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Review Article

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Pharmacological Activities of *Cotoneaster racemiflorus*- A Review

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Abstract Many compounds were isolated from *Cotoneaster racemiflora* included racemiside A; cotonoate A; cotonoate B; 7,8-dimethoxy-6-hydroxycoumarin; 3,3,4-Tri-o-methylellagic acid; cereotagloperoxide; scopoletin; β-sittosterol; ursolic acid; β- sittosterol 3-o-β-D-glucopyranoside; aromatic esters (cotonoates A and B); methyl 3,4-dihydroxy-5-methoxybenzoate; Racemiside, scopoletin, 7,8-dimethoxy-6-hydroxycoumarin, 3,3',4'-tri-o-methylellagic acid, cereotagloperoxide, a manna-like substance (shir-khist); sugars and phenolic compounds. The pharmacological investigation revealed that *Cotoneaster racemiflora* possessed antioxidant, cytotoxic, radioprotective, mutagenic, antimutagenic, antibacterial and enzyme inhibitory activities. In the current paper, the cemical constituents, pharmacological and therapeutic effects of *Cotoneaster racemiflora* are reviewed.

Keywords constituents, *Cotoneaster racemiflora*, pharmacology, terapeutic

Introduction

Since ancient times, plants have been used by communities to treat the diseases, the pharmacological investigations revealed that plant produced a wide range of secondary metabolites, which were used as pharmaceuticals, agrochemicals, flavours, fragrances, colours, biopesticides and food additives [1-30]. Many compounds were isolated from *Cotoneaster racemiflora* included racemiside A; cotonoate A; cotonoate B; 7,8-dimethoxy-6-hydroxycoumarin; 3,3,4-Tri-O-methylellagic acid; cereotagloperoxide; scopoletin; β- sittosterol; ursolic acid; β- sittosterol 3-O-β-D-glucopyranoside; aromatic esters (cotonoates A and B); methyl 3,4-dihydroxy-5-methoxybenzoate; Racemiside, scopoletin, 7,8-dimethoxy-6-hydroxycoumarin, 3,3',4'-tri-O-methylellagic acid, cereotagloperoxide, a manna-like substance (shir-khist); sugars and phenolic compounds. The pharmacological investigation revealed that *Cotoneaster racemiflora* possessed antioxidant, cytotoxic, radioprotective, mutagenic, antimutagenic, antibacterial and enzyme inhibitory activities. Thus, in the present work, the cemical constituents, pharmacological and therapeutic effects of *Cotoneaster racemiflora* are reviewed.

Plant Profile

Synonyms

Cotoneaster fontanesii Spach; *Cotoneaster fontanesii* var. *desfontainii* Regel; *Cotoneaster nummularius* subvar. fontanesii Maire; *Cotoneaster nummularius* var. *racemiflorus* (Desf.) Wenzig; *Cotoneaster racemiflorus* var. *desfontainii* Zabel and *Mespilus racemiflora* Desf [31].

Taxonomic Classification

Kingdom: Plantae; **Phylum**: Tracheophyta; **Class**: Magnoliopsida; **Order**: Rosales; **Family**: Rosaceae; **Genus**: *Cotoneaster*; **Species**: *Cotoneaster racemiflora* [31].

Common Names:

Arabic: safargelia, kutnia mutafarat elazhar; **English**: black-wood, redbead cotoneaster; **Estonia**: kobarjas tuhkpuu; **French**: cotonéaster sauvage; **German**: Dichtblütige, Zwergmispel [32].

Distribution:

It was distributed from the Mediterranean and Southwest Asia in the form of deciduous shrubs [33].

Description:

Tall shrub (growing to 2.4 m) with extended, arching branches. Lanceolate, acuminate, rough, dark green hairy white on its upper face and the inner leaves. Plurifloros white flowers arranged in corymbs. Red, bright fruit arching branches with their weight [34].

Traditional Uses:

The plant was used traditionally as aperient, expectorant and stomachic [35]. Using of extracts in breast-fed babies for reducing jaundice was popular in Iranian culture [36].

Chemical Constituents:

Many compounds were isolated from *Cotoneaster racemiflora* including: racemiside A; cotonoate A; cotonoate B; 7,8-dimethoxy-6-hydroxycoumarin; 3,3,4-Tri-o-methylellagic acid; cereotagloperoxide; scopoletin; β- sittosterol; ursolic acid and β- sittosterol 3-o-β-D-glucopyranoside [37-38].

Phytochemical investigation of the chloroform soluble fraction of the methanolic extract of *Cotoneaster racemiflora* resulted in the isolation of two aromatic esters named cotonoates A and B along with methyl 3,4-dihydroxy-5-methoxybenzoate [39].

Racemiside, scopoletin, 7,8-dimethoxy-6-hydroxycoumarin, 3,3',4'-tri-O-methylellagic acid, and cereotagloperoxide were isolated from the ethyl acetate-soluble fraction of *Cotoneaster racemiflora* [40].

The plant produced a manna-like substance called shir-khist, it was rich in sugars. It contained about 13% sacchrose, 37.5% dextrose, it was most likely to be produced by the stem [41-43].

Total phenolic contents of the plant extracts ranged from 81.11 to 266.39 mg GAEs/g extracts. Water extract had the highest total phenolics, followed by methanol and ethyl acetate. However, 16 phenolic components were identified in the plant, phenolic components in the ethyl acetate methanol and water extracts of the plant were included (respectively): Protocatechuic acid 1.64±0.04, not determined, 1.16±0.04; (+)- Catechin 6.14±0.16, 4.58±0.14, 3.26±0.12; p-Hydroxybenzoic acid 1.08±0.04, 0.94±0.04, 3.16±0.04; Chlorogenic acid 5.70±0.12, 16.66±0.26, 13.92±0.24; Caffeic acid 0.54±0.01, 0.56±0.01, not determined; (-)- Epicatechin 5.24±0.32, 6.50±0.32, 6.92±0.32; Syringic acid 0.12±0.01, not determined, not determined; Vanilin 0.08±0.01, not determined, not determined; p-Coumaric acid 0.26±0.02, 0.48±0.01, 0.18±0.01; Ferulic acid 25.54±0.62, 28.36±0.62, 22.60±0.62; Benzoic acid 1.32±0.04, not determined, 1.28±0.04; Rosmarinic acid 0.14±0.01, not determined, 0.28±0.01; Eriodictyol 1.16±0.01, 0.28±0.01, 1.00±0.01; trans-Cinnamic acid 0.16±0.02, 0.24±0.02, 0.02±0.01; Luteolin 0.08±0.01, not determined, not determined; Apigenin 0.22±0.01, not determined and 0.04±0.01 [44].

Pharmacological Effects

Antioxidant Effect:

Racemiside, scopoletin, 7,8-dimethoxy-6-hydroxycoumarin, 3,3',4'-tri-o-methylellagic acid, and cereotagloperoxide isolated from the ethyl acetate-soluble fraction of *Cotoneaster racemiflora*, showed profound antioxidative activities in the DPPH assay [40].

Free radical scavenging activity measured by 1,1- diphenyl-2-picryl-hydrazil (DPPH) showed that methyl 3,4-dihydroxy-5-methoxybenzoate isolated from the plant possessed significant antioxidant ($IC_{50:}$ 9.7±0.12µm). The spectrophotometric method showed that the same compound exerted lipoxygenase inhibitory activities ($IC_{50:}$ 19.5±0.07 µm) [39].

Antioxidant capacities of ethyl acetate, methanol and water extracts of the plant were evaluated by free radical scavenging assay (DPPH, ABTS and O_2), reducing power, phosphomolybdenum, β-carotene/linoleic acid bleaching and metal chelating assays. The highest DPPH and O_2 scavenging activities were exerted by water extract of the plant, followed by the methanol extract. However, the greatest ABTS inhibition was caused by the methanol extract

(IC_{50}:0.020 mg/ml) closely followed by the water extract (IC_{50}:0.023 mg/ml). There were no significant differences in free radical scavenging activities between methanol and water extracts [44].

Cytotoxic Effect:

The methanolic extract of *Cotoneaster racemiflora* showed strong toxicity in the shrimp lethality test [7]. The methanolic extract was subsequently divided into n-hexane, ethylacetate, n- butanol, and water soluble extracts. Out of these extracts, ethylacetate soluble fraction showed strong toxicity in brine shrimp lethality test [38].

Radioprotective Effect:

The radioprotective effect of aqueous as well as alcoholic extracts of the Mann of the plant, against 2 Gy Gamma irradiation, was analyzed using micronucleus assay on bone marrow cells of male mice. Different doses of 250, 500, 1000 mg/ kg/ bw for aqueous and 3750, 7500, 15000 mg/ kg/ bw for alcoholic extract were administered (ip), for five constitutive days prior to 2 Gy gamma irradiation. The result compared with the known radioprotective effect of vitamin E after the same treatment schedule. High frequency of micronucleus was observed in non treated gamma-exposed mice, which represented the clastogenic effect of irradiation. Vitamin E, aqueous and alcoholic extracts treated mice represented a 5.56, 3.32 and 2.1 times decrease in the gamma-induced micronucleus frequency respectively [45].

Mutagenic and Antimutagenic Activities:

The mutagenic and antimutagenic activities of the water extract of the plant (with doses of 10000 mg/plate and lower) were investigated. The Ames test was performed as a standard plate incorporation assay with *S. typhimurium* strains TA98 and TA100 in the presence or absence of S9 (metabolic activation enzymes) mix. The assays were performed using the standard plaque incorporation method. The strains were tested on the basis of associated genetic markers. For each tester strain, a specific positive control was always used to test the experimental flaws, if any. While 4-nitro-O-phenylenediamine (4- NPDA, 20 mg/plate) for TA 98 and sodium azide (SA, 5 mg/plate) for TA100 were used as positive controls without S9 mix. Spontaneous revertants were within normal values in all strains examined. The average revertant colony numbers in negative control were 40±8 for TA98 and 115±6 for TA100 with S9 and 22±1 and 118±6 without S9, respectively ($p>0.05$). While application of S9 in TA98 was increased revertant colony numbers, application of S9 in TA100 was decreased revertant colony numbers ($p>0.05$). On the contrary, the plates with the positive control mutagens (SA, 2-AF, 2-AA and 4-NPDA) showed significant increases relative to the spontaneous mutation rate in the two tested strains. Most of the results, increasing or decreasing relative to negative control group, were not statistically significant at ($p <0.05$) in examined strains. In order to establish a dose-response relationship, 5 different concentrations of cotoneaster extract were tested, and no induced revertants were observed along the dose range tested in either with or without S9 with two strains. According to the results, all tested doses of cotoneaster extract were not mutagenic for *S. typhimurium* TA98 and TA100 in the presence and absence of S9 mix. Cotoneaster extract exhibited moderate antimutagenic activities at doses of 10000, 5000 and 1000 mg (32%, 33%, and 31%, respectively) against 4-NPDA in the absence of S9 mix in *S. typhimurium* TA98. It was appeared that there was dose-response relationships between the tested concentrations ($p<0.05$). Induced inhibition ratios were observed along the dose range tested in the absence of S9 mix. On the other hand, 100 and 10 mg doses of the extract were found to be weak antimutagenic with a ratio of 19% and 20%, respectively. While, cotoneaster extracts showed strong antimutagenicity at doses of 10000 (50%) and 5000 mg (49%) against 2-AF. 1000, 100 and 10 mg doses of the extract exhibited moderate antimutagenic activities in the presence of S9 mix in TA98 strain with a ratio of 40%, 29%, and 25%, respectively ($p<0.05$). It was appeared that metabolic activation enzymes (S9 mix) induced the inhibition ratios of the extract compared to those of extracts in the absence of S9, and a dose response relationship was observed along the tested dose range. It was seen that cotoneaster extract manifested moderate antimutagenicity at concentrations of 10000, 5000, 1000, and 100 mg (40%, 38%, 36%, and 27%, respectively) against SA, while 10 mg dose of extract was found to be weak antimutagenic with a ratio of 20% in the absence of S9 mix in TA100 strain. Except for 100 and 10 mg, all tested doses exhibited strong antimutagenic activity against 2-AA in the presence of metabolic activation system. The highest inhibition ratio (59%) was observed in 10000 mg/plate dose of the extract, followed by 1000 mg (58%) and 5000 mg (55%). Meanwhile, the extracts at concentrations of 100 and 10 mg were found to be weak antimutagenic

capacities with S9 in TA 100 strain. Accordingly, it appeared that cotoneaster water extract had significant antimutagenic capacity in the presence of metabolic activation enzymes (S9) for TA98 at concentrations of 10000, 5000,1000, and 100 mg/plate against 2-AF, for TA100 strain at concentrations of 10000, 5000,1000 mg/plate against 2-AA [44].

Antibacterial Activity

The antibacterial and anti-methcillin resistant *S. aureus* (MRSA) activities of water, methanol and ethyl acetate extracts of the plant were investigated by broth microdilution method. Water extract possessed remarkable antibacterial against gram positive microorganisms. The MIC values were determined as 0.625 mg/ml for *S. aureus* (MSSA), *S. aureus* (MRSA), and *S. lutea.* It has been seen that water extract revealed a significant effect against MRSA. While *E. faecalis* was the most sensitive bacterium. *B. cereus* and *S. pneumonia* were resistant Gram-positive bacteria against water extract. The MIC value of water extract was determined as 0.039 mg/ml against *E. faecalis*. Although *E. coli* was affected by water extract at a 0.625 mg/ml dose, *K. pneumoniae, S. enteritidis,* and *P. aeruginosa* were found to be resistant to this extract. Gram-negative microorganisms were more resistant than Gram-positive bacteria against water extract of cotoneaster. Methanol extract exhibited significant antibacterial activity against *E. faecalis* at a concentration of 0.312 mg/ml. The MIC values of methanol extracts were determined as 2.5 mg/ml against *E. coli, P. aeruginosa* MSSA, and MRSA. *B. cereus, K. pneumoniae, S. lutea,* and *S. enteritidis* were not affected by this extract at all tested doses. The MIC value was determined as 0.625 mg/ml for *S. pneumoniae*. While, *P. aeruginosa and S. pneumoniae* which resisted water extract, they were affected by methanol extract. However, MIC values of the water extract were lower than those of methanol extract. Except for MRSA strain, the ethyl acetate extract of cotoneaster exhibited antimicrobial activity at a concentration of 2.5 mg/ml against both standard and isolated bacteria. The MIC value was determined as 1.25 mg/ml for MRSA strain. The authors concluded that *E. faecalis* was the most sensitive bacteria and *B. cereus, K. pneumoniae,* and *S. enteritidis* were the most resistant bacteria to the tested cotoneaster extracts except to ethyl acetate extract. The extracts of cotoneaster displayed antimicrobial activity against both *S. aureus* ATCC 43300 and all of the14 tested MRSA *S. aureus* strains. Water extract of Cotoneaster exhibited significant anti MRSA activity at doses of 0.625 mg/ml against 10 MRSA strains. The methanol extracts of Cotoneaster showed anti MRSA activity at a dose of 2.5 mg/ml against 7 MRSA strain [44].

Enzyme Inhibitory Activities

Resin extract of the plant caused 10.3 ± 0.47 % inhibition of urease enzyme at a concentration of 1 mg/ml of extract. The strong urease inhibitory activity reflected the antibacterial properties against *H. pylori* which at least partially due to inhibition of urease [46].

The ethyl acetate, methanol and water extracts were tested for AChE, BChE, tyrosinase, a-amylase and α-glucosidase inhibitory activities using colorimetric methods. These activities were expressed as equivalents of standard inhibitors (galatamine for AChE and BChE, kojic acid for tyrosinae and acarbose for α-amylase and α-glucosidase). The methanol and water extracts exhibited remarkable AChE inhibitory activity with 4.30 and 4.77 mg GALAEs/g extract, respectively. However; water extract had the lowest inhibitory activity on BChE. With regard to tyrosinase inhibitory activity, water extract showed a good inhibitory activity with 32.31 mg KAEs/g. The tyrosinase inhibitory activity of ethyl acetate (24.22 mg KAE/g) was slightly different from that of the methanol extract (24.01 mg KAEs/g). Methanol extract possessed very good inhibitory activity against α-glucosidase and α-amylase. In α- glucosidase inhibition assay the activity was methanol > water > ethyl acetate. In contrast to α-glucosidase assay, the lowest α-amylase inhibition activity was revealed by water extract [44].

Conclusion

The current review clarified the main active ingredients and pharmacological effects of *Cotoneaster racemiflora* as a promising plant as a result of effectiveness and safety.

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