PHYTO-PHARMACOLOGY OF *BERBERIS ARISTATA* DC: A REVIEW

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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. Plants are one of the richest sources of compounds. *Berberis aristata* is one of the plants used in Ayurveda for several remedies. *Berberis aristata* commonly known as "Daru haldhi and Chitra" is spinous herb native to northern Himalaya region. The plant is widely distributed from Himalayas to Srilanka, Bhutan and hilly areas of Nepal. *Berberis aristata* is used in ayurvedic medicines from very long time. It is used as a tonic, alternative, demulscent, diaphoretic, and diuretic, in the treatment of diarrhoea, jaundice and 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. The plant has effective pharmacological action and shows promising future for further researches. This review aims to highlight the ethnobotany, pharmacognostic and pharmacological uses of *Berberis aristata*.

Key Words: *Berberis aristata*, phytochemical constituents, pharmacological actions, inotropy.

INTRODUCTION

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 also 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. However among the estimated 250,000-400,000 plant species, only 6% have been studied for biological activity, and about 15% have been investigated phytochemically [1, 2]. Therefore it seems necessary to evaluate the herbs properly.

GENERAL INFORMATION

Berberis aristata DC. (Fam. 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. As it resembles in its properties to those of haridra, both the herbs have been mentioned together as haridra dvaya, meaning two haridras viz. haridra and daruharidra. Charaka has categorized daruharidra as stanyasodhana – lactode purant, lekhana – a reducing herb, arsoghna – anti – haemorrhoidal, kandughna – anti – haemorrhoidal, kandughna – anti – pruritic and as svedala – promotes sweating, rasayana-rejuvenative. Susruta have me ntioned it as ropana – a wound healer.

English names: Indian barberry, tree turmeric. **Indian names:** *darhaldi* (Bengal), *kashmoi* (Garhwal), *rasont, kashmal* (Himachal Pradesh), *chitra, dar-hald, rasaut, kashmal* (Hindi), *maradarisina, maramanjal*, (Kerala), *daruhald* (Maharashtra), *chitra, chutro* (Nepal),*chitra, kasmal. simlu, sumlu* (Punjab) *mullukala, usikkala* (Tamil Nadu), *daruharidra, darvi, kata, pitadaru, suvarnavarna* (Sanskrit).

There are 12 – 13 varieties like *Berberis asiatica, Berberis lycium, Berberis vulgaris, Berberis nepalensis* etc. The root and wood are rich in a yellow alkaloid berberine, a bitter substance, which dissolves in acids and forms salts of the alkaloid. The root contains two more alkaloids. A protoberberine alkaloid karachine is isolated and characterized, and taxalamine is also isolated. A protoberberine alkaloid – karachine – isolated and characterized and also taxilamine isolated. The plant is native of the whole range of Himalaya mountains at an elevation 2000 to 3500 metres. It also occurs in Nilagiri range in Southern India . The shrub grows upto 1.5 – 2.0 metres in height, with a thick woody root covered with a thin brittle bark. The leaves are cylindrical, straight, tapering, very sharp, hard, smooth spines. The flowers yellow, numerous, stalked, arranged in drooping racemes. The fruit is a small berry, ovoid and smooth. It flowers in April and May.

Berberis aristata DC. is an erect spinous shrub, often found in small patches on the bill slopes. It is one of very important medicinal plants. Almost every part of this plant

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has some medicinal value. Its roots, stem, bark and fruits are used in many *ayurvedic* preparations. This shrub is found growing wild in the sub-Himalayan tract at altitude ranging from 850-2,500 metres. It also grows in the Nilgiris and in Ceylon.

PHARMACOGNOSTICAL STUDIES

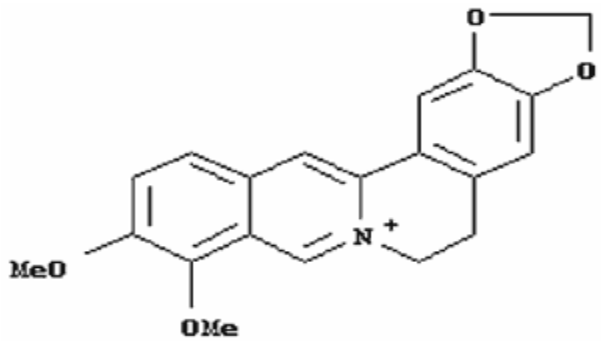
It is an erect spiny shrub, ranging between 2 and 3 metres in height wood, hard and yellow; bark, yellow to brown from outside and deep yellow from inside, removable in longitudinal strips by hand; spines (which, in fact, are modified leaves), three-branched and 1.5 cm long. Leaves, in tufts of 5 to 8, phyllotaxy verticillate, lanceolate, simple spiny, toothed, leathery, sessile, acuminate, with reticulate pinnate venation, 4.9 cm. long, 1.8 cm. broad, deep green on the dorsal surface and light green on the ventral surface.[3]

Flowers, stalked, yellow, complete, hermaphrodite, cyclic, actinomorphic, perigynous, the average diameter of a fully opened flower being 12.5 mm; inflorescence, a simple to corymbose raceme, with 11 to 16 flowers per cluster; calyx, yellow, polysepalous, with 6 sepals (3 small, 3 large), yellow, actinomorphic caducous, 4 to 5 mm long; corolla, polypetalous, with 6 petals, yellow, actinomorphic, 4 to 5 mm long; androecium, polyandrous, with 6 stamens, adnate, 5 to 6 mm long; gynoecium, one, 4 to 5 mm long, with a short style and a broad stigma. Fruits, globose to ovoid, usually covered with bloom as in plums, 7 mm long, 4 mm in diameter, weighing 227 mg, 237 microlitres in volume; fruit colour, aconite violet 937; colour of pulp and juice, plum purple 934/3. Seeds, 2 to 5, varying in colour from yellow to pink, each weighing 25 mg and being 29 microlitres in volume. Flowering in *Berberis aristata* starts from the first fortnight of March and remains in progress up to the end of April. The peak flowering season under Solan conditions 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. An average-sized bush of *Berberis aristata* was found to yield 657 g of fruits in about 4 pickings.

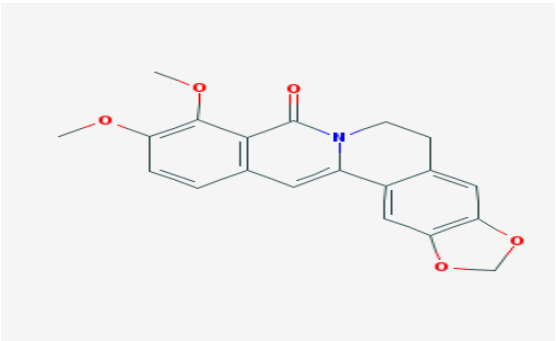
PHYTOCHEMISTRY

The plant contains barberine, oxyberberine, berbamine, aromoline, karachine, palmatine, oxyacanthine and taxilamine. [4] *Berberis aristata* contains protoberberine and bis isoquinoline type of alkaloid. Root of plant *Berberis aristata* contains alkaloid which are berbamine, Berberine, oxycanthine, epiberberine, palmatine, dehydrocaroline, jatrorhizine and columbamine,[5,6] karachine,[7] dihyrokarachine, taximaline,[8] oxyberberine, aromoline.[9] Four alkaloids, pakistanine, 1-O methyl pakistanine, pseudopalmatine chloride and pseudoberberine chloride were also isolated from *Berberis aristata*.[10,11] A secobisbenzlisoquinoline or simple isoquinoline alkaloid was isolated from *Berberis aristata*.[12] The major alkaloid found in *Berberis aristata* is Berberine having yield of 2.23% followed by palamatine.[13] Variation of Berberine content in root and stem of *Berrberis aristata* with altitude was determined. It was found that plants growing at lower altitude have more Berberine content. Berberine content in plant is also influenced by potassium and moisture content of soil.[14] HPTLC fingerprinting of Berberine in *Berberis aristata* was done to quantify the amount of Berberine. Total alkaloidal content of *Berberis aristata* was also done.[1]

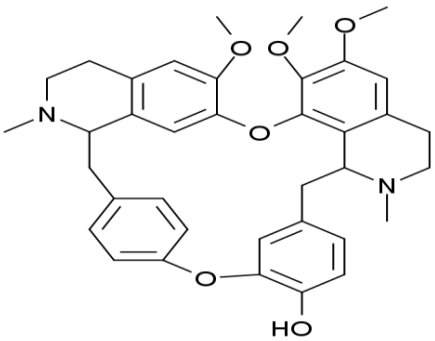
Berberine



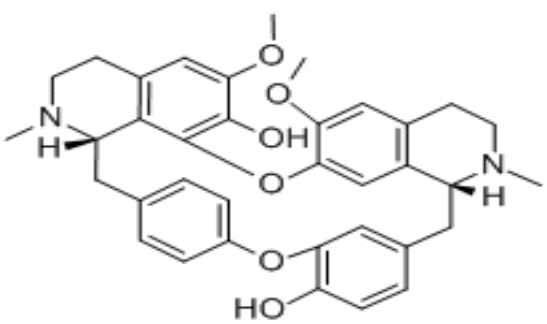
Oxyberberine



Berbamine



Aromoline



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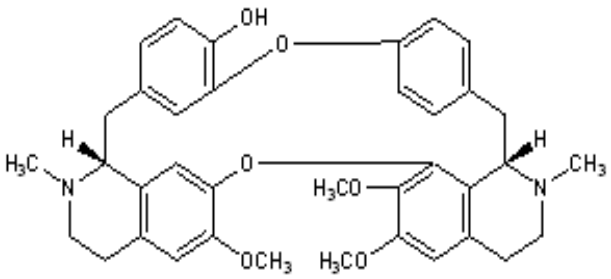
Oxyacanthine



TRADITIONAL MEDICINAL USES

Berberis aristata has played a prominent role in herbal healing for more than 2,500 years. The ancient Egyptians used it to prevent plagues. India's Ayurvedic healers used it foe dysentery. During the early middle ages, European herbalists used it to treat liver and gallbladder ailments. Russian healers used it for inflammations, high blood pressure, and for abnormal uterine bleeding. American Indians recognize barberry as similar to Oregon grape. Tincture made from *Berberis aristata* is used as a bitter tonic, stomachic, cholagogue, antiperiodic and alterative, in cases of remittent as well as intermittent fevers and also in debility consequent there from and is very effective in periodic neuralgia and menorrhagia.[12] As an antiperiodic on frequently repeated administration, it doses not produce is the case with cinchona and quinine and it may be used during the attack of fever. Rasaut a preparation of *Berberis aristata* mixed with honey is useful in the treatment of aphthous sores abrasions and ulcerations of the skin. The plant is an emmenagogue and is useful in the treatment of jaundice, enlargement of spleen, etc. the drug is also regarded as laxative, diaphoretic, antipyretic and antiseptic. *Berberis aristata* root bark decoction is externally used as a wash in painful eye affections, ulcers and hemorrhoids. In the Unani system of medicine, it is used for the treatment of leprosy. Decoction of roots of *Berberis aristata* is used for skin troubles and in blood purification. [13-16]

PHARMACOLOGY

Berberis aristata DC. are given as a cooling laxative to children. The stem is said to be diaphoretic and laxative and useful in rheumatism. The dried extract of the roots is used as an application in ophthalmia. It is also an excellent medication in the case of sun-blindness. The bark of its root is a valuable medicine in intermittent and remittent fevers. The root is one of the few really good medicines in India. In its efficacy, it is almost equal to quinine and Warburg's tincture. It does not produce any bad effects on the stomach, the bowels, the brain and the organs of hearing.[16-17]

A very valuable preparation called *rasaut* is prepared from this plant. For preparing *rasaut*, the bark of the root and of the lower part of the stem is boiled in water, strained and evaporated till a semi-solid mass (*rasaut*) is obtained. *Rasaut* is fairly soluble in water. It is mixed with butter and alum, or with opium and lime-juice and is applied externally to the eyelids to cure ophthalmia and other eye diseases.[18] It is also reported to be a mild laxative, a tonic and is useful in curing ulcers and fevers. [18]

Dastur in 1962 has reported that the chief constituent of *Berberis aristata* is barberine, which is a bitter alkaloid. According to him, rasaut is used as a purgative for children and as a blood-purifier, a tonic and a febrifuge. It is also given in diarrhoea, jaundice and skin diseases. A watery solution of this preparation is also used for washing piles, oriental sores and glandular swellings. [18]

ANTI – MICROBIAL

The antimicrobial activity of hydroalcoholic extracts of. *Berberis aristata*, were tested against eleven bacterial, *Micrococcus luteus, Bacillus subtilis, Berberis cereus, Enterobactor aerogenus, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus aureus, Salmonella typhimurium, Streptococcus pneumoniae,* and eight fungal strains. *Aspergillus nidulans, Candida albicans, Aspergillus terreus, Trichophyton rubrum, Aspergillus spinulosus, Cryptococcus albidus, Aspergillus flavus, Aspergillus niger. Berberis aristata* root extract gave low MICs values against *Bacillus cereus, Escherichia coli, Staphylococcus aureus* and *Aspergillus flavus* while stem extract against *Berberis cereus and Streptococcus pneumoniae*. The hydroalcoholic extracts of root of the *Berberis aristata* were effective against most of the tested bacteria. Like *Berberis lycium, Berberis aristata* and *Berberis asiatica* and also showed significant antifungal activity against *Aspergillus terreus* and *Aspergillus flavus*. *Berberis aristata* root and *Berberis lycium* stem extracts gave very low MIC values with the concentration of 0.3 µg/ml. The major alkaloid berberine may be responsible for antimicrobial activity. [19]

ANTI-DEPRESSANT

Berberine, an alkaloid isolated from *Berberis aristata* Linn. has been used in the Indian system of medicines as a stomachic, bitter tonic, antiamoebic and also in the treatment of oriental sores. Evidences have demonstrated that berberine possesses central nervous system activities, particularly the ability to inhibit monoamine oxidase-A, an enzyme involved in the degradation of norepinephrine and serotonin (5-HT). With this background, the present study was carried out to elucidate the antidepressant-like effect of berberine chloride in different behavioural paradigms of despair. Berberine (5, 10, 20 mg/kg, i.p.) inhibited the immobility period in mice in both forced swim and tail-suspension test, however, the effect was not dosedependent. Berberine (5 and 10 mg/kg, i.p.) also reversed the reserpine-induced behavioral despair. [20] Berberine (5 mg/kg, i.p.) enhanced the anti-immobility effect of subeffective doses of various typical but not atypical antidepressant drugs in forced swim test. Berberine (5 mg/kg, i.p.) following its acute administration in mice resulted in increased levels of norepinephrine (31%), serotonin (47%) and dopamine (31%) in the whole brain. Chronic administration of berberine (5 mg/kg, i.p.) for 15 days signi.cantly increased the levels of norepinephrine (29%), serotonin (19%) as well as dopamine (52%) but at higher dose (10 mg/kg, i.p.), there was no change in the norepinephrine (12%) levels but a significant increase in the serotonin (53%) and dopamine

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(31%) levels was found. The antidepressant-like effect of berberine (5 mg/kg, i.p.) in forced swim test was prevented by pretreatment with L-arginine (750 mg/kg, i.p.) or sildena.l (5 mg/kg, i.p.). On the contrary, pretreatment of mice with 7-nitroindazole (7-NI) (25 mg/kg, i.p.) or methylene blue (10 mg/kg, i.p.) potentiated the effect of berberine (2 mg/kg, i.p.) in the forced swim test. Pretreatment of mice with (+)- pentazocine (2.5 mg/kg, i.p.), a high-af.nity sigma1 receptor agonist, produced synergism with subeffective dose of berberine (2 mg/kg, i.p.). Pretreatment with various sigma receptor antagonists viz. progesterone (10 mg/kg, s.c.), rimcazole (5 mg/kg, i.p.) and N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(dimethylamino) ethylamine (BD1047; 1 mg/kg, i.p.) reversed the anti-immobility effects of berberine (5 mg/kg, i.p.). Berberine at lower dose did not affect the locomotor activity and barbiturate-induced sleep time. It produced mild hypothermic action in rats and displayed analgesic effect in mice. Taken together, theses finndings demonstrate that berberine exerted antidepressant-like effect in various behavioural paradigms of despair possibly by modulating brain biogenic amines (norepinephrine, serotonin and dopamine). Further, nitric oxide pathway and/or sigma receptors are involved in mediating its antidepressant-like activity in mouse forced swim test.[20]

DIABETES MELLITUS

An uncontrolled clinical trial investigated the effect of berberine on 60 patients with type 11 diabetes mellitus. The patients varied in severity of this disorder. Oral doses (0.3-0.5 g three times a day) were prescribed for 1-3 months, together with a therapeutic diet prescribed for 1 month. Major symptoms of diabetes disappeared patients strength improved, blood pressure became normal and blood lipids decreased. Fasting glycaemic levels in 60% of patients ere controlled. Further testing in animal models indicated that treatment with berberine led to healthier pancreatic tissue compared to controls. It is suggested that the mechanism of action of berberine may be associated with promoting regeneration and functional recovery of β-cells.[21,29]

HEPATOPROTECTIVE

In earlier studies, we demonstrated that this folkmedical use had scientifically justified basis, as the crude extract of *Berberis aristata* leaves and fruits showed hepatoprotection possibly through inhibitory action on hepatic drug metabolizing enzymes [21-22]. In this investigation we provide evidence that berberine is to be considered the active principle of these extracts. berberine, a known compound from *Berbris aristata* plant, was studied for its possible anti-hepatotoxicaction in rats. Pretreatment of animals with berberine 4 mg/kg; orally twice daily for 2 days prevented the acetaminophen or CCl_4 induced rise in serum levels of alkaline phosphatase ALP and aminotransaminases AST and ALT , suggestive of hepatoprotection. Post-treatment with three successive oral doses of berberine 4 mg/kg every 6 h reduced the hepatic damage induced by acetaminophen, while CCl_4 - induced hepatotoxicity was not modified, suggesting a selective curative effect against acetaminophen. Pretreatment of animals with a single oral dose of berberine 4 mg/kg induced prolongation of the pentobarbital 60 mg/kg, i.p. -induced sleeping time as well as increased strychnine 0.3 mg/kg; i.p. -induced toxicity, suggestive of inhibitory effect on microsomal drug metabolizing enzymes, cytochrome P450s CYPs.[25-27]

INOTROPIC ACTIVITY

Berberis aristata is an edible plant employed in South Asian traditional medicine; in particular, its fruit is used as a tonic remedy for liver and heart. In isolated cardiac tissues, *Berberis aristata* fruit extract exhibits a positive inotropic action. Activity-directed fractionation using organic solvents revealed that the cardiotonic activity is concentrated in the *n*-butanolic fraction (BF). The cardiac action of BF was investigated in spontaneously beating right atria and in electrically driven right ventricular strips and left atria obtained from reserpinized guinea pigs. The results show that this fraction produces a dose-dependent positive inotropic action with little effect on heart rate. To study its possible mode of action, guinea pig atria were pretreated with propranolol, a b-adrenoceptor blocking agent. This treatment abolished the cardiotonic effect of isoprenaline, whereas the cardiotonic effect of BF remained unaltered, suggesting that this effect does not involve stimulation of b-adrenoceptors. On the other hand, application of carbachol reverses only part of the BF-induced increase in ventricular force of contraction, indicating that besides a cyclic AMP (cAMP)-dependent mechanism, a cAMP-independent mechanism underlies the inotropic action of BF. This is in line with the observation that the dynamics of isometric twitch contractions are not significantly altered by BF. Investigations in skinned myocardial preparations showed that BF modulates the calcium-dependent interaction of actin and myosin, apparently by reducing the cooperativity of the calcium-dependent binding of myosin to actin, i.e., there is enhanced calcium activation at low to physiological intracellular calcium, and reduced calcium activation at high intracellular calcium concentrations as present, for example, in ischemic calcium overload. These data indicate that the edible plant, *Berberis aristata*, contains active principle(s) that cause(s) a selective inotropic effect, involving—in the form of the modulatory effect on actin myosin cooperativity—a novel mechanism of action. Further phytochemical and pharmacological studies may lead to isolation and structural identification of an attractive, new cardiotonic agent from *Berberis aristata* fruit.[16-20]

IMMUNOMODULATORY ACTIVITY

The activity of a crude extract formulation was evaluated in experimental immunomodulation studies. The formulation comprises the following five plants - *Boerhavia diffusa, Tinospora cordifolia, Berberis aristata, Terminalia chebula* and *Zingiber officinale*. In immunomodulation studies humoral immunity was enhanced as evidenced by the haemagglutination titre. The T-cell counts remained unaffected in the animals treated with the formulation but cell-mediated immune response was stimulated as observed in the leukocyte migration inhibition (LMI) tests.[17]

INFLUENCE ON T-CELL MEDIATED IMMUNITY

The protoberberine alkaloid berberin is isolated as a main alkaloid from the roots and bark of *Berberis vulgaris*. Berberine strongly inhibited in vitro the proliferative

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response of mouse spleen cells to Tdependent mitogens concanavalin A (con A) and phytochemagglutinin (PHA). Spleen cells obtained from berberine-treated mice (10 mg/kg/3) days) expressed enhanced proliferative response to both mitogens. Berberine was applied to mice at different intervals before or after the induction of adjuvant arhritis (AIA) and *Candida albicans (C. albicans)* infection. The application of the alkaloid to new born mice (5 days after birth at a dose of 5 mg/kg/3 days) did not change the course of AIA and C. albicans infection. Its application at three 10 day intervals (5 mg/kg), starting from the 5 day after birth increased the joint inflammation in AIA. The host resistance to C. albicans infection was not affected, while the delayed type hypersensitivity (DTH)-reaction against the pathogen was enhanced. The alkaloid inhibited the development of AIA when applied after its onset (10 mg/kg from day +3 to +12 day). Berberine treatment during the ongoing infection did not influence its outcome (from +2 to +10 day). Berbamine, an ingredient of Berberis, which itself is widely utilized in Chinese folk medicine has been used as a source of leukogenics, anti-arrhythmics and anti-hypertensives. In recent years the immunosuppressive effects of berbamine has been demonstrated. In order to further investigate the value of berbamine as an immunosuppressive agent, the delayed type hypersensitivity reaction (DTH) response with sheep red blood cells (SRBC), the mixed lymphocyte reaction (MLR) and a skin model of allograft rejection on mice were studied. Berbamine showed suppressive effects on DTH and MLR and significantly prolonged allograft survival compared with untreated transplanted mice. The results indicate that berbamine may be a potential agent in clinical transplantation. [16-17.]

HEPATIC AMOEBIASIS

The activity of a crude extract formulation was evaluated in experimental amoebic liver abscess in golden hamsters. The formulation comprises the following five plants - *Boerhavia diffusa, Tinospora cordifolia, Berberis aristata, Terminalia chebula* and *Zingiber officinale*. The formulation had a maximum cure rate of 73% at a dose of 800 mg/kg/day in hepatic amoebiasis reducing the average degree of infection (ADI) to 1.3 as compared to 4.2 for sham-treated controls. [18]

ANTI-CARCINOGENIC ACTIVITY

Berberin, an alkaloid isolated from the plant Berberis aristata, has been found to inhibit significantly the carcinogenesis induced by 20-methylcholanthrene (200 microg/0.1 mL/mouse) or N-nitrosodiethylamine (NDEA; 0.02% NDEA in distilled water, 2.5 mL/animal by gavage, five days a week for 20 weeks) in a dosedependent manner in small animals. Administration of berberine (0.5, 2.5 or 5.0 mg kg(-1) could reduce significantly the incidence of tumor in animals after an injection of 20-methylcholanthrene and increased their life span compared with the control. When berberine (10, 25 or 50 mg kg(-1)) was administered simultaneously with NDEA, the markers of liver injury (liver weight, gamma-glutamyl transpeptidase activity and glutathione S-transferase level) were reduced significantly compared with animals treated

with NDEA only, which resulted in all the values being elevated. A similar decrease was noted in the serum levels of lipid peroxide, bilirubin and glutamate pyruvate transaminase. Morphology of liver tissue and levels of marker enzymes indicated that berberine offered protection against chemicalcarcinogenesis. Methanolic extract of stems of *Berberis aristata* is also showing promising results against breast and colon cancer cell lines. Hence, it is effective against breast and colon cancers. [19,23,24.]

MISCELLANEOUS

Berberis aristata, an edible plant (family *Berberidaceae*, local name *Zarshik*), has been used since ancient times in South Asian traditional medicine as an herbal tonic for liver and heart. In our earlier studies we demon- that the folkloric use in hepatic damage has a scientifically justified basis, as the crude extract of *Berberis aristata* fruits and leaves showed hepatoprotection in an animal model of hepatotoxicity. [20-29]

CONCLUSION

Berberis aristata is commonly found throughout India. Studies have revealed 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 plethora of patents being awarded.

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