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A review on Pharmacological potential of Berberine; an active component of Himalayan *Berberis aristata*

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ABSTRACT

Plants have been the basis of many traditional medicines throughout the world for thousands of years and continue to provide new remedies to mankind. They are one of the richest sources of compounds. *Berberis aristata* is one of the major plants used in Ayurveda for several remedies. It is used as a tonic, alternative, demulscent, diaphoretic and diuretic, and in the treatment of diarrhoea, jaundice, skin diseases, syphilis, chronic rheumatism and urinary disorders. Scientific evidence suggests its versatile biological functions that support its traditional use in the orient. Phytochemical studies shows that plant *Berberis aristata* contains mainly yellow colored alkaloids Berberine, oxyberberine, berbamine, aromoline, a protoberberine alkaloid karachine, palmatine, oxycanthine and taxilamine and tannins, sugar, starch. Among the several compounds Berberine is main constitute having various pharmacological actions. It is, a benzylisoquinoline alkaloid, occurs as an active constituent in numerous medicinal plants and has an array of pharmacological properties. It has been used in Ayurvedic and Chinese medicine for its antimicrobial, antiprotozoal, antidiarrheal and antitrachoma activity. Moreover, several clinical and preclinical studies demonstrate ameliorative effect of berberine against several disorders including metabolic, neurological and cardiological problems. This review provides a summary regarding the pharmacokinetic and pharmacodynamic features of berberine, with a focus on the different mechanisms underlying its multispectrum activity..

Keywords: *Berberis aristata*, Berberine, Medicinal Chemistry, Pharmacology.

INTRODUCTION

Berberine is a plant alkaloid with a long history of medicinal use in both Ayurvedic and Chinese medicine.It is present in Hydrastis Canadensis (goldenseal), Coptis chinensis (Coptis or goldenthread), Berberis aquifolium (Oregon grape), Berberis vulgaris (barberry), and Berberis aristata (tree turmeric). The berberine alkaloid can be found in the roots, rhizomes, and stem bark of the plants. Berberine extracts and decoctions have demonstrated significant antimicrobial activity against a variety of organisms including bacteria, viruses, fungi, protozoans, helminths, and chlamydia. In China, berberine is an overthe-counter drug for the treatment of bacterial diarrhea. In 1988, the hypoglycemic effect of berberine was firstly reported when berberine was prescribed to treat diarrhea in diabetic patients[1]. Moreover, several clinical and preclinical studies demonstrate ameliorative effect of berberine against several disorders including metabolic, neurological and cardiological problems. This review provides a summary regarding the pharmacokinetic and pharmacodynamic features of berberine, with a focus on the different mechanisms underlying its multispectrum activity.However, numerous literatures had been published by various authors exploring the phytochemical and pharmaceutical aspects along with traditional uses yet there is no much more literature concerning so far the importance of Berberine, which is important constituent of this species.

Ayurveda is a traditional system of medicine using a wide range of modalities to create health and well being. The primary aim of Ayurveda health care is to restore the physical, mental and emotional balance in patients, thereby improving health, preventing disease and treating any current illness. The number of patients seeking alternate and herbal therapy is growing exponentially. Herbal medicines are now in great demand in the developing world for primary healthcare not because they are inexpensive but also for better cultural acceptability, better compatibility with the human body and minimal side effects. Herbal medicine is still the mainstay of about 75–80% of the world population, mainly in the developing countries for primary healthcare[2]. However among the estimated 250,000-400,000 plant species, only 6% have been studied for biological activity, and about 15% have been investigated phyto-chemically. Therefore, it seems necessary to evaluate the herbs properly. *Berberis aristata* DC. (Berberidaceae) is one of the herbs mentioned in all ancient scriptures of Ayurveda, Charaka and

Susruta have mentioned it's different properties along with various used for the treatment of numerous illnesses[3]. The genus *Berberis*represents the around 12 genera and 600 species worldwide and about 77 species have been reported fromIndia[4]. In Indian Himalayan ecosystem most of the species have reported from Nilgiri hills at an altitude of 1,000–3,000 mASL[5]. Among the various species of *Berberis* genus *Berberi aristata* DC is one of the most important species due to its wide medicinal properties and its occurrence has reported from sub-tropical areas (1800-3000 m ASL) of the mountain state of Uttarakhand and Himachal Pradesh[6]. It is used invarious crude drug formulations and in different ayurvedic and homeopathic medicines since ancient times[7,8].

It is erect spinous shrub, which is hard, yellowish useable part commonly used in Indian medicine system. The fruits of the species are eaten by inhabitants for curing various diseases. The whole plant is also a good source of dye and tannin which is used for dyeing clothes and for tanning leather[9]. Berberine is main constitute having various pharmacological actions. It isa benzylisoquinoline alkaloid, occurs as an active constituent in numerous medicinal plants and has an array of pharmacological properties. It has been used in Ayurvedic and Chinese medicine for its antimicrobial, antiprotozoal, antidiarrheal and antitrachoma activity. Therefore, in this reviewed article is introduced with the focus of its important ingredient berberine.

Phyto-chemical Examination Study

The plant contains barberine, oxyberberine, berbamine, aromoline, karachine, palmatine, oxyacanthine and taxilamine *Berberis aristata* contains protoberberine and bis isoquinoline type of alkaloid[10]. Root of plant *Berberis aristata* contains alkaloids which are berbamine, Berberine, oxycanthine, epiberberine, palmatine, dehydrocaroline, jatrorhizine, karachine dihyrokarachine, taximaline, oxyberberine, aromoline and columbamine[11-15]. Four alkaloids, pakistanine, 1-O methyl pakistanine, pseudopalmatine chloride and pseudoberberine chloride were also isolated from *Berberis aristata*[16,17]. A secobisbenzlisoquinoline or simple isoquinoline alkaloid was isolated from *Berberis aristata.* The major alkaloid found in *Berberis aristata* is Berberine having yield of 2.23% followed by palamatine[18,19].

Almost all the parts of different *Berberis* species plants have been explored by various research groups forgetting information on chemo-taxonomical identification, variability studies among the same or differentplants or species and isolation and identification of various medicinally important chemical constituentsfrom this genus. Although, the constituents reported from stem and roots of the plants were found almost same however, variability has been reported in the chemical constituents of leaves[20]. Various alkaloids, terpenoids, flavanoids, sterols, anthocyanins, lignans, vitamins, proteins, lipids and carotenoids have been isolated and characterized from different Berberis species plants. A numbers of alkaloids have been isolated and identified over the last 60 years across the globe from different *Berberis* species[21,22]. The chemical constituents isolated from the plants belonging to genus Berberis during the last two decades (Year 1991–2012). Alkaloids are the main bioactive chemical constituents of Berberis species reported by different researchers. Major alkaloids reported from various Berberis species are berberine, berbamine, palmatine, columbamine, jatrorrhizine, oxyacanthine[23-25]. The berberine and berbamine are the most biologically active compounds widely distributed in almost all *Berberis* species[26-28]. Fourteen isoquinoline alkaloids of aporphine, proaporphine, protoberberine, protopine, benzylisoquinoline, proaporphine-benzyliso-quinoline and simple isoquinoline have been reported from *B. sibirica* Pall. Pronuciferine N-oxide (1), aproaporphine N-methyl-N-oxide alkaloid are isolated from *B. coletioides* Lechl and identified a new isbenzyltetrahydroisoquinoline alkaloid from *B. tabiensis*[29,30]. An isoquinoline alkaloid pachycanthine was isolated from the methanolic extract of whole plant of *B. pachyacantha Koehne*[31]. Isolation of lignans from the stem and leaves of plants belonging to genus Berberis has also been reported[32]. Eight phenolic constituents including six lignans, hanultarin, (-)-secoisolariciresinol, (?)-lyoniresinol (?)-syringaresinol, syringaresinol-O-Dglucopyranoside, liriodendrin, and two phenylpropanoids, 4-glucosyloxy-3-methoxyphenyl trans-propenoic ethyl ester, transferulic acid are reported from the roots of *B. amurensis* Rupr[33]. Recently steroid, itesmol 3-O-palmitine has also been isolated from the methanol extract of trunk of *B. koreana* Palib[34]. Although, most of the phytochemical studies are reported from stem, stem bark, root and root bark of Berberis plant however, there are also reports of characterization of phytochemicals from other parts like leaves, fruits and flowers. Phenolic bases are isolated from leaves of *B. integerrima* Bunge[35]. Various polyphenolic flavonoids like (E) caffeic acid, quercetin, chlorogenic acid; meratin and rutin are reported from the flower extract of *B. aristata* DC[36]. Chemical constituents present in the fruits of *Berberis* have nutraceutical potential and provide health benefits. Recognizing their potential, many research groups in India are now exploring the phytochemical and pharmacological potential of fruits of different Indian species. Fruits of *B. lycium* Royle (Kasmal) are a good source of various nutrients like anthocyanin, b-carotene, and ascorbic acid and minerals[37]. Studies done on the five *Berberis* species of West Himalaya of India showed that the fruits contained high content of fiber (pulp 7.0–8.1 %; seeds 4.4–5.3 %), protein (pulp 4.7–7.2 %; seeds 5.9–8.5 %) and fat (pulp 2.6–4.0 %;seeds 4.6–5.3 %) and a good source of minerals, especially Ca and K[38]. However, they have lower food energy and anti-nutritional factors like tannins and phytic acid. Hence, care should be taken while selecting these fruits for value addition as health food. Many of antioxidants xanthophyll, phenol, caroteneare presence in the fruits and roots of *B. asiatica* Roxb[39]. Five aglycones and ten anthocyanins viz. petunidin-3-glucoside, delphinidin-3- glucoside, malvidin-3-glucoside, cyanidin-3-glucoside, petunidin-3-rutinoside, malvidin-3-rutinoside, cyanidin-3-rutinoside, delphinidin-3-rutinoside, peonidin-3-glucoside, and peonidin-3-Rutinoside are isolated and identified from the fruits of *B. boliviana* Lechl, a species native to the Pervian Andes[40]. Phenolic compounds rutin and chlogenic acid are also present in the leaves and fruits of B. crataegina DC. Rutin and apigenin 7-O-glucoside were more in fruits whereas, leaves contain more malic acid and citric acid[41].

Berberine is reported as the major active constituent in almost all Berberis species. Although it has been reported unanimously by all the research groups that maximum berberine content is accumulated in root part (1.6–4.3 %) in most of the Berberis species and low altitude plants contain more berberine in comparison to higher altitude plants[42-44]. But, no consistency could be established in the results with respect to species and season[45-47]. Higher berberine content in *B. asiatica* Roxb (4.3 %) in comparison to B. lycium Royle (4.0 %) and*B. aristata* DC (3.8 %) whereas another researcher reported higher content in *B. aristata* DC (2.8 %) in comparison to *B. asiatica* Roxb (2.4 %)[48,49]. Maximum yield of berberine in the roots (2.76 %) and stem bark (1.76 %) of *B. pseudumbellata* Parker harvested in summer season contrary to this higher berberine content (1.86 %) was reported in the winter samples in the roots of *B. aristata* DC. These variations

may be due to the difference in the species of the plants, location or the analytical techniques used for the analysis.

Structural Activity Relationship (SAR) of Berberine

Importantlyitcontains a quaternary base Berberine [Natural Yellow 18, 5,6-dihydro-9,10-dimethoxybenzo(g)-1,3-benzodioxolo (5,6-a) quinolizinium], a benzyl tetra isoquinoline plant alkaloid present in the roots and bark (figure 1), which is also commercially available as various salts such as berberine chloride and hemisulfate[50].

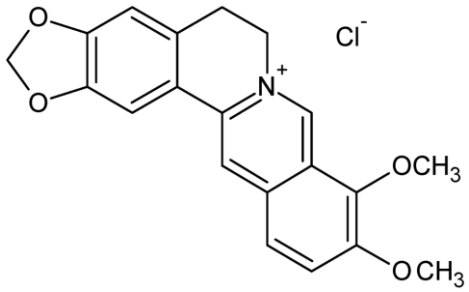

Figure 1: Chemical Structure of Berberine

Berberine the main bioactive component present in the plant is known as an AMP-activated protein kinase (AMPK) activator. It is insulin-independent hypoglycaemic. Its effect is related to inhibition of mitochondrial function, stimulation of glycolysis and activation of AMPK pathway and also prevents DNA replication[51]. Carbonyl moiety plays a key role in the activity of these compounds and partial reduction of the carbonyl moiety led to inactive dihydroonycine. Modification of the 4-methyl group to a chloromethyl moiety enhanced as well as broadened the antifungal profile of azafluorenones[52].Substitution at the 8-position in pseudoprotoberberine, especially an n-decyl, could significantly enhance the anti-TB activity. We consider 8-n-decylberberines to be a novel family of anti-tubercular agents with an advantage of inhibiting MDR strains of M. Tuberculosis[53].

Pharmacokinetics and Pharmacodynemics of Berberine

The plant also contains a number of importantphytochemicals, which are alkaloids (proto-berberine, isoquinoline, bisbenzyl-isoquinoline), flavonoids and phenolic acids. It is also important source of folklore medicine system in India[54]. Among several chemical constitutes present in the plant, the alkaloid berberine is the main bio-active component in the plant, which has property to lower blood glucose leveleffectively as the recommended drugmetformin[55]. *Berberisaristata*, contains active principle(s) that cause(s) a selective inotropic effect, involving—in the form of the modulatory effect on actin myosin cooperatively—a novel mechanism of action[56]. Berberine metabolized in the liver by cytochrome P450, suffering phase I metabolism and selectively accumulated by mitochondria on K1735-M2 melanoma cells, arresting cell proliferation, causing mitochondrial fragmentation, depolarization, oxidative stress and a decrease in ATP levels[57]. It inhibits the mitochondrial respiration and a decrease on calcium loading capacity through induction of the mitochondrial permeability transition (MPT)[50]. It also inhabit the cholinesterase (ChE) activity and increase *glucagon like peptide* (GLP1) release and break down the memory molecule acetylcholine, a neurotransmitter that is crucial for the important memory activities of focus and concentration[58]. It has strong potential to regulate glucose homeostasis through decreased gluconeogenesis and oxidative stress and theroot extract (250 mg/kg) reduced lipid peroxidation (41.6%) and protein carbonylation (30.15%), and it also increased the glucokinase and glucose-6-phosphate dehydrogenase activities and decreased glucose-6-phosphatase activity, which play a critical role in glucose homeostasis[59].

The methanolic extract at the dose of 500 mg/kg (198.2 to 89.7), which was compare to standard anti-diabetic drug Glibenclamide at 0.25 mg/kg dose (201.3 to 102.5)[60]. LD50 of >5000 mg/kg body weight was observed for both ethanolic and aqueous extracts of *B. aristata* in the acute oral toxicity[61].

Mode of Action (MoA) of Berberine

Berberine activated the adenosine monophosphate activated protein kinase (AMPK) and improvement of insulin sensitivity and the mechanism of action of berberine may be associated with promoting regeneration and functional recovery of β-cells[62].The effect of AMPK activation is stimulation of hepatic fatty acid oxidation and ketogenesis, inhibition of cholesterol synthesis, lipogenesis (the formation of fat), triglyceride synthesis, inhibition of adipocyte lipolysis, stimulation of skeletal muscle fatty acid oxidation, muscle glucose uptake and modulation of insulin secretion by pancreatic beta cells[63-66].Phosphorylationof Thr-172 within the catalytic domain of α subunit (AMPKα) is necessary for AMPK activity. Various studies demonstrate that berberine is a strong inducer for Thr-172 phosphorylation of AMPK. Liver kinase B1 (LKB1) and Ca2= calmodulin-dependent kinase II (CaMKK II) are two major upstream kinases for AMPK activation. Berberine may activate AMPK through increasing AMP/ATP ratio, which is mediated by inhibition of ATP biosynthesis in mitochondria[51].

Ethno-pharmacology

B. aristata DC, the official species of Ayurvedic Pharmacopeia of India has a niche over reported pharmacological and clinical uses. Attention has been paid to the antioxidant and anti-inflammatory activity of natural products and compounds isolated from natural products which are often characterized by high efficacy and low adverse effects. Berberine is an isoquinoline alkaloid, widely present in different medicinal herbs, especially in the genus *Berberis*. It is mainly used as antidiarrhoeal, antibacterial, antifungal, and antiprotozoal agent. However, current research has also highlighted on its beneficial role in neurodegenerative diseases, mainly due to its powerful antioxidant effect. The therapeutic potential of Berberine in different neurodegenerative diseases such as Alzheimer, Parkinson and Huntington disease has been brought to evidence by numerous studies[67]. According to Ayurvedic pharmacopeia of India *Berberis aristata* DC is also used in diabetes. Diabetes mellitus is one of the most common chronic diseases and is associated with hyperlipidemia and co-morbidities such as obesity and hypertension. In order to establish scientific facts for the utility of this plant in the treatment of diabetes, the hypoglycemic activityDiabetes mellitus study revealed that it is a heterogeneous metabolic disorder old as mankind and its incidence considered to be high (4-5%) all over world. The use of medicinal plants for the treatment of diabetes mellitus dates back from the Ebers papyrus of about 1550 B.C. A multitude of herbs spices and other plant materials have been described for the treatment of diabetes throughout the world. The medicinal plants might provide a useful source of new oral hypoglycemic compounds for development of pharmaceutical entities or as a dietary adjunct to existing therapies. Few of theplants used for the treatment of diabetes have received scientific or medicinal scrutiny and even the WHO expert committee on diabetesrecommends that this area warrant further attention.

Previous studies suggested that hyperglycemia and hyperlipidemia are the common characteristics of streptozotocin induced diabetes mellitus[68,69]. The maximum reduction in serum glucose levels was seen in methanolic extract of *Berberis aristata* DC at the dose of 500 mg/kg. Hence the methanolic extract of *Berberis aristata* DC had a beneficial effect on carbohydrate metabolism in diabetic condition.

A women's university in India, Shri Padmavathi Mahila Viswavidyalayam Tirupati, conducted a study to evaluate the effectiveness of ayurvedic medicine. They designed a study to provide scientific evidence for the use of Berberis aristata in the treatment of urinary troubles caused as a side effect of the anti-cancer chemotherapy drug, cisplatin. Cisplatin is known to cause nephrotoxicity which is a renal disease or dysfunction. In conclusion, the researchers found that the side effects of cisplatin were reversed by the antioxidant properties of the decoction of root bark of *Berberis aristata*[70]. Other research universities in India also studied the medicinal properties of *Berberis aristata* along with effects of berberine as active componentin various studies of the anti-diabetic activity of the plant, diabetic rats treated with the ethanol extract of the roots showed a significant reduction of serum glucose level, however, it also showed a significant increase in the level of HDL cholesterol. Additional research must be conducted to determine if thehypolipidemic properties of the plant could serve as a protective mechanism against the development of atherosclerosis (Atherosclerosis; also known as arteriosclerotic vascular disease or ASVD) is a specific form of arteriosclerosis in which an arterywall thickens as a result of invasion and accumulation of white blood cells (WBCs)), which is usually associated with diabetes[71].

Tincture of the root is found to be better than quinine and cinchona as it does not cause cardiac depression in the treatment of intermittent fever and powdered root mixed with butter is used for the treatment of bleeding piles[72]. Its ripe fruits are used as a mild laxative for children and exhibits hypochlolestrolemic activity[73]. The leaves forpreventing acetaminophen-induced liver damage and most important clinical use includes treatment of diarrhea due to bacterial, fungal, viral and protozoal infection[74]. Increased levels of calcium and phosphorus in serum and significant decreased in urine are due to the use of*Berberisaristata* aqueous-methanol extract, which possess the potent antiosteoporosis activity and substantiates the ethnic use in treatment of postmenopausal osteoporosis[75,76]. It also has property to reduce serum cholesterol, triglycerides and low density lipoprotein levels and moreover, there is an increase in thrombin and fibrinogen time[77].

The traditional Indian and Chinese medicine systems revealed that almost every part of the plant has some significant medicinal value. Its roots, stem, bark, leaves, rhizomes and fruits are used in many classical ayurvedic preparations like Rasaut, Darvyadikvatha, Darvyadileha, Darvyaditaila, Rasanjana, Dasangalepa and in formulations for eye care, wounds, skin diseases, jaundice, rheumatism and diabetes[78]. Traditionally a popular medicine Rasaut,prepared from the root of this plant for eye disorders[79] and also mixed with honey is useful in the treatment of aphthous sores abrasions and ulcerations of the skin[80]. Different extracts of *B. Aristata* have remarkable antibacterial and antifungal potentials against clinical and standard strains, thus could be used to derive antimicrobial agents especially against *V. cholerae*, *Staphylococcus*, *Candida* and *Aspergillus* species[81]. The antimicrobial (minimum inhibitory concentration (MIC)) and minimum actericidal concentration (MBC)against all strains of *Shigella*in both ethanolic and aqueous extract are between 125 to 500 µg/mL and 300 to 600 µg/mL, respectively and MIC& MBC values of berberine are almost comparable to standard ciprofloxacin[61]. Its methanolic extract is confirmed to be a potential anticancer herb against colon cancer due to its COX-II inhibitory property on proliferation of human colon cancer cell line (HT29)[82]. The decoction of root bark of *Berberisaristata* use in the treatment of urinary troubles caused as a side effect of the anti-cancer chemotherapy drug, cisplatin[83].

Table 2: Ethno-pharmacological activities of the different of *B. Aristata*

Part of the Plant	Ethno-pharmacological/clinical application	References
Fruits	Preventive and curative effects on paracetamol and CCl4 induced hepatotoxicity	84
Root	Anti-platelet activating factor activity	85
Stem, root bark and wood	Protection against ethanol-induced mitochondrial damage	86
Fruit extract	Inotropic effect	87
Root	Antihyperglycemic and antioxidant effect	59
Root bark	Scientific evidence for the folklore use of B. Aristata DC in urinary troubles.	83
Stem bark	Blood glucose lowering potential	88
Root	Anti-diabetic activity	89
Bark	Anti-diarrheal activity	61
Stem	Hypoglycemic and hypolipidemic activity	60
Root	Anti-osteoporotic activity in ovariectomized rats	75
Leaves and Root	Broad spectrum antimicrobial activity for the treatment of ear infections.	90
Root	Potentiation of thiopentone sodium induced hypnosis in rodents	91
Stem bark	Hypoglycemic activity of aqueous extract in STZ-induced rats	67
Leaves	Used in hepatobililary Disorders	92

Different types of oral hypoglycemicagents are available along with insulin for thetreatment of diabetes mellitus but their long-termuse produces undesirable side effects such as skinrashes, transient leucopenia**,** thrombocytopenia, severe hypoglycemia, and increase chances of cardiovascular death of unknown mechanism. The ethanol extract of root of *B. aristata* 71.42and 100 mg/kg body weight showed a significant (P<0.01) reduction of serum glucose level in alloxan induced diabetic rats at 15thday as compared to diabetic control group. Cholesterol and triglycerides level were increased very significantly (P<0.01), in diabeticanimal when compared with normal control group. The level of cholesterol and triglycerides reduced very significantly (P<0.01), when compared with diabetic control group. The level of HDL cholesterol was significantly (P<0.05) increased in the extract treated group when compared to diabetic control group. In oral glucose tolerance test ethanol extract of *B. aristata* increase the glucose tolerance. It is concluded that the ethanol extract of *B. aristata* possess anti-diabetic activity in alloxan induced diabetic rats. The ethanol extractof *B. aristata* is very promising to develop standardized phytomedicine for diabetes mellitus. *B. aristata*roots showed a significant reduction of serum glucose level, however, it also showed a significant increase in the level of HDL cholesterol and it is very promising to develop standardized phytomedicine for diabetes mellitus[54].The various ethno-pharmacological activities of different parts of *B. aristata* are in Table 1.

CONCLUSION

Berberis aristata is commonly found throughout India. Review of litratures has revealed that Berberine as active component its use in antimicrobial, hepatoprotective, immunomodulatory, and anti-depressant. However not much information is there to prove this plant for anti-neoplastic, anti-fertility, anti-leprotic etc. therefore further studies may be carried out to prove the potential of this plant. The plant is becoming the endangered species now so more work can be done on agricultural and climatic conditions to grow this plant. The translational potential and clues to possible novel bioactivities and novel targets yet to be discovered with this amazing plant species can be gauged from the period. It can be poteintial source for future drug discovery and drug development.

REFERENCES

1. Ahmeda T, Gilanib AH, Abdollahid M, Dagliae M, Nabavif SF, Nabavif SM. Berberine and neurodegeneration: A review of literature. Pharmacol Repo 2015;67:970–979.
2. Watt G. A dictionary of the economic products of India. Published under the authority of His Majesty's Secretary of State for India in Council, Kolkatta. London: Yohn Murry 1889:652.
3. Kirtikar KR, Basu BD. Indian medicinal plants. Allahabad: LM Basu Publica 1933:2422.
4. Anonymous. The wealth of India. Publications and Information Directorate CSIR, New Delhi 1985;1:176–179.
5. Rajasekaran A, Kumar N. Rasont—a traditional crude drug prepared from *Berberis* sp. and its uses. Indian J Tradit Know 2009;8:562–563.
6. Ray R, Gururaja KV, Ramchandra TV. Predictive distribution modeling for rare Himalayan medicinal plant *Berberis aristata* DC. J Environ Biol 2011;32:725-730 .
7. Shenoy PKR, Yoganarasimhan SN. Evaluation of antibacterial activity of Elanir kujambu—an Ayurvedic eye formulation. Indian J Tradit Know 2009;8:272–274.
8. Srivastava SK, Khatoon S, Rawat AKS, Mehrotra S, Pushpangadan P. Pharmacognostic Evaluation of the Root of *Berberis aristata* DC. Nat Prod Sci 2001;7:102–106.
9. Parmar C, Kaushal MK. *Berberis aristata*. In: Wild Fruits. Kalyani Publishers, New Delhi, India 1982:10–14 (http://www.hort.purdue.edu/newcrop/parmar/03.html)
10. Ambastha SP. The Wealth of India. Publication and Information Directorate, New Delhi, CSIR 1988;2:118.
11. Chatterjiee RP. Isolation of new phytoconstituents from the plants of *Berberidaceae* family. J Indian chem Soc 1951;28:225.
12. Saied S, Batool S, Naz S. Phytochemical studies of *berberis aristata*, J basic appl scienc 2007;3:1-4.
13. Blasko G, Karachine. An unusual protoberberine alkaloid. J Americ chem Socie 1982; 104:2039-2041.
14. Blasko, Sharma M. Taxilamine: a Pseudobenzlypyroquinoline alkaloid. Heterocycle 1982;19:257-9.
15. Rahman A, Ansari AA. Alkaloids of *Berberis aristata* - Isolation of Aromoline and Oxyberberine. J Chem Soc Pak 1983;5:283.
16. Bhakuni DS, Shoheb A, Popali SP. Medicinal plants: chemical constituent of *berberis aristata.* Indian journal of chemistry 1968; 6:123.
17. Lect EJ, Elango V, Hussain FS, Sharma M. Secobisbenzlisoquinoline or simple isoquinoline dimmer. Heterocycle 1983;20:425-9.
18. Chakarvarti KK, Dhar DC, Siddhiqui S. Alkaloidal constituent of the bark of *berberis aristata.* J of scientific and industrial research 1950;9b:161-4.
19. Ray, Roy. Folkloric uses of *Berneris aristata.* Sci and cult 1941; b13 (6).
20. Karimov A, Telezhenetskaya MV, Lutfullin KL, Yunusov SYu. The new alkaloid oblongamine. Chem Nat Compd 1977;13:68–70.
21. Karimov A. Berberis alkaloids. Chem Nat Compd 1993;29: 415-438.
22. Valencia E, Weiss I, Firdous S, Freyer AJ, Shamma M. The isoindolobenzazepine alkaloids. Tetrahydron 1984;40: 3957-3962.
23. Rashmi PJ, Rajasekaran A, Rekha P, Singh YP. Quantitative estimation of berberine in roots of different provenances of *Berberis aristata* DC by HPLC and study of their antifungal properties. Pharmacog Mag 2009;5:355-358.
24. Hussaini FA, Shoeb A. Isoquinoline derived alkaloids from Berberis chitria. Phytochemistry 1985;24:633.
25. Anonymous. The wealth of India, a dictionary of Indian Raw Materials. Publications and Information Directorate CSIR, New Delhi 1988;2(B):114-118.
26. Gorval LM, Grishkovets VL. Alkaloids of some species of the genus Berberis introduced into the Crimea. Chem Nat Compd 1999;35:223-224.
27. Dev S. A selection of prime ayurvedic plants drugsancient- modern concordance. Anamaya Publishers, New Delhi 2006.
28. Rashmi PJ, Rajasekaran A, Pant J. The Genus Berberis Linn.: a review. Phcog Rev 2008;2:369–385.
29. Fajardo V, Araya M, Cuadra P, Oyarzun A, Gallardo A, Cueto M, Diaz-Marrero AR, Daria J, Villarroel L, Alvarez C, Mora-Perez Y, Joseph-Nathan P. Pronuciferine N-oxide, a proaporphine N-oxide alkaloid from Berberis coletioides. J Nat Prod 2009;72:1355-1356.
30. Quevedo R, Valderrama K, Moreno-Murillo B, Laverde M, Fajardo V. A new bisbenzyltetrahydro isoquinoline alkaloid from *Berberis tabiensis* (Berberidaceae). Biochem Syst Ecol 2008;36:812-814.
31. Ahmed B, Masoodi MH, Khan S. Pachycanthine: a new isoquinoline alkaloid and its antihepatotoxic activity from Berberis pachyacantha Koehne. Indian J Chem B 2008;47:945-951.
32. Torres R, Delle Monache F, Marini-Bettolo GB. Biogenetic relationship between lignans and alkaloids in Berberis Genus. Lignans and berbamine from Berberis chilensis. Planta Med 1979;37:32-36.
33. Park HB, Lee KH, Kim KH, Lee IK, Noh HJ, Choi SU, Lee KR. Lignans from the roots of Berberis amurensis. Nat Prod Sci 2009;15:17-21.
34. Kim KH, Choi SU, Kim CS, Lee KR. Cytotoxic steroids from the trunk of *Berberis koreana*. Biosci Biotechnol Biochem 2012;76:825-827.
35. Karimov A, Telezhenetskaya MV, Lutfullin KL, Yunusov SY. Alkaloids of Berberis integerrima. Chem Nat Compd 1978;14:360-361.
36. Sivakumar R, Nair AGR. Polyphenolic constituents of the flowers of Berberis aristata. J Indian Chem Soc 1991;68: 531-532.
37. Sood P, Modgil R, Sood M. Physico-chemical and nutritional evaluation of indigenous wild fruit kasmal, Berberis lycium Royle. Indian J Nat Prod Resour 2010;1:362-366.
38. Andola HC, Rawal RS, Bhatt ID. Comparative studies on the nutritive and anti-nutritive properties of fruits in selected Berberis species of West Himalaya India. Food Res Int 2011;44:2352-2356.
39. Andola HC, Rawal RS, Bhatt ID. Antioxidants in fruits and roots of Berberis asiatica Rox. ex. DC: a highly valued Himalayan plant. Natl Acad Sc Lett 2008;31:337-340.
40. Del Carpio Jime´nez C, Serrano Flores C, He J, Tian Q, Schwartz SJ, Giusti MM. Characterisation and preliminary bioactivity determination of Berberis boliviana Lechler fruit anthocyanins. Food Chem 2011;128:717-724.
41. Gulsoy S, Ozkan G, Ozkan K. Mineral elements, phenolics and organic acids of leaves and fruits from Berberis crataegina DC. Asian J Chem 2011;23:3071-3074.
42. Chandra P, Purohit AN. Berberine contents and alkaloids profile of Berberis species from different altitudes. Biochem Syst Ecol 1980;8:379-380.

43. Andola HC, Gaira KS, Rawal RS, Muniyari MS, Bhatt ID. Habitat dependent variations in berberine content of Berberis asiatica Roxb.ex. DC in Kumaon Western Himalaya. Chem Biodivers 2010a;7:415–420
44. Mikage M, Mouri C. Pharmacognostical studies of Berberis plants (Berberidaceae) from Nepal (1) altitudinal, interspecific and partial variations of berberine content in the bark. Nat Med 1999;53(5): 249–254
45. Singh R, Tiwari SS, Shrivastava S, Rawat AKS. Botanicaland phytochemical studies on roots of Berberis umbellate Wall. ex G. Don. Indian J Nat Prod Resour 2012;3: 55–60.
46. Srivastava SK, Rawat AKS, Srivastava M, Mehrotra S. Pharmacognostic evaluation of the roots of Berberis chitria Lindl. Nat Prod Sci 2006a;12(1):19–23.
47. Srivastava SK, Rai V, Srivastava M, Rawat AKS, Mehrotra S. Estimation of heavy metals in different Berberis species and its market samples. Environ Monit Assess 2006b 116:315–320.
48. Srivastava SK, Rawat AKS, Mehrotra S. Pharmacognostic evaluation of the root of Berberis asiatica. Pharm Biol 2004;42:467–473.
49. Andola HC, Rawal RS, Rawat MSM, Bhatt ID, Purohit VK. Analysis of berberine content using HPTLC fingerprinting of root and bark of three Himalayan Berberis Species. Asian J Biotechnol 2010c;2:239–245
50. Pereira CV, Machado NG, Oliveira PJ. Mechanisms of Berberine (Natural Yellow 18)–Induced Mitochondrial Dysfunction: Interaction with the Adenine Nucleotide Translocator. Toxicolo Sci 2008;105: 408-417.
51. Yin J, Ye J, Jia W. Effects and mechanisms of berberine in diabetes treatment. Acta Pharmaceutica Sinica B 2012;2:327–334.
52. Enriz RD, Freile ML. Structure-Activity Relationship Of Berberine And Derivatives Acting As Antifungal Compounds. The J Argentine Chem Soci 2006;94:113-119
53. Li YH, Fu HG, Su F, Gao LM, Tang S, Bi1 CW, Li YH, Wang YX, Song DQ. Synthesis and structure−activity relationship of 8-substituted protoberberine derivatives as a novel class of antitubercular agents. Chem Central J 2013;7:117
54. Semwal B, Gupta J, Singh S, Kumar Y, Giri M. Antihyperglycemic activity of root of *Berberis aristata* DC in alloxan-induced diabetic rats. Int J Green Pharm 2009;3(3):259–262.
55. Chen C, Zhang Y, Huang C. Berberine inhibits PTP1B activity and mimics insulin action Biochem Biophys Res Commun 2010;397(3):5437
56. Gilani AH, Janbaz KH. Preventive and curative effects of *Berberis aristata* fruit extract on paracetamol and CCl4 induced hepatotoxicity. Phytother Res 1995;9(7):489–494.
57. Pereira GC, Branco AF, Matos JA, Pereira SL, Parke D, Perkins EL, Serafim TL, Sardao VA, Santos MS, Moreno AJ. Mitochondrially targeted effects of berberine [Natural Yellow 18, 5,6-dihydro-9,10-dimethoxybenzo(g)-1,3-benzodioxolo(5,6-a)quinolizinium] on K1735-M2 mouse melanoma cells: Comparison with direct effects on isolated mitochondrial fractions. J Pharmacol Exp Ther 2007;323: 636–649.
58. Hwang JT, Kwon DY, Yoon SH. AMP activated protein kinase: a potential target for the diseases prevention by natural occurring polyphenols. N Biotechnol2009;26:1722.
59. Singh J, Kakkar P. Antihyperglycemic and antioxidant effect of *Berberis aristata* root extract and its role in regulating carbohydrate metabolism in diabetic rats. J Ethnopharmacol 2009;123:22–26.
60. Upwar N, Patel R, Waseem N, Mahobia NK. Hypoglycemic effect of methanolic extract of *Berberis aristata* DC stem on normal and streptozotocin induced diabetic rats. Int J Pharm Pharm Sci 2011;3(1):222–224.
61. Joshi PV, Shirkhedkar AA, Prakash K, Maheshwari VL. Antidiarrheal activity, chemical and toxicity profile of *Berberis aristata*. Pharm Biol 2011;49(1):94–100.
62. Singh A, Duggal S, Kaur N, Singh J. Berberine: Alkaloid with wide spectrum of Pharmacological activities. J Natural Produ 2010;3:64-75.
63. Sabnis M. Chemistry and pharmacology of Ayurvedic medicinal plants. Varansi:Chaukhambha Surabharati Prakashan 2006:23-35.
64. Singhal GD, Sharma KR. Opthalmic and otorhinolaryngological considerations in ancient Indian surgery. Singhal Publications 1976:13-23
65. Ni Yanxia. Therapeutic effect of berberine on 60 patients with non-insulin dependent diabetes mellitus and experimental research. Chinese J Integrated Trad and Western Medic 1995;1:91-95
66. Winder WW, Hardie DG. MP activated protein kinase, a metabolic master switch: possible roles in type 2 diabetes. Am J Physiol 1999;277(1 Pt 1):E110
67. Ahamad J, Mir SR, Naquvi KJ. Hypoglycemic activity of aqueous extract of *Berberis aristata* stems bark in STZinduced rats. Int J Pharm Pharm Sci 2012;4(2):473–474
68. Pari L, Saravanan R. Effect of Cogent db, an herbal drug, on serum and tissue lipid metabolism in experimental hyperglycaemic rats. Diabetes Obesity and Metabolism 5th ed. 2003; 156–162.
69. Umesh CS, Yadav K, Moorthy K., Najma ZB. Combined treatment of sodium orthovanadate and *Mormodica charantia* fruit extract prevents alterations in lipid profile and lipogenic enzymes on Alloxan diabetic rats. Molecular and Cellular Biochemistry 2005:111–120.
70. Sreedevi A, Koganti B, Prasad K. Effect of Decoction of Root Bark of Berberis aristata Against Cisplatin-Induced Nephrotoxicity in Rats. Interna J Pharmacy and Pharma Scie 2010;2: 51-56.
71. Chander S, Bhupesh, Gupta J, Singh S, Kumar Y, Giri M. Antihyperglycemic activity of root of Berberis aristata D.C. in alloxan-induced diabetic rats. Intern J Green Pharm 2009:259-262.
72. Chatterjee A. The treatise on Indian medicinal plants. NISCAIR, CSIR Publication, Delhi, India, Satyesh Chandra Pakrashi 2005;1.
73. Chauhan NS () Medicinal and aromatic plants of Himachal Pradesh, 2nd edn. Indus Publishing Company, India 2006:36–37.
74. Musumeci R, Speciale A, Costanzo R, Annino A, Ragusa S, Rapisarda A, Pappalardo MS, Iauk L. *Berberis aetnensis* C. Presl. Extracts: antimicrobial properties and interaction with ciprofloxacin. Int J Antimicrob Agents 2003;22: 48–53
75. Yogesh HS, Chandrashekhar VM, Katti HR, Ganapaty S, Raghavendra HL, Gowda GK, Goplakhrishna B. Anti-osteoporotic activity of aqueous-methanol extract of *Berberis aristata* in ovariectomized rats. J Ethnopharmacol 2011,134:334–338
76. Potdar D, Hirwani RR, Dhulap S. Phyto-chemical and pharmacological applications of Berberis aristata. Fitoterapia 2012;83: 816-830.
77. Razzaq FA, Khan RA, Feroz Z, Afroz S Effect of *Berberis aristata* on lipid profile and coagulation parameters. Afr J Pharm Pharmacol 2011;5:943–947
78. Balasubramani SP, Goraya GS, Venkatasubramanian P. Development of ITS sequence-based markers to distinguish Berberis aristata DC. from B. lycium Royle and *B. asiatica Roxb*. 3 Biotech 2011;1:11–19
79. Srivastava S, Srivastava M, Misra A, Pandey G, Rawat AKS. A Review On Biological And Chemical Diversity In *Berberis* (Berberidaceae). EXCLI J 2015;14:247-267
80. Singh M, Sharma E. Preliminary Phytochemical Investigation Of *Berberis Aristata*, *Acacia Catechu* and *Ficus Benghalensis*- Important Medicinal Plants For Photoprotection. Int J Biologi & Pharma Res 2013;4: 614-617.
81. Shahid M, Rahim T, Shahzad A, Tajuddin, Latif A, Fatma T, Rashid M, Raza A, Mustafa S. Ethnobotanical studies on Berberis aristata DC. Root Extracts. African J Biotech 2009;8:556-563
82. Das S, Das MK, Mazumder PM, Das S, Basu SP. Cytotoxicity activity of methanolic extract of *Berberis aristata* DC on colon cancer. Global J Pharmacol 2009;3:137-140
83. Adikay S, Koganti B, Kvsrg P. Effect of decoction of root bark of *Berberis aristata* against cisplatin- induced nephrotoxicity in rats. Int J Pharm Pharm Sci 2010;2:51–56
84. Gilani AH, Janbaz KH. Preventive and curative effects of *Berberis aristata* fruit extract on paracetamol and CCl4 induced hepatotoxicity. Phytother Res 1995;9:489–494
85. Tripathi YB, Shukla SD. *Berberis aristata* inhibits PAF induced aggregation of rabbit platelets. Phytother Res 1996;10:628–630
86. Sebastian T, Setty OH. Protective effect of *Berberis aristata* against ethanol-induced mitochondrial damage in rats. J Clin Biochem nutr 1997;23:1–13
87. Gilani AH, Janbaz KH, Aziz N, Herzig MJU, Kazmi MM, Choudhary MI, Herzig JW. Possible mechanism of selective inotropic activity of the n-butanolic fraction from *Berberis aristata* fruit. Gen Pharmacol 1999;33:407–414
88. Gupta JK, Mishra P, Rani A, Mazumder M. Blood glucose lowering potential of Stem Bark of *Berberis aristata* DC in Alloxan-induced diabetic rats. Iran J Pharmacol Ther 2010;9:21–24
89. Pareek A, Suthar M. Antidiabetic activity of extract of *Berberis aristata* root in streptozotocin induced diabetic rats. Pharmacol online 2010;2:179–185
90. Sharma C, Aneja KR, Kasera R. Screening of *Berberis aristata* DC for antimicrobial potential against the pathogens causing ear infection. Int J Pharmacol 2011;7:536–541
91. Dehar N, Walia R, Ratol S. Potentiation of thiopentone sodium induced hypnosis by *Berberis aristata* in rodents. Asian J Pharm Clin Res 2012;5:131–133
92. Rathi B, Sahu J, Koul S, Kosha RL. Detailed pharmacognostical studies on *Berberis aristata* DC plant. Anc Sci Life 2013;32: 234–240.

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