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Perspectives of Rosmarinic Acid in the treatment of Multiple EmergingDiseases: an Insight Review

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ABSTRACT
Natural food-derived active components have drawn a lot of interest for their ability to treat a variety of ailments through chemotherapy and chemoprevention. A naturally occurring phenolic chemical found in many plants in the Lamiaceae family, including Rosmarinusofficinalis (rosemary), from which it was first isolated, is rosmarinic acid (RA), a caffeic acid ester. Through a variety of mechanisms, including tumor cell growth, apoptosis, metastasis, and inflammation, RA affects carcinogenesis. However, it also has potent antibacterial, anti-inflammatory, antioxidant, and even antidepressant and anti-aging properties. The purpose of this study is to discuss the therapeutic potential of RA against a wide range of disorders and to give an outline of its anticancer actions.According to the available research, RA may be included in the daily diet to treat a number of ailments, with certain levels that prevent cytotoxicity.

Keywords: Rosmarinic acid, Management, Disease, Therapeutics, Bioavailability, Cataract

I. INTRODUCTION

Rosmarinic acid (RA) is a naturally occurring phenolic molecule that is an ester of caffeic acid and 3,4-dihydroxyphenyl lactic acid. Its official name is (R)-α-[[3-(3,4-dihydroxyphenyl)-1-oxo-2E-propenyl]oxy]-3,4-dihydroxy-enzenepropanoic acid and its chemical formula is $C_{18}H_{16}O_8$. (**Figure 1**). Plants from the subfamily Nepetoideae of the Boraginaceae family are the primary causes of RA. In recent years, it has been identified in plants from the Lamiaceae family as well as Forsythia koreana (Rehder) Nakai, Hyptispectinate (L.) Poit.,Ocimumtenuiflorum L., and Thymus mastichina (L.) L. It was initially isolated in 1958 from the rosemary plant (Rosmarinusofficinalis L.).

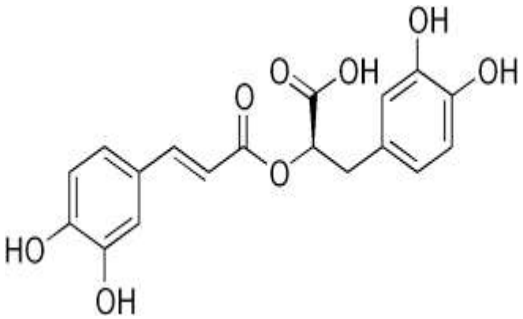

Figure 1. Structure of Rosmarinic acid.

Aside from its extraordinary antiviral, antibacterial, anticancer, antioxidant, anti-aging, antidiabetic, cardioprotective, hepatoprotective, nephroprotective, antidepressant, antiallergenic, and anti-inflammatory properties, RA also has significant biological effects. RA and several isolated components from rosemary extract, including as carnosic, ursolic acids, and carnosol, have also demonstrated the ability to lessen the risk of tumour growth in a number of human organs, including stomach, colon, liver, breast, and leukaemia cells.

II. BIOAVAILABILITY OF ROSMARINIC ACID AND ITS METABOLIC CHANGES IN THE HUMAN BODY

In the body of the rat, RA is largely converted to coumaric acid and caffeic acid [5], and its metabolites may potentially be responsible for the hypolipidemic impact of RA. For instance, caffeic acid boosted fatty acid -oxidation activity in high-fat diet-induced obese mice while decreasing the production of hepatic fatty acid synthase, 3-hydroxy-3-methylglutaryl CoA reductase, and acyl-CoA:cholesterolacyltransferase activities [6]. The observed metabolic effects may have been influenced by the elevated blood estradiol

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concentrations caused by caffeine and sinapic acid in rats with an oestrogen deficit [7]. Estradiol is produced by exterior ovarian tissues such adipose tissue, skin, bones, and the brain during rat ovarian ovulation. These locations are unable to synthesise C19.Aromatase is a steroid C19 (androgen) converting enzyme. Therefore, it is conceivable that RA or its byproducts boost aromatase activity. Only in rats fed normal food including soy did caffeine boost estradiol and lower total cholesterol levels; similar effects were not seen in rats fed standard diet without soy but with decreased phenolic acid contents [8]. It is therefore probable that the documented effects of RA, at least in part, are diet-related. Similar positive effects on a few lipid markers and insulin resistance (HOMA-IR) were seen with RA as were seen with sinapic acid in a related research [7].In addition, in diabetic rats, RA had favorable effects on the expression of hepatic genes or proteins involved in insulin signaling, glucose and lipid metabolism, including insulin receptor substrate-1 (IRS-1), 5′ AMP-activated protein kinase (AMPK), phosphoenolpyruvatecarboxykinase (PEPCK), glucose transporter 2 (GLUT2), forkhead box protein O1 (FOXO1), sterol regulatory element-binding protein 1 (SREBP1), and carnitinepalmitoyltransferase 1 (CPT1) in diabetic rats [9]. Peroxisome proliferator-activated receptor (PPAR) peroxidation may be a plausible pathway through which RA affects lipid and glucose metabolism; RA has been demonstrated to activate these receptors. It should be mentioned that the HOMA-IR index and fructosamine concentration may be reduced with a lower dose of RA (10 mg/kg), however the total cholesterol and triglyceride levels in rats with oestrogen shortage needed a larger dose (50 mg/kg). Additionally, RA and its metabolites have the ability to directly eliminate reactive oxygen species (ROS) [10], which lessens the production of oxidative damage-related products. The presence of two catecholic moieties and the four hydrogens in the phenolic system, which give this chemical its polar nature, are directly responsible for the antioxidant action of RA.According to electrochemical research, RA oxidises in two stages. The remaining caffeic acid is oxidised in the first stage, followed by the 3,4-dihydroxyphenyl lactic acid residue in the second.

Consequently, RA is regarded as the most potent antioxidant among all hydroxycinnamic acid derivatives [11]. RA has been shown to inhibit the synthesis of advanced glycation end products both in vitro and in vivo in the past [12]. In rats lacking in oestrogen, the administration of RA at dosages of 10 and 50 mg/kg had no effect on body mass. While RA at a level of 50 mg/kg of estradiol exhibited a tendency of growth, RA at a dose of 10 mg/kg of ovariectomized rats had no effect on estradiol and progesterone concentrations compared to ovariectomized control rats. It is feasible to ingest 5–10 g of these plants daily in the form of infusions and spices because RA-containing orchids are frequently employed in self-healing and everyday diets [13]. Since RA is water-soluble, literature studies indicate that roughly 90% of this molecule is effectively secreted during infusions [14]. As a result, it is feasible to eat around 110 mg of RA per day, or about 1.6 mg/kg for adult males who weigh 70 kg. In many diabetic models, using RA has been shown to increase the plasma concentration of reduced glutathione (GSH) [15]. In hematopoietic stem cells, RA has been found to increase the regulation of the catalytic subunits of glutamate cysteine ligase, an enzyme involved in the manufacture of GSH [16]. It is likely that the rise in GSH concentration following the administration of RA was caused by intensive GSH production rather than its recovery from the oxidised state.Additionally, it is important to remember that the RA appears to enter the rat mostly as its metabolites [5]. These metabolites could possibly be responsible for the elevated GSH concentration that was noticed. Additionally, serum GSH/oxidized glutathione (GSSG) was determined since it is considered to be a crucial marker of redox cell condition as well as for the state of redox at the tissue and overall body levels [17]. Rat serum has been demonstrated to have a higher ratio of GSH/GSSG due to the adventitious influence of RA on redox homeostasis.

III. HEALTH BENEFITS OF ROSMARINIC ACID

3.1. Arthritis

Petchi et al., 2013 An inflammatory condition called arthritis results in damage to one or more joints. It comes in more than a hundred varieties, with osteoarthritis and rheumatoid arthritis being the most prevalent. Osteoarthritis (OA) is a gradual degenerative condition that impairs mobility and causes discomfort. It is characterised by synovial inflammation, cartilage surface abrasion, subchondral sclerosis, and osteophyte formation. The only outcome of any action that increases strain on a specific joint or weakens the cartilage matrix is OA, which has long been recognised as a degenerative disease of the

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cartilage. Although the pathophysiology of OA is complex and not fully understood, a growing body of studies has shown that inflammation plays a significant role in the development of OA.The symptoms of rheumatoid arthritis (RA), a chronic inflammatory autoimmune disease, include significant mesenchymal and inflammatory cell infiltration and activation, synovial cell proliferation, neovascularization, and sporadic cartilage and bone loss. Nonsteroidal anti-inflammatory medicines (NSAIDs) and disease-resistant antirheumatic therapies (DMARDs) are often used to treat RA, but their side effects, possible toxicity, and high price limit their usage. In order to identify safe and effective medications, the area of arthritis research is currently quickly expanding in the direction of herbal research [18].

Articular cartilage loss is the main symptom of OA, a complex illness. The primary elements of cartilage extracellular matrix (ECM) are collagen 2 (COL2) and aggrecan (ACAN). The cartilage deteriorates in OA due to the loss of COL2 and ACAN. ACAN depletion in osteoarthritic cartilage is brought on by the metalloproteinases ADAMTS-4 and ADAMTS-5, which are disintegrins. Interleukin-1-beta (IL-1β), an inflammatory cytokine, also plays a significant role in the breakdown of the ECM. In rat chondrocytes, RosA has been shown to have an impact on OA. Chondrocytes from rat cartilage were taken out for this experiment, and they were then treated with RosA while being exposed to IL-1. It was discovered that RosA inhibits IL-6 secretion as well as ADAMTS-4 and ADAMTS-5 gene and protein expression.Additionally, RosA reduced the IL-1-induced gene expression of COL2 and ACAN. The findings suggest RosA can destroy ECM in OA and may have therapeutic benefits for OA. A other study discovered that consuming high-RosA spearmint tea may be an additional option for treating OA pain. According to the study, drinking high RosA tea for 16 weeks per day might dramatically lower pain and improve stiffness ratings in persons with knee OA. It could also greatly reduce physical disability scores.

The death of potentially harmful T-cells is seen as a key treatment strategy since T-cells play a critical role in the onset and progression of RA. According to the study, RosA can use the mitochondrial route to cause apoptosis in activated T-cell subsets in RA patients. According to the findings, 57.1% of RA patients who were exposed to RosA experienced CD3+CD25+ activated T-cell apoptosis in a dose-dependent manner. RosA also shown higher apoptotic activity against CD4+CD45RO+ effector T-cell subsets than it did against CD4+CD45RA+ naïve T-cell subsets. RosA also prevented the breakdown of MMPs, decreased the expression of Bcl-2, and promoted the release of Cyt c from mitochondria to the cytoplasm. These findings supported the hypothesis that RosA caused the mitochondrial pathway-mediated apoptosis of activated T cells from RA patients.In a different test, it was discovered that RosA can lessen the signs of arthritis in the mouse model of collagen-induced arthritis (CIA). RosA might considerably lower the number of paws with arthritis and the arthritis index. RosA prevents synovitis, according to histopathological pictures, and animals treated with RosA had a much lower frequency of COX-2-expressing cells in their synovial tissue. RosA was therefore administered in a clinical context, and this had therapeutic effects in the management of RA. Additionally, it has been found that the pomegranate peel extract RosA has strong anti-arthritic potential when used to treat arthritis brought on by Freund's complete adjuvant (FCA).

Colitis

Zhang and Li, 2014 Crohn's disease (CD) and ulcerative colitis (UC) are two examples of the chronic, recurring intestinal inflammation known as inflammatory bowel disease (IBD). IBD is believed to be brought on by an inappropriate and persistent immune response to intestinal bacteria brought on by the person's genetic vulnerability. The colon and rectal mucosa are diffusely inflamed in UC, a chronic illness. Bloody diarrhea is the usual clinical sign of UC. In contrast to CD, the afflicted colon and the colonic mucosa are the only areas of inflammation in UC. IBD has become more common in several parts of the world recently, particularly in poorer nations. Consequently, IBD patients are increasingly in need of potent and secure natural substances [19].

According to studies, RosA can treat colitis brought on by dextran sulphate sodium (DSS). In this work, RosA significantly reduced the disease activity index and prevented DSS-stimulated splenomegaly and colon length shortening in mice. RosA dramatically reduced the amount of inflammatory cell infiltration in the colitis model caused by DSS. RosA prevented the production of IL-1, IL-6, and IL-22 as well as the stimulation of COX-2 and iNOS expression. RosA dramatically reduced the expression of NF-κBp65 and pSTAT3 as well as their transport to the

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nucleus in the inflamed mucosa, according to immunohistochemistry analyses. RosA prevented the rise in NF-κB and STAT3-associated proteins in the colon of colitis animals, according to a Western blot study. In a different publication, the impact of RosA and black rice anthocyanin-rich extract (BRAE) on colitis brought on by DSS was demonstrated.When given in the proper dosage, the combination of BRAE and RosA dramatically decreased the DAI and suppressed the production of serum IL-1, TNF-α, and NO as well as IL-1 and TNF mRNA. Additionally, the combination of BRAE and RosA displayed its anti-inflammatory action by lowering the expressions of myeloperoxidase (MPO), NO, IL-6, IL-1β, and iNOS as well as MPO and NO levels.

By modifying RosA to have less hydrophilicity, some researchers were able to suppress the hypoxia-inducible factor-prolyl hydroxylase-2 (HPH) enzyme and activate the hypoxia-inducible factor (HIF)-1, which in turn prevented rats from developing colitis brought on by the TNBS.

3.2. Atopic Dermatitis

Cabanillas et al., 2017 Atopic eczema, commonly known as atopic dermatitis (AD), is a persistent, chronic inflammatory skin condition. The disease's clinical signs include flare-ups and reliefs of eczema skin, as well as inflammation, flaking and itching, desquamation, dry skin, and susceptibility to skin bacteria and mould infections. IgE-mediated hypersensitivity, barrier failure, alterations in the cell-mediated immune response, and environmental variables are all part of the complex and multifaceted pathophysiology of AD. Many researchers are working hard to create therapeutic medications that have powerful anti-inflammatory properties and little negative effects right now [20].

T cells are crucial to the pathophysiology of AD. In terms of its two separate phases, AD may be considered of as a bipolar inflammatory skin disease. The Th2 cytokines IL-4, IL-5, and IL-13 are mostly secreted by CD4+ T cells, which infiltrate AD skin lesions during the acute phase. However, Th1 cells release interferon (IFN) during the chronic phase. According to certain studies, RosA can reduce AD in NC/Nga mice that has been brought on by 2,4-dinitrofluorobenzene (DNFB) and has also been linked to a mechanism of action. In this study, the authors demonstrated that the production of IFN- and IL-4 by activated CD4+ T cells could be greatly inhibited by RosA. RosA effectively slowed the growth of cutaneous lesions, decreased blood total IgE levels, and decreased ear thickness.In DNFB-induced skin lesions in NC/Nga mice, RosA prevented CD4+ T cells, CD8+ T cells, and mast cells from infiltrating. According to the aforementioned findings, RosA prevented the onset of dermatitis resembling AD in NC/Nga mice induced by DNFB by lowering levels of total serum IgE and the generation of IFN- and IL-4 by activated T cells. Additionally, in clinical tests, RosA had the effect of treating AD. 21 patients with moderate AD received a topical application of a RosA (0.3%) emulsion twice daily, and this effect was seen in the elbow flexion. The statistically significant Severity Scoring of Atopic Dermatitis (SCORAD) score, pruritus, and transepidermal water loss (TEWL) were all dramatically decreased by RosA.RosA may be put to human skin without risk because no patient reacted to the patch test. These results demonstrate that RosA was effective as a treatment for AD. At the article's conclusion, the author added a suggestion that IKK-β inhibition by RosA could help alleviate AD symptoms.

3.3. Asthma

Manuyakorn et al., 2013 Airway obstruction, bronchial hyperresponsiveness (BHR), and airway inflammation combine intricately to cause the widespread chronic airway condition known as asthma. Many different types of cells and cellular elements play a part in this process, but mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells are particularly important. In a mouse model of asthma, RosA has been discovered to suppress ovalbumin (Ova)-stimulated airway inflammation. In the course of inflammation, the mitogen-activated protein kinases (MAPKs) control the production and release of pro-inflammatory mediators. The MAPK family includes the stress-activated protein kinase pathways p38, JNK, and ERK. In allergic asthma, NF-κB is continuously activated, and OVA-induced asthma is reduced when the NF-κB pathway is suppressed.In this study, the anti-inflammatory drug RosA lowered total IgE and Ova-specific IgE concentrations, considerably improved airway hyperresponsiveness (AHR), and greatly suppressed the growth of inflammatory cells and Th2 cytokines in bronchoalveolar lavage fluid (BALF). The amount of inflammatory cells and excessive mucus release in the airways were both dramatically decreased by RosA, according to a histological examination. In

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lung tissue, pretreatment with RosA significantly reduced the levels of the mRNAs for AMCase, CCL11, CCR3, Ym2, and E-selectin while also significantly regulating NF-κB and MAPK activity. RosA may thus represent a viable therapy option for asthma, according to this study. RosA may have a protective impact via activating NF-κB and inhibiting the phosphorylation of ERK, JNK, and p38 [21].

In a different experiment, a mouse respiratory allergy model induced by the Blomiatropicalis (Bt) mite was utilised to assess the immunomodulatory effects of Ocimumgratissimum (Og) and RosA. This study discovered that RosA dramatically reduced the quantity of eosinophils and overall inflammatory cells. RosA therapy decreased inflammatory cell infiltration surrounding the bronchi and perivascular regions, and also prevented mucus secretion in lung tissue, according to lung histopathology pictures. RosA may also lower the concentration of IL-4. The outcomes of this study provided solid evidence in favor of RosA's potential use as an anti-inflammatory medication to treat allergic asthma. Additionally, a study on asthmatics who had become resistant to conventional therapies described how Rosmarinusofficinalis extracts affected them.After receiving Rosmarinusofficinalis therapy, it was discovered that the Asthma Control Test (ACT) score showed a noticeable improvement. According to the clinical examination, the Rosmarinusofficinalis group had significantly reduced cough, sputum production, and wheeze. Exhaled nitric oxide (FENO) was also dramatically decreased following therapy with Rosmarinusofficinalis.

3.4. Allergic Rhinitis

Bousquet et al., 2008 The symptomatic inflammation of the nose known as allergic rhinitis (AR) is brought on by endocardial inflammation that is mediated by immunoglobulin E (IgE). With 10 to 20% of the global population affected, AR is one of the most widespread chronic disorders. Seasonal allergic rhinoconjunctivitis has pollen as the primary documented cause (SAR). According to prospective studies, SAR may operate as a risk factor for the development of asthma [22].

In the OVA-induced AR animal model, RosA reduced inflammation. Mice exposed to OVA had higher IgE levels in their blood, spleen, and nasal mucosa, which could be reduced by administering RosA. Histamine levels in the bloodstream considerably decreased following RosA therapy. In the spleen or nasal mucosa, RosA also inhibited the protein and mRNA expressions of IL-1, IL-6, and TNF-α. The study also discovered that the drug-administered group had a decreased increase in mast cell and eosinophil infiltration brought on by OVA sensitization. RosA administration to nasal mucosa tissue can also stop COX-2 expression and caspase-1 activity. RosA inhibited the activation of NF-κB and caspase-1 in activated human mast cells.The aforementioned outcomes illustrated RosA's therapeutic potential for allergic rhinitis and allergic rhinoconjunctivitis.

Clinical trials have been conducted by certain researchers to determine if orally administered RosA is useful in treating people with SAR, and animal studies have quantified RosA's anti-inflammatory effects in a model of ear edoema. RosA substantially decreased each symptom's rate of remission in clinical studies when used in addition to a placebo. Neutrophils and eosinophils were both significantly reduced by RosA in nasal lavage fluid. ICAM-1, VCAM-1 cyclooxygenase-2 (COX-2), keratinocyte chemoattractant (KC), and macrophage inflammatory protein-2 (MIP-2) up-regulation by TPA in the 12-tetradecanoylphorbol 13-acetate (TPA)-stimulated mouse ear edema model was considerably inhibited by pretreatment with RosA. According to histological analysis using hematoxylin-eosin staining, RosA can decrease neutrophil infiltration. RosA was said to provide therapeutic benefits for SAR patients in a different publication.Treatment with RosA-enriched Perillafrutescens extract significantly increased responder rates for itchy eyes, watery eyes, and overall symptoms when compared to placebo supplementation. RosA's ability to prevent polymorphonuclear leukocytes (PMNLs) from infiltrating the nostrils may help to effectively cure moderate SAR, at least in part.

3.5. Periodontal Diseases

Pietropaoli et al., 2010 It is believed that periodontal disease is a complex condition affected by a variety of environmental and genetic variables, as well as pathogenic infections, inflammation, and immunological responses to bacteria. Damage to the steady-state balance between the oral microbiota and the host, which may result in gingivitis and periodontitis, may have an impact on the intricate composition and structure of the periodontal ligament. Microbial plaques that build up at or close to the gingival sulcus are what cause gingivitis. It was discovered that plasma cells and

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B lymphocytes were the major causes of gingivitis. It is believed that gingivitis is a form of early periodontal disease that may or may not progress to periodontitis. A chronic inflammatory condition of the dental support tissue called periodontitis is common and can alternate between periods of acute relief and aggravation.Although its pathophysiology is not entirely understood, periodontitis is defined as chronic leukocyte infiltration that may be controlled by the generation of topical chemokines [23].

The development of plaque-induced gingivitis in a rhesus monkey model has been shown to be affected by the topical anti-inflammatory medicines ebselen and RosA. To measure the degree of gingival inflammation and plaque accumulation, nonparametric indicators (G.I.) and the plaque accumulation index (P.I.) were utilised. G.I. values vary from 0 (absence of erythema or edoema) to 4. (Serious erythema or edema, spontaneous bleeding, and ulceration). Between 0 (no plaque) and 4 is the P.I. (tooth completely covered by plaque). In this experiment, animals given rosA and ebselen had lower G.I. and P.I. levels than the control animals. As a result, the paper came to the conclusion that, at least in the short term, utilising a skin graft macaque model, RosA and ebselen were successful in reducing gingival inflammation and plaque development.

Additionally, Prunella vulgaris L. (PVE) and its component RosA have been shown to reduce oxidative stress and inflammation in human gingival fibroblasts stimulated by LPS. Reactive oxygen species (ROS) and antioxidant defence systems have an unbalanced equilibrium that contributes to the etiology of periodontitis. The scientists noted that in LPS-treated cells, PVE and RosA decreased lipid peroxidation, intracellular glutathione (GSH) consumption, and ROS generation. Along with preventing the LPS-induced elevation of IL-1, IL-6, and TNF-α, PVE and RosA also prevented the production of iNOS. These findings suggested that PVE and RosA may decrease the development of periodontitis by lowering gingival fibroblasts' inflammatory response and production of oxidative mediators.

3.6. Acute Pancreatitis

Irrera et al., 2014 An inflammatory condition known as acute pancreatitis (AP) is characterised by pancreatic parenchymal necrosis and acute inflammation. Acinar cells' early intracellular activation of digesting enzymes, which results in tissue self-digestion and may include distant organs, is thought to be a component of AP, which is seen as a topical inflammatory response. The release of chemokines and cytokines by secretory acinar cells is thought to also result in the recruitment of white blood cells and the onset of an inflammatory response that results in pancreatic edoema and neutrophil buildup. The likelihood of organ failure and infected pancreatic necrosis affects the prognosis of AP patients in a significant way. Despite its rising prevalence, the disease's symptoms and course are not currently treated with medication [24].

When AD is brought on by sodium taurocholate, RosA may provide protection. The pathogenesis of NaTC-induced rat AP is characterised by fast onset of necrosis and inflammation of the pancreas and/or peripancreatic tissue, and is strikingly comparable to that of severe acute pancreatitis in humans. Pro-inflammatory cytokines including IL-1, IL-6, and TNF-α, as well as inflammatory responses and NF-κB activation, play a significant role in AP. The results showed that pretreatment with RosA significantly reduced the pathological changes in the pancreas, as well as serum amylase and lipase activity, pancreatic myeloperoxidase activity, systemic and pancreatic leukocyte IL-1, IL-6, and TNF-α expression, and suppressed NF-κB translocation in the pancreas. Through inhibiting NF-B activation, RosA appeared to lessen the harm NaTC produced to AD and the production of inflammatory cytokines.

3.7. Mastitis

Aitken et al., 2011 Breast inflammation known as mastitis may affect any animal that is nursing and is often brought on by a bacterial infection. According to human epidemiological research, mastitis affects more than one-third of nursing women, and it's the primary cause of moms discontinuing breastfeeding due to its clinical symptoms. The degree of bacterial pathogen exposure to the breast affects the development of mastitis. Mastitis is brought on by several Gram-positive and Gram-negative bacteria. Lipopolysaccharide (LPS) from Gram-negative bacteria is thought to be crucial for creating animal models of inflammation [25].

Study described RosA's ability to reduce inflammation in LPS-induced murine mastitis. This study discovered that RosA therapy dramatically reduced myeloperoxidase activity and improved structural damage to the mammary glands. RosA lowered the amount of TNF-α, IL-1, and IL-6 in

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tissues and mMECs in a dose-dependent manner, according to the results of ELISA and qPCR. A crucial group of pathogen identification receptors are TLRs. The most distinctive TLR family member, TLR4, plays a critical role in the innate immune response to LPS infection. TLR4 has been linked to the generation of inflammatory cytokines and has been demonstrated to control the activation of the NF-κBsignalling pathway, according to a growing body of research.In HEK293-mTLR4/mMD-2 cells, RosA dose-dependently lowered TLR4 level, indicating that RosA can directly target TLR4 to prevent the inflammatory response. The levels of the TLR4 pathway's downstream signalling elements MyD88, IRAK1, TRAF6, and IKK were likewise markedly decreased. Additionally, the phosphorylation of I-κB and the activation of p65 were both markedly reduced by the injection of RosA. The DNA binding activity test provided additional evidence of the RosA-mediated reduction of NF-κB nuclear translocation. RosA can thereby reduce the severity of LPS-induced mastitis by inhibiting the TLR4/MyD88/NF-B signalling pathway.

3.8. Rosmarinic acid as anti-cataract agent

Tsai et al., 2019examined how rosmarinic acid shielded Sprague-Dawley rat pups from selenite-induced cataractogenesis. The animals were put into five groups of ten rat pups each at random. Group I acted as the standard control (vehicle administration). Animals from Groups II, III, IV, and V received a single subcutaneous injection of sodium selenite (2.46 mg/kg body weight) for the purpose of assessing cataract induction on postpartum day 12. Group-II acted as the control selenite after ingestion of sodium selenite. Groups III–V received 5, 10, and 50 mg/kg of rosmarinic acid intraperitoneally from the 11th to the 17th day, respectively. The rat pups were assessed for cataract development on postpartum day 24, and the lenses were extracted for further protein and oxidative damage markers examination.Significant cataract development was induced by selenite. The effects of selenite resulted in the downregulation of filensin and calpain 2 protein expressions and the upregulation of calcium concentrations, lipid peroxidation levels (TBARS), and inflammatory markers (iNOS, COX-2, and NF-B). Additionally, the GSH levels were downregulated, as were the antioxidant enzyme activities (GSH-Px, GSH-Rd, and catalase) and the protein expression of the antioxidant status (Nrf2, SOD, HO-1, and NQO1). Rosmarinic acid therapy, however, has the potential to greatly reduce the development of cataracts and lens oxidative damage. Additionally, the injection of rosmarinic acid markedly enhanced the protein expressions of filensin, calpain 2, Nrf2, SOD, HO-1, and NQO1, the antioxidant enzymes' activity, and the GSH level, in addition to lowering the calcium, lipid peroxidation, and inflammatory markers in the lens.Rosmarinic acid may slow the development and progression of cataracts brought on by sodium selenite when used in combination [26].

Chemerovski-Glikman et al., 2018posited that reducing lenticular protein aggregates' load of precipitates and altering their light-scattering characteristics would improve cataract. Researchers have created a unique ex vivo platform where human lens particles taken from patients after standard cataract surgery were treated with one of many protein aggregation modulators in order to examine this notion. They were able to directly examine the effects of the screened compounds on protein aggregates present in phacoemulsified human crystalline lens material thanks to the straightforward yet creative experimental technique. This is the first known instance of the systematic screening of possible therapeutic medicines using ex vivo human cataract material [27].

Zych et al., 2022 Rosmarinic acid (RA) and sinapic acid (SA) were studied for their impact on oxidative stress indicators in the lenses of type 2 diabetic female rats. Both of these phenolic acids were given to the rats by gavage for a total of 28 days after streptozotocin and a high-fat diet were used to develop diabetes. The dosages of phenolic acids for RA and SA were 10 and 50 mg/kg body weight (bw) and 5 and 25 mg/kg bw, respectively. The lenses were examined for oxidative stress markers, including as antioxidant enzymes, non-enzymatic antioxidants, and oxidative damage markers. The levels of both reduced and oxidised glutathione were lower in the lenses of diabetic female rats, indicating that type 2 diabetes primarily impacted glutathione.No of the amount, taking the tested phenolic acids orally did not reverse these alterations. Since glutathione is essential for maintaining lens clarity, neither RA nor SA may be viewed as promising medicines for preventing diabetic cataracts [28].

IV. CONCLUSION

The further investigation of RA as a prospective treatment agent against a wide range of contemporary lifestyle problems is supported by

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the available data. However, further research is necessary to determine the mechanisms behind RA's therapeutic efficacy. According to preliminary research, RA may exert its effects via a variety of pathways, including anti-inflammatory and antioxidant effects, cell proliferation and migration inhibition, and the selective induction of apoptosis in cancer cells. Additionally, RA's anti-angiogenic properties, which were shown by the suppression of human umbilical vein endothelial cells' migration, adhesion, and tube formation, imply that it may be helpful in inhibiting tumour development and metastasis. Given the aforementioned factors, rosemary extract may be seen as a rich source of candidates that might be added to the diet and have promising benefits at certain levels while avoiding toxicity.

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