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Medicinal Components and Pharmacological Effects of *Rosa rugosa*

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Abstract: *Rosa rugosa* is a widespread ornamental plant and generally utilized for food and medicinal purposes. The previous studies focused on the potent ingredients extracted from *R. rugosa*, such as essential oils, flavonoids, polyphenols, polysaccharides, pigments, vitamins and so on. Moreover, sufficient evidences and research data revealed that pharmacological effects of *R. rugosa* on various diseases were associated with these functional components. 19α-Hydroxyursane-type triterpenoids, such as euscaphic acid (EA) and tormentic acid (TA), are responsible for the anti-inflammatory action. Antioxidants such as flavonoids and polyphenols play a critical role against tumors and diabetes. Sesquiterpene and hydrolyzable tannins are essential for antimicrobial ability. Rosamultin reduces hepatotoxicity through enhancing the epoxide hydrolase activity. These studies suggest that *R. rugosa* has prospects of curing many diseases or assisting in traditional chemosynthetic drugs treatment.

Keywords: *Rosa rugosa* Thunb; medicines; secondary metabolites; pharmacological effects.

1. Introduction

Clinical applications of chemosynthetic drugs are important parts in modern medicine. Owing to the high difficulty and potential toxicity of synthetic pharmaceutical compounds, the utilization of natural antimicrobial, cytotoxic, as well as antiradical substances exhibits tremendous prospects for modern medicine [1]. Meanwhile, numerous clinical and medicinal studies have definitely demonstrated the importance of plant nutraceuticals for human health. These kinds of plants are usually called homologies of medicines and foods, which are not only a source of energy and nutrients, but can also antagonize a great variety of diseases, such as diabetes, cancers and cardiovascular disorders or slow down the process of aging, enhance the immune response and antibacterial function. According to the homologous catalogue of medicine and food issued by National Health and Family Planning Commission of the People's Republic of China, 101 plants including *Rosa rugosa* Thunb or animals are both used as medicines and foods.

R. rugosa, a member of Rosaceae, is indigenous to Eastern Asia. It was introduced into Europe and North America in the middle of nineteenth century, and generally utilized for food and medicinal purposes concurrently [2]. *R. rugosa* is economically important in many fields because their petals are a source of rose essential oils, which are known as "liquid gold", a particularly valuable natural raw materials, especially in perfumes, cosmetics, aromatherapy, spices, and nutrition [3]. Its petals and flower buds are commonly consumed for production of jams, teas, pies, juices and beverages. *R. rugosa* petals, hips and roots have been widely applied in China, Japan and Korea as an agent for treatment of diabetes, haemostatic, pain, anticancer, cardiovascular disorders and so on [4]. Particularly, *R. rugosa* is a widespread food in China and an extremely important drug resource

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included in the China Pharmacopeia. According to rationale of traditional Chinese medicine, *R. rugosa* can alleviate pains and reduce swelling, strengthen the spleen, relieve the depressed liver and promote the blood circulation to remove the stasis.

Research on the composition and activity of *R. rugosa* extract confirmed the great importance and potentials for medicine and human health. Many biologically active compounds have been identified in *R. rugosa*, a large proportion of them belongs to the various secondary metabolites [5], which are not directly involved in plant normal growth, development, or reproduction, but plays an extraordinarily important role in biotic and abiotic stress. In terms of human fitness, many of secondary metabolites act as potential natural antiradical, antitumor and antioxidative properties. Besides them, several minerals, vitamins and other botanicals from *R. rugosa* have been reported to elicit beneficial effects in the immune response and disease resistance [2,6,7].

In this review, we summarized the classification of the chemical substances extracted from *R. rugosa*, presented recent advances about the pharmacological effects of secondary metabolites extracted from *R. rugosa* and the metabolic regularity in the organisms.

2. Chemical Constituents

2.1. Essential Oils

Rose essential oils are the most important industrial products extracted from *R. rugosa*. As a matter of fact, the ingredients of traditional rose essential oils are extremely complex and different components form the rose fragrance.

Terpenoids are the indispensable components of rose fragrance and endow the native volatile of headspace. Rose oxides, linalool enrich the faint scent, while geraniol, citronellol, β-phenylethyl alcohol and their esters are the major headspace compounds of rose aroma. Eugenol, β-caryophyllene and other spicy ingredients are the main auxiliary components enhanced the sweetness of rose aroma [8]. The volatile monoterpene compounds such as geraniol, citronellol, nerol and their acetate esters are the foremost compounds of the traditional rose volatile oils, and their mass fraction account for over half of the total ingredients in the volatile oils. Other esters, alkanes, aldehydes, ketones and few other volatile ingredients compose the other parts of essential oils. [9].

In addition, the hemiterpenes, 2-methylbutan-2-ol and 3-methylbutan-l-ol were detected in trace amounts in the essential oil from the flowers and in the headspace of floral green parts, respectively, whereas 6-methyl-hept-5-en-2-one was mainly identified from the pollen, implying the composition differences between different organs of *R. rugosa* [10,11]. Furthermore, the essential oils constituents and contents are distinctly different during the several developmental stages. The main aroma constituents such as γ-muurolene, α-himachalene and α-pinene, format at the early opening stage, and most of them reach maximum concentration between half to full opening stage [12]. In Bulgaria, France, Turkey, Morocco, and other European countries, rose essential oil is principally extracted from the flowers of *Rosa damascena*, which has been introduced into China recently. Compared with the traditional Chinese rose, however, they display differences in the floral major headspace compounds, indicating that essential oils from flowers of different varieties and origins exhibit large differences in their composition and component [13,14]. Generally speaking, the aroma constituents and contents were obviously distinct at different development stages and organs, varieties and origins result in the imparities as well, which are the main considerations when choosing the raw materials of rose essential oils.

2.2 . Flavonoids

Flavonoids are currently widely studied because of their nutraceuticals and health benefits [15]. Recent research showed that some *R. rugosa* galenic chemical preparations, particularly those extracted from flowers and leaves, are also capable of providing large doses of flavonoids [16, 17].

The total flavonoid contents of *R. rugosa* vary from 1.37 to 7.21 mg RE/g (milligrams of rutin equivalents per gram of dry weight) with different phases of in vitro digestion [18]. However,

constituents of flavonoids extracted from *R. rugosa* are diverse in different parts of *R. rugosa*. Immature fruits of *R. rugosa* contain high amounts of quercetin and quercetin 3-*O*-β-glucoside (isoquercitrin), kaempferol and kaempferol 3-*O*-fl-glucoside, while rutin (quercetin 3-*O*-β-rutinoside) is the major flavonoid in the roots. Furthermore, more flavonoids, such as apigenin, tiliroside, apigenin-7-*O*-glucoside, kaempferol-3-*O*-rutinoside, kaempferol and related ester compounds have been also detected in leaves of *R. rugosa* by using spectrophotometric methods [19]. Among them, the simple flavonoids, apigenin and 7-*O*-methylkaempferol have been isolated as minor components [20].

2.3. Polyphenols

Polyphenols are the most generally studied group of secondary metabolites in various amounts in vegetables, fruits, cereals and beverages of plant origin [21]. All polyphenols have been characterized by the distinctive one or several phenolic groups, capable of reducing reactive oxygen species and other organic substrates and minerals. These redox properties are the origin of their commonly documented functions in the prevention of several chronic diseases such as cancers, diabetes, osteoporosis and cardiovascular diseases, which are associated with oxidative stress [22]. Therefore, polyphenols are the most available antioxidants in the diet and it is necessary to guarantee enough ingestion of polyphenols [23].

In the majority situations, rose was regarded as an abundant source of phenolic compounds. Phenolic constituents exist in both aerial and underground parts of *R. rugosa* and phenol content of ethanolic extracts from different organs ranged from 12.75 to 13.9 mg/mL (of gallic acid equivalents). The roots are rich in condensed tannins and catechin derivatives, but the aerial parts teem with more kinds of polyphenols. For example, 2-phenoxychromones and apigenin were found in exudate from the glandular trichomes of leaves [24]. By high performance liquid chromatography with the combination diode array detection and electrochemical detection, four more phenolic acids including ferulic acid, caffeic acid, *p*-coumaric and chlorogenic acid in dried flowers have been found [25]. Particularly notable, the amounts of phenols extracted from nut and flower tea was observed obviously decreased, ranging from 0.14 mg/mL to 1.52 mg/mL, respectively, which indicated flower tea might not be an appropriate utilization to get polyphenols than fresh flower [5].

2.4. Polysaccharides

Polysaccharides were shown to have significant synergistic effects which accounted for the antitumor activity and immunity enhancement [26-28]. It has been reported the widespread existence of polysaccharides in *R. rugosa*, particularly in the extract from pollen. Soluble polysaccharide, with the same as polysaccharide-peptides complexes, are the foremost components of polysaccharides extracted from *R. rugosa*. [29-31]. According to Wang's results, WRPP (for Water-soluble bee Pollen Polysaccharides from *R. rugosa*) were extracted and fractionated, and were purified to three types with DEAE-Cellulose, acidic polysaccharides (WRPP-1, WRPP-2) and neutral (WRPP-N). WRPP-1 primarily consisted of arabinose (53.9%), galactose (24.7%), galacturonic acid (12.4%) and rhamnose (3.0%), and contained a large proportion of arabinogalactan. WRPP-2 consisted of arabinose (48.7%), galacturonic acid (23.0%), galactose (15%) and rhamnose (7.8%), whereas WRPP-2 contained more galacturonic acid compared to WRPP-1. WRPP-N were mainly composed of galactose, mannose, glucose and arabinose, and mannoglucan, arabinogalactan and glucan were also detected [32].

2.5. Pigments and Others

Regarded as a common ornamental flower, *R. rugosa* is widely cultured on account of its abundant color and the various natural pigments in plants. Natural pigments are not only a kind of raw materials in industrial production and food processing, they act as antioxidant, antimicrobial and anti-inflammation as well mainly due to scavenging the radical groups mentioned above [33]. Pigments can be classified into pyrroles and their derivatives, polyenes, phenols, quinones and ketones according to the molecular structures. The main pigments extracted from flowers of *R. rugosa* are anthocyanin derivatives, which are phenolic compound accounted for the red colour of the flower. In addition, carotenoids such as phytoene and phytofluene, were identified in *R. rugosa* as well [34].

Together with the categories of different functional organics mentioned above, amino acids, vitamins, unsaturated fatty acids, microelements and dietary fibers are also available from *R. rugosa* [5,35,36].

3. Pharmacological Functions

3.1. Antioxidant Capacity

R. rugosa has been used for medicine purpose on account of the rich source of biologically active compounds, possessing antioxidant activity. The antioxidant abilities of *R. rugosa* were revealed not only in vitro, but also in cellular level and in vivo.

Tinctures and teas from different rose organs were analyzed for their antioxidant properties. Notable antioxidant potential (0.26 to 4.25 mmol Trolox/g) and reducing power (1092.04 to 9258.70 mmol Fe^{2+}/g) were revealed [37]. Free radical scavenging activities (FRSA) of the extraction from flowers of *R. rugosa* at different developmental stages on 1,1-diphenyl-2-picrylhydrazyl (DPPH), hydroxyl free radicals and superoxide were investigated. FRSA ranged from 40.2% to 73.5% for DPPH, from 14.3% to 32.2% for hydroxyl, and from 78.0% to 84.6% for superoxide.

Two antioxidant components, a polysaccharide-peptide complex and a kind of condensed tannin, extracted from *R. rugosa*, were incubated with mouse erythrocytes respectively to investigate their influence on erythrocyte catalase (CAT) and superoxide dismutase (SOD) activity. The result indicated that the activities of CAT and Zn-SOD were obviously increased after incubation for 3 hours with the rose flower extract, meanwhile, gene expression of SOD and CAT were also enhanced in the erythrocytes [38].

The effects of rose extract on antioxidant enzymes in senescence-accelerated mice (SAM mice) was also studied, the results showed that 9-month-old SAM mice were the most suitable objectives for the treatment because of the lower activities of glutathione peroxidase (GPx) and catalase (CAT) than those indices in 6-month-old SAM mice. The activities of GPx and CAT remarkably increased in whole blood and liver in the mice treated with rose extract. The gene expression level of GPx and CAT was up-regulated in the liver at the same time, nevertheless, malondialdehyde content in liver and brain reduced. Consequently, the longest life spans of SAM mice were longer than control after rose extract treatment [39].

3.2 . Anti-inflammatory Effects

The roots of *R. rugosa* have been widely used to treat chronic inflammatory disease in Eastern Asia. To clarify the principle, the MeOH extract was fractionated to isolate the anti-inflammatory substances from the roots of *R. rugosa*. From the active EtOAc fraction hydrolyzed in alkaline solution, euscaphic acid (2α,3β,19α-trihydroxyurs-28-oic acid) along with tormentic acid (2α,3α,19α-trihydroxyurs-28-oic acid), were isolated by column chromatography. Both anti-inflammatory extracts were tested for antiphlogistic abilities in a carrageenan-induced paw edema model in mice and rats. The anti-inflammatory effects indicated that the 19α-hydroxyursane-type triterpenoids, such as euscaphic acid (EA) and tormentic acid (TA), are responsible for the anti-inflammatory action of *R. rugosa* roots [40].

Further research suggested that the production of prostaglandin E2 (PGE2), nitric oxide (NO), interleukin-1β (IL-1β) and tumor necrosis factor- (TNF-), induced by lipopolysaccharide (LPS) in RAW 264.7 macrophages, was dose-dependently reduced by euscaphic acid (EA). The expression levels of related genes and IL-1β mRNA were inhibited by EA in accordance with the physiological data. In addition, EA interfered with the LPS-induced clustering of TNF receptor-associated factor 6 (TRAF6) with interleukin receptor associated kinase 1 (IRAK1) and transforming growth factor-β-activated kinase 1 (TAK1). Moreover, EA attenuated LPS-induced DNA binding and transcriptional activity of nuclear factor-kappa B (NF-κB), which was accompanied by a parallel reduction of degradation and phosphorylation of inhibitory kappa B (IκB) and consequently by decreased nuclear translocation of p65 subunit of NF-κB. In general, EA inhibits LPS-induced inflammatory responses mainly through the interference with the clustering of TRAF6 with IRAK1 and TAK1, resulting in

blocking the activation of IKK and MAPKs signal transduction to downregulate NF-κB activations [41].

Tormentic acid (TA), another 19α-hydroxyursane-type triterpenoid, similarly inhibited LPS-induced iNOS, COX-2, and TNF-α expression through inactivation of the NF-κB pathway in RAW 264.7 macrophages [42, 43]. Another research demonstrated that TA, remarkably decreased the IL-1β-stimulated expression of matrix metalloproteinase-3 (MMP-3). TA also inhibited the IL-1β-induced expression of derivable cyclooxygenase-2 (COX-2) nitric oxide (NO) synthase (iNOS), the production of prostaglandin E2 (PGE2) and NO in human OA chondrocytes reduced as well. It was originally demonstrated that TA possessed the ability to fight against inflammation in human OA chondrocytes. TA significantly suppresses the NF-κB signaling pathway to reduce the inflammatory response induced by IL-1β. Thus, *R. rugosa*, may be a potential galenic preparation in the treatment of OA because of the biologically active TA [44].

3.3. Anti-tumor Effects

Research on the anti-tumor effects about *Rosa rugosa* focused on the antioxidant and cytotoxicity. Radicals, more commonly known as reactive oxygen species (ROS) and mainly consisting of superoxide anion radical (O_2^-), hydrogen peroxide(H_2O_2), singlet oxygen and the highly reactive hydroxyl radicals, are well known for playing a double role as both beneficial and deleterious species [45]. The accumulation of ROS through either exogenous or endogenous injury generally existed for different types of cancer cells, which are related with altered redox regulation of cellular signaling pathways. Oxidative stress destroys the cellular redox balance in normal cells for oncogenic stimulation, induces the DNA mutation, an identified predominant step in carcinogenesis and enhancement of oxidative DNA lesions, such as 8-hydroxyguanine (8-OH-G). DNA lesions have been noted in various tumors and strongly implicating the damage in the etiology of cancer [46].

Secondary metabolites extracted from *R. rugosa*, such as flavonoids and polyphenols, have been demonstrated with potential anti-proliferative and cytotoxic activity. For example, the growth of ovarian and lung (A549) cancer line was significantly suppressed after been exposed to galenic preparations obtained from *R. rugosa*. Furthermore, preliminary anti-tumor activity analysis of flower-tea against breast and cervical cancer line has been conducted, showing viability decrease by 25% and 50%, respectively [5]. Another kind of flavonoid extracted from *R. rugosa*, along with its derivatives, were found dose-dependently cytotoxic towards breast cancer MCF-7 cell lines but nontoxic to normal NIH3T3 cell lines. Molecular mechanism implied that it may interacted with active site pocket of 1M17, a kind of tyrosine kinase epidermal growth factor receptor (EGFR), almost 90% of tumors found EGFR over-expressed [47].

P300 and CBP (CREB-binding protein) are two most important high molecular weight protein histone acetyltransferases (HAT). P300 and CBP are highly homologous, so normally they are all called P300/CBP together [48]. P300/CBP is involved the activation of many kinds of transcription factors and has the confirmed relationship with many human diseases, including diabetes, inflammation, heart diseases and especially cancers [49, 50].

Rosa rugosa methanol extract (RRME) has been shown as an effective histone acetyltransferase (HAT) inhibitor by reducing androgen receptor (AR) and histone acetylation, resulted in AR-mediated transcription decrease and ultimately reduced the growth of a human prostate cancer cell line (LNCaP). In the literature, RRME inhibited both CBP (CREB-binding protein) and P300 activity, mediated agonist-dependent AR activation and suppressed antagonist-dependent inhibition. Transcription of genes regulated by AR was also decreased with RRME treatment [4].

Heterocyclic amines (HCAs), occurred in meat and meat products at high temperatures, have been identified as potent carcinogens and a causative factor for human cancer. Therefore, the effect of *Rosa rugosa* tea extract (RTE), which is rich in phenolic compounds and antioxidants, on the formation of HCAs during cooking was assayed. The total HCAs obviously decreased by 75% at 160 °C and 46% at 220 °C with the treatment of RTE, respectively, proposing a novel aspect of rose anti-tumor effects [51].

3.4. Anti-diabetic Activity

Diabetes mellitus, a chronic disease widely distributed, leads to multiple complications and is one of the supreme causes of morbidity in human populations [52]. Medicinal plants including *R. rugosa* have been widely used as rich sources of potential therapeutic agents for diabetes. Roots extract of *R. rugosa* contains 13 triterpenoid saponins, whose functions are known as various diseases inhibitors. Marvelously, the *n*-BuOH fraction showed potent rat intestinal sucrase inhibitory activity, with inhibition value of 50.96 % to 87.62 % relative to the acarbose control at different concentration. Most of other compounds in the root extract exhibited similar attractive sucrase inhibitory activity, with the inhibition values ranging from 13.26% to 46.80% at the same doses. The result illustrated *R. rugosa* as a significantly new sucrose inhibitor, may be effective for the new therapies for the diabetes mellitus treatments [53].

It was also confirmed that the effects of *R. rugosa* on the diabetes were related with oxidative stress. The oral administration of *R. rugosa* at different doses attenuated the abnormal physiological changes in rats with streptozotocin (STZ)-induced diabetes. Diabetic rats had higher serum levels of superoxide and nitrite/nitrate. However, the ingestion of *R. rugosa* reduced the over-production of radicals associated with diabetes, thiobarbituric acid-reactive substance levels in serum, hepatic and renal mitochondria, suggesting *R. rugosa* is an effective radical scavenger and would alleviate the oxidative stress associated with diabetes by inhibiting lipid peroxidation [54]. In another related research, the significant of the function with the treatment of *R, rugosa* polyphenols enriched extract (RPE) was revealed. In vitro, PRE inhibited α-glucosidase and exhibited antioxidant activity in livers of diabetic rats. In addition, the extract decreased the fasting blood glucose, improved various indexes related to insulin sensitivity and blood lipid profile. The hexokinase activity and glycogen synthesis raised together with the increased insulin signal activity, such as p-IR, p-IRS, p-GSK-3β and p-AKT. These results suggest that *R. rugosa* reduced blood glucose in diabetic rats by improvement of insulin sensitivity and the effect is associated with the inhibition of oxidative stress and α-glucosidase [55].

3.5. Antimicrobial Activity

In 1989, an antimicrobial sesquiterpene was isolated from bleeding sap composition of damaged leaves of *R. rugosa* [56]. Antimicrobial activities of *R. rugosa* petals are effective against the pathogenic and intestinal bacteria, and the selective ability was similar with the capacity of prebiotics. In addition, hydrolyzable tannins played an essential role in the antimicrobial ability according to the research [57]. *R. rugosa* galenic preparations showed positive effects against both Gram-positive and Gram-negative bacteria. Remarkably, tinctures exerted superior antimicrobial abilities than those of infusions and samples from different parts revealed the existing differences in antibacterial properties [5].

3.6. Other Effects

Rosamultin, the main compound from distillation of *R. rugosa*, may reduce hepatotoxicity induced by bromobenzene partly through enhancing the epoxide hydrolase activity, and antioxidant properties of the extract may account for the alleviation [58].

The antihypertensive ability of the flowers of *R. rugosa* had also been reported. Evidences illustrated that both ethanolic (RE95) extract and water (RW) extract showed the ability of activity inhibiting of Angiotensin I Converting Enzyme (ACE). Nevertheless, RW extract exhibited inferior inhibition activities than RE95 extract. Additionally, the antihypertensive effect of the extracts was also observed by oral treatment in naturally hypertensive rats as well [59].

In addition, *Rosa rugosa* can alleviate endurance exercise-induced stress by decreasing oxidative stress levels, turning against the 5-hydroxytryptamine 6 (5-HT6) receptor and resulting the suppression of cAMP activity [36].

3. Concluding remarks

This review summarized the different kinds of biologically active compounds contained in *R. rugosa*. Among them, various secondary metabolites played a critical role in its functions as antioxidants and chemical messengers. The secondary metabolites and other functional components extracted from *R. rugosa* endowed this ornamental plant the abilities to maintain physical well-being and antagonize a great variety of diseases. Additionally, with the development of modern medicine, pharmacological effects of these constituents have been revealed gradually. It means that *R. rugosa* is a potential source of beneficial substances, and required been well known, fully appreciated and efficiently utilized.

Conflict of interest

The author(s) confirm that this article content has no conflict of interest.

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