INTRODUCTION
Rosmarinic acid is a phenolic acid that is active constituent of several medicinal plants, predominantly those which belong to the families Lamiaceae e.g. sage 1, rosemary 1-3, lemon balm 1, sweet basil 1, hyssop 1, marjoram 1, numerous mint species 1-3, oregano 1, Self-heal (Prunella vulgaris) L 4, Chinese basil (Perilla frutescens L Britton) 5, wild mint (Hyptis verticillata Jacq), and Boraginaceae (e.g. Anchusa officinalis L) 6,7, and comfrey (Symphytum officinale L) 8,9. RA commonly found in species of the Boraginaceae and the subfamily Nepetoideae of the Lamiaceae. RA species of Labiatae named Salvia officinalis, Rosmarinus officinalis. RA exhibits important biological activities including its anti-carcinogenic, antiviral, antibacterial antimicrobial, antidepresant qualities. Plants of Labiatae family have been used in traditional medicine for examination, psychotherapy, weakness, depression, and memory enhancement, circulation improvement, strengthening of fragile blood vessels, inflammation, and infection CNS disorder. RA showed the highest concentrations of antioxidant all the polyphenols. It is a red-orange powder that is slightly soluble in water, but well soluble in most organic solvents. RA polyphenolic compounds have been associated with antioxidative action in biological systems, acting as scavengers of singlet oxygen and free radicals. RA protects neurons from oxidative stress significantly attenuated H2O2-induced reactive oxygen species (ROS) generation and apoptotic cell death and could contribute at least in part to neuroprotective effects because this natural compound exerts neuroprotective and anti-oxidative effects against neurotoxin insult in dopaminergic cells. This review focused on pharmacokinetics and use different uses of RA as antioxidant agent, anti-inflammatory, antiviral, photo protective, anticancer, antidepressant, and possible neuroprotective agent mechanism of actions. Keywords: Antioxidant, Anti Inflammatory, AntiAllergic, Huntington, Rosmarinic acid (RA), Angiogenesis.

ABSTRACT
Rosmarinic acid is a natural polyphenol antioxidant isolated from Rosmarinus officinalis L. and commonly found in species of the Boraginaceae and the subfamily Nepetoideae of the Lamiaceae. RA species of Labiatae named Salvia officinalis, Rosmarinus officinalis. RA exhibits important biological activities including its anti-carcinogenic, antiviral, antibacterial antimicrobial, antidepresant qualities. Plants of Labiatae family have been used in traditional medicine for examination, psychotherapy, weakness, depression, and memory enhancement, circulation improvement, strengthening of fragile blood vessels, inflammation, and infection CNS disorder. RA showed the highest concentrations of antioxidant all the polyphenols. It is a red-orange powder that is slightly soluble in water, but well soluble in most organic solvents. RA polyphenolic compounds have been associated with antioxidative action in biological systems, acting as scavengers of singlet oxygen and free radicals. RA protects neurons from oxidative stress significantly attenuated H2O2-induced reactive oxygen species (ROS) generation and apoptotic cell death and could contribute at least in part to neuroprotective effects because this natural compound exerts neuroprotective and anti-oxidative effects against neurotoxin insult in dopaminergic cells. This review focused on pharmacokinetics and use different uses of RA as antioxidant agent, anti-inflammatory, antiviral, photo protective, anticancer, antidepressant, and possible neuroprotective agent mechanism of actions. Keywords: Antioxidant, Anti Inflammatory, AntiAllergic, Huntington, Rosmarinic acid (RA), Angiogenesis.

INTRODUCTION
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Medicinal species are comprising more than 3% RA, based on dry weight 8. RA can be absorbed through the skin, and the build-up of rosmarinic acid favors skin, muscle, and bone deposition rather than organ deposition percutaneously 14. RA does not affect prostaglandin synthesis 15. RA contributes to endothelial (blood vessel) and blood cell health. RA (typically via Perilla Oil) is used topically to combat skin carcinogenesis. This has been shown in rat models 16,17 alongside general topical anti-inflammatory benefits, and appears to also be absorbed via the skin in humans in the form of perillyl alcohol 18,19. However, unconjugated rosmarinic acid and its metabolites remain in the bloodstream of rats for enough time to reach the brain and decrease acetylcholinesterase activity, which is useful in the treatment of Alzheimer's disease 20.

Description

Structure

Figure 1: Structure of Rosmarinic Acid

IUPAC Name (2R)-2-[[2(E)-3-(3,4-Dihydroxyphenyl)-1-oxo-2-propenyl][oxy]-3-(3,4-dihydroxyphenyl)propanoic acid.

Pharmacokinetic parameters of Rosmarinic acid
The pharmacokinetic, tissue distribution, metabolism, and excretion of the RA in the target organs and their metabolic fate in serum, however unclear. The elimination half-lives for RA were 0.75h, when 60 mg/kg S. miltiorrhiza depside salts were administrated 26. Pharmacokinetic parameters of RA, in Sprague-Dawley rats following intravenous administration of 60 mg/kg S. miltiorrhiza depside salts. AUC0-t(h) (mg. h/l) 6.6 ± 1.8, Mean residence time (h) 0.32 ± 0.07, t1/2(h) 0.12 ± 0.04, Clearance (l/h/kg) 1.02 ± 0.32 26. RA contained in PE (perilla extract) absorbed, conjugated and methylated ensuing ingestion, with a small proportion of RA being degraded into numerous components, such as

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conjugated forms of CAA (caffèic acid), FA (ferulic acid) and COA (m cuminaric acid). These metabolites were then rapidly excreted in the urine 27.

X.J. Lai et al. (2007) pharmacokinetics studies on rosmarinic acid was applied to the evaluation of RA, in rats following intravenous and oral administrations demonstrated more rapid distribution and was eliminated more rapidly from the systemic circulation with a t1/2,λZ of (56.45±0.67) min after intravenous administration as described in Table 1. After being administered orally, RA was absorbed and eliminated more rapidly, with a Tmax1 of 10 min, a Tmax2 of 45 min and a t1/2,λZ of (63.68±13.11) min.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Rosmarinic acid Oral route</th>
<th>Rosmarinic acid I.V. Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>t1/2,λZ (min)</td>
<td>63.68±1.11</td>
<td>56.45±0.67</td>
</tr>
<tr>
<td>AUC inf (µg•ml⁻¹•min⁻¹)</td>
<td>185.15±20.61</td>
<td>425.57±61.36</td>
</tr>
<tr>
<td>MRT inf (min)</td>
<td>104.19±2.52</td>
<td>51.43±2.36</td>
</tr>
<tr>
<td>Tmax (min)</td>
<td>10.00±0.00</td>
<td>NA</td>
</tr>
</tbody>
</table>

Various plants contain Rosmarinic acid including its biological activities
RA present various plant along plant extract and having different biological activity like Anticarcinogenic, Antioxidant activity, Immunomodulatory, anti-inflammatory, which is depicted in Table 2. Various plants contain RA including its biological activities.

Pharmacological and Biological activities of RA
Role of Rosmarinic Acid as Antioxidant: RA possesses four phenolic hydrogens that underwrite to its ability to control free radical oxidation (Figure 3). In addition, it contains two catechol (1,2-dihydroxybenzene) rings which gives it a quality of polarity 37.

RA can form intermolecular hydrogen bonds between the free hydrogen of its hydroxyl and of its phenoxy radical, improving its radical stability (Figure 4) 37,38.
Role of rosmarinic acid as anti-Inflammatory Agent:
In order to alleviate inflammation, natural compounds that are capable of reducing or eliminating leukotriene production and modulating the complement system without adverse reactions have been sought. RA has been reported to inhibit complement activation in vitro as well as in vivo and additionally inhibit complement activation by both the classical and alternative pathways. In vivo, RA has inhibited cobra venom factor (CVF)-induced paw edema, and complement-dependent inhibitor of prostacyclin synthesis. Experimental evidence shows that rosmarinic acid predominantly inhibits complement activation by covalently reacting with the activated complement component C3b. In this way it blocks C3b attachment to activating surfaces and prostanoid release at the site of inflammation where lipoxygenase response and effects on 5-

In vitro and in vivo experiments proved the exceptional antioxidant activity of rosmarinic acid against peroxidative damage to biomembranes. Compared to caffeic acid and its other derivatives, rosmarinic acid was one of the compounds which strongly inhibited the extremely reactive 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical.

Figure 4: Hydrogen Donation Mechanism of Rosmarinic Acid

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Table 1: Phytochemical, pharmacological and pharmacokinetics effects of Rosmarinic acid

<table>
<thead>
<tr>
<th>Plant Name</th>
<th>Plant Part &amp; type of extract contains Rosmarinic acid</th>
<th>Type of activity</th>
<th>Mechanism of action</th>
<th>Animal model</th>
<th>Parameters evaluated</th>
<th>Result</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perilla frutescens</td>
<td>Perilla extract</td>
<td>Anticarcinogenic</td>
<td>Inhibition of the inflammatory response and scavenging of reactive oxygen radicals.</td>
<td>Seven- to nine-week-old male, BALB/c mice</td>
<td>Histological evaluative Statistical analysis</td>
<td>Reactive oxygen radical production, detected as this habitrubic acid reactive substance and lipid peroxide, by double treatment of TPA was reduced by pre-treatment with PE or RA.</td>
<td>17</td>
</tr>
<tr>
<td>Rosmarinus officinalis (L.), Carnosic acid</td>
<td>Carnosic acid extract of Og leaves</td>
<td>Antioxidant activity</td>
<td>free radical scavenging activity</td>
<td>-</td>
<td>-</td>
<td>The correlation was broadly confirmed by the production of volatile aldehydes as measured by the hexanal assay.</td>
<td>31</td>
</tr>
<tr>
<td>Ocimum gratissimum (Og)</td>
<td>methanolic extract of Og leaves</td>
<td>Immunomodulatory</td>
<td>-</td>
<td>Male AJ mice (25–30 g)</td>
<td>Histopathological analysis Eosinophil peroxidase (EPO) activity</td>
<td>RA have therapeutic potential in this marine model of respiratory allergy to a clinically relevant human sensitizer allergen.</td>
<td>12</td>
</tr>
<tr>
<td>Eryngium alpinum L.</td>
<td>R(+)-3 -O-β-d-glucopyranosyl</td>
<td>Antioxidant capacity</td>
<td>-</td>
<td>-</td>
<td>Quantitative determination</td>
<td>The results indicate that the new derivative R(+)-3 -O-β-d-glucopyranosyl rosmarinic acid is a potential chemotaxonomic marker of the Saniculoideae subfamily.</td>
<td>33</td>
</tr>
<tr>
<td>Cordia americana</td>
<td>ethanolic extract</td>
<td>anti-inflammatory</td>
<td>inhibitory effects on 5-lipoxygenase</td>
<td>-</td>
<td>HPLC analysis</td>
<td>The effective compound in Cordia americana and supports its use in traditional medicine</td>
<td>34</td>
</tr>
<tr>
<td>Origanum vulgare</td>
<td>-</td>
<td>antioxidant activities</td>
<td>radical-scavenging activities</td>
<td>embryonic liver BNCL2 cells</td>
<td>Cell viability Cellular tyrosinase activity assay, Melanin content</td>
<td>Ov-8 exhibits antioxidant and depigmentation activities that may be useful in food additives and in the control of skin pigmentation.</td>
<td>35</td>
</tr>
<tr>
<td>Heliotropium foertherianum</td>
<td>H. foertherianum</td>
<td>Inhibitory activities</td>
<td>-</td>
<td>Mouse neuroblastoma cells</td>
<td>Neuroblastomacytotoxicity assay, Cell viability measurement H.foertherianum aqueous extract and Rosmarinic acid effects in brosausys</td>
<td>The potential of H. foertherianum in the treatment of Ciguatera Fish Poisoning.</td>
<td>36</td>
</tr>
</tbody>
</table>
complement activation is taking place. Thus side effects due to action on other parts of the organism may be reduced 44. Effects of caffeic acid-containing compounds such as chlorogenic acid, rosmarinic acid and rabdosin on anti-allergic activities involving active oxygen scavenging activity as well as inhibitory activities of hyaluronidase and \( \beta \)-hexosaminidase release. Rabdosin exhibited the highest hyaluronidase-inhibitory activity and scavenging activities against active oxygen species such as superoxide anion radicals and hydroxyl radicals among the tested compounds. Both rabdosin and caffeic acid inhibited \( \beta \)-hexosaminidase release from cultured cells more than 90% at 2 mM 45. Rosmarinic acid furnished notable antibacterial activity against Bacillus subtilis, Micrococcus luteus, and Escherichia coli 46. RA effective in reducing both gingival inflammation and plaque accumulation as the synthetic antioxidant and anti-inflammatory compound ebselen when topically applied in the Rhesus monkey model 49. RA antibacterial activity and its proven reduction of inflammation make it ideal for topical skin infections of the epidermis and oral mucosa 39.

**Role of rosmarinic acid in photo protective agent:**
Solar UV and other ionizing radiations cause a generation of reactive oxygen species, induce cellular DNA damage and alter skin homeostasis 50. The expenditure of exogenous antioxidants is increasingly frequent, RA extract acts as a photo-protector; both free radical scavenger as an inducer of the body’s own endogenous defence mechanisms by regulating tyrosinase activity and stimulating melanin production 50. Plant compounds/extracts with screening, antioxidant and anti-inflammatory activities may also successfully protect the skin against UV-caused injury 51.

**Role of rosmarinic acid in anticancer agent:**
Mutagenicity assays showed no increase in the frequency of micronuclei in animals treated with different concentrations of RA when compared to the negative controls 52. Inhibitory effects of rosmarinic acid against 7,12-dimethylbenz anthracene (DMBA)-induced oral carcinogenesis by evaluating the status of biochemical markers (lipid peroxidation, antioxidants, and detoxification enzymes) and immune expression patterns of p53 and bcl-2 proteins 53. Natural antioxidant and chemopreventive rosmery phytocemicals, carnosic acid, carnosol, and ursolic acid, have inhibitory effects on P-glycoprotein and the potential to cause food–drug interactions 54.

**Role of rosmarinic acid in antidepressive agent:**
Rosmarinic acid from the leaves of Perilla frutescens Britton var. acuta Kudo (Perillae Herba) has antidepressive-like activity. Rosmarinic acid, its major metabolite caffeic acid also significantly reduced the duration of immobility of mice in the forced swimming test, RA inhibits the histamine release from mast cells produced a noteworthy antidepressive like effect at only one dose, and that caffeic acid can activate the α1-adrenergic receptor system and inhibit the production and release of nitric oxide. It has been suggested adrenergic systems in the brain may contribute to stress and depression. Forced swimming increased the brain content of histamine and histamine turnover, and H1 and H3 receptor antagonists reduced the duration of immobility in the forced swimming test. Some antidepressants such as doxepin, mianserin and amitriptyline are potent competitive H1 receptor antagonists, as determined in several different assay systems Therefore, these brain systems should be examined in future studies to elucidate the detailed mechanisms involved in the antidepressive effects of rosmarinic acid and caffeic acid 55. Rosmarinic acid from Perillae Herba acts as a novel antidepressive-like substance 55. RA is one of major polyphenolic ingredients of Perillae Herba (a leaf of Perilla frutescens), and has an antidepressant-like property in animal models of depression 50. RA-induced cell proliferation may be one of the mechanism(s) of the antidepressant-like effect of RA 56.

**Role of rosmarinic acid in inhibitors angiogenesis:**
Rosmarinic acid (RA), a water-soluble polyphenolic compound with anti-oxidative and anti-inflammatory activities, inhibited several important steps of angiogenesis containing proliferation, migration, adhesion and tube formation of human umbilical vein endothelial cells (HUVEC) in a concentration-dependent manner. RA also reduced intracellular reactive oxygen species (ROS) level, \( H_2O_2 \)-dependent VEGF expression and IL-8 release of endothelial cells 57.

**Role of rosmarinic acid in neurodegenerative disease:**
Parkinson’s disease (PD) is a neurodegenerative disorder categorized by progressive motor dysfunction. The key neuropathological features of PD are the loss of dopaminergic neurons in the substantia nigra pars compacta (SNPC) and thus the dopamine diminution in the striatum 58. RA provides some protection against the apoptotic cell death by oxidative stress 59. Rosmarinus officinalis a culinary aromatic and medicinal plant is very rich in polyphenols and flavonoids with high antioxidant properties. Alzheimer’s disease (AD) is the most common form of dementia and is characterized by progressive impairment in cognitive function and behavior. AD represents the most frequently occurring form of dementia, especially if considered alongside concomitant cerebrovascular disease. Pharmacological basis for the use of sage in AD, effect of a standardized extract from the leaves of S. Officinatis and its main active ingredient RA use in AD 50. Huntington’s disease is an autosomal dominant, fully penetrant, progressive, and fatal neurodegenerative disease 61 characterized by progressively worsening chorea (dance like movement) cognitive and psychiatric disturbance involving the basal ganglia and cerebral cortex that is the region, which controls body movement 62, 63. The protein huntingtin (htt) is widely expressed within the central nervous system and in extraneural tissues apoptosis. Huntington is expressed more intensely in neurons than in glial cells 54.

Rosmarinic acid protects neurons from oxidative stress 65. RA significantly attenuated \( H_2O_2 \)-induced reactive oxygen species (ROS) generation and apoptotic cell death 59. RA could contribute at least in part to neuroprotective effects because this natural compound exerts neuroprotective and anti-oxidative effects against neurotoxin insult in dopaminergic cells 66. Rosmarinic acid significantly protected neurons. These effects are mediated by the prevention of oxidative stress, intracellular Ca\(^{2+} \) overload and c-fos expression 67.

In case of neurodegenerative disease where oxidative stress underlying causal? A has shown potential application, thus its assessment as a therapeutics agent in these disorders is warranted. Some potential targets of RA are shown (Figure 5). The figure depicts various events such as
mitochondrial dysfunction, excitotoxicity, apoptosis and oxidative stress as contributing factors to pathogenesis of various disorders that can be targeted by RA. These events specifically in brain lead to neurodegenerative disorders such as Alzheimer’s, Parkinson’s and Huntington’s disease.

**CONCLUSION**

Rosmarinic acid as discussed earlier having antioxidant, anti-inflammatory, anti-allergic, immunoenhancer, antiviral, antibacterial, anti-inflammatory, antimicrobial, anticancer and antidepressant properties. RA has shown promising results in many in-vitro and in-vivo studies which are carried out in animals (male, BALB/c mice, male AJ mice, mouse neuroblastoma cells). RA has been implicated as a potent antioxidant and therapeutic agent with numerous application in many disorders. RA as natural antioxidant can also be used in Parkinson’s and Huntington’s disease. In Huntington (HD) and Parkinson (PD) due to oxidative stress neuronal cell loss and amount of reactive oxygen species (ROS) and free radical in much higher amount in brain. RA can used as antioxidant in the HD and PD because RA have free radical scavenger activity. RA reduce the free radical amount in HD and PD brain. RA can also be used in Alzheimer disease, as it has been shown to be protective against memory impairments in AD. Its role in treatment of many diseases where oxidative stress is the underlying cause is required to be evaluated. Thus specific targeting using RA, specifically in brain regions where oxidative stress is associated shall be effective as a therapeutic strategy.

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