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Review

Rosmarinic acid: modes of action, medicinal values and health benefits

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Abstract

The supplementation of livestock rations with herbs containing bioactive components, such as rosmarinic acid (RA), have shown promising results as a natural feed additive in promoting growth, productive and reproductive performance, feed utilization, fertility, anti-oxidant status and immunologic indices. Furthermore, RA reportedly reduces the risks of various animal diseases and mitigates side effects of chemical and synthetic drugs. RA is a natural polyphenol present in several Lamiaceae herbs like *Perilla frutescens*, and RA is becoming an integral component of animal nutrition as it counters the effect of reactive oxygen species induced in the body as a consequence of different kinds of stressors. Studies have further ascertained the capability of RA to work as an anti-microbial, immunomodulatory, anti-diabetic, anti-allergic, anti-inflammatory, hepato- and renal-protectant agent, as well as to have beneficial effects during skin afflictions. Additionally, RA is favored in meat industries due to enhancing the quality of meat products by reportedly improving shelf-life and imparting desirable flavor. This review describes the beneficial applications and recent findings with RA, including its natural sources, modes of action and various useful applications in safeguarding livestock health as well as important aspects of human health.

Keywords: Rosmarinic acid, mode of action, beneficial application, health benefits, animal.

Introduction

Polyphenolic compounds have been demonstrated to play vital roles against several diseases and health risks, including tumor cell proliferation, carcinogenesis, bronchial asthma, peptic ulcer, atherosclerosis, spasmogenic disorders, apoptosis, ischaemic heart disease, hyperglycemia, hepatotoxicity, depression, cataract, poor sperm motility and metastasis, in addition to roles as powerful antioxidant, anti-allergy, anti-microbial, anti-carcinogenic and anti-inflammatory agents (Bulgakov *et al.*, 2012; Karthikkumar *et al.*, 2012).

Rosmarinic acid (RA) is considered one of the most important polyphenols. It is an ester of 3, 4-dihydroxyphenyllactic and

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caffeic acids. RA is present in herbal plants such as rosemary (*Rosmarinus officinalis* L.), basil (*Ocimum basilicum*), oregano (*Origanum vulgare)*, sage (*Salvia officinalis*), *Melissa officinalis* and many others (Corral-Lugo *et al*., 2016).

Several studies have shown biologic activities and protective efficacies of RA, including anti-bacterial, anti-oxidant, anti-cancer, anti-inflammatory, immunomodulatory and health-enhancing activities (Chun *et al*., 2014; Alagawany and Abd El-Hack, 2015; Rocío-Teruel *et al*., 2015). Similarly, several studies also reported the dietary supplementation of certain herbs (e.g., rosemary, thyme and garlic), and their products such as cold pressed oil, essential oil or bioactive components such as RA, carvacrol, thymol, resveratrol and curcumin, in animals and poultry to improve performance, immune responses, anti-oxidant parameters, carcass criteria and quality, and to lower morbidity and mortality rates (Yesil-Celiktas *et al*., 2010; Kim *et al*., 2013; Alagawany and Abd El-Hack, 2015).

In this review, we have described the natural sources, chemical structure, modes of action, beneficial applications and biological activities of RA in animal and poultry health, nutrition and production, as well as covering some of its important aspects for safeguarding human health. The information presented here is expected to be useful for students, nutritionists, researchers, veterinarians, medical professionals, pharmacists and livestock producers. Additionally, this information can help to popularize and propagate the multidimensional health benefits of this molecule with its multitude of beneficial applications. The source of information presented herein has been retrieved and compiled from different database searches such as ScienceDirect, SCOPUS and PubMed.

RA sources

Rosmarinic acid, which was first isolated from *R. officinalis*, is a polyphenolic compound that is an ester of caffeic acid and 3, 4-dihydroxyphenyllactic acid (Scarpati and Oriente, 1958; Petersen *et al*., 2009). Its structure is derived from two amino acids, caffeic acid from phenylalanine and 3, 4-dihydroxyphenyllactic acid from tyrosine (Ellis and Towers, 1970). The structure of RA was first described by Scarpati and Oriente in 1958 (Petersen, 2013). RA is present in certain family Lamiaceae (=Labiatae) herbs, such as *Perilla frutescens*, which are the richest source of RA (Hossain *et al*., 2010; Vladimir *et al*., 2014). Also, the presence of RA in spices, herbs and medicinal plants has health-promoting and other beneficial properties. The other sources of RA are marjoram, lemon balm, sage (*S. officinalis* L.), thyme (*Thymus vulgaris*), rosemary (*Rosmarinus officinalis)*, *Artemisia capillaris*, *Calendulla officinalis*, basil (*O. basilicum* L.), *Salvia miltiorrhiza*, *S. officinalis* (sage tea), oregano (*O. majorana*), *Cordia sinensis*, *Sanicula europaea*, *Salvia euphratica*, mint (*Mentha arvense* L.), *M. officinalis*, *Prunella vulgaris*, *Symphytum officinale* and *Heliotropium foertherianum* (Petersen *et al*., 2009; Rossi *et al*., 2012; Corral-Lugo *et al*., 2016). A study with 29 species of family Labiatae revealed that *Mentha spicata* possessed the highest amount of RA among the studied species, hence this herb can be considered for extracting RA in good quantity (Shekarchi *et al*., 2012).

Chemical structure and physical characteristics

The chemical structure of RA (3, 4-dihydroxyphenyllactic acid) derived from hydroxycinnamic acid (Rossi *et al*., 2012) is shown in Fig. 1. A natural anti-oxidant isolated from many plants, RA is a molecule of highly lipophilic and slightly hydrophilic properties, which is usually in the form of a red-orange powder. Solubility of this molecule is higher in most organic solvents. The melting point of RA is 171–175°C (340–347°F) and the molar mass is 360.32 g mol^{-1} (Petersen *et al*., 2009).

Metabolism and excretion

Biosynthesis of RA begins with amino acids such as L-tyrosine and L-phenylalanine (Petersen and Simmonds, 2003). Information about absorption, metabolism, degradation and excretion of RA are limited. RA and its related metabolites (caffeic acid, methylated RA, m-coumaric acid and ferulic acid) were observed in human urine after intake of 200 mg of RA. In plasma, peak levels of RA and ferulic acid were observed 0.5 h after RA intake, while the highest level of methylated RA was detected after 2 h and related compounds were excreted through 6 h after RA intake. The excreted amount in the urine from RA and its derivatives was 6.3% of the total dose (Baba *et al*., 2005).

Compounds related to RA, including m-coumaric and m-hydroxyphenylpropionic acids as well as caffeic and ferulic acids, were detected in urine of rats after oral administration of RA (Nakazawa and Ohsawa, 1998). RA was absorbed percutaneously and entered to many parts of the body such as skin, blood, bone, and meat after its topical application to the skin of rats. After intravenous administration, RA residue was detected in certain tissues like spleen, lung, liver and heart (Ritschel *et al*., 1989). Also, in rats, RA could be absorbed from gastrointestinal tract and skin and distributed in different tissues. Nakazawa and Ohsawa (2000) found that there were some differences in metabolism of RA between rats and human beings. They pointed out that human intake of RA resulted in 2, 4, 5-trimethoxycinnamoyl being excreted in the urine, which is derived from RA. To improve the bioavailability of RA, nanoparticle-based RAs were recently studied to bypass gastric degradation. RA loaded on Witepsol and Carnauba waxes were tested both *in vitro* and *in vivo* (in rats), and, without affecting the activity of RA, these results confirmed that there was no cytotoxicity or genotoxicity (Madureira *et al*., 2016). Chitosan-based nanoparticle delivery was also evaluated for ocular delivery of RA (da Silva *et al*., 2016).

Modes of action, biological activities and beneficial aspects

The modes of action and beneficial activities of RA are presented in Table 1. Using RA as natural feed additive/supplement has been described to exert multiple beneficial activities on health. These reports include use of RA as an antioxidant, anti-

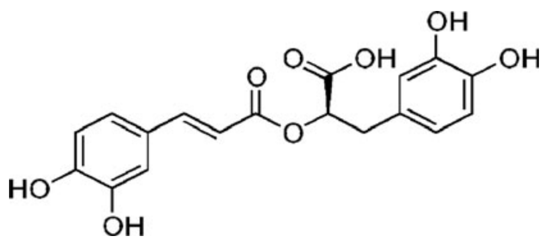

Fig. 1. Basic st Basic structural formula of rosmarinic acid ($C_{18}H_{16}O_8$).

microbial, anthelminthic, coccidiostat and anti-inflammatory agent, and as an endocrine and immune stimulant. In addition, improving the secretion of endogenous digestive enzymes, motility of the gut, motility of sperm, enhancing growth and production, as well as proven anti-allergy, anti-diabetic anti-angiogenic, anti-tumor and neuroprotective functions (Bulgakov *et al.*, 2012; Petersen, 2013; Hossan *et al.*, 2014; Stansbury, 2014; Kim *et al.*, 2015; Nabavi *et al.*, 2015). RA also affects feed conversion and utilization, growth and reproductive performance in addition to egg and meat quality of poultry (Bulgakov *et al.*, 2012). Gao *et al.* (2005) and Abd El-Hack *et al.* (2015) confirmed the anti-microbial, anti-bacterial and anti-oxidant activity of the bioactive compounds and oils (cold pressed and essential) extracted from medicinal plants in a large number of experiments (*in vitro* and *in vivo*), but certain queries still remain unanswered concerning the optimal level, mode of action, absorption and metabolism of these additives in animals. Many trials were carried out to determine the dependency and functionality of RA and its supplementation in animal and poultry diets. There are many studies on the anti-oxidant and anti-cancer effects of RA; however, reports on its activities as an anti-inflammatory, anti-Alzheimer, anti-allergy or anti-diabetic agent are few (Ferreira *et al.*, 2013). Ozturk *et al.* (2014) reported a reduction in circulatory levels of creatinine, blood urea nitrogen, focal glomerular necrosis, dilatation of Bowman's capsule, degeneration of tubular epithelium and tubular dilatation in unilaterally nephrectomized rats treated with RA.

Advances in science and especially the field of biotechnology by employing new high-throughput techniques have provided newer trends and avenues for achieving better production and exploiting the useful applications of RA to its full potential (Kim *et al.*, 2015). The salient beneficial applications of RA are presented in Fig. 2.

Anti-microbial effects

RA is used in animal and poultry nutrition, in particular as a natural phytogenic additive to enhance the general health, performance parameters, activation of digestive system structure and function, as well as its ability to alter the gut microbiota and to reduce numbers pathogenic bacteria such as *Escherichia coli*, *Salmonella* spp. and many other harmful bacteria species (Yesilbag *et al.*, 2011; Chung *et al.*, 2015). RA may be the main bioactive anti-microbial compound present in rosemary extracts. However, a methanol extract containing 30% carnosic acid, 16% carnosol and 5% RA was an effective anti-microbial against Gram-positive and -negative bacteria, while water extract containing 15% RA showed narrower effects (Moreno *et al.*, 2006).

In the present era of emerging and rising drug resistance of pathogenic microorganisms to common anti-microbials, medicinal plants, herbs and their oils have gained wide attention as novel and alternative drugs, such as RA, on account of their potent anti-microbial activities (Ekambaram *et al.*, 2016). Benedec *et al.* (2015) reported that RA showed higher *in vitro* anti-oxidant activity (DPPH method) and expressed profound activity against Gram-positive bacteria, inhibition by *R. officinalis* extract was even higher than the Gentamicin control, and RA also suppressed fungal growth (*Candida albicans*). However, the same group reported that this extract was ineffective against Gram-negative organisms like *E. coli* and *S.* Typhimurium. RA extracted from *O. vulgare* L., *M. officinalis* L., *R. officinalis* L., *O. basilicum* L., *S. officinalis* L. and *Hyssopus officinalis* L. had an anti-microbial effect against *L. monocytogenes*, *S. aureus* and *C. albicans* (Benedec *et al.*, 2015). The mortality rate of mice infected with Japanese encephalitis virus was reduced with RA supplementation. The viral load was significantly ($P < 0.001$) decreased in infected rats treated with RA in comparison with infected animals without RA treatment at 8–9 days after infection (Swarup *et al.*, 2007). *Aeromonas hydrophila* is an important pathogenic bacterium of zebra fish, and *A. hydrophila* can cause biofilm formation. RA was found to inhibit biofilm formation *in vitro*, due to quorum sensing activity of *A. hydrophila*, at a concentration of 750 $\mu g\ ml^{-1}$ (Rama Devi *et al.*, 2016). RA has synergistic activity with antibiotics like vancomycin, to act against methicillin-resistant *Staphylococcus aureus* (MRSA) under *in vitro* conditions (Ekambaram *et al.*, 2016). In this context, further exploitation of the anti-microbial properties of RA has been suggested for finding a useful role against several other important pathogens affecting animals.

Immunomodulatory effects

Beneficial polyphenols such as RA, carnosic acid and carnosol present in the rosemary herb also have immunomodulatory effects (Chun *et al.*, 2014; Rocío-Teruel *et al.*, 2015). The immunomodulatory impacts of RA may also make it a novel agent for the treatment of autoimmune disorders (Friedman, 2015). The use of RA at a concentration of 100 or 200 mg oil kg^{-1} of broiler chicken diet, increased immunologic indices like phagocytic activity and phagocytic index along with the concentrations of some biochemical blood parameters like triglycerides, total cholesterol, low density lipoprotein and high-density lipoprotein. It has also been reported to improve the immune function by reducing pro-inflammatory mediators and increasing IL-10 levels (Lembo *et al.*, 2014).

Analgesic and anti-inflammatory effects

RA was reportedly beneficial against colon cancer, owing to its anti-inflammatory activities and ability to suppress

Table 1. Mechanisms of action and activities of rosmarinic acid

Type of study	Activities	Results/mechanisms	Literatures
In vivo	Anti-microbial	Decreased counts of pathogenic bacteria such as *E. coli*, *L. monocytogenes*, *S. aureus*, *C. albicans*, and HSV	Moreno *et al.* (2006), Benedec *et al.* (2015)
In vivo	Immunomodulatory	Increased weight of lymphoid organs and improved macrophage function	Rocío-Teruel *et al.* (2015)
In vivo	Immunomodulatory	Inducement of apoptosis in T and NK cells via eliciting mitochondrial dysfunction	Hur *et al.* (2003)
In vivo	Immunomodulatory	Reduced pro-inflammatory mediators and enhanced IL-10 level	Lembo *et al.* (2014)
In vitro and *in vivo*	Anti-inflammatory Immunomodulatory	Inhibition of eosinophilic inflammation, mucus cell accumulation, Th2 cytokines and inhibition of allergen-specific IgG and decreased IL-4 and IL-5	Sanbongi *et al.* (2004), Rocha *et al.* (2015)
In vitro	Anti-inflammatory Immunomodulatory	Inhibition of synovial tissue damage, reduced arthritic index scores and COX-2 expression, as well as inhibition of TCR-mediated T cell proliferation and activation	Youn *et al.* (2003)
In vitro	Anti-viral Anti-inflammatory	Reduction in IL-12, TNF-α, IFN-γ and IL-6, increased survival rate, inhibited expression of viral proteins and reduced viral mRNA transcripts	Swarup *et al.* (2007)
In vitro and *in vivo*	Anti-inflammatory Immunomodulatory	Reduced concentrations of histamine, IgE, IL-1β, IL-6, TNF-α, reduced levels of COX-2 and NF-κB, reduced mast cell and eosinophil infiltration	Oh *et al.* (2011)
In vitro and *in vivo*	Anti-oxidant	Reduced the production of hydrogen peroxide (H_2O_2) and superoxide ($O_2\cdot$) radicals. Upregulated catalase, heme oxygenase-1, and superoxide dismutase, reduced malondialdehyde	Fadel *et al.* (2011), Fernando *et al.* (2016)
In vitro	Anti-oxidant Neuroprotection	Inhibited NF- κB translocation and increased PPAR-g expression, inhibited cell death under oxidative stress, excitotoxicity and ischemia–reperfusion conditions	Fallarini *et al.* (2009)
In vitro	Anti-oxidant Neuroprotection	Prevented the impairment of memory and nitration of proteins	Alkam *et al.* (2007)
In vivo	Anti-allergic	Inhibited the activity of α-glucosidase	Zhu *et al.* (2014)
In vivo	Anti-cancer	Reduced the transcription factor through inhibition of AP-I which is responsible for the activation of COX-2	Hossan *et al.* (2014), Scheckel *et al.* (2008)
In vivo	Fertility stimulator	Improved the progressive and total motility of sperm and maintained acrosomal and plasma membrane integrity	Bulgakov *et al.* (2012), Luño *et al.* (2014)
In vivo	Anti-hyperglycemic Anti-diabetes	Inhibited α-glucosidase, reduced glomerular hypertrophy, glomerular number loss and glomerulosclerosis	Tavafi *et al.* (2010)
In vivo	Anti-hyperglycemic Anti-diabetes	Increased GLUT4 expression and decreased PEPCK expression	Runtuwene *et al.* (2016)
In vivo	Anti-Alzheimer	Inhibited NF-κB activation, decreased histopathological damage and brain edema	Luan *et al.* (2013)
In vivo	Nephro-protective	Reduced glomerulus necrosis, dilatation of Bowman's capsule and degeneration of renal tubular epithelial cells	Ozturk *et al.* (2014)
In vivo	Burn injuries	Reduced edema formation, reduced hepatic injury	Rocha *et al.* (2015)

cyclooxygenase-2 (COX-2) activation via activator protein-1 inducing factors (Ferrández *et al.*, 2003). The beneficial aspects of RA as an anti-inflammatory agent have been also reported against skin cancer after topical use (Roland *et al.*, 2010). The analgesic and anti-inflammatory activities of the acetyl ester derivative of RA were evaluated by employing abdominal constriction and carrageenan-induced paw edema in rats, respectively, revealing significant effects via a peripheral-mediated mechanism and reduced the number of paw licks, which also indicated a potential role for the management of pain and inflammation (Lucarini *et al.*, 2013). The anti-inflammatory activities and protective effect of RA against local and systemic inflammation in the rats have been evaluated by Rocha *et al.* (2015). RA also showed anti-inflammatory effects against chronic and acute inflammation, particularly at doses of 50, 100 and 150 mg kg^{-1} (Boonyarikpunchai *et al.*, 2014). Inhibitory effects of rosemary (*R. officinalis*) ethanolic extract on *Propionibacterium acnes*-induced inflammation has been documented *in vitro*, and attributed to suppression of pro-inflammatory cytokines (interleukin [IL]-8, IL-1β and tumor necrosis factor [TNF]-α) in the monocytic THP-1 cell line, along with *in vivo* attenuation of the *P. acnes*-induced ear swelling and granulomatous inflammation in an intradermally injected mouse model, via suppression of nuclear factor kappa-B (NF-κB) and Toll-like receptor -2 (TLR-2) mediated signaling pathways (Tsai *et al.*, 2013). In the same context,

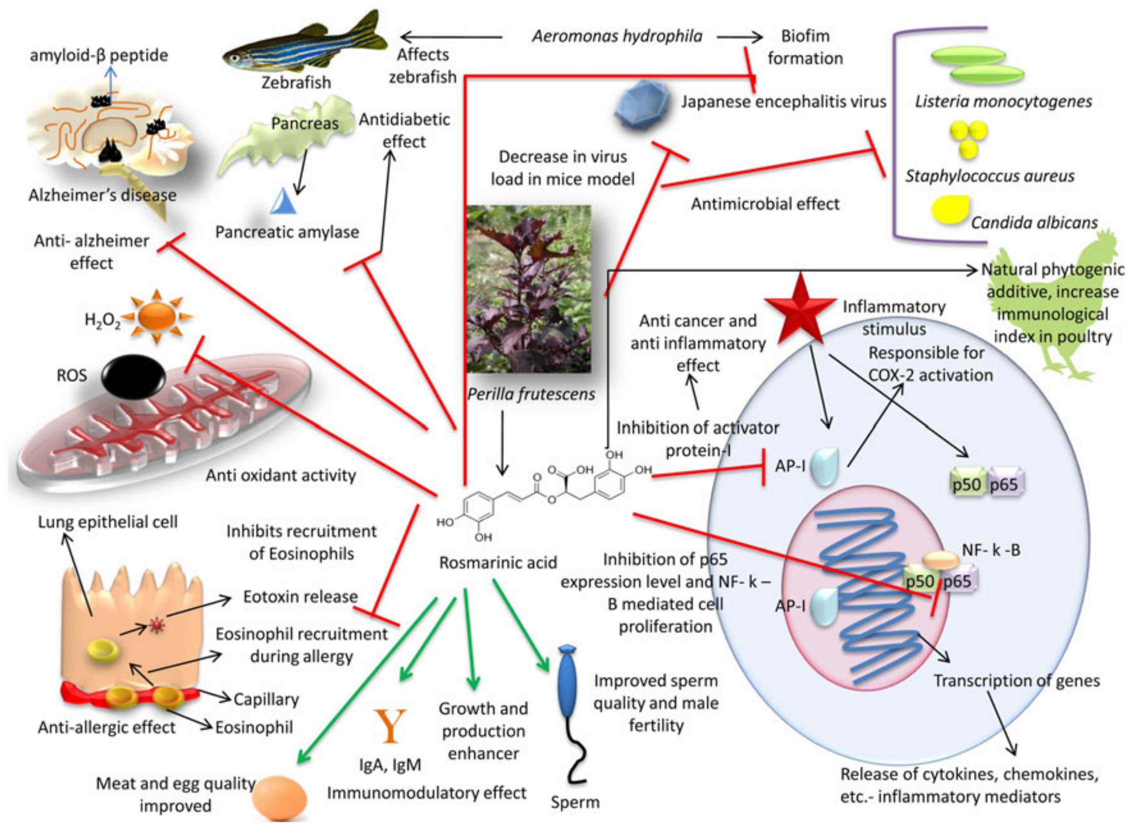

Fig. 2. Mechanisms of action and beneficial effects of rosmarinic acid.

Friedman (2015) pointed out that the concentrations of TNF-α, interferon-γ, IL-6 and IL-12 were decreased in infected animals treated with RA when compared with infected animals without RA. Neuropathic pain due to chronic constriction injury of sciatic nerves in rats was tested with RA, and it was found that there was pain relief due to the anti-inflammatory effect of RA (Ghasemzadeh Rahbardar *et al.*, 2017).

Rocha *et al.* (2015) observed that pretreatment of male Wistar rats with 25 mg kg^{-1} *R. officinalis* extract reduced inflammation and paw edema formation by 60%, suggesting anti-inflammatory activity of this plant extract. These preparations also possessed anti-inflammatory activity, resulting from ischemic reperfusion and decreased hepatic injury. The administration of RA also reduced the inflammatory response during thermal or burn injuries. RA reduced the release of cytokines into general circulation during the periods of burn and scald injuries, which affect various vital organs in the system, including lungs, kidney and liver; hence, this administration protects the entire system. In addition to its other anti-inflammatory actions, the oxidative burst from the neutrophils was also reduced (Rocha *et al.*, 2015). The anti-allergenic effect of RA shows high potential for allergy treatments via suppressing inflammatory activity by decreasing IgE and COX-2 levels (Zhu *et al.*, 2014, 2015). RA also exhibits anti-inflammatory and anti-allergic inhibition of seasonal allergic rhinoconjunctivitis (Osakabe *et al.*, 2004) via reduced IgE and COX-2 levels (Oh *et al.*, 2011).

Anti-cancer effects

Rosemary herb use has spread widely due to its high content of many important constituents such as carnosic acid, caffeic acid, ursolic acid and carnosal, as well as its derivatives like RA, which were mainly used as a food additive (spice, flavoring and coloring agent) in food processing (Alagawany and Abd El-Hack, 2015; Ramanauskiene *et al.*, 2016). These constituents provide the rosemary plant with powerful antioxidant and therapeutic effects in prevention and treatment of several diseases, and inhibiting the development of tumors in many organs such as the colon, liver, stomach and breast, as well as leukemia and melanoma cells (Hossan *et al.*, 2014; Wu *et al.*, 2015).

It has been suggested that the RA molecule can reduce rectum and colon cancer, as well as increase tumor regression, in animal models of colorectal cancer. Hossan *et al.* (2014) reported that the administration of RA in colon cancer cell lines (HT-29) reduced a transcription factor through inhibition of activator protein-I (AP-I), which is responsible for the activation of COX-2 (Scheckel *et al.*, 2008). Karthikkumar *et al.* (2015) supplemented RA in colon cancer-induced rats. These authors found that RA reduced the levels of p65 protein expression and NF-kB-mediated cell proliferation during the treatment regimen. The spectrum of RA's anti-cancer activity was not restricted only to the colon, but also included skin cancer and melanoma (Osakabe *et al.*, 2004), pancreatic cancer (Roland *et al.*, 2010), breast cancer (Chen *et al.*, 2011), lung cancer

(Tao *et al.*, 2014), leukemia, hepatoma and ovarian cancer (Inyushkina *et al.*, 2007). RA at a concentration of 5 mg kg^{-1} BW in rats showed good effect against colon cancer induced by 1, 2-dimethylhydrazine, suggesting it could be considered as a chemotherapeutic agent candidate for colon cancer (Venkatachalam *et al.*, 2013). A subsequent study reported that RA could reduce lipid peroxidation byproducts and expression of pro-apoptotic proteins in rats with colon cancer (Venkatachalam *et al.*, 2016).

RA could play a crucial role against skin, breast and pancreatic cancer and melanoma. The beneficial roles of this compound may be advanced by topical uses, with reports that RA acted against skin cancer by exerting antioxidant and anti-inflammatory effects (Roland *et al.*, 2010). RA improved the expression of an enzyme, tyrosinase, and increased melanin content in melanoma cells, suggesting melanin plays a role against skin cancer (photocarcinogenesis). Also, there is an increasing appreciation of the importance of RA in melanogenesis (melanin formation), and RA was found to increase the activity and expression of tyrosinase in B16 melanoma cells (Lin *et al.*, 2014). Diterpenes from *R. officinalis* were also shown to possess potent anti-cancer activities (Petiwala and Johnson, 2015). Moreover, Xu *et al.* (2016) reported that RA has a radioprotective impact in animals. RA is therefore a promising anti-cancer factor with potential radioprotective and chemopreventive impacts.

Antioxidant effects

The RA molecule is a polyphenolic compound that is considered a powerful free-radical scavenger, which enhances the anti-oxidant defense mechanism against oxidative reactive oxygen species (ROS) (Kuo *et al.*, 2011; Ramanauskiene *et al.*, 2016). Gao *et al.* (2005) studied the anti-apoptotic and anti-oxidant effects of RA on H_2O_2-induced apoptosis in astrocytes, and these authors found that RA reduced levels of ROS, malondialdehyde (MDA) and H_2O_2-induced cell injury. They showed the effectiveness of RA as an antioxidant and anti-apoptotic agent. In this context, RA strongly decreased ROS generation and apoptosis (Lee *et al.*, 2008). Fadel *et al.* (2011) investigated the efficacy of RA as a natural antioxidant in reducing and preventing the alterations (lipid peroxidation) of lipid membranes by oxidative stress. There was negative correlation between RA and concentration of lipid peroxidation, including MDA ($P <$ 0.05) (Luño *et al.*, 2014).

RA was shown to have both anti-oxidant and anti-inflammatory action by inhibiting lipoxygenase activity (Stansbury, 2014). In animals, Bacanli *et al.* (2016) assessed the ability of RA to attenuate sepsis-induced oxidative stress by improving anti-oxidant indices and DNA repair capacity. In serum, total anti-oxidant capacity was improved ($P < 0.05$) in groups that received RA, while MDA was reduced with RA treatment (Hajhosseini *et al.*, 2013). This antioxidant activity is attributed to the phenolic hydroxyl (–OH) group (Rice-Evans *et al.*, 1996). The supplementation of RA in aged mice elevated the activity of anti-oxidant enzymes superoxide dismutase, catalase and glutathione peroxidase, and reduced malonaldehyde production in liver and kidney (Zhang *et al.*, 2015), and these responses seemed to be dependent on the dose of RA.

Regarding the cytoprotective effect of RA against ultraviolet B (UVB) radiation, Fernando *et al.* (2016) showed that RA is an effective eliminator of intracellular ROS induced by UVB and improves the activities of anti-oxidant enzymes such as catalase, heme oxygenase-1, superoxide dismutase and their transcription factor Nrf2, which are lowered by the radiation of UVB.

RA augments the D-galactosamine and lipopolysaccharide-induced injuries in liver through their effect on superoxide dismutase and COX-2 production (Won *et al.*, 2003). Pérez-Fons *et al.* (2010) reported that the presence of diterpenes and RA were responsible for rosemary leaf extract's anti-oxidant activity. Makino *et al.* (2000) observed that RA exhibited an anti-proliferative effect in murine mesangial cells.

Anti-diabetic effect

Herbal preparations that include RA play an important role in the treatment of diabetes. The main goals of diabetes treatment are to maintain the concentration of blood glucose, to reduce insulin resistance and to improve β-cell function. Meanwhile, medications used to treat diabetic problems must not only reduce the levels of blood glucose, but also improve insulin sensitivity and glucose homeostasis (Wilcox, 2005; Runtuwene *et al.*, 2016). Hasanein and Zaheri (2014) reported that RA is a bioactive component and a good strategy for diabetic neuropathic treatment in animals. Pancreatic amylase inhibitors seemed to be good option to control hyperglycemia by preventing the release of glucose from starch, hence these inhibitors can be used as a drug for treatment for diabetes. RA has the potential to inhibit pancreatic amylase, which can be used as anti-diabetic drug (McCue and Shetty, 2004).

RA reduced glomerular hypertrophy, glomerular loss, glomerulosclerosis and also attenuated serum creatinine and urea levels in rats with diabetes (Tavafi *et al.*, 2010). A group receiving 10 mg kg^{-1} of RA had significantly attenuated lipid peroxidation in the hippocampus, cortex, and striatum by 28, 38 and 47%, respectively, of diabetic rats in comparison with the control group. Moreover, RA played important role as an anti-hyperglycemic agent, and the acetylcholinesterase activity was increased in the hippocampus, cortex and striatum by 58, 46, and 30%, respectively, with hyperglycemia in diabetic rats compared with the control rats, but the use of RA reduced this effect to control levels after 3 weeks (Mushtaq *et al.*, 2014). The inhibitory activity of α-glucosidase is a potential mechanism behind the control of diabetes mellitus, which was also exhibited by RA, thus it could be considered as a hypoglycemic agent (Zhu *et al.*, 2014). Runtuwene *et al.* (2016) observed that RA reduced hyperglycemia and ameliorated insulin sensitivity by increasing GLUT4 expression and decreasing PEPCK expression. In diabetic animals, Sotnikova *et al.* (2013) and Jayanthy and Subramanian (2014) reported that RA may control blood glucose by regulating SGLT1 trafficking to the intestinal brush-border membrane to mitigate hyperglycemia.

Neuroprotective and anti-Alzheimer effects

RA has a beneficial role as a neuroprotective agent that helps to reduce or prevent cell damage and disorders caused by free radicals and other factors (Zhang *et al.*, 2011; Hasanein and Mahtaj, 2015). The neuroprotective effects of RA at cellular levels, with a special focus on effects against neuroinflammation, neurodegeneration, neurotoxicity and oxidative stress, were recently reviewed by Nabavi *et al.* (2015). Ghaffari *et al.* (2014) studied the neuroprotective effect of RA against oxidative stress in N2A cells and found that hydrogen peroxide-induced cytotoxicity in N2A cells was inhibited by RA treatment. Also, they recommended that RA can be potentially used as a factor for reduction of human neurodegenerative diseases which are caused by oxidative stress. In another human study, Lee *et al.* (2008) investigated the neuroprotective impacts of RA against H_2O_2-induced apoptotic cell death, and they pointed out that RA significantly ($P < 0.05$) reduced H_2O_2-induced ROS generation and apoptosis. Furthermore, RA enhanced heme oxygenase-1 as an anti-oxidant enzyme. In rats, Pereira *et al.* (2005) investigated the effect of RA administration at levels of 1, 2, 4 or 8 mg kg^{-1} on behavioral alterations and its genotoxic impact on brain tissue. They noted that the level of 8 mg kg^{-1} of RA was enough to increase the motivation and locomotion of the rats, but the lower levels (1, 2, and 4 mg kg^{-1}) of this acid produced anxiolytic-like impact without any alterations in locomotor or DNA damage in brain.

Oxidative stress plays an important role in the development of Alzheimer's disease. Amyloid beta peptides are deposited, interacting with mitochondria, leading to free radical production, dysfunction of the mitochondria and death of the cell. In one study, RA reduced amyloid beta-induced nitrite and malondialdehyde production, suggesting a beneficial effect of RA (Baluchnejadmojarad *et al.*, 2014). Memory impairments may be mediated by daily consumption of RA, due to a protective effect against neurotoxicity of $A\beta_{25-35}$ that may be attributed to scavenging of Peroxynitrite (Alkam *et al.*, 2007). Luan *et al.* (2013) pointed out that using of RA at 50 mg kg^{-1} decreased histopathological damage, brain edema and high-mobility group Box1 protein expression and inhibited NF-κB activation. They also observed that RA at levels of 25, 50, 100 and 200 mg kg^{-1} reduced cerebral infarct volume, neurological deficit scores and water content in brain, but did not decrease concentration of blood glucose.

Fertility stimulator

Rosemary herb and its extracts reportedly improved sperm quality and male fertility (Uyeturk *et al.*, 2014). Progressive and total motility of sperm were statistically increased ($P < 0.05$) by experimental treatments with RA (26.25, 52.5 and 105 μM) compared with controls. Acrosomal and plasma membranes were enhanced by RA (at 105 μM), while spermatozoa numbers were unaffected by the different treatments (Luño *et al.*, 2014). In rats, Hajhosseini *et al.* (2013) studied the protective effect of RA against sertoli cell apoptosis caused by electromagnetic fields. The concentration of testosterone and total anti-oxidant capacity were improved ($P < 0.05$) in a treatment group that received RA at a level of 5 mg per rat. Moreover, RA administration had an increasing effect on lowered testosterone caused by an electromagnetic field. In animals, using RA in food or feed was reportedly effective for overcoming problems and side effects caused by environmental pollution via electromagnetic waves (Farsi *et al.*, 2013). Khaki *et al.* (2012) demonstrated that herbal plants and their derivatives, like RA, have useful roles in enhancing sex hormones, including testosterone; these benefits may be attributed to antioxidant activity and flavonoids, which have beneficial effects on androgenic hormones and increase sperm counts.

Conclusion and future perspectives

RA appears to be an effective candidate for inclusion in functional foods and pharmaceutical plant-based products. The benefits of dietary RA supplementation as a phytogenic additive are promising. RA acts as a powerful anti-oxidant, which could protect the cell membrane and decrease the induction of ROS by enhancing the activity of the antioxidant defense mechanism through multiple enzymes throughout the body. It also has an advantageous role in promoting growth and improving both productive and reproductive performance due to its beneficial effect on nutrient absorption. RA also exhibits many nutritional benefits by lowering the lipid peroxidation in eggs, meats and sera. Additionally, RA, as a natural antioxidant, showed many healthy and pharmacologic activities such as anti-spasmodic, anti-microbial, anti-fungal, neuroprotective, anti-cancer, immunomodulatory, anti-allergy, anti-inflammatory and anti-Alzheimer disease effects. Further studies are warranted to further define the growth enhancing activity of RA, to evaluate its safety and toxicity in different animal species, and to provide new approaches for its use in human and veterinary medicine. A better understanding of RA's practical applications for various health issues and the exact mechanisms of its action will further add to its acception. Advances in biotechnology to improve utilization of RA for animal production will help determine *in vivo* applications of RA in safeguarding animal health.

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Disclosure statement

Authors would hereby like to declare that there is no conflict of interests that could possibly arise, and all authors have contributed significantly.

References

Abd El-Hack ME, Mahgoub SA, Alagawany M and Dhama K (2015). Influences of dietary supplementation of antimicrobial cold pressed oils mixture on growth performance and intestinal microflora of growing Japanese quails. *International Journal of Pharmacology* **11**: 689–696.

Alagawany M and Abd El-Hack ME (2015). The effect of rosemary herb as a dietary supplement on performance, egg quality, serum biochemical parameters, and oxidative status in laying hens. *Journal of Animal and Feed Science* **24**: 341–347.

Alkam T, Nitta A, Mizoguchi H, Itoh A and Nabeshima T (2007). A natural scavenger of peroxynitrites, rosmarinic acid, protects against impairment of memory induced by Aβ25–35. *Behavioural Brain Research* **180**: 139–145.

Baba S, Osakabe N, Natsume M, Yasuda A, Muto Y, Hiyoshi K, Takano H, Yoshikawa T and Terao J (2005). Absorption, metabolism, degradation and urinary excretion of rosmarinic acid after intake of *Perilla frutescens* extract in humans. *European Journal of Nutrition* **44**: 1–9.

Bacanli M, Aydın S, Taner G, Göktaş HG, Şahin T, Başaran AA and Başaran N (2016). Does rosmarinic acid treatment have protective role against sepsis-induced oxidative damage in Wistar Albino rats? *Human and Experimental Toxicology* **35**: 877–886.

Baluchnejadmojarad T, Roghani M and Kazemloo P (2014). Rosmarinic acid mitigates learning and memory disturbances in amyloid β (25–35)-induced model of Alzheimer's disease in rat. *Journal of Basic and Clinical Pathophysiology* **2**: 7–14.

Benedec D, Hanganu D, Oniga I, Tiperciuc B, Olah NK, Raita O, Bischin C, Dumitrescu RS and Vlase L (2015). Assessment of rosmarinic acid content in six *Lamiaceae* species extracts and their antioxidant and antimicrobial potential. *Pakistan Journal of Pharmaceutical Sciences* **28**: 2297–2303.

Boonyarikpunchai W, Sukrong S and Towiwat P (2014). Antinociceptive and anti-inflammatory effects of rosmarinic acid isolated from *Thunbergia laurifolia* Lindl. *Pharmacology Biochemistry and Behavior* **124**: 67–73.

Bulgakov VP, Inyushkina YV and Fedoreyev SA (2012). Rosmarinic acid and its derivatives: biotechnology and applications. *Critical Reviews in Biotechnology* **32**: 203–217.

Chen Q, Zhang XH and Massagué J (2011). Macrophage binding to receptor VCAM-1 transmits survival signals in breast cancer cells that invade the lungs. *Cancer Cell* **20**: 538–549.

Chun KS, Kundu J, Chae IG and Kundu JK (2014). Carnosol: a phenolic diterpene with cancer chemopreventive potential. *Journal of Cancer Prevention* **19**: 103–110.

Chung YC, Hsieh FC, Lin YJ, Wu TY, Lin CW, Lin CT, Tang NY and Jinn TR (2015). Magnesium lithospermate B and rosmarinic acid, two compounds present in salvia miltiorrhiza, have potent antiviral activity against enterovirus 71 infections. *European Journal of Pharmacology* **755**: 127–133.

Corral-Lugo A, Daddaoua A, Ortega A, Espinosa-Urgel M and Krell T (2016). Rosmarinic acid is a homoserine lactone mimic produced by plants that activates a bacterial quorum-sensing regulator. *Science Signaling* **9**, ra1. doi: 10.1126/scisignal.aaa8271.

da Silva SB, Ferreira D, Pintado M and Sarmento B (2016). Chitosan-based nanoparticles for rosmarinic acid ocular delivery – in vitro tests. *International Journal of Biological Macromolecules* **84**: 112–120.

Ekambaram SP, Perumal SS, Balakrishnan A, Marappan N, Gajendran SS and Viswanathan V (2016). Antibacterial synergy between rosmarinic acid and antibiotics against methicillin-resistant *Staphylococcus aureus*. *Journal of Intercultural Ethnopharmacology* **5**: 358–363.

Ellis BE and Towers GHN (1970). Biogenesis of rosmarinic acid in Mentha. *Biochemical Journal* **118**: 291–297.

Fadel O, El Kirat K and Morandat S (2011). The natural antioxidant rosmarinic acid spontaneously penetrates membranes to inhibit lipid peroxidation in situ. *Biochimica et Biophysica Acta* **1808**: 2973–2980.

Fallarini S, Miglio G and Paoletti T (2009). Clovamide and rosmarinic acid induce neuroprotective effects in *in vitro* models of neuronal death. *British Journal of Pharmacology* **157**: 1072–1084.

Farsi A, Khaki A, Fathiazad F, Afshari F, Hajhossini L and Kahki AA (2013). Improvement effect of rosmarinic acid on serum testosterone level after exposing with electromagnetic fields. *International Journal of Women's Health and Reproduction Sciences* **1**: 45–50.

Fernando PM, Piao MJ, Kang KA, Ryu YS, Hewage SR, Chae SW and Hyun JW (2016). Rosmarinic acid attenuates cell damage against UVB radiation-induced oxidative stress via enhancing antioxidant effects in human HaCaT cells. Biomolecules & Therapeutics *(Seoul)* **24**: 75–84.

Ferrández A, Prescott S and Burt RW (2003). COX-2 and colorectal cancer. *Current Pharmaceutical Design* **9**: 2229–2251.

Ferreira LG, Celotto AC, Capellini VK, Albuquerque AA, Nadai TR, Carvalho MT and Evora PR (2013). Is rosmarinic acid underestimated as an experimental cardiovascular drug? *Acta Cirurgica Brasileira* **28**: 83–87.

Friedman T (2015). The effect of rosmarinic acid on immunological and neurological systems: a basic science and clinical review. *Journal of Restorative Medicine* **4**: 50–59.

Gao LP, Wei HL, Zhao HS, Xiao SY and Zheng RL (2005). Antiapoptotic and antioxidant effects of rosmarinic acid in astrocytes. *Pharmazie* **60**: 62–65.

Ghaffari H, Venkataramana M, Ghassam BJ, Nayaka SC, Nataraju A, Geetha NP and Prakash HS (2014). Rosmarinic acid mediated neuroprotective effects against H2O2-induced neuronal cell damage in N2A cells. *Life Sciences* **113**: 7–13.

Ghasemzadeh Rahbardar M, Amin B, Mehri S, Mirnajafi-Zadeh SJ and Hosseinzadeh H (2017). Anti-inflammatory effects of ethanolic extract of *Rosmarinus officinalis* L. and rosmarinic acid in a rat model of neuropathic pain. *Biomed Pharmacotherapy* **86**: 441–449.

Hajhosseini L, Khaki A, Merat E and Ainehchi N (2013). Effect of rosmarinic acid on sertoli cells apoptosis and serum antioxidant levels in rats after exposure to electromagnetic fields. *African Journal of Traditional, Complementary and Alternative Medicines* **10**: 477–480.

Hasanein P and Mahtaj AK (2015). Ameliorative effect of rosmarinic acid on scopolamine-induced memory impairment in rats. *Neuroscience Letters* **585**: 23–27.

Hasanein P and Zaheri ML (2014). Effects of rosmarinic acid on an experimental model of painful diabetic neuropathy in rats. *Pharmaceutical Biology* **52**: 1398–1402.

Hossain MB, Rai DK, Brunton NP, Martin-Diana AB and Barry-Ryan C (2010). Characterization of phenolic composition in Lamiaceae species by LC-ESI-MS/MS. *Journal of Agricultural and Food Chemistry* **58**: 10576–10581.

Hossan MS, Rahman S, Anwarul Bashar ABM, Jahan R, Al-Nahain A and Rahmatullah M (2014). Rosmarinic acid: a review of its anticancer action. *World Journal of Pharmaceutical Sciences* **3**: 57–70.

Hur Y-G, Yun Y and Won J (2003). Rosmarinic acid induces p56lck-dependent apoptosis in Jurkat and peripheral T cells via mitochondrial pathway independent from Fas/Fas ligand interaction. *Journal of Immunology* **172**: 79–87.

Inyushkina YV, Bulgakov VP, Veselova MV, Bryukhanov VM, Zverev YF, Lampatov VV, Azarova OV, Tchernoded GK, Fedoreyev SA and Zhuravlev YN (2007). High rabdosiin and rosmarinic acid production in *Eritrichium sericeum* callus cultures and the effect of the calli on masugi-nephritis in rats. *Bioscience, Biotechnology, and Biochemistry* **71**: 1286–1293.

Jayanthy G and Subramanian S (2014). Rosmarinic acid, a polyphenol, ameliorates hyperglycemia by regulating the key enzymes of carbohydrate metabolism in high fat diet – STZ induced experimental diabetes mellitus. *Biomedicine and Preventive Nutrition* **4**: 431–437.

Karthikkumar V, Sivagami G, Vinothkumar R, Rajkumar D and Nalini N (2012). Modulatory efficacy of rosmarinic acid on premalignant lesions and antioxidant status in 1, 2-dimethylhydrazine induced rat colon carcinogenesis. *Environmental Toxicology and Pharmacology* **34**: 949–958.

Karthikkumar V, Sivagami G, Viswanathan P and Nalini N (2015). Rosmarinic acid inhibits DMH-induced cell proliferation in experimental rats. *Journal of Basic and Clinical Physiology and Pharmacology* **26**: 185–200.

Khaki A, Imani SAM and Golzar F (2012). Effects of rosmarinic acid on male sex hormones (testosterone-FSH-LH) and testis tissue apoptosis after exposure to electromagnetic field (EMF) in rats. *African Journal of Pharmacy and Pharmacology* **6**: 248–252.

Kim GD, Park YS, Jin YH and Park CS (2015). Production and applications of rosmarinic acid and structurally related compounds. *Applied Microbiology and Biotechnology* **99**: 2083–2092.

Kim SJ, Um JY, Kim SH and Hong SH (2013). Protective effect of rosmarinic acid is through regulation of inflammatory cytokine in cadmium-induced ototoxicity. *The American Journal of Chinese Medicine* **41**: 391–404.

Kuo CF, Su JD, Chiu CH, Peng CC, Chang CH and Sung TY (2011). Anti-inflammatory effects of supercritical carbon dioxide extract and its isolated carnosic acid from *Rosmarinus officinalis* leaves. *Journal of Agricultural and Food Chemistry* **59**: 3674–3685.

Lee HJ, Cho HS, Park E, Kim S, Lee SY, Kim CS, Kim DK, Kim SJ and Chun HS (2008). Rosmarinic acid protects human dopaminergic neuronal cells against hydrogen peroxide-induced apoptosis. *Toxicology* **250**: 109–115.

Lembo S, Balato A, Di Caprio R, Cirillo T, Giannini V, Gasparri F and Monfrecola G (2014). The modulatory effect of ellagic acid and rosmarinic acid on ultraviolet-B-induced cytokine/chemokine gene expression in skin keratinocyte (HaCaT) cells. *Biomed Research International* **2014**: 346793. doi: 10.1155/2014/346793.

Lin M, Zhang BX, Zhang C, Shen N, Zhang YY, Wang AX and Tu CX (2014). Ginsenosides Rb1 and Rg1 stimulate melanogenesis in human epidermal melanocytes via PKA/CREB/MITF signaling. *Evidence-based Complementary and Alternative Medicine* **2014**: 892073. doi: 10.1155/2014/892073.

Luan H, Kan Z, Xu Y, Lv C and Jiang W (2013). Rosmarinic acid protects against experimental diabetes with cerebral ischemia: relation to inflammation response. *Journal of Neuroinflammation* **10**: 28.

Lucarini R, Bernardes WA, Ferreira DS, Tozatti MG, Furtado R, Bastos JK, Pauletti PM, Januário AH, Silva ML and Cunha WR (2013). *In vivo* analgesic and anti-inflammatory activities of *Rosmarinus officinalis* aqueous extracts, rosmarinic acid and its acetyl ester derivative. *Pharmaceutical Biology* **51**: 1087–1090.

Luño V, Gil L, Olaciregui M, González N, Jerez RA and de Blas I (2014). Rosmarinic acid improves function and *in vitro* fertilising ability of boar sperm after cryopreservation. *Cryobiology* **69**: 157–162.

Madureira AR, Nunes S, Campos DA, Fernandes JC, Marques C, Zuzarte M, Gullón B, Rodríguez-Alcalá LM, Calhau C, Sarmento B, Gomes AM, Pintado MM and Reis F (2016). Safety profile of solid lipid nanoparticles loaded with rosmarinic acid for oral use: *in vitro* and animal approaches. *International Journal of Nanomedicine* **4**: 3621–3640.

Makino T, Ono T, Muso E, Yoshida H, Honda G and Sasayama S (2000). Inhibitory effects of rosmarinic acid on the proliferation of cultured murine mesangial cells. *Nephrology Dialysis Transplantation* **15**: 1140–1145.

McCue P and Shetty K (2004). Inhibitory effects of rosmarinic acid extracts on porcine pancreatic amylase *in vitro*. *Asia Pacific Journal of Clinical Nutrition* **13**: 101–106.

Moreno S, Scheyer T, Romano CS and Vojnov AA (2006). Antioxidant and antimicrobial activities of rosemary extracts linked to their polyphenol composition. *Free Radical Research* **40**: 223–231.

Mushtaq N, Schmatz R, Pereira LB, Ahmad M, Stefanello N, Vieira JM, Abdalla F, Rodrigues MV, Baldissarelli J and Pelinson LP (2014). Rosmarinic acid prevents lipid peroxidation and increase in acetylcholinesterase activity in brain of streptozotocin-induced diabetic rats. *Cell Biochemistry and Function* **32**: 287–293.

Nabavi SF, Tenore GC, Daglia M, Tundis R, Loizzo MR and Nabavi SM (2015). The cellular protective effects of rosmarinic acid: from bench to bedside. *Current Neurovascular Research* **2**: 98–105.

Nakazawa T and Ohsawa K (1998). Metabolism of rosmarinic acid in rats. *Journal of Natural Products* **61**: 993–996.

Nakazawa T and Ohsawa K (2000). Metabolites of orally administered Perilla frutescens extract in rats and humans. *Biological & Pharmaceutical Bulletin* **23**: 122–127.

Oh H-A, Park C-S, Ahn H-J, Park YS and Kim H-M (2011). Effect of Perilla frutescens var. Acuta Kudo and rosmarinic acid on allergic inflammatory reactions. *Experimental Biology and Medicine* **236**: 99–106.

Osakabe N, Takano H, Sanbongi C, Yasuda A, Yanagisawa R, Inoue K and Yoshikawa T (2004). Anti-inflammatory and anti-allergic effect of rosmarinic acid (RA); inhibition of seasonal allergic rhinoconjunctivities (SAR) and its mechanism. *Biofactors* **21**: 127–131.

Ozturk H, Ozturk H, Terzi EH, Ozgen U, Duran A and Uygun I (2014). Protective effects of rosmarinic acid against renal ischaemia/reperfusion injury in rats. *Journal Pakistan Medicine Association* **64**: 260–265.

Pereira P, Tysca D, Oliveira P, da Silva Brum LF, Picada JN and Ardenghi P (2005). Neurobehavioral and genotoxic aspects of rosmarinic acid. *Pharmacological Research* **52**: 199–203.

Pérez-Fons L, Garzón MT and Micol V (2010). Relationship between the antioxidant capacity and effect of rosemary (*Rosmarinus officinalis L.*) polyphenols on membrane phospholipid order. *Journal of Agricultural and Food Chemistry* **58**: 161–171.

Petersen M (2013). Rosmarinic acid: new aspects. *Phytochemistry Reviews* **12**: 207–227.

Petersen M and Simmonds MSJ (2003). Rosmarinic acid. *Photochemistry* **62**: 121–125.

Petersen M, Abdullah Y, Benner J, Eberle D, Gehlen K, Hücherig S, Janiak V, Kim KH, Sander M, Weitzel C and Wolters S (2009). Evolution of rosmarinic acid biosynthesis. *Phytochemistry* **70**: 1663–1679.

Petiwala SM and Johnson JJ (2015). Diterpenes from rosemary (*Rosmarinus officinalis*): defining their potential for anti-cancer activity. *Cancer Letter* **367**: 93–102.

Rama Devi K, Srinivasan R, Kannappan A, Santhakumari S, Bhuvaneswari M, Rajasekar P, Prabhu NM and Veera Ravi A (2016). *In vitro* and *in vivo* efficacy of rosmarinic acid on quorum sensing mediated biofilm formation and virulence factor production in *Aeromonas hydrophila*. *Biofouling* **32**: 1171–1183.

Ramanauskiene K, Raudonis R and Majiene D (2016). Rosmarinic acid and melissa officinalis extracts differently affect glioblastoma cells. *Oxidative Medicine and Cellular Longevity* **2016**: 1564257. doi: 10.1155/2016/1564257.

Rice-Evans CA, Miller NJ and Paganga G (1996). Structure-antioxidant activity relationships of flavonoids and phenolic acids. *Free Radical Biology and Medicine* **20**: 933–956.

Ritschel WA, Starzacher A, Sabouni A, Hussain AS and Koch HP (1989). Percutaneous absorption of rosmarinic acid in the rat. *Methods and Findings in Experimental and Clinical Pharmacology* **11**: 345–352.

Rocha J, Eduardo-Figueira M, Barateiro A, Fernandes A, Brites D, Bronze R, Duarte CM, Serra AT, Pinto R and Freitas M (2015). Anti-inflammatory effect of rosmarinic acid and an extract of *Rosmarinus officinalis* in rat models of local and systemic inflammation. *Basic and Clinical Pharmacology and Toxicology* **116**: 398–413.

Rocío-Teruel RM, Garrido MD, Espinosa MC and Linares MB (2015). Effect of different format-solvent rosemary extracts (*Rosmarinus officinalis*) on frozen chicken nuggets quality. *Food Chemistry* **172**: 40–46.

Roland CL, Dineen SP, Toombs JE, Carbon JG, Smith CW, Brekken RA and Barnett CC Jr (2010). Tumour-derived intercellular adhesion molecule-1 mediates tumour-associated leukocyte infiltration in orthotopic pancreatic xenografts. *Experimental Biology and Medicine (Maywood)* **235**: 263–270.

Rossi F, Jullian V, Pawlowiez R, Kumar-Roiné S, Haddad M, Darius HT, Gaertner-Mazouni N, Chinain M and Laurent D (2012). Protective effect of Heliotropium foertherianum (*Boraginaceae*) folk remedy and its active compound, rosmarinic acid, against a Pacific ciguatoxin. *Journal of Ethnopharmacology* **143**: 33–40.

Runtuwene J, Cheng KC, Asakawa A, Amitani H, Amitani M, Morinaga A, Takimoto Y, Kairupan BHR and Inui A (2016). Rosmarinic acid ameliorates hyperglycemia and insulin sensitivity in diabetic rats, potentially by modulating the expression of PEPCK and GLUT4. *Journal of Drug Design, Development and Therapy* **10**: 2193–2202.

Sanbongi C, Takano H and Osakabe N (2004). Rosmarinic acid in perilla extract inhibits allergic inflammation induced by mite allergen, in a mouse model. *Clinical and Experimental Allergy* **34**: 971–977.

Scarpati ML and Oriente G (1958). Isolamento e costituzione dell'acido rosmarinico (*dal Rosmarinus off.*). *Ricerca Science* **28**: 2329–2333.

Scheckel KA, Degner SC and Romagnolo DF (2008). Rosmarinic acid antagonizes activator protein-1-dependent activation of cyclooxygenase-2 expression in human cancer and non-malignant cell lines. *Journal of Nutrition* **138**: 2098–2105.

Shekarchi M, Hajimehdipoor H, Saeidnia S, Gohari AR and Hamedani MP (2012). Comparative study of rosmarinic acid content in some plants of Labiatae family. *Pharmacognosy Magazine* **8**: 37–41.

Sotnikova R, Okruhlicova L, Vlkovicova J, Navarova J, Gajdacova B, Pivackova L, Fialova S and Krenek P (2013). Rosmarinic acid administration attenuates diabetes-induced vascular dysfunction of the rat aorta. *Journal of Pharmacy and Pharmacology* **65**: 713–723.

Stansbury J (2014). Rosmarinic acid as a novel agent in the treatment of allergies and asthma. *Journal of Restorative Medicine* **3**: 121–126.

Swarup V, Ghosh J, Ghosh S, Saxena A and Basu A (2007). Antiviral and anti-inflammatory effects of rosmarinic acid in an experimental murine model of Japanese encephalitis. *Antimicrobial Agents and Chemotherapy* **51**: 3367–3370.

Tao L, Wang S, Zhao Y, Sheng X, Wang A, Zheng S and Lu Y (2014). Phenolcarboxylic acids from medicinal herbs exert anticancer effects through disruption of COX-2 activity. *Phytomedicine* **21**: 1473–1482.

Tavafi M, Ahmadvand H, Khalatbari A and Tamjidipoor A (2010). Rosmarinic acid ameliorates diabetic nephropathy in uninephrectomized diabetic rats. *Iranian Journal of Basic Medical Sciences* **14**: 275–283.

Tsai TH, Chuang LT, Lien TJ, Liing YR, Chen WY and Tsai PJ (2013). *Rosmarinus officinalis* extract suppresses *Propionibacterium acnes*-induced inflammatory responses. *Journal of Medicinal Food* **16**: 324–333.

Uyeturk U, Firat T, Cetinkaya A, Kin Tekce B and Cakir S (2014). Protective effects of rosmarinic acid on doxorubicin-induced testicular damage. *Chemotherapy* **60**: 7–12.

Venkatachalam K, Gunasekaran S, Jesudoss VA and Namasivayam N (2013). The effect of rosmarinic acid on 1,2-dimethylhydrazine induced colon carcinogenesis. *Experimental and Toxicologic Pathology* **65**: 409–418.

Venkatachalam K, Gunasekaran S and Namasivayam N (2016). Biochemical and molecular mechanisms underlying the chemopreventive efficacy of rosmarinic acid in a rat colon cancer. *European Journal of Pharmacology* **791**: 37–50.

Vladimir-Knežević S, Blažeković B, Kindl M, Vladić J, Lower-Nedza AD and Brantner AH (2014). Acetylcholinesterase inhibitory, antioxidant and phytochemical properties of selected medicinal plants of the *Lamiaceae* family. *Molecules* **19**: 767–782.

Wilcox G (2005). Insulin and insulin resistance. *The Clinical Biochemist Reviews* **26**: 19–39.

Won J, Hur YG, Hur EM, Park SH, Kang MA and Choi Y (2003). Rosmarinic acid inhibits TCR-induced T cell activation and proliferation in an Lck-dependent manner. *European Journal of Immunology* **33**: 870–879.

Wu CF, Hong C, Klauck SM, Lin YL and Efferth T (2015). Molecular mechanisms of rosmarinic acid from salvia miltiorrhiza in acute lymphoblastic leukemia cells. *Journal of Ethnopharmacology* **176**: 55–68.

Xu W, Yang F, Zhang Y and Shen X (2016). Protective effects of rosmarinic acid against radiation-induced damage to the hematopoietic system in mice. *Journal of Radiation Research* **57**: 356–362.

Yesilbag D, Eren M, Agel H, Kovanlikaya A and Balci F (2011). Effects of dietary rosemary, rosemary volatile oil and vitamin E on broiler performance, meat quality and serum SOD activity. *British Poultry Science* **52**: 472–482.

Yesil-Celiktas O, Sevimli C, Bedir E and Vardar-Sukan F (2010). Inhibitory effects of rosemary extracts, carnosic acid and rosmarinic acid on the growth of various human cancer cell lines. *Plant Foods and Human Nutrition* **65**: 158–163.

Youn J, Lee KH and Won J (2003). Beneficial effects of rosmarinic acid on suppression of collagen induced arthritis. *The Journal of Rheumatology* **30**: 1203–1207.

Zhang JJ, Wang YL, Feng XB, Song XD and Liu WB (2011). Rosmarinic acid inhibits proliferation and induces apoptosis of hepatic stellate cells. *China Biological & Pharmaceutical Bulletin* **34**: 343–348.

Zhang Y, Chen X, Yang L, Zu Y and Lu Q (2015). Effects of rosmarinic acid on liver and kidney antioxidant enzymes, lipid peroxidation and tissue ultrastructure in aging mice. *Food Function* **6**: 927–931.

Zhu F, Asada T, Sato A, Koi Y, Nishiwaki H and Tamura H (2014). Rosmarinic acid extract for antioxidant, antiallergic and α-glucosidase inhibitory activities, isolated by supramolecular technique and solvent extraction from perilla leaves. *Journal of Agricultural and Food Chemistry* **62**: 885–892.

Zhu F, Xu Z, Yonekura L, Yang R and Tamura H (2015). Antiallergic activity of rosmarinic acid esters is modulated by hydrophobicity, and bulkiness of alkyl side chain. *Bioscience, Biotechnology, and Biochemistry* **79**: 1178–1182.