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AN OVERVIEW OF THERAPEUTIC POTENTIALS OF *ROSA CANINA*: A TRADITIONALLY VALUABLE HERB

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Abstract – Rosa canina L. *(*Rosacea *family) is an ornamental plant with erect prickly shrub and fragrant pink or white flowers, grown for decorative purposes in gardens and landscape designs projects. It is native to Europe, northwest Africa, and western Asia. Its fruits are extensively used worldwide in food preparation. It is traditionally proposed as a dietary supplement and herbal remedy for the prevention and treatment of different human diseases. This review aimed to investigate the pharmacological and therapeutic properties of* R. canina *in traditional medicine and scientific papers. Results from numerous studies indicated that this plant owned many biological potencies, including anti-inflammatory, anti-tumor, immunomodulatory, anti-microbial, anti-oxidant, pain reduction, anti-diabetic, anti-hyperlipidemic, neuroprotective, genoprotective, anti-obesity, skin-whitening, and anti-biotic resistance reversal activity as well as exerting a positive influence on the osteoarthritis, anxiety, depression, recognition memory, urinary and reproductive systems disorders, and neutrophil respiratory burst. Nevertheless, the exact mechanism of action for these properties is not fully recognized. Due to the lack of toxicity and side effects, this plant has been considered as a valuable complementary drug for various diseases. Further clinical trials are needed to confirm the reported promising experimental effects in clinical use.*

KEYWORDS: Rosa canina*, Anti-oxidant, Anti-cancer, Anti-diabetes, Osteoarthritis.*

INTRODUCTION

Herbal medicine has a long history in the treatment of several types of diseases. Many of the traditional remedies described by oriental scientists are still used by herbalists[1]. Herbs are also used in Iranian traditional medicine[2]. Today, several studies have demonstrated the relationship between plant's consumption and human health, and many epidemiological and clinical tests have confirmed the relationship between diet and health. These findings raise the global interest towards introducing new nutraceuticals and functional foods, which have the health benefit and the therapeutic effect on numerous diseases[3].

Among various medicinal plants, *Rosa canina L.* (*R. canina*, Nastaran or Nasrin in Persian) with reach historical background, revealed a wide spectrum of pharmacological potential. This plant owned many biological potencies, including anti-inflammatory, anti-tumor, immunomodulatory, anti-microbial, anti-oxidant, pain reduction, anti-diabetic, anti-hyperlipidemic, neuroprotective, genoprotective, anti-obesity, skin-whitening, and anti-biotic resistance reversal activity as well as exerting a positive influence on the osteoarthritis, anxiety, depression, recognition memory, urinary and reproductive systems disorders, and neutrophil respiratory burst.

BOTANICAL CHARACTERISTIC

The genus Rosa (from *Rosaceae* family) includes about 200 species and 20,000 widely cultivars, dis-

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Fig. 1. *A,* Flowers and (*B*) pseudocarps or false fruits R. canina (rosehips)[6].

tributed in some parts of the world, especially in the temperate and subtropical regions of the northern hemisphere. Biological phenomena in reproductive biology, inadequate morphological and anatomical characters to discriminate between species and the human impact by rose breeding have made it a very diverse genus. Conventionally, it is divided into four subgenera (Hulthemia Focke, Platyrhodon Rehder, Hesperhodos Cockerell, and Rosa). Rosa's subgenus comprises more than 95% of all species and is subdivided into ten sections[4].

R. canina, also referred to as the dog rose, is the most familiar Rosa species. It is an ornamental plant with erect prickly shrub (1–3 m high) and fragrant pink or white flowers, grown for decorative purposes in gardens and landscape designs projects (Figure 1 a). Its branches are often curved or arched, and fruits ripen late[5]. It produces pseudocarps or false fruits, which have one seed covered with achenes and surrounded by a fleshy outer layer (Figure 1 b).

CHEMICAL COMPOSITION

The phytochemical profile and biological potential of *R. canina* are extensively investigated. The Rosa canina fruits (RCFs) are the valuable source of phytonutrients, sugars, organic acids, pectins, flavonoids, tannins, carotenoids (β-carotene, lycopene, and isomeres of rubixanthin), vitamins (especially ascorbic acid, and also vitamins B1, B2, K, PP, D, and E), fatty acids (linoleic, oleic, linolenic, palmitic, stearic and arachidonic acid), macro- and microelements[7]. Structures of common phytochemicals in *R. canina* are shown in Figure 2. Pectins, polymers of neutral sugars, recently have been investigated for the development of medicines and health products. The results of studies about the bioactivity of pectic polysaccharides (pectins) indicated their various pharmacological applications, such as its immunoregulatory, anti-inflammatory, hypoglycemic, anti-bacterial, anti-oxidant and anti-tumor activities. They also improve the drug-delivery systems[8]. Flavonoids present a great diversity of biological and pharmaeutical activities[9]. Tannins, the major bioactive components of the fruits, have anti-cancer, anti-diabetic, anti-microbial, anti-inflammatory, and immune-regulating activities. They also have a protective effect on organs/tissues from damages induced by chemicals, stresses, and aging[10]. Carotenoids possess the capacity to scavenge DNA damaging free radicals, suppress angiogenesis, inhibit cell proliferation and induce apoptosis. There is a significant association between dietary intake and circulating levels of carotenoids and reduction in cancer risk/carcinoma[11].

RCFs are known to have the highest ascorbic acid content (30-1300 mg/100 g) among fruits and vegetables[6]. The most studied part of this herb is the fruits which is a valuable source of bioactive compounds, such as carotenoids, ascorbic acid, mineral elements, phenolics, and fatty acids. The full nutritional compositions of *R. canina* fruits (RCFs) are provided in a review by Fan et al[12].

NUTRITIONAL USES

The RCFs are extensively used worldwide in food preparation[13]. Common foodstuffs with *R. canina* fruits include juice, wine, syrups, tea, jelly, liquor, and jam, mixed with dried salmon eggs and nowadays; it is also used as an ingredient in probiotic drinks, yogurts, and soups. It is also used predominantly in the manufacture of canning[14].

TRADITIONAL USES

R. canina traditionally recommended as a dietary supplement and a natural remedy for the prevention and treatment of several human diseases[14]. The use of it as a medicinal plant dates back to the time of Hippocrates in ancient Greek. During the 2nd World War, when Britain was unable to import cit-

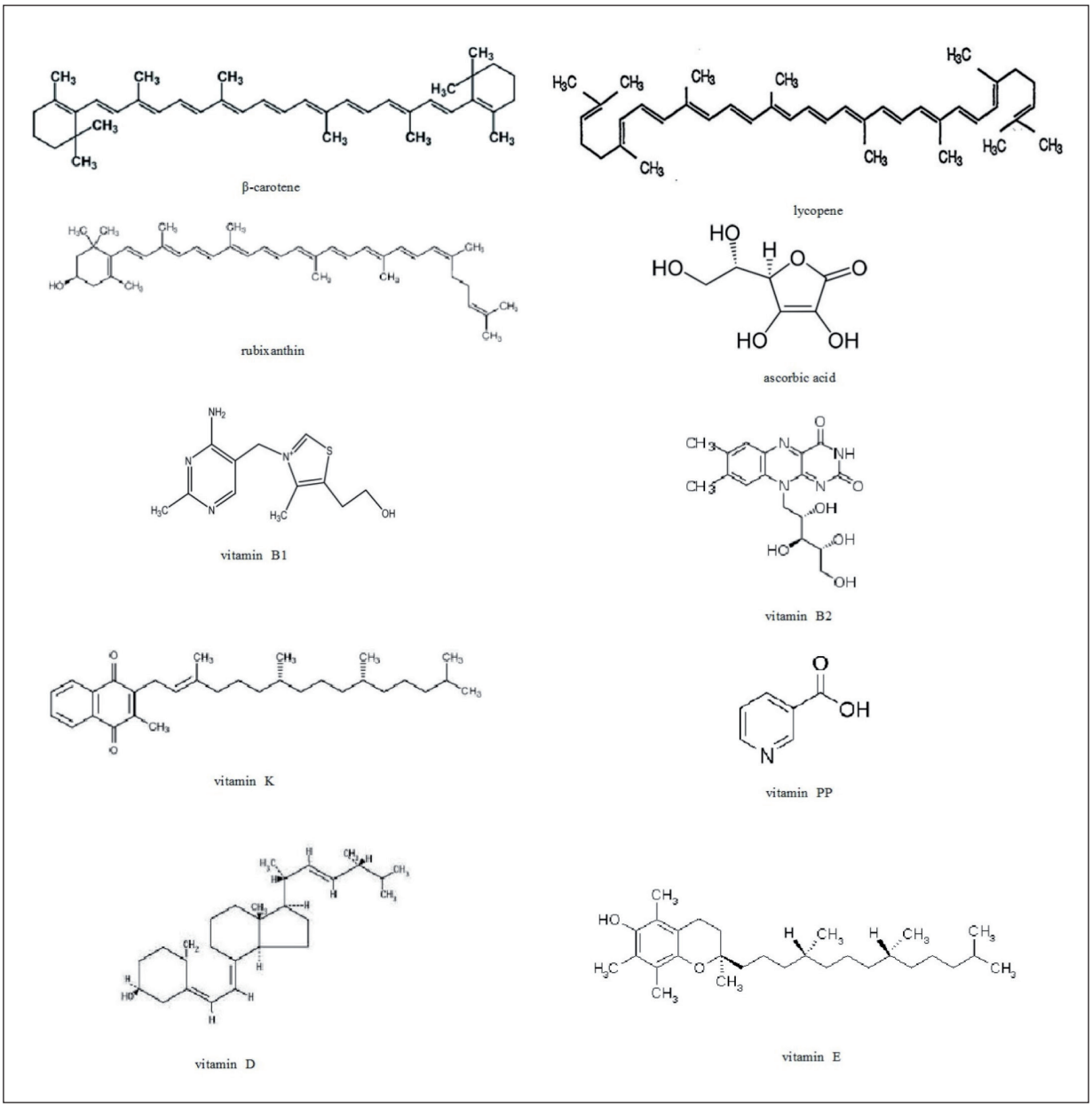


Fig. 2. Structures of common phytochemicals of *R. canina*.

rus fruits, the syrup of RCFs was added in the diet for preventing scurvy (it was rich in ascorbic acid). In traditional medicine, 2-5 g of the dried RCF is used in tea to strengthening the body´s immune system against infections. It is used in common colds, influenza, scurvy, diarrhea, gastritis, cough, vaginitis and urinary tract infections[15]. This plant also has a long history in traditional Persian medicine. In the Canon of Medicine written by Avicenna (Ibn-e-Sina), it was suggested for treating headaches and some neural and gastrointestinal diseases. Furthermore, Aghili in The Storehouse of Medicaments recommended it as a tonic for heart and brain, and for treating some hepatic disorders[16].

SCIENTIFIC RESEARCHES AND PHARMACOLOGICAL POTENTIALS

The medicinal potentials of *R. canina* have been reported by many different *in vitro* and animal models studies and also by a few human studies (Table 1). These properties have been mainly attributed to the phytochemicals of the plant.

TABLE 1. Pharmacological activities of *R. canina*.

NO.	Parts of plant	Active constituents/ preparations	Study design	Results	Refs.
Anti-microbial					
1	Aerial parts	kaempferol 3-O-(6≤-O-E-pcoumaroyl)-b-D-glucopyranoside and kaempferol 3-O-(6≤-O-Z-p-coumaroyl)-b-D-glucopyranoside	*In vitro*	Inhibition of the growth of Lactobacillus plantarum, Proteus mirabilis and Staphylococcus epidermedis	17
2	Aerial parts	Extracts in n-hexane, ethyl acetate, chloroform, acetone, water, and methanol.	*In vitro*	1. Anti-microbial effect against Staphylococcus aureus (PTCC1431), Bacillus cereus (PTCC 1015), *Bacillus subtilis Escherichia coli*, (PTCC1399) and *Candida albicans* (PTCC 5027) by the methanolic and water extract 2. Anti-bacterial activity against Escherichia coli, Staphylococcus aureus, and Candida albicans by the acetone extract 3. The chloroform and n-hexane extracts showed no inhibition activity	18
3	Flowers	Ethanolic and methanolic extracts	*In vitro*	The best anti-microbial effects of ethanolic and methanolic extracts were against Pseudomonas aeruginosa, and Escherichia coli	19
Anti-inflammatory					
4	Fruits	Dry powder from R. canina with minimal essential medium (MEM)	*In vitro* and *in vivo*	1. Inhibition of the chemotaxis and chemiluminescence of peripheral blood PMNs 2. Reducion in chemotaxis of peripheral blood PMNs 3. reduced the level of serum creatinine and acute phase protein C-reactive protein	20
5	Fruits	Galactolipid (2S)-1,2-di-O-[(9Z,12Z,15Z)-octadeca-9,12,15-trienoyl]-3-O-beta-d-galactopyranosyl glycerol	*In vitro*	Inhibition of chemotaxis of human peripheral blood neutrophils through cyclooxygenase (COX) inhibition	21,22
6	Fruits	Linoleic and alpha linolenic acids	*In vitro*	Inhibition of COX-1 and COX-2 activities	23,24
7	Fruits	Hydro alcoholic extract	*In vivo* (Rat)	Management of the inflammatory-related diseases	25
Effect on osteoarthritis					
8	Aerial parts	Chloroform extract	*In vitro* (canine articular chondrocyte)	1. Suppression of interleukin-1β-induced NF-κB activation by inhibition of IκBα phosphorylation, IκBα degradation, p65 phosphorylation, and p65 nuclear translocation 2. Down-regulation of NF-κB targets including COX-2 and MMPs 3. Reversion the interleukin-1β-induced down-regulation of collagen type II, CSPG, β1-integrin, and cartilage-specific transcription factor SOX-9 protein expression 4. Stimulation of new cartilage formation even in the presence of IL-1β	30
9	Fruits	Dried fruits	Human study	Reduction in serum C-reactive protein levels and chemotaxis of peripheral blood neutrophils	31
10	Fruits	Dried fruits	Clinical trial	Reduction in symptoms of OA	32
11	Fruits	Hyben vital powder	Clinical trial	The positive effect on the symptoms of OA	33,34

Continued

TABLE 1 *(CONTINUED)*. Pharmacological activities of *R. canina*.

NO.	Parts of plant	Active constituents/ preparations	Study design	Results	Refs.
Anti-oxidant activity					
12	Leaves	Methanol and ethyl acetate extracts	*In vitro*	Presence of anti-oxidant phenolic compounds in extracts	37
13	Fruits	Water extract	*In vitro*	The maximum anti-oxidant activity at 3% concentration	38
14	Fruits	Water extract	*In vitro*	Anti-oxidant and pro-oxidant activity depending on concentrations	39
15	25 types of R. canina fruits	Hydro-alcoholic extract	*In vitro*	All rose genotypes were sources of phenolic contents and had a good anti-oxidant capacity	40
16	Fruits from Bulgaria	Hydro-alcoholic extract	*In vitro*	Wild-growing R. canina is a rich source of anti-oxidants	41
17	Fruits from Iran	N-hexane, ethyl acetate, chloroform, acetone, water and methanol extract	*In vitro*	The methanol fraction was the most powerful one	18
18	Aerial parts from Transylvania	Water extract	*In vitro*	Anti-oxidant effect of RCF	5
19	Seeds, Petals, Flowers, Galls, and Fruits from Portugal	Methanol extract	*In vitro*	Galls revealed the highest anti-oxidant potential.	42
Pain reduction effect					
20	Fruits	Aqueous extract	*In vivo* (Mice)	The dose-dependent analgesic effects	43
21	Fruits and seed powder (LitozinR)	A dose of 5 g LitozinR per day	Human	The pain reduction effects	44
22	Fruits powder	Not mentioned	Clinical trials	A small to moderate effect on pain	45
Anti-cancer properties					
23	Dried fruits	Ascorbic acid, flavonoids, and phenolic acids	*In vitro* (HeLa, MCF7 and HT-29 cell lines)	Only polyphenols contribute to R. canina anti-proliferative activity	46
24	Fruits	Acetone extract, ascorbic acid, neutral polyphenols, acidic polyphenols, and dimethyl sulfoxide extract	*In vitro* (colon cancer cell line (Caco-2) and (WiDr))	1. Proliferation inhibitory effect on Caco-2 cell line 2. Selective cytotoxic effect on WiDr cells compared with normal colon cells 3. Induction of cell cycle arrest at the S phase and apoptosis via reduced mitochondrial membrane potential 4. Repression of telomerase expressions	47,48
25	Fruits	Hydroalcoholic extract	In vitro (U-1242 MG, U-251 MG, and A-172 glio-blastoma cell line)	Prevention of cell proliferation through inhibition of the AKT and MAPK signaling pathways	52

Continued

TABLE 1 *(CONTINUED).* Pharmacological activities of *R. canina*.

NO.	Parts of plant	Active constituents/ preparations	Study design	Results	Refs.
Effect on the urinary system disorders					
26	Aerial parts	Hydro-methanolic extract	*In vivo* (Rat)	Disruption and prevention of the calcium oxalate kidney stones formation	54
27	Aerial parts	Dried herb (5 g/1) for 12 days	*In vivo* (Rat)	Reduction of the urinary risk factors of calcium oxalate urolithiasis	55
28	Fruits	Hydro-alcoholic extract	*In vivo* (Rat)	Protective effect against kidney function disturbances, oxidative stress, and histological damages	56
29	Fruits	500 mg R. canina capsules for 20 days	Human	Reduction the incidence of urinary tract infection after cesarean section	58
Anxiolytic effect					
30	Flowers	Hydroalcoholic extract	*In vivo* (Rat)	Increased the number of open arm entries in a dose-dependent manner 2. increased the time of stay in the open arms	59
Effect on depression and recognition memory					
31	Aerial parts	Hydro-Alcoholic Extract	*In vivo* (Rat)	1. Attenuation of depressive-like behavior 2. Recognition memory impairment	61
Skin-whitening effect					
32	Fruits	A water extract was divided into four fraction.	*In vitro* (mouse melanoma cells) and *in vivo* (brown guinea pigs)	Proanthocyanidins from RCFs inhibited melanogenesis	62
33	Fruits	Quercetin	*In vitro*	The inhibition of melanogenesis by quercetin due to the inhibition of tyrosinase activity	63
Effect on neutrophil respiratory burst					
34	Fruits	Acetone/water extract without ascorbic acid	*In vitro*	The anti-oxidative effects of R. canina are due not only to ascorbic acid but also to polyphenolics	64
Anti-diabetic effect					
35	Fruits	Hydro-alcoholic extract	*In vivo* (Rat)	1. Improved islets necrotic 2. regenerated pancreatic islet cells	16
36	Fruits	Water extract	*In vitro*	Act as a growth factor for pancreatic β-cell line	66
37	Fruits	Oligosaccharide fraction	*In vivo* (Rat) and *in vitro* (Pancreatic β cell line RIN5F)	1. Inhibition of Gluconeogenesis and α-glucosidase activity 2. Improvement of the oral glucose tolerance 3. Improvement pancreatic β-cells and tissue 4. Increase the expression of Ngn3, Nkx6.1 and insulin genes 5. increase the insulin levels due to the regeneration of beta-cells in the islands of langerhans 6. Increase cell death at high concentration and protection of cells from streptozotocin-induced apoptosis at low concentration 7. Increase the expression of Ins1, Pdx1, Gck and Ptp1b genes 8. Reduction the expression of the Slc2a2 gene	67,68

Continued

TABLE 1 *(CONTINUED).* Pharmacological activities of *R. canina*.

NO.	Parts of plant	Active constituents/ preparations	Study design	Results	Refs.
Anti-hyperlipidemic and anti-obese effect					
38	Fruits and seeds	Kaempferol 3-O-b-D-glucopyranoside and *p*-coumaroyl moieties	*In vivo* (mice)	The importance of both kaempferol 3-O-b-D-glucopyranoside and p-coumaroyl moieties for anti-obese effects	70
39	Fruits	Hydro-alcoholic extract	*In vivo* (Rat)	Decreased levels of cholesterol and triglyceride concentrations Anti-biotic resistance reversal effect	71
40	Fruits	Methanol extract	*In vitro*	1. A mild to poor anti-bacterial activity against the panel of bacteria 2. Strongly potentiation of tetracycline activity against XU212, a Tetracycline-effluxing, and resistant strain	72
41	Petals	Tellimagrandin I and rugosin B	*In vitro*	1. Tellimagrandin I was very effective regarding the reduction of the minimum inhibitory concentration of tetracycline 2. Rugosin B showed some effect	73
Neuroprotective effect					
42	Aerial parts	Ethanol extract	*In vivo* (Rat)	1. Increased the expression level of SYP 2. Decreased the expression level of Psen1. 3. No significant changes in spatial learning	74
Immunomodulatory effects					
43	Fruits	Hydro-alcoholic extract	*In vivo* (Rat)	1. Increased gamma globulin level, neutrophil and monocyte counts and phagocyte activity. 2. Increased thiobarbituric acid reactive substances. 3. Decreased glutathione level	75
44	Fruits	Oleanolic acid, betulinic acid, and ursolic acid	*In vitro* (Mono Mac 6 or MM6 cell line)	Inhibition of the lipopolysaccharide-induced interleukin-6 release by oleanolic acid and ursolic acid, but not betulinic acid	76
Genoprotective effect					
45	Fruits	Water extract	*In vivo* (Drosophila Melanogaster)	Genoprotective effect	77
Effect on the reproductive system					
46	Fruits	Water extract	In vitro (mice)	Protective effect on reproductive system	79

ANTI-MICROBIAL ACTIVITY

The strong anti-microbial activity of *R. canina* against certain micro-organisms has been reported. Preparative reversed phase high-performance liquid chromatography (RP-HPLC) analysis of a methanolic extract of *R. canina* seeds yielded kaempferol 3-O-(6≤-O-E-pcoumaroyl)-b-D-glucopyranoside and kaempferol 3-O-(6≤-O-Z-p-coumaroyl)-b-D-glucopyranoside. The anti-bacterial activity of these compounds was determined. The compound mixture inhibited the growth of *Lactobacillus plantarum, Proteus mirabilis* and *Staphylococcus epidermedis*[17].

In vitro anti-microbial activity of *R. canina* extracts in n-hexane, ethyl acetate, chloroform, acetone, water, and methanol, was studied against the following bacterial and yeast strains: *Staphylococcus aureus* (PTCC1431), *Bacillus cereus* (PTCC 1015), *Bacillus subtilis* (isolated and biochemically characterized in the laboratory), *Escherichia coli* (PTCC1399) and *Candida albicans* (PTCC 5027). The methanolic extract was the most effective extract against these micro-organisms. Besides, the water extracts exhibited toxicity against both gram-positive and gram-negative bacteria. The acetone extracts showed anti-bacterial activity against *Escherichia coli, Staphylococcus aureus, and Candida albicans*. Furthermore, the chloroform and n-hexane extracts showed no inhibition activity against tested micro-organisms. Some extracts of *R. canina* might, therefore, be useful for their anti-bacterial activity[18].

Ethanolic and methanolic extracts of *R. canina* flowers were screened utilizing agar well diffusion method against two gram-negative bacteria, including *Escherichia coli* (CCM 3988) and *Pseudomonas aeruginosa* (CCM 1960) and three microscopic filamentous fungi strains *Aspergillus niger, Fusarium culmorum*, and *Alternaria alternata*, respectively. The best anti-microbial effects of ethanolic and methanolic extracts were against *Pseudomonas aeruginosa* and *Escherichia coli*, respectively[19].

ANTI-INFLAMMATORY ACTIVITY

The effect of RCFs on a number of inflammatory parameters (chemotaxis and chemiluminescence of peripheral blood polymorphonuclear leucocytes (PMNs), serum levels of creatinine and C-reactive protein) was assessed. RCFs extract inhibited the chemotaxis and chemiluminescence of peripheral blood PMNs *in vitro*. Daily consumption of dried fruit by healthy individuals resulted in reduced chemotaxis of peripheral blood PMNs and reduced the level of serum creatinine and acute phase protein C-reactive protein. These results confirmed the anti-inflammatory properties of these fruits[20].

The galactolipid (2S)-1,2-di-O-[(9Z,12Z,15Z)-octadeca-9,12,15-trienoyl]-3-O-beta-d-galactopyranosyl glycerol isolated from dried and milled RCFs by bioassay-guided fractionation is responsible for the anti-inflammatory and inhibitory effect on chemotaxis of human peripheral blood neutrophils[21]. This anti-inflammatory activity is probably through cyclooxygenase (COX) inhibition[22]. Linoleic and alpha linolenic acids from these fruits inhibit COX-1 and COX-2 activities. Moreover, three triterpene acids of *R. canina* extract show COX and lipooxygenase inhibitory properties[23, 24] (Figure 3).

In vivo anti-inflammatory activity was also examined in the rat model. *R. canina* extract inhibited the development of carrageenin-induced edema, and this anti-inflammatory power was comparable to that of indomethacin (a FDA approved nonsteroidal anti-inflammatory drug commonly used to reduce fever, pain, stiffness, and swelling from inflammation). The gastric damage was lower in *R. canina* pre-treated stomachs compared to control, although the anti-ulcerogenic effect was not statistically significant[25]. Therefore, these results suggest the potential use of this plant as an adjuvant therapeutic agent for the management of inflammatory-related diseases.

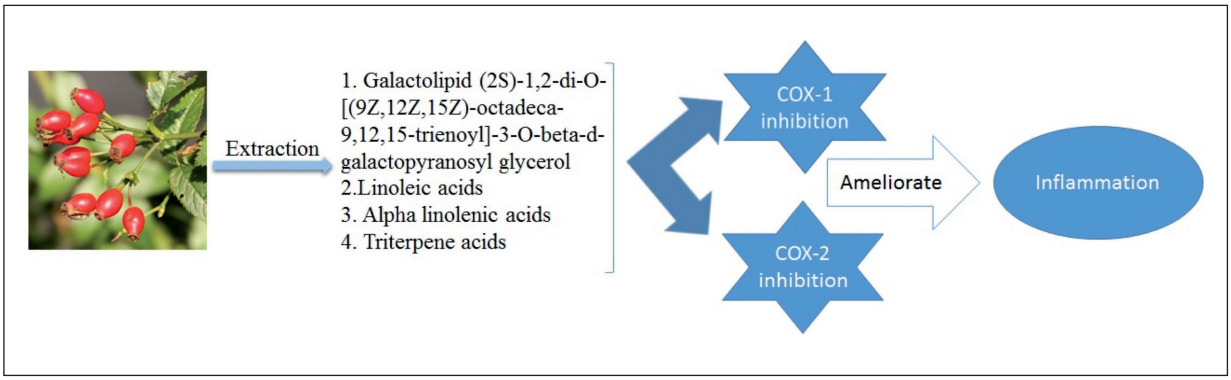


Fig. 3. Anti-inflammatory activity of RCFs.

EFFECT ON OSTEOARTHRITIS

Osteoarthritis (OA) is the most prevalent joint disorder. It involves articular cartilage, the synovial membrane, subchondral bone and periarticular soft tissues[26]. It may appear after injury or infection of the joint or as a result of aging. The most common symptoms and signs of OA are heat, swelling, pain, stiffness and limited mobility of the affected joints. Other more severe complications include osteophyte formation and joint malalignment. These symptoms are variable, depending on joint location and disease severity[27]. At the molecular level, an imbalance between extracellular matrix destruction and replacement causes the loss of cartilage matrix components, particularly type II collagen and aggrecan[28]. Although in chondrocytes, the expression of both anabolic and catabolic matrix genes was increased[29], their catabolic ability is considered to dominate their anabolic capacity resulting in cartilage loss in OA.

The effect of *R. canina* extract on the expression of collagen type II (the main structural component of the cartilage tissue), cartilage-specific proteoglycan (CSPG) (specific types of sugar-coated proteins), β1-integrin (a transmembrane signal transduction receptor mediating cell-matrix interactions in cartilage), SOX-9 (a transcription factor that is essential for cartilage extracellular matrix formation), cyclooxygenase (COX)-2 (an enzyme that is responsible for conversion of arachidonic acid to prostanoids), and matrix metalloproteinase (MMP) -9 (a zinc-metalloproteinase enzyme that involved in the degradation of the extracellular matrix) and MMP-13 (a zinc-metalloproteinase enzyme that degrades collagenous extracellular matrix) in primary canine articular chondrocytes model was investigated. The herb extract suppressed interleukin-1β-induced NF-κB activation by inhibition of IκBα phosphorylation, IκBα degradation, p65 phosphorylation, and p65 nuclear translocation. These events connected with the down-regulation of NF-κB targets including COX-2 and MMPs. The extract also reversed the interleukin-1β-induced down-regulation of collagen type II, CSPG, β1-integrin, and cartilage-specific transcription factor SOX-9 protein expression. In high-density cultures, herbs extract stimulated new cartilage formation even in the presence of IL-1β[30].

In a short report, it was suggested that daily consumption of *R. canina* dried fruits for four weeks by healthy volunteers and OA patients, resulted in reduced serum C-reactive protein levels and chemotaxis of peripheral blood neutrophils. Therefore, it can be used as a dietary supplement in OA patients[31].

The clinical efficacy of this plant has been approved for OA. A double-blind, randomized, placebo-controlled clinical for testing the impact of standardized RCFs powder on mobility of the hip and knee joints, activities of daily living, quality of life, and pain in patients with OA in 2003 showed that this powder reduced symptoms of OA, and 64.6% of patients had at least some reduction of pain after treatment. It is also improved hip flexion[32].

Hyben vital powder (HVp) is a standardized dry powder from the seeds and fruits of a special subtype of *R. canina* (Lito). The plants used for HVp are grown in standardized fields according to good agricultural practice. Harvesting takes place when the fruits are ripe, and they freeze without delay. The selection of optimal fruits is done by a laser technique and the temperature of the drying process never exceeds 40°C. The powder of seeds and fruits is finally standardized to contain at least 500 mg ascorbic acid per 100 g HVp. The phytochemicals and their structure presented in HVp are listed in Table 2. In addition to these components, HVp contains some essential elements such as Magnesium (1.70 mg/g), Zinc (0.01 mg/g) and Copper (0.109 mg/g) which are required for the function of many enzymes and transcription factors[33].

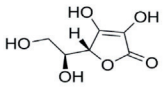
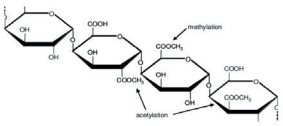
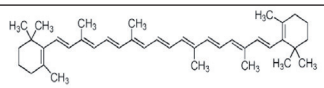
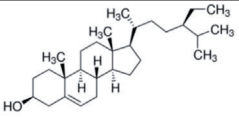
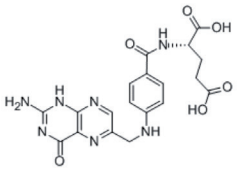
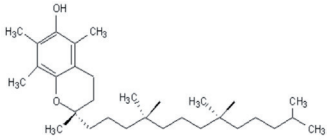
In two double-blind, placebo-controlled, randomized trial in 2004 and 2005, the positive effect of HVp on the symptoms of OA was confirmed[33,34].

ANTI-OXIDANT ACTIVITY

There is an association between the consumption of fruits and vegetables and overall health and it is mainly attributed to their potential anti-oxidant capacity. On the other hand, there is an agreement among food industries that some synthetic anti-oxidants should be replaced with their natural kinds because of their potential health risks and toxicity. Therefore, anti-oxidants from natural sources have received much attention, and efforts have been made to identify new natural resources for active anti-oxidant compounds. Also, natural anti-oxidants can be formulated to give nutraceuticals (a food containing health-giving additives and having the medicinal benefit), which can prevent oxidative damage in the body[35]. The most common anti-oxidant compounds in fruits are ascorbic acid, carotenoids, and polyphenol substances. The quality of natural anti-oxidant depends not only on the nature of the plant source, geographical origin, weather conditions, time of harvesting and storage, but also on the method of extraction and the used solvent[36]. The anti-oxidant potential of various extracts of *R. canina* in different geographical areas has been studied.

In a study phenolic composition and anti-oxidant properties of methanol and ethyl acetate extracts of *R. canina* leaves from Tunisia were characterized. Fifteen phenolic compounds were identified using the high performance liquid chromatography with

TABLE 2. Constituents of Hyben Vital powder:

Constituents	*Amount*	*Chemical formula*	*Structure*	*Importance*
Ascorbic acid	5 mg/g	C6H8O6		Essential for tissue repair and several enzymes activity
Pectin	58.0 mg/g	C6H10O7		Presented in most cell walls and a source of dietary fiber
β-carotene	57.9 mg/kg	C40H56		A precursor (inactive form) of vitamin A
β-sitosterol	0.5 mg/g	C29H50O		Reduction in benign prostatic hyperplasia and blood cholesterol levels
Folic acid	1.6 mg/kg	C19H19N7O6		Essential for DNA and RNA production, and amino acids metabolism
Vitamin E	0.046 mg/g	C29H50O2		Protecting cell membranes from ROS

diode array detector (HPLC-DAD) and HPLC-DAD-ESI–MS technologies. The phenolic composition of extracts includes two kaempferol derivatives (Kaempferol 3-O-glucoside and kaempferol7-O-glucoside). The data suggested that these extracts were a rich source of antioxidant phenolics[37].

In order to determine the actual dose being consumed for better anti-oxidant effect, five different concentrations (1%, 2%, 3%, 4%, 8%) of *R. canina* infusions were used in different *in vitro* test systems. According to the data the best anti-oxidant activity was at 3% concentration. Therefore, it is suitable to achieve this concentration at the tissue level when used as a supplement to therapeutic regimens and for healthy individuals[38]. It was suggested that *R. canina* extract may act not only as an anti-oxidant but also as a pro-oxidant with the effects depending on its concentrations[39]. The anti-oxidant potential of the fruits of twenty-five *R. canina* types from Bolu province in the northwest region of Turkey and their total phenolic content were analyzed by various methods. Their total phenolic contents ranged from 20.12 to 32.2 mg gallic acid equivalents/g. This study showed that all rose genotypes were valuable sources of phenolic contents and had a good anti-oxidant capacity[40].

The high values of the anti-oxidant activity of RCFs extract is probably due to synergism interaction between polysaccharides and organic acids (gallic, cinnamic, ellagic), with phenolic antioxidants: flavonoids (rutin, kaempferol, quercetin). The anti-oxidant potential and polyphenolic content of water and hydroethanolic extracts from wild growing Bulgarian RCFs were investigated *in vitro*. The highest ascorbic acid content was observed in the ethanolic extract, while the total tannins dominated in the water extracts. The ethanolic extract had the highest total phenolic contents and the anti-oxidant activity. So, wild-growing *R. canina* from Bulgaria is a rich source of anti-oxidants and revealed their potential application as food and herbal cosmetic preparations[41].

The phytochemicals (phenols and flavonoids) content and anti-oxidant characteristics of the various extracts of RCFs from Iran were studied through various *in vitro* methods. Among the extracts, the methanol fraction was the most powerful one. The study of the relationship between anti-oxidant capacity and total phenolic and flavonoid content indicated that anti-oxidant activity is mainly attributed to these compounds[18]. The results obtained from a study about bioactive compounds and anti-oxidant activity of *R. canina* biotypes extracts from wild

Transylvania populations showed that there is a good correlation between anti-oxidant activity with ascorbic acid content and total polyphenols[5].

The comparison between chemical compounds and anti-oxidant activity of different parts (seeds, petals, flowers, galls, and fruits) of this plant indicated the presence of bioactive compounds in different parts. Phytochemical characterization included determination of sugars by HPLC-RI, fatty acids by GC FID, tocopherols by HPLC-fluorescence, phenolics, flavonoids, carotenoids, chlorophylls, and ascorbic acid, by spectrophotometric techniques was shown that galls had the highest anti-oxidant potential, ripen fruits had the highest tocopherols and β-carotene contents, as also the most adequate n-6/n-3 fatty acids ratios. Unripe fruits had the highest levels of ascorbic acid, and petals revealed the highest concentration of sugars. Furthermore, the levels of *R. canina* anti-oxidants make it a suitable source of compounds to be used commercially to retard rancidity in fatty materials in food manufacturing, to reduce the effects of aging and to prevent oxidative-stress related diseases such as cancer and heart diseases[42].

PAIN REDUCTION EFFECT

R. canina has been traditionally used in Iran as an herbal medicine for pain reduction[43]. An *in vivo* study evaluated the analgesic activity of the aqueous extract using animal models of pain. The analgesic effect was assessed with hot plates a model of visceral pain in mice. The extract increased the latency time in mice in a dose-dependent manner. The pre-treatment augmented the anti-nociceptive effects of *R. canina* and this was even more pronounced than sodium salicylate[35]. A one-year survey on the effectiveness of powder from *R. canina* in acute exacerbations of chronic pain confirmed the pain reduction effect[44]. Also, a meta-analysis of randomized controlled trials investigated whether the fruit powder reduce pain in OA patients or not. Results showed that RCFs powder had a small to moderate effect on pain and proposed it as an analgesic herbal remedy[45].

ANTI-CANCER PROPERTIES

As previously discussed, *R. canina* extract can scavenge reactive oxygen species (ROS) and have a strong anti-oxidant capacity. ROS are produced as a result of cellular metabolism and their concentration can be increased in body due to ambience pollution, tobacco consumption, etc. An excess of these reactive compounds damage some macromolecules in cells such as lipids, proteins, and DNA. In humans, ROS causes problems like aging, atherosclerosis, inflammatory disorders and cancer. Given the difficulty of synthesizing molecules with anti-oxidant ability, the extraction of these compounds from natural sources such as vegetables or fruits is very interesting. It has been reported that most dietetic products with anti-cancer activity act as strong anti-oxidants and/or alter the activity of one or more protein kinases involved in cell cycle control[46].

Natural anti-oxidants from dried RCFs (*R. canina* tea) were separated by solid-phase extraction (SPE) into ascorbic acid, flavonoids, and phenolic acids. These three fractions were then screened for their anti-proliferative activity on the growth of three human tumor cell lines, HeLa (cervix epitheloid carcinoma), MCF7 (breast adenocarcinoma, estrogen receptor-positive) and HT-29 (colon adenocarcinoma). Data showed the lowest IC50 values for *R. canina* flavonoids, (80.63, 248.03 and 363.95 mg L−1 respectively). However, the ascorbic acid fraction did not inhibit the growth of tumor cells. So, only polyphenols contribute to *R. canina* anti-proliferative activity[46]. The anti-cancer properties of different concentrations of RCFs extract on colon cancer cell line (Caco-2) were studied. Total extract, ascorbic acid, neutral polyphenols, and acidic polyphenols were tested. All of them, in both low and high concentrations, showed cell proliferation inhibitory effect and caused disturbances in the cell cycle resulting in concomitant cell death by the apoptotic pathways[47]. Also, in WiDr colon cancer cell line *R. canina* extract exhibited a selective cytotoxic effect compared with normal colon cells. The extract induced cell cycle arrest at the S phase and apoptosis via reduced mitochondrial membrane potential. It significantly repressed telomerase expressions. Based on these two studies, this natural plant could be an effective component of functional foods for patients with colon cancer[48].

GBM multiforme (GBM) is the most malignant and aggressive form of primary astrocytic brain tumors[49]. It is among the most lethal types of human cancers, and the median survival time of patients is about 14 months[50]. Some studies indicated the effect of plant extract on GMB cell lines[51]. *R. canina* extracts were able to prevent cell proliferation through a mechanism that involves inhibition of both the AKT (associated with increased cell proliferation, invasion, angiogenesis, and inhibition of apoptosis in GBMs) and MAPK (contribute to the development and promotion of brain tumors, especially gliomas) signaling pathways, but does not promote apoptosis in GBM cell lines[52]. Temozolomide is the most widely used chemotherapy for patients with GBM[53]. *R. canina* extracts prevent cell proliferation more effectively than temozolomide. Therefore, it can be used as an alternative or complement to standard chemotherapeutic agent for GBMs[52].

EFFECT ON THE URINARY SYSTEM DISORDERS

Nephrolithiasis is a crystal concretion formed usually in the kidneys. It is one of the prevalent disorders of the urinary tract, affecting about 12% of the world population. There is a relation between nephrolithiasis and increased risk of renal failure. The most prevalent type of kidney stone (up to 80%) is predominately composed of calcium oxalate (CaOx). Its formation involves a cascade of events, such as crystal nucleation, supersaturation, growth, aggregation, retention within renal tubules and migration to the renal papillary surfaces. Treatments have been developed to remove kidney stones with minimal renal damage; however, there is no satisfactory drug that can be used in clinical therapy. Herbal medicines and phytotherapy are novel strategies for the prevention and treatment of nephrolithiasis. Many of the available herbal remedies have been used to treat kidney stones[54].

The possible therapeutic potential of *R. canina* as a preventive agent in experimentally induced CaOx nephrolithiasis in rats was examined. Ethylene glycol (1%) was used to induction of nephrolithiasis in the animal models. The hydro-methanolic extract contributed to reducing the kidney and liver lipid peroxides to optimum levels in rats that had been treated with EG-induced CaOx nephrolithiasis. The extract also decreased renal and urinary calcium contents and the size and number of CaOx calculi in the kidneys. It increased citrate excretion without changing the volume, pH, or urinary concentrations of oxalate. Therefore, *R. canina* can be useful in disrupting and preventing the formation of the CaOx kidney stones[54].

The effect of *R. canina* extract (in herb infusion form) on the CaOx urolithiasis (the formation of stony concretions in the bladder or urinary tract) risk factors was studied using rats under balanced dietary conditions. There was not observed any significant effects on the volume of liquids drunk or on creatinine, phosphate, and oxalate urinary concentrations and excretions. The herb infusion did not cause any diuretic effect. Calciuria (the presence of calcium salts in the urine) decreased and citraturia (The presence of citrate (or citric acid) in the urine) increased when taking the herb infusion, and vice versa when taking magnesium chloride. Magnesium chloride decreased the urinary pH value, but this effect was not observed when magnesium chloride was administered with herb infusion. So, the same beneficial effects of the studied infusion herb on CaOx urolithiasis urinary risk factors can be clearly detected. It seems that some possible effects depend on dietary components, thus, an increase in the urinary pH was only detected when the intake of the herb infusion was studied in a magnesium chloride-supplemented diet[55].

Two major challenges in the management of acute kidney injury, which cause and develop renal disturbances, are inflammation and oxidative stress. The effects of the oral administration of RCFs extract on kidney function disturbances, histological damages, and oxidative stress induced by bilateral renal ischemia was investigated *in vivo*. Ischemia and reperfusion were induced on the kidneys. Extract solvent and plant extract were administered. In addition, in the sham group, surgery was done without ischemia. Some reductions in creatinine clearance, absolute excretion of potassium, urine osmolarity, and an increase in absolute excretion of sodium in the reperfusion group was reported compared with sham group. These changes were less pronounced with RCFs extract. In addition, blood creatinine and urea concentrations which increased in the reperfusion group were lower in the plant group. In this group, the degree of histological damages and the level of malondialdehyde were lower than the reperfusion group, while ferric reducing/anti-oxidant power level was higher. So, RCF extract possesses protective effects against kidney function disturbances, oxidative stress, and histological damages[56].

Urinary tract infection (UTI) is an inflammatory response of squamous urinary tract tissue to bacterial invasion and is divided into asymptomatic bacteriuria and symptomatic infection (cystitis and pyelonephritis). Pregnant women, post-partum women, patients with spinal cord injuries or catheterization, older people, infants, patients with diabetes or sclerosis, patients with acquired immune deficiency or human immunodeficiency virus, and those with underlying urological disorders are among most susceptible cases to this kind of infection. UTI can be effectively treated with herbal medicine[57].

The effect of RCF in preventing UTI in women following the cesarean section (CS) was investigated. This triple-blind randomized clinical trial was conducted in 2016 on 400 women following CS with a negative urine culture (U/C) in Iran. Participants received a twice-daily dose of 500 mg capsules containing *R. canina* or placebo. RCF capsules were able to reduce the incidence of UTI after CS. Thus, it is likely that the administration of this medication can promote maternal health following CS[58].

EFFECT ON ANXIETY, DEPRESSION AND RECOGNITION MEMORY

Depression and anxiety commonly occur together. They are among the most prevalent diseases in the world. Patients with depression often have features of anxiety disorders, and those with anxiety

disorders commonly also have depression. Anxiety is a natural psychophysiological reaction against known, unknown, and even imagined dangerous situations. High levels of anxiety are characterized as a diffuse, unpleasant and vague sense of apprehension. This state in humans is often accompanied by autonomic symptoms (headache, perspiration, palpitations, tightness in the chest, and mild stomach discomfort). High-anxiety states are among the most important factors responsible for the development of pathological stresses. Benzodiazepines are the main class of pharmacological agents used for suppression of anxiety. However, they present undesired side effects. Attempts have been made to develop new compounds with fewer side effects. Compounds derived from natural resources may have therapeutic value in the treatment of anxiety. Extensive efforts are underway to identify natural anxiolytic agents[59].

In one of these efforts, the anxiolytic effect of a hydroalcoholic extract of *R. canina* flowers on rats using the elevated plus-maze (EPM) test was investigated. Animal behavior in the EPM was videotaped, and conventional indices related to the anxiety level were scored. Flowers extract increased the number of open arm entries in a dose-dependent manner and also increased the time of stay in the open arms at a high dose. The number of closed arm entries interpreted as a correlate of the locomotion intensity did not differ from the control[59].

Depression is the second most common cause of disability in the world. Approximately 17% of the world's population experience major depression in their lifetime. The suicidal rate is four times higher among those with depression. The use of herbal medicine is an important part of depression treatment. Now more patients are interested in herbal medicine. Numerous studies approved the anti-depression of various herbal extracts[60].

R. canina extract improved depressive-like behavior and recognition memory in diabetic mice. In this *in vivo* experience, forced swimming and novel object recognition (NOR) tests were used. Malondialdehyde levels and total anti-oxidant capacity were measured in the mouse brain homogenate to evaluate oxidative stress. The results showed that the groups receiving *R. canina* had lower immobility time compared to the control group in the forced swimming test, and a higher discrimination index was seen in diabetic animals in the NOR task compared to the control group. Also, the groups receiving treatment had a higher total anti-oxidant capacity and lower malondialdehyde levels in the brains. So, *R. canina* attenuated impairment of recognition memory and depressive-like behavior probably through modulation of oxidative stress in diabetic mouse brains[61].

SKIN-WHITENING EFFECT

Melanin plays an important role in protecting human skin from the harmful influence of solar ultraviolet radiation. However, an abnormal accumulation of melanin as highly pigmented patches on specific parts of the skin is an aesthetic problem. Skin lighteners are applied in Western countries to prevent and treat such an irregular hyperpigmentation as melasma, freckles and age spots. There has also been a long cultural tradition in Asia of trying to make the skin look whiter. The effect of various fractions from an aqueous extract of RCFs on melanogenesis in B16 mouse melanoma cells was tested, and the active melanogenesis-inhibiting compounds were isolated[62]. Also, the inhibitory effects of this herb on skin pigmentation on brown guinea pigs were confirmed and compared to the mechanisms responsible for this inhibition of melanogenesis between B16 mouse melanoma cells and brown guinea pigs. The 50% ethanol eluate from a DIAION HP-20 column reduced the production of melanin and was mainly composed of procyanidin glycosides. This eluate reduced the intracellular tyrosinase activity and had a direct inhibitory effect on impure tyrosinase in melanoma cell extract. The effect of *R. canina* on skin pigmentation in brown guinea pigs showed that the pigmentation was inhibited together with the tyrosinase activity in the skin. Altogether, proanthocyanidins from RCFs inhibited melanogenesis in mouse melanoma cells and guinea pig skin and could be useful as a skin-whitening agent[62].

Among the isolated compounds from a methanolic extract of RCFs, quercetin was a particularly potent melanogenesis inhibitor. Quercetin decreased the intracellular tyrosinase activity as well as the tyrosinase activity in a cell culture-free system. It also decreased the cellular level of tyrosinase mRNA and protein. So, the inhibition of melanogenesis by quercetin was due to the inhibition of both tyrosinase activity and of the protein expression[63].

EFFECT ON NEUTROPHIL RESPIRATORY BURST

Respiratory burst, which occurs during inflammatory disorders, is a cellular response to pathogenic agents. It is characterized by an increase in oxygen consumption by phagocytes. Like other phagocytes, polymorphonuclear neutrophils (PMN) are activated through the activation of a membrane-associated NADPH oxidase converting molecular oxygen into superoxide anion. Superoxide anion is produced by the dismutation of hydrogen peroxide. Hypochlorous acid is produced by the myeloperoxidase– hydrogen peroxide system. These strongly reactive

substances released by the neutrophils are intended to participate in the destruction of viruses and bacteria within phagosomes, but they also have several harmful effects on the body. Polyphenolics are a class of well-known anti-oxidative natural substances that eliminate these reactive molecule activities. These components are mainly present in plants[64]. As described earlier, *R. canina* anti-oxidant activity was confirmed by several studies.

In this concern, the *in vitro* effect of the *R. canina* extract without ascorbic acid on superoxide anion, hydrogen peroxide, hypochlorous acid in both cell-free systems and in cellular systems, was evaluated. Cell-free systems were used in which each ROS, and the extract was brought together in order to prove a direct interaction between the phenolic extract and ROS. Secondly, tests were undertaken with PMNs isolated from human blood. In these cellular models, inflammatory conditions were reproduced *in vitro* by chemical stimulation of PMN. ROS was released by stimulated PMNs, and the effect of the RCFs extract on PMN oxidative metabolism was investigated. This extract decreased ROS in acellular and cellular systems. The IC50s obtained were 5.73 mg/L, 1.33 mg/L and 2.34 mg/L, respectively, for superoxide anion, hypochlorous acid and hydrogen peroxide in acellular experiments. In cellular experiments, the IC50 values were nearly similar. This extract did not affect the PMN metabolism. Therefore, the anti-oxidative effects of *R. canina* are due not only to ascorbic acid but also to polyphenolics[64].

ANTI-DIABETIC ACTIVITY

Diabetes is one of the most prevalent metabolic disorders characterized by high blood glucose level (hyperglycemia). It is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the produced insulin. Chronic hyperglycemia in diabetic patients damages many of the body's systems, in particular, eyes, kidneys, nerves, heart, and blood vessels. The incidence of diabetes has increased rapidly over the past two decades and it may become the strongest and deadliest leading cause of humans' death in the future. Due to the limitation of currently available anti-diabetic drugs, especially in terms of efficacy and safety, the development of new strategies is necessary for the prevention and management of this kind of disease. Herbal remedies are among the best existing alternative therapies, which have been used since ancient times in the treatment of diabetes. To the date, more than 400 traditional plants have been reported with anti-diabetic potential, although only a small number of them have received clinical evaluation to assess their efficacy[65].

A study about the anti-diabetic effect of *R. canina* in STZ-induced diabetic rats showed the reduction of the blood glucose by fruits extract. Furthermore, this extract improved islets necrotic and regenerated pancreatic islet cells. So, it represented the hypoglycemic activity in diabetic rats[16]. *R. canina* extract can act as a growth factor for pancreatic beta cells providing a novel mechanism for the observed anti-diabetic effect of this natural extract[66]. An oligosaccharide was purified, characterized and identified from *R. canina* exttract with regenerative effects on β-cells and the ability to complete reverse of STZ-induced diabetes. The efficacy of this oligosaccharide was confirmed using *in vivo* and *in vitro* studies. Owing to the verified anti-diabetic effects and regenerative potential, this oligosaccharide could be considered as the promising drug in the management of diabetes[67,68].

ANTI-HYPERLIPIDEMIC AND ANTI-OBESE EFFECT

Obesity has increased at an alarming rate in recent years and considered a global health problem. It is believed that obesity results from disequilibrium between energy intake and expenditure, and it is known to be a strong risk factor for many disorders. Overweight and obese people are at higher risk of developing hyperlipidemia. Hyperlipidemia is elevations of fasting plasma lipid concentration. Elevated levels of blood lipids increase the risk of chronic metabolic disorders, such as cardiovascular disease and type II diabetes[69].

It has been shown that 80% aqueous acetone extracts from fruits and seeds of *R. canina* had a substantial inhibitory effect on the gain of body weight and/or weight of visceral fat without affecting food intake in mice. Trans-tiliroside in this extract potently inhibited the gain of body weight, especially visceral fat weight. On the other hand, kaempferol and p-coumaric acid lacked such effect and kaempferol 3-O-b-D-glucopyranoside tended to reduce the gain of body weight and visceral fat weight. These results indicated the importance of both kaempferol 3-O-b-D-glucopyranoside and p-coumaroyl moieties for anti-obese effects[70]. Evaluation of the hypolipidemic activity of *R. canina* fruits extract in STZ induced diabetic rats showed that the levels of cholesterol and triglyceride concentrations were decreased in the treatment groups in comparison with the diabetic control group[71].

ANTI-BIOTIC RESISTANCE REVERSAL EFFECT

The rapid emergence and spread of multidrug-resistant (MDR) bacteria is a serious global health threat and a major problem in the treatment of hos-

pital- and community- acquired infections over the last decades. Nowadays, the treatment of infections caused by MDR bacteria strain is difficult with available anti-biotic. This is in part due to the ability of bacteria to develop mechanisms that counteract anti-microbial action. Unfortunately, synthetic plasmid-curing agents such as acridine orange, ethidium bromide, and sodium dodecyl sulfate are unsuitable for therapeutic application due to their toxic nature. Therefore, the development of new antibiotics with alternative mechanisms to overcome bacterial resistance seems to be necessary. Plant-derived products have been proposed as potential candidates. In this context, the crude methanol extract of RCFs was tested against multidrug-resistant (MDR) bacterial strains, including methicillin-resistant Staphylococcus aureus SA1199B, EMRSA16 and XU212 harbouring NorA, PBP2a, and TetK resistance mechanisms, respectively, as well as Staphylococcus aureus (ATCC25923), a standard anti-microbial susceptible laboratory strain. The inhibition of the conjugal transfer of plasmid PKM101 and TP114 by the extract were also evaluated[72].

The extract demonstrated a mild to poor anti-bacterial activity against the panel of bacteria but strongly potentiated tetracycline activity (64-fold) against XU212, a tetracycline-effluxing, and resistant strain. Furthermore, the extract showed a moderate capacity to inhibit the conjugal transfer of TP114 and PKM101. Cytotoxicity analysis against HepG2 cells line showed that it was non-toxic towards human cells. The inhibition of bacterial plasmid conjugation opens the possibility of combination therapies to overcome antibiotic resistance[80]. Methicillin-resistant Staphylococcus aureus (MRSA) is a major cause of hospital-acquired infections. Treatment of patients infected with MRSA is very difficult because MRSA is resistant not only to L-lactams but also to many other anti-microbial agents. Although the mechanisms of MRSA resistance to L-lactams are not clear, several genes are proposed for this resistance. Currently, glycopeptides such as vancomycin and teicoplanin are the only antibiotic to which most clinically isolated MRSA strains are susceptible[73].

The emergence of MRSA strains with intermediate resistance to glycopeptides may become a serious clinical problem soon. Extract from petals of *R. canina* reduced the minimum inhibitory concentration of L-lactams in methicillin-resistant Staphylococcus aureus. Two compounds that reduced the minimum inhibitory concentrations of L-lactams from the extract, tellimagrandin I and rugosin B were isolated. Tellimagrandin I was very effective regarding the reduction of the minimum inhibitory concentration, and rugosin B showed some effect. Tellimagrandin I showed a weak bactericidal action when added together with oxacillin. The effect of tellimagrandin I plus oxacillin was synergistic. Tellimagrandin I also reduced the minimum inhibitory concentration of tetracycline in some strains of methicillin-resistant Staphylococcus aureus[73].

NEUROPROTECTIVE EFFECT

Sporadic Alzheimer's disease (SAD) is a chronic neurodegenerative disorder, characterized by progressive cognitive impairment, memory loss, and behavioral disturbances. It is the most controllable type of Alzheimer's disease (AD) by drug administration and a multifactorial disease affected by genetic risk factors, aging, and oxidative stresses. The impairment of memory and cognition in AD patients is caused by synaptic loss, enhanced inflammatory signaling, and the progressive deposition of senile plaques, neurofibrillary tangles and neurodegeneration. Synapses are believed to be the basis of AD pathology and synaptophysin (SYP) is one of the best targets that are often measured to quantify synapses function. SYP mRNA level is reduced in the post-mortem AD brain. Presenilin1 (PSEN1) is the catalytic subunit of γ-secretase. Neuronal inflammation and oxidative stresses activate Psen1 gene expression leading to synaptic dysfunction and the effect could be enhanced by hypoxia. A study on the neuroprotective effects of *R. canina* extracts in the rat model of SAD showed that herbal extract increased the expression level of SYP up to 12 fold. Meanwhile, the expression level of Psen1 was decreased one-half-fold. Significant changes in spatial learning were observed in herbal-treated rats. So, *R. canina* extract have anti-dementia properties and improve spatial learning and memory[74].

IMMUNOMODULATORY EFFECTS

The potential of *R. canina* as an immunomodulator agent and its effects on some biochemical parameters of the immune system were tested in rats. The gamma globulin level, neutrophil and monocyte counts and phagocyte activity were increased by *R. canina* extract. Alanine aminotransferase, aspartate aminotransferase, and alkaline phosphates had no significant changes in extract-treated rats. Plant extract increased thiobarbituric acid reactive substances and also decreased glutathione levels. Therefore, *R. canina* possess immunomodulatory effects[75].

Treatment of Mono Mac 6 or MM6 cell line (Human acute monocytic leukemia derived cells) with a crude dichloromethane extract of RCFs significantly and dose-dependently inhibited the lipopolysaccharide-induced interleukin-6 release. The immunomodulatory effect of this extract was correlated to

a mixture of three triterpene acids; oleanolic acid, betulinic acid, and ursolic acid. Further studies revealed that only oleanolic acid and ursolic acid, but not betulinic acid, could inhibit the lipopolysaccharide-induced interleukin-6 release from MM6 cell when tested separately. Interestingly, a combination of either oleanolic acid or ursolic acid with betulinic acid enhanced the immunomodulatory effect of the two triterpene acids[76].

GENOPROTECTIVE EFFECT

Alkylating agents are very potent mutagens and generate various types of mutations. Ethyl methanesulfonate is one of the most recognized examples of them. It leads to both point mutations and chromosomal damage by ethylating the thymine or guanine directly and incorrect base pairing between nucleotides during replication. It has been used in genotoxicity studies due to the mutagenic and carcinogenic effects. Extracts of several plants are used against different effects of chemicals at the present. As it was explained earlier, the *R. canina* has anti-oxidant properties, so, the possible protective effects of its fruits against the genotoxic effects of ethyl methanesulfonate were investigated with Drosophila wing somatic mutation and recombination test. Test results demonstrated the potential of *R. canina* as a natural genoprotective product[77].

EFFECT ON THE REPRODUCTIVE SYSTEM

Recently, reproductive system disorders have become one of the major health problems worldwide and its incidence has been increasing rapidly. Synthetic drugs imponer high costs and serious side effects. Studies showed that herbal products can be used effectively in the management and treatment of male and female reproductive disorders[78]. An *in vivo* study about the effects of *R. canina* extract on body and testicular weights, serum levels of testosterone, the number of germ cells and Sertoli cells, sperm parameters, the mean testis seminiferous luminal, and tubular and epithelial height in mice showed that the extract has protective effects against doxorubicin-induced reproductive toxicity[79].

CONCLUSIONS

An increase in the popularity of alternative medicine and natural products has renewed interest in plant compounds and their derivatives as potential natural remedies. Although the results from this review are completely promising for the use of *R. canina* as a medicinal agent, however, three limitations currently exist in the published literature. 1) More clinical trial should be conducted to support its beneficial use; 2) long-term trials with reasonable duration would provide insights into the possible side-effects of different extract of this plant; 3) The detailed mechanisms of action underlying the therapeutic potentials of *R. canina* should be understood.

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Author's contributions:
M. Khazaei designed the study and co-authored the manuscript. M.R. Khazaei performed the entire search. M. Pazhouhi wrote the manuscript. All authors read and approved the final manuscript.

Conflict of Interest:
The authors declare that they have no conflict of interest.

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