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FUNCTIONAL AND PHYTOCHEMICAL POTENTIAL OF BERBERIS

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Abstract

The plant is wide source for possible medications and in the ongoing years there has been a good understanding about the significance of medicinal plants. Medications from the plants are effectively accessible, more affordable, protected, and productive without causing harm unlike allopathic medicines. Different phytochemicals are extracted in the form of primary and secondary metabolites from these plants. These phytochemicals mainly comprise of alkaloids, glycosides, polyphenols and terpenes. These extracts have a wide range of activities like analgesic, sedative, laxative, anti-inflammatory, antioxidant, antibacterial and neuropharmacological activities. Berberis baluchistanica plant locally called as Karoskai (Pashtu), Zrolg and Korae (Balochi), belongs to the family Berberidaceae, potentially contains phytochemicals with antioxidant activities. These phytochemicals are selected to discover its uses as an antioxidant. The genus Berberis (Berberdaceae) entails of almost 500 species occurring in many areas of central and southern Europe, the northeastern parts of the United States and in South Asia including the north of Pakistan. Berberis is applicable for wound healing. It is also indicated in some studies that Berberis species are useful for treatment of insomnia, lungs diseases, unease of gastrointestinal tract (GIT), liver disorder and urinary incontinence. It can also be used as anti-rheumatic, antifungal, antipyretic, and antibacterial infection. Berberine and palmatine play the vital role as phytochemical. Cancer prevention agent capability of fifty percent aqueous ethanolic root extract of B. aristata was investigated. Its effect on antioxidant enzymes of liver was studied in diabetic rats. The root extract of B. aristata can possibly reduce oxidative stress. Antioxidant capability of dried parts of B. aristata were explored in fluid and methanolic separate and berberine, against CCl4 actuated liver injury.

Keywords: *Berberidaceae, Baluchistanamine, Anti- cancer activity, Anti-rheumatic*

INTRODUCTION

All the new and ancient chemotherapies arose from the plants and they are the basic ingredients of medicines. People have been using e plants to treat infections and as preventives from the diseases, from their forefathers till new generation of modern era. Some chemicals/medicines are not in pure form but straight extracts of plant material that have been acceptably developed and systematized (1). The plant world is a treasury of possible medications and in the ongoing years there has been a good understanding about the significance of medicinal plants. Medications from the plants are effectively accessible, more affordable, protected, and productive without causing harm unlike allopathic medicines. Plants are the most extravagant asset of medications of conventional methods of medication, nutraceuticals, and food supplements, locally made medicines, drug intermediates and substance elements for modern day drugs (2). In recent years, a lot of work is done in the field of antibacterial agents. Various concentrates from medicinal plants have been tried to investigate for their healing potential. Therefore, some of the products obtained

from medicinal plants have been affirmed as new antibacterial medications, yet there is a need to distinguish novel substances that are dynamic towards microbes with better results (3). Ethnobotany is a subject that deals with the local use of plants for medicinal, food and fodder purposes. The knowledge is passed on from generation to generation since prehistoric times (4).

Local healing system which was adopted traditionally in world that uses plant-based products as remedies are a vital source to find new antibiotics (5). Almost all the parts of plants are used for medicinal purposes including root, shoot, bark, seed, bulb, flowers, fruit, resins, gum, rhizome, and tuber. Different phytochemicals are extracted in the form of primary and secondary metabolites from these plants. These phytochemicals mainly comprise of alkaloids, glycosides, polyphenols and terpenes. These extracts have a wide range of activities like analgesic, sedative, laxative, anti-inflammatory, antioxidant, antibacterial and neuropharmacological activities.

Internally, Daruharidra (Indian barberry extract) is used against many diseases, some studies show that it is routinely used in diseases like skin diseases, eye infection, menorrhagia, cholera ENT infections, injury healing, lower urinary tract infection and vaginal disorders (3). In this plant there are many bioactive substances such as carbohydrates, flavonoids, steroids, alkaloids, tannins and terpenoids that gives specific functional action on human being (2).

Almost all the parts including root, bark, leaves and flowers of plant have been utilized in preparation of various medicines. Powdered bark is used for looseness of the bowels, injuries and sore throat. Root and bark extract is used for diabetes, pustules and scabies while root powder paste has been used in bone crack (6).

Berberis baluchistanica: A, flowering branch; **B**, fruiting branch; **C**, flower; **D**, outer sepal; **E**, inner sepal; **F**, petal.

Fig. 1. An illustration showing different parts of *Berberis baluchistanica* (Source; Flora of Pakistan)

Many studies have specified that plants which are medically significant have divergent nutrients and non-nutrients particles and some particles have antimicrobial and antioxidant actions which protect human body from microorganisms and oxidation. *Berberis baluchistanica* (Fig. 1) plant locally called as *Karoskai* (Pashtu), *Zrolg* and *Korae* (Balochi), which belongs to the family Berberidaceae potentially contains phytochemicals with antioxidant activities. These phytochemicals are selected to discover its uses as an antioxidant. The genus Berberis (Berberdaceae) entails of almost 500 species occurring in many areas of central and southern Europe, Northeastern parts of the United States and in South Asia including the North of Pakistan (7).

TAXONOMY OF *B. BALUCHISTANICA* AND *B. ARISTATA*

Berberis spp. is found worldwide especially in India, Pakistan, Nepal, South East Asia, Europe and South America. In Pakistan it is found in hilly areas and in parts of Balochistan. These are found at an altitude of 1400-3500 meters above sea levels. According to recent reports, there are only 14 Berberis species out of 650 in total, in Pakistan (8). They could be trees and shrubs both in deciduous or evergreen forms. The leaves are compound and bi-pinnate. The flowers are yellow or white with six petals. They could be individual or in raceme with almost twenty flowers in one raceme. The fruit is berry with oval shape and a size of 5-15 mm. In sub-continent the flowering season starts from February and ends in June. The flowering season attracts bees.

Table I. Taxonomical classification of Berberis

Kingdom	Plantae
Division	Magnoliophyta
Class	Mangoliopsida
Order	Ranunculales
Family	Berberidaceae
Genus	Berberis
Example	*Berberis aristata*

PHYTOCHEMICAL PROFILE OF *BERBERIS*

Alkaloids are the major type of phytoconstituents present in *B. aristata*. Almost all the plant parts are used for medicinal purposes. Fruit is edible with lots of sugars. Its stem, roots and fruits are used in Ayurveda. The root bark of the plant contains a protoberberine alkaloid — karachine (22). *B. aristata* flower contains various polyphenolic flavonoids like quercetin, rutin, meratin and acids like E- caffeic acid and chlorogenic acid (23). *B. aristata* has been extensively studied for its pharmacological potentials. Extracts from this plant have been used effectively for malaria, bleeding piles, rheumatism, diarrhea, constipation in children and diabetes (4).

Alkaloids are the main constituents of Berberis phytochemistry. Researchers have been isolating and studying these chemicals for last sixty years Some of the types of alkaloids reported from various Berberis species are berberine, berbamine, palmatine, columbamine, jatrorrhizine, oxyacanthine (15). Alkaloid content may vary depending upon nature of plant species for instance, deciduous or evergreen, wild or deomesticated have different amounts of alkaloids e.g. it was found that evergreen Berberis spp. contain more alkaloids than wild species (24). Similarly lower altitudes has plants with higher berberine content than the plants found at high altitudes. Soils also play their role in high alkaloid content as soils with high potassium had populations with high alkaloids and vice versa. Low moisture also affected the alkaloid content positively (25).

There are 4 types of alkaloids for example pakistanine, 1-O-methylpakistanine, pseudo-palmatine chloride and pseudo-berberine chloride which have been obtained from *B. aristata*. While berberine is the most common alkaloid present in *B. aristata* and palamatine is the second most common alkaloid (26). An isoquinoline alkaloid was also extracted from *B. aristata*. The medicinal values of the plant lie in some organic compounds and the most important of these previous investigations on this plant showed isolation of different types of compounds including alkaloids and steroid (7).

Table II shows some of the most common phytochemicals in Berberis sp. along with the parts from which these constituents are normally extracted. One common method used to extract such phytochemicals is the use of methanol which is considered as a good solvent. Being highly volatile, the methanol is vaporized and the plant contents are isolated later on (40).

Berberine being the common most compound isolated from numerous Berberis species is an organic cation and are secondary metabolites in nature. These metabolites have a wide range of activities including antimicrobial and anticancer activities. There is a need to explore more about these metabolites because of their potential. Their use is not only limited to human disorders and disease, but also to the agriculture and livestock in addition to their use in research (23).

Table II. Biochemical Profile of Berberis

S#	Compounds	Presence	Importance	References
1.	Alkaloids	Roots, bark	used as purgative and	(27)
2.	Pakistanine,	Leaves and stem	treatment for both	(8)
3.	Jatrorrhizine	Stem	diarrhea and rheumatism	(28)
4.	Oxyacanthine	Leaves	treatment of	(29)
5.	Isoquinoline	Roots	neuropsychiatric and	(30)
6.	Steroids	Stem	neurodegenerative diseases	(31)
7.	Saponins	Roots	Anticancer, Antioxidant, Immuno- modulatory, Anti-malarial, Anti-bacterial, Eczema	(32)
8.	Triterpenoids	Trunk		(33)
9.	Isoquinoline	Rhizomes	antibacterial and	(34)
10.	Columbamine	Roots, Stem	antitumor	(35)
11.	Berberine	Rhizomes	properties,various eye conditions andanti-inflammatory activity	(36)
12.	Palmatine	Leaves	Antileshmenial	(37)
13.	Berbamin	Roots	antibacterial, anti amoebic, antifungal,	(38)
14.	Aromoline	Leaves	antihelminthic,	(39)
15.	Oxyacanthine	Leaves	leishmanicidal, and	(40)
16.	Sterole	Roots	tuberculostatic properties	(41)
17.	Baluchistanamine	Root bark		(42)
18.	Oxyberberine	Leaves and stem		(43)

MEDICINAL USES OF BERBERIS

Berberis can be used for treatment of bleeding. It is also indicated in some studies that Berberis species are useful for treatment of insomnia, lungs diseases, unease of gastrointestinal tract (GIT), liver disorder and urinary incontinence. It can also be used as anti-rheumatic, antifungal, antipyretic, and antibacterial infection (9). It has customarily used to treat tooth pain, common cold and fight bad breath (10). Roots with a bitter taste is utilized in splenic difficulty, intestinal infection, chest difficulty, throat inconveniences, eye infection, menorrhagia, used for gargling which strengthens the gums. In Balochistan the leaves are used as a cure for Jaundice. Berberis plants have been successfully utilized for treating gynecological sicknesses (8). Due to above mentioned fact that this plant is very useful and the fact that little information is available on its biological activity, there is a need to find out more about the potential of this plant as antimicrobial agent (11).

Recently a group of researchers from Czech Republic isolated three new alkaloids from *B. vulgaris* and found them effective against Alzheimer disease (31). These alkaloids are named as bersavine, muraricine and berbostrejdine. It was also shown recently, that berberine plays acetylcholinesterase inhibitory role in treating Alzheimer's disease by increasing acetylecholine levels (14). Berberine is a type of alkaloid which has antioxidant activity and it also depletes reactive oxygen species (10).

Berberine

Berberine is important alkaloid isolated from Berberis spp. It has an antimicrobial activity and effectively kills microbes when administered orally (12). The chief constituent of *B. aristata* DC. is berberine, which is bitter alkaloid. Berberine is a plant quaternary ammonium salt from the group of isoquinoline alkaloid (2, 3 methylenedioxy-9, 10-dimethoxyprotoberberine chloride; $C_{20}H_{18}NO_4^+$) with a molar mass of 336.36122 g/mol (Fig. 2) (17).

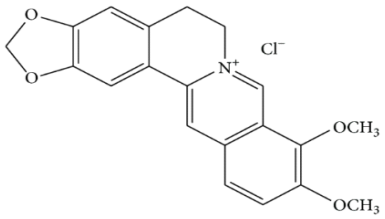

Fig. 2. Berberine found in *B. aristata*

Another important class of alkaloids isolated from *B. vulgaris* is Isoquinoline alkaloids. *B. vulgaris* is abundantly found in Europe and Iran. Extracts from this plant are used as additives in Northern Iran. Almost twenty such alkaloids have been isolated up till now. These alkaloids have been effective against Alzheimer's disease (42).

Berberine belongs to benzylisoquinoline alkaloids. This alkaloid has been effectively used against many diseases like diabetes and other metabolic diseases (MD) (43, 19). Extracts from Berberis have shown effective results against type II Diabetes Milletus (T2DM) (45). Increased amounts of mitochondrial sirtuin-3 (SIRT3) are linked to metabolite syndrome. In an experiment, on rats, Berberis showed effective results by lowering the SIRT3 levels (20). This alkaloid is mainly extracted from the roots of the plant. Trace amounts are also present in leaves and fruit. *B. aristata* was found to have high amounts of berberine (5).

Remedial Properties of Berberine

Berberine has got great interest because it decreases the level of glucose in human blood and lowers the lipid in blood too (13). Along the above properties it lowers the triglycerides too by around 35%. In both animals and humans these lipid profile decreasing effect has been detected (14). An isoquinoline, berberine alkaloid of the protoberberine is a type of protoberberine, found in many different species of plant. For many years it has been used in Chinese and Indian medicines. It is present in *Berberis aquifolium* (Oregon grape), *Coptic chinensis* (Coptis or goldthread), *Berberis vulgaris* (barberry), *Berberis aristata* (tree turmeric), and *Hydrastis canadensis* (goldenseal) (15). It is also used as anti-inflammatory and immunomodulatory (Gupta *et al.,* 2008). In different parts of world, the aqueous extract of *B. aristata* roots is broadly used as treatment of malaria (16). These foods which have the phytochemical activity obtaining importance due to its good securing property from many diseases (17).

Berberine, oxy acanthine and palmatine play vital role as phytochemical (18). Berberine is used to treat parasitic infections, diarrhea and ocular infections (trachoma, conjunctivitis) (19). Plants bearing berberine are assessed and they have smart action against Acquired Immune Deficiency Syndrome (AIDS) (20). Berberine coordination compound is also having vital activity against the fungi *Candida albicans*, *C. glabrata* and *C. tropicalis* (21).

Hepatoprotective Activity

The roots of *B. aristata* have been utilized in treatment of jaundice in Ayurveda. This plant has been found promising to treat liver disorders and the aerial parts of this plant used as aqueous and methanolic compositions have been successfully used against liver disorders caused by CCl4. The healing potential of this extract was practically identical to a standard medicine called silymarin used to treat liver injuries and disorders (32).

Antidiabetic Activity

Lower blood sugar levels were assessed through roots of *B. aristata*. Dried and powdered root extract with water and methanol and rough concentrate was administrated to typical and alloxan induced diabetic rabbit. It was found that roots of this plant contain antidiabetic compounds which help in raising the levels of insulin or mimic the action of insulin by bringing the glucose levels to normal (44).

Anticancer Activity

Extract of *B. aristata* obtained from stem by using methanol was screened for anticancer potential against human colon cancer cell line.These extracts were found significantly effective against colon cancer, inhibiting the HT29 cancer cells(need to give number wise reference here) An alkaloid namely Berberine obtained from the plant *B. aristata*, has been found to hinder altogether the carcinogenesis actuated by 20-methylcholanthrene or N-nitrosodiethylamin (45).

Antimalarial Activity

Antiplasmodial adequacy of root bark of *B. aristata* has been found to apply critical schizont development hindrance of *P. berghei* isolates in vitro (46).

Antimicrobial Activities of Genus Berberis Species

Three types of extracts i.e. aqueous, alcoholic and powdered root of *B. aristata* were tried for antifungal action. All the three extracts demonstrated antifungal action against the Candida and Aspergillus species tried, aside from *C. krusei* out of the three sorts of extratcs, the best outcomes were gotten by utilizing the alcoholic extract. Significant antifungal action was found against Candida species and Aspergillus species (47).

Berberine from the plant *B. aristata* has been referred since old times as an antidiarrheal drug hindered by around 70% the secretory reactions of the heat labile enterotoxins of *Vibrio cholerae* and *Escherichia coli* in the rabbit ligated intestinal loop model (48).

B. aristata shows impact against hepatitis disease (49). In vitro near investigation of antimicrobial action of *B. aristata* and berberine was additionally performed. The ethanolic (by maceration) and fluid (by Soxhlet) extracts of *B. aristata* bark were utilized for the assessment of the in vitro and in vivo antidiarrheal action. The antimicrobial, bactericidal and antidiarrheal (castor oil initiated loose bowels, charcoal motility) tests were conducted. The results were found to be promising (50).

B. aristata, *B. chitria* and *B. lycium* are three main types of Berberis found in Pakistan. Extracts of these species have shown significant antimicrobial results. Berberine, an alkaloid from Berberis, has good results against Gram positive and Gram negative bacteria just as antifungal activity. These distinctions in susceptibilities may be because Gram negative and Gram positive bacteria are different in their cell walls. In addition, extracts got from *B. lycium* have solid antibacterial action when compared with those of *B. aristata* and *B. chitria* (8). It was also found that ethanolic root extracts of *B. aristata* show antifungal activity. It was also demonstrated that all three types of extracts mentioned above from *B. aristata* have antifungal activity against Candida and Aspergillus species (51).

Anti-inflammatory Activity

Alcoholic and watery extracts of *B. aristata* indicated significant results against intense aggravation and critical action was accomplished at two hours after Carrageen injection. Fluid extract was successful in the beginning stage of intense aggravation and alcoholic extract in the later period of intense irritation. This recommends that the alcoholic extract might be acting by hindering the mediators delivered in the later stage (for example prostaglandin), while the fluid extract might be acting by impeding the mediators delivered in the beginning stage (for example bradykinin, histamine, and serotonin), just as by obstructing the mediators delivered in the later stage (for example prostaglandin) (53).

Antioxidant Activity

Cancer prevention agent capability of fifty percent aqueous ethanolic root extract of *B. aristata* was investigated. Its effect on antioxidant enzymes of liver was studied in diabetic rats. The root extract of *B. aristata* can possibly reduce oxidative stress. Antioxidant capability of dried parts of *B. aristata* were explored in fluid and methanolic separate and berberine, against CCl4 actuated liver injury. The outcome was promising (54).

Domestic Applications

Berberis aristata has various uses such as fruit, medicinal purpose, fuel wood, live-fence and fodder for goats. The barberry fruits are consumed by the villagers in the hills. A well-flavored fruit, it has a sweet taste with a mixture of acid, although the seeds cause a mild bitterness (61). In India, the fruit is sold in local markets. *Berberis aristata* D.C has been known for their medicinal and pharmaceutical properties (56) and it is also used in the dyeing and printing industry. The roots, wood, bark and extract of barberry have been used in Hindu medicine since time long-established. The wood is used as a fuel. The spikey branches are used for making fencing around fields (59). The roots of this plant are also used by the villagers in the hills to make an alcoholic drink. The fruits are juicy and contain lots of sugars and other beneficial components (60) In India; it is dried and used like raisins. They can also be dried and used as a raisin substitute. Buds of flowers are added to sauces (57).

CONCLUSION AND RECOMMENDATIONS

Berberis species is common to South America and Asia. In Asia it is found in India (Himachal Perdesh), Pakistan and Nepal. This species has long been used for a wide range of medicinal, food and fodder purposes throughout the world. It has been found to have antibacterial, anti-inflammatory, antidiabetic, antidiarrheal, antioxidant, antimicrobial and anti-osteoporotic activities. Extracts from all the parts of different plants are being used to cure a wide range of diseases. This species is getting endangered in recent years. There is need to conserve this valuable resource of therapeutic potential in Pakistan and there is also a need to investigate more about it. The real potential of phytochemicals found in this species is still to be explored. This can be a source of drug development in coming days. It was earlier reported that there are 19 Berberis species in Pakistan, but recently there are reports claiming that only 14 species are present here. Experts are needed to identify all the locally available species and botanical gardens are required to establish herbaria in order to conserve the rapidly diminishing Berberis spp. Moreover, *B. baluchistanica* has not been investigated for its pharmacological and clinical uses. Each plant having unique phytochemicals needs to be studied properly. Only three (*B. aristata*, *B. vulgaris* and *B. lycium*) have been studied in Pakistan. Rest of the 11 species are yet to be explored for their medicinal potential. There is also a need to study the anticancer and antidiabetic potential of Berberis species.

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