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ROSEMARY: AN OVERVIEW OF POTENTIAL HEALTH BENEFITS

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ABSTRACT

The rosemary plant, Rosmarinus officinalis L (family Lamiaceae), is an aromatic evergreen shrub originating in the Mediterranean region and now growing widely in Europe, Asia, and Africa. The genus name Rosmarinus is derived from the Latin "Dew of the Sea" and has traditionally been associated with remembrance, love, and fidelity. This plant has been used extensively as a culinary spice in a variety of contexts. In Mexico, it is used in preparation of tea, and it seasons meats in the cuisines of Europe and the Middle East. Another use of rosemary is as part of a marinade for lamb, pork, and chicken dishes. Rosemary leaves flavor soups and beverages in India. Rosemary and its extracts also are used as food preservatives and enhancers of sensory and functional properties. Furthermore, rosemary and its constituents have been incorporated into cosmetics and cosmeceuticals in the hope of enhancing the health of skin and hair. This plant has been an ingredient in folk medicines with associated claims for relief of such diverse symptoms and conditions as mental decline, epilepsy, pain relief, and infertility. It also has been promoted as a treatment for hair loss, dermatitis, anxiety, cognitive improvement, constipation, joint and muscle pain, and improvement of circulation. Today research attention is focusing more closely on whether this herb may have potential of antidiabetic, antioxidant and antimicrobial properties.

Rosemary and its constituents has been the subject of considerable research interest because of their potential antioxidant, anti-inflammatory, and neurological activities, some of which are discussed in this article.

Composition and Bioavailability

The referenced studies evaluate the effects of diverse rosemary samples, including its dried powder, essential oil, and water and organic solvent extracts. Although the composition of

these oils and extracts can vary widely depending on the specific preparation protocols used, the growth conditions of the plant and the specific portion of the plant selected, some general descriptions of content can be noted. For example, the essential oil of rosemary may contain 6% to 41% 1, 8-cineole, 18–28% camphor, 9% to 14% α-pinene, and 4% to 10% borneol. Several different essential oil chemotypes of indigenous and cultivated plants exist. Each essential oil from these has a different composition and thus potentially different biological activity. An ethanol extract of rosemary was reported to contain (mg/g dry extract) rosmarinic acid (RA;), rosmanol, carnosol , and CA . An acetone extract contained as major constituents RA, carnosol, carnosic acid (CA), methyl carnosate, and 12-methyl CA. A water extract has been reported to contain 1,8-cineole, camphor, borneol, and 2-carene as major ingredients. A methanolic extract consisted of carnosol and CA as major diterpenes, hesperidin and genkwanin as major flavonoids, and RA and gallic acids as major phenolic acids. The variety of extract compositions reported underscores the need to characterize the phytochemical profile of rosemary samples used in preclinical and clinical studies in order to better compare studies and to more fully determine the role of bioactive constituents contributing to a biological action. Rosemary and other spices in the Lamiaceae family are well-known sources of diverse natural antioxidants. Several extracts of rosemary have been prepared for commercial use as food flavorings and antioxidant preservatives.

Unfortunately, the systematic characterization of major rosemary constituents' bioavailability in animals and humans is incomplete. The oral bioavailability of rosemary bioactive constituents can affect systemic exposure and biological outcomes and is an important factor in determining their potential health effects. In humans, it was reported that, following acute oral dosing with an extract of Perilla frutescens leaves containing 200 mg RA, a plasma RA concentration of 1.15 μM was achieved.33 A placebo-controlled trial was conducted with 11 healthy individuals receiving 100, 250, or 500 mg RA administered in an extract of Melissa officinalis. Participants were evaluated in both fasting and fed states. Maximum serum concentration of RA for those fasting and given 250 and 500 mg RA was 72.2 and 162.2 nmol/L, respectively. Food intake increased the exposure of RA and delayed absorption. In another study, normal subjects were fed 2.8 g/d of rosemary powder for 7 days, and blood subsequently drawn. Although levels of rosemary constituents were not measured in the blood, some rosemary components were sufficiently bioavailable so that, compared with controls, serum markers of inflammation were significantly suppressed. It is evident from these findings that in order to better understand the potential human health benefits of these

rosemary constituents the impact of various oral doses, length of exposure, and presence of other dietary factors on the bioavailability and metabolism of CA, RA, and other prominent rosemary phytochemicals need to be more thoroughly assessed in humans.

Scientific Evidence for Select Potential Benefits

Rosemary Powder

Rosmarinus officinalis L (crushed and encapsulated) was given orally (2.8 g/d) to 12 subjects for 7 days. Human serum isolated from these subjects was added ex vivo to cultures of oxidized low density lipoprotein (oxLDL)-stimulated THP-1 human monocytes. Serum from those fed rosemary showed significantly lower expression of inflammatory markers interleukin 6 (IL-6) and tumor necrosis factor α, compared with controls. These findings suggest that the rosemary constituents were sufficiently bioavailable so that subjects' serum samples had a significant impact on THP-1 inflammatory markers. No adverse effects were noted.

Extracts of Rosemary

Limited human data are available regarding use of rosemary extract. A proprietary formulation containing reduced iso-α acids from hops, a rosemary extract, and oleanolic acid was given (1320-1760 mg/d) to patients (open-label, observational 8-week study) with rheumatic disease. A trend toward decreasing levels of C-reactive protein in blood was observed for those subjects initially presenting with elevated C-reactive protein. The individual contribution of rosemary cannot be determined. In another study of 46 osteoarthritis patients, a similar phytochemical combination, when given orally for 4 weeks (600 mg/d), decreased reports of disease symptoms in patients with osteoarthritis. A randomized double-blind study of 52 individuals with medically diagnosed knee osteoarthritis was conducted to evaluate the effects of a high RA spearmint tea. For 16 weeks, participants in the treatment group consumed 2 cups of tea/d, which contained 130 to 150 mg RA/cup, and controls consumed 13 mg RA/cup of tea. Pain scores significantly decreased for the high-RA group, compared with controls, and there was improvement in physical function as measured in the 6-minute walk test.

Individual Constituents

Rosmarinic Acid

In a human study of subjects with mild atopic dermatitis, topical application of RA (0.3% cream emulsion) twice a day for 8 weeks to elbow flexures significantly reduced erythema

and transepidermal water loss on the antecubital fossa, compared with cream controls. Treated subjects also self-reported noticeable improvements in dryness and pruritus. A randomized, double-blind, age-matched, placebo-controlled clinical trial was conducted with patients with seasonal allergic rhino conjunctivitis who were treated orally with RA (50 mg/d or 200 mg/d) for 21 days. Based on patients' daily records, compared with controls, those treated with 50 mg RA exhibited significantly improved symptoms for itchy nose, watery eyes, and itchy eyes. Rosmarinic acid also significantly reduced the numbers of neutrophils and eosinophils in nasal lavage fluid. Neither adverse events nor significant abnormalities in blood tests were detected. These results were similar to those reported by the same authors when patients with seasonal allergic rhino conjunctivitis were treated orally with an extract of P frutescens enriched for RA (50 or 200 mg RA) daily for 21 days.

Alleviation of Metabolic Disorders (Obesity and Diabetes)

Rosemary Extracts

Several studies show consistent effects of rosemary extracts on signs of diabetes and the metabolic syndrome. In normoglycemic mice provided a water extract of rosemary (10 g/L) in place of tap water, plasma glucose levels decreased a significant 12% after 3 months, compared with controls. For alloxan-treated hyperglycemic mice consuming the same water extract for 1 month, plasma glucose levels significantly decreased by 45%. No toxic effects during chronic application were noted, and no mechanisms for this hypoglycemic effect were identified. Two experiments with rosemary were reported for normal and alloxan-induced rabbits. An undefined ethanol extract of rosemary administered orally to fasting normal rabbits (100–200 mg/kg) produced a significant drop in blood glucose levels of up to 21% within 6 hours, without changing insulin levels. In alloxan-treated rabbits, dosing with this extract (100–200 mg/kg, orally) for 8 days produced a significant decrease in blood glucose and an increase in serum insulin levels, compared with controls, an effect determined in part to be due to the extract's potent antioxidant activity. The authors speculated that the elevation of circulating insulin levels in the rosemary-treated alloxan-diabetic rabbits could be due to components that either protect functional β cells from additional damage or stimulate regeneration of β cells. These possibilities need to be further examined. A recent study found that combining treatment of streptozotocin-induced diabetic rats with an aqueous extract of rosemary (200 mg/kg per day, intragastrically) with a regimen of endurance exercise for 8 weeks resulted in lowered blood indices of oxidative stress by enhancing antioxidant enzyme activates and decreasing lipid peroxidation levels approaching normal levels seen in healthy

controls. In 2 rodent experiments, a rosemary extract rich in CA was evaluated. Mice were provided for 16 weeks a high-fat diet supplemented (500-mg/kg diet) with a rosemary extract standardized to 20% CA. Diet supplementation with the extract decreased fasting blood glucose and plasma cholesterol levels, compared with controls. Moreover, body and epididymal fat weights for mice fed the rosemary supplemented high-fat diets were less than those for mice fed the control high-fat diet. This suggested that this effect may partly be associated with activation of peroxisome proliferator-activated receptor γ. In a second investigation, an ethanol extract of rosemary containing 39% CA, 6.5% carnosol, and 6.9% methyl carnosate was added to diets (0.5% wt/wt) of lean and obese Zucker rats for 64 days. Compared with controls, the rosemary-supplemented diet moderated the weight gain of both groups of rats without affecting food intake. Moreover, primarily in the lean rats, the plasma lipid profile was improved. This diet significantly inhibited gastric lipase and thus was hypothesized to reduce fat absorption. Of note is that animals consuming rosemary extract exhibited increased liver weights and enzymatic activities, a response to rosemary extract reported by others. This suggested that long-term consumption of rosemary extracts rich in CA may be beneficial for weight maintenance and normalization of lipid profiles. However, the consequences of increased liver weight and liver enzyme induction would need to be better characterized. This report led to a subsequent opinion article suggesting that CA should be considered for the treatment of nonalcoholic liver disease or the metabolic syndrome. Of additional interest, an ethanol extract of rosemary (39% CA, 7% carnosol) was supplemented to diets (0.5% wt/wt) for 64 days to both lean and obese Zucker rats. Compared with controls, feeding of the extract to lean rats led to an increase in circulating adiponectin in contrast to that seen for obese rats in which feeding of the extract resulted in decreased circulating adiponectin. In lean rats, consumption of the rosemary extract led to a significant decrease in circulating IL-1β and tumor necrosis factor α, compared with controls, in contrast to that for obese rats in which no changes were noted. Activated AMP-activated protein kinase in perivisceral adipose tissue of rosemary fed rats was significantly decreased in obese rats, whereas no effect of dietary supplementation was seen for lean rats. Based on the observation that AMP-activated protein kinase may mediate the metabolic effects of leptin and adiponectin, the authors speculated that a functioning leptin signaling pathway is required for the rosemary extract to exert metabolic regulatory effects on obese Zucker rats. A recent study using cultures of human primary omental preadipocytes and adipocytes found exposure to rosemary extract modulated adipocyte differentiation and interfered with adipogenesis and lipid metabolism. Furthermore, extract supplementation increased short-chain fatty acid

excretion in the feces of obese rats but decreased excretion in lean rats, compared with their controls, which, according to the authors likely reflects differential uptake and metabolism of short-chain fatty acid between the lean and obese animals. In contrast to other reports, rosemary supplementation had no significant effect on the intraperitoneal glucose tolerance test and fasting insulin levels in this study. The authors suggested that rosemary extract may have potential use in strategies to limit weight gain and liver disease associated with obesity. Supplementation of diets with rosemary extract significantly reduced body weight gain, percent body fat composition, plasma transaminases, glucose and insulin levels, and liver triglycerides, compared with the high-fat controls. Moreover, in similar comparisons among groups, liver peroxidation and lipid accumulation were decreased for the mice fed the rosemary supplemented diets, and fecal lipid excretion was elevated, compared with controls. A recent review highlighted the potential benefits of rosemary in preventing obesity and the metabolic syndrome. The effect of a natural product mixture containing 0.02% rosemary extract on urine metabolite profiles of diabetic humans was reported. Although some treatment-related effects were observed, interpretation of the urine patterns was not entirely straightforward, and further exploration of these profiles and the metabolic changes they reflect is needed.

CONCLUSIONS

Several actions of rosemary are evident that warrant further confirmation. This suggests that, although identifying specific rosemary phytochemicals that are biologically active is important for mechanistic characterizations, the mix of constituents in rosemary is likely to have a broader impact on health end points than 1 component alone. Moreover, examining rosemary's effects on neurological end points at lower doses approximating dietary exposures in humans would certainly be worthwhile. Comparisons of findings between animal studies are often difficult not only because of dosing and sample identity disparities, but also because recognized markers of rosemary bioavailability are not reported. Future rosemary feeding studies in animals evaluating neurological benefits need to identify and measure chemical profiles in the blood and brain associated with rosemary exposure and bioavailability. For example, 1,8-cineole could be measured when essential oils are administered, or, similarly, total CA and CA-glucuronides could be measured when water or alcohol extracts of rosemary are used. Reports of rosemary's anti-inflammatory actions, particularly following oral exposure in animals, provide emerging evidence that rosemary essential oil, rosemary extracts, and individual constituents can improve diverse respiratory, vascular, and

dermatological conditions. Rosmarinic acid and 1,8-cineole in particular has demonstrated potential benefits in human studies evaluating skin and respiratory responses, respectively. Evaluation of different rosemary samples provided mixed evidence of efficacy in improving symptoms of metabolic disorders. For example, oral rosemary oil elicited inconsistent effects on blood glucose levels in several animal models. In contrast, water and alcohol extracts of rosemary provided orally to normal and diabetic animals resulted in hypoglycemic responses, improved blood lipid profiles, and lower weight gains. Oral CA in particular was associated with hypoglycemic and antiadipogenic responses. Besides further confirmation of the extracts' effects on these end points and identification of the active constituents, an assessment of rosemary's effects on energy balance, and body weight regulation also would be worthwhile, especially when provided at levels consistent with amounts typically consumed by humans.

SUMMARY

Rosmarinus officinalis contains a cocktail of biologically active phytochemicals with diverse health benefits that have only begun to be elucidated. An emerging body of literature supports rosemary as having the potential to improve inflammatory conditions, and some complications associated with obesity and diabetes. Animal and well-controlled human studies are needed to characterize dose-response relationships for those biological actions that follow dietary administration of rosemary samples at culinary-relevant levels. Specific phytochemicals responsible for any benefits need to be identified along with mechanisms of action and possible toxicities in vivo. In animal models of disease, interactions of dietary rosemary with drug efficacies should be clarified. The composition of rosemary samples used for in vivo investigations must be provided in more detail, and quantitation of blood and tissue markers of rosemary bioavailability would aid in comparisons among experiments. It also would be valuable to determine whether dietary intake of culinary-relevant levels of rosemary leads to biologically relevant circulating levels of the major rosemary bioactive constituents and whether other dietary factors influence this bioavailability. Such progress in understanding rosemary's biological activities and in defining dietary rosemary's health benefits is possible, because preclinical disease models and clinical capabilities to monitor established biomarkers are available.

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