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Review Article

Pharmacology of rosemary (*Rosmarinus officinalis* Linn.) and its therapeutic potentials

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The use of plants is as old as the mankind. Natural products are cheap and claimed to be safe. They are also suitable raw material for production of new synthetic agents. Rosemary (*Rosmarinus officinalis* Linn.) is a common household plant grown in many parts of the world. It is used for flavouring food, a beverage drink, as well as in cosmetics; in folk medicine it is used as an antispasmodic in renal colic and dysmenorrhoea, in relieving respiratory disorders and to stimulate growth of hair. Extract of rosemary relaxes smooth muscles of trachea and intestine, and has choleretic, hepatoprotective and antitumerogenic activity. The most important constituents of rosemary are caffeic acid and its derivatives such as rosmarinic acid. These compounds have antioxidant effect. The phenolic compound, rosmarinic acid, obtains one of its phenolic rings from phenylalanine via caffeic acid and the other from tyrosine via dihydroxyphenyl-lactic acid. Relatively large-scale production of rosmarinic acid can be obtained from the cell culture of *Coleus blumei* Benth when supplied exogenously with phenylalanine and tyrosine. Rosmarinic acid is well absorbed from gastrointestinal tract and from the skin. It increases the production of prostaglandin E_2 and reduces the production of leukotriene B_4 in human polymorphonuclear leucocytes, and inhibits the complement system. It is concluded that rosemary and its constituents especially caffeic acid derivatives such as rosmarinic acid have a therapeutic potential in treatment or prevention of bronchial asthma, spasmogenic disorders, peptic ulcer, inflammatory diseases, hepatotoxicity, atherosclerosis, ischaemic heart disease, cataract, cancer and poor sperm motility.

Nature is a great chemist. Starting with water, carbon dioxide and mineral elements, nature has shown her synthetic skill of producing carbohydrates, proteins, fats, vitamins and innumerable secondary metabolites of natural products[1,2]. The use of plant preparations as food stuff, flavouring agents, dyes, insecticides as well as CNS active, cardioactive, hypolipidaemic, antimicrobial and antitumour agents are some examples of immense chemical diversity in plants which are as old as mankind. No wonder that we are still looking more and more into the synthetic skill of plants for cheap and potentially unlimited source of a suitable raw material for the production of new therapeutic agents. With the development of various analytical methods of high precision, and advances in molecular biology and genetic engineering, it is now possible to isolate compounds in extremely small quantities, study their chemical structure and therapeutic potentialities and then to alter the molecule to be suitable for production of novel and more selective new therapeutic agents. Explosion of research works on plants like *Azadirachta indica*[3], *Taxus brevifolia*[4], *Bacopa officinalis*[4] and *Ocimum sanctum*[5] are some examples that can be mentioned in this regard. Recently, another plant that has aroused great interest for its therapeutic potentialities is rosemary, a very common household plant.

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Botany, geographical distribution and folklore of rosemary

Rosemary (*Rosmarinus officinalis* Linn. Fam. *Labiatae*) is an evergreen branched bushy shrub, attaining a height of about one metre with upright stems, whitish-blue flowers and dark green leaves which are small with edges turned over backward. Underneath these rolled edges are little glands containing aromatic oils. It grows wildly along the north and south coasts of the Mediterranean sea, and also in the sub-Himalayan areas[6-8]. It has been cultivated since ancient days in England, Germany, France, Denmark and other Scandinavian countries, Central America, Venezuela and the Philippines[6]. Rosemary is one of the ancient cult plants, closely associated with love and marriage, birth and death. In England and Germany it is considered as a symbol of remembrance and is still used in bridal bouquets and a spring is put in the cradle of a newly born child to protect against evil influences and forces; it is also placed in books and among clothes to protect them from moths and to produce a pleasant odour[9]. The name of the plant is mentioned in some world classics such as Hamlet and Don Quixote[9]. "*Rosmarinus*" is a Latin word which means "Dew of the Sea" (*Ros*=Dew; *Marinus*=Sea).

Traditional uses of rosemary

Rosemary plant is cultivated for its aromatic oil which is called "rosemary oil" and is obtained by steam distillation of the fresh leaves and flowering tops of the plant[6]. It is a colourless or pale yellow liquid having the characteristic odour of the plant. It is an ingredient for Eau-de-cologne, hair tonics, hair lotion, cold cream etc. The leaves are used for flavouring foods as condiment. Since the ancient days rosemary has been used in folk medicine for manifold conditions[10-12], some of which may be enumerated as follows:

It has been used as an antispasmodic in renal colic and dysmenorrhoea and in relieving respiratory disorders. It has also been used as an analgesic, antirheumatic, carminative, cholagogue, diuretic, expectorant, antiepileptic and for effects on human fertility. Other uses are as a general tonic in case of excessive physical or intellectual works and in heart diseases; and also as an insecticide and herbicide. Externally, it is a rubefacient, and is used to stimulate the growth of hair and treatment of eczema of the scalp, boils and wounds.

It is needless to say that such diverse activities of rosemary has generated great interest and its volatile oil, plant extracts and some of its isolated constituents have been subjected for many pharmacological investigations.

Chemistry of rosemary

When the aqueous extract of rosemary was analyzed to identify the active principles, its chemical composition revealed the presence of many substances whose antioxidant and anti-lipoperoxidant activities have been demonstrated, namely rosmarinic acid (RA), caffeic acid (CA), chlorogenic acid, carnosolic acid, rosmanol, carnosol and different diterpenes[13,14], rosmari-diphenol[15], rosmariquinone[16] and many other natural antioxidants, ursolic acid, glucocolic acid and the alkaloid rosmaricine[7]. The rosemary oil contains esters (2-6%) largely as borneol, cineoles and several terpenes, chiefly α-pinene and camphene[6].

Amongst these compounds, CA and RA became the focus of attention of researchers as potential therapeutic agents. They were found to be widely present in many members of the plant kingdom including rosemary. A list of plants containing CA and RA is given in Table 1.

Chemistry of rosmarinic acid

The biosynthetic pathways of the phenolic compounds,CA, dihydroxy-phenyl-lactic acid (DOPL) and RA[1,28,32] are depicted in Fig. 1. The chemical structure of CA, DOPL and RA are given in Fig. 2.

Briefly, shikimic acid which is present widely in plants, is a compound of far reaching importance in biosynthesis of aromatic essential amino acids viz. phenylalanine, tyrosine and tryptophan. Synthesis of cinnamic acid arises from phenylalanine by enzymatic elimination of ammonia (phenylalanine ammonia lyase), followed by aromatic hydroxylation to give CA. RA* (α-O-caffeoyl-3,4-dihydroxyphenyl lactic acid) is an ester of DOPL and CA, with different origins for its two C_6-C_3 units: independently phenylalanine for A ring and tyrosine for B ring (Figs 1&2).

Important enzymes in the biosynthetic pathway of RA have been identified, purified and attempts to enhance or inhibit their activities have been worked out as well. Prephenate aminotransferase (PAT) from RA-producing cell cultures of *Anchusa officinalis* has been purified to apparent homogeneity using a combination of high-performance anion-exchange, chromatofocusing and gel filtration chromatography[17]. The purified PAT displays high affinity for prephenate and it is not subject to feedback inhibition from *L*-Phenylalanine or tyrosine, but its activity is affected by the RA metabolite, 3,4-dihydroxyphenyl-lactic acid.

Another enzyme, tyrosine aminotransferase (TAT) was purified from the cell culture of *Anchusa officinalis* and subsequently has been characterized as TAT-1, TAT-2 and TAT-3, all of them show a pronounced preference for *L*-Tyrosine over other aromatic amino acids, and are inhibited by the tyrosine metabolite, 3,4-dihydroxyphenyl-lactate[18].

In plants, these phenolic acids form esters with tannins containing OH-group, this link known as depside bond. A new analytical method for separation and determination of aqueous depsides has been developed[31].

Table 1—List of some plants containing caffeic acid (CA) and rosmarinic acid (RA)

Plant	Antioxidant	Reference
1 *Anchusa officinalis* L.	RA	17,18
2 *Artemisia campestris*	CA	19
3 *Artemisia capillaris*	RA	20
4 *Artemisia montana*	RA	20
5 *Artemisia princeps*	RA	20
6 *Calendulla officinalis* L.	CA	21
7 *Carissa spinarum*	CA	22
8 *Coleus blumei* Benth	RA	23
9 *Helianthus annuus* L.	CA	24
10 *Lavandula officinalis* Chaix	RA	7
11 *Lithospermum officinalis* L.	CA	7
12 *Lithospermum ruderale*	CA	25
13 *Lycopus europaeus* L.	RA	26, 27
14 *Melissa officinalis*	CA, RA	26, 27
15 *Mentha piperita*	RA	26, 28
16 *Nicotiana tabacuum*	CA	29
17 *Olea europea* L.	CA	29
18 *Origanum vulgare* L.	RA	26, 27
19 *Prunella vulgaris* L.	RA	27
20 *Pyrus comunis* L.	CA	29
21 *Rosmarinus officinalis* L.	CA, RA	7, 38, 27, 30
22 *Salvia aegyptiaca* L.	RA	7
23 *Salvia miltiorrhiza*	CA, RA	31
24 *Salvia officinalis* L.	RA	26, 27
25 *Strychnos innocua* Del	CA	29
26 *Strychnos stuhlmannii* Gilg	CA	29
27 *Thymus vulgaris* L.	CA	29

Production of rosmarinic acid by plant cell culture

Plant cell culture techniques potentially offer the possibility for large-scale production of the desired natural products. RA production has been studied in cell suspension cultures of *Coleus blumei Benth* which has been found to accumulate 8-11% of their dry weight as RA[23]. Actively growing tissue converts > 20% of exogenously supplied phenylalanine and tyrosine to the caffeoyl ester and this high rate of synthesis coincides with an increase in phenylalanine ammonia-lyase specific activity.

Pharmacological actions of rosemary

Effects of rosemary on central nervous system—Administration of rosemary oil, both by inhalation and by oral route, stimulates the CNS, respiratory and locomotor activity in mice, suggesting a direct action of one or more of its constituents[33]. Alcoholic extract of *R. officinalis* showed antidepressant activity on forced swimming induced immobility test model in mice[34].

Effects of rosemary on circulation—Use of rosemary oil bath is reported to stimulate the skin, improve circulation and to improve haemodynamics in occlusive arterial diseases[35].

Effects of rosemary on smooth muscle—The volatile oil inhibited the contraction of tracheal smooth muscle induced by acetylcholine and histamine in rabbits and guinea pigs in Ca^{2+} containing as well as Ca^{2+} free solutions, and also inhibited the contraction induced by high K^+ containing solution[36]. Aqueous extract of rosemary leaves inhibited the spontaneous contractions of the rabbit jejunum and inhibited contractions induced by acetylcholine, histamine and barium chloride[37].

Choleretic and hepatoprotective effects of rosemary—Rosemary has been used empirically as a choleretic and hepatoprotective agent in tradi-tional medicine. These effects were proved experimentally by using the lyophilized ethanol and aqueous extracts of young sprouts of *R. officinalis* which have shown a choleretic activity and offered protection against carbon tetrachloride induced hepatotoxicity in rats[13]. This was evident by a significant increase in bile flow and a significant reduction in plasma liver enzymes when extracts were given as pretreatment before carbon tetrachloride, but there was no protection when extracts were given after it. Using an organic hydroperoxide (tert-butyl-hydroperoxide) to induce injury in freshly isolated rat hepatocytes, it has been shown that the aqueous extract of the young sprouts of *R.officinalis* had an antilipoperoxidant activity, as it reduced the formation of malonaldehyde significantly, in a dose dependent manner and significantly decreased the release of lactico-dehydrogenase (LDH) and aspartate aminotransferase (ASAT), thus confirming the antihepatotoxic action of *R. officinalis*[38].

Antitumorigenic effect of rosemary—The incidence of cancer is associated with multiple factors including dietary and nutritional status. In particular, minor, non-nutrient dietary constituents have been reported to be effective inhibitors of experimental carcinogenesis [39-41]. Some of

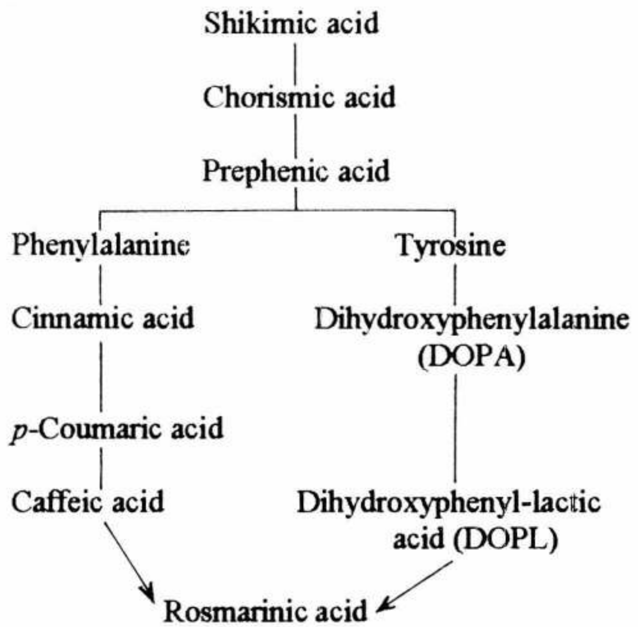

Fig. 1—Biosynthetic pathway of caffeic acid (CA), dihydroxyphenyl-lactic acid (DOPL) and rosmarinic acid in some higher plants. Shikimic acid gives the aromatic essential amino acids: phenylalanine and tyrosine. Rosmarinic acid comes from both, CA and DOPL

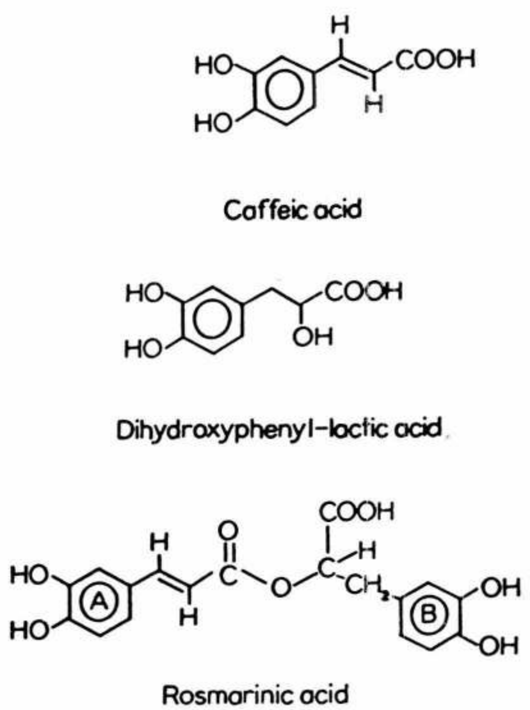

Fig. 2—Chemical structure of caffeic acid, dihydroxyphenyl-lactic acid and rosmarinic acid

these inhibitors have been found to possess a potent antioxidant activity. extracts of leaves of *R. officinalis* are widely used as antioxidant in the food industry and are shown to be safe by not producing any acute toxicity in animal tests[42-45]. Extracts of this plant have also been shown to exhibit an inhibitory activity against KB cells[46], an assay which is widely used to identify anticancer agents in natural products. The potentiality of rosemary extract to inhibit chemically-induced mammary tumorigenesis in female rats and to prevent carcinogen-DNA adduct formation in mammary epithelial cells was investigated[47]. Dietary supplement with 1% (w/w) rosemary extract in rats treated with 7, 12-dimethylbenz (α) anthracene (DMBA) significantly decreased the mammary tumorigenesis by 47% and inhibited total in *vivo* binding of DMBA to mammary epithelial cell DNA by an average of 42%, suggesting that the use of rosemary extract and its individual antioxidant constituents as chemopreventive agents for tumorigenesis warrant further investigation.

Antimycotic activity of rosemary—The problem of infection with oral candidiasis in immuno-compromised patients and following the use of drugs such as broad spectrum antibiotics, corticosteroids and cytotoxic drugs which may not respond to the commonly used remedies such as nystatin, has become increasingly manifested recently. Rosemary oil remarkably inhibited the growth of *Candida albicans in vitro*[48]. *In vivo,* it has been reported that when an aqueous emulsion of rosemary oil in water (1:10) is applied with a cotton swab in the mouth, five times a day, of patients with different types of cancer and pneumonia having candidiasis which did not respond to treatment with nystatin, the growth of the yeast disappeared completely in 2-4 days[49].

Pharmacology of rosemarinic acid

Pharmacokinetics of RA in rats—RA is absorbed by both oral and parenteral routes of administration with t-half of about 1.8h; half an hour after i.v. administration, it was detected and measured in brain, heart, liver, lung, muscle, spleen and bone, with the highest concentration in the lung tissue (13 times the blood concentration). Upon topical administration of RA in the form of ointment on the hind limb, its bioavailability was about 60% and peak time was 4.5 hr; and it was measurable in blood, skin, muscle and bone. Alcohol promotes topical absorption of RA[50].

Antiinflammatory action of RA—RA is a naturally occurring non-steroidal antiinflammatory agent with novel properties which are as follows:

(a) Effects of RA on cell mediators—RA strongly inhibits the formation of 5-hydroxy-6, 8, 11, 14-ecosatetraenoic acid (5 HETE) and leukotriene B_4 in human polymorphonuclear leucocytes, while the formation of prostaglandin E_2 is enhanced by CA and several of its derivatives including RA[51].

(b) Free radical scavenging activity of RA—Hydroalcoholic extracts of some medicinal plants with high amount of hydroxycinnamic derivative content (of which RA is present in more than 3-6% of the dry weight) were tested and have shown significant antioxidative activities, by free radical scavenging effect on DPPH. The antioxidative activity was attributed partly to the high RA content of these plants[26,27].

In another study with the use of spin trapping methods, rosemary extract was reported to have a scavenging effect on the active oxygen free radical in stimulated polymorphonuclear leucocyte system[52].

(c) Effect of RA on the complement system—Activation of the complement system can contribute to the inflammatory reaction in a number of ways, such as by increasing the vascular permeability and formation of oedema; by stimulating chemotaxis of leucocytes; by enhancing platelet activation and aggregation; by enhancing prostaglandin synthesis in macrophages, and by releasing lysosomal enzymes. Several drugs have been shown to modulate the bactericidal activity of serum complement[53,54].

RA was reported to produce an inhibitory activity when tested in three *in vivo* models in which complement activation plays a role[30]. Thus, it inhibited passive cutaneous anaphylaxis for egg ovalbumin in the rat in a dose of 1-100 mg/kg given orally; it impaired *in vivo* activation of mouse macrophages by heat killed *C. pervum* (ip) in a dose of 10 mg/kg i.m. and in still smaller dose (0.316-3.16 mg/kg, i.m.) reduced paw oedema induced by cobra venom factor (CVF) in the rat. The fact that RA did not inhibit *t*-butyl-hydroperoxide induced paw oedema in the rat indicates the selectivity of RA for the complement dependent processes[30]. Experiments with *in vitro* immunohaemolysis of antibody coated sheep red blood cells by guinea pig serum revealed that rosmarinic acid causes inhibition of haemolysis by 70% in a concentration as low as 5-10 μmol/L by acting on the C_3-convertase of the classical complement pathway.

In another study RA was reported to inhibit the chemiluminescence of porcine and human polymorphonuclear leucocytes by pre-opsonized zymosan or phorbol myristate acetate[55]. The killing of *E. coli* was inhibited by RA at a concentration of 2 m*M*, but not that of *Staph. aureus*. The inhibition of the killing was due to an impaired opsonization, caused by an adverse influence of RA on the complement activation. Direct effects of RA on the killing mechanisms of polymorpho-nuclear leucocytes were not observed.

Conclusion and future prospects

It is well established that the increased formation of oxygen free radicals may cause tissue damage and degeneration and hence may play a role in the pathogenesis of some diseases and acceleration of ageing process. Epidemiological evidence suggests that maintaining high intakes of antioxidants such as vitamin E, vitamin C, β-

carotene and some types of food constituents may help to protect against life-threatening diseases such as heart disease and cancer[56].

Oxidative stress is probably an inevitable accompaniment of disease with an increase in the activity of the radical-generation enzymes such as xanthine oxidase, and activation of phagocytes which may contribute to the disease pathology. This free radical initiation of the propagation of a "chain reaction", can only be halted by an antioxidant substance like vitamin E (tocopherol)[57], and will be exaggerated in the deficiency of antioxidants because of the uncontrolled lipid peroxidation, protein damage and DNA adduction.

The accumulated evidence supports that rosemary is one of the important antioxidants which are commonly used in different nations folk medicine and as a beverage drink. It inhibits lipid peroxidation[38] and prevents carcinogen-DNA adduct formation[47]. Increasing utilization of this plant, which has been shown to be safe in toxicity studies in animals and when added as antioxidant to food [42-44], can be achieved simply by adding it to food for flavouring and by taking it as a beverage drink.

The potential benefits of rosemary and its constituents like RA and the caffeoyl derivatives in the following diseases, in which oxygen free radicals may play a role (Table 2), remain to be evaluated by clinical trials.

Rheumatoid arthritis—The rheumatoid joint is a site of intense oxidative stress, as the large number of phagocytic cells, like the polymorphonuclear leukocytes and macrophages, at the onset of phagocytosis use membrane NADPH oxidase to generate superoxide anions[58,59]. The reactive oxygen will cause local damage to proteins like collagen and denaturation of immunoglobulins which in certain circumstances like in rheumatoid arthritis both might become as autoantigens[60]. Generally in inflammation eicosanoid production switches from the formation of prostaglandin E_2, which dampens cellular activation, to the synthesis of leukotrienes which are oxidized forms of arachidonate and this switching promotes aggressive cellular reactions by macrophages, polymorphs and lymphocytes[61]. RA has been shown to increase the production of prostaglandin E_2 and decrease the production of leukotrienes[51] and above all it inhibits the complement C_3-convertase[30] resulting in an inhibition of the inflammatory process. Rosemary as antioxidant may reduce the damage caused by the oxygen free radicals to the joint and surrounding tissues.

Atherosclerosis—Atherosclerotic lesions are now thought to be specifically promoted by low density lipoprotein particles that are oxidized in endothelial cells, macrophages and smooth muscle cells[62,63]. These particles will be phagocytozed with production of lipid peroxide which will cause chemoattraction of more monocyte/macrophages and inhibits their motility resulting in the development of atheromatous plaque. This can be reduced by lowering the low density lipoprotein levels, administration of antioxidants and to increase the production of the beneficial prostaglandins which inhibit platelet aggregation[57]. Rosemary increases production of prostaglandin E_2[51] and has an antioxidant effect, so it may be beneficial in atherosclerosis.

Table 2—Therapeutic potentials of rosemary plant

Pharmacological actions	Therapeutic potential
1. Relaxation of bronchial smooth muscle	Bronchial asthma
2. Relaxation of intestinal smooth muscle	Antispasmodic
3. Reduction of leukotrienes and increase PGE_2 production	Bronchial asthma Peptic ulcer Inflammatory diseases
4. Inhibition of lipid peroxidation	Hepatotoxicity Atherosclerosis and Ischaemic heart disease Inflammatory diseases Asthenozoospermia
5. Inhibition of the complement	Inflammatory diseases
6. Prevention of the carcinogen-DNA adduct formation	Cancer (protection)

Coronary artery disease—The consequences of coronary artery disease can be minimized by reducing the damage resulting from the release of free radicals produced by xanthine oxidase after the reperfusion (reoxygenation) which may be more pronounced than the damage due to the ischaemic anoxia[64]. Antioxidants may help in reducing this effect.

Hepatotoxicity—Fatty changes and necrosis are due to free radical mediated lipid peroxidation and damage to proteins caused by many noxious agents such as ethanol[65], large dose of paracetamol[66] and carbon tetrachloride can be reduced by anti-oxidants[38]. Rosemary may have a beneficial use in cholestasis as it increases bile flow[13].

Carcinogenesis—Various initiators and promoters of carcinogenesis act via the generation of oxygen free radicals[67] which cause lipid peroxidation[68] and oxidative DNA damage[69]. Antioxidants suppress lipid peroxidation and stop action of promoters[67,70,71]. Rosemary has been shown to have antioxidant effect with prevention of the carcinogen-DNA adduct formation[47] and so it may be useful in prevention of cancer.

Ulcerative colitis—Excessive accumulation and activation of phagocytes in the gut may cause severe damage[56] and may be reduced by antioxidants.

Cataract—Cataract in old people involves oxidation and cross-linking of lens proteins. Its development can be accelerated by free radicals[56] and may be delayed by antioxidants.

Bronchial asthma—RA increases the production of prostaglandin E_2 which is generally bronchodilator while reduces leukotrienes which are bronchoconstrictors[51]. This effect can be enhanced by the inhibition by rosemary of the histamine constricting action on the bronchial smooth muscle[36] and by its relaxant effect on the smooth muscle[36,37]. The antioxidant effect of rosemary against the free radicals, which may have a role in the pathogenesis of bronchial asthma, adds to its potential preventive use in bronchospasm diseases.

Peptic ulcer—Prostaglandin E_2 is well known to offer a protective effect for the gastric mucosa against the harmful effect of gastric acid. RA has been shown to increase the production of prostaglandin E_2[51]and hence a potential use in peptic ulcer may exist.

Sperm motility—It has been shown that lipid peroxidation of the sperm membrane makes it more rigid hence decreases its motility and that antioxidants like ferulic acid (a derivative of caffeic acid) improve sperm motility in people with asthenozoospermia[72].

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