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Review Article

Phytopharmacological and ethnomedicinal uses of the Genus Berberis (Berberidaceae): A review

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Abstract

Plants belonging to Berberis are reported in several folklore medicinal pharmacopeias and are used in traditional medicines in Asia and European countries. The plants have been used in the preparation of various traditional and synthetic medicines since pre-historic times for wound healing, fever, eye disease, jaundice, vomiting during pregnancy, rheumatism, kidney and gall balder stones, and several other illnesses. Their healing properties are appear to be due to the presence of secondary metabolites and important alkaloids with different pharmacological activities. Their antibacterial, antifungal, antiviral, anti-diabetic, and anti-tumor activities as well as positive effects on the cardiovascular and body immune systems have been reported. Root extracts of some species of the plant genus contain quinine which acts as a powerful anti-malarial agent. The main chemical constituents of Berberis plants are alkaloids, steroids, glycosides, flavonoids, saponins, terpenoids and reducing sugars. Of these alkaloids, berberine is the most important. The present review focuses on recent advances in phytopharmacological and ethnomedicinal uses of plants belonging to Berberis genus.

Keywords: *Berberis, Alkaloids, Berberine, Pharmacology, Phytochemistry, Ethnomedicinal uses*

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INTRODUCTION

Traditionally medicinal plants have been used in the preparation of medicines [1,2]; In developing countries, about 25 % of ingredients in prescribed medicines are derived from medicinal plants [2,3]. Most of these preparations include plant extracts and their active components. In addition, a number of modern drugs are isolated from natural medicinal plants [4].

The genus, *Berberis*, is a major dicotyledonous genus belonging to the Berberidaceae family; mainly spiny, woody, deciduous or evergreen shrubs or small trees with characteristic yellow wood and flowers. Different taxonomists have reported different number of species in this genus. Recent reports indicate 17 genera and 650 species of Berberidaceae [5]. The genus has wide distribution all over the world mainly in India, Pakistan, Japan, China, Central and West Asia, South-East Asia, Europe, East Africa, South America and North America [6]. In Pakistan, species belonging to this genus are found across most of the mountainous regions (1400m – 3500 m above sea level) and are key components of both traditional and modern medicines [5,7-9]. Based on habitat, these plants are clustered into three groups namely Rocky Mountain group which includes *B. aquifolium* Pursh, the Asiatic group which includes *B. aristata* and the European group which includes *B. vulgaris* [11]. Apart from their medicinal uses,

some of the species are also used as sources of natural dyes [10,12].

Research findings have been published by various groups on the phytochemical and pharmacological properties of *Berberis* species. Ikram [13] reviewed studies on the chemical and pharmacological aspects of 24 *Berberis* species. The number of chemical studies on *Berberis* species increased immensely between 1975 and 1990. Karimov [14] also tabulated 76 *Berberis* species and listed 129 distinct new alkaloids belonging to 16 different classes. The present review focuses mainly on recent advances in different ethno-medicinal uses and pharmacological studies of chemical substances from plants belonging to genus *Berberis*. In addition we discussed the biological activities of chemical compounds found in *Berberis* species, and their relevance to phyto-medicinal properties.

PHYTOCHEMISTRY OF GENUS *BERBERIS*

Almost similar types of chemical constituents are present in the roots and stems of *Berberis* plants. However, variations exist in the chemical constituents of leaves of different species of the genus [11]. These include alkaloids, flavanoids, terpenoids, anthocyanins, sterols, vitamins, lignins, carotenoids, proteins and lipids which have been isolated and characterized from different *Berberis* species (Table 1 and 2). Some of the main alkaloids reported are berberine, berbamine, columbamine, palmatine, jatrorrhizine and oxyacanthine [10,14-16]. From methanolic extract of all parts of *B. pachyacantha* an isoquinoline alkaloid, pachycanthine, was isolated [17]. Furthermore, Torres *et al* [18] isolated lignins from the stem and leaves of these plants.

Although most of the phytochemical studies focused on wild species, some of the research groups have carried out comparative studies on the phytochemical compositions of wild and cultivated plants of this genus. For example, differences have been reported in the amount of alkaloids isolated from wild and cultivated plants [19, 20]. For example, Gorval and Grishkovets [21] reported that evergreen *Berberis* species contain more alkaloids than deciduous species.

While most of the phytochemical studies were carried out on the stem, stem bark, root and root bark of *Berberis* plants, there are reports of characterization of phytochemicals from other parts like leaves, fruits and flowers. Various polyphenolic flavonoids like caffeic acid, quercetin; meratin, chlorogenic acid and rutin have been extracted from the flowers of *B. aristata*. Chemical constituents present in the fruits have nutraceutical potential and provide health benefits [22]. *B. lycium* is a good source of various nutrients like β-carotene, anthocyanin, ascorbic acid and minerals.

Studies carried out on five different species of *Berberis* from West Himalaya showed that the fruits contained appreciable amounts of protein (seeds 5.9–8.5 %; pulp 4.7–7.2 %); fat (seeds 4.6–5.3 %; pulp 2.6–4.0 %); fiber (seeds 4.4–5.3 %; pulp 7.0–8.1 %), and minerals, especially potassium and calcium [23]. However, they have anti-nutritional factors like tannins and phytic-acid which lower food energy. Hence, care should be taken while selecting these fruits for value addition as health foods.

The major chemical constituents of different species of the genus *Berberis* are illustrated in Figure 1.

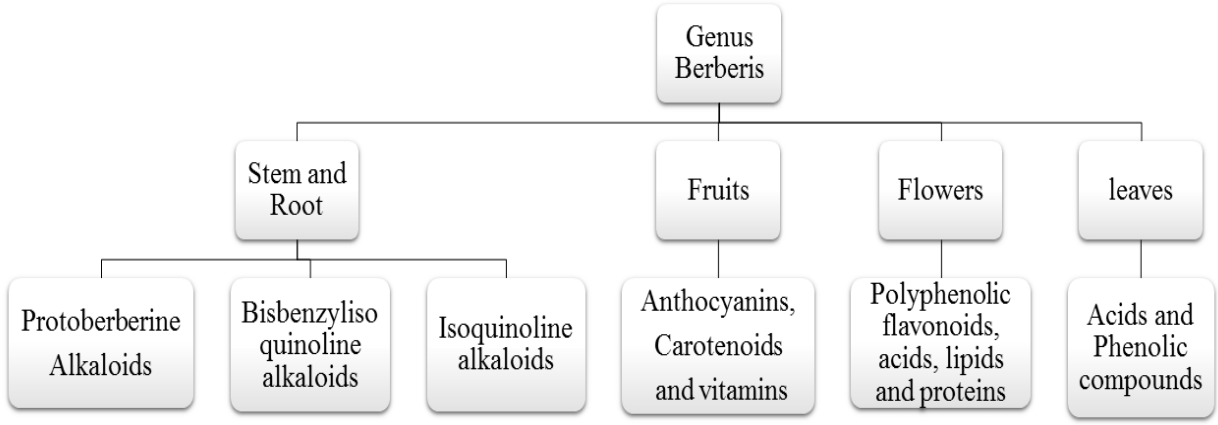

Figure 1: Major chemical constituents of different species of the genus *Berberis*

Table 1: Photochemistry of *Berberis* plants

No	Botanical Name	The compounds isolated	Parts used	References
1	*B. aristata*	Berbamine, Berberine, Colunbamamine, Jatrrohirine,, Karachine , Oxyacanthine, Oxyberberine , Palmatine, Palmitine, Taxilamine, Tetrahydropalmitine	Roots and leaves	Srivastava *et al*., [14]; Bhardwaj and Kaushik, [9]
2	*B. lycium*	Baberine, Berbericine hydrochloride, Berbericine hydroiodide, Berberine chloride, Berberine-chlorofrom, Chenabine, Diphenolic, Palmatine, Gilgitine, Jhelumine, Kara-koramine, Palmitine chloroform along with oxyberberine, Punjabine, Seco-bisbenzylisoquinolines, Sindamine, Umbellatine	Roots , Leaves, Stems and Decoctions	Ikram *et al*., [11]; Miana, [26]
3	*B. pachycantha*	Berbamine, Cyanidin- 3 glucoside, Isotetrandrine, Jatrorrhizine, Magnoflorine, Oxyacanthine, Oxyberberine, Polar gonidin - 3 glucoside	Roots and Fruits	Reviewed by Srivastava *et al*., [14]
4	*B. vulgaris*	8-Oxyberberine, Aromoline, Auroxanthin, Baluchistanamine, Berbamine, Berberine Chloride, Capsanthin, Carbohydrates, Chilenine Chrysanthemaxanthin, Flavoxanthin, Palmatine, Isotetrandrine, Jatrorrhizine Chloride, Lutein, Obaberine, Obamegine, Organic acids, Oxycanthine, Palmitine Chloride, Pectic substances, Tannin, Tejedine, Thalifoline, Thaligrisine, Vitamin C, Zea xanthin, β – carotene	Fruits, Root bark, Decoctions and Fruits	Reviewed by Srivastava *et al*., [14]
5	*B. coriaria*	1, 4-Bis (2' - hydroxy-5'-methylphenyl)-butan-1, 4-dione (I) (a ketone), ketone -7 methyltetracosan along with berberine, Anthocyanins –cyanidin, Pelargonidin, Petunidin, Peonidin and delphinidin aglycons bounded with glucose and rutinose.	Stem, Bark and Fruits	Tiwari and Singh, [29] Srivastava *et al*., [14]
6	*B. calliobotrys*	1-0-methylpakistanine, Chitraline, Kalashine, New dimeric aporphine Benzylisoquinoline- Khyberine, Pakistanamine, Pakistanine	Roots	Hussain and Shamma, [30]
7	*B. orthobotrys*	Dimer of kalashine with the pakistanamine and pakistanine, 1-0 methyl kalashine, armeparvine	Roots	Hussain and Shamma, [30]
8	*B. brandisiana*	Berbamine-2'-β-N-oxide, Berbamine, Palmitine, Berbernine, Thalifoline, Reticuline, Apoglaziovine, Isoboldine, Isotetrandrine	Aerial parts	Hussain *et al*., [31]; Karimov *et al*., [12]
9	*B. pseudoumbellata*	Berberine, Palmitine, Pisbenzy isoquinoline alkaloid oxyaoanthine, O-methyl oxyacanthine	Aerial part	Reviewed by Rajasekaran and Pant, [32]
10	*B. baluchistanica*	Free base baluchistanamine, Phenolic aprophine benzylisoquinoline alkaloid, pakistanine, Proaphorphin, benzylisoquinoline alkaloid, pakistanamine	Roots	Kakar *et al*., [33]
11	*B. calliobotrys*	*Berberine, Oxyberberine, Karachine, Corydaldine, Methylcorydaldine, Nmethyl- 6, 7-Dimethoxy-isoquinoline, Aromoline, Pakistanine, Waziristanine*	*Root bark*	*Ahmed, [34]*
12	*B. jaeschkeana*	Alkaloids, Glycosides, Flavonoids, Steroids, Saponins, Reducing Sugars, Terpenoids	Roots and Stems	Alamzeb *et al*., [35]

Table 1: *Photochemistry of Berberis plants (continued)*

No	Botanical Name	The compounds isolated	Parts used	References
13	*B. chitria*	Alkaloids named chitrian A, B, C, Aporphine base-o-methyl corydine N-oxide, Berbamine, Berbamunine, Berberine, Berlambine, Cetyl alcohol, Columbamine, Dihydro kaempferol, Dihydropalmitine N-oxid, Glucose, fructose and rhamnose, Hentriacontane, Hydroxyacanthine, Jatrorrhizine, Lambertine, Linoleic acids, Oleic acids, Oxyacanthine, Palmitic, Palmitine, Palmitine, Quercetin, Steric acids, Triacontan, Trimethoxyl dibenzo- quinoliziaium chloride, Umbellatine, Yuziphine, β-sitosterol	Roots	Hussaini and Shoeb, [36]

Table 2: Major alkaloids present in species belonging to the genus *Berberis*

S/no.	Alkaloid	Species	Reference
1	Berberine	*B. aristata, B. lycium, B. vulgaris, B. chitria, B. corearia, B. umbellata, B. pseudumbellata, B. jaeschkeana, B. waziristanica, Berberis brevissima*	Rashmi *et al* [34]
2	Berbamine	*B. aristata, B. vulgaris, B. coriaria, B. jaeschkeana, B. pachycantha, B. brandisiana, B. chitria*	Rashmi *et al* [34]
3	Palmatine	*B. aristata, B. lycium, B. vulgaris, B. chitria, B. jaeschkeana*	Rashmi *et al* [46]; Bhardwaj and Kaushik [11]
4	Columbamine	*B. vulgaris, B. chitria*	Hussaini and Shoeb [38]
5	Jatrorrhizine	*B. aristata, B. lycium, B. vulgaris, B. chitria, B. pachycantha,B. vulgaris*	Rashmi *et al* [46]
6	Oxyacanthine	*B. aristata, B. chitria, B. coriaria, B. pachycantha, B. pseudoumbellata,*	Rashmi *et al* [46];

Different parts of the plants have been explored for different purpose viz. the fruits of *B. vulgaris* have been explored more broadly for their neutraceutical properties in comparison to other parts. Also, the stem and roots of *B. aristata and B. lyceum* (these species mainly found in Asia) have been extensively studied for their medicinal rather than for neutraceutical properties [23,24].

PHARMACOLOGY OF GENUS *BERBERIS*

A number of pharmacological and clinical studies have been reported for different *Berberis* species, thus indicating their importance as medicinal plants (Table 3). Traditionally, in 668 BC Assyrian (present day Iraqi) people used *Berberis* species, especially barberry fruit extracts, for blood purification [14]. In a number of homeopathic and ethno-medicines, the stem and roots of *Berberis* species have been extensively used as ingredients or raw materials; they are used in Ayurveda (traditional Indian medicine system) for quick healing of wounds, various infections of ear, eye and mouth, piles and hemorrhoids; for reducing obesity, for the treatment of dysentery, indigestion and vaginal diseases, and as antidotes for snake bites [39]. Extracts prepared by boiling the roots and stem barks of *B. aristata, B. chitria* and *B. lyciumin* in water have been used since ancient times as domestic cure for conjunctivitis, bleeding piles, ophthalmic problems, skin diseases, ulcers, jaundice, inflamed spleen and inflamed liver [40]. A decoction of some *Berberis* species is mixed with honey and used for treatment of jaundice and painful micturition. Extracts of *Berberis* plants have been effectively used for treating gynecological inflammatory diseases [11]. Attempts have been made at synthesizing some alkaloid products originally isolated from *Berberis* species; some of the synthetic berbamine derivatives have been found to have anti-leukemia activity [41].

Two important alkaloids (Table 2 for details), berberine and berbamine, found in *Berberis* plants have antioxidant, anti-hyperglycemic, anti-inflammatory, heptoprotective, and hypotensive properties [42]. Aqueous extract of *B. lyceum*

Table 3: Ethnomedicinal claims of *Berberis* species

S/N	Botanical name	Local Name	Ethnomedicinal uses*									Reference
			R	Se	F	St	B	W	Fr	De		
1.	*B. aitchisonii*	Kwary	+	-	-	+	+	-	+	-	Has Activity against carrageenan and serotonin-induced hind paw oedema, acetic acid-induced increased vascular permeability, castor oil-induced diarrhea and Freund's complete adjuvant-induced arthritis models.	Küpeli *et al* [65]
2.	*B. vulgaris*	Zarlog/ Tor kwaray/ Zarch/Zralga	+	-	-	+	+	-	+	+	Used to heal internal injuries in man and cattle. For the relief of joint pain. Used the roots decoction for the cure of internal injuries and for the removal of kidney stones. Used for sore throat and fever. Poultice of pounded root or bark used for sore throat. Cold and compound decoctions are taken in fever. Roots are boiled in water and decoction is used in both human and cattle for the treatment of internal injuries and also used for tanning skin.	Tantaquidgeon, [66] Chaudhary *et al* [67]
3.	*B. brandisiana*	Shugloo	-	-	-	-	+	+	+	-	Leaves decoction is useful in dysentery and sore throat. Root and stem bark is tonic and is frequently utilized for healing of wounds and arthritis.	Khan *et al* [5]
4.	*B. brevissima*	Zeyar largy	+	-	-	+	-	-	-	-	Antidiabetic and antimicrobial activities.	Ali *et al* [58]
5.	*B. calliobotrys*	Shin zaralga	-	-	-	-	+	-	+	+	Traditionally used as a gargle for pharyngitis for the relief of intestinal colic.	Singh *et al* [30]
6.	*B. aristata*	Kingore/Daru haldhi	+	-	-	-	+	-	+	+	Anti-microbial, anti-pyretic, anti-hepatotoxic, anti-hyperglycaemic, anti-lipidemic, anti-cancer, and anti-oxidant agent. Useful in the treatment of gynaecological disorders, diarrhoea, haemorrhoids, osteoporosis, HIV-AIDS, diabetes, ear and eye infections, jaundice, wound healing, malarial fever and skin diseases. Root extract and decoction is used for eye disorders. The decoction of the root of this plant is used in Piles, gastric disorders and other allied complaint. Used in snake and scorpion bite. Extract of root with butter used for the treatment of bleeding piles.	Küpeli *et al* [65] Bhattacharjee *et al* [68]
7.	*B. Jaeschkeana*	Jaeschke's /kaymali	+	+	-	-	-	-	+	-	Used in Eye trouble, fever, stomach disorders, skin diseases, blood purifier, astringent, diuretic, jaundice and menorrhea. Root extract is commonly, used as an astringent, diuretic, blood purifier and alternative. It is also used in eye disorders, menorrhea, jaundice and skin diseases by the local tribes.	Singh *et al* [30] Gaur *et al* [69]
8.	*B. lycium*	Speen Kwaray	+	+	+	+	-	+	-	+	Antibacterial, anticarcinogenic, carminative febrifuge and ophthalmic. Fruit is used medicinally for stomachache. Fruits are used as coagulant.	Jee *et al* [70]

Table 3: *Ethnomedicinal claims of Berberis species (continued)*

S/N	Botanical name	Local Name	Ethnomedicinal uses*									Reference
			R	Se	F	St	B	W	Fr	De		
9.	*B. orthobotrys*	Kishmal	+	-	-	+	+	-	-	-	Used for external and internal wounds, infections, jaundice, piles, liver problems, kidney stone, swellings, sore throat, diabetes, bleeding, leucorrhoea, uterine tumors and its related problems. The extract of stem and root bark has been used in stomach ulcers and other related problems.	Khan and Khatoon [64] Akhtar *et al* [71]
10.	*B. pachyacantha*	Karpa	+	-	-	-	-	-	+	-	Traditionally used to treat stomach trouble, fever and dye	Singh *et al* [30]
11.	*B. parkeriana*	Kala Simbloo									Antidiabetic and antimicrobial activities.	Ali *et al* [58]
12.	*B. pseudumbellata*	Kashmal/kwarai	+	-	-	-	+	+	+	-	Traditionally used as astringent, diuretic and as cure for jaundice, Intestinal disorders, eye trouble, oxytocic and throat ache.	Singh *et al* [30]
13.	*B. ulicina*	Gorse Barberry	+	-	-	-	+	-	-	-	Against ringworm. cholagogue, antidiarrhoeal, stomachic, laxative, Diaphoretic, antipyretic, antiseptic. Used externally in opthalmia, conjunctivitis, ulcers, sores, swollen gums. Have Anti-inflammatory, hypoglycaemic, hypotensive, antiamoebic, anticoagulant, antibacterial activities. Bark used in liver complaints, diarrhoea, dysentery, cholera, gastric disorders enlargement of spleen and for regulating metabolism. Berries are used as antiscorbutic and laxative.	Khare [72]

**R (Roots), Se (Seeds), F (Flower), St (Stem), B (Bark), L (Leaves), W (Whole plant), Fr (Fruit), D (Decoction)*

showed hypotensive effects in dogs, and reduced mean arterial pressure in cats [43].

B. aristata, an extensively studied species of *Berberis* genus, is reported to have a number of pharmacological and clinical uses. Extracts of its root appear to be better treatment option for malaria (compared to cinchona and quinine), because it does not cause cardiac depression during treatment of intermittent fever in malaria [65,68]. Butter is mixed with powdered root and used for the treatment of bleeding piles. Cambium paste of *B. aristata* is used for the treatment of rheumatism [44]. The best clinical use includes treatment of diarrhea due to viral, protozoal, bacterial and fungal infections [45]. Ripe *B. aristata* exhibits hypochlolestrolemic activity and is used as a mild laxative for children [34].

ANTIMICROBIAL ACTIVITIES OF GENUS *BERBERIS* SPECIES

B. aristata, B. chitria and *B. lycium* are three important species of *Berberis* found in Pakistan. Extracts of these species have very good antimicrobial activities. Details of medicinal uses of *Berberis* species are indicated in Table 3. Berberine, an alkaloid from *Berberis*, has activity against Gram positive and Gram negative bacteria as well as antifungal activities [26,47,48]. These differences in susceptibilities might be due to the differences in the cell wall composition of Gram negative and Gram positive bacteria. Moreover, extracts obtained from *B. lycium* have strong antibacterial activity as compared to those of *B. aristata* and *B. chitria*. [48]. Sharma and colleagues reported that ethanolic root extract of *B. aristata* shows

antifungal activity [47]. More detailed studies showed that extracts from *B. aristata* (aqueous andalcoholic extracts; and colloidal suspension of powdered root in distilled water) have antifungal activities against *Candida* and *Aspergillus* species [26]. These extracts also exhibit antibacterial activity against gram-negative bacteria (*Salmonella typhimurium, Escherichia coli, Shigella dysenteriae* type 1 and *Vibrio cholerae*. *B. aristata* root extracts have low minimum inhibitory concentration (MICs) values against *Bacillus cereus, Escherichia coli, Staphylococcus aureus* and *Aspergillus flavus*, while the stem extract has been reported effective against *Bacillus cereus* and *Streptococcus pneumonia* [26,47,48]. *In vitro*, ethanolic extracts of *B. aristata* showed inhibitory effects against *Propionibacterium acnes* [50].

Berberine; an alkaloid isolated from *Berberis* species has been used as anti-diarrheal medication from time immemorial. It has been reported to inhibit the secretory responses of heat-labile enterotoxins of *E. coli* and *V. cholera* in rabbit ligated intestinal loop model [49]. Orally administered berberine resulted in more effective elimination of parasites than other established drugs [51].

Hydro-alcohol (50 %) extract of air-dried roots and stems of *B. lycium* has exhibit antibacterial activity against *Micrococcus luteum, B. cereus, Enterobacter aerogenes, Klebsiella pneumonia, E. coli, Proteus mirabilis, Staphylococcus aureus, Pseudomonas aeruginosa* and *Streptococcus pneumonia* [52]. The root extract also showed antifungal activities against fungal strains of *Aspergillus terreus, Aspergillus flavus* and *Aspergillus spinulosus*, while the stem extract inhibited only *Aspergillus spinulosus*. The hydro-alcoholic extract exhibited stronger and broader range against bacterial strains than fungal strains [52]. These findings show that main berberine might be has promising antimicrobial potential. When *B. lycium* was mixed in drinking water of broilers along with other medicinal plants showed good immune boosting activity against Newcastle disease, infectious bursal disease and infectious bronchitis. A significant reduction in coccidial oocysts per gram of feces was also noticed [53].

ANTI-DIABETIC ACTIVITY

Studies have shown that *B. aristata* roots have potent and orally effective anti-diabetic constituents which either promote insulin secretion or have insulin-like effects [54]. Ethanolic and methanolic extracts of stem bark of *B. aristata* have significant anti-hyperglycemic effect in alloxan-induced diabetic rats. The antioxidant and anti-hyperglycemic activity of 50 % aqueous ethanolic extracts of *B. aristata* roots have been reported in alloxan induced diabetic rats. Aqueous ethanolic extracts, besides being safe also lowered blood glucose significantly with no hypoglycemic effect on the control groups. Root extracts of *B. aristata* are also reported to have strong tendencies to regulate glucose homeostasis through decreased gluconeo-genesis [45].

Crude powder *Berberis* species has been reported to decrease level of glucose in blood both in diabetic and normal rabbits [17,55]. The root bark extracts of *B. lycium* in various solvents including water, aqueous methanolic, methanolic, chloroform and n-hexane were prepared and screened for their antidiabetic activities in alloxanized rabbits. Results revealed that amongst the extracts, water extract (500 mg/kg) showed maximum hypoglycemic activity when administered orally, for almost 6 h. Similar doses of aqueous methanol, methanol, and n-hexane extract reduced blood glucose levels for 4 h. The chloroform extract did not show any significant anti-diabetic activity [17,55]. 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. Water extract was further compared in combination with insulin. The 50 and 100 mg/kg doses reduced hyperglycemia after 3 to 5 h of administration. Oral glucose tolerance tests showed that the plant extracts decreased serum glucose in a dose-dependent manner [55]. The mechanism involved in the hypoglycemic effects may involve insulin-like effects, possibly through increased peripheral glucose consumption [56]. Anti-diabetic activity of pure berberine was compared with that of ethanolic root extract of *B. lycium* in normal and alloxan-induced diabetic rats using similar doses (50 mg/kg) of each. Both treatments reduced blood glucose levels significantly and demonstrated significant effects on glycosylated haemoglobin, glucose tolerance, serum lipid profiles and animal body weights. Thus the root extract was comparable in efficacy with berberine [56]. Moreover, aqueous root extract of *B. vulgaris* shows potent and significant hypoglycemic effects in streptozotocin-induced diabetic rats, with significant increases in serum cholesterol and serum triglycerides levels [57]. *B. brevissima* and *B. parkeriana* are also have anti-diabetic activities [58].

ANTI-INFLAMMATORY ACTIVITIES

Topical application of aqueous extracts *B. aristata* showed potent anti-inflammatory activity against endotoxin-induced uveitis in rabbits. Anterior uveitis was induced in rabbits by intravitreal injection of lipopolysaccharide from *E. coli* after pre-treatment with *B. aristata* aqueous extracts [59]. Alcoholic extract of *B. aristata* was found to have moderate anti-proteolytic activity toward trypsin-induced hydrolysis of bovine serum albumin, but no inhibitory activity against β.-glucuronidase [60]. Aqueous extracts of the plant were effective in arresting the initial phases of acute inflammation, while the alcoholic extracts worked better at the later phases of acute inflammation. Studies indicate that the alcoholic extract acts by hindering the release of mediators of late-phase mediators e.g. prostaglandin, while the aqueous extracts blocks the mediators released in the early phase (i.e. bradykinin, serotonin and histamine), as well as mediators released in the later phase e.g.. prostaglandin [26].

B. baluchistanicais is a popular species found in Pakistan (Balochistan). This plant is reported in folklore pharmacopeias for its different medicinal uses. Decoction of roots is used against cough and internal injury of livestock and human beings. Two new alkaloids (pakistanamine and pakistanine) and a new phenolic bisbenzylisoquinoline alkaloid, (+)-baluchistine, have been isolated from *B. baluchistanica* [35].

ANTIOXIDANT ACTIVITIES

Aqueous and ethanolic extracts of roots of *B. aristata* roots have been studied for their antioxidant potential, and results obtained showed that they decreased oxidative stress [45]. In addition, aqueous and methanolic extracts of the aerial parts of *B. aristata*, significantly improved antioxidant status in CCl_4-induced liver injury [61]. The antioxidant properties of the fruits of *B. lycium* have also been studied, with respect to DPPH radical scavenging potential of its phytochemicals [62]. These compounds include, 4, 4 dimethyl hexadeca 3-ol, berberine, β-sitosterol, 3-[4-(6-methyl butyl) phenyl] propan-1-ol and butyl -3-hydroxypropyl phthalate.

ANTICANCER ACTIVITIES

Methanolic extract of the stem of *B. aristata* was screened for anticancer potential against human colon cancer cell line and found to be effective. The extract also showed concentration-dependent inhibition of HT29 cells. Indeed, berberine, an alkaloid isolated from the plant *B. aristata*, has been reported to significantly inhibit carcinogenesis induced by 20-methylcholan-threne or nitrosodiethylamine, in a dose-dependent manner in small animals [63].

WOUND HEALING PROPERTIES

Root extracts of *B. lycium* have been studied in Swiss Wistar rats for their wound-healing potential. Methanolic and aqueous extracts of the plant roots were examined using incision, excision and dead wound space models of wound repair. Both extracts increased the area of epithelization and also showed increase in breaking potency. In aqueous extract-treated group, moderate collagen deposition, fibroblasts and macrophages were found, whereas a significant increase in collagen deposition with lesser macrophages and fibroblasts were observed in methanol extract-treated group. A significant increase in dry weight and hydroxyproline content of granulation tissue was also observed. It was shown that methanolic extract was more effective than the aqueous extract [64].

Pakistani perspective

The altitudes in Pakistan range from 0 to 8611 m, with a unique geography rich in floral diversity. Therefore the public interest is focused on indigenous plants and these medicinal plants have great value for scientists like ethno-botanists, anthropologists, pharmaceutical chemists, and physicians [2]. Pakistan has more than 6,000 species of valuable medicinal plants [73]. It is one of the leading countries which export medicinal plants to international markets [74]. The medicinal plants are mostly collected by untrained hands, and their identification and storage depends on inherited knowledge from elders. Some plant species are considered for a specific disease and illness, while some have mixed usage. In many cases, closely related species to the desired one, are collected and sold under one name, leading to non-achievement of the desired results. Recent reports indicate only 14 species of *Berberis* in Pakistan which contradicts the earlier figure of 19 species. A trained plant taxonomist and good herbaria are necessary for identification and collection of desired plant species but their numbers are decreasing worldwide especially in Pakistan [5,64].

CONCLUSION

The actual number of *Berberis* species could be more than those discovered so far. Therefore, conservation strategies are needed for these medicinal plants. Trained plant taxonomists and good herbaria are necessary for identification and collection of desired plant species. *Berberis* species are rich sources of phytonutrients and have important pharmacological properties such as anti-cancer, antibacterial, anti-viral, anti-daibetic, antioxidant, cholesterol-lowering and anti-hypertensive potential (table 3). A good number of phytochemical and pharmacological studies in Pakistan have been carried out on *B. aristata*, followed by *B. vulgaris* and *B. lycium*. Studies reported from Western countries mainly emphasized the chemistry of the different *Berberis* plants and isolation of new lead compounds. In view of their bioactive compounds the development and discovery of new activities in related species are very important.

Phytochemical and pharmacological studies (Table 1 and 2) of the genus *Berberis* have received more interest in the recent past. These include investigation of its potential towards cardiovascular, hepato-protective, anti-microbial and anti-cancer activities. *Berberis* species from Pakistan are not well investigated for anti-cancer and anti-diabetic potential. Further research should be focused on human cell culture systems to elucidate the anti-cancer potential and anti-diabetes activities of the species from this genus.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. ZKS conceived the study. IK and SN drafted the manuscript. MA and IK revised the manuscript. All the authors read approved the manuscript.

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