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Review Article

Berberis lycium Royle (Royle, 1837): A Threatened Medicinal Plant and Its Biological Activities

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Abstract

Berberis lycium Royle belongs from the genus Berberidaceae and is a hedge plant native to Pakistan, India and whole region of Himalayas. In Pakistan, it grows in Baluchistan, NWFP, Punjab and Azad Kashmir at elevation of 900 to 2900 m. Different portions of the plant such as roots, leaves and fruits etc. are utilized to heal different diseases and also used as food supplements. The plant is identified to impede renal disorders, skin infections, abdominal disorders, common cold and cough, typhoid etc. Traditionally, this plant has been employed against diarrhea, intestinal colic, piles, jaundice, internal wounds, rheumatism, diabetes, ophthalmia, gingivitis, throat pain, backache, scabies, bone fractures, sun blindness, pustules, menorrhagia, fever and as diuretic, expectorant and diaphoretic. *Berberis lycium* is also known to have antidiabetic, antihyperlipidemic, hepatoprotective, antibacterial, antifungal, anticoccidial, pesticidal and wound healing properties. There is only a little published information on the *in vitro* and cutting propagation of *Berberis lycium*. According to International Union for Conservation of Nature (IUCN), categories *Berberis lycium* species are vulnerable.In this review an attempt has been made to sum up various characteristics of *Berberis lycium*.

Keywords: *Berberis lycium; Berberine; Alkaloids; Hepatoprotective effect; Antihyperlipidemic effect*

Introduction

Medicinal plants are the plants that comprise of constituents having curative effects therefore have been employed from a long time to cure different diseases. In the recent times, due to the fact that pathogens had developed resistance against existing antibiotics, several traditional medicines are recognized as a substitute of health care which has recommenced the research area for the medicinal plants to check their biological activities [1].

Medicinal plants are considered as the vital natural sources for potentially secure drugs which play an essential part in assuage human health by contributing as an herbal medicine. In Pakistan, many native plants are utilized in herbal medicine to treat diseases and heal different injuries. Such flora frequently shows a broad spectrum of biologic and pharmacologic activities, for instance they are intended to reduce inflammation, shows bactericidal and fungicidal properties [2]. The root, bark, seed and fruit extracts of these plants are exploit in the development of syrups and infusions in traditional medicine [3]. Al-Biruni named one of such medicinal plant (*Berberis lycium*) as Ambaribis. He referred its name in Persian as Zirkash as well. It is commonly called as Indian barberry in English and Kashmal or Ishkeen in Urdu. It was illustrated by John Forbes Royle in 1837 [4].

Berberis lycium is a spiky plant which is the member of the genus Berberis of family Berberidaceae. It is dispersed in the moderate and semitropical Asian, European and American divisions [5,6]. In Pakistan it is extensively distributed in Baluchistan, NWFP, Punjab and in northerly regions like Gilgit, Baltistan, Ghizer, Astor, Diamer, Swat and Azad Kashmir at elevation of 900 to 2900 m [7,8].

Medicinal plants are the essential source of medical and a lot of other pharmaceutical products. The conventionally used breeding techniques are the major means of multiplication which acquires a large period for development caused due to the small rate of fruit set or deprived germination and occasionally clonal homogeny is not sustained by seeds as well. In the recent time, because of the increase in the demand for the naturally occurring drugs, the plants are being overutilization, menacing the endurance of numerous rate species. Furthermore, numerous medicinal plant species are vanishing at a disquieting rate because of the quick rural and urban growth, unrestrained disforestation, and unsystematic assemblage of the plants. Modern biotechnological techniques of culturing plant cells and tissues are supposed to supply novel ways for preserving and quickly proliferating important, exceptional, and endangered medicinal plant species [9]. According to International Union for Conservation of Nature (IUCN), categories *Berberis lycium* species are vulnerable [10,11]. Hamayun *et al*., also stated it as one of the endangered medicinal plant species in Pakistan [12]. Therefore a quick clonal proliferation method for *Berberis lycium* a threatened therapeutic shrub is needed. *In-vitro* multiplication of *Berberis lycium* was reported with different concentrations of growth hormones utilizing cotyledonary node explants obtained from germinated seeds. Regenerated plantlets were formed and successfully shifted to the field after 12 weeks [13].

Berberis lycium is a vertical flowering bush plant that increases to a length of 3-4 meters, having a solid timber stem and is enclosed in a slight fragile bark. The plant has androgynous (containing both sex organs) flowers which are self pollinated but pollination occurs via insects too [5,6] (Jafri, n.d.; Irshad *et al*., 2013). The branches of *Berberis lycium* are light white to grayish and have thorns alternatively fixed on them. Leaves of the plant have vibrant color [14]. The plant blooms from May to June. The flowers have a cupped shape which are arranged in racemes and are mostly pale yellow in color, and are larger than the leaves [15]. The fruit of this plant are the berries which are oval in shape having bright red or purplish color on ripening. In average the fruit of the plant is 7 mm in length, 4 mm in width and have weight of 227 mg. Its pulp or juice is plum purplish in color and contains approximately 2-5 seeds. Root is stiff, branched and 3-8cm in width while its timber is leveled and intense yellow in color. Root bark could be approximately 3mm solid, from the outside fractured and inside smooth [14].

Berberis lycium is extensively utilized for medical purposes. A general method is to boil small parts of its root and bark in water which is then drained and boiled further until it forms a partially firm accumulate, known as "Rasaut". The root extract is applied for curing UTI, swelling of spleen, stomach and intestinal ulcer and liver diseases. The extract is also used for the external application of the eyelids in acute conjunctivitis, in combination with butter and alum [4]. The local population utilizes the powdered form of dried root bark after combining with dissolved animal fat for bone fractures as a bandage. In Asian countries, for the treatment of renal disorders the fruit of the plant is utilized and for gum and tooth diseases the fruit juice is employed. For typhoid and common cold, fruit extract is used [16]. Shoots of the plant are employed for the belly ache, jaundice and loose bowels [4]. The bark of the plant has wound healing activity [17]. The leaves of the plant are used as an alternative to the tea. The local population utilizes the entire plant for curing bulging and stinging eyes, fractured bones, internal wounds, ulcer, jaundice and rheumatism [18].

Numerous biologically significant isolated compounds are berberine, palmatine, berbamine, aromoline, oxyacanithine, umbellatine, ß-sitosterole, punjabine, balochistanamine, oxyberberine, berberine chloroform and palmatine chloroform (some of them are shown in Figure 1). The major biological activities are characterized to its most important element, berberine which is an alkaloid [4].

Berberine has a wide spectrum of pharmacological and biological properties which includes anti-inflammatory, antimicrobial properties and antidiabetic properties. Furthermore, *Berberis lycium* had shown antidepressant effects in a variety of behavioral animal models [19]. Leng *et al*., (2004) have illustrated the effect of berberine to lower glucose levels, and quite a lot of works have been carried out concerning about its function in the cure of diabetes mellitus, but it is still not clear that how the mechanism is triggered [20].

Berberine is also useful against amoebiasis, cholera and dysentery [18], alleviates fever and has pain-relieving effects [21], and was also stated to show antiarrhythmic, anti-tumor [22], anti-inflammatory [23], and rheumatic properties [21]. There is a very little

knowledge about the cellular and molecular anti-tumorous mechanisms which are activated via berberine or through the extracts of *Berberis* species [18].

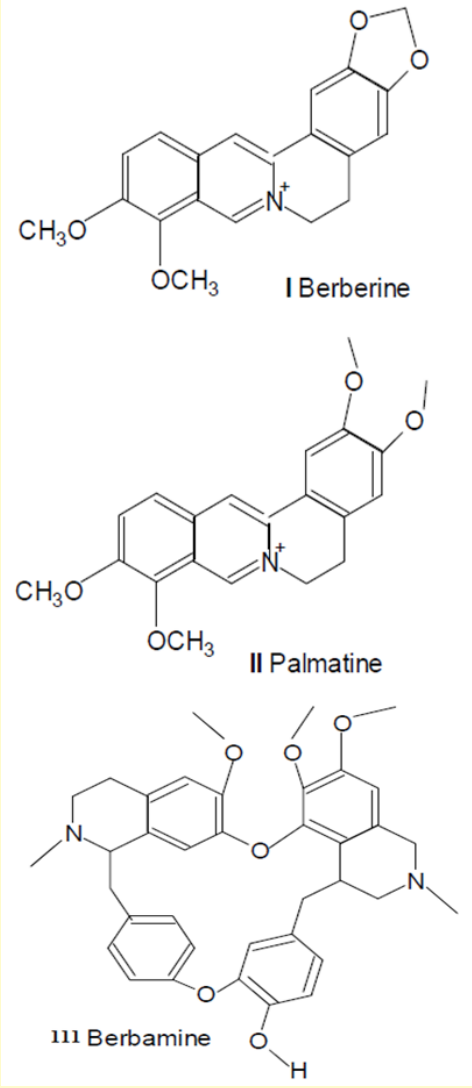

Figure 1: *Alkaloids of Berberis lycium.*

Biological Activities

Antimicrobial Activity

Hydro alcoholic (50%) extract of air dried root and stem of *Berberis lycium* were used to find out antibacterial property via micro-dilution technique. Plant extract showed antibacterial activity against *Micrococcus luteum, Bacillus subtilis, Bacillus cereus, Enterobacter aerogenes, Escherichia coli, Klebsiella pneumonia, Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus aureus,*

and *Streptococcus pneumonia*. Minimum inhibitory concentration (MIC) of root and stem extract against each test organism is shown in Table 1. Root extract also found active against fungal strains of *Aspergillus flavus, Aspergillus terreus* and *Aspergillus spinulosus*. Whereas stem extract inhibited *Aspergillus spinulosus* only, the MIC of root and stem extracts against these fungal strains are shown in Table 2. The main alkaloid berberine might be dependable for antimicrobial activity [24]. The hydro-alcoholic extract demonstrated stronger and broader range against bacterial strains in contrast to fungal strains [25].

Micro-organisms	Extracts	MIC	Extracts	MIC
Micrococcus luteum	Root Extract	1.25 µg/mL	Stem Extract	0.31 µg/mL
Bacillus subtilis	Root Extract	0.62 µg/mL	Stem Extract	0.31 µg/mL
Bacillus cereus	Root Extract	2.50 µg/mL	Stem Extract	2.50 µg/mL
Enterobactor aerogenus	Root Extract	2.50 µg/mL	Stem Extract	1.25 µg/mL
Escherichia coli	Root Extract	0.31 µg/mL	Stem Extract	0.62 µg/mL
Klebsiella pneumonia	Root Extract	1.25 µg/mL	Stem Extract	0.31 µg/mL
Proteus mirabilis	Root Extract	1.25 µg/mL	Stem Extract	0.31 µg/mL
Pseudomonas aeruginosa	Root Extract	0.62 µg/mL	Stem Extract	0.31 µg/mL
Staphylococcus aureus	Root Extract	0.62 µg/mL	Stem Extract	0.62 µg/mL
Salmonella typhimurium	Root Extract	2.5 µg/mL	Stem Extract	0.62 µg/mL
Streptococcus pneumonia	Root Extract	0.62 µg/mL	Stem Extract	1.25 µg/mL

Table 1: *MIC against bacterial strains.*

Micro-organisms	Extracts	MIC
Aspergillus terreus	Root Extract	0.31 µg/mL
Aspergillus spinulosus	Root Extract	0.62 µg/mL
Aspergillus flavus	Root Extract	1.25 µg/mL
Aspergillus terreus	Stem Extract	0.62 µg/mL

Table 2: *MIC against fungal strains.*

Different extracts i.e. methanolic, isopropanol, ethanol and aqueous extracts were examined against the mixture of human pathogenic bacteria namely *Pseudomonas sp., Escherichia coli, Streptococci sp*. and *Staphylococcus sp*., the methanolic extract exhibits the highest zone of inhibition then isopropanol extract and ethanol extract while the aqueous extract exhibited the smallest inhibitory zone that are shown in Table 3. In the methanolic extract, the maximum inhibition is possibly characterized based upon the fact that alkaloids are extremely solvable in polar solvents. The methanolic extract was when used alone to analyze the bacterial pathogenic strains, *E. coli* exhibited greatest zone of inhibition followed by *Pseudomonas* and *Staphylococcus*, shown in Table 4. Though, there was no effect on *Streptococcus* [6]. The highest inhibition levels that occurred in *E. coli* and *Pseudomonas* might be predictable by the fact that the root extract of *Berberis lycium* has a number of components that hinders the protein synthesis mechanism of these bacterial species [26]. Stermitz *et al.*, also reported the inhibitory effect of plant extracts against *Staphylococcus sp* [27].

In the drinking water of broilers *Berberis lycium* was added along with other medicinal plants which exhibited improved immunity response to Newcastle syndrome, contagious bursal disease and contagious bronchitis. A noteworthy reduction in coccidial oocysts was also observed [28].

Root Extracts	Zone of Inhibition
Methanol	16 mm
Isopropanol	13 mm
Ethanol	12 mm
Aqueous	10 mm

Table 3: *Zone of inhibition formed against human pathogenic bacteria (Pseudomonas sp., Escherichia coli, Streptococci sp. and Staphylococcus sp.) using different solvent root extracts of Berberis lycium.*

Bacteria	Zone of Inhibition
Streptococcus	None
Staphylococcus	10mm
Pseudomonas	11mm
E. coli	12mm

Table 4: *Zone of inhibition formed against human pathogenic bacterial strains by using 10% methanolic root extract of Berberis lycium.*

The antifungal effect of root, stem and leaf extract of *Berberis lycium* was tested against the fungal pathogen *Sclerotium rolfsii* Sacc. The extracts that were tested in various concentrations decreased the mycelial growth of *S. rolfsii* in contrast to the control. The root extract was more effective as compared to the other extracts. There was maximum production of *Sclerotia* in control while a few *Sclerotia* was produced in the root, stem and leaf extracts at 20 and 25% extract concentrations [29].

Antidiabetic Activity

Berberis lycium shows antidiabetic activity in rabbits therefore aids in the reduction of sugar intensity in the blood. The root bark extract of Effect of *Berberis lycium* was determined in an alloxan induced diabetic rabbits. Simple powder of *Berberis lycium* decreased the blood glucose levels of both diabetic and normal rabbits. Water, methanolic, aqueous methanolic, n-hexane and chloroform extracts of plant were made to screen their antidiabetic activity in alloxanized rabbits. Results showed that amongst the extracts, water extract (500 mg/kg) showed greatest hypoglycemic activity when administered orally, for almost 6 hours. Similar dosage of methanol, aqueous methanol and n-hexane extract decreased glucose intensity in the blood for 4 hours. There was no significant change showed by the chloroform extract [8].

Ethanolic and aqueous extracts of the roots of the plant were administered in normal and alloxanized rats and 20 mg/kg glibenclamide was utilized as a control drug. The 50 and 100 mg/kg dosage quantity decreased the blood glucose level after 3 to 5 hours of administration but there was more prominent effect of the dose used later on. Oral glucose tolerance test showed that the plant extracts decreased serum glucose intensity in a dose-reliant behavior. The observed procedure concerned in hypoglycemia has insulin-like effect, maybe by the peripheral glucose utilization [30].

Hepatoprotective Effect

Berberis lycium also comprises antihepatotoxicity effect. *Berberis lycium* was mixed with *Galium aparine* and *Pistacia integerrima* and was tested in rats that were treated with carbon tetra chloride; the results revealed that the combination of these three medicinal plants encompasses antihepatotoxicity effects. The three medicinal plants used in the present study showed high curative effect as a therapeutic agent relatively than protective agent [31].

To estimate hepatoprotective effect of *Berberis lycium*, crude powder and methanolic extract of plant were used. Paracetamol was given to the rabbits to induce hepatotoxicity. Results showed that plant considerably decreased the elevated levels of serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase and alkaline phosphatase enzymes in hepatotoxic rabbits [32]. In a

further study, six poly herbal formulations comprising Livokin (Herbo-med, Kolkata) and *Berberis lycium* were studied in mice. This formulation showed hepatoprotective effect in paracetamol stimulated hepatotoxic mice [33].

Anti-hyperlipidemic Effect

In alloxanized rabbits the rough root powder of *Berberis lycium* shows lipid-lowering effect. In alloxan induced diabetic rabbits, hypertriglyceridemia and dyslipidemia have been stated to arise [34]. Anti-hyperlipidemic effect was examined and roots of *Berberis lycium* Royle were collected for this reason. Results showed that oral administration of 250 and 500 mg/kg crude powder showed a major decline in the levels of low density lipids (LDLs), total cholesterol and triglyceride in male albino rabbits, while high density lipids (HDLs) were increased. Also the same doses stabilize the weight of diabetic rabbits. An enhancement in HDL and reduction in LDL levels was found when treated with root of the plant and this effect most likely prevents the patients suffering from diabetes from having heart problems. Plant root bark powder when frequently administrated showed a positive result on hyperlipidaemia linked with high blood glucose levels [8].

Another study concerning about the function of *Berberis lycium* for the reduction of serum cholesterol level in broilers has also been demonstrated. 240 broiler chicks were fed to the root extract of *Berberis lycium*, at the dosage percentage of 0, 0.5, 1, 1.5, 2 and 2.5%. The results suggested that the plantconsiderably helped in enhancing the HDL level and also helped in decreasing the levels of LDL, triglycerides and serum total cholesterol [35].

Wound Healing Activity

The root extract of *Berberis lycium* was used to study its wound healing ability in Swiss Wistar rats. Methanolic and aqueous extracts of the roots were tested using, excision, incision and deceased wound space forms of wound repair. Both extracts enhanced the region of epithelialization and also displayed enhancement in breaking potency. Results revealed that aqueous extract was less efficient than the methanolic extract [17].

Pesticidal Activity

Petroleum ether and aqueous methanol extracts of *Berberis lycium* root was made employing Soxhlet apparatus and dried out under vacuum. The pesticidal activity of plant extracts wereexamined at two high doses (5000 and 10000 ppm) against pests. Petroleum ether extract given 25% death rate against *Helicoverpa armigera* Hub and 92% death rate against *Aphis craccivora* Koch at the dose of 5000 ppm and also exhibited 26% mortality rate against *Tetranychus urticae* Koch, 98% mortality rate against *A. craccivora* Koch, while 28% mortality rateagainst *H. armigera* Hub and *Plutella xylostella* L. each at the dose of 10,000 ppm. Petroleum ether extract inhibited *A. craccivora* Koch at 458.65 ppm lethal concentration at 50% (LC50) after 24 hour contact time and 57.79 ppm LC50 after 48 hour contact time. The LC50 at 48 hour disclosure was almost analogous with that of Dimethoate (a compound insecticide) at 24 hour disclosure.

Aqueous methanolic extract showed 26% death rate against *A. craccivora* Koch at the dose of 5000 ppm and also showed 44% death rate against *H. armigera* Hub, 41% against *P. xylostella* L., 43% against *T. urticae* Koch and 68% against *A. craccivora* Koch [36].

Conclusion

Berberis lycium (Berberidaceae) is an essential conventional hedge plant local to Pakistan and India however is located in the other regions of the world as well. Residents of these regions use *Berberis lycium* to cure different diseases such as diabetes, lesions, bone fractures, ulcers, curative piles and aching eyes [37]. It is a significant plant with a variety of healing properties which is widely used for medicinal purposes in Pakistan [38].

Berberis lycium has a significant potential for future research. Plant is identified to have tannins and anthocyanins which both encompass antioxidant property [39,40], but only a smaller amount of research work have been conducted in this area. Therefore future research should be assumed using plant extracts and different antioxidant models. *Berberis lycium* has been used traditionally in

diarrhea and in intestinal colic since centuries. Berberine, a plant component is also recognized to have anti-diarrheal property but the exact mechanism is still unsure. So, *in vitro* spasmolytic activities and *in vivo* anti-diarrheal activities of different plant extracts should be estimated in a view to find the mechanism. Some other *Berberis* species have also been assessed for a range of potential pharmacological properties. *Berberis aristata* has been observed for anti-inflammatory and cardio-tonic properties [41]. *Berberis vulgaris* was found to possess antioxidant [42], anti-histaminic, anticholinergic [43], and anti-inflammatory property [44]. The results specify that *Berberis lycium* Royle [45] may possess similar activities as well. Thus, research must be aimed at to evaluate *Berberis lycium* Royle for these pharmacological properties in future.

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