



POTENTIALITIES OF BERBERINE CONTAINING MEDICINAL PLANTS-A REVIEW

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ABSTRACT

Economically developed countries are evincing a greater interest in natural medicines which are referred as herbal drugs or phytomedicines. Several medicinal plants of Ayurvedic material medica were subjected to scientific scrutiny for producing scientific validation. During search of molecular therapeutic agents from higher plants, several researches were carried out and successfully developed certain active components like reserpine (Antihypertensive), vinblastine & vincristine (Anti cancerous), Bromohexine (expectorant), glycyrrhizin (Antiulcer) etc. Secondary metabolites (Alkaloids & glycosides etc) of the plant act as the therapeutically valuable molecules against a targeted disorder. Berberine an alkaloid which is widely distributed not only in *Berberis cristata* but also in several plants like *Tinospora cordifolia*, *Fumaria indica*, *Coscinium fenestratum*, *Argemone mexicana* etc. Berberine is enlisted under Anti-diarrheal agents or is used as intestinal antiseptic & bitter stomachic in modern pharmacology. A review of research studies carried out on the medicinal plants containing Berberine is enumerated in this paper.

Key words: Berberine, *Berberis cristata*, *Tinospora cordifolia*, *Fumaria indica*, *Coscinium fenestratum*, *Argemone mexicana*.

INTRODUCTION

The industrial demand for the medicinal plant resources has been on the rise due to the worldwide buoyancy in the herbal sector engaged in production of herbal health care formulations; herbal based cosmetics products and herbal nutritional supplements. In India, many registered herbal industries and a multitude of unregistered cottage-level units depend upon the continuous supply of medicinal plants for manufacture of herbal medicinal formulations based on Indian systems of medicine. In addition to the industrial consumption, significant quantities of medicinal plant resources are consumed in the country under its traditional health care practices at the household level, by traditional healers and by practitioners of Indian Systems of Medicine.

A list of 960 medicinal plant species forming source of 1289 botanical raw drugs in trade of our country has been worked out by Foundation of revitalization of local health traditions (FRLHT) from the (a) literature and (b) data collected during the study on (i) consumption of botanicals by the herbal manufacturing units, and (ii) the plant raw drugs traded in the mandis (raw drug trading

centers). This list also includes the known equivalent species, substitutes, and the adulterants in trade of the major botanical raw drugs. Species that are harvested in large quantities from the wild, whether or not recorded during the survey of herbal industry or the raw drug markets, have also been included in this list.

The annual demand of botanical raw drugs in the country has been estimated at 3,19,500 MT for the year 2005-06. The annual trade value corresponding to the trade of 3,19,500 MT botanical raw drugs in the country works out to Rs.1069crores for the year 2005-06. The annual turnover of the herbal industry in the country, for the year 2005-06, has been estimated at Rs.8800crores. The total annual turnover of the domestic herbal industry has been estimated by employing this correlation to the total procurement costs of Rs.627,90crores, pertaining to the botanical raw drugs, consumed by this sector. Analysis of data obtained from the herbal industries has revealed that the annual procurement costs of botanical raw drugs account for about 7% of the annual turnover of the herbal manufacturing units. Some berberine containing plants

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have been scrutinized with their estimated consumption and source which are mentioned below in table 1.

Berberine containing plants

The information with regards to Berberine containing medicinal plants in terms of part used and indications described in the literature of Ayurvedic classics and works on medicinal plants are furnished in the following table 2.

Activities carried out on plants

Research activities reported on 13 medicinal plants containing Berberine alkaloid are as follows.

Berberis aquifolium

The antipsoriatic *Berberis aquifolium* drug which were analysed for an in vitro inhibiting effect on cyclooxygenase (CO) of sheep seminal vesicles and 5-lipoxygenase (5-LO) of porcine leucocytes. The same extracts exhibited also immunostimulating activities.

Berberis aristata

Berberis aristata possess the potent antiosteoporosis activity, anticancer activity, hypoglycaemic activity.

Berberis vulgaris

Berberis vulgaris possess the potent antibacterial activity, antioxidant activities, antihistaminic & anticholinergic activities.

Coptis chinensis

Coptis chinensis possess the potent Vasoconstrictive activity & cytotoxic activity.

Hydrastis canadensis

Hydrastis canadensis exhibited the potent Antibacterial activity & Anti-cancerous activity

Tinospora cordifolia

Tinospora cordifolia possess the potent radio protective & cytoprotective activity, antipsychotic activity, In-vitro antimicrobial activity, antioxidant activity, anti-diabetic activity.

Coscinium fenestratum

Coscinium fenestratum shown the potent anti-proliferative activity, antimicrobial & Antioxidant activity, Anti-hepatotoxic effect.

Fumaria indica

Fumaria indica exhibited the potent Anti-anxiety activity & Cytotoxic activity.

Argemone mexicana

Argemone mexicana possess the potent Bacteriostatic activity, Hypoglycaemic activity & wound healing activity.

Cissampelos pareira

Cissampelos pareira possess the potent anti-oxidant & immunomodulatory activity, In-vivo & In-vitro hepatoprotective activity & anti-anxiety activity.

Cyclea peltata

Cyclea peltata possess the potent diuretic activity, Antibacterial activity, In-vitro pediculocidal activity, Antioxidant & anti-ulcer activity.

Phellodendron chinense

Phellodendron chinense possess the potent Anti-osteoporotic activity, Immunomodulator activity & antifungal activity.

Mahonia palensis

Mahonia palensis has shown the potent anti-hypertensive activity & pesticidal activity.

(A) Experimental research

Berberine suppresses gero-conversion from cell cycle arrest to senescence Berberine (BRB), a natural alkaloid, has a long history of medicinal use in both Ayurvedic and old Chinese medicine. This findings reveal that: (a) in cells induced to senescence BRB exhibits gero-suppressive properties by means of mTOR/S6 inhibition; (b) in parallel, BRB reduces the level of constitutive DNA damage response, previously shown to report oxidative DNA damage by endogenous ROS; (c) there appears to a causal linkage between the (a) and (b) activities; (d) the in vitro model of premature stress-induced senescence can be used to assess effectiveness of potential gero-suppressive agents targeting mTOR/S6 and ROS signaling; (e) since most of the reported beneficial effects of BRB are in age-related diseases, it is likely that gero-suppression is the primary activity of this alkaloid.

Berberine promotes the development of atherosclerosis and foam cell formation by inducing scavenger receptor A expression in macrophage

Berberine is identified to lower the serum cholesterol level in human and hamster through the induction of low density lipoproteins (LDL) receptor in hepatic cells. To evaluate its potential in preventing atherosclerosis, the effect of berberine on atherosclerosis development in apolipoprotein E-deficient (apoE^{-/-}) mice was investigated. In apoE^{-/-} mice, berberine induced in vivo foam cell formation and prevented atherosclerosis development. Results suggest that to evaluate the potential of a cholesterol-reducing compound in alleviating atherosclerosis, its effect on the cells involved in atherosclerosis development, such as macrophages, should also be considered. Promotion of foam cell formation could counter-balance the beneficial effect of lowering serum cholesterol.

Berberine improves glucose metabolism through induction of glycolysis

Berberine, a botanical alkaloid used to control blood glucose in type 2 diabetes in China, has recently been reported to activate AMPK. However, it is not clear how AMPK is activated by berberine. In this study, activity and action mechanism of berberine were investigated in vivo and in vitro. In dietary obese rats, berberine increased insulin sensitivity after 5-wk

administration. Results suggest that berberine enhances glucose metabolism by stimulation of glycolysis, which is related to inhibition of glucose oxidation in mitochondria. Berberine-induced AMPK activation is likely a consequence of mitochondria inhibition that increases the AMP/ATP ratio.

Antioxidant activities of Berberine hydrochloride

In order to explore the mechanism of berberine hydrochloride in treating diabetes, antioxidant activities of the berberine hydrochloride *in vitro* were carried out. This study aimed to examine the antioxidant activity of berberine hydrochloride using different assays including: reducing power, 2,2-diphenyl 1-picrylhydrazyl (DPPH) radical scavenging assay, ABTS radical scavenging assay, superoxide anion and hydroxyl radical scavenging activity. The results exhibited that berberine hydrochloride has significant reductive ability and radicals scavenging effects, especially on ABTS, hydroxyl radicals and DPPH radicals.

→Biological assessment of Berberis vulgaris and its active constituent, berberine:Antibacterial, antifungal and anti-hepatitis C virus (HCV) effect.

Berberis vulgaris is a shrub in the family Berberidaceae. *B. vulgaris* as well as other berberine (BER) containing plants are used medicinally in virtually all-traditional medical systems. In this study, the efficacy of ethanolic extract of dried root powder of *B. vulgaris* as anti bacterial, anti fungal and anti hepatitis C was evaluated. Also, its efficacy for induction of phagocytosis and lymphoproliferation was determined. In conclusion, *B. vulgaris* extract can be considered an efficient antimicrobial especially hepatitis C virus (HCV) and *Aspergillus flavus*. This effect could be referred to its immunostimulant capacity as it enhances the activity of peripheral blood mono nuclear cells (PMNC), especially phagocytic cells.

→Inhibition of lipid synthesis through activation of AMP kinase: an additional mechanism for the hypolipidemic effects of berberine.

The alkaloid drug berberine (BBR) was recently described to decrease plasma cholesterol and triglycerides (TGs) in hypercholesterolemic patients by increasing expression of the hepatic low density lipoprotein receptor (LDLR). Using HepG2 human hepatoma cells, it was found that BBR inhibits cholesterol and TG synthesis in a similar manner to the AMP-activated protein kinase (AMPK) activator 5-aminoimidazole-4-carboxamide 1-beta-ribofuranoside (AICAR). Significant increases in AMPK phosphorylation and AMPK activity were observed when the cells were incubated with BBR. findings indicate that BBR, in addition to upregulating the LDLR, inhibits lipid synthesis in human hepatocytes through the activation of AMPK. These effects could account for the strong reduction of plasma TGs observed with this drug in clinical trials.

(B) Phytochemical studies

Validated HPLC-UV method for the determination of berberine in raw herb *Daruharidra (Berberis aristata DC)*, its extract, and in commercially marketed Ayurvedic dosage forms

A new, simple, sensitive, selective, and precise high-performance liquid chromatography (HPLC) method for analysis of berberine in crude plant material, herbal extract, and ayurvedic dosage forms was developed and validated. The linear regression analysis data for the calibration plots showed good linear relationship, with $r(2) = 0.9942$ in the concentration range of 16380-30420 $\mu\text{g/ml}$ with respect to the peak area. The method was validated for specificity, precision, recovery, and linearity according to the International Conference on Harmonization guidelines. Statistical analysis of the data showed that the method is reproducible and selective for the estimation of berberine.

Multicomponent Therapeutics of Berberine Alkaloids

Although berberine alkaloids (BAs) are reported to be with broad-spectrum antibacterial and antiviral activities, methicillin-resistant *Staphylococcus aureus* (MRSA) was chosen as a model organism, and modified broth microdilution was applied for the determination of the fluorescence absorption values to calculate the anti-MRSA activity of BAs. The synergetic combinations included berberine and epiberberine, jatrorrhizine and palmatine and jatrorrhizine and coptisine ; the antagonistic combinations included "coptisine and epiberberine". The optimal combination was berberine : coptisine : jatrorrhizine : palmatine : epiberberine = 0.702 : 0.863 : 1 : 0.491 : 0.526 and the potency of the optimal combination on cyclophosphamide-immunocompromised mouse model was better than the natural combinations of herbs containing BAs.

Synergy in a medicinal plant: Antimicrobial action of berberine potentiated by 5'-methoxyhydnocarpin, a multidrug pump inhibitor

Berberine alkaloids, which are cationic antimicrobials produced by a variety of plants, are readily extruded by MDRs. Several *Berberis* medicinal plants producing berberine were found also to synthesize an inhibitor of the NorA MDR pump of a human pathogen *Staphylococcus aureus*. The inhibitor was identified as 5'-methoxyhydnocarpin (5'-MHC), previously reported as a minor component of chaulmoogra oil, a traditional therapy for leprosy. 5'-MHC is an amphipathic weak acid and is distinctly different from the cationic substrates of NorA. 5'-MHC had no antimicrobial activity alone but strongly potentiated the action of berberine and other NorA substrates against *S. aureus*. MDR-dependent efflux of ethidium bromide and berberine from *S. aureus* cells was completely inhibited by 5'-MHC. The level of accumulation of berberine in the cells was increased strongly in the presence of 5'-MHC, indicating that this plant compound effectively disabled the bacterial resistance mechanism against the berberine antimicrobial.

Berberine chloride can ameliorate the spatial memory impairment and increase the expression of interleukin-1beta and inducible nitric oxide synthase in the rat model of Alzheimer's disease

Berberine is the major alkaloidal component of *Rhizoma coptidis*, and has multiple pharmacological effects including inhibiting acetyl cholinesterase, reducing cholesterol and glucose, lowering mortality in patients with chronic congestive heart failure, arthritis etc. The study was carried out to investigate the effect of berberine chloride on the spatial memory, inflammation factors interleukin-1 beta (IL-1beta) and inducible nitric oxide synthase (iNOS) expression in the rat model of Alzheimer's disease (AD) which was established by injecting Abeta (1-40) (5 microgram) into the rat hippocampus bilaterally.

Determination of berberine and strychnine in medicinal plants and herbal preparations by pressurized liquid extraction with capillary zone electrophoresis

A simple and rapid method for the determination of berberine and strychnine in medicinal plants and herbal preparations for regulatory purposes using a home-made pressurized liquid extraction (PLE) system with capillary zone electrophoresis (CZE) using ultraviolet detection at 254 nm was developed. The effects of pH, concentration of buffer, and organic modifiers in the electrophoretic separation were investigated. The buffer used for CZE contained 50 mM ammonium acetate, pH 3.1. The effect of temperature on the extraction efficiency of strychnine in medicinal plants by PLE was demonstrated. Comparable or higher extraction efficiency was achieved with PLE for strychnine in medicinal plants and berberine in herbal preparations compared to Soxhlet extraction. The effect of matrix interference in medicinal plants and herbal preparations containing a number of medicinal plants samples using CZE was investigated by standard additional experiments. The reproducibility of the method using PLE with CZE was found to vary between 2.4 and 10.7% ($n = 5/6$) for different types of samples on different days.

(C) Clinical studies

Relationship between the clinical effects of berberine on severe congestive heart failure and its concentration in plasma studied by HPLC

It has been reported that berberine is valuable for long-term treatment of ventricular premature beats (VPBs) and leads to a decrease in mortality for patients with congestive heart failure (CHF).

DISCUSSION

The medicinal plants containing Berberine namely Daruharidra (*Berberis aristata* D.C), Patha (*Cissampelos pareira* Linn.), Guduchi (*Tinospora cordifolia* (Willd.) Miers) or popular drugs indicated in various condition by ayurvedic classics and compendia. Among them Guduchi (*Tinospora cordifolia* (Willd.) Miers), is categorised under prime drugs indicated

in the management of vatarakta (Arthritis, Gouty arthritis, Rheumatoid Arthritis). The other indications include kamla (Jaundice), Prameha (Urinary disorders including DI), Vishamjwara & Jirnajwara (Intermittent & Chronic fever), Atisara (Diarrhoea), Pleehodar (Splenomegaly) and Arshas (Haemorrhoids). Charaka considered Guduchi as Medhya rasayana (memory enhancing rejuvenating agent) Patha is indicated in Atisara (Diarrhoea), Arshas (Haemorrhoids), Jwara (Fever), Pleehodar (Splenomegaly), Prameha (Urinary disorders including DM), Ardhavbedak (Migraine).

Both these drugs are indicated in similar conditions like fever, splenomegaly, piles, diarrhoea, urinary diseases including in diabetes. Tribal folk are mainly using these two drugs in the management of malarial fever. Patha is indicated to induce labour while Guduchi is prescribed to purify the breast milk and the claims refer to presume the activity of Patha's and Guduchi on certain hormones like oxytocin and prolactin. Guduchi and Patha are reported to have hypoglycaemic activity by monitoring insulin secretions. The analysis of information furnished in ayurvedic classics clearly indicate that berberine monitors the different hormones by specifically acting on the gut.

Acharyas of Ayurved identified the hypofunction of agni (Digestive and enzymatic complex substance) as the root cause for majority of diseases. It may be reported that gut is the important endocrinal organ which exerts an influence on the secretion of other hormone in the body.

Berberis aristata (Berberidaceae) is considered as the source plant of Daruharidra while south Indian ayurvedic physicians prefer *Coscinium fenestratum* Gaertn. (Menispermaceae) for the same. The phytochemical analysis reports that both drugs are having berberine alkaloid. Daruharidra is indicated in vrana (Wound), Prameha (Urinary disorders including DM), Kamla (Jaundice), Shvetpradar (Leucorrhoea), Netraroga & mukharoga (Diseases of eye & ENT), and sarpavisha (snake poisoning). Sodhala observes that Haridra (*Curcuma longa*). And Daruharidra (*Berberis aristata* D.C) are the prime drugs for the management of snake bites, So far the researchers have not attempted to provide the scientific evidence about the anti-venom activity of Berberine.

Satyanashi (*Argemone mexicana* L) is an exotic plant which is native to America and naturalised throughout India is being considered as a source plant of svarnakshiri which appears to be controversial. The fresh latex contain protein dissolving constituents, berberine and is used externally to treat the warts, wounds & tumours. Folklore medicine confirms its application in inflammatory condition of the eye. The review of indications of berberine containing medicinal plants in Ayurvedic literature as well as scientific validation produced clearly denote anti-microbial, anti-ulcer, anti-oxidant, hypoglycaemic, anti-cancer, anti-inflammatory and immunomodulatory activities. The role of berberine in the conditions like in the management of eye diseases, malaria and snake bites are yet to be explored.

Table 1. Consumption and source of medicinal plants

Sr.no	Botanical name	name	Estimated consumption (MT)	Source (W/C) (wild/cult.)
1.	<i>Berberis aristata</i>	Daruharidra	521	W
2.	<i>Cosconium fenestratum</i>	Kaliyaka	114	W
3.	<i>Cyclea peltata</i>	Rajpatha	183	W
4.	<i>Tinospora cordifolia</i>	Guduchi	3845	W

Table 2. Traditional indications of medicinal plants

Sr. No.	Latin name	Family	English name & Sanskrit name	Part used	Indications
1.	<i>Argemone mexicana</i> L	Papavaraceae	Mexican poppy/Satyanashini	Whole plant	Skin related ailments, Arthritis, constipation, Indigestion, Fever, Inflammation.
2.	<i>Berberis aristata</i> D.C	Berberidaceae	Tree Turmeric Root/Daruharidra	Root	Fever, Arthritis, Diarrhoea.
3.	<i>Coscinium fenestratum</i> Gaertn.	Menispermaceae	False calumba root/Kaliyaka	Stem, roots	Fever, Arthritis, Diarrhoea.
4.	<i>Cissampelos pareira</i> Linn.	Menispermaceae	Pereira brava/ Patha	Root	Skin diseases, inflammation, indigestion, asthma, fever, dysurea, dysentery.
5.	<i>Cyclea peltata</i> Hook.f & Thomson	Menispermaceae	Buckler-leaved moon-seed/Raj patha	Root	Fever, Anorexia, Indigestion, Abdominal pain.
6.	<i>Tinospora cordifolia</i> (Willd). Miers	Menispermaceae	Heart-leaved Moonseed/Guduchi	Stem	Fever, Arthritis Jaundice and Urinary disorders.
7.	<i>Berberis aquifolium</i> Pursh.	Berberidaceae	Oregon Grape	Rhizome, Roots	Syphilis, constitutional syphilis, chronic skin affections
8.	<i>Berberis vulgaris</i> .L.	Berberidaceae	Common Barberry	Outer Bark of Stem, Root	Used in Ailments of GI tract, liver, gall bladder, urinary tract, respiratory tract.
9.	<i>Coptis chinensis</i> Franch	Ranunculaceae	Coptis or Goldenthread	Rhizome	Anorexia, malarial fever,
10.	<i>Fumaria indica</i> Hausskn	Papavaraceae	Indian fumitory	Whole plant	helminthiasis, jaundice, fever.
11.	<i>Hydrastis canadensis</i> L	Ranunculaceae	Goldenseal	Rhizome, Roots.	Infections (Bacterial & virus)
12.	<i>Mahonia napalensis</i> DC	Berberidaceae	Holly leaved barberry	Root	Infections (Bacterial & virus)
13.	<i>Phellodendro chinense</i> C.K.Schneid	Rutaceae	Phellodendron Bark	Bark	Arthritis, Infections (Bacterial & virus)

CONCLUSION

Medicinal plants contain active drug molecules often referred as secondary metabolites. Herbal healthcare division is expanding with a rapid scale. In India currently 7494 Ayurvedic pharmacies are manufacturing classical and other herbal products adhering to standardized good manufacturing practices (GMP). Various scientific methodologies including chromatographic analysis are being adopted to evolve standards of herbal products. Exclusive studies on berberine isolated alkaloid are very limited. The reported activities include immune

stimulating, antiosteoporosis, anticancer, hypoglycaemic, antibacterial, antioxidant, antihistaminic, anticholinergic, vasoconstrictive, radioprotective, anti-anxiety, wound healing, hepatoprotective, diuretic, pediculocidal, antioxidant, antifungal, antihypertensive & pesticidal activities. The analysis clearly indicate that berberine containing medicinal plants requires further clinical evaluation to document their role in the management of Diabetes, Diseases due to dyslipidemia including heart disease and liver diseases; and Alzheimer diseases.

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