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BERBERIS ASIATICA: POTENTIAL FRUITS AS NUTRCEUTICALS

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Abstract

Berberis asiatica (Barberry) is a popular wild edible fruits bearing plant of Indian Himalaya having good nutritional and medicinal potential. These will be the best source of the nutraceuticals. Since fruits are richer in micronutrients and bioactive secondary metabolites, which are produced in adaptation to local environmental conditions. These metabolites trigger further adaptive responses by producing 'protective', bioactive compounds which, when ingested, result in the transfer of protective effects to our organism. Fruits have a different taste, flavour, colour, ripening season than that of cultivated fruits and free from pesticides, insecticides, and fertilizers. These are natural ingredients, which are gathered, grown or produced locally and prepared into dishes, which often represent local specialties. They are harvested from the forest, as plants are safe and ready to produced fruits for next year and we get highly nutritive fruits without any environmental loss. This renewable resource of raw materials is ecofriendly processes. Natural colour, nutrients, phytochemical constituents of the fruits provides health benefits. Carotenoids flavonoids, phenolics, anthocynins are pigments currently recognized for their value as antioxidants. This article reviews the nutritional value, pharmacological effects and the active ingredient of Berberis asiatica**.**

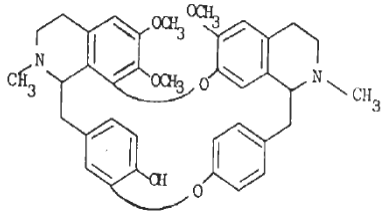
Key Words: Berberis asiatica, Antioxidants, Anthocynins, Flavonoids, Nutraceuticals, Nutrients, Wild Edible Fruits,

Introduction

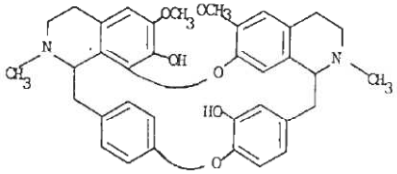
Berberis asiatica (Barberry) fruits have been used as a healthy food and traditional drug in India. Berberis Linn. (Family: Berberidaceae), a genus of shrubs or small trees, distributed in the temperate and sub-tropical parts of

Asia, Europe and America. In India this shrub is found growing wild in the sub-Himalayan tract at altitude ranging from 850-2,500 meter. B. asiatica is an erect spinous shrub, often found in small patches on the hill slopes. It is one of very important medicinal plants. Almost every part of this plant has some medicinal value. Its roots, stem, bark and fruits are used in many ayurvedic preparations. A Plant is erect spiny shrub, ranging between 2 and 3 meters in height wood, hard and yellow; bark, yellow to brown from outside and deep yellow from inside, removable in longitudinal strips by hand; spines (which, in fact, are modified leaves), three-branched and 1.5 cm long. Flowering in B. aristata starts from the first fortnight of March and remains in progress up to the end of April. The peak flowering seasons was recorded to be from 8-25 April. The fruits start ripening from the second week of May and continue to do so throughout June. They can be retained on the shrub after ripening for quite a long period, but they fall off soon after the onset of rains. The fruiting season, therefore, ends abruptly with the commencement of the rainy season. Fruits are offered for sale at some places, mostly near schools, because they are very much liked by children. Even sun-dried fruits are eaten, being quite palatable. Fruits are important sources of minerals, fibre, and vitamins, which provides essential nutrients for maintaining good health (1). The plant has long history of use, dating back to the middle ages. Salishan native elders have used berberry to treat acne (2). , and native American Indians utilized to treat scurvy (3). A decoction of the root plant has been used to treat GI ailments and coughs (4). The alkaloid berberine was included as an astringent in eye drops. More than 3 dozen medicinal uses for berberry, including cancer, cholera and hypertension have been listed (5, 6). Other reported uses of Berberis asiatica included the treatment of the followings: fever,goat, renal and biliary diseases, rheumatic symptoms and dermatitis (7,8). Alkaloids isolated from B. asiatica have found to be antibacterial, antifungal anti inflammetry, antidiarrheal, antioxidant (9), and also has current use for psoriasis (10,11). Constituents: Medicinally used parts of B. asiatica (barberry) include the stem bark and root bark, although the berries have also been traditionally used. The chief constituent of barberry is berberine, a yellow crystalline, bitter alkaloid, one of the few that occurs in plants belonging to several different natural orders. Other constituents of Berberis asiatica are oxyacanthine, berbamine, berberrubine, bervulcine, columbamine, isotetrandine, jatorrhizine, oxycanthine, palmatine, vulcracine (12,13), carbohydrates, organic acids, some

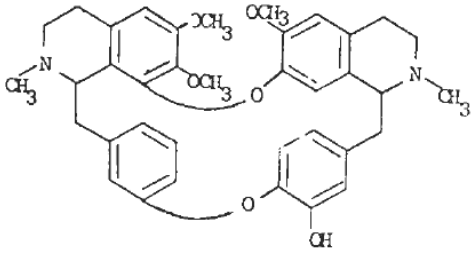
vitamins, poliphenolic compounds, pectin, tannin, and mineral elements (14).The structures of some alkaloids are as bellow.



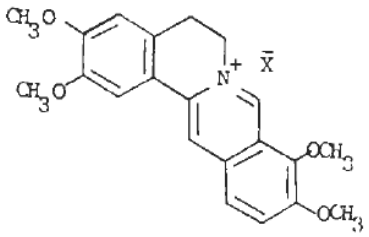
Berberine



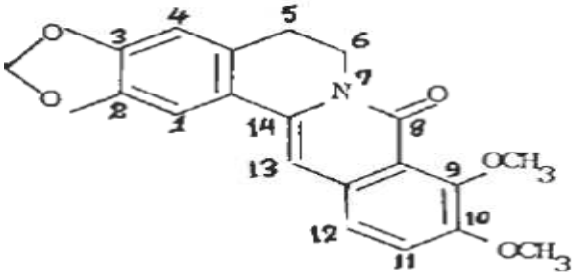
Berbamine



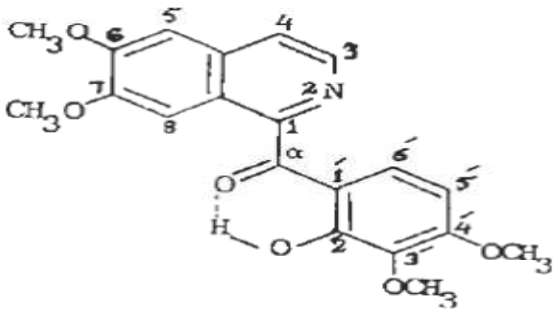
Aromoline



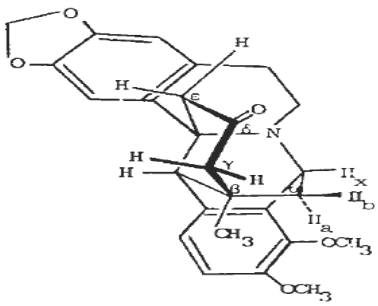
Oxycanthine



Oxyberberine



taxilamine



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The extractable juice of the fruit is 26.6 per cent. The fruit contains 63.4 per cent moisture. The total soluble solids of the juice amount to 18.90 per cent, having 1.07 per cent acidity, 11.97 per cent total sugars, most of which are in the from of reducing sugars. The fruit contains 0.64 per cent tannins and 0.37 per cent pectin. Its vitamin C content is only 4.60 mg per 100 ml of juice. The protein content of the fruit is 2.31 per cent. Its total mineral content, as represented by ash, is 2.052 per cent. In the fruit, the percentage of different mineral elements, viz. phosphorus, potassium, calcium, magnesium and iron are 0.079, 0.439, 0.065, 0.061 and 0.011 respectively (15).

Anti-amoebic activity:

In an animal in vivo study, berberine has been shown to be effective at treating amoebiasis in a dose dependent manner in both mice and hamsters (16). The greatest effect was seen at doses of 100mg/kg in mice and 150mg/kg in hamsters. Berberine, in doses of 2mg/kg intramuscularly or 3mg/kg given orally, was shown to prevent the development of hepatic amoebiasis in hamsters when given in three doses (every four hours) (17).

Antihypertensive activity:

Berberine sulfate solution (5mg/mL) produced a dose-dependent decrease in blood pressure in anesthetized dogs, cats, frogs, and rats that was not inhibited by intravenous atropine, mepyramine maleate, pentolinium tartrate, propranolol or phenoxybenzamine (18). An in vitro study found that intravenous berberine caused a hypotensive effect in rats at a dose of 4mg/kg ($p<0.01$ for systolic; $p<0.001$ for diastolic); bradycardia occurred at 6mg/kg ($p<0.01$) (19).

The antihypertensive and vasodilatory effects of fruit extract are mainly endothelial-independent and it may be used to treat hypertension, a status with endothelial dysfunction. The aqueous extract of barberry has beneficial effects on both cardiovascular and neural system suggesting a potential use for treatment of hypertension, tachycardia and some neuronal disorders, such as epilepsy and convulsion.

Anti-inflammatory activity:

Berberine has been shown to inhibit activator protein-1 activity, which is essential for inflammation in an in vitro study (20). Berberine sulfate administered subcutaneously to the ears of mice in doses of 4 and 8mg/kg

significantly inhibited xylene-induced swelling (21). The addition of berberine significantly inhibited the transformation of lymphocytes despite the presence of known mitogens in vitro, as measured by [^{3}H] thymidine uptake by lymphocytes (22). Berberine has been shown to inhibit the transcriptional activity of cyclo-oxygenase 2 (COX-2) enzymes in vitro studies. COX-2 is induced by cytokines to engage in inflammation. Berberine was shown to have statistically significant inhibition of interleukin 1 (IL-1) at doses of 10 and 20μg/mL(23). In an in vitro study, berberine was studied for its effects on the inhibition of interleukin-8 (IL-8)(24) IL-8 is a cytokine that is actively involved in inflammatory processes and was shown to decrease IL-8 production by 40% when compared to control. However, a study conducted by Kostalova et al. showed that while a crude extract of berberine can decrease IL-8 production, the polysaccharide isolated from the crude extract can be a potent inducer of IL-8(25). Berberine was shown to significantly decrease leukotriene formation via an in vitro study. Monocyte production was decreased by 14%. In addition, PGE2 generation by monocytes was significantly inhibited by berberine by 78%. Berberine inhibited edema and inflammation induced in the guinea pig paw by carrageenan or zymosan solution (26).

Antimicrobial activity (bacterial, fungal):

Berberis heterophylla leaves, stems and root aqueous extracts, has purported antimicrobial activity in vitro on Gram-positive and Gram-negative bacteria and fungi (27). Berberine, at concentrations of 10mg/mL, exhibited antifungal activity versus Alternaria, Candida albicans, Curvularia, Drchslera, Fusarium, Mucor and Rhizopus oryzae; and concentrations of 25mg/mL were able to inhibit the growth of Aspergillus flavus and Aspergillus fumigates in vitro (28). Berberine was shown to have weak to moderate activity against Malassezia species (29). Berberine (0.5mg) injected into chick embryos, reduced the mortality rate of the embryos due to the injection of trachoma organisms into the yolk sac (30). Berberine demonstrated activity against Streptococcus pneumoniae in an in vivo study with white mice (31). The mice were given 6mg intraperitoneally every six trachoma hours for 24 hours. Only 57% of the infected mice were protected against infection in comparison to 100% in the arm that received ampicillin. Furthermore, a methanol extract of berberine has demonstrated cidal activity against T. vaginalis, G. lamblia, and E. histolytica in vitro (32). Berberine sulfate was shown to possess antimicrobial

activity versus Gram-positive, Gram-negative, fungal and protozoan organisms in vitro, through the inhibition of RNA and protein synthesis(33).It has also been found to be bactericidal versus Vibrio cholera at concentrations of 35mcg/mL and versus Staphylococcus aureus at a concentration of 50mcg/mL. An in vitro study conducted by Chung et al. showed berberine to be effective in suppressing the growth of Helicobacter pylori in a dose dependent manner (34).

Antineoplastic activity:

A study showed that berberrubin, an isolate of barberry, is effective against sarcoma-180 ascities and that it has strong antitumor effects (35). In vitro study berberine to induce differentiation of human teratocarcinoma cells into cells with neuronal cell morphology, beginning one day after the addition of 0.1mg/mL berberine to the culture medium (36). Evaluating the ability of 9-substituent protoberberine compounds to inhibit DNA topoisomerase I and II, found that 9-ethoxycarbonyl berberine significantly inhibits topoisomerase II (37). Proberberine exhibited similar actions to that of topoisomerase I and II poisons (sic), from three up to more than 10 times cytotoxic against solid cell tumors (38). The most potent against SF-268 cells was DM-II-24. Berberine was shown in vitro to inhibit the DNA fragmentation and apoptosis of thymocytes induced by etoposide and camptothecin(39). Berberine has also been shown to inhibit activator. In vitro, berberine activated macrophages to inhibit the growth of tumor cells at concentrations above 0.15mcg/mL (40). Additionally, at concentrations above 1.5(/mL, berberine successfully inhibited DNA synthesis in the tumor cells.The addition of berberine to culture of six human brain tumor cell lines resulted in a mean 91% cell kill. In the rat model of gliosarcoma, berberine administration resulted in a mean 80.9% cell kill(41). In an experiment on mouse skin, berberine inhibited the action of tumor promoters, teleocidin and 12-O-tetradecanoylphorbol-13-acetate (42). Intravenous berberine, administered at a concentration of 0.2mg/kg/min, significantly raised left ventricular end-diastolic pressure in anesthetized dogs with embolized left main coronary arteries, simulating left ventricular heart failure (43). Li et al. have found that protoberberines, organic cations, are able to intercalate DNA and inhibit the enzyme topisomerase I with differing affinities dependent upon their substituent structures (44).

Anti-oxidant activity:

Berberine was shown to have antioxidant effects similar to that of vitamin E in the riboflavin system(45). Its effects are greater than vitamin E in the xanthine oxidase system. In a comparative study, protoberberine, a constituent of barberry, was shown to inhibit lipoxygenase and lipid perioxidation leading to its antioxidant properties (46, 47). It shown to have more activity in oxyberberine, corytuberine, and columbamine than in berberine.

Anti-parasitic activity:

In vitro study has demonstrated the ability of berberine to completely inhibit the growth of promastigotes at a concentration of 5(/mL, while inhibiting endogenous respiration of the organism and inhibiting nucleic acid and protein synthesis (48). Subsequent study has shown berberine chloride to interact with Leishmania donovani nuclear DNA, inhibiting the multiplication of amastigotes in macrophage culture in vitro and to decrease the parasite load in animals (49).

Anti-platelet activity:

In vitro study has found that berberine inhibits platelet-activating factor aggregation of platelets with 50% inhibition at a concentration of 38(/mL; and, berberine inhibits the binding of platelet-activating factor to rabbit platelets with 50% inhibition seen at a concentration of 480(/mL(50). Anti-complementary activity was found to be due to the alkaloid fraction especially bisbenzylisoquinoline, a derivative of barberry (51). Xuan et al. conducted an animal study that showed that tetrahydroberberine, related to barberry, inhibited platelet aggregation in vivo and in vitro, which lead to the prevention of venous thrombosis (52).

Antiproliferative activity:

Some of the main constituents on barberry (berberine, berbamine, and oxyacanthine) have been shown to be effective in suppressing the proliferative activity of keratinocyes(53). In an in vitro study, berberine was shown with statistical significance to slow proliferation ($p<0.05$). In addition, the other two constituents tested, berbamine and oxyacanthine, was shown to be three times more effective than berberine ($p<0.05$).

Anti-secretory activity:

Berberine, an active ingredient in barberry, has been shown to inhibit the secretory response to E. coli heat-stable toxin in the intestines of Wistar rats when both berberine and toxin were administered together(54). Berberine was shown to have antisecretory effects on V. cholerae in rabbits even after the enterotoxin has already settled in the host (55).

Cardiovascular activity:

Berberine extract showed inhibitory activity on adrenaline-induced aortic contraction (56). In vitro, berberine caused bradycardia in isolated right and left atria excised from guinea pigs, which was not prevented by atropine (57). Berberine also has exhibited positive inotropic effects, preventing and abolishing ouabain-induced ventricular arrhythmias (58-60) in experiments in anesthetized dogs. In guinea pigs, berberine had positive inotropic and negative chronotropic effects. Additional experiments in animals with induced ventricular arrhythmias and atrial fibrillation have also demonstrated the ability of berberine to restore normal sinus rhythm (61). Berberine also showed to have a concentration-dependent time to peak tension and cardiac relaxation time. Huang conducted an animal study showing the benefits of berberine on the ability to suppress ventricular premature beats ($p<0.001$) and ventricular tachycardia (62,63).Zalewski, et al. have found through animal study that berberine, in doses of 0.2mg/kg/min and 0.7mg/kg/min, increased cardiac output, and decreased total peripheral resistance and heart rate; while doses of 0.02mg/kg/min only increased cardiac output(64). Tetrahydroberberine, similar to berberine, was shown to reduce the infarct size of the left anterior descending artery four hours after ligation (65). The results of this study suggest that tetrahydroberberine can protect the myocardium from ischemic and reperfusion injury.

Cholinergic activity:

The administration of Berberine (0.1 and 0.5g/kg) for 14 days was effective in improving scopolamine-induced amnesia in rats, an effect that was augmented by physostigmine and neostigmine (66). Results suggest that the anti-amnesic effect of berberine administration may be related to the increase in the peripheral and central cholinergic neuronal system activity.

Diuretic activity:

Barberry contains vitamin C and may have a mild diuretic activity due to the acid content.

Gastrointestinal activity:

Berberine given orally at doses of 0.06 to 20mg/kg daily significantly prolonged the latent period and decreased the frequency of purging ($p<0.05$) (67). Also, in intact mice that received 10mg/kg daily, it delayed intestinal motility ($p=0.01$). Oral berberine sulfate (40 and 80mg/kg) significantly decreased the occurrence of diarrhea induced by the ingestion of castor oil and Cassia angustifolia in mice (68). Sack et al. found through animal experiments with rabbit ligated intestinal loops, that berberine sulfate significantly inhibited the actions of V. cholera crude enterotoxin and E. coli heat-labile enterotoxin when administered before or up to 4 hours after toxin injection (69). In addition, berberine sulfate, at concentrations of 0.05 and 0.1mg, significantly inhibited the secretory response of infant mice to E. coli heat stable enterotoxin. Swabb et al. found that berberine reduced the secretion of water, sodium, chloride and bicarbonate induced by cholera-toxin in rat ilea and prevented the edema seen in non-berberine treated controls (70).

Hepatic activity:

Berberine has been shown to increase the secretion of bilirubin in rats with hyperbilirubinemia acutely, but the effect diminished with continued berberine exposure (71). A more recent study has shown berberine to displace bilirubin from albumin in both in vitro and animal studies, resulting in an increase in serum total- and direct-bilirubin concentrations (72). In an in vitro study, berberine was shown to be hepatoprotective when administered twice daily for two days before receiving toxic doses of acetaminophen (73).

Hypoglycemic activity:

Rats with alloxan-induced diabetes mellitus treated with berberine had significantly lower blood sugar concentrations than control rats (74). Berberine also improved insulin resistance and liver glycogen levels similarly to metformin when given to rats fed a high fat diet (75) It is unclear whether bayberry exhibits the same effects.

Immunomodulating activity:

An in vivo study was conducted using mice to test the immunosuppressant effects of berbamine at doses of 25mg/kg daily and 50mg/kg daily compared to control(76). With higher doses of berbamine, more splenic cells were suppressed; statistically significant when the mitogen is concanacalin A (ConA) at both doses and at 50mg/kg delay the mixed lymphocyte reaction (MLR) ($p<0.01$). Berbamine wash shown to significantly inhibit mitogen induced lymphocyte transformation ($p<0.01$)(77). Berbamine 10μg/mL has been shown to inhibit neutrophil adherence and chemotaxis ($p<0.05$). Berbamine was also shown to suppress the uptake of neutrophil locomotion and neutrophil deoxyglucose uptake ($p<0.05$).

Muscle relaxant activity:

In an animal study, berberine sulphate (20mcg/mL) pretreatment blocked the response of ileum, trachea and rectal muscles to acetylcholine (78). Berberine was shown to increase the amplitude of slow-response action potentials induced by histamine by 6.2%; increase the maximum rate of depolarization by 21.1%; increase the action potential duration (APD) by 50.1% (APD 50) and 47.2% (APD 100) and effective refractory period by 92.2%(80).

Osteoporosis activity:

Berberine has been shown to inhibit parathyroid hormone-stimulated bone resorption in animal study (81). Berberine, in doses of 30 to 50mg/kg daily, has demonstrated an ability to prevent a decrease in bone mineral density of lumbar vertebra in ovariectomized rats and induce apoptosis of osteoclastic cells (82).

Sedative activity:

In animal study, berberine, an active ingredient in barberry, produced sedation and potentiated the sedative effects of pentobarbitone when administered via the intraperitoneal or intraventricular routes. Berberine has been shown to lower rectal temperature, reduce spontaneous motor activity and prolong hexobarbitone-induced sleeping time when administered to mice (83).

Interest in Nutraceuticals:

Nutraceutical have the potential to play a role in healthy eating and to contribute to the prevention and treatment of diseases so that how functional components in foods could expand the role of disease prevention and treatment (35,36).

1. since new molecule is difficult to discover, more expensive and risky

2. The belief among consumers that these "food like substances" are either harmless or least toxic as compared to conventional pharmaceuticals.

3. Increased healthcare costs with conventional pharmaceuticals, recent legislation and scientific discoveries.

4. Inappropriate dietary habits are seen as contributing to the leading cause of deaths of due to coronary heart disease, certain type of cancers etc. the role of nutraceuticals in treating these conditions is thus speculated (37)

5. The emergence of diet-disease relations have lead to search of specific constituents of plants, and minerals having a beneficial role for our mental and physical health(38).

6. Nutraceuticals are gaining popularity as people are relying on them for safe guarding their health and avoiding side effects associated with drugs as well.

7. As public knowledge in this field has evolved.

8. Long history of use and better patient tolerance as well as public acceptance.

9. Renewable source, Cultivation and processing environmental friendly and local availability.

10. Plants constitute to be a major source of new lead generation (39,40).

11. Consumer today are more aware when it come to health, which makes them go for nutritional supplements (41).

12. Increase acceptance of alternative treatments

13. Use in diseases which are untreated by modern medicine

The secondary metabolites of plants provide humans with numerous biologically active products, which have been used extensively as food additives, flavors, colors, insecticides, drugs, fragrances, and other fine chemicals. These plant secondary metabolites include several classes such as terpenoids, flavonoids, Phenolic, carotene, and

alkaloids; have diverse chemical structures and biological activities. It is important to identify in which class a phytonutrient belongs, because each class offers a unique kind of protection for the body. To play the "wellness game," however, all classes of phytonutrients need to be consumed (42, 43). Fruits of Berberis asiatica as nutraceuticals are very simple and risk free. These fruits have the potential to play an important role as nutaceuticals in healthy diet and to contribute to the prevention and treatment of diseases.A food based approach instead of a drug based approach to conquer malnutrition is the need. They have stood the test of time for their safety, efficacy, cultural acceptability and lesser side effects. The chemical constituents present in these fruits are a part of the physiological functions of living flora and hence they are believed to have better compatibility with the human body. Fruits of B. aristata are richer in micronutrients and bioactive secondary metabolites, which are produced in adaptation to local environmental conditions. These metabolites trigger further adaptive responses by producing 'protective', bioactive compounds which, when ingested, result in the transfer of protective effects to our organism. These wild edible fruits ensure improve productivity, nutrition, food diversity, income generation, health security of the users. Many of the multinational drug firms are shifting over to the nutraceutical manufacturing the old proverb "an apple a day will keep the doctor away" is now replaced by "a nutraceutical a day may keep the doctor away". Consumers are turning massively to food supplements to improve well being where pharmaceuticals fail.

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