Research Journal of Pharmacognosy (RJP) 1(3), 2014: 47-54
Received: Nov 2013
Accepted: Jan 2014

Review article

An overview on phytochemical and pharmacological properties of *Rhus coriaria* L.

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Abstract

Rhus coriaria L. is known as Sumac. *R. coriaria* extracts are important in drug development with numerous pharmacological reputations in the South-Eastern Anatolia, Mediterranean area and Western Asia especially in Iran. Regarding the new multi-functional properties of *R. coriaria* and the related valuable ongoing reports, we were prompted to review the phytochemical and pharmacological properties of this species. The data were collected using scientific journals, books and websites such as Scopus, PubMed and Google Scholar. For a long time, *R. coriaria* has been used as a spice by grinding the dried fruits with salt, and it has also been widely used as a medicinal herb in traditional medicine for its atheroprotective effect and its ability to treat eye diseases, wounds, bowel disorders, ring worms and skin disorders. In addition, *R. coriaria* has recently shown to have hepatoprotective, anti-ischemic, antimicrobial as well as hypoglycemic and hyperlipidemic effects. Volatile substances, flavonoids, tannins and xanthones have been reported from this plant. Due to its easy collection and the remarkable biological activities, *R. coriaria* has been used both as food and medicine in some parts of the world especially Iran. This article presents comprehensive analyzed information on the botanical, chemical and pharmacological aspects of *R. coriaria.*

Keywords*:* Anacardiaceae, pharmacology, phytochemistry, *Rhus coriaria*

Introduction

Rhus coriaria commonly known as Sumac is a flowering shrub which belongs to Anacardiaceae family in the order of Sapindales that contains about 81 genera and more than 800 species. *Rhus* species are widely distributed in subtropical and temperate regions throughout the world, especially in Africa, South Eastern Anatolia, Mediterranean area and Western Asia. This genus includes approximately 250 species in the world [1]. *R. coriaria* is a shrub and a small tree that can reach to the height of 10 meters (figure 1). The leaves are spirally arranged and are usually pinnately compound, some species have trifoliate or simple leaves (figure 2). The flowers are in dense panicles or spikes 5–30 cm long, each flower is very small, greenish, creamy white or red, with five petals (figure 3). The fruits form dense clusters of reddish drupes called sumac bobs (figure 4). The dried drupes are usually ground to produce a tangy purple spice. Sumac propagates both by seed (spreading by birds and other animals through their droppings), and by new shoots from rhizomes, forming large colonial colonies [2].

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The acidic tasty fruits of *R. coriaria* are used as a condiment and sour drink in the Middle East dishes. Its sour taste is due to the citric and malic acids content of its juice [3].

The fruits are used as tonic and diuretic, and are also believed to be useful in dysentery and diarrhea. A gargle prepared from the fruits is used in catarrhal infections of the pharynx, and the paste is topically applied to ulcers and piles [4].

In folk medicine, it is used for treatment of indigestion, anorexia, hemorrhages, and hyperglycemia [5-7]. The main compounds in sumac are hydrolysable tannins and substantial amounts of flavonoids. The leaves are used as condiment and for tanning leather. The fruits are prescribed to relieve stomach diseases, bowel complaints, fever, dermatitis, as appetizer, diuretic and antiseptic [1,8,9]. *R. coriaria* berries are beneficial to prevent diabetes, obesity, paralysis and colitis [10,11]. The seeds are appetizer, astringent, diuretic, styptic and tonic; prescribed to treat dysentery, hemoptysis and conjunctivitis [12].

Since review and systemic analysis of chemistry, pharmacology and clinical properties of *R. coriaria* had not been reported before, we were prompted to provide the currently available information on local knowledge, ethno medicinal issues and pharmacologically important molecules existing in this useful plant. The aim of the present article was to introduce *R. coriaria* as a potent medicinal plant by highlighting its traditional applications as well as the recent findings for novel pharmacological and clinical applications.

Chemical composition

The commonly known phytochemical compounds from *R. coriaria* are volatile substances, flavonoids, tannins and xanthons [13-16]. Main constituents of the essential oil of the berries are terpene hydrocarbons such as α-pinene, β-caryophyllene and cembrene; oxygenated terpenes such as α-terpineol, carvacrol and β-caryophyllene alcohol as well as farnesyl acetone, hexahydrofarnesylacetone and aliphatic aldehydes [13].

Figure 1. *Rhus coriaria* (Sumac) available at: http://www.divine-journeys.com/blog/wp-content/uploads/2012/06/sumac-bush.jpg

Figure 2. *R. coriaria* leaves available at: http://davesgarden.com/guides/pf/showimage/76678

Figure 3. *R. coriaria* flowers available at: http://wildeherb.com/2010/07/06/sumac-flower-buds-and-red-berries

Figure 4. *R. coriaria* fruits available at: http://en.wikipedia.org/wiki/Sumac

Some xanthones which have been isolated from seeds are characterized as 2,3-dihydroxy-7-methyl xanthone, 2,3,6-trihydroxy-7-hydroxymethylene xanthone-1-carboxylic acid and 2- methoxy- 4- hydroxy-7- methyl-3-*O*-beta-D-glucopyranosyl xanthone-1,8-dicarboxylic acid, beta-sitosterol-beta-D-glucoside, has also been isolated from the seeds [16].

Sumac is rich in tannins [17]. Tannins present in *R. coriaria* berries are hydrolysable, susceptible to cleavage by hydrolysis and have small molecular size. Their small size has made them to be easier to digest and absorb and have many health benefits [18].

Myricetin has been found to be the major flavonol in *R. coriaria* berries, followed by minor quantities of quercetin and kaempferol [14].

The berries of *R. coriaria* are reported to be rich in oils, fatty acids and minerals, suggesting that they could be valuable for using in foods. The oil includes oleic, linoleic, palmitic and stearic acids [19].

Three aromatic compounds have been isolated from the fruits. They have been identified as coriarianaphtyl ether, coriariaoic acid and coriarianthracenyl ester [16]. Compounds such as *n*-tetracosane, *n*- pentacosane, anise alcohol, *p*-hydroxybenzyl alcohol, methyl lawson and 2-hydroxymethylene naphtaquinone have been also identified as aromatic compounds in sumac fruits [16]. Also, myrtillin, delphidin and crysanthemin have been characterized as the main anthocyanins in the fruits [20].

Biological properties

Antimicrobial effects

In recent years, an explosive spread of multiple drug resistance bacterial pathogens has become a serious concern worldwide in terms of public health and economic issues.

The majority of the antimicrobial studies on sumac have focused specifically on the fruits because of their widespread use in the Mediterranean and Middle East as a dried spice. All of the studies have used either ethanol or water based extracts [1]. Ethanol extracts of the ripe and unripe fruits of the plant have exhibited a broad range of antimicrobial activity by inhibiting the growth of Gram positive and Gram negative species such as *Bacillus cereus, Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris, Pseudomonas aeruginosa, Shigella dysentariae, Staphylococcus aureus, S. epidermidis, Streptococcus pyogenes, Enterococcus faecalis,* and *Yersinia enterocolitica* [21]. The observed antimicrobial activity has been ascribed to the tannins in the ethanol extracts, with MICs in the range of 10 to 26 mg/mL depending on the bacterial species. Ripe fruits were also found to have a significant higher antimicrobial activity compared to unripe fruits. Dried seeds have shown antibacterial effect against *Pseudomonas aeruginosa* [22]. The antibacterial activity of *R. coriaria* leaf methanol extract has been also shown against Gram-positive and Gram-negative bacteria along with antimycotic activity against some *Candida* species [23].

Xanthones and aromatic components isolated from the seeds have been active against *Candida albicans* and *Aspergillus flavus* [16].

Protective properties

The aqueous extract of *R. coriaria* fruit (75 µg/mL) and also gallic acid (100 µM) as one of its main components have shown protective effects against oxidative stress toxicity induced by cumene hydroperoxide (CHP) in isolated rat

hepatocytes. Both the extract and gallic acid have significantly protected the hepatocytes against oxidative stress markers including cell lysis, lipid peroxidation, glutathione depletion, mitochondrial membrane potential decrease, lysosomal membrane oxidative damage and cellular proteolysis. Aqueous extract of the plant have been more effective than gallic acid in protecting hepatocytes against CHP induced lipid peroxidation. Gallic acid has been more effective than the aqueous extract of *R. coriaria* in preventing hepatocyte membrane lysis. In addition, H_2O_2 scavenging effect of the extract has been determined in hepatocytes and compared with gallic acid but gallic acid has been more effective than the aqueous extract of the plant at H_2O_2 scavenging activity [24].

R. coriaria has shown DNA-protective effects in human and animals. Prevention of the formation of strand breaks and oxidized DNA bases as well as the protection against H_2O_2 and benzo [a] pyrene-7,8-dihydro-diol-9,10-epoxide (BPDE)-induced DNA-damage has been demonstrated in human lymphocytes with ethanol extract of *R. coriaria* (3.0 g/day, 3 days) in single cell gel electrophoresis assays. Furthermore, DNA-protective effects of the plant have been monitored in different inner organs of rats in identical conditions. No alteration of DNA-migration has been detectable in human lymphocytes in standard conditions, but a decrease of the tail-lengths due to formation of oxidized purines and pyrimidines has been found with lesion-specific enzymes. Also damage caused by H_2O_2 and BPDE was significantly reduced by 30% and 69%, respectively. The later effect may be due to induction of glutathione S-transferase (GST). After the intervention, the overall GST activity in plasma was increased by 40%, GST-alpha by 52% and GST-pi by 26% (ELISA). The antioxidant effects of the extract were probably due to scavenging which has been observed in *in vitro* experiments, which also indicated that gallic acid could be the active principle of *R. coriaria*. The animal experiments have shown that *R. coriaria* also has caused protection in inner organs. Supplementation of the drinking water (0.02 g/kg per animal) has decreased the formation of oxidized DNA bases in colon, liver, lung and lymphocytes; also after gamma-irradiation pronounced effects have been obsereved [25].

Cardioprotective activity of hydrolysable gallotannins from the leaves extract has been reported in isolated rabbit hearts. The leaves have induced a dose-dependent normalization of coronary perfusion pressure, reducing left ventricular contracture during ischemia, and improving left ventricular developed pressure and the maximum rate of rise and fall of left ventricular pressure at reperfusion. Creatinine kinase and lactate dehydrogenase outflow have been significantly reduced during reperfusion. In parallel, there has been a rise in the release of the cytoprotective 6-ketoprostaglandin F and a decrease of tumor necrosis factor-alpha (TNF-alpha), both significant only at dose of 150-500 µg/mL. The vasorelaxant activity of *R. coriaria* leaves extract was studied in isolated rabbit aorta rings precontracted with norepinephrine with and without endothelium. *R. coriaria* leaves extract has been able to modulate the coronary endothelium cyclooxygenase (COX) pathway. The antioxidant activity of the leaves extract, investigated in the 1,1-diphenyl-2-picrylhydrazyl (DPPH) model and in living cell systems (rat erythrocytes), has been stronger than that of gallic acid, ascorbic acid and trolox. The structures of the leaves main bioactive constituents have comprised a mixture of polygalloylated D-glucopyranose with different degrees of galloylation and 3-*O*-methylgallic acid. The cardiovascular protective effect of the plant leaves extract has seemed to be due to interplay of different factors: COX pathway modulation, TNF-alpha inhibition, endothelial nitric oxide synthase (eNOS) activation, and free radical scavenging [15].

Antihyperglycemic activity

Results of the recent studies have clearly indicated that the methanol extract of the fruits

have potential hypoglycemic activity [10]. The crude extract has been further fractionated and the ethyl acetate extract has exhibited significant hypoglycemic activity through α-amylase inhibition (87% inhibition at 50 μg/mL), compared to the *n*-hexane fraction (77% inhibition at 250 μg/mL). The higher biological activity of the ethyl acetate extract has been attributed to the presence of flavonoids as tentatively identified by thin-layer chromatography [1,10].

Antioxidant activity

Developing safe, new and naturally derived antioxidants for food and health applications is a major goal in sustainable bio-products. Synthetic antioxidants such as butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) are widely used in spite of concerns regarding their toxicity and a sustainable supply [26]. An antioxidant is defined as 'any substance that, when present at low concentrations compared to those of an oxidizable substrate, significantly delays or prevents oxidation of that substrate' [27,29]. Antioxidants are of interest to biologists and clinicians because they help to protect the human body against damages induced by reactive free radicals generated in atherosclerosis, ischemic heart disease, cancer, Alzheimer's disease, Parkinson's disease and even in the aging process [30,31]. There are many evidences that natural products and their derivatives have efficient anti-oxidative characteristics, consequently linked to anti-cancer, hypolipidemic, anti-aging and anti-inflammatory activities [27-33].

Anti-oxidative capacity of *R. coriaria* fruits has been evaluated by determining their effects using free radical-generating systems *in vitro*. The IC_{50} value of the extracts for lipid peroxidation inhibition has been estimated as 1200 μg/mL in the Fe^{+2}-ascorbate system while those for superoxide-scavenging activity in the xanthine-xanthine oxidase method and hydroxyl radical scavenging activity in the deoxyribose decomposition method were 282.92 μg/mL and 3850 μg/mL, respectively. These data suggest that the methanol extracts of the fruits have considerable antioxidant activity against free radicals and lipid peroxidation *in vitro* [34].

Other work about stabilizing food products with sumac extracts includes the use of a methanol extract of the fruits tested in sunflower oil stored at 70 °C by measuring peroxide values in regular intervals [35] and sumac extract have been found to be very effective in stabilizing the sunflower oil.

Antioxidant properties for stabilizing peanut oil have been also reported for the methanol extracts of *R. coriaria* fruits and leaves [36]. Fruit extract addition to peanut oil from 1 to 5% (w/v) has inhibited the formation of hydroperoxide during the initial 7 day after addition [36], but at 28 days of storage, the antioxidant potential of sumac extract has substantially lowered compared to BHA controls.

Anti-ischemic activity and endothelium-dependent vasorelaxant effect

Atherosclerosis of the coronary arteries evokes the most serious clinical manifestations of this disease, including unstable angina, acute myocardial infarction, and sudden death. Atherosclerosis is characterized by endothelial dysfunction, vascular inflammation, and the buildup of lipids, cholesterol, calcium, and cellular debris within the vessel walls. The release of cytokines and growth factors from activated platelets and macrophages at the lesion sites culminates in the heightened migratory activity of vascular smooth muscle cells (VSMCs) [37]. Any strategy to inhibit VSMC migration would benefit the treatment of atherosclerosis. Tannin and its derivatives are strong antioxidants and it is known that antioxidants can inhibit mechanisms leading to VSMC migration [38,39]. *R. coriaria* fruits as a rich source of tannin have been able to inhibit VSMC migration. Pure tannins extracted from the fruits have reduced VSMC migration at an optimal dosage by 62%. Tannins present in this plant are hydrolysable and therefore may be

easier to digest and absorb and they can increase nitric oxide, thereby reducing the process of atherosclerosis [37].

Conclusion

The objective of the present work was to show the recent advances in the exploration of *R. coriaria* in phytotherapy and to illustrate its potential as a therapeutic agent. With the current information, it is evident that the species possesses pharmacological functions including antibacterial, antifungal, antioxidant and hypoglycemic activities. It could be suggested that flavonoids, aromatic components and xanthones might be useful in the development of new drugs to treat various diseases. Besides, the present results suggest a possibility that these compounds can be further developed as a potential disease-curing remedy. It must be kept in mind that clinicians should remain cautious until more definitive studies demonstrate the safety, quality and efficacy of *R. coriaria*. For these reasons, extensive pharmacological and chemical experiments, together with human metabolism studies will be a focus for future researches. Last but not the least, this article emphasizes the potential of *R. coriaria* to be employed in new therapeutic drugs and provide the basis for future research on the application of medicinal plants.

Acknowledgments

This study is the outcome of an in-house study and has not been supported financially.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the content of the paper.

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