Berberis aristata DC.
(Berberidaceae)

(**Syns.**: *B. bussmul* K. Koch ex Miq.; *B. coccinea* K. Koch; *B. elegans* K. Koch; *B. gracilis* Lindl.; *B. macrophylla* K. Koch; *B. umbellata* Lindl.)

Abstract

A deciduous evergreen shrub found in temperate and subtropical regions of Asia, Africa, Europe and North and South Americas. It is useful as antipyretic, antimicrobial, hepatoprotective, antihyperglycemic, anticancer, antioxidant, and antilipidemic agent. Bark and stem are tonic, diaphoretic, stomachic, antiperiodic, and gentle aperients, and used in malarial fevers, diarrhea, dyspepsia, dysentery, ague, during convalescence from fevers and acute diseases; the root is purgative. The extract and its formulations have also been used in the treatment of diarrhea, hemorrhoids, gynecological disorders, HIV-AIDS, osteoporosis, diabetes, wound healing, eye and ear infections, jaundice, skin diseases, enlargement of spleen, leprosy, rheumatism, morning/evening sickness, and snakebite. The plant mainly contains isoquinoline alkaloids; major alkaloids identified are berberine, berberrubine, jatrorrhizine, ketoberberine, palmatine, dihydropalmatine, berbamine and pakistanamine. Aqueous-alcoholic root extract significantly lowered FBG in diabetic rats, without causing hypoglycemia, increased glucokinase and G-6-PD activities, and decreased activity of glucose-6-phosphatase. Hydroalcoholic bark extract produced significant anti-inflammatory and antigranuloma effects with significant reduction in proinflammatory markers. A pilot study of a combination product of *B. aristata* extract and *Silybum marianum* extract to twenty-six Italian type-2 diabetic patients with suboptimal glycemic control, showed significant reduction in HbA1c, basal insulin, TC, LDL-C, and TGs, after 90-days of treatment. A comparative study of the standardized extract of *B. aristata* with the fixed combination containing the same standardized extract of *B. aristata* plus standardized extract of *S. marianum* showed similar improved fasting glucose, TC, LDL-C, TGs, and liver enzyme levels in both groups, except the HbA1c

B. aristata and *B. vulgaris* are used interchangeably in *Unani* and *Ayurveda*.

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values were reduced to a greater extent by the fixed combination. Addition of the combination to statin regimen was effective in reducing doses of statins by half in dyslipidemic patients who could not tolerate high doses of statins, without affecting the lipid profile.

Keywords
Amber baarees · Begrannter sauerdorn · Chitra · Darhalad · Darchoba · Dãruharidrã · Indian barberry · Lofiyun · Rasaut · Zarishk

Vernaculars: Urd.: Darchoba, Darhald (stem wood), Rasot (extract), Zarishk (fruit); **Hin.**: Chitra, Darhalad (stem wood), Jharki-halad, Kash-mal, Rasaut, Raswanti (extract), Raswat; **San.**: Chitra, Dãruharidrã, Dãruniśã, Darvi, Katamkateri, Rasãñjana (dry extract), Pitã, Pitadãru, Parjanyã; **Ben.**: Darhaldi, Daruharidra; **Mal.**: Kasturimanjal, Maramanjal, Maradarisina; **Mar.**: Daruhalad; **Tam.**: Kasturimanjal, Maramanjal, Mullabubla, Puttar; **Tel.**: Daruharidra, Kasturipaspu, Manupasupu; **Ara.**: Amber baarees (fruit); **Eng.**: Indian barberry, Nepal barberry, Root bark of berberis, Turmeric wood, Tree turmeric; **Ger.**: Begrannter sauerdorn; **Gre.**: Lofiyun; **Nep.**: Chitra; **Per.**: Darchob (stem wood), Darhald, Filzahrah, Zarishk (fruit).

Description: A deciduous evergreen shrub found in temperate and subtropical regions of Asia (north India, Nepal, Sri Lanka), Africa, Europe and North and South Americas. The roots of *B. aristata* are considered as the official drug in the *Ayurvedic* Pharmacopoeia of India. However, in different parts of India, other species of Berberis, namely *B. asiatica*, *B. chitria*, and *B. lycium* are also used under the name of *Daruharidra* [24]. Rasout is the water extract of powdered stem or wood.[LXXXI] In India, *Darhalad* is available as pieces of 2.5–5.0 cm in diameter, covered by a soft, corky, light brown bark, with a hard layer of stony cells beneath, forming a complete coating of the stem. *Rasot* or *rusot* is the dark brown extract of the consistence of opium, having a bitter and astringent taste. *Zarishk* is a moist sticky mass of small black fruit; most of them abortive, but a few contain one or two oblong seeds about 0.4 cm long, with a thin roughish brown testa. Root bark is brittle, externally light-brown and corky, beneath which is a dark brown layer, with a greenish-yellow tinge, fibrous, and very bitter (Figs. 1 and 2).[XL]

Actions and Uses: Ibn-al-Baitar[LXIX] quoted Ghafiqi that the decoction of the root in wine or vinegar is beneficial for inflammation and pain of liver. Rose-water in which *Zarishk* has been soaked is preventive and curative as eye drops for chronic inflammation. Ibn al-Baitar also quoted Galen that it is beneficial for gastric ulcers, diarrhea and nosebleed in women. Galen assigned the temperament of moderately hot and dry 2° to this plant; some authors consider it cold 1° and dry 2°. Dioscorides mentioned it useful for cough and hemoptysis. In Iran, fruits of *B. vulgaris* are known as *Zereshk*. The tree is called *Zarishk* in *Unani* medicine, the bark is known as *Dar-e-hald*, and the resin obtained from the tree is called *Rasaut*. Externally, *Rasaut* is astringent, anti-inflammatory and counterirritant; and internally, astringent, blood purifier, and styptic; internally it is used after dissolving in

Fig. 1 *Berberis aristata*, Plant, L. Shyamal, WikimediaCommons; ShareAlike 3.0 Unported CC BY-SA 3.0, https://commons.wikimedia.org/wiki/File:BerberisAculeata.jpg; https://creativecommons.org/licenses/by-sa/3.0/deed.en

Fig. 2 *Berberis aristata*, Fruits, Buddhika.jm, WikimediaCommons; ShareAlike 3.0 Unported CC BY-SA 3.0, https://commons.wikimedia.org/wiki/File:Berberis_aristata_fruit.jpg; https://creativecommons.org/licenses/by-sa/3.0/deed.en

rose-water.[1] Decoction of *Zarishk* as enema is beneficial for ulcerative colitis. Kabeeruddin[LXXVII] mentions that *Zarishk* reduces excessive heat due to blood and

[1]Tayyab M: Personal Communication.

yellow bile, reduces stomach and liver heat, and relieves thirst, nausea and vomiting. It is useful as antipyretic, antimicrobial, hepatoprotective, antihyperglycemic, anticancer, antioxidant, and antilipidemic agent. Bark and stem are tonic, diaphoretic, stomachic, antiperiodic, and gentle aperients, and used in malarial fevers, diarrhea, dyspepsia, dysentery, ague, during convalescence from fevers and acute diseases[LXXXI]; the root is purgative.[CV] The extract and its formulations have also been used in the treatment of hemorrhoids, gynecological disorders, HIV-AIDS, osteoporosis, diabetes, wound healing, eye and ear infections, jaundice, skin diseases, and malarial fever [22], enlargement of spleen, leprosy, rheumatism, fever, morning/evening sickness, and snakebite [28]. In *Ayurveda*, the stem is used in the treatment of *kapharoga*, *amatisara*, *medoroga*, *urustambha*, *karnaroga*, *mukharoga*, *netraroga*, *kandū*, *vrana*, and *meha*.[LX] The alkaloid, berberine, isolated from the plant has also shown significant antimicrobial activity against bacteria, viruses, fungi, protozoans, helminths, and chlamydia; and is clinically used for bacterial diarrhea, intestinal parasitic infections, and ocular trachoma infections [2].

Phytoconstituents: The plant mainly contains isoquinoline alkaloids; major alkaloids identified are berberine, berberrubine, jatrorrhizine, ketoberberine, palmatine, dihydropalmatine or 7,8-dihydro-8-hydroxyberberine, berbamine and pakistanamine. Berberine, mainly reported from root and stem bark, was also identified in leaves along with chlorogenic acid [3]. Hydroalcoholic stem bark extract showed the presence of 25.44% alkaloids (the isoquinoline alkaloids: berbamine, berberine, reticuline, jatrorrhizine, palmatine and piperazine) [29].

Pharmacology: Aqueous-alcoholic (50%) root extract, mainly containing berberine, berbamine and palmatine, significantly lowered FBG in diabetic rats, without causing hypoglycemia. The glucokinase and G-6-PD activities were increased, and activity of glucose-6-phosphatase was decreased [25]. Berberine shows hypoglycemic activity comparable to metformin in diabetic mice [4]. Aqueous fruit extract exhibited a positive inotropic action, and activity-directed fractionation led to *n*-butanolic fraction (BF) with cardiotonic activity; that produced a dose-dependent positive inotropic action with little effect on HR. Pretreatment of atria with propranolol did not abolish the cardiotonic effect of BF, and carbachol partially reversed the effect, indicating that a cAMP-independent mechanism underlies the inotropic action [14].

Pretreatment of rats with hydroalcoholic bark extract produced significant anti-inflammatory and antigranuloma effects with significant reduction in proinflammatory markers, IL-1β, IL-6, TNF-R1, and COX-2 [20]. Hydroalcohol root extract inhibited growth of *B. cereus*, *E. coli*, *S. aureus* and *A. flavus*; while the stem extract was active against *B. cereus* and *S. pneumoniae* [26]. Ethanol and aqueous bark extracts inhibited growth of Shigella, with MIC and MBC between 125–500 and 300–600 μg/mL, respectively. Both extracts delayed the onset of castor oil-induced diarrhea and reduced the number of diarrheal episodes [17]. The extract significantly inhibits generation of ROS from *H. pylori*-infected gastric epithelial cells [33]. Hydroalcoholic stem bark extract exhibited synergistic effect with colistin, tigecycline and amoxicillin/clavulanate, and antagonism with ertapenem and meropenem [29], produced synergistic bactericidal effect against carbapenem-resistant *E. coli*

[30], and ameliorated carbapenem-resistant *E. coli*-induced peritonitis in rats [31]. *B. aristata* extract protected rats against anti-TB drugs (INH, RIF, and PZA)-induced testicular damage [24]. Administration of aqueous-methanol extract to ovariectomized rats for 42-days exhibited antiosteoporotic effect, significantly increased uterine weight, femur BMD and lumber hardness, and increased serum levels of calcium and phosphorus [32]. Ethanol extract (i.p.) attenuated percent increase in weight gain due to tumor cell proliferation, increased survival time, reversed alterations in hematology of EAC-bearing mice [21]. Berberine also significantly inhibited incidence of tumors, induced by 20-MCA or NDEA in mice and rats, and increased their life span [1]. Topical instillation of aqueous extract showed potent anti-inflammatory activity against endotoxin-induced uveitis in rabbits [15].

Berberine exhibited antidepressant activity, and enhanced antimobility effect of subeffective doses of desipramine, imipramine, fluoxetine, venlafaxine, bupropion and tranylcypromine in forced-swim test of mice, and increased levels of NE, 5-HT and DA [19]. Chronic administration of berberine for 15-days significantly increased brain levels of NE, 5-HT, as well as DA; but at a higher dose of 10 mg/kg, i.p., only 5-HT and DA were significantly increased [18]. Berberine was effective against *T. vaginalis*, comparable to metronidazole [27], and markedly diminished parasitic load, improved hematological picture of *L. donovani*-infected hamsters, with less toxicity than pentamidine [13]. Berberine inhibits secretory responses of heat-labile enterotoxins of *V. cholerae* and *E. coli*, and also markedly inhibits secretory response of *E. coli* heat-stable enterotoxin; however it does not inhibit stimulation of adenylate cyclase by cholera enterotoxin [23]. Pretreatment with berberine for 2-days also prevented APAP- or CCl_4-hepatotoxicity, and post-treatment with three successive oral doses reduced APAP-induced hepatic damage, but not the CCl_4-hepatotoxicity [16].

Clinical Studies: Berberine has poor oral bioavailability due to the presence of *P*-glycoprotein in enterocytes—that extrudes berberine back into the intestinal lumen, thus limiting its absorption. Silymarin, derived from *Silybum marianum*, is considered a *P*-glycoprotein inhibitor by some. A pilot study of a combination product of *B. aristata* extract and *Silybum marianum* extract (Berberol®) to twenty-six Italian type-2 diabetic patients with suboptimal glycemic control, showed significant reduction in HbA1c, basal insulin, TC, LDL-C, and TGs, after 90-days of treatment [12]. In another RCT of dyslipidemic, euglycemic patients, the same combination reduced TC, TGs and LDL-C, and increased HDL-C and insulin secretion after three-months of treatment. However, the lipid profile worsened when treatment was interrupted for two months, and improved again when the treatment was reintroduced [5, 6]. A comparative study of the standardized extract of *B. aristata* with the fixed combination containing the same standardized extract of *B. aristata* plus standardized extract of *S. marianum* (Berberol®) showed similar improved fasting glucose, TC, LDL-C, TGs, and liver enzyme levels in both groups, except the HbA1c values were reduced to a greater extent by the fixed combination [11]. Addition of the combination (Berberol®) to statin regimen was effective in reducing doses of statins by half in dyslipidemic patients who could not tolerate high doses of

statins, without affecting the lipid profile [8]. Similar results were reported in hypercholesterolemic, type-2 diabetic patients, wherein addition of Berberol® either as a single therapy or as an add-on therapy to low-dose statin or to ezetimibe reduced TGs, LDL-C, FBG, and HbA1c in a significant manner without inducing toxicity [10]. The combination also reduced fasting plasma glucose, insulin, and HOMA-index in euglycemic, dyslipidemic subjects, intolerant to high dosages of statins after six-months of treatment, with no reduction in levels of TC, LDL-C and TGs [9]. Addition of the combination to insulin therapy in type 1 DM patients resulted in reduction of insulin dose for the same level of glycemic control [7].

Human A/Es, Allergy and Toxicity: Harmful in individuals with phlegmatic constitution.[LXXVII]

Animal Toxicity: Oral LD50 of both ethanol and aqueous bark extracts were >5,000 mg/kg body weight in the acute toxicity studies with Swiss albino mice [15]. The no observed adverse effect level (NOAEL) of hydroalcoholic stem bark extract in rats was up to a dose of 2,000 mg/kg BW [31].

CYP450 and Potential for Drug-Herb Interactions: Hepatic mRNA levels of CYP1A1, CYP2B9, CYP2B10, CYP3A11, CYP4A10, and CYP4A14 are increased in STZ-diabetic mice. Berberine restores expression of CYP3A11, CYP4A10, and CYP4A14 to normal levels, but suppresses the expression of CYP2E1, an adverse hepatic event-associated enzyme. Berberine treatment alone increases the expression of CYP2B9 and CYP2B10 in primary mouse hepatocytes [4].

Commentary: Antidiabetic and antidyslipidemic effects obtained in RCTs of the combination of standardized extracts of *B. aristata* and *S. marianum* as adjunct to standard treatments are encouraging, and worthy of consideration in patients with suboptimal glycemic control.

References

1. Anis KV, Rajeshkumar NV, Kuttan R. Inhibition of chemical carcinogenesis by berberine in rats and mice. J Pharm Pharmacol. 2001;53:763–8.
2. Anonymous. Berberine. Altern Med Rev. 2000;5:175–7.
3. Bajpai V, Singh A, Arya KR, Srivastava M, Kumar B. Rapid screening for the adulterants of *Berberis aristata* using direct analysis in real-time mass spectrometry and principal component analysis for discrimination. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2015;32:799–807.
4. Chatuphonprasert W, Nemoto N, Sakuma T, Jarukamjorn K. Modulations of cytochrome P450 expression in diabetic mice by berberine. Chem Biol Interact. 2012;196:23–9.
5. Derosa G, Bonaventura A, Bianchi L, et al. *Berberis aristata*/*Silybum marianum* fixed combination on lipid profile and insulin secretion in dyslipidemic patients. Expert Opin Biol Ther. 2013;13:1495–506.
6. Derosa G, Bonaventura A, Bianchi L, et al. Effects of *Berberis aristata*/*Silybum marianum* association on metabolic parameters and adipocytokines

in overweight dyslipidemic patients. J Biol Regul Homeost Agents. 2013;27: 717–28.
7. Derosa G, D'Angelo A, Maffioli P. The role of a fixed *Berberis aristata*/*Silybum marianum* combination in the treatment of type 1 diabetes mellitus. Clin Nutr. 2016;35:1091–5.
8. Derosa G, Romano D, D'Angelo A, Maffioli P. *Berberis aristata* combined with *Silybum marianum* on lipid profile in patients not tolerating statins at high doses. Atherosclerosis. 2015;239:87–92.
9. Derosa G, Romano D, D'Angelo A, Maffioli P. *Berberis aristata*/*Silybum marianum* fixed combination (Berberol®) effects on lipid profile in dyslipidemic patients intolerant to statins at high dosages: a randomized, placebo-controlled, clinical trial. Phytomedicine. 2015;22:231–7.
10. Di Pierro F, Bellone I, Rapacioli G, Putignano P. Clinical role of a fixed combination of standardized *Berberis aristata* and *Silybum marianum* extracts in diabetic and hypercholesterolemic patients intolerant to statins. Diabetes Metab Syndr Obes. 2015;8:89–96.
11. Di Pierro F, Putignano P, Villanova N, et al. Preliminary study about the possible glycemic clinical advantage in using a fixed combination of *Berberis aristata* and *Silybum marianum* standardized extracts versus only *Berberis aristata* in patients with type 2 diabetes. Clin Pharmacol. 2013;5: 167–74.
12. Di Pierro F, Villanova N, Agostini F, et al. Pilot study on the additive effects of berberine and oral type 2 diabetes agents for patients with suboptimal glycemic control. Diabetes Metab Syndr Obes. 2012;5:213–7.
13. Ghosh AK, Bhattacharyya FK, Ghosh DK. *Leishmania donovani*: amastigote inhibition and mode of action of berberine. Exp Parasitol. 1985;60: 404–13.
14. Gilani AH, Janbaz KH, Aziz N, et al. Possible mechanism of selective inotropic activity of the n-butanolic fraction from *Berberis aristata* fruit. Gen Pharmacol. 1999;33:407–14.
15. Gupta SK, Agarwal R, Srivastava S, et al. The anti-inflammatory effects of *Curcuma longa* and *Berberis aristata* in endotoxin-induced uveitis in rabbits. Invest Ophthalmol Vis Sci. 2008;49:4036–40.
16. Janbaz KH, Gilani AH. Studies on preventive and curative effects of berberine on chemical-induced hepatotoxicity in rodents. Fitoterapia. 2000;71:25–33.
17. Joshi PV, Shirkhedkar AA, Prakash K, Maheshwari VL. Antidiarrheal activity, chemical and toxicity profile of *Berberis aristata*. Pharm Biol. 2011;49:94–100.
18. Kulkarni SK, Dhir A. On the mechanism of antidepressant-like action of berberine chloride. Eur J Pharmacol. 2008;589:163–72.
19. Kulkarni SK, Dhir A. Possible involvement of L-arginine-nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) signaling pathway in the antidepressant activity of berberine chloride. Eur J Pharmacol. 2007;569:77–83.

20. Kumar R, Gupta YK, Singh S. Anti-inflammatory and antigranuloma activity of *Berberis aristata* DC. in experimental models of inflammation. Indian J Pharmacol. 2016;48:155–61.
21. Pai KS, Srilatha P, Suryakant K, et al. Anticancer activity of *Berberis aristata* in Ehrlich ascites carcinoma-bearing mice: a preliminary study. Pharm Biol. 2012;50:270–7.
22. Potdar D, Hirwani RR, Dhulap S. Phytochemical and pharmacological applications of *Berberis aristata*. Fitoterapia. 2012;83:817–30.
23. Sack RB, Froehlich JL. Berberine inhibits intestinal secretory response of *Vibrio cholerae* and *Escherichia coli* enterotoxins. Inf Immun. 1982;35:471–5.
24. Sharma R, Goyal N, Singla M, Sharma VL. *Berberis aristata* ameliorates testicular toxicity induced by combination of first-line tuberculosis drugs (rifampicin + isoniazid + pyrazinamide) in normal Wistar rats. J Diet Suppl. 2018;28:1–14.
25. 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;123:22–6.
26. Singh M, Srivastava S, Rawat AK. Antimicrobial activities of Indian Berberis species. Fitoterapia. 2007;78:574–6.
27. Soffar SA, Metwali DM, Abdel-Aziz SS, et al. Evaluation of the effect of a plant alkaloid (berberine derived from *Berberis aristata*) on *Trichomonas vaginalis in vitro*. J Egypt Soc Parasitol. 2001;31:893–904.
28. Srivastava S, Rawat AK. Quality evaluation of ayurvedic crude drug daruharidra, its allied species, and commercial samples from herbal drug markets of India. Evid Based Complement Alter Med. 2013;2013:472973.
29. Thakur P, Chawla R, Goel R, et al. Augmenting the potency of third-line antibiotics with *Berberis aristata*: *in vitro* synergistic activity against carbapenem-resistant *Escherichia coli*. J Glob Antimicrob Resist. 2016;6:10–6.
30. Thakur P, Chawla R, Narula A, et al. *In vitro* bactericidal activity of *Berberis aristate* extract against clinical isolates of carbapenem-resistant *Escherichia coli*. J Complement Integr Med. 2016;13:229–37.
31. Thakur P, Chawla R, Narula A, Sharma RK. Protective effect of *Berberis aristata* against peritonitis induced by carbapenem-resistant *Escherichia coli* in a mammalian model. J Glob Antimicrob Resist. 2017;9:21–9.
32. Yogesh HS, Chandrashekhar VM, Katti HR, et al. Antiosteoporotic activity of aqueous-methanol extract of *Berberis aristata* in ovariectomized rats. J Ethnopharmacol. 2011;134:334–8.
33. Zaidi SF, Muhammad JS, Shahryar S, et al. Anti-inflammatory and cytoprotective effects of selected Pakistani medicinal plants in *Helicobacter pylori*-infected gastric epithelial cells. J Ethnopharmacol. 2012;141:403–10.