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Berberis vulgaris: specifications and traditional uses

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ABSTRACT

The medicinal plants from genus *Berberis* are particularly important in traditional medicine and the food basket of Iranians. Given various plants from genus *Berberis* and their economic, nutritional, and medicinal status in Iran, this study seeks to investigate the findings of recent studies on the phytochemical characteristics, specifications, and uses of *Berberis vulgaris*. In this review article, 350 articles were initially retrieved from reliable scientific databases using relevant search terms. Then, 230 articles were selected and 120 were excluded after a primary analysis. Finally, 98 articles related to the subject under study were meticulously examined and the required data were extracted and classified according to the research purposes. The findings were divided into eight separate sections: Introducing Berberidaceae family, different species of Berberis, pharmaceutical organs, *B. vulgaris* nutrition facts and minerals, the antioxidants and alkaloids compounds in fruit and other organs, action mechanisms of preventing and treating diseases, traditional uses of *B. vulgaris*, and its properties reported by recent studies. The results briefly indicate that *B. vulgaris* contains a large number of phytochemical materials including ascorbic acid, vitamin K, several triterpenoids, more than 10 phenolic compounds and more than 30 alkaloids. Therefore *B. vulgaris* may have anti-cancer, anti-inflammatory, antioxidant, antidiabetic, antibacterial, analgesic and anti-nociceptive and hepato-protective effects. Regarding the use of different organs of *B. vulgaris* in traditional medicine and their confirmed effects in the recent studies, it is possible to use different organs of *B. vulgaris*, especially fruit, to develop new drugs.

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Introduction

Medicinal plants have been known among different nations since thousands of years ago and have been used throughout many centuries according to the traditional medicine of most countries. In recent decades and despite the emergence of synthetic drugs, medicinal plants continue to be welcomed and are being used in many countries due to safe use, efficiency, cultural acceptance, and fewer side effects than synthetic drugs (1, 2). As with other countries, in Iran, different medicinal plants, including those from genus *Berberis*, are used to treat diseases according to traditional medicine (3, 4).

Genus *Berberis* is native to moderate and semitropical regions of Asia, Europe, Africa, North America, and South America. Different plants of genus *Berberis* can occur in many regions across the world including Iran (5). Iran is the biggest producer of *B. vulgaris* fruit in the world, with 11000 hectares of land under cultivation. Over 10000 tons of dried *B. vulgaris* fruit are produced in Iran per year. Among the provinces of Iran, Southern Khorasan is one of the biggest producers of *B. vulgaris*. Over 97% of all the lands under *B. vulgaris* cultivation are located in Ghaenat County, Southern Khorasan province, producing 95% of the whole *B. vulgaris* fruit in Iran (6, 7).

Various species of the genus *Berberis* which occur around the world are cultivated and grown up for specific purposes (8). *B. vulgaris* is the most widely known *Berberis* which is mainly used as a food is cooked with rice (seedless or red), *B. integerrima*, also referred to as black barberry and wild *barberry,* are used mainly for juice extraction in food industries and as medication (9, 10).

Medicinal uses of *B. vulgaris* in Chinese medicine date back to over 3000 years ago and in some other countries to over 2500 years ago (3, 5). In Iran, Rhazes was the first one to introduce the medicinal properties of *B. vulgaris* and considered its use to be helpful for human being (11). There are a variety

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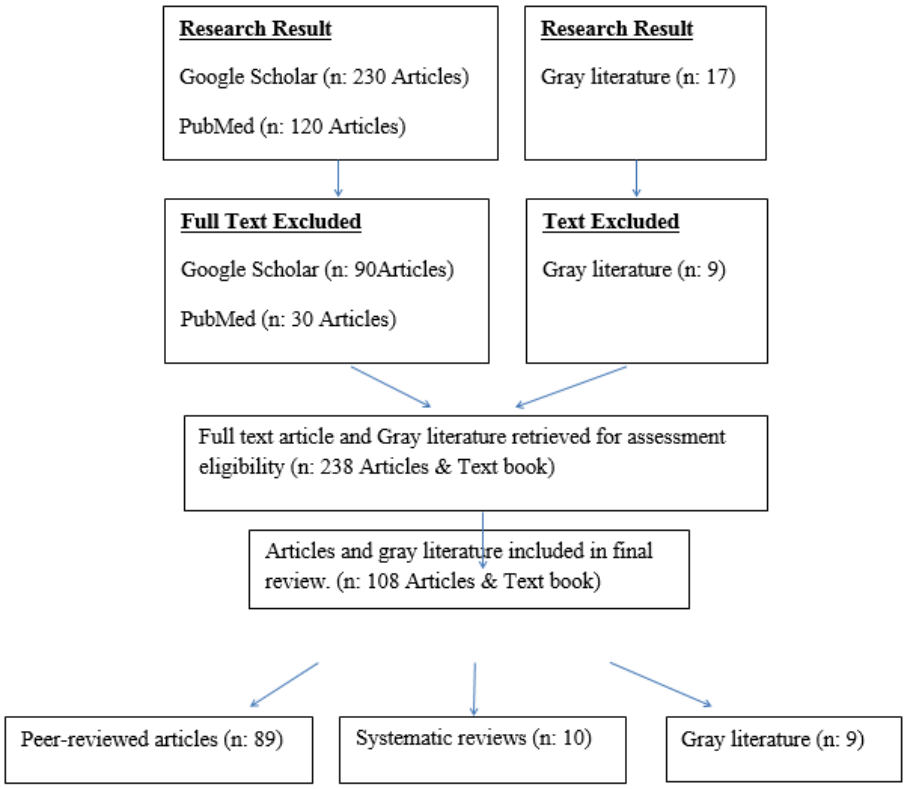


Figure 1. Flow chart of research design

of alkaloids in the various organs of this plant, most important of which is berberine. This alkaloid can exert different effects, including antioxidant, anti-inflammatory, hypoglycemic, hypotensive, and hypolipidemic activities (12, 13).

Different organs of *B. vulgaris* are used in food and pharmaceutical industries and the decorative species are used to decorate different places. According to traditional medicine, *B. vulgaris* is used to treat fever, cough, liver disease, depression, hyperlipidemia, hyperglycemia and bleeding (14, 15).

Over 500 plants from genus *Berberis* are accessible to people across the world with four pharmaceutical organs being used to treat different diseases. *B. vulgaris*, *B. orthobotrys*, *B. khorasanica*, *B. integerrima*, *B. crataegina*, *B. lycium, and B. aristata* are used in traditional medicine more frequently in Iran and other parts of the world (16-18). Hence, this study was conducted to present the phytochemical characteristics, the findings of the experimental studies and the clinical trials conducted on the most frequently used species of the plants from this genus in traditional medicine, focusing on *B. vulgaris* which is the most frequently used plant of this genus.

Therefore, the present review is mainly focusing the research reports on the pharmacological effects in traditional and modern medicine and various chemical constituents in *B. vulgaris.*

Materials and Methods

In this review article, 350 articles were initially retrieved from reliable scientific databases using relevant search terms. Then, 230 articles were selected and 132 ones were excluded after a primary analysis. Finally, 98 articles that were related to the subject under study were meticulously examined and the required data were extracted according to the research purposes and classified. In summary our method is presented as flow chart in Figure 1.

Results

The findings were presented in eight separate sections: Introducing *Berberidaceae,* family different plants of genus *Berberis*, pharmaceutical organs, *B. vulgaris* nutrition facts, vitamins, and minerals, the antioxidants and alkaloids in fruit and other pharmaceutical organs, action mechanisms of preventing and treating diseases, uses of *B. vulgaris*, and its properties reported by recent studies. Besides that, the pharmaceutical and therapeutic properties of the pharmaceutical organs of some species from Berberidaceae family are shown in Table 1.

Berberidaceae

The plants from Berberidaceae family *a*re often acanaceous shrubs with 1-5 m height and rarely small. The internal surface of the bark and wood of these plants are yellow, brown, or purple.

The branches of these plants are cylindrical, angular, or striate and sometimes covered by wax. The leaves of long branches are transformed to single, binary, or triple thistles, sometimes clawed or leaf-like and located in short branches or short small branches with batch oriented, lint-less, without petioles or with short petioles, the lower surface is sometimes covered with a waxed layer.

The flowers are yellow and sometimes with a differently colored strip, red-stripped, and with senary sepals or petals. Petals are often smaller than sepals. The stamens are scenery and often smaller than petals. The fruits of the plants from Berberidaceae family are bright red or blackish red and taste sour (19, 20). After falling leaves in autumn and passing through winter, the shrubs of barberries begin to flourish in March and flower in June. The fruits are rape and can be harvested in October (21).

Genus *Berberis*

The genus *Berberis* (Berberidaceae) includes about 500 species worldwide (22). Berberidaceae family includes approximate 14 genera and 700 species (23). *Berberis* is a major genus in dicotyledonous woody plants of Berberidaceae family. Different taxonomists have reported disparate number of species and in the family likewise species in the genus. For many, the family comprises upon *ca.* 17 genera containing 650 species (24), while for several others there are 14 genera and *ca.* 715 species (25). Furthermore, Whetstone *et al* (1997) and Nickol (1995) are in favor of 15 and 13 genera with *ca.* 650 and 570 species respectively in the family (26). Similarly, according to Ahrendt (1961) and Adhikari (2010), *Berberis* includes *ca*. 450 (excluding *Mahonia ca.* 100) and more than 500 (inc. *Mahonia*) species correspondingly. Berberis is the largest woody plant genus of the basal eudicots (12, 27). The genus includes four species in Iran: *B. integerrima* Bunge, *B. crataegina* DC, *B. vulgaris* L. and *B. orthobotrys* Bienert (28).

Two species, *B. orthobotrys* and *B. khorasanica* occur exclusively in Iran, and *B. integerrima, B. crataegina* and black barberry, occur also in Eastern Anatolia, eastern Iraq, Afghanistan, Upper Caucasus, Turkmenistan, western Pakistan, Kashmir, and Central Asia. Some species of genus *Berberis* have recently been imported into Iran and cultivated and propagated in different regions for decorative uses (8).

Pharmaceutical organs of B. vulgaris

In traditional medicine, different organs of this plant are used to treat diseases. Fruit, bark, root, and stem are the pharmaceutical organs of *B. vulgaris*. Fruit is the most frequently used organ of this plant in traditional and modern medicine (21, 29).

Nutrition facts of B. vulgaris fruit

B. vulgaris fruit is sour and contains different nutrients including dextrose, fructose, malic acid, tartaric acid, citric acid, pectin, and resin. It is also rich in vitamins C and A, calcium, iron, and potassium (16, 30). In *B. vulgaris* fruit, the concentrations of iron, zinc, copper, and manganese are estimated 2650 mg/kg, 27.5 mg/kg, 33.7 mg/kg, and 58.6 mg/kg, respectively (10). Decomposition of *B. vulgaris* fruit shows that this fruit contains 79.6% humidity, 1.16% fat, 2% protein, 16.24% carbohydrate, and 0.99% ash. The amount of anthocyanin is estimated 281 mg/l (31).

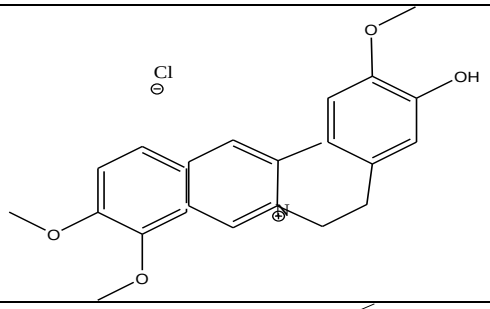
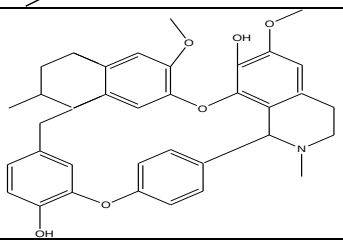
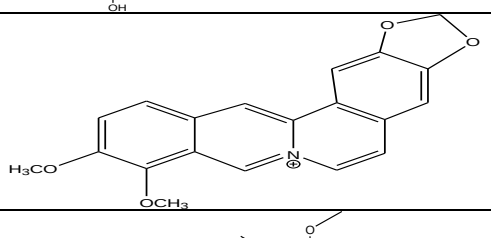
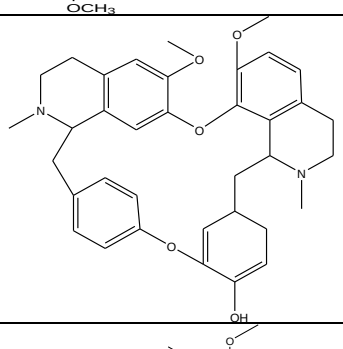
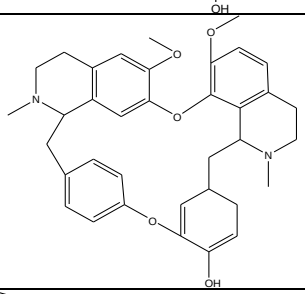
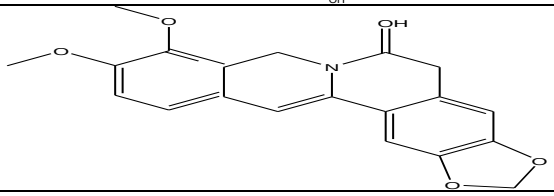
In Iran, dried *B. vulgaris* fruit is used in many foods. As well, the fruit or its derivatives are used to produce certain products such as sauce, jelly, juice, jam, marmalade, and carbonated drinks. Besides that, *B. vulgaris,* considered of nature-based and useful substance, is used to season, flavor, and garnish foods to satisfy different sapors (32, 33). This fruit is also used in industries. For example, the anthocyanin found in *B. vulgaris* fruit is used as a nature-based color (6).

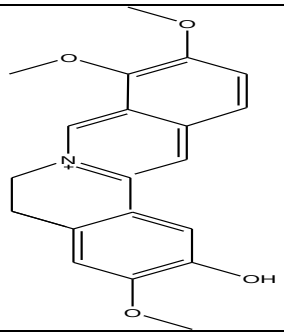
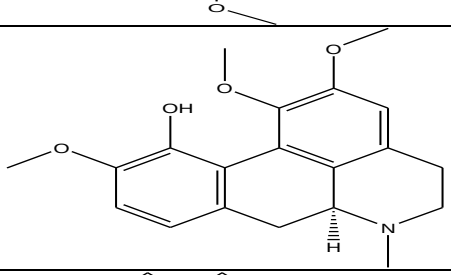
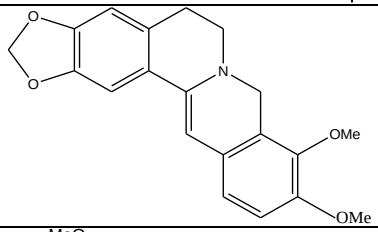
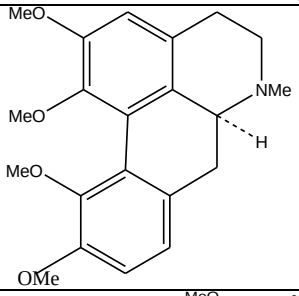
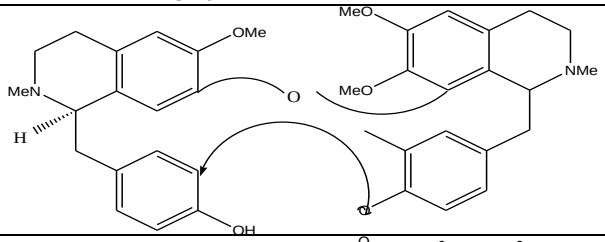
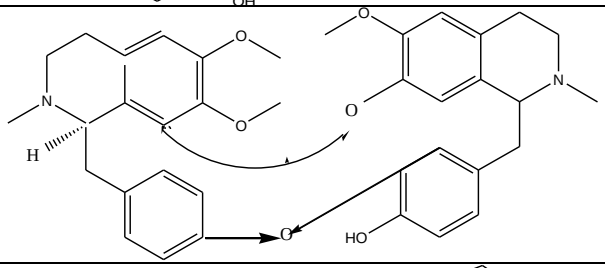
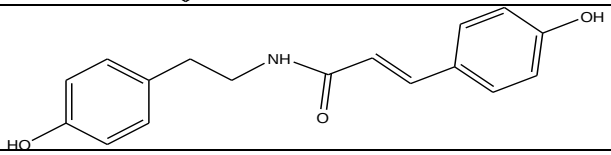
Secondary metabolites of B. vulgaris fruit and other medicinal organs

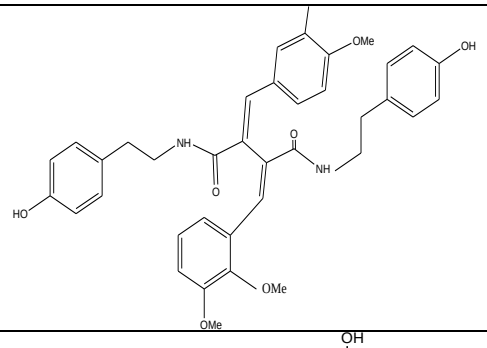
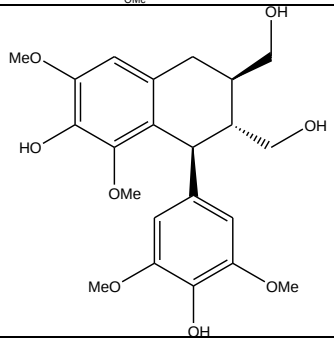
Many metabolites of various species of *B. vulgaris* have been reported. Phytochemical analysis revealed the presence of alkaloids, tannins, carotenoid, vitamin, protein, lipid, anthocyanin and phenolic compounds. Most compounds are summarized in Table1. The highest amounts of phenolic compounds and anthocyanins can be found in *B. vulgaris* juice and the highest amount of flavonoid compounds in *B. vulgaris* leaves. Regarding the importance of investigating *B. vulgaris* quality, the amount of anthocyanin in the fruit to be an important index of *B. vulgaris* quality (21). The concentrations of flavonol, flavonoid, and phenol of *B. vulgaris* fruit are 25.3 mg/g, 12.2 mg/g, and 0.54 mg/g, respectively (10).

Action mechanism of B. vulgaris in preventing and treating diseases

In all organs of *B. vulgaris*, certain alkaloids such as berberine, oxyaconthine, berbamine, brolicin, and columbamine are found. The amount of alkaloid is higher in the root bark than other organs of *B. vulgaris*. Berberine is one of the most important alkaloids of this plant that can be effective in preventing coronary artery disease and possibly reducing the levels of total cholesterol and triglyceride (36). The most important property of berbamine is to block calcium channels. This alkaloid was found to be active in the tests of lipids peroxidation in red blood cells and can exert anti-myocardial ischemia and antiarrhythmic effects. Besides that, oxyaconthine has a sympatholytic and vasodilatory agent (37).

Secondary Metabolite	Structure	References
Alkaloids		
Jatrorrhizine Chloride		(13)
Aromoline		(12, 13)
Berberine		(12, 13)
Berbamine		(12, 13)
Palmatine Chloride		(12, 13)
Oxyberberine		(12)

Columbamine		(12)
Isocorydine		(12, 14)
Lambertine		(12)
Magniflorine		(12)
Bisbenzlisoquinolines		(12)
(+)-Oxycanthine		(12, 13)
N-(*P-Trans*-Coumaroyl) Tyramine		(12)

Cannabisin G		(12)
(±)-Lyoniresinol		(12)
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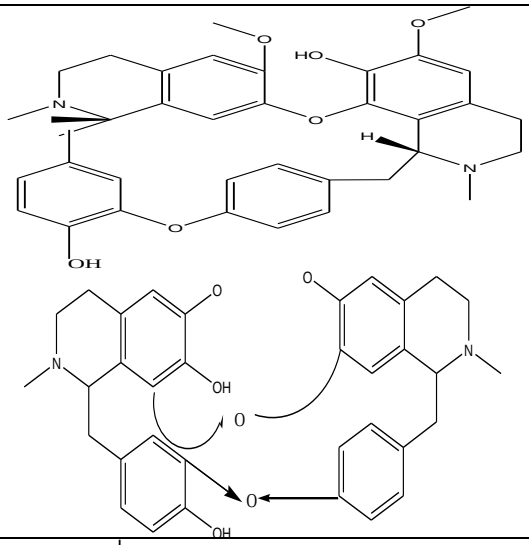
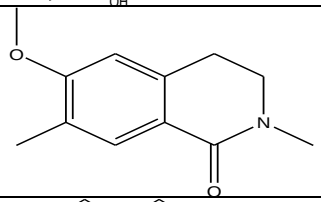
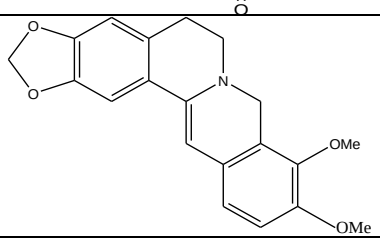
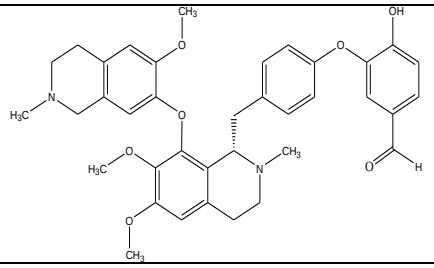
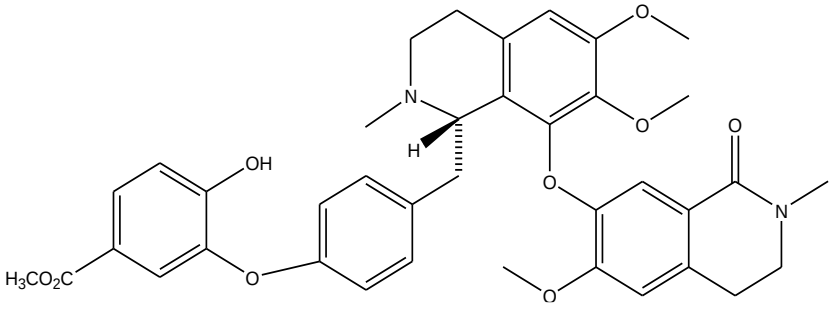
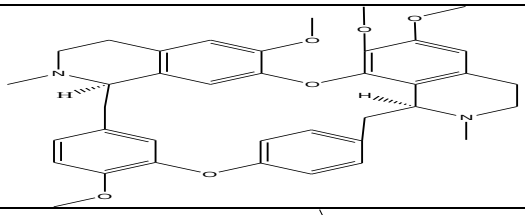
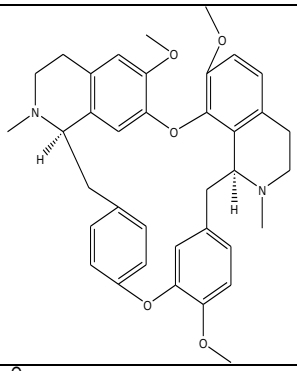
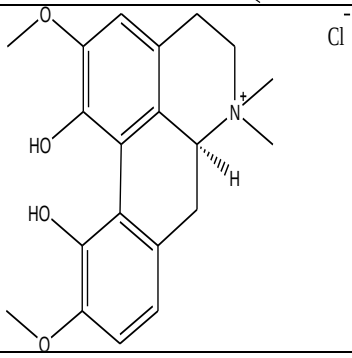
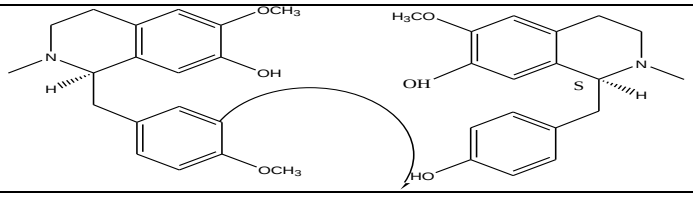
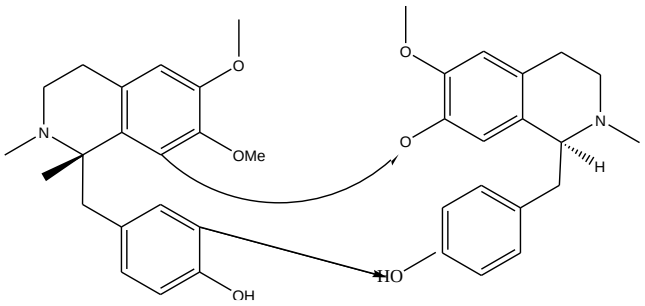
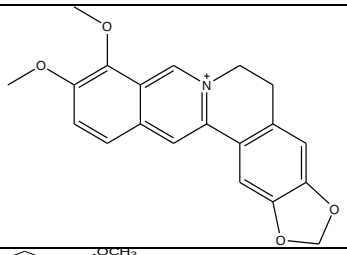
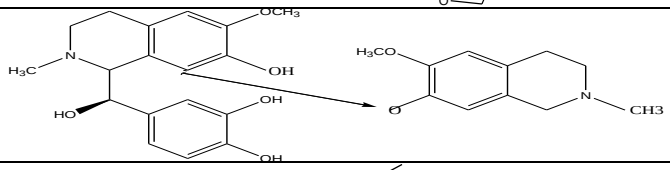
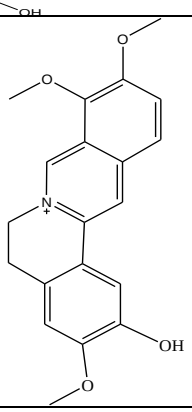
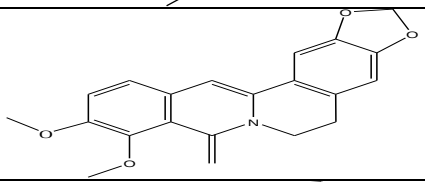
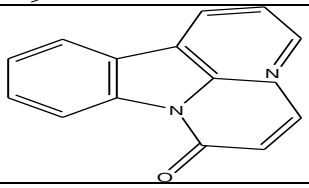
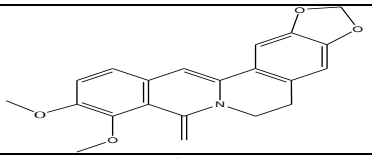
(+)-Obamegine		(13)
Thalifoline		(13)
8-Oxyberberine		(13)

Baluchistanamine		(13)
(−)-Tejedine		(13)
(+)-Obaberine		(13)
(+)-Isotetrandrine		(13)
Magnoflorine Chloride		(13)

(+)-Thaligrisine		(13)
Beriambine		(34)
Berberrubine		(34)
Bargustanine		(34)
Columbamine		(14)
Berlambine		(34)
Hydroxycanthine		(14)

Berlambine		(14)
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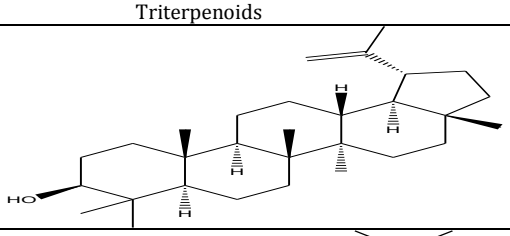
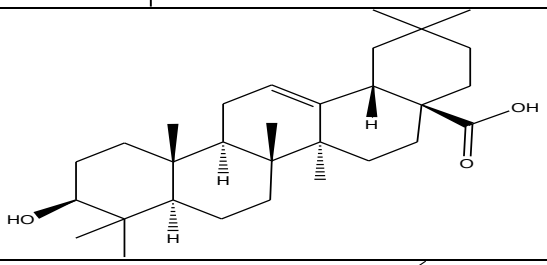
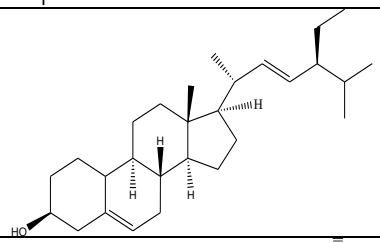
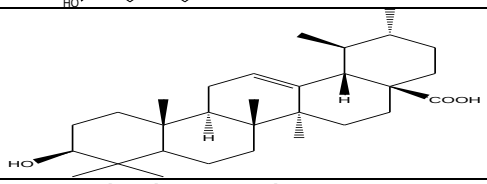
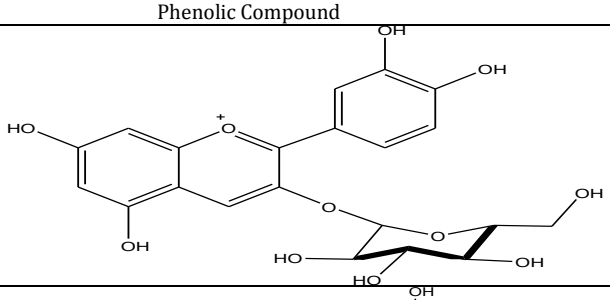
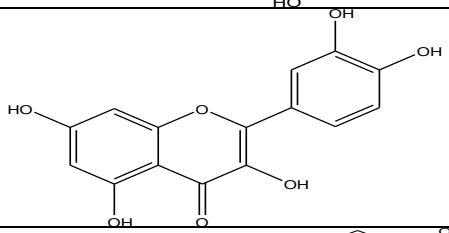
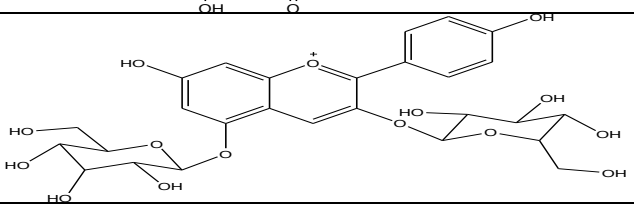
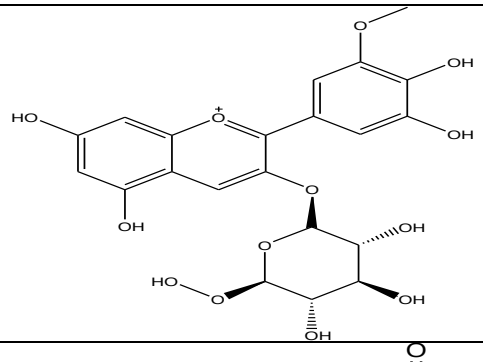
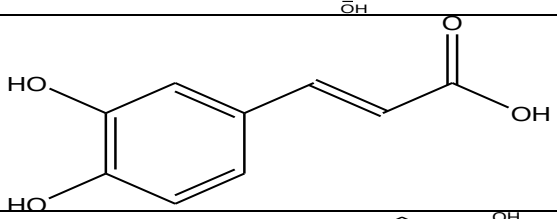
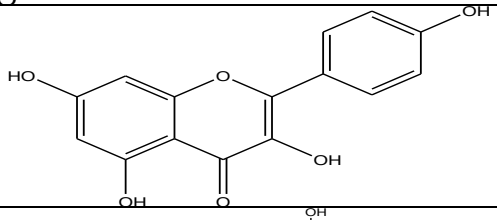
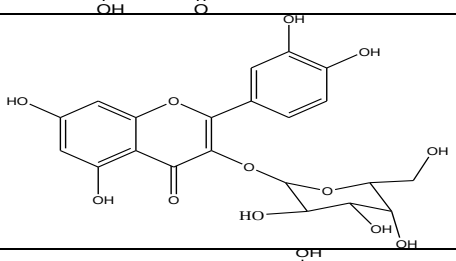
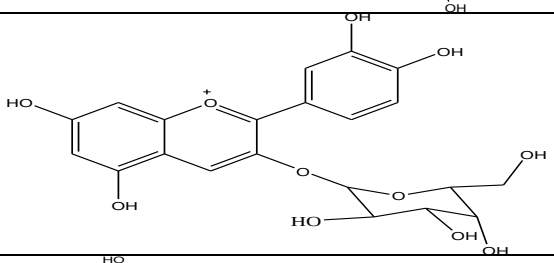
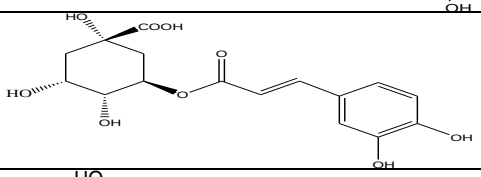
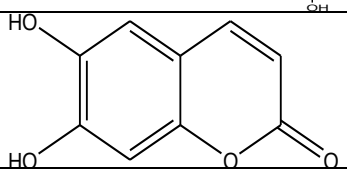
Lupeol		(12)
Oleanolic Acid		(12)
Stigmasterol		(12)
Urosolic Acid		(34)
Phenolic Compound		
Chrysanthemin		(34)
Quercetin,		(13, 35)
Pelargonin		(34)

Petunidin-3-O-Beta-D-Glucoside		(34)
Caffeic Acid		(34)
Kaempferol		(13, 35)
Hyperoside		(34)
Chrysanthemin		(34)
Chlorogenic Acid		(34)
Aesculetin		(34)
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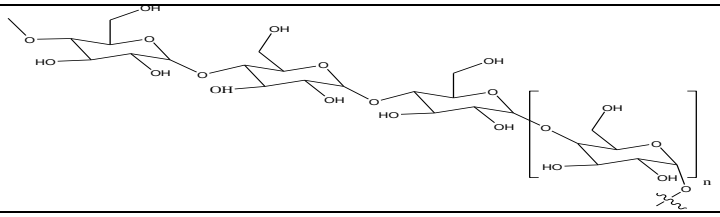
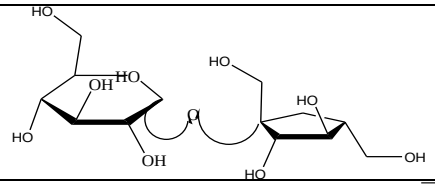
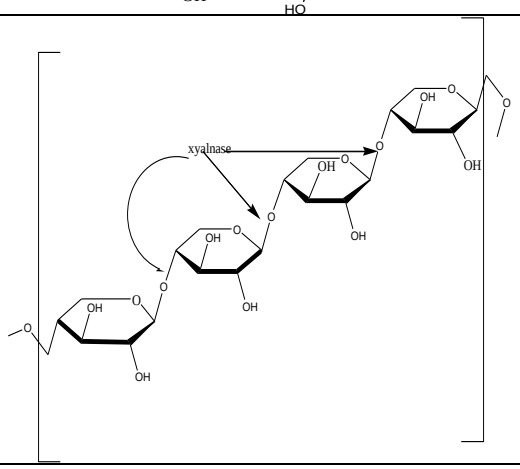
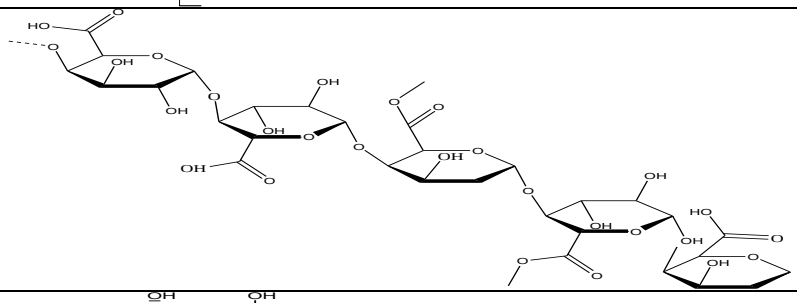
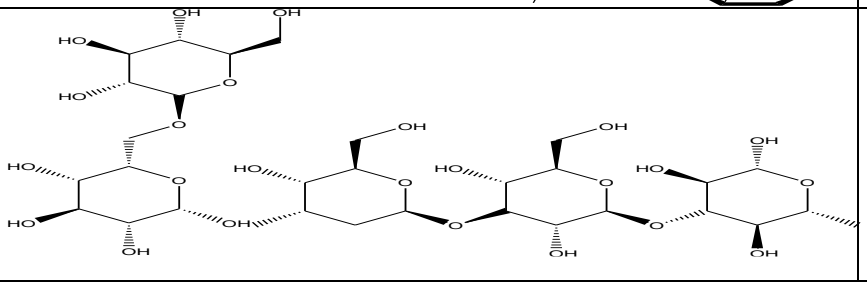
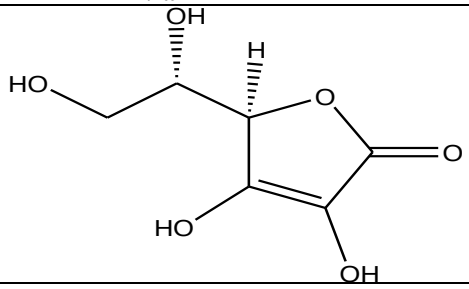
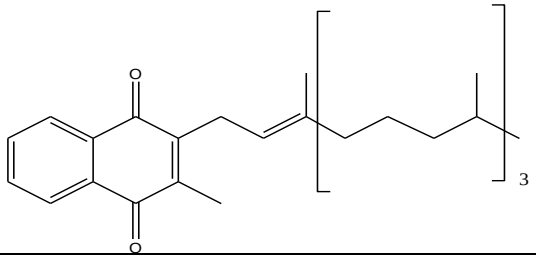
Polysaccharide		(34)

Sucrose		(34)
Xylan, Beta		(34)
Pectin		(34)
Glucan, Alpha		(34)
Vitamin		
Ascorbic Acid		(34)
Vitamin K		(34)

Recently, berberine has been reported to decrease cholesterol through a mechanism different from that through which statins decrease cholesterol. If a statin and berberine are used simultaneously, they seem to control cholesterol more efficiently. In a controlled study, berberine was found to cause increase in a type of protein receptor in the liver, which could bond to cholesterol and facilitate its excretion (38). Despite extensive use and several properties of different organs of *B. vulgaris*, the action mechanisms of this plant remain to be clearly known. Some of these properties can be attributed to the antihistaminic and anticholinergic effects of this plant (39). There are large amounts of vitamin C in *B. vulgaris* fruit. Vitamin C is an antioxidant and water-soluble organic compound.

This vitamin is essential to the production and maintenance of collagen tissue and the strength of other tissues, and can help to reinforce immunity system and to speed up wound healing (40, 41). As well, vitamin C prevents the formation of carcinogenic nitrosamines and nitrous ureas, and is considered a strong antioxidant agent and an effective cause of restoring cell enzymatic activities and electron transfer processes (42). It is also involved in the metabolism of carbohydrates, the conversion of folic acid to folinic acid, the metabolism of phenylalanine and thyrosine, the conversion of plasma transferine to liver ferritin, and the production of serotonin in the body (43, 44).

A study on aqueous *B. vulgaris* fruit extract on antihistaminic and anticholinergic activities in guinea pig ileum confirmed that this extract could exert these effects (5).

Uses of B. vulgaris in traditional medicine

The oldest findings on the use of barberry fruit to purify blood were inscribed on the clay tablets in the library of Assyrian (present day Iraq) emperor Asurbanipal during 650BC. The stem bark, stem, roots and root bark of *Berberis* species have been widely used in Ayurvedic, Homeopathic and ethno-medicines as raw materials or ingredients. In Ayurveda, it is traditionally used to cure various infections of eye, ear and mouth, to lose weight, to heal wounds quickly, to cure piles and hemorrhoids, to treat dysentery, indigestion, uterine and vaginal disorders as well as to treat snake or Scorpion bite as an antidote. In Iranian traditional medicine, it is used to cure jaundice, enlarged liver, enlarged spleen, eye sores, toothache, asthma and skin pigmentation, to dry unhealthy ulcers as well as to eliminate swelling and inflammation as orally and topically (13, 45, 46). *B. vulgaris* is also used to treat scorbutus, Alzheimer's disease, depression, diabetes, icterus, kidney stones, gout, rheumatism, and skin diseases (33, 47-49). In traditional medicine of Bulgaria and Eastern world, the extracts of the roots of different species from family Berberidaceae are used to treat rheumatoid arthritis and other chronic inflammatory diseases (50). Sarangdhara acclaims that decoction of barberry mixed with honey can be used to treat jaundice. A decoction of barberry and *Emblic myrobalan* combined with honey is prescribed to treat acrid urine or painful micturition from bilius (13).

The properties of B. vulgaris according to recent studies

Many researchers reported pharmacological effects of *B. vulgaris* (Table 2 and 3). *B. aristata* root extract caused decrease in glycemia and helped to regulate carbohydrate metabolism in diabetic rats (51). Moreover, the extract of *B. vulgaris* tree root is effective in treating and preventing the formation of stones in gastrointestinal tract (52). *B. croatica* Horvat is rich in berberine, phenol, and flavonol. The root extract of this plant can exert antimicrobial effects against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Candida albicans* (53). One of the main compounds of *B. integerrima* is berberine. Berberine can exert protective effects on central nervous system and help to treat the diseases of this system (54).

Moreover, this alkaloid can protect islets of Langerhans in diabetic mice and cause increase in insulin secretion, decrease in cholesterol and low-density lipoprotein, and increase in high-density lipoprotein (55). As with other fruits, *B. vulgaris* fruit contains salts and different vitamins including vitamin C. Ascorbic acid was found to exert positive effects on dementia progression in Alzheimer's disease patients (56). In addition, the plasma levels of ascorbic acid were found to be lower in patients with dementia compared to the controls, representing the protective effect of ascorbic acid on the brain function and in preventing cognitive disorders (57). Moreover, ascorbic acid, a nature-based agent, has been reported to be effective in improving memory in patients and older animals (58).

Ascorbic acid has been reported to be effective in improving learning disabilities and memory disorders in several experimental models (59). The effect of the administration of aqueous and hydroalcoholic *B. vulgaris* extract on the rate of insulin secretion in islets of Langerhans in mice confirmed the *in vitro* antidiabetic effects in low concentrations of glycemia, and that affecting islets of Langerhans was a hypoglycemic mechanism of *B. vulgaris* (60). The useful effect of long-term consumption of processed *B. integerrima* has been confirmed on some of the components of metabolic syndrome (61). Moreover, this plant has morphine-like properties and is therefore effective in quitting

substance abuse. *B. vulgaris* fruit has been shown to have hypotensive effects in patients with type 2 diabetes (5). Besides that, scientific studies have confirmed the control of inflammatory markers in animal models through the use of *B. vulgaris* fruit (62).

Aqueous *B. integerrima* fruit extract can have a highly important role in lowering cholesterolemia and triglyceridemia in patients (63). The protective effects of *B. vulgaris* extract on carbon tetrachloride-induced cytotoxicity in liver demonstrated that this extract could prevent liver damage in mice (64). *B. vulgaris* antioxidant effect on oxidative systems such as liver cells oxidation, red blood cells hemolysis, and hemoglobin non-enzymatic glycosilation demonstrated that the highest inhibitory effect was exerted on glycosilation, and that lipid peroxidation was adequately inhibited in the presence of different concentrations of *B. vulgaris* (65). Oral use of aqueous *B. vulgaris* fruit extract was demonstrated to be effective on moderate Acne vulgaris in adolescents (66). Hydroalcoholic *B. integerrima* extract was reported to be effective in inhibiting the growth of *E. coli* and *S. aureus* (67).

A study on the protective effect of aqueous *B. vulgaris* extract in rat model of Parkinson's disease demonstrated that the aqueous *B. vulgaris* extract could decrease the behavioral symptoms of this disease due probably to inhibiting ACE enzyme in brain tissue (68). The inhibition of some markers and the activation of some others by two-week oral use of *B. vulgaris* caused inhibition of T lymphocytes and prevented the progression of type 1 diabetes in mice (69). Use of *B. vulgaris* root extract alongside drinking water inhibited the deposition of calcium oxalate crystals in kidney tubules, improved oxidative stress in kidney and polyuria, and prevented weight loss in rats (70). *B. integerrima* is a rich source of antioxidants that can contribute significantly to promoting community health (31).

Aqueous *B. vulgaris* fruit extract caused a significant decrease in the liver enzymes and total bilirubin and an increase in total serum protein in mice with streptomycin-induced diabetes. It is therefore concluded that *B. vulgaris* fruit is likely to improve diabetes mellitus-induced liver damage in diabetic mice through modulating detoxifying enzymes and antioxidant factors (71). The optimal effects of *B. integerrima* extract have been confirmed on weight loss and decrease in systolic and diastolic blood pressure. If clinical trials are conducted with the populations of large sample size, the findings can be more definitely generalized to the whole community and this extract can be recommended to lose weight and lower blood pressure in patients with alcoholic fatty liver (72). Moreover, use of hydroalcoholic *B. vulgaris* extract can cause a considerable decrease in the lipid profile of diabetic rats (29).

Table 1. Summary of metabolites in *Berberis vulgaris*

Disease	Type of study	Berberis species	Part of plant	Results	Reference
Cancer	Experimental (mice)	*Berberis aristata*	Fruit	Ethanolic extract was observed to be efficient and the presence of alkaloids and flavonoids may be responsible for the observed anticancer effects.	(42)
	Human colon cancer cell line	*B. aristata*	*S*tem	Methanolic extract induces a concentration-dependent inhibition of HT29 cells, with an IC_{50} of 1.8964 µg/ml after 72 hours of incubation.	(73)
	Experimental (rat)	*Berberis vulgaris*	Fruit	The fruit can reduce the activity of liver enzymes and inhibit the gene expression of alpha-fetoprotein in rats during hepatocarcinogenesis.	(74)
	Human prostate cancer cell lines	*Berberis libanotica*	Root	Ammonia-dichloromethane extract showed a high therapeutic potential to target prostate cancer and its cancer stem cells.	(75)
	P_{53}-deficient HL-60 cells	*Berberis lycium*	Root	Berberine and the butanolic extract inhibited the expression of the proto-oncogene cyclin D1 and induced the acetylation of α-tubulin. This correlated with the induction of apoptosis. The data demonstrate that berberine is a potent anti-neoplastic compound that acts via anti-proliferative and pro-apoptotic mechanisms independent of genotoxicity.	(76)
	Experimental (Rat)	*Berberis vulgaris*	Fruit	Microscopic examinations of the TUNEL-positive apoptotic cells demonstrated a significant difference between cancer control and normal control group. Increasing concentration of *B. vulgaris* aqueous extract in cancerous treated groups showed considerable increase in TUNEL-positive cells compared with the cancer control group, and apoptotic	(77)

				cells increased with increase in *B. vulgaris* extract concentration in cancerous groups.	
Antihistaminic	Experimental (guinea-pig ileum)	*Berberis vulgaris*	Fruit	The results indicated antihistaminic and anticholinergic activities of the extract, potentially competitive.	(5)
	Experimental (male Sprague–Dawley rats)	*Berberis vulgaris*	Fruit	Aqueous extract has beneficial effects on both cardiovascular and neural systems, suggesting a potential use to treat hypertension, tachycardia, and some neurological disorders, such as epilepsy and convulsion.	(78)
Cardiovascular / Hypertension	Experimental (rat)	*Berberis orthobotrys*	Root	It causes decrease in systolic blood pressure	(79)
	Experimental (rat)	*Berberis integerrima*	Fruit	*B. integerrima* reduced systolic blood pressure in the right ventricle.	(80)
	Experimental (rat)	*B. vulgaris*	Fruit	Aqueous extract has beneficial effects on both cardiovascular and neural systems, suggesting a potential use to treat hypertension, tachycardia, and some neurological disorders, such as epilepsy and convulsion.	(78)
	Experimental (mice and rat)	*Berberis crataegina*	Root	The anti-inflammatory activity of the extracts and fractions, inhibited oil-induced diarrhea. The active constituent, berberine also showed a dose-dependent and potent analgesic activity against acetic acid-induced writhing reflex in mice	(81)
Gastrointestinal	In vitro and in vivo	*B. aristata*	Bark	The onset of castor oil-induced diarrhea was delayed and the number of diarrheal episodes was reduced by the extract in a dose-dependent manner.	(82)
	Experimental (Swiss albino mice)	*B. aristata*	Stem	*B. aristata* produces antidiarrheal effect through decreasing intestinal secretions and antispasmodic effect through inhibiting intestinal motility.	(83)
	Experimental (mice)	*Berberis integerrima* L.	Root	*B. integerrima* has anticonvulsant activity in pentylenetetrazol-induced seizures.	(54)
Epilepsy	Experimental (mice)	*B. vulgaris*	isoquinoline alkaloid of berberine.	Berberine exhibits anticonvulsant activity by modulating neurotransmitter systems and may have clinical uses.	(84)
	laboratory experimental	*B. aristata*	Root and Stem	*B. aristata* root extract gave low MICs values against *Bacillus cereus*, *Escherichia coli*, *Staphylococcus aureus*, and *Aspergillus flavus* while stem extract against *B. cereus* and *Streptococcus pneumoniae*.	(85)
Fever / Antibacterial	laboratory experimental	*B. vulgaris*	Bark of barberry root	The root bark exhibited anti-parasitic and antiseptic effects and is prescribed to lower fever.	(48)
	Experimental (rat)	*B. vulgaris*	Root	The amount of cholesterol, triglyceride, and LDL decreased significantly.	(86)
	Experimental (white rabbits)	*B. aristata*	-	*B. aristata* caused a significant reduction in serum cholesterol, triglycerides, and LDL levels; moreover, there was an increase in thrombin and fibrinogen time.	(87)
	Experimental (rat)	*B. aristata* DC	Stem	Significant hypoglycemic activity and hypolipidemic activity was exhibited by the methanolic extract.	(88)
lipid profile	Experimental (rat)	*B. orthobotrys*	Rroot	The crude extract significantly prevented the increase in LDL, VLDL, total cholesterol, triglyceride, atherogenic index, and coronary risk index in high fat diet, cholesterol, fructose and olive oil-induced hyperlipidemic rat model.	(89)
	Experimental (rabbit)	*B. lycium*	Root	*B. lycium* treatment increased the levels of high density lipids.	(90)
	Experimental (rat)	*B. lycium*	Root	The extracts also lowered the levels of cholesterol, triglycerides, LDL,VLDL, serum glutamic oxaloacetic transaminase, serum glutamic-pyruvic transaminase, and serum ALP in diabetic rats.	(91)
Diabetes	Experimental (rat)	*B. vulgaris*	Bark of barberry root	Blood glucose levels of the diabetic rats treated with aqueous extract decreased on the first day. This condition remained roughly constant for three weeks. Both extracts also declined	(92)

			biochemical parameters significantly.	
Experimental (rat)	*B. aristata*	Root	The extract has strong potential to regulate glucose homeostasis through decreased gluconeogenesis and oxidative stress.	(51)
Experimental (rat)	*B. lyceum*	Root	Oral administration of 50 mg/kg of the extract and berberine to normal and experimental diabetic rats caused a significant reduction in blood glucose levels from day 3 to day 7 of treatment. As well, significant effects were observed on the glucose tolerance, glycosylated hemoglobin, serum lipid profiles, and body weight of experimental animals.	(93)
Experimental (rat)	*B. integerrima*	Root	Aqueous extract improves renal dysfunction in streptozotocin-induced diabetes in rats through controlling blood glucose and renal protective effects.	(94)
Experimental (rat)	*B. integerrima*	Root	Aqueous extract has hypoglycemic, hypolipidemic, and antioxidant effects in streptozocin-induced diabetes in rats.	(95)
Experimental (rat)	*B. integerrima*	Root	Aqueous extract had a desirable effect on the testosterone level, blood glucose, and histological changes of testes during the course of diabetes.	(96)

Table 2. Summary of the findings on some species from genus *Berberis* most frequently used to treat different diseases

Disease	Title of article	Berberis species	Part of plant	Results	Reference
Acne vulgaris	Aqueous extract of dried fruit of *Berberis vulgaris* L. in acne vulgaris, a clinical trial	*Berberis vulgaris*	Fruit	Oral aqueous extract of dried barberry is a safe, well-tolerated, and effective choice in teenagers with moderate to severe acne vulgaris.	(97)
Cardio vascular / Hypertention	The Effect of *Berberis Vulgaris* extract on blood pressure and weight of the patients suffered from Non-alcoholic fatty liver disease	*B.vulgaris*	Fruit	Mean systolic and diastolic blood pressure was significant compared to control group.	(72)
Cardio vascular / Hypertention	Effect of processed *Berberis vulgaris* in apple vinegar on blood pressure and inflammatory markers in type 2 diabetic patients	*B.vulgaris*	Fruit Of *B.vulgaris* in apple vinegar	findings had shown processed *B.vulgaris* had no effect on systolic- and diastolic blood pressure but apple vinegar had positive effect on interleukin-6. Nevertheless, further investigations about *B.vulgaris* effect on blood pressure and inflammatory markers are necessary.	(98)
Diabetes	Clinical trial (patients with diabetes type 2)	*Berberis*	Fruit	The fruit had a significant reducing effect on serum glucose and decreased HbA1c levels during the 8 weeks of study.	(99)
Diabetes	Clinical trial (type 2 diabetic patients)	*B.vulgaris*	Fruit	Mean nutritional intake, anthropometric indices, hs CRP concentration, and systolic and diastolic blood pressure did not change in processed *B. vulgaris*. Also, interleukin-6 concentration did not change in processed *B. vulgaris* and control groups.	(98)
Diabetes	The effects of *Berberis vulgaris* fruit extract on serum lipoproteins, apoB, apoA-I, homocysteine, glycemic control and total antioxidant capacity in type 2 diabetic patients	*Berberis vulgaris*	Fruit	The intake of 3 g/d *B. vulgaris* fruit extract for 3 months may have benefical effects on lipoproteins, apoproteins, glycemic control and total antioxidant capacity in type 2 diabetic patients.	(100)
Lipid profile	Clinical trial (dyslipidemic patients)	*Berberis aristata*	Fruit	*B. aristata* reduced total cholesterol, triglycerides, and LDL cholesterol and increased HDL cholesterol after three months.	(101)

Discussion

This study was conducted to investigate the phytochemical characteristics, the findings of the experimental studies and the clinical trials conducted on the most frequently used species of the plants from this genus in traditional medicine, focusing on *B. vulgaris* which is the most frequently used plant of this genus.

Because no single pattern has been used to refer to different species of barberries in the articles published in Persian language and the recently published works, the readers and examiners of the texts might become confused. For example, Mozaffarian, in "A Dictionary of Iranian Plant Names", classified the *B. integerrima* and *B. crataegina* as black or seeded berbery (8). However, in several studies, *B. vulgaris* has been referred to as

black barberry (61-63) . *B. vulgaris* has been considered to be the same as *B. khorasanica* in some references and different from this plant in some others (73, 102). This can affect the interpretation of the findings and the conclusions drawn.

The fruits of most plants from family Berberidaceae are rich in antioxidants (51, 75, 76). Free radicals are the normal by-products of metabolism in the body, and can cause cell damage by bonding to other molecules and stimulating the growth of anomalous cells, or intervening in the function of normal cells such as nerve and brain cells (74, 77). However, in the presence of antioxidants, the effects of free radicals are neutralized and the damage due to them is minimized (78). Antioxidants therefore play a significant role in preventing a variety of diseases such as cancer and diabetes and hypertension(49, 103).

The results briefly indicate that *B. vulgaris* contains a large number of phytochemical materials including ascorbic acid, vitamin K, several triterpenoids, more than 10 phenolic compounds and more than 30 alkaloids. Therefore *B. vulgaris* may have antihypertensive, anti-cancer, anti-inflammatory, antioxidant, antibacterial, analgesic and anti-nociceptive and hepato-protective effects (15, 29, 79).

The fruits of most plants from Berberidaceae family have a sour taste which is due mainly to the presence of ascorbic acid or vitamin C. We can discuss vitamin C in these fruits with regard to affecting physiological functions of the body in both antioxidants and vitamins. As vitamin C, an antioxidant, enters into bloodstream, it neutralizes or minimizes the damage to the body's tissues due to the effect and destruction caused by chemicals (62).

This vitamin can protect the skin of human body against adverse effects of the sun ultraviolet radiation. Besides that, vitamin C improves the body's immunity and contributes to the increased strength of gums and teeth (80).

Collagen is a connective tissue which keeps the body parts together. Vitamin C is required to produce and maintain collagen tissue in the body (104).

This vitamin can prevent hypercholesterolemia and clots formation in blood vessels (81). Moreover, vitamin C facilitates iron absorption in gastrointestinal tract, and therefore people with anemia are recommended to use vitamin C alongside iron-containing foods and medications (82). This important vitamin that is found in the fruits of the plants from Berberidaceae family can be used to prevent osteoporosis and osteomalacia and to treat stroke and atherosclerosis (83, 84).

Plants are the richest sources of alkaloids, and alkaloids can cause strong physiological reactions with special effects in human beings. These compounds are particularly effective on nervous system(105, 106).

The aerial organs of the plants from Berberidaceae family contain several compounds that are effective in treating diseases. Alkaloids are a group of these compounds (85, 107). Alkaloids can exert strong physiological effects in the body of mammals, including human beings. Lack of alkaloids may cause various problems in the body of human being. For example, deficiency of phenylalanine, as a non-polar alkaloid, can lead to disturbed process of thyrosine production in converting levodopa in the brain to dopamine or noradrenaline to adrenaline. Phenylalanine deficiency can lead finally to certain disorders such as depression and declined pain tolerance (85, 86, 108).

Conclusion

In the light of use of different organs of *B. vulgaris* in traditional medicine and certain properties of these organs that were confirmed in the recent studies, it is possible to use them, especially fruit, to develop new drugs.

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