A REVIEW ON ROSMARINIC ACID RICH EXTRACT FOR SKIN REGENERATION THROUGH RAPAMYCIN SIGNALING PATHWAY

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ABSTRACT: Rosmarinic acid is a phenolic compound procured from the species of the Boraginaceae and the Lamiaceae subfamily Nepetoideae. Rosmarinic acid has numeral of biologically stimulating properties. Rosmarinic acid is a chemical constituent which is a major compound found in *Orthosiphon aristatus* leaves and it is about 5-10% w/w in the ethanolic extract of the leaves. The skin is the largest organ of a human body and a variety of environmental conditions, frequently affects it such as skin infections, skin oxidation, wounds, UV radiation exposure and skin aging. In both physiological and pathological conditions, the phosphatidylinositol 3-kinase (PI3K) / protein kinase B (AKT) enzyme aids in the preservation and repair of the epidermis, dermis, and hair follicles layer of the skin. PI3K/Akt manages cell proliferation, differentiation, migration, angiogenesis and metabolism. This review paper compiles, summarizes and considers on skin regenerative and wound healing.

KEY WORDS: *Rosmarinic acid; Orthosiphon aristatus; wound healing; anti-aging; PI3K/Akt/mTOR signaling pathway*

1. INTRODUCTION

Many medicinal herbs and herbal remedies have recently gained popularity, and they are commonly used in traditional medicine. Not only that, their application in modern medicine for a variety of maladies and disorders is quickly increasing. Natural rosmarinic acid (RA) is one of the most appealing phytochemicals among the various medicinal herbs because of its outstanding pharmacological activity [1]. Before the molecular structure of RA was identified, it is known as "Labiatengerbstoffe," a sort of tannin found in Lamiaceae plants. Scarpati and Oriente, two Italian chemists, isolated RA as a pure substance for the first time and named it RA after the plant from which they extracted it, Rosmarinus officinalis. The structure composed of an ester of caffeic acid and 3,4-dihydroxyphenyllactic acid [2], as shown in Fig. 1.

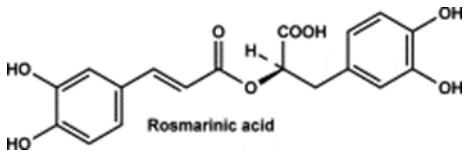

Fig. 1. Chemical structure of rosmarinic acid

RA is a very important phenolic compound derived from plants. It is predominantly found throughout the Boraginaceae family, while in the Lamiaceae family, it is only found in the subfamily of Nepetoideae [3]. Despite that, it may also be found in both higher and lower plant groups. For example, in higher plant groups like ferns from the family of Blechnaceae and in lower plant groups like hornworts species [4]. It is also commonly found in monocotyledonous plants like the sea grass from Zosteraceae family [5]. As this dispersion shows, the presence of RA cannot be used as a chemotaxonomic marker to distinguish between families. It grows naturally in the Mediterranean Sea and West Asia, and is widely grown throughout Europe and North America [6].

Many RA derivatives that are discovered in higher plants, as well as natural compounds, contains one or two RA with extra aromatic moieties. 30-deoxyrosmarinic acid, for example, is isorinic acid [7]. The most well-known RA derivatives are lithospermic acid, a rosmarinic acid-caffeic acid conjugate, and lithospermic acid B, a dimer RA [8].

This compound is recognized to have biological activities like anticancer, anti-inflamatory, anti-aging, antidiabetic, antibacterial, antidepressant, antiallergic, antiviral and antioxidant activities. Caffeoyl ester is a highly sought-after chemical with numerous applications, including food preservatives and cosmetics [9]. Natural antioxidants also avoid the health concerns associated with synthetic antioxidants as like butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA), both of which have been related to cancer [10]. It has also proven RA to lessen the risk of tumor formation in a variety of human organs, including the colon, breast, stomach, liver, and leukemia cells [11].

RA's antioxidant activity is greater than vitamin E. RA protects cells from free radical damage, which lowers the risk of atherosclerosis. Anti-inflammatory effects are found in RA. Perilla is utilized for its antiallergic properties due to its high RA content. A study by Osakabe et al., has shown that RA, when taken orally, is an excellent treatment for allergic asthma [12]. Youn et al. found that RA decreases synovitis in mice, suggesting that it might be useful in the treatment of rheumatoid arthritis [13]. Despite antihistamines, RA stops immune responder cells from becoming activated, causing swelling and fluid accumulation. Hence, RA is chosen in this review paper to study on its antioxidant activity in wound healing and anti-aging.

2. ROSMARINIC ACID ACTS AS THE MAIN ANTI-OXIDANT IN ORTHOSIPHON ARISTATUS

Orthosiphon aristatus (OA) is known as one of the dominant traditional folk medicines which is widely found in Africa and Southeast Asia. Because of its delicate purple blossoms with long wispy filaments that resemble like cat whiskers, it is known locally as "Misai Kucing" [14]. This herb belongs to the Lamiaceae family. The leaves of OA are found to be the vital part of the plant. Southeast Asians uses the leave extract of the plant as an herbal tea called ‘Java Tea’ [15]. These leaves are rich in bioactive components that promote diuretic, anti-fungal, bacteriostatic and antitumor properties. Due to a phenolic group in their structure, most flavonoids are bioactive chemicals.

This plant yielded twenty phenolic compounds, including nine lipophilic flavones, two flavanol glycosides, nine caffeic acid derivatives, and the newly discovered 5,6,7,8-tetra hydroxy-6-methoxy flavone. The polyphenol content of this leaves aids in the therapeutic effects of this herb, which has effects on antioxidant activity and enzyme inhibition. The main flavonoid in this plant are RA, eupatorin, scutellarein and sinestin [16]. Since this plant is relatively easy to cultivate, hence it has become a plantation crop in tropical nations like Thailand, Indonesia, the Philippines, Brunei, and Malaysia, it should investigate its antioxidant potential [17].

Numerous studies have showed the antioxidant activity of OA, and earlier research has found that OA shields the gut from damages caused by a high-fat diet. However, the chemical mechanism underlying in the OA protective effect was unknown. After the researcher separated OA by polarity and molecular weight, it compared the antioxidant activity of each constituent. RA was shown to be the most beneficial compound in OA after high performance liquid chromatography (HPLC) analysis of the components with the highest antioxidant activity [18]. The major ingredient in OA is RA. OA contains about 5.3 percent w/w RA, according to researchers. Furthermore, when compared to other plants that contain RA, OA is considered having the highest quantity of RA [19].

3. ROSMARINIC ACID FOR WOUND HEALING

The skin, which is known as the protective shield of the body from the external environment, skin is always exposed to potential injuries and hence, wound healing is an important process for the survival of humans [20]. Skin wound may cause severe problems to human like microbial infections depending on the severity of the wound. Damaged skins such as scratches, cuts and burns have to be treated and healed the soonest possible to avoid infections [21]. An efficient and correct wound healing process will aid in the restoration of the wounded tissue's structure and function. A normal wound healing process in the human body has to go through four phases to heal a wound successfully. The first phase will be homeostasis, inflammation, proliferation and remodeling. All these four phases have to occur at a specific time in the proper sequence and continue for a specific duration at an optimal intensity [22].

RA is well-known for its therapeutic properties, including antiviral, anti-inflammatory, antimutagenic, antioxidant, antibacterial and astringent properties. We performed an excisional wound model on Wistar albino female rats in a previous study to test the wound healing efficacy of RA, the primary component extracted from OA [23]. Lymphocytic density, vascular proliferation, edema development, and fibrosis were assessed histopathological, and it did grading between groups. Researchers discovered that the group given RA (120 mg/kg, 0.1 %) had a statistically significant difference from the other groups. To comprehend the processes underlying the antioxidant properties of RA, further research is required [24].

4. ROSMARINIC ACID FOR ANTI-AGING

Aging of the skin is a common process that all humans go through, and it has become visible in numerous organs, tissues, and cells. While it hid the aging symptoms of our internal organs from view, the skin is the first visible sign of the aging process. The biological process of skin aging is complex and involves both intrinsic and extrinsic factors. Extrinsic factors are typically brought on by exposure to the sun, where the progression of time brings intrinsic factors on time [25]. UV radiation causes physical alteration on the skin via multiplex pathways, resulting in the production of reactive oxygen species (ROS),

matrix metalloproteinases (MMPs), and elastase [26]. The elasticity and resistance of the skin results from these proteins. Skin ages as a result of the stimulation of elastase and collagenase enzymes by free radicals. It linked wrinkles to the breakdown of elastin and collagenase proteins [27].

RA is a strong antioxidant with the capacity to bind and stabilize free radicals. The presence of free radicals has an inhibitory influence on the amounts of RA that are absorbed through the skin of mouse abdomen. It measured the induced levels of collagenase and elastase enzymes using kits. Additionally, 1-methyl-4-phenypyridinium effects were inhibited and RA protected MES23.5 dopaminergic cells from 6-hydroxydopamine-facilitated neurotoxicity. When cells are treated with 1-methyl-4-phenylpyridinium, dopamine levels and viability changes related to apoptosis are decreased. Furthermore, 1-methyl-4-phenylpyridinium, which may be detected by suppressing mitochondrial respiratory chain complex 1-associated activity, indicates mitochondrial transmembrane collapse and the formation of ROS [28].

As a result, RA pretreatment was able to partially restore mitochondrial respiratory chain complex 1 activity while also partially reversing the other mitochondrial processing peptidase (MPP) negative effects. In mice, RA lowers oxidative stress while also increases mitochondrial effectiveness. RA was effective in delaying disease progression and reducing amyloid peptide aggregation in vitro in animal models. It also suppressed phosphorylated p38 MAPK levels generation, lipid peroxidation, DNA, and ROS generation providing neuroprotection against A-induced damage [29].

5. ACTIVATION OF PI3K/AKT/mTOR PATHWAY IN WOUND HEALING

One of the comprehensive and complex process is proliferation and migration of various cell types such as inflammatory cells, keratinocytes, fibroblasts, and platelets to restore the integrity of wound healing. Inflammation, new tissue development, and tissue remodeling are all part of this process [30]. The establishment of an epidermal barrier, which predominantly depends on keratinocyte proliferation and differentiation, has long been connected to the PI3K/Akt pathway [31]. According to a recent study, miR126 binding to its target gene PLK2 enhances keratinocyte proliferation and migration, activating the PI3K/Akt pathway and aiding skin wound healing [32]. A researcher has reported that miR26a inhibits wound healing by reducing keratinocyte migration via modulating its target gene, ITGA5. The epithelial–mesenchymal transition (EMT) has been linked to skin wound healing, and PI3K activation is thought to speed up the EMT by stimulating mTOR via Akt [33]. Another study indicated that using ozone oil speed up the activation of the PI3K/Akt/mTOR pathway, promoting EMT and improving wound healing. Soon, drugs that target the PI3K/Akt/mTOR pathways may offer new hope for skin wound healing [34].

6. HERBS OR PLANTS THAT CONTAINS ROSMARINIC ACID

6.1 *Rosmarinus officinalis* L.

Rosmarinus officinalis L. (Rosemary) is a Lamiaceae plant that is native to the Mediterranean and parts of Asia, but can also withstand cold and dry conditions. It derived the name Rosmarinus from the Latin word ros-marinus, which means "dew of the sea," because of the reason where it was supposed to survive without water and only on sea dew [35]. This plant is known as one of the most well-known antioxidant plants. Its extract is presently the sole natural antioxidant permitted in the EU (Directive 95/2/EC). Phenolic

diterpenes, carnosic acid, and carnosol, as well as RA and additional hydroxycinnamic acids, such as caffeic acid and small flavonoid components, handle the antioxidant action in this plant [36].

6.2 *Origanum Vulgare*

The *Origanum Vulgare* (Oregano) from the Lamiaceae family is one of the most common and significant aromatic and therapeutic plants. Thousands of tones are used as a spice every year, and the flavor is popular all around the world. Dry oregano is used as a spice in snacks and salad dressings in the food sector, where it may provide antioxidant protection and a pleasant flavor. Its essential oil (EO) has been demonstrated in multiple studies to have antiviral, anti-inflammatory, and anticancer properties due to its high level of carvacrol and thymol [37]. Although rosemary extract is the only Lamiaceae herb extract allowed as a food antioxidant (additive) by EU legislation, oregano EO has also been recognized as a safe and powerful compound by the US Foods and Drug Administration (FDA) [38].

It has recognized oregano as one of the most promising sources to recover polyphenols and this gives out antioxidant benefits. In many studies, they have proven that the antioxidant properties highly depend on the total phenolic contents [39]. Flavonoids (such as quercetin, apigenin, luteolin, glycosides) and also the phenolic acids are the two major classes of bioactive compounds found in oregano, primarily RA. Previous study has found that the major phenolic component of oregano, with a maximum concentration of roughly 23 mg/g of plant material is RA. Among oregano plants of various origins, including Turkish, Syrian, and Spanish, the Syrian oregano exhibited the highest quantities of rosmarinic and caffeic acid, according to a study [40].

6.3 *Satureja thymbra*

Satureja thymbra (Pink savory) belongs to the Satureja genus, which contains over 200 species and can be found in sunny, dry, rocky regions in the Mediterranean, Asia, and North America. Extracts of *Satureja thymbra* contain a variety of antioxidant and pharmacologically active compounds. SARS-CoV and HSV-1 infections were both resistant to the plant's antiviral capabilities. The oxygenated monoterpene content of this plant's EO is exceptionally high. Among them, the most well-known are thymol and carvacrol. The phenolic acids and flavonoid components in *Satureja thymbra* preparations is very large in quantity [41]. The most prevalent phenolic acid is RA, which is followed by salvianolic acid A and lithospermic acid, both of which are caffeic acid derivatives. The extraction took 20 minutes at 30 °C in an ultrasonic bath, with RA accounting for 88% of the flavonoids [42].

6.4 *Melissa officinalis* L.

Melissa officinalis L. (Lemon balm) is a Lamiaceae family plant that is native to Europe, Central Asia, and Iran, but now thrives all over the world. It is used for desserts, drinks, and a few foods, as well as in traditional medicine. Its EO is used in aromatherapy and for fragrance. Because it blooms in the summer with white small flowers rich of nectar, the plant is also used to attract bees, hence the Greek name Melissa, which means "bee". We have found the antioxidant has antibacterial, anti-inflammatory, antiplatelet, anticancer, depressive, anxiolytic, hypolipidemic, and other biological properties in several studies. The major components connected to these activities are triterpenoid acids, phenolic acids, and flavonoids [43].

Ursolic and oleanolic acid, as well as their derivatives, are the most well-known triterpenoids. RA was discovered to be the most abundant phenolic acid in *Melissa officinalis L.* extracts, accounting for 1.50–6.8% of the plant's dry leaves, and it was linked to the extract's antioxidant properties. Furthermore, RA had antibacterial activity, but triterpene derivatives had very little or no antimicrobial activity. From this study, we can see that *Melissa officinalis L.* has a high content of RA concentration [44].

7. CONCLUSION

There is currently a surge of interest in rosmarinic acid and its variants. In the near future, someone will undoubtedly actively exploit rosmarinic acid and its derivatives to improve human health. RA seems to be a phytochemical that could be used in dietary supplements and pharmaceuticals. The pharmacological properties of RA and its antioxidant potential have been described in much research. RA is a health-promoting compound found in medicinal plants, herbs, and spices. Plants are thought to use RA as a preformed, constitutively accumulating defense component. Because of its high RA content, OA extract has wound healing and anti-aging capabilities. In fact, when compared to other plants in the same family, OA is believed to have the highest concentration of RA. Many research papers have demonstrated various benefits of RA that can be used in traditional folk medicine but there are very few research papers on the effect of wound healing and anti-aging. Therefore, this review paper is to mainly outline the therapeutic actions of RA in wound healing and skin regenerative. I hope that we can use this review paper as a reference for future studies.

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