The traditional uses and pharmacological effects of different parts Berberis Vulgaris (berberine) in Iran

Seyyed Mahdi Javadzadeh, Ahmad Ebrahimi

Department of Agriculture, Iranshahr Branch, Islamic Azad University, Iranshahr, Iran

Corresponding author: Email: s.m.javadzadeh@gmail.com

Keywords
Berberis vulgaris
Therapeutic application

ABSTRACT
Barberry (Berberis vulgaris L.), family Berberidaceae grows in Asia and Europe; the plant is well known in Iran and has been used extensively as a medicinal plant in traditional medicine. The fruits of the plant have been also used as a food additive. The plants is a shrub, 1–3 m tall, spiny, with yellow wood and obviolate leaves, bearing pendulous yellow flowers succeeded by oblong red fruits (barberry). Barberries is an important production of South Khorasan; biggest producer of barberries in Iran. The different parts of Berberis vulgaris have several applications. In this article we are going to discuss the matter according to the latest references. Due to their cold and dry nature, barberries are used to reinforce the heart and liver, as an analgesic for the stomach and anticoagulant and their leaves are used in affections resulting from the lack of Vitamin C, to treat gastric ulcer, Treating diarrhea, edema, and treating scurvy. Based on more studies, the majority of the medical properties of barberries are related to the different alkaloids existing in the different parts of this plant.

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Introduction

The barberry (Berberis vulgaris L., Var. asperma Don, family Berberidaceae) plant also grows in Asia and Europe; in Iran more than 5,000 tons of barberries are produced each year (FAO, 2005) Barberry has been used extensively as a medicinal plant in traditional medicine. Mention has been made of barberry in writings of the medieval times (medical books in southern Italy) and probably its origin is Arabic. It seems that Simon Janunsi was the first person who acquainted people with the Arabic name "Berberis" in the 8th century. Barberry wood and possibly its fruit were used in the Himalayan slopes since ancient times and in the first century A.C. the Greeks were familiar with its extract which they termed Indian Lycemum, and the Arabs called it Honduras (Abu Ali S, Ibn S .1971). The fruit of the plant has been used as food additive. The plant is a shrub, 1-3 m tall, spiny, with yellow wood and obviolate leaves, bearing pendulous yellow flowers succeeded by oblong red berries (Zargari, 1983, Amin, 1991). It has leathery leaves that are egg-shaped and little red fruits in the form of clusters hanging from the branches. The various parts of B. vulgaris including its root, bark, leaf and fruit have been used as folk medicine for a long time in Iran and other countries. In pharmacological research, there is some evidence for different effects of the B. vulgaris or isoquinoline alkaloids of the genus Berberis (particularly berberine) there are also some clinical trials of the therapeutic effects of this plant or berberine. Barberries contain organic acids and phenol compounds that contain anthocyanin and carotenoids pigments as well as phenolase, polyphenolase and glycocidase enzymes. Medicinal properties for all parts of the plant have been reported, includingtonic, antimicrobial, aantimetic, antipyretic, antipruritic and cholagogue actions and it has been used in some cases like cholecystitis, cholelithiasis, jaundice, dysentery, leishmaniasis, malaria and gall stones (Zargari, 1983, Amin, 1991, Nafissi, 1990). In spite of extensive applications and numerous properties, the mechanism of action in most of its effects is not exactly clear. Some of these properties may occur due to antihistaminic or anticholinergic effects. Historical testimonies show that Rhazes was the first person to know about the medical properties of this plant and he advised drinking barberry juice for treating fever, thirst, and inflammation. In Iran people drink barberry juice and use its extract in preparing food, jam, pickles, syrup, round flat candy, dried barberry concentrate, and Sohan Asali (a traditional Iranian sweet). In recent years in order to make industrial use of barberries much research has been conducted on preparing different products such as beverages, sauce, jelly, candy, pastilles, colored edible powder etc. from barberries (Kafe et al., 2001). Due to their cold and dry nature, barberries are used to reinforce the heart and liver, as an analgesic for the stomach and anticoagulant and their leaves are used in affections resulting from the lack of Vitamin C, to treat gastric ulcer, Treating diarrhea, edema, and treating scurvy. Based on more studies, the majority of the medical properties of barberries are related to the different alkaloids existing in the different parts of this plant. Berberis vulgaris was macerated along with Foeniculum vulgare in Ancient Egypt for fevers. It was also used by the Catawba for peptic ulcers. South Khorasan province, located at the northeastern Iran, is the production center with about 6,442 hectares of field growing barberry. Each year, more than 8,400 tones are harvested in Khorasan region alone. Barberry cultivation in Khorasan is concentrated in the south of the province, especially around Birjand and Ghayen...
where environmental condition (i.e. hot weather, low relative humidity, and water shortage and soil condition) are unfavorable for the growing of other horticultural crops. Cultivation and production of seedless barberry took place in Afin village located in Ghayen city’s Zirkuh district for the first time. Until 50 years ago, seedless barberry was mainly cultivated in Afin and Darmiyan villages, however, ever since seedless barberry is cultivated in most of the villages and regions. South Khorasan province is renowned for the production of seedless barberry as the main agricultural product. In Iran, Southern Khorasan province and mainly the cities of Ghayen and Birjand (Fig 1) are the most important regions where barberries are produced and around 95% of the country’s barberries are produced in these 2 cities (Kafe et al ,2001).

Production of seedless barberry as a garden product is confined to South Khorasan province; however, seeded barberries grow in various parts of the world. Seedless barberry is resistant to cold weather and grows well in mountain areas with cold winters. Decorative barberry species appear in three categories i.e. perishable, ever green and semi ever green. Yellowish-orange flowers and reddish-bluish-purple fruits hang from the beautiful shrubs of barberry. In fall, you can observe shift of colors in the branches of shrubs which appear in heights ranging from 30 centimeters to 5.2 meters. These shrubs can be used for decorative purposes (Kafe et al .2001).

This article reviews the Therapeutic application of different parts, pharmacological effects and the most active ingredient of B. vulgaris (berberine).

Materials And Methods
A computerized search of published articles was performed using the MEDLINE database from 1990 to 2013. Search terms utilized including barberry, application. All articles were obtained as reprints from their original authors. Additional sources were identified through cross-referencing.

Results and discussion
A) barberry - virtues and uses virtues of barberry fruit
To explore the characteristics, medicinal uses and prescribing considerations of this herb in more detail, Boon H, Smith M (2009) and Godfrey A, Saunders P, Barlow K, Gowan M (2011) check out the references indicated.
cold and dry by nature. In traditional medicine, barberry is ant bilious and it is calmative for stomach heat. It is used to strengthen liver and heart and it staunches the flow of hemorrhoids blood. It also prevents chronic bleeding. For those of cold nature, it is very useful to mix barberry with medicines like Valerian (which has a hot nature) in order to strengthen liver and avoid its clogging. In Mongolia, they use barberry to send out body moisture, to staunch bleeding and for diseases with mucosa secretion. Barberry juice (100 ml) or barberry fruit (100 grams) has an anti-alcohol effect and it can be used as an anti-alcohol medicine (Fig 2).

Barberry fruit is an astringent medicine. This plant quiets arthralgia (joint pain), rheumatism and inflammation. Barberry can be effective in treatment of some infections such as throat, urethra, gastrointestinal, pulmonary, yeast infections and diarrhea. Barberry juice includes a large amount of Vitamin C and so it increases the activity of immune system, stimulates to absorb iron and avoids scurvy. Barberry fruit includes organic acids and so it is diuretic and it is useful to treat kidney stone. Barberry juice also purifies blood and is a disinfectant.

Also, it is mentioned that barberry fruit constricts vessels and it is suggested to strengthen stomach and avoid vomiting during pregnancy. Barberry juice reduces fever and blood pressure, alleviates inflammation and helps to regulate heart beat and to constrict heart muscles. Barberry can bring delight and freshness. Barberrypowder or barberry tea is very useful for treatment of constipation. Barberry extract made of barberry fruit reduces blood cholesterol, strengthens stomach, treat dyspepsia and enteritis and it is anti-thirst and anti-itch. Recent researches conducted Arayne MS, Sultana N and Bahadur SS (2007) and Stargrove MB, Treasure J, McKee DL (2008) tested on animals prove that barberry should not be used during pregnancy, as traditional medicine has suggested. According to results of the researches, berberin which is one of main alkaloids in barberry fruit can constrict uterus and so increase of the constriction can end in miscarriage.

It should be considered that large doses of berberin can also have teratogenicity effects. All parts of the Berberis vulgaris plant have long been used as a herbal remedy for the treatment of a variety of complaints including Liver dysfunction, gallbladder disease, diarrhea, indigestion and urinary tract diseases. Barberry fruit includes dihydro-palimitinum hydroxide which is anti-estrogen that cause to atrophy endometer and to crumple stroma glands. These changes avoid the fetus to be nourished and cause disorders in its growth.Barberry juice is a tonic popular juice used in some regions of Iran such as Shahrud, Sabzevar, Birjand and Qaen. Thus, it is necessary to be aware of the effects that barberry can have during pregnancy. Therefore, it is possible to avoid probable problems mentioned above.

A) Units 3-2 Virtues of barberry

Leaf

Barberry leaf alone or mixed with some other medicine is used to treat intestine wounds and chronic diarrhea caused by weakness of viscera inside the stomach.

![Fig 3. leaf of Berberis Vulgaris](image)

For treatment of chronic diarrhea, 15-30 grams of dried leaf is boiled in half a liter of cold water. Then it is strained and sweetened by honey. A cup of it should be used three times a day between main foods. Also, barberry leaf has been used to cure chronic dysentery, scurvy and tissue edema. Chewing barberry leaf hardens gums. Barberry leaf tea can be gargled and it is useful for treatment of angina and sore throat.

B) Virtues of bark of barberry stem and barberry root

Bark of stem in barberry is dry and hot by nature. However, it is somehow cold in nature too. It is laxative and its juice tastes bitter. Its tea is good for cold liver. Bark of stem and bark of root have been used in medicine from many years ago especially from the age of Galenus, Dave Securid and Pollini (Greek scientists) as a purgative, antibilious, laxative, tonic and appetizer. Root and extract of barberry include many iso-kinolin alkaloids. Scientists and researchers have studied about
these chemicals for years, but they come up with the fact that these can act as antibiotics. Some of them can reduce fever and blood pressure, alleviate inflammation, regulate hear beat and constrict heart muscles. It cures varicose, gout, rheumatism, anorexia, dyspepsia, jaundice, hemorrhoid, splenalgia and urodynia and it regulates the digestive system. For treatment of kidney stone and vesica stone (bladder stone), it is useful to boil dried bark of barberry root and then serve with honey. For curing those who have been poisoned by opium, usually barberry root boiled in water is used. Having a similar virtue of morphine, it is also used to kick taking drugs. It is also useful for kidney stone, jaundice and gall stone. In China and Japan, they use bark of barberry root as an anti-parasite and antiseptic and it is prescribed for reducing fever and curing much bleeding in menses. In Europe and America, bark of barberry stem and bark of barberry root were used as antisepic, laxative, antipyretic, anti-vomiting, tonic and as an antidepressant. They were also used to treat jaundice and stomachache. Flowers (fig 4) and bark of stems were used to treat rheumatism. Bark of root is laxative, and it opens hepatic duct and cystic duct. For this purpose, 25 grams of dried bark of barberry root is boiled in half a liter of cold water for half an hour. Then it is strained and sweetened (usually by honey) and a cup of it is served after each meal. Besides curing hepatic disorders and problems, it cures jaundice, gall stone and kidney stone as well.

C) The latest researches on medicinal uses of barberry

The results of the researches show that berberin which is an iso-kinolin alkaloid and exists in bark of barberry root is a strong anti-oxidant and it is useful in treating fibrosis caused by anti-cancer medicines such as bleomycin. In pathology, it has been known that bleomycin simulates bronchial tubes a lot and berberin can reduce its effect noticeably. According to a research done in the school of pharmacy in Mashhad and testing the extract of barberry root on mice and hamsters, barberry plant was found to be very useful in treating oriental sore. Forming plaque on teeth is common in Iran which is the main reason for causing dental caries and gingivitis. Regarding the bacterial nature of plaque and anti-bacterial virtue in the extract of bark of barberry root and barberry stem which includes almost 1.5% berberin, a kind of gel toothpaste was formulated and produced showing that it reduces forming plaque on teeth and avoids gingivitis. Bark of barberry root includes a very noticeable amount of berberin which is of alkaloids and is anti-infection. Recent researches show that it kills infectious microorganisms such as Staphylococci and Streptococci, Salmonella and Shigella (microbes causing diarrhoea), Endamoebahystolotica (a microbe causing dysentery), vibrio cholerae (a microbe causing cholera) and Escherichia coli (a microbe causing urethra infection) as an effective antibiotic. Besides, berberin alkaloid causes to simulate and strengthen immune system through attacking infectious agents and microbes. The researchers also show that berberin increases the activity of macrophages, i.e. white corpuscle eating microbes. In Germany, they use bark of barberry root for treating eye problems. Ophthalmie is the name of a medicine including berberin and is used to cure eye allergy, conjunctivitis and ophthalmitis. Including iso-kinolin alkaloids (berberin), bark of barberry root is a fungicide, anti-oxidant, anti-psoriatic, antibacterial and anti-inflammatory.

Lipoxygenase metabolism products cause psoriasis. Each of 6 bisbenziliso-kinolin alkaloids can control different types of lipoxygenase and as a result, they act as anti-oxidants and anti-inflammatory. Berberin also reduces synthesis of 5-lipoxygenase. Berberin and dependant alkaloids are bactericides and prescription of barberry alone or with tetracycline is useful in treatment of watery diarrhea. Studies show that extract made from barberry root has a fungicidal effect against trichoderma viride and is more effective than Nystatin. According to some studies, extract of barberry root made blood pressure reduce in cats for several hours. Several alkaloids such as berberin, berbamin and oxyacantine control the flow and falling of calcium and probably play a role in mechanism of loosening vessels and controlling alpha-adrenoreceptors. Berberin is antiepilepsy, hypnotic and is a womb stimulant. Local anesthesia can happen after subcutaneous injection of berberin. According to the tests done on animals, injecting Syrian mice some extract of barberry on the 7th, 8th and 9th days of pregnancy which equals the 3rd month in human beings caused some disorders in spinal column, nervous system, eyes, face and hands and it avoided fetuses to grow and mature well. Studies carried out on the chemical composition of the extracts show that the alkaloid constituents with an isoquinolinic nucleus such as berberine, berbamine and palmatine are important compounds of this plant (Ivanovska and Philipov, 1996). In a quantitative HPLC analysis of the main alkaloids in the roots, barks and stems of B. vulgaris, the amounts of berberine and berbamine were 1.24% and 2.5%, respectively. Although berberin is the most important alkaloid that is generally claimed to be responsible for their beneficial effects and numerous studies have been conducted so far (Küpeli et al., 2002) but it is pointed out that other alkaloids also have some roles in the effects of the plant (Ye8ilada and Küpeli, 2002).

Berberine, an isoquinoline plant alkaloid, belongs to the structural class of protoberberines. Berberine represents one of the most studied among the naturally occurring protoberberine alkaloids (Mazzini et al., 2003). In addition to B. vulgaris (barberry), berberine is present in many other plants including Hydrastis Canadensis (goldenseal) (Ranunculaceae), Coptischinensis (Coptis or goldenthread) (Ranunculaceae), Arcangelisia flavula (Menispermaceae), B. aquifolium (Oregon grape) and B. aristata (tree turmeric) (Wang et al., 2004a; Peng et al., 2004). Berberine is used for the treatment of different diseases.
E) Side effects of barberry

Improper and irregular use of barberry can cause nausea, regurgitation, vertigo, convulsion, nosebleed, kidney failure, skin and eye inflammation and decrease blood sugar. Mixture of dried barberry should not be used by children, pregnant women and nursing mothers. In case of overusing barberry, there appear symptoms of toxicity by decreasing consciousness and by vertigo, numbness, diarrhea and nausea.

F) Usage of barberry in medicine

The safety and prescribing considerations for Berberis include: (Brinker et al., 2010, Vedel et al., 1973) generally regarded as safe. Side-effects are generally not seen. Contraindicated in pregnancy as it may cause uterine stimulation (in vitro, animal) and lactation as it can be toxic and cause jaundice in the newborn Caution: not to be used without skilled therapeutic knowledge and not for more than 4-6 weeks Drug-Herb Interactions (Godfrey et al., 2011) Reverses leucopenia induced by benzene, cancer chemotherapy (human study) Eliminates inclusion bodies of Chlamydia trachomatis in conjunction with sulphacetamide (eye drops, human study) Potentiates barbiturates Improves outcomes in patients with congestive heart failure taking ACE inhibitors, digoxin, nitrates, and diuretics/spironolactone (human study) Unfortunately, nowadays barberry is not used much in medicine. And medicinal uses of this valuable plant have been limited to traditional medicine and home uses of making its tea and extract. Here, we mention the medicines that have already been produced from barberry and also the different types of other medicines that can be produced:

Raha: a liquid medicine which includes 42% barberry is used to reduce symptoms of quitting addiction. Since most symptoms of quitting opium and its derivations appear through simulating sympathetic nervous system, berberin in barberry weakens sympathetic system and helps to quit addiction remarkably. Also, other symptoms of quitting addiction such as diarrhea and stomachache can be controlled because berberin acts as an anticholinergic. On the other hand, berberin is anti-convulsion and anti-spasm and so it alleviates the symptoms of convulsion in addicts.

Barberry distillate: it is made from distilling barberry juice and has many virtues such as: decreasing blood sugar and blood cholesterol, strengthening stomach and treating dyspepsia, stomach ulcer and rheumatism. Barberry tincture: an alcoholic infusion of barberry fruit or bark of barberry stem which has the same virtues of barberry fruit or bark of barberry stem and barberry root. Barberry expressed juice, medicinal draught of barberry, ointment and capsule of barberry are other different medicines that can be also produced and used.

G) Effect of barberry on heart diseases

Nowadays, cardiovascular diseases are regarded as severe problems in all societies and studies show that this problem is increasing all over the world. Many medicines have been produced to cure these diseases, but they come along with many side effects which limits their clinic uses. Thus, researches on making new powerful medicines with fewer side effects are in progress. Barberry includes berberin, oxyacantine and other alkaloids such as berbamin, columbamine and...
berberinin. Recent studies show that berberin has useful cardiovascular effects such as positive inotropic effect (tested in a separated atrium of guinea pigs), negative chronotropic effect, anti-arrhythmic effect and anti-high blood pressure effects and it reduces vascular resistance. Several therapeutic effects have been described for Berberis vulgaris. In present study, the effects of ethanolic extract from Berberis vulgaris on isolated heart were examined. The heart mounted on a Langendorff apparatus and perfused through aorta. Heart contractility were determined on the presence of four concentrations of ethanolic extract (0.5, 1, 2 and 5 g%) and diltiazem, (0.1, 1, 10 and 100 μM) in comparison with baseline values in two group: 1) Perfused heart with ordinary Krebs (group1, n=10). 2) Perfused heart with calcium free Krebs solution (group 2, n=8). Results: In group 1 three larger concentrations of diltiazem showed significant decrease and two last concentrations of ethanolic extract significantly increased heart contractility in this group (p<0.01 to P<0.001). In group 2 only last concentrations of diltiazem showed significant reduction in contractility in this group (p<0.05).These results showed that ethanolic extract of Berberis vulgaris has strong effect on heart contractility. The results of the present study may also indicate an activation of the calcium channel of isolated heart by the extract.

Acknowledgment

This study was supported by research, research vice president of technology. Thanks for your support in providing the necessary facilities for this study.

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