A glance at *Berberis integerrima* pharmacological effects and its active constituents

Mahmoodreza Moein¹,², Zahra Sabahi¹,*, Hasti Salim¹

¹Medicinal Plants Processing Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.
²Department of Pharmacognosy, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran.

Abstract

*Berberis integerrima* (family: Berberidaceae) is broadly used in the pharmacological studies as a rich source of active compounds. Among different compounds, alkaloids are the most isolated ones from various parts of this plant. Research in available databases including Web of Science, Pub Med and Google Scholar was used to reveal the pharmacological effects and active compounds of *B. integerrima*. The present review attempts to give a short overview on biological effects and active components of *B. integerrima* with emphasis on some mechanisms of activities. Scientific evidences suggested the possible therapeutic properties of this plant on diseases such as diabetes, inflammation, free radicals associated diseases, seizure and cancer. In this review, we evaluated the most correlated original articles to determine the effects of *B. integerrima* on different medical conditions. It seems that *B. integerrima* would be able to manage various types of disease; however more studies, particularly pharmacokinetic and clinical trials, need to be considered to improve our knowledge about toxicity and possible side effects of this plant.

Keywords: *Berberis integerrima*, alkaloid, berberine, phytochemical constituents.

1. Introduction

According to different taxonomy reports, Berberidaceae family comprises about 14 genera and 700 species and *Berberis* is the major genus in this family (1).

Phylogeny based study showed this genus have two source of diversity: Asia (or Eurasia) and South America. Taxonomists have described different classification. Among them, *Berberis khorasanica* Browicz and Zielinski, *Berberis scrataegina* DC., *Berberis orthobotrys* Bienert ex Schneid, *Berberis integerrima* Bunge (*B. integerrima*) and *Berberis vulgaris* L are grown in various region of Iran.

*B. integerrima* is famous as integrifolious barberry, distributing in the most region of Iran (2, 3) particularly in Tash valley, Shahrood and Semnan province (4). This plant has been known as ornamental herb. Fresh fruits are food additive in syrups, jellies, jams, juices, etc; also, root and fruits have mostly therapeutic applications (4).

This review focus on phytochemical characteristics and the pharmacological and experimental studies conducted to *B. integerrima* (Figure 1).

2. Active constituents

Alkaloids are the most isolated compound from various parts of this plant. The alkaloids derive which were isolated from leaves, stem and root have been listed below (Table 1).

Moreover, the oil content of *B. integerrima* seed was extracted by the solvent method. This oil have fatty acids (linolenic, linoleic and oleic as well as ω-3 and ω-6 fatty acid),
phytosterols comprise: β-sitosterol, campesterol, Δ5-avenasterol and stigmasterol as well as α- and γ-tocopherol are other contents of this oil (5). Also, 1-methyl malate (butanedioic acid, hydroxy, 1-methyl ester) is a simple organic acids, was isolated from fruits of B. integerrima. This compound has been used in β-lactam rings synthesis which is a part of different penicillin derivatives structure (6).

3. Pharmacological studies

3.1. Antioxidant effects

Potency of antioxidant capacity of the B. integerrima seed oil has been measured by evaluating 2,2 diphenyl-1-picryl hydrazyl (DPPH) scavenging activity (IC\textsubscript{50}:5.47±0.01 mL/L) and ferric-reducing antioxidant power. Reducing power result was 5.68 µmol Fe (II) per gram of oil. Indeed, This seed oil was able to protect soybean oil against oxidation as compared to commercial antioxidants (5). In other study, antioxidant activity of fruit extract of four samples of B. integerrima (collecting from various region of Iran) were measured by DPPH and ferric reducing antioxidant power (FRAP).

The DPPH inhibition percentages were 74.72, 20.69, 48, 61%; Trolox equivalent (TE) were 70.39, 20.36, 40.98, 60.27 and Fe\textsuperscript{2+} chelating activity were 41.46, 18.56, 40.53, 46.21%. These results related to high amount of phenolic compounds, anthocyanins and flavonoids in these fruits. Also, they are source of antioxidant enzymes such as guaiacol peroxidase (G POD) and catalase (CAT)(10).

In another study, these fruits exhibited low TE in Oxygen radical absorbance capacity assay (ORAC) test and low EC\textsubscript{50} in cellular antioxidant assay. Moreover, the fraction of these fruits strongly inhibits xanthine oxidase activity, which playing critical role in free radicals production. This fraction also protect human lymphocyte against H\textsubscript{2}O\textsubscript{2} induced DNA damages (11). Since this fraction is rich source of polyphenols, these activities can be due to their content(12).

<table>
<thead>
<tr>
<th>Parts of plant</th>
<th>Isolated alkaloids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaves (7)</td>
<td>reticuline, isoboldine, isocorydine, glaucine, armepavine, oxyacanthine, and heliamine, intebrinine, intebrimine</td>
</tr>
<tr>
<td>Stem (8)</td>
<td>glaucine, thalicmidine, isocorydine, oxyacanthine, berberine, armepavine, berbamime, palmatine, jatrorrhizine, columbamine, 8-trichloromethylhydroberberine, 8-trichloromethylhydrodipalmatine</td>
</tr>
<tr>
<td>Roots (9)</td>
<td>Palmatine, Berberine, Jatrorrhizine, columbamine</td>
</tr>
</tbody>
</table>
3.2. Antibacterial effects

The ethanol extract of *B. integerrima* fruits showed antibacterial activity against clinical isolate *Staphylococcus aureus*. 1-Methyl Malate which was isolated from these fruits enhanced the antibacterial activity of ampicillin against this strain. 1-methyl malate (2 mg/ml) was able to reduce the MIC of ampicillin from 128 to 1 μg/ml (6). In other study, four isolated alkaloids from *B. integerrima* root (columbamine, palmatine, berberine and jatrorhizine) exhibited antibacterial activity against *Brucella abortus*. 15 μg/ml of jatrorhizine and columbamine were comparative to 10 μg/ml streptomycin (9).

3.3. Antidiabetic effects

According to ethnopharmacological study, *B. integerrima* has been known as an antidiabetic plant in persian folk medicine (13). Several investigates have been evaluated antidiabetic effect of this plant and mechanisms of action in animal models. These studies were focused on antidiabetic effects of fruits and root. Fallah *et al*. examined...
ined the effect of aqueous extract of *B. integerrima* fruits on insulin resistance in high fructose-fed insulin-resistant rats. In this evaluation, rats were fed with a high-fructose diet then the extract was administrated (1000 mg/kg). This treatment showed significant decrease in the levels of insulin and blood glucose. The results show elevated level of adiponectin, while in treated and non-treated groups there is no significant difference between mRNA and protein level of GLUT4 and PPAR-γ. Hence, this mechanism was not related to GLUT4 and PPARγ pathway. The suggested mechanism of this extract was insulin-like effect and an enhancement of adiponectin levels (14). Adiponectin is secreted by adipocytes and show critical role in obesity-related diseases like insulin resistance and type 2 diabetes (15-17). Also, administration of adiponectin in humans and rodents lead to insulin-sensitization(15), therefore if the probable mechanism of this extract is adiponectine enhancement it would be proper candidate in management of diabetic complications.

Ashraf et al. examined hypoglycaemic effects of fruit aqueous extract in Streptozotocin-induced diabetic Rats. In this research, While, treatment of diabetic rats with glibenclamide (0.6 mg/Kg) for 42 days decreases hyperglycemia but their treatment with the aqueous extract was not able to improve the glucose concentration in comparison to untreated ones (18). In other study, the administration of anthocyanin fraction from the fruits of *B. integerrima* (400, 1000 mg/kg) to streptozotocin-induced diabetic rats decreased blood glucose, increased liver glycogen and body weight as compared with control. Though, they could not see any synergistic effects between this fraction and metformin or glibenclamide to improve these factors (13). In this study possible antidiabetic mechanisms of fruit anthocyanin were refered to antioxidant activity, protection of pancreatic β-cells against oxidative stress, induction of insulin secretion, activation of phosphorylation of AMP activated protein kinase (AMPK) and increase glucose intake by skeletal muscle (13). Phenolic compound like anthocyanin improve glucose metabolism, lipid profile, regulating the hormones and enzymes. Consequently the molecular mechanisms in glucose and lipid metabolism would offer novel insights in antidiabete effects of herbal medicine (19, 20).

In other research administration of aqueous extract of *B. integerrima* root (500 mg/kg) for 6 weeks improve kidney parameters and renal function to near normal (serum creatinine, blood urea nitrogen, urine glucose, urine urea and urine creatinine, urine protein, urine albumin, and water intake) and increased body weight as well. Also, histopathological study confirmed renal protective effect of this extract in diabetic samples (21).

Moreover, intra gastric consumption of root aqueous extract (500 mg/Kg) for 6 weeks (3 weeks before STZ injection and continued for another three weeks) was resulted in significant improvement in the levels of blood glucose, malondialdehyde (MDA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total bilirubin. This treatment also increased body weight, total protein, SOD, CAT and glutathione (GSH) in comparison to diabetic control rats. So, administration of this extract can be considered as ameliorating factor in diabetic liver complications. Berberine and alkaloids present in *B. integerrima* root can play critical role as α-glucosidase inhibitors, glucose absorption inhibitor and peripheral glucose uptake induction. Furthermore, SOD and CAT play critical role improving ROS cellular damages in diabetes complications (22). It is also suggested that hypoglycemic effects of berberine can be mediated by other mechanism such as improvement of gut-derived hormones, reduce defect of mucosal barrier function and decrease the proinflammatory fluctuations of intestinal immune cells and cytokines(23).

In other study, STZ- injection in rats lead to significant increases in the biochemical factors such as blood glucose, triglycerides (TG), total cholesterol (TC), low density lipoprotein LDL-cholesterol (LDL-C), creatinine (Cr), urea, ALT, AST, ALP and total bilirubin. Diabetic rats were treated by 250 and 500 mg/kg of root extract of *B. integerrima* for six weeks. Results exhibited significant reduction in blood glucose, TG, TC, LDL-cholesterol, ALT, AST, ALP, total bilirubin, creatinine and urea compared to untreated diabetic rats. This extract in dose of 500 mg/Kg is more
effective on all parameters except blood glucose when compare to glibenclamide (0.6 mg/Kg) as standard drug. This study suggested root of *B. integerrima* as antihypoglycemic, antihypolipidemic and antioxidant candidate in diabetes (24).

3.4. Antiinflammatory effect

In other research the impact of *B. integerrima* fruit on lymphocytic immune responses was evaluated. So, splenocytes of Balb/c mice expose to the phytohemagglutinin and lipopolysaccharide as mitogens and aquatic and alcoholic extract of *B. integerrima* (0.001–1000 μg/ml) simultaneously. Both extracts inhibited production of IFN-γ from splenocytes and boosted release of IL-4, IL-10 and TGF-β. Other effects comprise suppress T-cell expansion and increase B-cell proliferation. This extract could be considered as humoral immunity stimulant (25).

In other study, macrophages and lipopolysaccharide-stimulated macrophages were treated by alcoholic and aqueous extracts. Both extracts blocked nitric oxide production. Low dose of them were able to suppressed TNF-α production while aqueous extract induce that. Furthermore, release of IL-6 was inhibited while release of IL-12 was increased. These data suggested that extract showed anti-inflammatory functions by altering cytokine production and release (26). Previously anti-inflammatory activity of other *Berberis* genus has been reported for *B. aristata* (27), *B. vulgaris* (28) and *B. crataegina* (29).

3.5. Anticancer

Potency of anticancer effects of *B. integerrima* was carried out by Malayeri *et al.* In this study, colon cancer was induced in male wistar rats by injecting 1,2-dimethyl hydrazine (DMH). They received *B. integerrima* fruit hydroalcoholic extract (50 and 100 mg/kg b.w). To some extent, this treatment improved the levels of ferric reducing ability of plasma (FRAP), the hepatic glutathione S-transferase (GST), cytochrome P450 (CYP450) and β-catenin. Also, aberrant crypt foci (ACF) formation in colon tissue of DMH-treated rats was reduced by this extracts. So, this extract could be potent chemotherapeutic agent against colon carcinogenesis in future studies (30).

*B. integerrima* pharmacological effects and active constituents

3.6. Protective effect

*B. integerrima* root extract has been reported as an effective agent in protecting against CCl4-induced testicular damages in wistar rats. This extract improve different factors such as serum testosterone level, testis weight, testosterone level, seminiferous tubules diameter, thickness of the epithelium, tubule differentiation index, spermiogenesis index and catalase activity. Other parameters such as interstitial tissue thickness and malondialdehyde reduced significantly. The 500 mg/kg of extract is more effective than silymarin (50 mg/kg) as a reference drug. Since carbon tetrachloride induce toxicity by tissue oxidative damage and

*B. integerrima* root are rich source of alka-loids hence, these effects would be related to anti-oxidant activity of this natural compounds (31).

Other studies have confirmed that anthocyanin fraction of *B. integerrima* fruits protected HepG2 and MCF7 cells against hydrogen peroxide (H2O2) induced cytotoxicity. In this assay, the cells were pre-exposed (24 h) to anthocyanin fraction then cytotoxic concentration of H2O2 was added.

Anthocyanin fraction (200 and 400 μg/ml) increased viability of MCF7 cells when compared with the control. But there is no difference between viability of treated and non-treated HepG2 cells. In other test, the cells were exposed to anthocyanin fraction and toxic concentration of H2O2, simultaneously. The results showed anthocyanin (25-400 μg/ml) protected MCF7 cells against H2O2 cytotoxicity. While 100, 200 and 400 μg/ml of fraction increased HepG2 cells viability (32). Interaction of the H2O2 and the superoxide (O2•- ) resulted in formation of hydroxyl radicals, which are highly reactive free radical (33, 34). Subsequently, this protective effect would be associated with anti-oxidant activities of anthocyanin in this fraction. Meanwhile flavonoids are considered to reduce risky effects of free radicals by different mech-anisms: scavenging free radical through dihydroxy groups in their structure and conjugation with transition metals consequently free radical formation is inhibited (12, 35).
3.7. Anticonvulsant

Epilepsy is a neurological disorder with abnormal brain activity, seizures or unusual behavior.

Hosseinzadeh et al. and coworkers evaluated the anticonvulsant activity of methanolic extract, hydromethanolic and chloroform fraction of *B. integerrima* root.

Pentylenetetrazole (PTZ) and maximal electroshock (MES)-induced seizure models were considered in this study. In the PTZ test, extract and fractions improved the onset time of hind limb tonic extensions (HLTEs).

While in the MES test, these samples were unable to reduce HLTE duration significantly. So, it seems that *B. integerrima* can be an anticonvulsant factor in PTZ-induced seizures and may be worthwhile in petit mal epilepsy. As the methanolic extract show better results in comparison to chloroform fraction in petit mal epilepsy, consequently it can be related to the presence of alkaloids and tannins, which have been found in its methanolic extract (36). Other studies confirmed anticonvulsant activity of some alkaloids and berberine which were detected in root and stem bark of *Berberis* species (37, 38). These compounds are effective in mental depression, anxiety. The anticonvulsant effect of this plant may be related to these mentioned effects on central nervous system (36). Sadeghnia et al. used 4-aminopyridine (4-AP) as a convulsant factor by inducing the neurotransmitter (glutamate) release and lead to seizures. According to the results berberine reduced release of hippocampal aspartate and glutamate and play as an anticonvulsant factor properly (38). Other studies also suggested modulating neurotransmitter systems as a mechanism of berberine anticonvulsant effect (39, 40).

3.8. Antinociceptive effect

Hajhashemi et al. studied antinociceptive effect of total extract and its alkaloid fractions of *B. integerrima* root. According to the results of various test, probable antinociceptive mechanism was mediated by suppressing pains with inflammatory origins and anti inflammation mechanism (41).

3.9. Anti hypertension effect

To evaluation of *B. integerrima* fruits effects on hypertension, monocrotaline was injected to rats, after two weeks they received aqueous fruit extracts (50, 100, and 200mg/kg) or sildenafil (30mg/kg/d) for 2 weeks. Extract (200mg/kg) and sildenafil significantly reduced the right ventricular systolic pressure, right ventricular hypertrophy and the medial wall thickness. It seems that *B. integerrima* extract was more effective than sildenafil on improvement of the monocrotaline-induced pulmonary hypertension (42).

In other study, the effects of aqueous extract of this plant on hemodynamic and electrocardiogram (ECG) indices of rat were evaluated. The rats received 50, 100, and 200 mg/kg/day of fruit extract for two weeks and after 15th days, data were collected. Electrocardiogram evaluation showed these administrations had no significant effects on heart rate, RR interval, P duration, and Q wave amplitude of electrocardiogram as well as blood pressure. The doses of 100 and 200 mg/kg increased the QRS interval but decreased the QTc interval, the JT interval and TpTe interval when compared to control and 50 mg/kg. According to these results, high dose of extract extended the depolarization phase and decreased the repolarization phase of ventricular muscle so this extract would play as an antiarrhythmic factor and in some cases could be even arrhythmogenesis. It seems that these pharmacological effects are not associated with berberine and other components (43).

4. Discussion

As discussed previously, the most considered bioactive compounds isolated from this plant are alkaloids. isoquinoline alkaloids were isolated from stem and Quaternary benzylisoquinoline alkaloids isolated from root. Some other alkaloids are isolated from leaves.

Based on in vitro and in vivo pharmacological studies, *B. integerrima* can be considered as natural source in pharmaceutical development in order to treatment of various diseases such as diabetes, cancers, hypertension, inflammation, and bacterial infections. Antidiabetic effects were more investigated followed by antioxidant and
protective effects. Moreover, the antioxidant and chemopreventive properties of this herb may reveal the potential of *B. integerrima* as an adjuvant therapy for free radicals associated diseases.

Further investigations should be completed to improve our information about toxicity, probable side effects and herb-drug interaction. Other drawback of this field is lack of pharmacokinetic data to reveal absorption, distribution, metabolism of this plant. These types of studies help to increase our knowledge about metabolism and choose proper formulations for this plant product.

**Conflict of Interest**

None declared.

**5. References**


13. Ghoshal K, Bhattacharyya M. Adiponectin: Probe of the molecular paradigm associating


38. Sadeghnia HR, Taji AR, Forouzanfar F, Hosseinzadeh H. Berberine attenuates convulsing behavior and extracellular glutamate and aspar-


