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Review Article

Anti-inflammatory properties of Rosmarinic acid - A review

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ABSTRACT

Phytochemicals are natural, non nutritive chemicals rich in pharmacological activities. They show a very potent antioxidant activity and this activity is closely linked to various beneficial actions, including anti-aging, prevention of cancer, cardiovascular disease, etc. Medicinal plants play a vital role in drug discovery that can be used to cure various ailments in humans. A safe new phytochemical compound as drugs is one of the major searches world-wide. Rosmarinic acid, a polyphenolic compound is generally available in the wide species of the Boraginaceae and Lamiaceae family (Nepetoideae subfamily). The phytochemical has two phenolic rings with ortho positioned hydroxyl groups. A carboxylic acid, carbonyl group and an unsaturated double bond is present between the two phenolic rings. The compound is thus an ester linked caffeic acid and 3, 4-dihydroxyphenyllactic acid. It has a broad range of biological activity that includes antiviral, antibacterial, antitumor, antihepatitis, anti-inflammation and inhibiting blood clots. Inflammation, a localized protective response elicited by injury or destructions of tissues, is mediated by various proinflammatory cytokines, is associated with every health condition. Inflammation is also important cause for many allergic diseases. Rosmarinic acid, being one of the promising active principles, can be developed for various pharmacological activities through clinical trials and applications further. This review aimed to describe the antiinflammatory properties of rosmarinic acid in various diseased conditions and to understand its basic mechanisms.

Keywords: Anti-inflammatory properties; Phytochemicals; inflammation; Rosmarinic acid.

INTRODUCTION

The mammalian tissues show inflammatory response against harmful stimuli caused by hostile agents such as toxic chemical substances, physical injury, infectious organisms, tumor growth etc, (Sobota et al., 2000) further local accumulation of plasmic fluid and blood cells occurs. Inflammation can be either acute or chronic conditions. The process of Inflammation is characterized by the production of mediators such as histamine, bradykinin, prostaglandins, platelet-activating factor, leukotrienes and the release of chemicals from tissues and migrating cells (Tomlinson et al., 1994; Cuzzocrea et al., 2004). Prostanoids is synthesized by Cyclooxygenase (COX), it is involved in platelet aggregation, pain and inflammation (Pilotto et al., 2010). Central role of inflammatory responses is through p38α MAPK, a serine / threonine kinase. It is involved in the biosynthesis and release of pro-inflammatory cytokines e.g. IL-1β and TNF α. The production is controlled at the level of transcription and the translation (Laufer et al., 2002). These reaction mediators provoke, maintain and aggravate many disorders. The key feature of inflammatory activity is production of reactive species by phagocytic cells that injures cell and tissue by oxidative degradation of essential cellular components (Halliwell et al., 1988).

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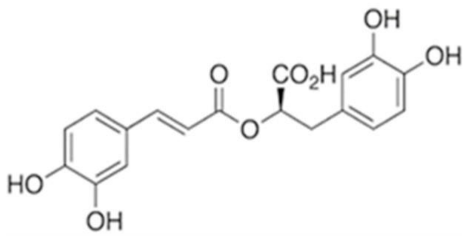

Figure 1: Rosmarinic acid - Chemical Structure

Plants are potential sources for producing new drugs to treat many chronic and infectious diseases. The parts of many medicinal plants possess bioactive compounds that have varied medicinal properties; hence they are used as raw drugs (Mahesh et al., 2008). Phytochemicals are low molecular weight active secondary metabolites in plants, few examples are caffeine, nicotine, ginkgo, ginseng, valerian, curcumin, resveratrol, epigallocatechin-3-gallate etc. (Kennedy et al., 2011). They are the potential sources of natural anti-inflammatory, antioxidant, antimicrobial, anticancer, hepatoprotective and nephroprotective activities (Parnham et al., 1985; Petersen M., 1994). They protect the plant against ultraviolet radiation, pathogens, and herbivores (Harborne et al., 2000). Also they are used to effectively treat the various ailments for mankind. In recent years, the importance of medicinal plants for treating many diseased conditions were increasing. They exhibit potent pharmacological properties that are proved by different epidemiological and in vitro/in vivo experimental studies. The phytochemicals such as epigallocatechin gallate, resveratrol, phytosterol, myricetin, gingerol, etc., directly impacts various molecular signal transduction pathways like oxidative stress, cell proliferation/migration, inflammation cascade and metabolic disorders that are involved in the development of diseased conditions (Upadhyay et al., 2015).

Rosmarinic acid

In Boraginaceae species and in the Nepetoideae subfamily of the Lamiaceae herbs, (rosemary, sweet basil, perilla) a polyphenolic compound, Rosmarinic acid (RA) is found (del Bano et al., 2003; Kintzios et al., 2003; Osakabe et al., 2002) with biological activities. RA is also found in other plant kingdoms which taxonomically belong to non-related families (Holzmannova 1996; Petersen 2003). It (α-*o*-caffeoyl-3,4-dihydroxyphenyl lactic acid; RA), occurs in the form of hydroxylated phenolic compound naturally as an ester of caffeic acid and 3, 4- dihydroxy phenyl lactic acid. RA posses extensive pharmacological activities such as anti-oxidant, anti- inflammatory, anti-tumor and anti-angiogenic activities (Osakabe et al., 2004; McKay et al., 2006; Huang et al., 2006; Kosar et al., 2008). In addition they causes attenuation of T cell receptor mediated signaling, blocking of complement fixation and suppression of inhibitor of nuclear factor kappa-B (IKK-β) downstream signaling during the upregulation of C-C motif chemokine 11(CCL11) induced by tumor necrosis factor (TNF)-α, CCL11 is a potent chemo attractant and an activator of T helper 2 cells, eosinophils and basophils (Sahu et al., 1999; Lee et al., 2006; Kang et al., 2003). Approximately 3% RA was found in medicinal plants by dry weight (Lamaison et al., 1989).

The anti-inflammatory properties of rosmarinic acid is due to the inhibition of activity of enzymes such as lipoxygenase (LOX) and cyclooxygenases (COX), inhibition of inflammatory cytokines expression (Sanbongi et al., 2003) and alteration in the complement cascade pathway (Parnham et al., 1985; Mirzoeva et al., 1996; Krol et al., 1996; Petersen et al, 2003). Basic mechanism underlying in anti-inflammatory and anti-atheroesclerotic activity of rosmarinic acid by *in-vitro* and *in-vivo* models confirm high specific antioxidant activity with less production of pro-inflammatory molecules and also by preventing the low density lipoprotein oxidation. This review focuses on the reported antiinflammatory activities of rosmarinic acid.

Reported anti-inflammatory activities of Rosmarinic acid

Lung injury

Exposure of animals as well as humans to diesel exhaust particles (DEP) induces an acute inflammatory response (Salvi et al., 1999), by generating reactive oxygen species (Sagai et al., 1993 & 1996; Ichinose et al., 1995; Lim et al., 1998), by inducing the production of P450 reductase and/or P450 in the inflammatory process (Kumagai et al., 1997; Lim et al., 1998; Takano et al., 2002). Sanbongi et al., (2003) observed that exposure of male ICR mice to DEP caused pathophysiological changes such as neutrophilic inflammation and edema in the lung by decreasing the local expression of keratinocyte chemoattractant, interleukin -1β, monocyte chemoattractant protein -1 and macrophage inflammatory protein -1α. Rosmarinic acid is found to inhibit the expression of iNOS mRNA and formation of nitrotyrosine, 8-hydroxyguanosine that is enhanced by exposure to DEP. These effects also reduce the expression of proinflammatory cytokine and chemokines, which play a major role in inflammatory response in initiation and progression. The inflammatory response to allergens in the lungs of allergic asthma is a consequence of increased expression of several inflammatory proteins like interleukin-4 in lung tissue and it is also associated with infiltration of the airway wall by eosinophils (inflammatory cells) (Lee et al., 2010).

Kang et al., (2003) reported that *Ocimum gratissimum* has rich contents of polyphenols, such as rosmarinic acid (Ola et al., 2009) and possess immunomodulatory activity by suppressing T-cell receptor (TCR) signaling. 100 mg/Kg methanolic extract of *Ocimum gratissimum* and 200 mg/Kg RA was analyzed by Costa et al., (2012) for the treatment of murine model of respiratory allergy. There was reduction in the leukocytes/eosinophils numbers, eosinophil peroxidase activity in bronchoalveolar lavage (BAL), presence of mucus in respiratory tract, histopathological changes in the lung, and interleukin - 4 in BAL suggesting their therapeutic potential.

Corsini et al., (2005) identified that pleurisy induced by intrapleural administration of carrageenan leads to immediate recruitment of polymorphonuclear cells (PMN) in the pleural space. The respiratory pathway inflammation is also due to mediators such as cytokines, histamine, leukotrienes, nitric oxide release and thromboxane A2 (Eum et al., 2003). Gamaro etal., (2011) proved that migration of polymorphonuclear and mononuclear cells stimulated by carrageenan into pleural space was reduced by caffeic acid and rosmarinic acid, suggesting that the anti-inflammatory property of rosmarinic acid in carrageenan induced rats is due to its breakdown products, like caffeic acid.

Hepatoprotective activity

The hepatoprotective effects of rosmarinic acid have been proved on liver ischemia/reperfusion injury in rats. The treatment with rosmarinic acid reduced neutrophil infiltration, hepatocellular damage and oxidative/nitrosative stress parameters caused by the injury. It also attenuated nuclear factor -κB activation and down-regulated interleukin-1β and tumor necrosis factor –α gene expression, the liver content of eNOS/iNOS and NO was also decreased. These data by Ramalho et al., (2014) indicates that in the ischemic liver, rosmarinic acid protects hepatocytes against ischemia/reperfusion injury by its anti-inflammatory and antioxidant effects.

The anti-inflammatory properties of rosmarinic acid from *Rosmarinus officinalis* in local inflammation of paw oedema rat model induced by carrageenin was assessed by Rocha et al, (2015). They found that by 6 hr by 60% of paw oedema has been reduced at the dose of 25 mg/kg of rosmarinic acid (Boonyarikpunchai et al., 2014). They also evaluated that, in systemic inflammation of liver ischaemia-reperfusion of rat models, there was a remarkable reduction in the serum concentration of transaminases and lactate dehydrogenase due to the prior administration of rosmarinic acid. Rosmarinic acid also reduced multi-organ dysfunction markers in liver, kidney and lung by modulating metalloproteinase-9 and nuclear factor- κB in the thermal injury rat model. *In vivo* studies also shown that rosmarinic acid will inhibits cobra venom factor induced paw edema (Leyck et al, 1983; Englberger et al, 1988).

Nephroprotective activities

Nephrotoxicity is the most serious dose-limiting side effects of chemotherapy with Cisplatin (CP) for cancer in bladder, testicular, ovarian, cervical, esophageal, head and neck (Giaccone 2000). The oxidative stress, tubular necrosis, inflammation and apoptosis are the major mechanisms underlying CP-induced nephrotoxicity (Miller et al., 2010). Domitrovic et al., (2014) examined that the treatment of nephrotoxicity induced by cisplatin (CP) in mice models with rosmarinic acid showed antiapoptotic activity by reducing p53, expression of active caspase-3 and phosphorylated p53. CP also cause considerable histopathological changes, increased blood urea nitrogen and serum creatinine. RA inhibited the tumor necrosis factor-α and nuclear factor-kappa B expression, and reduced the oxidative stress induced by CP, indicating the rosmarinic acid anti-inflammatory effect.

Pro-inflammatory mediators Inhibition

Pro-inflammatory mediators such as Tumor Necrosis Factor –α, Interleukin-1β & 6 possess many biological activities associated to chronic inflammatory diseases (Okada et al., 1998). Through the arachidonic acid cascade catalysed by cyclooxygenase isoforms, COX-1 and COX-2, inflammatory mediator Prostaglandin E2 (PGE2) was produced. Intracellular glutathione depletion, lipid peroxidation as well as production of reactive oxygen species in Lipopolysaccharide (LPS) induced human gingival fibroblasts cells was reduced by *Prunella vulgaris* L. extract and rosmarinic acid. They also suppressed, expression of inducible nitric oxide synthase and inhibited LPS-induced up-regulation of interleukin - 1β, interleukin – 6 and tumor necrosis factor- α.

Zdarilova et al., (2009) showed LPS-induced inflammatory process in gingival fibroblasts, including periodontal disease can be suppressed and modulated by *Prunella vulgaris* L. extract and rosmarinic acid. LPS mimicks an inflammatory response *in vitro* by stimulating macrophage cells to produce PGE2 (Patel et al., 1999). Meehye (2012) reported that rosmarinic acid is the key phytochemical in ethanol extracts of *Prunella vulgaris* which inhibits the production of PGE2 in RAW264.7 mouse cell line showing the anti-inflammatory properties.

Inhibition of diabetes-induced damage

Chronic hyperglycemia accelerates the advanced glycation end products (AGEs) formation and accumulation in various tissues. Diabetic vascular complications study showed that inflammatory state triggered by hyperglycaemia is by means of AGEs and their receptors together with Toll-like receptors and high mobility-group box-1 protein (Nogueira-Machado et al., 2011). mRNA of proinflammatory mediators like tumour necrosis factor-α and interleukin-1β, was increased in aorta of diabetic rats induced by streptozocin (Sotnikova et al., 2013). Rosmarinic acid protects aortas of endothelial injury induced by diabetes by controlling the overexpression of proinflammatory mediators.

Seasonal Allergic Rhinoconjunctivitis (SAR) Inhibition by Rosmarinic acid

Rosmarinic acids inhibit Polymorphonuclear Leukocyte Infiltration and have effective control of seasonal allergic rhinoconjunctivitis. Takano et al., (2004) determined that in nasal lavage fluid of seasonal allergic rhinoconjunctivitis patients, there was significant reduction in the production of eosinophils and neutrophils, after oral supplementation with rosmarinic acid obtained from *Perilla frutescens* and inhibited PMNL infiltration into the nostrils, thus exhibiting the anti-inflammatory properties.

Inhibition of epidermal inflammatory responses

Osakabe et al., (2004) found that topical application of the extract of perilla containing 68% rosmarinic acid or commercially available rosmarinic acid with equivalent quantity, showed anti-inflammatory activity in two-stage skin carcinogenesis model (initiated by application of 7,12-dimethylbenz[a]anthracene and promoted by application of 12-tetradecanoylphorbol 13-acetate). RA treatment showed noticeable inhibition of neutrophil infiltration, decreased activity of myeloperoxidase, a neutrophil recruitment marker, reduced vascular cell adhesion molecule-1 and intercellular adhesion molecule 1 mRNA expression levels. Decrease in the levels of synthesis of chemokine, macrophage inflammatory protein-2, leukotriene B4 and Prostaglandin E2 were also observed with perilla extract.

Anti-inflammatory effects on Japanese Encephalitis

In children, acute encephalopathy is caused by Japanese encephalitis virus (JEV) that particularly targets the central nervous system (Chambers et al., 1997). In serum and cerebrospinal fluid, JEV infection showed elevated levels of inflammatory mediators such as Interleukins - 6 & 8, tumor necrosis factor alpha (TNF)-α and RANTES (Regulated on Activation, Normal T Cell Expressed and Secreted) (Ravi, et al., 1997; Kolson, et al., 1998; Singh, et al., 2000). JEV infection also sways the viral pathogenesis by stimulating microglial activation and proinflammatory mediators (IL-6, Monocyte Chemo attractant Protein-1 and TNF- α) (Ghoshal et al., 2007). Swarup et al., (2007) observed that rosmarinic acid significantly reduced the mortality of JEV infected mice and also decreased the viral loads and proinflammatory cytokine levels.

RA Inhibits complement factors

The classical and alternative pathways of complement activation were inhibited by rosmarinic acid (Peake et al, 1991; Englberger et al., 1988), it also stimulate prostacyclin synthesis via complement factors (Rampart et al., 1986) thereby proving its anti-inflammatory property.

CONCLUSION

The inflammation process is a complex network involved by different proinflammatory mediators. Oxidative stress and neutrophil oxidative burst initiates and mediates the inflammatory process and tissue injury. RA has been found to be effective against a number of diseases such as lung injury, liver injury, kidney disorders and other inflammatory disorders. The inhibition of the proinflammatory mediator's synthesis by lipoxygenase and cyclooxygenases enzymes activity, inhibition and prevention of reactive oxygen metabolites that promotes direct toxicity to activate the inflammation process are the major causes for anti-inflammatory effect of the rosmarinic acid. The effect of rosmarinic acid in *in-vitro* and *in-vivo* models shows that the compound may be useful in the treatment of inflammation and oxidative stress. A deeper insight on the pharmacological activity and its mechanism with promising results is required to show that rosmarinic acid is a potential therapeutic compound for treating various inflammatory diseases.

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