial. The essential oils used were lavender, marjoram, eucalyptus, rosemary, and peppermint blended in proportions of 2:1:2:1:1, mixed with a carrier oil consisting of almond (45%), apricot (45%), and jojoba oil (10%), diluted to 1.5% after blending. Aromatherapy significantly decreased both the pain and the depression scores of the experimental group compared with the control group. However, aromatherapy did not increase the feeling of satisfaction in life of the experimental group compared with the control group. The effects of rosemary alone cannot be determined from this study.

Brands Used in Human Studies

- Tisserand pure rosemary essential oil (Tisserand Aromatherapy, Newtown Road, Hove, Sussex, UK) (Moss et al., 2003).
- Botanical supplement formula (combination is as follows: 100 mg of *C. longa* (turmeric) root extract standardized to 95% curcumin; 100 mg of *C. scolymus* (artichoke) leaf 6:1 extract; 100 mg of *R. officinalis* (rosemary) leaf 5:1 extract; 100 mg of *S. marianum* (milk thistle) seed extract standardized to 80% silybin, silichristin, silidianin, and silymarin; 100 mg of *T. officinalis* (dandelion) root 4:1 extract; and 50 mg of *S. chinensis* (schisandra) berry 20:1 extract) (Vital Nutrients) (Greenlee et al., 2007).
- Meta050 (standardized combination is as follows: reduced iso-alpha acids from hops, rosemary extract, and oleanolic acid) (Lukaczer et al., 2005).

Brands Shown to Contain Claimed Ingredients Through Third-Party Testing

- *Consumer Laboratory*: Not applicable.
- *Consumer Reports*: Consumer Reports Health presented a list of products containing rosemary.
- *Natural Products Association*: Not applicable.
- *NSF International*: Not applicable.
- *US Pharmacopeia*: Not applicable.

Select Patents Outside the United States

- JP2009132662 Glutathione production promoter.
- MX2007010360 herbal composition for the treatment of psoriasis.
- JP2008303165 hair improving agent.

US Patents

- US5939050: Antimicrobial compositions.
- US6060061: Method for preventing or treating disorders involving an inflammatory process.
- US6248309: Gums containing antimicrobial agents.

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REFERENCES

Abascal K, Yarnell E. Herbs and breast cancer: research review of seaweed, rosemary and ginseng. Alt Complement Ther. 2001;6:32–36.

Abascal K, Yarnell E. A botanical approach to Alzheimer's disease. Nat Pharm. 2004a;8:1–17.

Abascal K, Yarnell E. Alzheimer's disease – Part 2 – A botanical treatment plan. Altern. Complement Ther. 2004b;10:67–72.

Abdel-Fatah MK, El-Hawa MA, Samia EM, Rabie G, Amer AM. Antimicrobial activities of some local medicinal plants. J Drug Res. 2002;24:179–186.

Abdul-Ghani AS, El-Lati SG, Sacaan AI, Suleiman MS, Amin RM. Anticonvulsant effects of some Arab medicinal plants. Int J Crude Drug Res. 1987;25:39–43.

Abe F, Yamauchi T, Nagao T, Kinjo J, Okabe H, Higo H, Akahane H. Ursolic acid as a trypanocidal constituent in rosemary. Biol Pharm Bull. 2002;25:1485–1487.

Adams M, Gmunder F, Hamburger M. Plants traditionally used in age-related brain disorders—a survey of ethnobotanical literature. J Ethnopharmacol. 2007;113:363–381.

Adsersen A, Gauguin B, Gudiksen L, Jager AK. Screening of plants used in Danish folk medicine to treat memory dysfunction for acetylcholinesterase inhibitory activity. J Ethnopharmacol. 2006;104:418–422.

Aggarwal BB, Kunnumakkara AB, Harikumar KB, Tharakan ST, Sung B, Anand P. Potential of spice-derived phytochemicals for cancer prevention. Planta Med. 2008;74:1560–1569.

Aggarwal BB, Shishodia S. Suppression of the nuclear factor-kappaB activation pathway by spice-derived phytochemicals: reasoning for seasoning. Ann NY Acad Sci. 2004;1030:434–441.

Aherne SA, Kerry JP, O'Brien NM. Effects of plant extracts on antioxidant status and oxidant-induced stress in Caco-2 cells. Br. J Nutr. 2007;97:321–328.

Ahn J, Grun IU, Mustapha A. Antimicrobial and antioxidant activities of natural extracts in vitro and in ground beef. J Food Prot. 2004;67:148–155.
Ahn J, Grun IU, Mustapha A. Effects of plant extracts on microbial growth, color change, and lipid oxidation in cooked beef. Food Microbiol. 2007;24:7–14.
Akbar W, Lord JC, Nechols JR, Loughin TM. Efficacy of Bauveria bassiana for red flour beetle when applied with plant essential oils or in mineral oil and organosilicone carriers. J Econ Entomol. 2005;98:683–688.
al Hader AA, Hasan ZA, Aqel MB. Hyperglycemic and insulin release inhibitory effects of Rosmarinus officinalis. J Ethnopharmacol. 1994;43:217–221.
Al Qura'n S. Ethnopharmacological survey of wild medicinal plants in Showbak, Jordan. J Ethnopharmacol. 2009;123:45–50.
al Sereiti MR, Abu-Amer KM, Sen P. Pharmacology of rosemary (Rosmarinus officinalis Linn.) and its therapeutic potentials. Indian J Exp Biol. 1999;37:124–130.
Albu S, Joyce E, Paniwnyk L, Lorimer JP, Mason TJ. Potential for the use of ultrasound in the extraction of antioxidants from Rosmarinus officinalis for the food and pharmaceutical industry. Ultrason Sonochem. 2004;11:261–265.
Aleisa AM. Cytological and biochemical effects of St. John's Wort supplement (a complex mixture of St. John's Wort, Rosemary, and Spirulina) on somatic and germ cells of Swiss Albino mice. Int J Environ Res Public Health 2008;5:408–417.
Alippi AM, Ringuelet JA, Cerimele EL, Re MS, Henning CP. Antimicrobial activity of some essential oils against Paenibacillus larvae, the causal agent of American foulbrood disease. J Herbs, Spices, Med Plants 1996;4:9–16.
Almela L, Sanchez-Munoz B, Fernandez-Lopez JA, Roca MJ, Rabe V. Liquid chromatograpic-mass spectrometric analysis of phenolics and free radical scavenging activity of rosemary extract from different raw material. J Chromatogr. A 2006;1120:221–229.
Altinier G, Sosa S, Aquino RP, Mencherini T, Della LR, Tubaro A. Characterization of topical anti-inflammatory compounds in Rosmarinus officinalis L. J Agric Food Chem. 2007;55:1718–1723.
Amin A, Hamza AA. Hepatoprotective effects of Hibiscus, Rosmarinus, and Salvia on azathioprine-induced toxicity in rats. Life Sci. 2005;77:266–278.
Angelini LG, Carpanese G, Cioni PL, Morelli I, Macchia M, Flamini G. Essential oils from Mediterranean lamiaceae as weed germination inhibitors. J Agric. Food Chem. 2003;51:6158–6164.
Angioni A, Barra A, Cereti E, Barile D, Coisson JD, Arlorio M, Dessi S, Coroneo V, Cabras P. Cchemical composition, plant genetic differences, antimicrobial and antifungal activity investigation of the essential oil of Rosmarinus officinalis L. J Agric Food Chem. 2004;52:3530–3535.
Antonio CM, Abriouel H, Lopez RL, Omar NB, Valdivia E, Galvez A. Enhanced bactericidal activity of enterocin AS-48 in combination with essential oils, natural bioactive compounds and chemical preservatives against Listeria monocytogenes in ready-to-eat salad. Food Chem Toxicol. 2009;47:2216–2223.
Aqel MB. Relaxant effect of the volatile oil of Rosmarinus officinalis on tracheal smooth muscle. J Ethnopharmacol. 1991;33:57–62.
Ariana A, Ebadi R, Tahmasebi G. Laboratory evaluation of some plant essences to control Varroa destructor (Acari: varroidae). Exp Appl Acarol. 2002;27:319–327.
Arican E. Inhibition of crown-gall tumorigenesis with plant extracts. Pharm Biol. 2009;47:463–466.
Armisen M, Rodriguez V, Vidal C. Photoaggravated allergic contact dermatitis due to Rosmarinus officinalis cross-reactive with Thymus vulgaris. Contact Derm. 2003;48:52–53.
Arraez-Roman D, Gomez-Caravaca AM, Gomez-Romero M, Segura-Carretero A, Fernandez-Gutierrez A. Identification of phenolic compounds in rosemary honey using solid-phase extraction by capillary electrophoresis-electrospray ionization-mass spectrometry. J Pharm Biomed Anal. 2006;41:1648–1656.
Arslan D, Musa Ozcan M. Evaluation of drying methods with respect to drying kinetics, mineral content, and colour characteristics of rosemary leaves. Energ Convers Manag. 2008;49:1258–1264.
Artico M, Cervoni L, Nucci F, Giuffre R. Birthday of peripheral nervous system surgery: the contribution of Gabriele Ferrara (1543–1627). Neurosurgery 1996;39:380–382.
Aruoma OI. Antioxidant actions of plant foods: use of oxidative DNA damage as a tool for studying antioxidant efficacy. Free Radic Res. 1999;30:419–427.

Aruoma OI, Halliwell B, Aeschbach R, Loligers J. Antioxidant and pro-oxidant properties of active rosemary constituents: carnosol and carnosic acid. Xenobiotica 1992;22:257–268.
Aruoma OI, Spencer JP, Rossi R, Aeschbach R, Khan A, Mahmood N, Munoz A, Murcia A, Butler J, Halliwell B. An evaluation of the antioxidant and antiviral action of extracts of rosemary and Provencal herbs. Food Chem Toxicol. 1996;34:449–456.
Asai A, Nakagawa K, Miyazawa T. Antioxidative effects of turmeric, rosemary, and capsicum extracts on membrane phospholipid peroxidation and liver lipid metabolism in mice. Biosci Biotechnol Biochem. 1999;63:2118–2122.
Atsumi T, Tonosaki K. Smelling lavender and rosemary increases free radical scavenging activity and decreases cortisol level in saliva. Psychiatry Res. 2007;150:89–96.
Awney HA, Sindi H. The effect of rosemary on the mutagenic activity of heterocyclic amines extracted from common food consumed in Saudi Arabia. Int J Food Sci Nutr. 2010;61:192–203.
Ayadi MA, Grati-Kamoun N, Attia H. Physico-chemical change and heat stability of extra virgin olive oils flavoured by selected Tunisian aromatic plants. Food Chem Toxicol. 2009;47:2613–2619.
Baardseth P. Effect of selected antioxidants on the stability of dehydrated mashed potatoes. Food Addit Contam. 1989;6:201–207.
Babu US, Wiesenfeld PL, Jenkins MY. Effect of dietary rosemary extract on cell-mediated immunity of young rats. Plant Foods Hum Nutr. 1999;53:169–174.
Backleh M, Leupold G, Parlar H. Rapid quantitative enrichment of carnosic acid from rosemary (Rosmarinus officinalis L.) by isoelectric focused adsorptive bubble chromatography. J Agric Food Chem. 2003;51:1297–1301.
Bagamboula CF, Uyttendaele M, Debevere J. Inhibitory effects of spices and herbs toward Shigella sonnei and S. flexneri. Meded. Rijksuniv. Gent Fak. Landbouwkd. Toegep Biol Wet. 2001;66:523–530.
Bagamboula CF, Uyttendaele M, Debevere J. Antimicrobial effect of spices and herbs on Shigella sonnei and Shigella flexneri. J Food Prot. 2003;66:668–673.
Bajer T, Adam M, Galla L, Ventura K. Comparison of various extraction techniques for isolation and determination of isoflavonoids in plants. J Sep Sci. 2007;30:122–127.
Bakirel T, Bakirel U, Keles OU, Ulgen SG, Yardibi H. In vivo assessment of antidiabetic and antioxidant activities of rosemary (Rosmarinus officinalis) in alloxan-diabetic rabbits. J Ethnopharmacol. 2008;116:64–73.
Ball LJ, Shoker J, Miles JN. Odour-based context reinstatement effects with indirect measures of memory: the curious case of rosemary. Br J Psychol. 2009 (E-pub ahead of print).
Balogh Z, Gray JI, Gomaa EA, Booren AM. Formation and inhibition of heterocyclic aromatic amines in fried ground beef patties. Food Chem Toxicol. 2000;38:395–401.
Bassani V, Casadebaig J, Jacob M, Menut C, Lamaty G. Preparation of a low-alcohol extract of Rosmarinus officinalis using a reverse osmosis membrane. Int J Pharm. 1990;63:57–63.
Baumann LS. Less-known botanical cosmeceuticals. Dermatol Ther. 2007;20:330–342.
Baylac S, Racine P. Inhibition of human leukocyte elastase by natural fragrant extracts of aromatic plants. Int J Aromather. 2004;14:179–182.
Beaulieu JE. Herbal therapy interactions with immunosuppressive agents. US Pharmacist. 2001;26:13–22.
Beddows CG, Jagait C, Kelly MJ. Preservation of alpha-tocopherol in sunflower oil by herbs and spices. Int J Food Sci Nutr. 2000;51:327–339.
Benhabiles NE, Ait-Amar H, Boutekdjiret C, Belabbes R. Comparative study of Algeria's Rosmarinus eriocalyx and Rosmarinus officinalis L. Perfum. Flavor. 2001;26:40–48.
Bentayeb K, Rubio C, Batlle R, Nerin C. Direct determination of carnosic acid in a new active packaging based on natural extract of rosemary. Anal. Bioanal. Chem. 2007;389:1989–1996.
Bentayeb K, Vera P, Rubio C, Nerin C. Adaptation of the ORAC assay to the common laboratory equipment and subsequent application to antioxidant plastic films. Anal. Bioanal. Chem. 2009;394:903–910.
Bezanger BL, Guilbert N. On the flavonoids in rosemary leaves. C. R. Hebd. Seances Acad Sci. 1965;260:3202–3203.
Bhale SD, Xu Z, Prinyawiwatkul W, King JM, Godber JS. Oregano and rosemary extracts inhibit oxidation of long-chain N-3 fatty acids in menhaden oil. J Food Sci. 2007;72:C504–C508.

Bogdadi H, Abdelsalam A, Kokoska L, Havlik J, Kloucek P, Rada V, Vorisek K. In vitro antimicrobial activity of some Libyan medicinal plant extracts. Pharm Biol. 2007;45:386–391.
Boot C, Mayer J. 2 new finds in the old German delivery of the rosemary treatise. Sudhoffs Arch. 1990;74:104–111.
Botsoglou NA, Govaris A, Giannenas I, Botsoglou E, Papageorgiou G. The incorporation of dehydrated rosemary leaves in the rations of turkeys and their impact on the oxidative stability of the produced raw and cooked meat. Int J Food Sci Nutr. 2007;58:312–320.
Boyraz N, Ozcan M. Antifungal effect of some spice hydrosols. Fitoterapia. 2005;76:661–665.
Bozin B, Mimica-Dukic N, Samojlik I, Jovin E. Antimicrobial and antioxidant properties of rosemary and sage (Rosmarinus officinalis L. and Salvia officinalis L., Lamiaceae) essential oils. J Agric Food Chem. 2007;55:7879–7885.
Brieskorn CH, Domling HJ. On the presence of 5-hydroxy-7, 4′-dimethoxyflavone in the leaves of Rosmarinus officinalis L. Arch Pharm Ber Dtsch Pharm Ges. 1967;300:1042–1044.
Brieskorn CH, Zweyrohn G. Incidence of 3 further triterpene acids in the leaves of Rosmarinus officinalis L. Pharmazie. 1970;25:488–490.
Brooks JC, Alvarado M, Stephens TP, Kellermeier JD, Tittor AW, Miller MF, Brashears MM. Spoilage and safety characteristics of ground beef packaged in traditional and modified atmosphere packages. J Food Prot. 2008;71:293–301.
Burkhard PR, Burkhardt K, Haenggeli CA, Landis T. Plant-induced seizures: reappearance of an old problem. J Neurol. 1999;246:667–670.
Burnett KM, Solterbeck LA, Strapp CM. Scent and mood state following an anxiety-provoking task. Psychol Rep. 2004;95:707–722.
Calabrese V, Scapagnini G, Catalano C, Bates TE, Dinotta F, Micali G, Giuffrida Stella AM. Induction of heat shock protein synthesis in human skin fibroblasts in response to oxidative stress: regulation by a natural antioxidant from rosemary extract. Int J Tissue React. 2001;23:51–58.
Calabrese V, Scapagnini G, Catalano C, Dinotta F, Geraci D, Morganti P. Biochemical studies of a natural antioxidant isolated from rosemary and its application in cosmetic dermatology. Int J Tissue React. 2000;22:5–13.
Calucci L, Pinzino C, Zandomeneghi M, Capocchi A, Ghiringhelli S, Saviozzi F, Tozzi S, Galleschi L. Effects of gamma-irradiation on the free radical and antioxidant contents in nine aromatic herbs and spices. J Agric Food Chem. 2003;51:927–934.
Campbell W, Drake MA, Larick DK. The impact of fortification with conjugated linoleic acid (CLA) on the quality of fluid milk. J Dairy Sci. 2003;86:43–51.
Cantrell CL, Richheimer SL, Nicholas GM, Schmidt BK, Bailey DT. Seco-Hinokiol, a new abietane diterpenoid from Rosmarinus officinalis. J Nat Prod. 2005;68:98–100.
Carraminana JJ, Rota C, Burillo J, Herrera A. Antibacterial efficiency of Spanish Satureja montana essential oil against Listeria monocytogenes among natural flora in minced pork. J Food Prot. 2008;71:502–508.
Carrillo JD, Tena MT. Determination of volatile compounds in antioxidant rosemary extracts by solid-phase microextraction and gas chromatography. Anal Lett. 2005;38:1193–1212.
Castrillo M, Vizcaino D, Moreno E, Latorraca Z. Specific leaf mass, fresh: dry weight ratio sugar and protein contents in species of Lamiaceae from different light environments. Rev Biol Trop. 2005;53:23–28.
Cervellati R, Renzulli C, Guerra MC, Speroni E. Evaluation of antioxidant activity of some natural polyphenolic compounds using the Briggs-Rauscher reaction method. J Agric. Food Chem. 2002;50:7504–7509.
Chan MM, Ho CT, Huang HI. Effects of three dietary phytochemicals from tea, rosemary, and turmeric on inflammation-induced nitrite production. Cancer Lett. 1995;96:23–29.
Chang CH, Chyau CC, Hsieh CL, Wu YY, Ker YB, Tsen HY, Peng RY. Relevance of phenolic diterpene constituents to antioxidant activity of supercritical CO_2 extract from the leaves of rosemary. Nat Prod Res. 2008;22:76–90.
Chang MH, Chen TC. "Hotness" stability of chicken hot-wing products as affected by preparation methods and storage. Poult Sci. 1998;77:627–631.
Cheng SC, Huang MZ, Shiea J. Thin-layer chromatography/laser-induced acoustic desorption/electrospray ionization mass spectrometry. Anal Chem. 2009;81:9274–9281.

Cheung S, Tai J. Anti-proliferative and antioxidant properties of rosemary Rosmarinus officinalis. Oncol Rep. 2007;17:1525–1531.
Chohan M, Forster-Wilkins G, Opara EI. Determination of the antioxidant capacity of culinary herbs subjected to various cooking and storage processes using the ABTS(*+) radical cation assay. Plant Foods Hum Nutr. 2008;63:47–52.
Choi HR, Choi JS, Han YN, Bae SJ, Chung HY. Peroxynitrite scavenging activity of herb extracts. Phytother Res. 2002a;16:364–367.
Choi WS, Park BS, Ku SK, Lee SE. Repellent activities of essential oils and monoterpenes against Culex pipiens pallens. J Am Mosq Control Assoc. 2002b;18:348–351.
Cloyd RA, Galle CL, Keith SR, Kalscheur NA, Kemp KE. Effect of commercially available plant-derived essential oil products on arthropod pests. J Econ Entomol. 2009a;102:1567–1579.
Cloyd RA, Timmons NR, Goebel JM, Kemp KE. Effect of pesticides on adult rove beetle Atheta coriaria (Coleoptera: staphylinidae) survival in growing medium. J Econ Entomol. 2009b;102:1750–1758.
Cordeiro CH, do Sacramento LV, Correa MA, Pizzolitto AC, Bauab TM. Herbal extracts in an experimental mouthwash: pharmacognostics analysis and antibacterial activity. Braz J Pharm Sci. 2006;42:395–404.
Costa S, Utan A, Speroni E, Cervellati R, Piva G, Prandini A, Guerra MC. Carnosic acid from rosemary extracts: a potential chemoprotective agent against aflatoxin B1. An in vitro study. J Appl Toxicol. 2007;27:152–159.
Cross DE, Acamovic T, McDevitt, RM. The productive performance of chicks from 0–21 days, when fed diets containing secondary plant compounds in the presence of an enzyme. Br Poult Sci. 2004a;45(Suppl 1):S50–S51.
Cross DE, McDevitt RM, Acamovic T. Phytochemicals in broiler diets and their effect on nutrient digestibility at 21 days of age. Br Poult Sci. 2004b;45(Suppl 1):S49–S50.
Cross DE, McDevitt RM, Hillman K, Acamovic T. The effect of herbs and their associated essential oils on performance, dietary digestibility and gut microflora in chickens from 7 to 28 days of age. Br Poult Sci. 2007;48:496–506.
Croteau R, Kolattukudy PE. Biosynthesis of pentahydroxystearic acid of cutin from linoleic acid in Rosmarinus officinalis. Arch Biochem Biophys. 1974;162:458–470.
Culotta L, Melati MR, Orecchio S. The use of leaves of Rosmarinus officinalis L. as samplers for polycyclic aromatic hydrocarbons. Assessment of air quality in the area of Palermo. Ann Chim. 2002;92:837–845.
Cuppett S, Hall C, III, Conway H, Birt D, Lawson T. Inhibition of the mutagenicity of alkylating agents by rosmariquinone, a component of Rosmarinus officinalis L. Cancer Prev Int. 1995;2:25–31.
da Silva LV, Prinyawiwatkul W, King JM, No HK, Bankston JD, Jr, Ge B. Effect of preservatives on microbial safety and quality of smoked blue catfish (Ictalurus furcatus) steaks during room-temperature storage. Food Microbiol. 2008;25:958–963.
Daferera DJ, Ziogas BN, Polissiou MG. GC-MS analysis of essential oils from some Greek aromatic plants and their fungitoxicity on Penicillium digitatum. J Agric Food Chem. 2000;48:2576–2581.
de la FE, Martinez-Castro I, Sanz J. Characterization of Spanish unifloral honeys by solid phase microextraction and gas chromatography-mass spectrometry. J Sep Sci. 2005;28:1093–1100.
de Loreto ES, Pozzatti P, Alves SL, Santurio D, Morais SJ, Alves SH. Differentiation of Candida dubliniensis from Candida albicans on rosemary extract agar and oregano extract agar. J Clin Lab Anal. 2008;22:172–177.
Dearlove RP, Greenspan P, Hartle DK, Swanson RB, Hargrove JL. Inhibition of protein glycation by extracts of culinary herbs and spices. J Med Food. 2008;11:275–281.
Debersac P, Heydel JM, Amiot MJ, Goudonnet H, Artur Y, Suschetet M, Siess MH. Induction of cytochrome P450 and/or detoxication enzymes by various extracts of rosemary: description of specific patterns. Food Chem Toxicol. 2001a;39(9):907–918.
Debersac P, Vernevaut MF, Amiot MJ, Suschetet M, Siess MH. Effects of a water-soluble extract of rosemary and its purified component rosmarinic acid on xenobiotic-metabolizing enzymes in rat liver. Food Chem Toxicol. 2001b;39:109–117.
del Bano MJ, Lorente J, Castillo J, Benavente-Garcia O, Del Rio JA, Ortuno A, Quirin KW, Gerard D. Phenolic diterpenes, flavones, and rosmarinic acid distribution during the development of leaves,

flowers, stems, and roots of Rosmarinus officinalis. Antioxidant activity. J Agric Food Chem. 2003;51:4247–4253.
del Bano MJ, Lorente J, Castillo J, Benavente-Garcia O, Marin MP, Del Rio JA, Ortuno A, Ibarra I. Flavonoid distribution during the development of leaves, flowers, stems, and roots of Rosmarinus officinalis. Postulation of a biosynthetic pathway. J Agric Food Chem. 2004;52:4987–4992.
Del Campo J, Amiot MJ, Nguyen-The C. Antimicrobial effect of rosemary extracts. J Food Prot. 2000;63:1359–1368.
Dias PC, Foglio MA, Possenti A, de Carvalho JE. Antiulcerogenic activity of crude hydroalcoholic extract of Rosmarinus officinalis L. J Ethnopharmacol. 2000;69:57–62.
Diego MA, Jones NA, Field T, Hernandez-Reif M, Schanberg S, Kuhn C, McAdam V, Galamaga R, Galamaga M. Aromatherapy positively affects mood, EEG patterns of alertness and math computations. Int J Neurosci. 1998;96:217–224.
Doolaege EH, Raes K, Smet K, Andjelkovic M, Van Poucke C, De Smet S, Verhe R. Characterization of two unknown compounds in methanol extracts of rosemary oil. J Agric Food Chem. 2007;55:7283–7287.
Dorrie J, Sapala K, Zunino SJ. Carnosol-induced apoptosis and downregulation of Bcl-2 in B-lineage leukemia cells. Cancer Lett. 2001;170:33–39.
Dragan S, Nicola T, Ilina R, Ursoniu S, Kimar A, Nimade S, Nicola T. Role of multi-component functional foods in the complex treatment of patients with advanced breast cancer. Rev Med Chir Soc Med Nat Iasi. 2007;111:877–884.
Du M, Ahn DU. Effect of antioxidants on the quality of irradiated sausages prepared with turkey thigh meat. Poult Sci. 2002;81:1251–1256.
Durakovic Z, Durakovic S. The effect of rosemary oil on Candida albicans. J Indian Med Assoc. 1979;72:175–176.
Elgayyar M, Draughon FA, Golden DA, Mount JR. Antimicrobial activity of essential oils from plants against selected pathogenic and saprophytic microorganisms. J Food Prot. 2001;64:1019–1024.
Englberger W, Hadding U, Etschenberg E, Graf E, Leyck S, Winkelmann J, Parnham MJ. Rosmarinic acid: a new inhibitor of complement C3-convertase with anti-inflammatory activity. Int J Immunopharmacol. 1988;10:729–737.
Erdogrul OT. Antibacterial activities of some plant extracts used in folk medicine. Pharm Biol. 2002;40:269–273.
Erenmemisoglu A, Saraymen R, Ustun S. Effect of a Rosmarinus officinalis leave extract on plasma glucose levels in normoglycaemic and diabetic mice. Pharmazie. 1997;52:645–646.
Erkr F, Erdemir T, Ceylan FO, Toker C. Fumigant toxicity of three essential oils and their binary and tertiary mixtures against the pulse beetle, Callosobruchus maculates F. (Coleoptera: bruchidae). Fresen Environ Bull. 2009;18:975–981.
Esiyok D, Otles S, Akcicek E. Herbs as a food source in Turkey. Asian Pac J Cancer Prev. 2004;5:334–339.
Etter SC. Rosmarinus officinalis as an Antioxidant. J Herbs Spices Med Plants 2004;11:121–159.
Fabio A, Corona A, Forte E, Quaglio P. Inhibitory activity of spices and essential oils on psychrotrophic bacteria. New Microbiol. 2003;26:115–120.
Fahim FA, Esmat AY, Fadel HM, Hassan KF. Allied studies on the effect of Rosmarinus officinalis L. on experimental hepatotoxicity and mutagenesis. Int J Food Sci Nutr. 1999;50:413–427.
Fan X, Sommers CH, Sokorai KJ. Ionizing radiation and antioxidants affect volatile sulfur compounds, lipid oxidation, and color of ready-to-eat Turkey bologna. J Agric Food Chem. 2004;52:3509–3515.
Fenner R, Betti AH, Mentz LA, Rates SM. Plants with potential antifungal activity employed in Brazilian folk medicine. Braz J Pharm Sci. 2006;42:369–394.
Fernandez L, Duque S, Sanchez I, Quinones D, Rodriguez F, Garcia-Abujeta JL. Allergic contact dermatitis from rosemary (Rosmarinus officinalis L.). Contact Derm. 1997;37:248–249.
Fernandez-Torres R, Perez-Bernal JL, Bello-Lopez MA, Callejon-Mochon M, Jimenez-Sanchez JC, Guiraum-Perez A. Mineral content and botanical origin of Spanish honeys. Talanta. 2005;65:686–691.
Flamini G, Cioni PL, Morelli I, Macchia M, Ceccarini L. Main agronomic-productive characteristics of two ecotypes of Rosmarinus officinalis L. and chemical composition of their essential oils. J Agric Food Chem. 2002;50:3512–3517.

Forster HB, Niklas H, Lutz S. Antispasmodic effects of some medicinal plants. Planta Med. 1980;40:309–319.

Frackowiak A, Fiszer-Kuc M, Maliszewska I, Bruziewicz-Mikla-Szewska B, Gancarz R. Attempt of using extracts of plants helpful in treatment of oral disease – Halitosi. Herba Polonica. 2003;49:371–372.

Fu Y, Zu Y, Chen L, Efferth T, Liang H, Liu Z, Liu W. Investigation of antibacterial activity of rosemary essential oil against Propionibacterium acnes with atomic force microscopy. Planta Med. 2007a;73:1275–1280.

Fu Y, Zu Y, Chen L, Shi X, Wang Z, Sun S, Efferth T. Antimicrobial activity of clove and rosemary essential oils alone and in combination. Phytother Res. 2007b;21:989–994.

Fuchs SM, Schliemann-Willers S, Fischer TW, Elsner P. Protective effects of different marigold (Calendula officinalis L.) and rosemary cream preparations against sodium-lauryl-sulfate-induced irritant contact dermatitis. Skin Pharmacol Physiol. 2005;18:195–200.

Fuhrman B, Volkova N, Rosenblat M, Aviram M. Lycopene synergistically inhibits LDL oxidation in combination with vitamin E, glabridin, rosmarinic acid, carnosic acid, or garlic. Antioxid Redox Signal. 2000;2:491–506.

Galobart J, Barroeta AC, Baucells MD, Codony R, Ternes W. Effect of dietary supplementation with rosemary extract and alpha-tocopheryl acetate on lipid oxidation in eggs enriched with omega3-fatty acids. Poult Sci. 2001;80:460–467.

Ganeva Y, Tsankova E, Simova S, Apostolova B, Zaharieva E. Rofficerone: a new triterpenoid from Rosmarinus officinalis. Planta Med. 1993;59:276–277.

Garcia S, Dos Santos EP, Da Salva AJ, Di Giacomo CG, Soares HC. Application of rosemary extracts as sunscreen. Rev Bras Farm. 1992;73:35–36.

Gedney JJ, Glover TL, Fillingim RB. Sensory and affective pain discrimination after inhalation of essential oils. Psychosom Med. 2004;66:599–606.

Geoffroy M, Lambelet P, Richert P. Radical intermediates and antioxidants: an ESR study of radicals formed on carnosic acid in the presence of oxidized lipids. Free Radic Res. 1994;21:247–258.

Giachetti D, Taddei E, Taddei I. Pharmacological activity of Mentha piperita, Salvia officinalis and Rosmarinus officinalis essences on Oddi's sphincter. Planta Med. 1986;52:543–544.

Gillij YG, Gleiser RM, Zygadlo JA. Mosquito repellent activity of essential oils of aromatic plants growing in Argentina. Bioresour Technol. 2008;99:2507–2515.

Giordani R, Regli P, Kaloustian J, Mikail C, Abou L, Portugal H. Antifungal effect of various essential oils against Candida albicans. Potentiation of antifungal action of amphotericin B by essential oil from Thymus vulgaris. Phytother Res. 2004;18:990–995.

Giron LM, Freire V, Alonzo A, Caceres A. Ethnobotanical survey of the medicinal flora used by the Caribs of Guatemala. J Ethnopharmacol. 1991;34:173–187.

Gladine C, Rock E, Morand C, Bauchart D, Durand D. Bioavailability and antioxidant capacity of plant extracts rich in polyphenols, given as a single acute dose, in sheep made highly susceptible to lipoperoxidation. Br J Nutr. 2007;98:691–701.

Gobert M, Martin B, Ferlay A, Chilliard Y, Graulet B, Pradel P, Bauchart D, Durand D. Plant polyphenols associated with vitamin E can reduce plasma lipoperoxidation in dairy cows given N-3 polyunsaturated fatty acids. J Dairy Sci. 2009;92:6095–6104.

Gonzalez-Miret ML, Terrab A, Hernanz D, Fernandez-Recamales MA, Heredia FJ. Multivariate correlation between color and mineral composition of honeys and by their botanical origin. J Agric Food Chem. 2005;53:2574–2580.

Gonzalez-Trujano ME, Pena EI, Martinez AL, Moreno J, Guevara-Fefer P, Deciga-Campos M, Lopez-Munoz FJ. Evaluation of the antinociceptive effect of Rosmarinus officinalis L. using three different experimental models in rodents. J Ethnopharmacol. 2007;111:476–482.

Grabensteiner E, Arshad N, Hess M. Differences in the in vitro susceptibility of mono-eukaryotic cultures of Histomonas meleagridis, Tetratrichomonas gallinarum, and Blastocystis sp. to natural organic compounds. Parasitol Res. 2007;101:193–199.

Gramza-Michalowska A, Korczak J, Regula J. Use of plant extracts in summer and winter seasons butter oxidative stability improvement. Asia Pac J Clin Nutr. 2007;16(Suppl 1):85–88.

Granger R, Passet J, Arbousset G, Girard JP. Biogenetic relations between verbenone and alpha-pinene in Rosmarinus officinalis L. C R Hebd Seances Acad Sci D. 1970;270:209–212.

Grayer RJ, Eckert MR, Veitch NC, Kite GC, Marin PD, Kokubun T, Simmonds MS, Paton AJ. The chemotaxonomic significance of two bioactive caffeic acid esters, nepetoidins A and B, in the Lamiaceae. Phytochemistry. 2003;64:519–528.

Greenlee H, Atkinson C, Stanczyk FZ, Lampe JW. A pilot and feasibility study on the effects of naturopathic botanical and dietary interventions on sex steroid hormone metabolism in premenopausal women. Cancer Epidemiol Biomarkers Prev. 2007;16:1601–1609.

Guin JD. Rosemary cheilitis: one to remember. Contact Derm. 2001;45:63.

Gutierrez J, Barry-Ryan C, Bourke P. The antimicrobial efficacy of plant essential oil combinations and interactions with food ingredients. Int J Food Microbiol. 2008a;124:91–97.

Gutierrez J, Rodriguez G, Barry-Ryan C, Bourke P. Efficacy of plant essential oils against foodborne pathogens and spoilage bacteria associated with ready-to-eat vegetables: antimicrobial and sensory screening. J Food Prot. 2008b;71:1846–1854.

Gutierrez ME, Garcia AF, Africa DM, Sagrista ML, Casado FJ, Mora M. Interaction of tocopherols and phenolic compounds with membrane lipid components: evaluation of their antioxidant activity in a liposomal model system. Life Sci. 2003;72:2337–2360.

Gutierrez R, Alvarado JL, Presno M, Perez-Veyna O, Serrano CJ, Yahuaca P. Oxidative stress modulation by Rosmarinus officinalis in CCl(4)-induced liver cirrhosis. Phytother Res. 2010;24:595–601.

Haddad PS, Depot M, Settaf A, Chabli A, Cherrah Y. Comparative study on the medicinal plants most recommended by traditional practitioners in Morocco and Canada. J Herbs Spices Med Plants. 2003;10:25–45.

Hafez HM, Hauck R. Efficacy of a herbal product against Histomonas meleagridis after experimental infection of turkey poults. Arch Anim Nutr. 2006;60:436–442.

Haloui M, Louedec L, Michel JB, Lyoussi B. Experimental diuretic effects of Rosmarinus officinalis and Centaurium erythraea. J Ethnopharmacol. 2000;71:465–472.

Harach T, Aprikian O, Monnard I, Moulin J, Membrez M, Beolor JC, Raab T, Mace K, Darimont C. Rosemary (Rosmarinus officinalis L.) leaf extract limits weight gain and liver steatosis in mice fed a high-fat diet. Planta Med. 2010;76:566–571.

Haraguchi H, Saito T, Okamura N, Yagi A. Inhibition of lipid peroxidation and superoxide generation by diterpenoids from Rosmarinus officinalis. Planta Med. 2009;61:333–336.

Hasani-Ranjbar S, Larijani B, Abdollahi M. A systematic review of the potential herbal sources of future drugs effective in oxidant-related diseases. Inflamm Allergy Drug Targets. 2009;8:2–10.

Hay IC, Jamieson M, Ormerod AD. Randomized trial of aromatherapy. Successful treatment for alopecia areata. Arch Dermatol. 1998;134:1349–1352.

Heinrich M, Kufer J, Leonti M, Pardo-de-Santayana M. Ethnobotany and ethnopharmacology—interdisciplinary links with the historical sciences. J Ethnopharmacol. 2006;107:157–160.

Hernandez F, Madrid J, Garcia V, Orengo J, Megias MD. Influence of two plant extracts on broilers performance, digestibility, and digestive organ size. Poult Sci. 2004;83:169–174.

Herrero M, Arraez-Roman D, Segura A, Kenndler E, Gius B, Raggid MA, Ibanez E, Cifuentes A. Pressurized liquid extraction-capillary electrophoresis-mass spectrometry for the analysis of polar antioxidants in rosemary extracts. J Chromatogr A. 2005;1084:54–62.

Herrero M, Plaza M, Cifuentes A, Ibanez E. Green processes for the extraction of bioactives from Rosemary: chemical and functional characterization via ultra-performance liquid chromatography-tandem mass spectrometry and in-vitro assays. J Chromatogr A. 2010;1217:2512–2520.

Hethelyi E, Kaposi P, Domonkos J, Kernoczi Z. GC/MS investigation of the essential oils Rosmarinus officinalis L. Acta Pharm Hung. 2009;57:159–169.

Hjorther AB, Christophersen C, Hausen BM, Menne T. Occupational allergic contact dermatitis from carnosol, a naturally occurring compound present in rosemary. Contact Derm. 1997;37:99–100.

Ho CT, Wang M, Wei GJ, Huang TC, Huang MT. Chemistry and antioxidative factors in rosemary and sage. Biofactors. 2000;13:161–166.

Ho SC, Tsai TH, Tsai PJ, Lin CC. Protective capacities of certain spices against peroxynitrite-mediated biomolecular damage. Food Chem Toxicol. 2008;46:920–928.

Hoefler C, Fleurentin J, Mortier F, Pelt JM, Guillemain J. Comparative choleretic and hepatoprotective properties of young sprouts and total plant extracts of Rosmarinus officinalis in rats. J Ethnopharmacol. 1987;19:133–143.

Hosny M, Johnson HA, Ueltschy AK, Rosazza JP. Oxidation, reduction, and methylation of carnosic acid by Nocardia. J Nat Prod. 2002;65:1266–1269.

Hosseinzadeh H, Nourbakhsh M. Effect of Rosmarinus officinalis L. aerial parts extract on morphine withdrawal syndrome in mice. Phytother Res. 2003;17:938–941.

Hsieh CL, Peng CH, Chyau CC, Lin YC, Wang HE, Peng RY. Low-density lipoprotein, collagen, and thrombin models reveal that Rosemarinus officinalis L. exhibits potent antiglycative effects. J Agric Food Chem. 2007;55:2884–2891.

Hsu S. Green tea and the skin. J Am Acad Dermatol. 2005;52:1049–1059.

Huang HC, Huang CY, Lin-Shiau SY, Lin JK. Ursolic acid inhibits IL-1beta or TNF-alpha-induced C6 glioma invasion through suppressing the association ZIP/p62 with PKC-zeta and downregulating the MMP-9 expression. Mol Carcinog. 2009;48:517–531.

Huang MT, Ho CT, Wang ZY, Ferraro T, Lou YR, Stauber K, Ma W, Georgiadis C, Laskin JD, Conney AH. Inhibition of skin tumorigenesis by rosemary and its constituents carnosol and ursolic acid. Cancer Res. 1994;54:701–708.

Huang SC, Ho CT, Lin-Shiau SY, Lin JK. Carnosol inhibits the invasion of B16/F10 mouse melanoma cells by suppressing metalloproteinase-9 through downregulating nuclear factor-kappa B and c-Jun. Biochem Pharmacol. 2005;69:221–232.

Ibanez E, Cifuentes A, Crego AL, Senorans FJ, Cavero S, Reglero G. Combined use of supercritical fluid extraction, micellar electrokinetic chromatography, and reverse phase high-performance liquid chromatography for the analysis of antioxidants from rosemary (Rosmarinus officinalis L.). J Agric Food Chem. 2000;48:4060–4065.

Ibanez E, Kubatova A, Senorans FJ, Cavero S, Reglero G, Hawthorne SB. Subcritical water extraction of antioxidant compounds from rosemary plants. J Agric Food Chem. 2003;51:375–382.

Inoue K, Takano H, Shiga A, Fujita Y, Makino H, Yanagisawa R, Ichinose T, Kato Y, Yamada T, Yoshikawa T. Effects of volatile constituents of a rosemary extract on allergic airway inflammation related to house dust mite allergen in mice. Int J Mol Med. 2005;16:315–319.

Inui S, Katayama I. Allergic contact dermatitis induced by rosemary leaf extract in a cleansing gel. J Dermatol. 2005;32:667–669.

Ismail SA, Dea T, Abd El-Rahman H, Yassien MA, Beuchat LR. Effectiveness of immersion treatments with acids, trisodium phosphate, and herb decoctions in reducing populations of Yarrowia lipolytica and naturally occurring aerobic microorganisms on raw chicken. Int J Food Microbiol. 2001;64:13–19.

Isman MB, Wilson JA, Bradbury R. Insecticidal activities of commercial rosemary oils (Rosmarinus officinalis) against larvae of Pseudaletia unipuncta and Trichoplusia ni in relation to their chemical compositions. Pharm Biol. 2008;46:82–87.

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1–12.

Jager S, Trojan H, Kopp T, Laszczyk MN, Scheffler A. Pentacyclic triterpene distribution in various plants – rich sources for a new group of multi-potent plant extracts. Molecules. 2009;14:2016–2031.

Jaswir I, Che Man YB, Hassan TH. Performance of phytochemical antioxidant systems in refined-bleached-deodorized palm olein during frying. Asia Pac J Clin Nutr. 2005;14:402–413.

Jimenez MM, Fresno Contreras MJ, Selles E. Pharmacotechnical characterization and effectiveness testing of a proposed emulsion for the treatment of dry skin. Boll Chim Farm. 2002;141: 333–342.

Jirovetz L, Buchbauer G, Denkova Z, Stoyanova A, Murgov I, Schmidt E, Geissler M. Antimicrobial testings and gas chromatographic analysis of pure oxygenated monoterpenes 1,8-cineole, α-terpineol, terpinen-4-ol and camphor as well as target compounds in essential oils of pine (Pinus pinaster), rosemary (Rosmarinus officinalis), tea tree (Melaleuca alternifolia). Sci Pharm. 2005;73:27–38.

Johnson BM, Bolton JL, van Breemen RB. Screening botanical extracts for quinoid metabolites. Chem Res Toxicol. 2001;14:1546–1551.

Jozsa LG. Histologic diagnoses of tissues from two nineteenth-century Habsburgs. Paleopathol Newsl. 2008;141:12–18.

Kahkonen MP, Hopia AI, Vuorela HJ, Rauha JP, Pihlaja K, Kujala TS, Heinonen M. Antioxidant activity of plant extracts containing phenolic compounds. J Agric Food Chem. 1999;47:3954–3962.

Kaliora AC, Andrikopoulos NK. Effect of Alkanna albugam root on LDL oxidation. A comparative study with species of the Lamiaceae family. Phytother Res. 2005;19:1077–1079.

Karamarkovic AR, Djuranovic SP, Popovic NP, Bumbasirevic VD, Sijacki AD, Blazic IV. Hepatic abscess secondary to a rosemary twig migrating from the stomach into the liver. World J Gastroenterol. 2007;13:5530–5532.
Karanika MS, Komaitis M, Aggelis G. Effect of aqueous extracts of some plants of Lamiaceae family on the growth of Yarrowia lipolytica. Int J Food Microbiol. 2001;64:175–181.
Karlsen J, Svendsen AB. Composition of etheric oil in the leaves of Rosmarinus officinalis L. 1. Monoterpenchydrocarbons. Terpenes and related materials VI. Planta Med. 1968;16:95–98.
Karpinska M, Borowski J, Danowska-Oziewicz M. Antioxidative activity of rosemary extract in lipid fraction of minced meat balls during storage in a freezer. Nahrung 2000;44:38–41.
Karpinska-Tymoszczyk M. Effect of the addition of ground rosemary on the quality and shelf-life of turkey meatballs during refrigerated storage. Br Poult Sci. 2008;49:742–750.
Katerinopoulos HE, Pagona G, Afratis A, Stratigakis N, Roditakis N. Composition and insect attracting activity of the essential oil of Rosmarinus officinalis. J Chem Ecol. 2005;31:111–122.
Kaziulin AN, Petukhov AB, Kucheriavyi I. Efficiency of includes of bioactive substances in diet of patient with hepatic encephalopathy. Vopr Pitan. 2006;75:40–44.
Keokamnerd T, Acton JC, Han IY, Dawson PL. Effect of commercial rosemary oleoresin preparations on ground chicken thigh meat quality packaged in a high-oxygen atmosphere. Poult Sci. 2008;87:170–179.
Khater HF, Ramadan MY, El Madawy RS. Lousicidal, ovicidal, and repellent efficacy of some essential oils against lice and flies infesting water buffaloes in Egypt. Vet Parasitol. 2009;164:257–266.
Kim HY, Kim K. Protein glycation inhibitory and antioxidative activities of some plant extracts in vitro. J Agric Food Chem. 2003;51:1586–1591.
Kim MA, Sakong JK, Kim EJ, Kim EH, Kim EH. Effect of aromatherapy massage for the relief of constipation in the elderly. Taehan Kanho Hakhoe Chi. 2005a;35:56–64.
Kim MJ, Nam ES, Paik SI. The effects of aromatherapy on pain, depression, and life satisfaction of arthritis patients. Taehan Kanho Hakhoe Chi. 2005b;35:186–194.
Kim SJ, Han D, Moon KD, Rhee JS. Measurement of superoxide dismutase-like activity of natural antioxidants. Biosci Biotechnol Biochem. 1995;59:822–826.
Kitano M, Wanibuchi H, Kikuzaki H, Nakatani N, Imaoka S, Funae Y, Hayashi S, Fukushima S. Chemopreventive effects of coumaperine from pepper on the initiation stage of chemical hepatocarcinogenesis in the rat. Jpn J Cancer Res. 2000;91:674–680.
Klancnik A, Guzej B, Kolar MH, Abramovic H, Mozina SS. In vitro antimicrobial and antioxidant activity of commercial rosemary extract formulations. J Food Prot. 2009;72:1744–1752.
Kosaka K, Mimura J, Itoh K, Satoh T, Shimojo Y, Kitajima C, Maruyama A, Yamamoto M, Shirasawa T. Role of Nrf2 and p62/ZIP in the neurite outgrowth by carnosic acid in PC12h cells. J Biochem. 2010;147:73–81.
Kosaka K, Yokoi T. Carnosic acid, a component of rosemary (Rosmarinus officinalis L.), promotes synthesis of nerve growth factor in T98G human glioblastoma cells. Biol Pharm Bull. 2003;26:1620–1622.
Kovar KA, Gropper B, Friess D, Ammon HP. Blood levels of 1, 8-cineole and locomotor activity of mice after inhalation and oral administration of rosemary oil. Planta Med. 1987;53:315–318.
Kreis P, Dietrich A, Mosandl A. Chiral compounds of essential oils. Part 18. On the authenticity of assessment of the essential oil of Rosmarinus officinalis L. Die Pharmazie. 1994;49:761–765.
Kuhlmann A, Rohl C. Phenolic antioxidant compounds produced by in vitro cultures of rosemary (Rosmarinus officinalis) and their anti-inflammatory effect on lipopolysaccharide-activated microglia. Pharm Biol. 2006;44:401–410.
Kwon YI, Vattem DA, Shetty K. Evaluation of clonal herbs of Lamiaceae species for management of diabetes and hypertension. Asia Pac J Clin Nutr. 2006;15:107–118.
Lai CS, Lee JH, Ho CT, Liu CB, Wang JM, Wang YJ, Pan MH. Rosmanol potently inhibits lipopolysaccharide-induced iNOS and COX-2 expression through downregulating MAPK, NF-kappaB, STAT3, and C/EBP signaling pathways. J Agric Food Chem. 2009;57:10990–10998.
Lai PK, Roy J. Antimicrobial and chemopreventive properties of herbs and spices. Curr Med Chem. 2004;11:1451–1460.
Laitinen LA, Tammela PS, Galkin A, Vuorela HJ, Marvola ML, Vuorela PM. Effects of extracts of commonly consumed food supplements and food fractions on the permeability of drugs across Caco-2 cell monolayers. Pharm Res. 2004;21:1904–1916.

Lamaison JL, Petitjean-Freytet C, Carnat A. Medicinal Lamiaceae with antioxidant properties, a potential source of rosmarinic acid. Pharm Acta Helv. 1991;66:185–188.
Larrondo JV, Agut M, Calvo-Torras MA. Antimicrobial activity of essences from labiates. Microbios. 1995;82:171–172.
Laszczyk MN. Pentacyclic triterpenes of the lupane, oleanane, and ursane group as tools in cancer therapy. Planta Med. 2009;75:1549–1560.
Leal PF, Braga ME, Sato DN, Carvalho JE, Marques MO, Meireles MA. Functional properties of spice extracts obtained via supercritical fluid extraction. J Agric Food Chem. 2003;51: 2520–2525.
Lee JJ, Jin YR, Lee JH, Yu JY, Han XH, Oh KW, Hong JT, Kim TJ, Yun YP. Antiplatelet activity of carnosic acid, a phenolic diterpene from Rosmarinus officinalis. Planta Med. 2007;73:121–127.
Lee KG, Shibamoto T. Determination of antioxidant potential of volatile extracts isolated from various herbs and spices. J Agric Food Chem. 2002;50:4947–4952.
Lee SY, Gwon SY, Kim SJ, Moon BK. Inhibitory effect of commercial green tea and rosemary leaf powders on the growth of foodborne pathogens in laboratory media and oriental-style rice cakes. J Food Prot. 2009;72:1107–1111.
Lee TG, Williams SK, Sloan D, Littell R. Development and evaluation of a chicken breakfast sausage manufactured with mechanically deboned chicken meat. Poult Sci. 1997;76:415–421.
Lemberkovics E, Kery A, Simandi B, Kakasy A, Balazs A, Hethelyi E, Szoke E. Influence of extraction methods on the composition of essential oils. Acta Pharm Hung. 2004;74:166–170.
Lemiere C, Cartier A, Lehrer SB, Malo JL. Occupational asthma caused by aromatic herbs. Allergy. 1996;51:647–649.
Lemonica IP, Damasceno DC, di Stasi LC. Study of the embryotoxic effects of an extract of rosemary (Rosmarinus officinalis L.). Braz J Med Biol Res. 1996;29:223–227.
Lev E. Drugs held and sold by pharmacists of the Jewish community of medieval (11–14th centuries) Cairo according to lists of materia medica found at the Taylor–Schechter Genizah collection, Cambridge. J Ethnopharmacol. 2007;110:275–293.
Llewellyn GC, Burkett ML, Eadie T. Potential mold growth, aflatoxin production, and antimycotic activity of selected natural spices and herbs. J Assoc. Off Anal Chem. 1981;64:955–960.
Lo AH, Liang YC, Lin-Shiau SY, Ho CT, Lin JK. Carnosol, an antioxidant in rosemary, suppresses inducible nitric oxide synthase through downregulating nuclear factor-kappaB in mouse macrophages. Carcinogenesis. 2002;23:983–991.
Lopez P, Sanchez C, Batlle R, Nerin C. Solid- and vapor-phase antimicrobial activities of six essential oils: susceptibility of selected foodborne bacterial and fungal strains. J Agric Food Chem. 2005;53:6939–6946.
Lopez-Bote CJ, Gray JI, Gomaa EA, Flegal CJ. Effect of dietary administration of oil extracts from rosemary and sage on lipid oxidation in broiler meat. Br Poult Sci. 1998;39:235–240.
Lopez-Lazaro M. Distribution and biological activities of the flavonoid luteolin. Mini Rev Med Chem. 2009;9:31–59.
Lopez-Munoz F, Alamo C, Garcia-Garcia P. "The herbs that have the property of healing . . . ,": the phytotherapy in Don Quixote. J Ethnopharmacol. 2006;106:429–441.
Lopez-Munoz F, Garcia-Garcia P, Alamo C. The virtue of that precious balsam . . . : approach to Don Quixote from the psychopharmacological perspective. Actas Esp Psiquiatr. 2007;35:149–220.
Lopez-Sebastian S, Ramos E, Ibanez E, Bueno JM, Ballester L, Tabera J, Reglero G. Dearomatization of antioxidant rosemary extracts by treatment with supercritical carbon dioxide. J Agric Food Chem. 1998;46:13–19.
Louli V, Ragoussis N, Magoulas K. Recovery of phenolic antioxidants from wine industry by-products. Bioresour Technol. 2004;92:201–208.
Luis JC, Martin R, Frias I, Valdes F. Enhanced carnosic acid levels in two rosemary accessions exposed to cold stress conditions. J Agric Food Chem. 2007;55:8062–8066.
Lukaczer D, Darland G, Tripp M, Liska D, Lerman RH, Schiltz B, Bland JS. A pilot trial evaluating Meta050, a proprietary combination of reduced iso-alpha acids, rosemary extract, and oleanolic acid in patients with arthritis and fibromyalgia. Phytother Res. 2005;19:864–869.
Luqman S, Dwivedi GR, Darokar MP, Kalra A, Khanuja SP. Potential of rosemary oil to be used in drug-resistant infections. Altern Ther Health Med. 2007;13:54–59.

Mace K, Offord EA, Harris CC, Pfeifer AM. Development of in vitro models for cellular and molecular studies in toxicology and chemoprevention. Arch Toxicol Suppl. 1998;20:227–236.
Machado DG, Bettio LE, Cunha MP, Capra JC, Dalmarco JB, Pizzolatti MG, Rodrigues AL. Antidepressant-like effect of the extract of Rosmarinus officinalis in mice: involvement of the monoaminergic system. Prog Neuropsychopharmacol Biol Psychiatry 2009;33:642–650.
Mahady GB, Pendland SL, Stoia A, Hamill FA, Fabricant D, Dietz BM, Chadwick LR. In vitro susceptibility of Helicobacter pylori to botanical extracts used traditionally for the treatment of gastrointestinal disorders. Phytother Res. 2005;19:988–991.
Mahmoud AA, Al Shihry SS, Son BW. Diterpenoid quinones from rosemary (Rosmarinus officinalis L.). Phytochemistry. 2005;66:1685–1690.
Makino T, Ono T, Liu N, Nakamura T, Muso E, Honda G. Suppressive effects of rosmarinic acid on mesangioproliferative glomerulonephritis in rats. Nephron. 2002;92:898–904.
Makino T, Ono T, Muso E, Yoshida H, Honda G, Sasayama S. Inhibitory effects of rosmarinic acid on the proliferation of cultured murine mesangial cells. Nephrol Dial Transplant. 2000;15:1140–1145.
Mancini DA, Torres RP, Pinto JR, Mancini J. Inhibition of DNA virus: herpes-1 (HSV-1) in cellular culture replication, through an antioxidant treatment extracted from rosemary spice. Braz J Pharm Sci. 2009;45:127–133.
Mangena T, Muyima NY. Comparative evaluation of the antimicrobial activities of essential oils of Artemisia afra, Pteronia incana, and Rosmarinus officinalis on selected bacteria and yeast strains. Lett Appl Microbiol. 1999;28:291–296.
Martin R, Pierrard C, Lejeune F, Hilaire P, Breton L, Bernerd F. Photoprotective effect of a water-soluble extract of Rosmarinus officinalis L. against UV-induced matrix metalloproteinase-1 in human dermal fibroblasts and reconstructed skin. Eur J Dermatol. 2008;18:128–135.
Martinez AL, Gonzalez-Trujano ME, Pellicer F, Lopez-Munoz FJ, Navarrete A. Antinociceptive effect and GC/MS analysis of Rosmarinus officinalis L. essential oil from its aerial parts. Planta Med. 2009;75:508–511.
Martinez L, Cilla I, Beltran JA, Roncales P. Combined effect of modified atmosphere packaging and addition of rosemary (Rosmarinus officinalis), ascorbic acid, red beet root (beta vulgaris), and sodium lactate and their mixtures on the stability of fresh pork sausages. J Agric Food Chem. 2006;54:4674–4680.
Martinez-Gonzalez MC, Goday Bujan JJ, Martinez GW, Fonseca CE. Concomitant allergic contact dermatitis due to Rosmarinus officinalis (rosemary) and Thymus vulgaris (thyme). Contact Derm. 2007;56:49–50.
Martinez-Tome M, Jimenez AM, Ruggieri S, Frega N, Strabbioli R, Murcia MA. Antioxidant properties of Mediterranean spices compared with common food additives. J Food Prot. 2001;64:1412–1419.
Mastelic J, Kustrak D. Essential oil and glycosidically-bound volatiles in aromatic plants. Part 2. Rosemary (Rosmarinus officinalis L., Lamiaceae). Acta Pharmaceutica. 1997;47:139–142.
Masuda T, Inaba Y, Maekawa T, Takeda Y, Tamura H, Yamaguchi H. Recovery mechanism of the antioxidant activity from carnosic acid quinone, an oxidized sage, and rosemary antioxidant. J Agric Food Chem. 2002;50:5863–5869.
Masuda T, Inaba Y, Takeda Y. Antioxidant mechanism of carnosic acid: structural identification of two oxidation products. J Agric Food Chem. 2001;49:5560–5565.
Masuda T, Kirikihira T, Takeda Y. Recovery of antioxidant activity from carnosol quinone: antioxidants obtained from a water-promoted conversion of carnosol quinone. J Agric Food Chem. 2005;53:6831–6834.
Matsubara S, Shibata H, Ishikawa F, Yokokura T, Takahashi M, Sugimura T, Wakabayashi K. Suppression of Helicobacter pylori-induced gastritis by green tea extract in Mongolian gerbils. Biochem Biophys Res Commun. 2003;310:715–719.
Mazzio E, Huber J, Darling S, Harris N, Soliman KF. Effect of antioxidants on L-glutamate and N-methyl-4-phenylpyridinium ion-induced neurotoxicity in PC12 cells. Neurotoxicology. 2001;22:283–288.
McCaffrey R, Thomas DJ, Kinzelman AO. The effects of lavender and rosemary essential oils on test-taking anxiety among graduate nursing students. Holist Nurs Pract. 2009;23:88–93.
Milovic I. Medical manuscript of mihail plamenac, a priest. Srp Arh Celok Lek. 1998;126:63–67.

Minich DM, Bland JS, Katke J, Darland G, Hall A, Lerman RH, Lamb J, Carroll B, Tripp M. Clinical safety and efficacy of NG440: a novel combination of rho iso-alpha acids from hops, rosemary, and oleanolic acid for inflammatory conditions. Can J Physiol Pharmacol. 2007;85:872–883.
Minnunni M, Wolleb U, Mueller O, Pfeifer A, Aeschbacher HU. Natural antioxidants as inhibitors of oxygen species-induced mutagenicity. Mutat Res. 1992;269:193–200.
Mirshekar R, Dastar B, Shabanpour B. Effect of rosemary, echinacea, green tea extracts and ascorbic acid on broiler meat quality. Pak J Biol Sci. 2009;12:1069–1074.
Miyazawa M, Sugie A, Shimada T. Roles of human CYP2A6 and 2B6 and rat CYP2C11 and 2B1 in the 10-hydroxylation of (-)-verbenone by liver microsomes. Drug Metab Dispos. 2003;31:1049–1053.
Miyazawa M, Sugie A, Shindo M. Biotransformation of (-)-verbenone by human liver microsomes. Biosci Biotechnol Biochem. 2002;66:2458–2460.
Monino I, Martinez C, Sotomayor JA, Lafuente A, Jordan MJ. Polyphenolic transmission to Segureno lamb meat from ewes' diet supplemented with the distillate from rosemary (Rosmarinus officinalis) leaves. J Agric Food Chem. 2008;56:3363–3367.
Montes MA, Wilkomirsky T, Valenzuela L, Bello H, Osses F. Essential oils from some Labiatae growing in the Bio-Bio region, Chile, Rosmarinus officinalis L., Mentha pulegium L., Mentha spicata L.: components and antimicrobial activity. Anales de la real Academia de Farmacia. 1991;57:425–438.
Moran AE, Carothers AM, Weyant MJ, Redston M, Bertagnolli MM. Carnosol inhibits beta-catenin tyrosine phosphorylation and prevents adenoma formation in the C57BL/6J/Min/+ (Min/+) mouse. Cancer Res. 2005;65:1097–1104.
Moreno S, Scheyer T, Romano CS, Vojnov AA. Antioxidant and antimicrobial activities of rosemary extracts linked to their polyphenol composition. Free Radic. Res. 2006;40:223–231.
Moss M, Cook J, Wesnes K, Duckett P. Aromas of rosemary and lavender essential oils differentially affect cognition and mood in healthy adults. Int J Neurosci. 2003;113:15–38.
Muhlbauer RC, Lozano A, Palacio S, Reinli A, Felix R. Common herbs, essential oils, and monoterpenes potently modulate bone metabolism. Bone. 2003;32:372–380.
Munne-Bosch S, Alegre L. Changes in carotenoids, tocopherols, and diterpenes during drought and recovery, and the biological significance of chlorophyll loss in Rosmarinus officinalis plants. Planta. 2000;210:925–931.
Munne-Bosch S, Alegre L. Subcellular compartmentation of the diterpene carnosic acid and its derivatives in the leaves of rosemary. Plant Physiol. 2001;125:1094–1102.
Munne-Bosch S, Schwarz K, Alegre L. Enhanced formation of alpha-tocopherol and highly oxidized abietane diterpenes in water-stressed rosemary plants. Plant Physiol. 1999a;121: 1047–1052.
Munne-Bosch S, Schwarz K, Alegre L. Response of abietane diterpenes to stress in Rosmarinus officinalis L.: new insights into the function of diterpenes in plants. Free Radic Res. 1999b;31(Suppl):S107–S112.
Nabekura T, Yamaki T, Hiroi T, Ueno K, Kitagawa S. Inhibition of anticancer drug efflux transporter P-glycoprotein by rosemary phytochemicals. Pharmacol Res. 2010;61:259–263.
Naemura A, Ura M, Yamashita T, Arai R, Yamamoto J. Long-term intake of rosemary and common thyme herbs inhibits experimental thrombosis without prolongation of bleeding time. Thromb Res. 2009;122:517–522.
Nakatani N. Phenolic antioxidants from herbs and spices. Biofactors. 2000;13:141–146.
Negroni M, D'Agostina A, Arnoldi A. Effects of olive, canola, and sunflower oils on the formation of volatiles from the Maillard reaction of lysine with xylose and glucose. J Agric Food Chem. 2001;49:439–445.
Nicolato E, Boschi F, Marzola P, Sbarbati A. Secretory response induced by essential oils on airway surface fluid: a pharmacological MRI study. J Ethnopharmacol. 2009;124:630–634.
Nissen LR, Mansson L, Bertelsen G, Huynh-Ba T, Skibsted LH. Protection of dehydrated chicken meat by natural antioxidants as evaluated by electron spin resonance spectrometry. J Agric Food Chem. 2000;48:5548–5556.
Nogues S, Munne-Bosch S, Casadesus J, Lopez-Carbonell M, Alegre L. Daily time course of whole-shoot gas exchange rates in two drought-exposed Mediterranean shrubs. Tree Physiol. 2001;21:51–58.

Nolkemper S, Reichling J, Stintzing FC, Carle R, Schnitzler P. Antiviral effect of aqueous extracts from species of the lamiaceae family against herpes simplex virus type 1 and type 2 in vitro. Planta Med. 2006;72:1378–1382.
Nozal Nalda MJ, Bernal Yague JL, Diego Calva JC, Martin Gomez MT. Classifying honeys from the Soria Province of Spain via multivariate analysis. Anal Bioanal Chem. 2005;382:311–319.
Nusier MK, Bataineh HN, Daradkah HM. Adverse effects of rosemary (Rosmarinus officinalis L.) on reproductive function in adult male rats. Exp Biol Med (Maywood). 2007;232:809–813.
Offord EA, Gautier JC, Avanti O, Scaletta C, Runge F, Kramer K, Applegate LA. Photoprotective potential of lycopene, beta-carotene, vitamin E, vitamin C, and carnosic acid in UVA-irradiated human skin fibroblasts. Free Radic Biol Med. 2002;32:1293–1303.
Offord EA, Mace K, Avanti O, Pfeifer AM. Mechanisms involved in the chemoprotective effects of rosemary extract studied in human liver and bronchial cells. Cancer Lett. 1997;114:275–281.
Offord EA, Mace K, Ruffieux C, Malnoe A, Pfeifer AM. Rosemary components inhibit benzo[a]pyrene-induced genotoxicity in human bronchial cells. Carcinogenesis. 1995;16:2057–2062.
Oh HK, Jones MB, Longhurst WM. Comparison of rumen microbial inhibition resulting from various essential oils isolated from relatively unpalatable plant species. Appl Microbiol. 1968;16:39–44.
Okamura N, Haraguchi H, Hashimoto K, Yagi A. Flavonoids in Rosmarinus officinalis leaves. Phytochemistry. 1994;37:1463–1466.
Olmos E, Sanchez-Blanco MJ, Ferrandez T, Alarcon JJ. Subcellular effects of drought stress in Rosmarinus officinalis. Plant Biol (Stuttg). 2007;9:77–84.
Oluwatuyi M, Kaatz GW, Gibbons S. Antibacterial and resistance modifying activity of Rosmarinus officinalis. Phytochemistry. 2004;65:3249–3254.
Ormeno E, Baldy V, Ballini C, Fernandez C. Production and diversity of volatile terpenes from plants on calcareous and siliceous soils: effect of soil nutrients. J Chem Ecol. 2008;34:1219–1229.
Ormeno E, Fernandez C, Mevy JP. Plant coexistence alters terpene emission and content of Mediterranean species. Phytochemistry. 2007a;68:840–852.
Ormeno E, Mevy JP, Vila B, Bousquet-Melou A, Greff S, Bonin G, Fernandez C. Water-deficit stress induces different monoterpene and sesquiterpene emission changes in Mediterranean species. Relationship between terpene emissions and plant water potential. Chemosphere. 2007b;67:276–284.
Oskay M, Sari D. Antimicrobial screening of some Turkish medicinal plants. Pharm Biol. 2007;45:176–181.
Ozcan M. Antioxidant activities of rosemary, sage, and sumac extracts and their combinations on stability of natural peanut oil. J Med Food. 2003;6:267–270.
Ozcan M. Effect of spice hydrosols on the growth of Aspergillus parasiticus NRRL 2999 strain. J Med Food. 2005;8:275–278.
Ozcan MM, Chalchat JC. Chemical composition and antifungal activity of rosemary (Rosmarinus officinalis L.) oil from Turkey. Int J Food Sci Nutr. 2008;59:691–698.
Panizzi L, Flamini G, Cioni PL, Morelli I. Composition and antimicrobial properties of essential oils of four Mediterranean Lamiaceae. J Ethnopharmacol. 1993;39:167–170.
Papageorgiou V, Gardeli C, Mallouchos A, Papaioannou M, Komaitis M. Variation of the chemical profile and antioxidant behavior of Rosmarinus officinalis L. and Salvia Fruticosa Miller grown in Greece. J Agric Food Chem. 2008a;56:7254–7264.
Papageorgiou V, Mallouchos A, Komaitis M. Investigation of the antioxidant behavior of air- and freeze-dried aromatic plant materials in relation to their phenolic content and vegetative cycle. J Agric Food Chem. 2008b;56:5743–5752.
Parada M, Carrio E, Bonet MA, Valles J. Ethnobotany of the Alt Emporda region (Catalonia, Iberian Peninsula): plants used in human traditional medicine. J Ethnopharmacol. 2009;124:609–618.
Paris A, Strukelj B, Renko M, Turk V, Pukl M, Umek A, Korant BD. Inhibitory effect of carnosic acid on HIV-1 protease in cell-free assays [corrected]. J Nat Prod. 1993;56:1426–1430.
Park JA, Kim S, Lee SY, Kim CS, Kim DK, Kim SJ, Chun HS. Beneficial effects of carnosic acid on dieldrin-induced dopaminergic neuronal cell death. Neuroreport. 2008;19:1301–1304.
Park MK, Lee ES. The effect of aroma inhalation method on stress responses of nursing students. Taehan Kanho Hakhoe Chi. 2004;34:344–351.

Peng CH, Su JD, Chyau CC, Sung TY, Ho SS, Peng CC, Peng RY. Supercritical fluid extracts of rosemary leaves exhibit potent anti-inflammation and anti-tumor effects. Biosci Biotechnol Biochem. 2007;71:2223–2232.

Peng Y, Yuan J, Liu F, Ye J. Determination of active components in rosemary by capillary electrophoresis with electrochemical detection. J Pharm Biomed Anal. 2005;39:431–437.

Perez-Fons L, Aranda FJ, Guillen J, Villalain J, Micol V. Rosemary (Rosmarinus officinalis) diterpenes affect lipid polymorphism and fluidity in phospholipid membranes. Arch Biochem Biophys. 2006;453:224–236.

Perez-Fons L, Garzon MT, Micol V. Relationship between the antioxidant capacity and effect of rosemary (Rosmarinus officinalis L.) polyphenols on membrane phospholipid order. J Agric Food Chem. 2010;58:161–171.

Perrucci S, Mancianti F, Cioni PL, Flamini G, Morelli I, Macchioni G. In vitro antifungal activity of essential oils against some isolates of Microsporum canis and Microsporum gypseum. Planta Med. 1994;60:184–187.

Persson E, Graziani G, Ferracane R, Fogliano V, Skog K. Influence of antioxidants in virgin olive oil on the formation of heterocyclic amines in fried beefburgers. Food Chem Toxicol. 2003;41:1587–1597.

Pertino MW, Schmeda-Hirschmann G. The corrected structure of rosmaridiphenol, a bioactive diterpene from Rosmarinus officinalis. Planta Med. 2010;76:629–632.

Pezo D, Salafranca J, Nerin C. Determination of the antioxidant capacity of active food packagings by in situ gas-phase hydroxyl radical generation and high-performance liquid chromatography-fluorescence detection. J Chromatogr. A 2008;1178:126–133.

Plouzek CA, Ciolino HP, Clarke R, Yeh GC. Inhibition of P-glycoprotein activity and reversal of multidrug resistance in vitro by rosemary extract. Eur J Cancer. 1999;35:1541–1545.

Poeckel D, Greiner C, Verhoff M, Rau O, Tausch L, Hornig C, Steinhilber D, Schubert-Zsilavecz M, Werz O. Carnosic acid and carnosol potently inhibit human 5-lipoxygenase and suppress pro-inflammatory responses of stimulated human polymorphonuclear leukocytes. Biochem Pharmacol. 2008;76:91–97.

Posadas SJ, Caz V, Largo C, De la GB, Matallanas B, Reglero G, De Miguel E. Protective effect of supercritical fluid rosemary extract, Rosmarinus officinalis, on antioxidants of major organs of aged rats. Exp Gerontol. 2009;44:383–389.

Pozo-Insfran D, Follo-Martinez A, Talcott ST, Brenes CH. Stability of copigmented anthocyanins and ascorbic acid in muscadine grape juice processed by high hydrostatic pressure. J Food Sci. 2007;72:S247–S253.

Pozzatti P, Scheid LA, Spader TB, Atayde ML, Santurio JM, Alves SH. In vitro activity of essential oils extracted from plants used as spices against fluconazole-resistant and fluconazole-susceptible Candida spp. Can J Microbiol. 2008;54:950–956.

Prat ML, Lopez-Gonzalvez A, Ruiz MA, Barbas C. Ultrasound-assisted extraction for rapid determination of Zn, Cu, Fe, Mg, and Mn in liver of diabetic rats under different antioxidant treatments. J Pharm Biomed Anal. 2009;49:1040–1044.

Presti ML, Ragusa S, Trozzi A, Dugo P, Visinoni F, Fazio A, Dugo G, Mondello L. A comparison between different techniques for the isolation of rosemary essential oil. J Sep Sci. 2005;28:273–280.

Proenca da Cunha A, Roque OR. Contribution to the study of the essential oil of Portuguese rosemary. Part 2. Quantitative variations of the main constituents during the spring blooming. Boletim da Faculdade de Farmacia de Coimbra. 1986;10:5–13.

Pukalskas A, van Beek TA, de Waard P. Development of a triple hyphenated HPLC-radical scavenging detection-DAD-SPE-NMR system for the rapid identification of antioxidants in complex plant extracts. J Chromatogr A. 2005;1074:81–88.

Putnam SE, Scutt AM, Bicknell K, Priestley CM, Williamson EM. Natural products as alternative treatments for metabolic bone disorders and for maintenance of bone health. Phytother Res. 2007;21:99–112.

Pyevich D, Bogenschutz MP. Herbal diuretics and lithium toxicity. Am J Psychiatry. 2001;158:1329.

Quave CL, Plano LR, Pantuso T, Bennett BC. Effects of extracts from Italian medicinal plants on planktonic growth, biofilm formation and adherence of methicillin-resistant Staphylococcus aureus. J Ethnopharmacol. 2008;118:418–428.

Rababah TM, Hettiarachchy NS, Horax R. Total phenolics and antioxidant activities of fenugreek, green tea, black tea, grape seed, ginger, rosemary, gotu kola, and ginkgo extracts, vitamin E, and tert-butylhydroquinone. J Agric Food Chem. 2004;52:5183–5186.

Rakover Y, Ben Arye E, Goldstein LH. The treatment of respiratory ailments with essential oils of some aromatic medicinal plants. Harefuah. 2008;147:783–788, 838.

Ramirez P, Garcia-Risco MR, Santoyo S, Senorans FJ, Ibanez E, Reglero G. Isolation of functional ingredients from rosemary by preparative-supercritical fluid chromatography (Prep-SFC). J Pharm Biomed Anal. 2006;41:1606–1613.

Ranger CM, Reding ME, Oliver JB, Moyseenko JJ, Youssef NN. Toxicity of botanical formulations to nursery-infesting white grubs (Coleoptera: scarabaeidae). J Econ Entomol. 2009;102: 304–308.

Rasmussen KE, Rasmussen S, Baerheim SA. Quantitative variations of some components of the foliage volatile oil of Rosmarinus officinalis L. in the spring. Terpenes and related compounds. XIX Pharm Weekbl. 1972;107:309–313.

Rasooli I, Fakoor MH, Yadegarinia D, Gachkar L, Allameh A, Rezaei MB. Antimycotoxigenic characteristics of Rosmarinus officinalis and Trachyspermum copticum L. essential oils. Int J Food Microbiol. 2008a;122:135–139.

Rasooli I, Shayegh S, Taghizadeh M, Astaneh SD. Phytotherapeutic prevention of dental biofilm formation. Phytother Res. 2008b;22:1162–1167.

Rau O, Wurglics M, Paulke A, Zitzkowski J, Meindl N, Bock A, Dingermann T, Abdel-Tawab M, Schubert-Zsilavecz M. Carnosic acid and carnosol, phenolic diterpene compounds of the labiate herbs rosemary and sage, are activators of the human peroxisome proliferator-activated receptor gamma. Planta Med. 2006;72:881–887.

Reichling J, Nolkemper S, Stintzing FC, Schnitzler P. Impact of ethanolic lamiaceae extracts on herpesvirus infectivity in cell culture. Forsch Komplementmed. 2008;15:313–320.

Ribeiro A, Arnaud P, Frazao S, Venancio F, Chaumeil JC. Development of vegetable extracts by microencapsulation. J Microencapsul. 1997;14:735–742.

Ritschel WA, Starzacher A, Sabouni A, Hussain AS, Koch HP. Percutaneous absorption of rosmarinic acid in the rat. Methods Find Exp Clin Pharmacol. 1989;11:345–352.

Rota C, Carraminana JJ, Burillo J, Herrera A. In vitro antimicrobial activity of essential oils from aromatic plants against selected foodborne pathogens. J Food Prot. 2004;67:1252–1256.

Rudzinska M, Korczak J, Gramza A, Wasowicz E, Dutta PC. Inhibition of stigmasterol oxidation by antioxidants in purified sunflower oil. J AOAC Int. 2004;87:499–504.

Ruiz Del Castillo ML, Blanch GP. Enantiomeric purity of (+/−) -methyl jasmonate in fresh leaf samples and commercial fragrances. J Sep Sci. 2007;30:2117–2122.

Ruiz A, Williams SK, Djeri N, Hinton A, Jr, Rodrick GE. Nisin, rosemary, and ethylenediaminetetraacetic acid affect the growth of Listeria monocytogenes on ready-to-eat turkey ham stored at four degrees celsius for sixty-three days. Poult Sci. 2009;88:1765–1772.

Saenz-Lopez R, Fernandez-Zurbano P, Tena MT. Capillary electrophoretic separation of phenolic diterpenes from rosemary. J Chromatogr A. 2002;953:251–256.

Sagorchev P, Lukanov J, Beer AM. Investigations into the specific effects of rosemary oil at the receptor level. Phytomedicine. 2010;17:693–697.

Saito Y, Shiga A, Yoshida Y, Furuhashi T, Fujita Y, Niki E. Effects of a novel gaseous antioxidative system containing a rosemary extract on the oxidation induced by nitrogen dioxide and ultraviolet radiation. Biosci Biotechnol Biochem. 2009;68:781–786.

Samman S, Sandstrom B, Toft MB, Bukhave K, Jensen M, Sorensen SS, Hansen M. Green tea or rosemary extract added to foods reduces nonheme-iron absorption. Am J Clin Nutr. 2001;73: 607–612.

Sancheti G, Goyal P. Modulatory influence of Rosemarinus officinalis on DMBA-induced mouse skin tumorigenesis. Asian Pac J Cancer Prev. 2006a;7:331–335.

Sancheti G, Goyal PK. Effect of Rosmarinus officinalis in modulating 7, 12-dimethyl benz(a)anthracene induced skin tumorigenesis in mice. Phytother Res. 2006b;20:981–986.

Sandasi M, Leonard CM, Viljoen AM. The in vitro antibiofilm activity of selected culinary herbs and medicinal plants against Listeria monocytogenes. Lett Appl Microbiol. 2010;50:30–35.

Sanders C, Diego M, Fernandez M, Field T, Hernandez-Reif M, Roca A. EEG asymmetry responses to lavender and rosemary aromas in adults and infants. Int J Neurosci. 2002;112:1305–1320.

Santos FA, Rao VS. Mast cell involvement in the rat paw oedema response to 1, 8-cineole, the main constituent of eucalyptus and rosemary oils. Eur J Pharmacol. 1997;331:253–258.

Santoyo S, Cavero S, Jaime L, Ibanez E, Senorans FJ, Reglero G. Chemical composition and antimicrobial activity of Rosmarinus officinalis L. essential oil obtained via supercritical fluid extraction. J Food Prot. 2005;68:790–795.

Sasse A, Colindres P, Brewer MS. Effect of natural and synthetic antioxidants on the oxidative stability of cooked, frozen pork patties. J Food Sci. 2009;74:S30–S35.

Satoh T, Kosaka K, Itoh K, Kobayashi A, Yamamoto M, Shimojo Y, Kitajima C, Cui J, Kamins J, Okamoto S, Izumi M, Shirasawa T, Lipton SA. Carnosic acid, a catechol-type electrophilic compound, protects neurons both in vitro and in vivo through activation of the Keap1/Nrf2 pathway via S-alkylation of targeted cysteines on Keap1. J Neurochem. 2008;104:1116–1131.

Scheckel KA, Degner SC, Romagnolo DF. Rosmarinic acid antagonizes activator protein-1-dependent activation of cyclooxygenase-2 expression in human cancer and nonmalignant cell lines. J Nutr. 2008;138:2098–2105.

Schelz Z, Molnar J, Hohmann J. Antimicrobial and antiplasmid activities of essential oils. Fitoterapia. 2006;77:279–285.

Schwarz K, Ternes W. Antioxidative constituents of Rosmarinus officinalis and Salvia officinalis. I. Determination of phenolic diterpenes with antioxidative activity amongst tocochromanols using HPLC. Z Lebensm Unters Forsch. 1992a;195:95–98.

Schwarz K, Ternes W. Antioxidative constituents of Rosmarinus officinalis and Salvia officinalis. II. Isolation of carnosic acid and formation of other phenolic diterpenes. Z Lebensm Unters Forsch. 1992b;195:99–103.

Schwarz K, Ternes W, Schmauderer E. Antioxidative constituents of Rosmarinus officinalis and Salvia officinalis. III. Stability of phenolic diterpenes of rosemary extracts under thermal stress as required for technological processes. Z Lebensm Unters Forsch. 1992c;195:104–107.

Schwiertz A, Duttke C, Hild J, Muller HJ. In vitro activity of essential oils on microorganisms isolated from vaginal infections. Int J Aromather. 2006;16:169–174.

Scollard J, Francis GA, O'Beirne D. Effects of essential oil treatment, gas atmosphere, and storage temperature on Listeria monocytogenes in a model vegetable system. J Food Prot. 2009;72:1209–1215.

Selmi G. Therapeutic use of rosemary through the centuries. Policlinico Prat. 1967;74:439–441.

Seyfert M, Hunt MC, Mancini RA, Hachmeister KA, Kropf DH, Unruh JA, Loughin TM. Beef quadriceps hot boning and modified-atmosphere packaging influence properties of injection-enhanced beef round muscles. J Anim Sci. 2005;83:686–693.

Shabtay A, Sharabani H, Barvish Z, Kafka M, Amichay D, Levy J, Sharoni Y, Uskokovic MR, Studzinski GP, Danilenko M. Synergistic antileukemic activity of carnosic acid-rich rosemary extract and the 19-nor Gemini vitamin D analogue in a mouse model of systemic acute myeloid leukemia. Oncology. 2008;75:203–214.

Shahidi F. Antioxidants in food and food antioxidants. Nahrung. 2000;44:158–163.

Sharabani H, Izumchenko E, Wang Q, Kreinin R, Steiner M, Barvish Z, Kafka M, Sharoni Y, Levy J, Uskokovic M, Studzinski GP, Danilenko M. Cooperative antitumor effects of vitamin D3 derivatives and rosemary preparations in a mouse model of myeloid leukemia. Int J Cancer. 2006;118:3012–3021.

Shimojo Y, Kosaka K, Noda Y, Shimizu T, Shirasawa T. Effect of rosmarinic acid in motor dysfunction and life span in a mouse model of familial amyotrophic lateral sclerosis. J Neurosci Res. 2010;88:896–904.

Shin S. Anti-aspergillus activities of plant essential oils and their combination effects with ketoconazole or amphotericin B. Arch Pharm Res. 2003;26:389–393.

Shukla VK, Bhattacharya K. Extending the shelf life of cosmetic products through novel stabilization of exotic butters and oils. SOFW. 2003;129:38–44.

Silva MD, Silva MA, Higino JS, Pereira MS, Carvalho AD. In vitro antimicrobial activity and anti-adherence of Rosmarinus officinalis Linn. against oral planktonic bacteria. Rev Bras Farmacogn. 2008;18:236–240.

Singletary K, MacDonald C, Wallig M. Inhibition by rosemary and carnosol of 7, 12-dimethylbenz[a]anthracene (DMBA)-induced rat mammary tumorigenesis and in vivo DMBA-DNA adduct formation. Cancer Lett. 1996;104:43–48.

Singletary KW. Rosemary extract and carnosol stimulate rat liver glutathione-S-transferase and quinone reductase activities. Cancer Lett. 1996;100:139–144.
Singletary KW, Nelshoppen JM. Inhibition of 7, 12-dimethylbenz[a]anthracene (DMBA)-induced mammary tumorigenesis and of in vivo formation of mammary DMBA-DNA adducts by rosemary extract. Cancer Lett. 1991;60:169–175.
Singletary KW, Rokusek JT. Tissue-specific enhancement of xenobiotic detoxification enzymes in mice by dietary rosemary extract. Plant Foods Hum Nutr. 1997;50:47–53.
Siurin SA. Effects of essential oil on lipid peroxidation and lipid metabolism in patients with chronic bronchitis. Klin Med (Mosk). 1997;75:43–45.
Slamenova D, Kuboskova K, Horvathova E, Robichova S. Rosemary-stimulated reduction of DNA strand breaks and FPG-sensitive sites in mammalian cells treated with H_2O_2 or visible light-excited methylene blue. Cancer Lett. 2002;177:145–153.
Smet K, Raes K, Huyghebaert G, Haak L, Arnouts S, De Smet S. Lipid and protein oxidation of broiler meat as influenced by dietary natural antioxidant supplementation. Poult Sci. 2008;87:1682–1688.
Smith C, Halliwell B, Aruoma OI. Protection by albumin against the pro-oxidant actions of phenolic dietary components. Food Chem Toxicol. 1992;30:483–489.
Soler-Rivas C, Marin FR, Santoyo S, Garcia-Risco MR, Senorans FJ, Reglero G. Testing and enhancing the in vitro bioaccessibility and bioavailability of Rosmarinus officinalis extracts with a high level of antioxidant abietanes. J Agric Food Chem. 2010;58:1144–1152.
Sotelo-Felix JI, Martinez-Fong D, Muriel DLT. Protective effect of carnosol on CCl(4)-induced acute liver damage in rats. Eur J Gastroenterol Hepatol. 2002a;14:1001–1006.
Sotelo-Felix JI, Martinez-Fong D, Muriel P, Santillan RL, Castillo D, Yahuaca P. Evaluation of the effectiveness of Rosmarinus officinalis (Lamiaceae) in the alleviation of carbon tetrachloride-induced acute hepatotoxicity in the rat. J Ethnopharmacol. 2002b;81:145–154.
Soyal D, Jindal A, Singh I, Goyal PK. Modulation of radiation-induced biochemical alterations in mice by rosemary (Rosemarinus officinalis) extract. Phytomedicine. 2007;14:701–705.
Stashenko EE, Puertas MA, Martinez JR. SPME determination of volatile aldehydes for evaluation of in vitro antioxidant activity. Anal Bioanal Chem. 2002;373:70–74.
Steiner M, Priel I, Giat J, Levy J, Sharoni Y, Danilenko M. Carnosic acid inhibits proliferation and augments differentiation of human leukemic cells induced by 1, 25-dihydroxyvitamin D3 and retinoic acid. Nutr Cancer. 2001;41:135–144.
Steinmetz MD, Moulin-Traffort J, Regli P. Transmission and scanning electronmicroscopy study of the action of sage and rosemary essential oils and eucalyptol on Candida albicans. Mycoses. 1988;31:40–51.
Steinmetz MD, Vial M, Millet Y. Actions of essential oils of rosemary and certain of its constituents (eucalyptol and camphor) on the cerebral cortex of the rat in vitro. J Toxicol Clin Exp. 1987;7:259–271.
Suhr KI, Nielsen PV. Antifungal activity of essential oils evaluated by two different application techniques against rye bread spoilage fungi. J Appl Microbiol. 2003;94:665–674.
Swain AR, Dutton SP, Truswell AS. Salicylates in foods. J Am Diet Assoc. 1985;85:950–960.
Szabo MA, Varga GZ, Hohmann J, Schelz Z, Szegedi E, Amaral L, Molnar J. Inhibition of quorum-sensing signals by essential oils. Phytother Res. 2010;24:782–786.
Tada M, Ohkanda T, Kurabe J. Syntheses of carnosic acid and carnosol, anti-oxidants in Rosemary, from pisiferic acid, the major constituent of Sawara. Chem Pharm Bull (Tokyo). 2010;58:27–29.
Tahraoui A, El Hilaly J, Israili ZH, Lyoussi B. Ethnopharmacological survey of plants used in the traditional treatment of hypertension and diabetes in south-eastern Morocco (Errachidia province). J Ethnopharmacol. 2007;110:105–117.
Takahashi T, Tabuchi T, Tamaki Y, Kosaka K, Takikawa Y, Satoh T. Carnosic acid and carnosol inhibit adipocyte differentiation in mouse 3T3-L1 cells through induction of phase 2 enzymes and activation of glutathione metabolism. Biochem Biophys Res Commun. 2006;382:549–554.
Takaki I, Bersani-Amado LE, Vendruscolo A, Sartoretto SM, Diniz SP, Bersani-Amado CA, Cuman RK. Anti-inflammatory and antinociceptive effects of Rosmarinus officinalis L. essential oil in experimental animal models. J Med Food. 2008;11:741–746.
Talcott ST, Brenes CH, Pires DM, Pozo-Insfran D. Phytochemical stability and color retention of copigmented and processed muscadine grape juice. J Agric Food Chem. 2003;51:957–963.

Tamaki Y, Tabuchi T, Takahashi T, Kosaka K, Satoh T. Activated glutathione metabolism participates in protective effects of carnosic acid against oxidative stress in neuronal HT22 cells. Planta Med. 2010;76:683–688.

Tantaoui-Elaraki A, Beraoud L. Inhibition of growth and aflatoxin production in Aspergillus parasiticus by essential oils of selected plant materials. J Environ Pathol Toxicol Oncol. 1994;13:67–72.

Tawfiq N, Wanigatunga S, Heaney RK, Musk SR, Williamson G, Fenwick GR. Induction of the anti-carcinogenic enzyme quinone reductase by food extracts using murine hepatoma cells. Eur J Cancer Prev. 1994;3:285–292.

Tayel AA, El Tras WF. Possibility of fighting food borne bacteria by Egyptian folk medicinal herbs and spices extracts. J Egypt Public Health Assoc. 2009;84:21–32.

Thorsen MA, Hildebrandt KS. Quantitative determination of phenolic diterpenes in rosemary extracts. Aspects of accurate quantification. J Chromatogr A. 2003;995:119–125.

Topal U, Sasaki M, Goto M, Otles S. Chemical compositions and antioxidant properties of essential oils from nine species of Turkish plants obtained by supercritical carbon dioxide extraction and steam distillation. Int J Food Sci Nutr. 2008;59:619–634.

Torre J, Lorenzo MP, Martinez-Alcazar MP, Barbas C. Simple high-performance liquid chromatography method for alpha-tocopherol measurement in Rosmarinus officinalis leaves. New data on alpha-tocopherol content. J Chromatogr A. 2001;919:305–311.

Tovar L, Salafranca J, Sanchez C, Nerin C. Migration studies to assess the safety in use of a new antioxidant active packaging. J Agric Food Chem. 2005;53:5270–5275.

Tsai PJ, Tsai TH, Yu CH, Ho SC. Evaluation of NO-suppressing activity of several Mediterranean culinary spices. Food Chem Toxicol. 2007;45:440–447.

Valenzuela A, Sanhueza J, Alonso P, Corbari A, Nieto S. Inhibitory action of conventional food-grade natural antioxidants and natural antioxidants of new development on the thermal-induced oxidation of cholesterol. Int J Food Sci Nutr. 2004;55:155–162.

Valenzuela A, Sanhueza J, Nieto S. Cholesterol oxidation: health hazard and the role of antioxidants in prevention. Biol Res. 2003;36:291–302.

Valero M, Salmeron MC. Antibacterial activity of 11 essential oils against Bacillus cereus in tyndallized carrot broth. Int J Food Microbiol. 2003;85:73–81.

van Vuuren SF, Suliman S, Viljoen AM. The antimicrobial activity of four commercial essential oils in combination with conventional antimicrobials. Lett Appl Microbiol. 2009;48:440–446.

Veal L. The potential effectiveness of essential oils as a treatment for headlice, Pediculus humanus capitis. Complement Ther Nurs Midwifery. 1996;2:97–101.

Verluyten J, Leroy F, De Vuyst L. Effects of different spices used in production of fermented sausages on growth of and curvacin A production by Lactobacillus curvatus LTH 1174. Appl Environ Microbiol. 2004;70:4807–4813.

Vijayan P, Raghu C, Ashok G, Dhanaraj SA, Suresh B. Antiviral activity of medicinal plants of Nilgiris. Indian J Med Res. 2004;120:24–29.

Vitaglione P, Morisco F, Caporaso N, Fogliano V. Dietary antioxidant compounds and liver health. Crit Rev Food Sci Nutr. 2004;44:575–586.

Waliwitiya R, Kennedy CJ, Lowenberger CA. Larvicidal and oviposition-altering activity of monoterpenoids, trans-anithole and rosemary oil to the yellow fever mosquito Aedes aegypti (Diptera: culicidae). Pest Manag Sci. 2009;65:241–248.

Wang LH, Wang CC, Kuo SC. Vehicle and enhancer effects on human skin penetration of aminophylline from cream formulations: evaluation in vivo. J Cosmet Sci. 2007;58:245–254.

Wang R, Li H, Guo G, Li X, Yu X, Li H, Wang J, Liu F, Chen X. Augmentation by carnosic acid of apoptosis in human leukaemia cells induced by arsenic trioxide via upregulation of the tumour suppressor PTEN. J Int Med Res. 2008;36:682–690.

Wargovich MJ, Woods C, Hollis DM, Zander ME. Herbals, cancer prevention, and health. J Nutr. 2001;131:3034S–3036S.

Watt K, Christofi N, Young R. The detection of antibacterial actions of whole herb tinctures using luminescent Escherichia coli. Phytother Res. 2007;21:1193–1199.

Weckesser S, Engel K, Simon-Haarhaus B, Wittmer A, Pelz K, Schempp CM. Screening of plant extracts for antimicrobial activity against bacteria and yeasts with dermatological relevance. Phytomedicine 2007;14:508–516.

Wei FX, Liu JX, Wang L, Li HZ, Luo JB. Expression of bcl-2 and bax genes in the liver cancer cell line HepG2 after apoptosis induced by essential oils from Rosmarinus officinalis. Zhong Yao Cai. 2008;31:877–879.

Wellwood CR, Cole RA. Relevance of carnosic acid concentrations to the selection of rosemary, Rosmarinus officinalis (L.), accessions for optimization of antioxidant yield. J Agric Food Chem. 2004;52:6101–6107.

Wijeratne SS, Cuppett SL. Potential of rosemary (Rosemarinus officinalis L.) diterpenes in preventing lipid hydroperoxide-mediated oxidative stress in Caco-2 cells. J Agric Food Chem. 2007;55:1193–1199.

Winkler V. Bioactive substances: spices as remedies spice of life. OAZ. 2004;58:1242.

Xiao C, Dai H, Liu H, Wang Y, Tang H. Revealing the metabonomic variation of rosemary extracts using 1H NMR spectroscopy and multivariate data analysis. J Agric Food Chem. 2008;56:10142–10153.

Yamamoto J, Yamada K, Naemura A, Yamashita T, Arai R. Testing various herbs for antithrombotic effect. Nutrition. 2005;21:580–587.

Yang YC, Lee HS, Clark JM, Ahn YJ. Insecticidal activity of plant essential oils against Pediculus humanus capitis (Anoplura: pediculidae). J Med Entomol. 2004;41:699–704.

Yarnell E, Abascal K. Botanical medicine for thyroid regulation. Altern Complement Ther. 2006;12:107–112.

Yarnell E, Abascal K. Botanical medicines for headache. Altern Complement Ther. 2007;13:148–152.

Yarnell E, Abascal K. Herbal Support for methicillin-resistant Staphylococcus aureus infections. Altern Complement Ther. 2009;15:189–195.

Yassaa N, Williams J. Analysis of enantiomeric and non-enantiomeric monoterpenes in plant emissions using portable dynamic air sampling/solid-phase microextraction (PDAS-SPME) and chiral gas chromatography/mass spectrometry. Atmos Environ. 2005;39:4875–4884.

Yesil-Celiktas O, Nartop P, Gurel A, Bedir E, Vardar-Sukan F. Determination of phenolic content and antioxidant activity of extracts obtained from Rosmarinus officinalis' calli. J Plant Physiol. 2007;164:1536–1542.

Yu YM, Lin HC, Chang WC. Carnosic acid prevents the migration of human aortic smooth muscle cells by inhibiting the activation and expression of matrix metalloproteinase-9. Br J Nutr. 2008;100:731–738.

Zandi P, Ahmadi L. Antioxidant effect of plant extracts of Labiatae family. J Food Microbiol. 2000;37:436–439.

Zeng HH, Tu PF, Zhou K, Wang H, Wang BH, Lu JF. Antioxidant properties of phenolic diterpenes from Rosmarinus officinalis. Acta Pharmacol Sin. 2001;22:1094–1098.

Zhao BL, Li XJ, He RG, Cheng SJ, Xin WJ. Scavenging effect of extracts of green tea and natural antioxidants on active oxygen radicals. Cell Biophys. 1989;14:175–185.

Zhu BT, Loder DP, Cai MX, Ho CT, Huang MT, Conney AH. Dietary administration of an extract from rosemary leaves enhances the liver microsomal metabolism of endogenous estrogens and decreases their uterotropic action in CD-1 mice. Carcinogenesis. 1998;19:1821–1827.

Zimmermann V. Rosemary as a medicinal plant and wonder-drug. A report on the medieval drug monographs. Sudhoffs Arch. 1980;64:351–370.

Zochling S, Murkovic M, Pfannhauser W. Effects of industrially produced flavours with pro- and antioxidative properties on the formation of the heterocyclic amine PhIP in a model system. J Biochem Biophys Methods. 2002;53:37–44.

Zunino SJ, Storms DH. Carnosol delays chemotherapy-induced DNA fragmentation and morphological changes associated with apoptosis in leukemic cells. Nutr Cancer. 2009;61:94–102.