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ROLE OF MEDICINAL PLANT PASHANBHEDA IN MAINTAINING HUMAN HEALTH

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ABSTRACT

Plants have been playing a vital role in maintaining human health and contributing towards improvement of human life. They are important components of medicines, cosmetics, dyes, beverages etc. In the present time, focus on plant research has increased all over the world enormously. Plants are considered as state-of-art laboratories capable of biosynthesizing number of biomolecules of different chemical classes. There are a number of herbal agents which are successfully used for gastrointestinal, cardiovascular, metabolic disorders, diabetes etc. The ethno-botanical and ethno-pharmacological studies on such plants continue to attract investigators throughout the world. In India 75% population rely on herbal drugs for the treatment of diseases due to unavailability of modern medicines in remote areas.

The objective of present review is to provide the up-to-date information that is available on the botany, pharmacognosy, traditional uses, phytochemistry, pharmacopeal standards, pharmacology and toxicology of B. ligulata and to highlight the biological activities of bergenin (active constituent from Bergenialigulata) with its pharmacokinetics, analytical methods of estimation and to provide a basis for future research. It covers the information collected from scientific journals, books, theses and reports via a library and electronic search (Google Scholar, Web of Science and Science Direct) and literature available from 1962 to 2013, which will guide in proper identification and authentication of B. ligulataand will contribute towards further exploration of this potential clinical candidate.

Keywords: *Antioxidant, Bergeniaciliata, Phenolic content, Flavonoid content, Sikkim Himalaya.*

I. INTRODUCTION

In recent years there has been resurgence in herbal system, but due to the depletion of forests with valuable herbs and their supply has reduced drastically as compared to their demand. As a result of increase in demand there arise ample chances for adulteration with crude drug, which is altogether different from the genuine drug. As per the WHO guidelines the standardization of the plant drugs for their quality, identity, devoid of toxic compounds etc. are essential. Further it is not at all uncommon that several distinct species that may or may not be taxonomically related possessing very different therapeutic characteristics might share the same Sanskrit names. Consequently there are large numbers of plant species whose botanical identities remained unresolved and such are referred as 'controversial drugs' 1.

II. MATERIALS AND METHOD

Dissolution of stones

Bergenialigulata Wall is considered amongst the high valued, endangered temperate medicinal herbs and one of the important examples of controversial drugs. It is popularly known as 'Paashanbheda' (meaning 'to dissolve the stone') in Indian systems of medicine as the rhizomes of B. ligulata have been used for centuries in herbal formulations for dissolution of kidney and bladder stones 2.

Paashanbheda is mentioned in CharakSanhita

Though drug has been listed in the CharakSamhita, SushrutaSamhita and Ashtang- Hridaya, it remains controversial because several plants are used and sold under the name of 'Pashanabheda' in different parts of country. About nine

different plants species are known with the single name i.e. Paashanbheda in different regions (Table 1) 3, 4, 5. Hence comprehensive scientific knowledge would help in proper identification of present plant.Pashanbheda is a medicinal plant belonging to the family SAXIFRAGACEAE and the genus BERGENIA which is mostly found in temperate regions of the Himalayas from Kashmir to Bhutan.

Constitution

The major Contents of bergenialingulatacontains a phenolic compound bergenin and afzelechin, a type of flavon-3-ol. It is used as medicinal plant because of its following constituent:-

The rhizome of the plant Bergenialinulata contains- bergenin,galicacid,starch glucose,tannins,mucilage and wax C-glycoside and beta-sitosterol.Useful part:Root

Plant Profile

Bergenialigulata Wall belonging to family Saxifragaceae is popularly known as a 'stone flower/stone breaker'. It is also known as Saxifragaligulata Wall.

Kingdom	: Plantae- Plants
Subkingdom	: Tracheobionta-Vascular plants
Super divison	: Spermatophyta- Seed plants
Division	: MagnoliphytaFloweringplants
Class	: Magnoliopsida- Dicotyledons
Subclass	: Rosidae
Order	: Rosales
Family	: Saxifragaceae- Saxifrage family
Genus	: BergeniaMoench- elephant ear
Species	: Bergenialigulata (Wall.)
Synonyms	: Bergeniaciliata (Haw.) Sternb.,Megaseaciliata (Haw.), Saxifragaciliata (Haw.) Royle., Saxifragaligulata Wall., SaxifragathysanodesLindl

The phytochemical studies have shown the presence of many secondary metabolites belonging to coumarins, flavonoids, benzenoids, lactone, carbohydrate, tannins, phenols and sterols. Crude extracts and isolated compounds from B. ligulatashow a wide spectrum of pharmacological activities, such as antiurolithic, antiviral, free radical scavenging, antidiabetic, hepatoprotective, diuretic, antipyretic, antioxaluria, antitumor, antibacterial, antifungal, anti-inflammatory, anti-implantation and cardioprotective activities.

Geographical distribution

The B. ligulata is perennial herb upto 50 cm tall, succulent. It is distributed in the temperate Himalaya (from Kashmir to Nepal) from Macroscopic features The rhizomes are compact solid, barrel shaped, somewhat cylindrical, measuring 1-3 cm long and 1-2 cm in diameter. The outer surface is brown colored with small roots, ridges, furrows wrinkles and covered with root scars. It possesses aromatic odor and astringent taste.

Microscopic features

Transverse section of rhizome shows cork divided into two zones; outer and inner. Outer zone is with few layers of slightly compressed and brown colored cells whereas inner zone is multilayered consisting of thin walled, tangentially elongated and colorless cells. Cork is followed by single layered cambium and two to three layers of secondary cortex. Cortex consists of a narrow zone of parenchymatous cells containing a number of simple starch grains whereas most of cortical cells contain large rosette crystals of calcium oxalate (CaC2O4) and starch grains. Endodermis and pericycle are absent whereas vascular bundles arranged on a ring. Cambium is present as continuous ring composed of two to three layers of thin walled, tangentially elongated cells. Xylem consists of fibres, tracheids, vessels and parenchyma000-2700 m and very common in Pakistan, Central and East Asia.

Description

B. ligulata is a perennial herb with short, thick, fleshy and procumbent stems and very stout rootstock. Leaves are ovate or round and 5-15 cm long at flowering time (Flowering period March- May). In the autumn leaves turn to

bright red with short stiff hairs and attain about 30 cm lengths. Upper and lower surfaces of leaves are hairy, becoming almost hairless in age. Flowers are white, pink or purple, 3.2 cm in diameter, forming a cymose panicle with flexible flowering stem, 10-25 cm long leafless and styles (Fig. 1)11, 7,

III. DISCUSSION

It plays an important role in various diagnosis. The Research work done in this field is as follows:-

Antiurolithic effect
The study indicates the anti urolithic effect of Bergenialinguatapossibily through crystal inhibition, di-uretic and anti-oxidating effect. It works as different type like diuretic, antidiabetic, astringent, cardio tonic, wound-healer,anti pyretic, expectorant, anti inflammatory,anti protozoal due to certain phytochemical constituents:

Bergenin, tannicacid, galicacid, stigmestrol, sitosterol, catechin, (+)Afzelechin1, 8 cinecole,Isovaleric acid, (+)-(6S)-paraascorbic acid, arbutin, phytol,caryophyllene, damascenone,eudesmol,3-methyl-2-buten-1-ol,(Z)-asarone, Terpinen-4-ol, pashanlactone.

Antipyretic activity
The assessment of antipyretic activity was carried out using Brewer's Yeast induced pyrexia method in wistar rats 50. The findings revealed that the alcoholic extract of roots of B. ligulata has shown the significant antipyretic activity at the dose 500 mg/kg body weight as compared to standard paracetamol at the dose 20 mg/kg with significant fall in body temperature up to 4 h following its administration.

Analgesic activity
The analgesic activity was evaluated by using hydroalcoholic extract of rhizomes of B. ligulata, (250 mg/kg) administering intra-gastrically in the mouse by employing hot plate and tail clip methods 51. Consequently it was inferred that the extract was devoid of analgesic activity.

Antioxaluria activity
Pendseetal.have carried out an antioxaluria evaluation on Indian human adults 52. They prepared tablets each containing Didymocarpuspedicellata (65 mg), B. ligulata (16mg), Rubiacordifolia (16 mg), Cyprus artosus (16 mg) and Veronica cinerea (16 mg). Thirty two healthy volunteers and forty eight stone formers were selected for present study. All selectee were given two tablets each for three times a day and advised to avoid oxalate rich foods. The treatment continued for eight weeks. A gradual reduction in oxalate excretion was found in persons having stone in their kidney, but the level of oxalate excretion was not as low as those observed in normal human adults. From this study it was claimed that present formulation could prove a promising drug in controlling the propensity of oxaluria.

Antitumor activity
In another study, hydroalcoholic extract of B. ligulata was administered to rat intraperitoneally for the determination of antitumor activity. Test results exhibited activity against SARCOMA-WM1256 IM which showed that the hydroalcoholic extract of the B. ligulata exhibited cytotoxic activity with ED50 on cell culture at the dose of 20 mcg/ml 53.

Cardioprotective activity
The hypotensive activity of hydroalcoholic extract of B. ligulata was conducted in different animal models. Administration of 50 mg/kg dose through intravenous route in dogs resulted into positive hypotensive activity 53. On frog's heart, the extract exerted a positive chronotropic and inotropic effect. On continuous rabbit's heart perfusion, the extracts showed negative inotropic and chronotropic effect with a reduction of coronary flow. The alcoholic extract elicited marked anti-bradykinin activity (in-vivo and in-vitro) but did not modify the response of 5-HT and acetylcholine on isolated guinea pig ileum. It potentiated the action of adrenaline on guinea pig tracheal chain and ileum 54

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Hepatoprotective,diuretic and anti-pyretic action

When ethanolic extract of the plant BeregeniaLingulata was assessed for diuretic, hepato-protective and anti pyretic actionand compared with standard drugs.It showed significant action to control the diseased Albino eat

Anti microbial activity

When the rhizome was screened for its antimicrobial activity against Escherchia coli,staphylococcus aureus,streptolococcus,pneumonia and salmonella typhi using agar gel diffusion method it was found effective,scientific exploration of B. ciliata, growing in the Sikkim Himalaya, for phytochemicals and pharmacological properties is in infancy. With this view, the present study was undertaken to investigate B. ciliata leaf extracts for antioxidant, antimicrobial activity and bioactive compounds. Three solvents viz., methanol, ethyl acetate and hexane were used for extraction and the respective leaf extracts were analyzed for total phenolic and flavonoid contents along with the antioxidant and antimicrobial activities. Amongst the tested solvents, methanol was found to be the best solvent for extraction with highest total phenolic contents and the lowest IC50 values for the 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assays. Methanol extract also exhibited effective antimicrobial activity, particularly against bacteria and actinomycetes. Further, high performance liquid chromatography (HPLC) analysis revealed that methanolic extract contains the highest amount of all the three analyzed bioactive compounds viz. bergenin, catechin and gallic acid. The current study suggests that the methanol extract of B. ciliata is a potential source of natural antioxidant and antimicrobial compounds that can be used in food and drug industriesAcute toxicity study

Acute toxicity studies were carried out for alcoholic extract of B. ligulata on healthy Swiss albino mice of body weight 25- 35 g by using Up and Down or Stair case method. The maximum non lethal dose was found to 5 g/ kg-body weight 48.

Other activities

Alcoholic extract of B. ligulata has exhibited significant anti-inflammatory, analgesic, antibacterial and diuretic properties 55, 56. Paashanolactone and other constituents of the rhizomes possess anti-inflammatory properties 29. In an anti-implantation study, 100 mg/kg of the hydroalcoholic extract of B. ligulata to the pregnant hamster through gastric intubation showed negative results whereas when used in the concentration of 125 mcg/ml exhibited positive results on Entamoebahistolytica 53.

Activities of bergenin

When bergenin was incubated into hepatocyte medium for 14 hrs with 1.5mM galactosamine, it showed hepatoprotective effect at the dose of 100 μM. The hepatoprotective effects against galactosamine-intoxicated rat hepatocytes might be by inhibiting the release of glutamic pyruvic transaminase and sorbitol dehydrogenase as well as by increasing RNA synthesis 57.

Bergenin was tested with CCl4-induced cytotoxicity in primary cultured rat hepatocytes. Bergenin significantly reduced the activities of glutamic pyruvic transaminase and sorbitol dehydrogenase released from the CCl4-intoxicated hepatocytes 58, 59. The antihepatotoxicity of bergenin was also evidenced by elevating the activities of glutathione S-transferase, glutathione reductase and content of glutathione in the CCl4-intoxicated hepatocytes. Therefore it is assumed that bergenin exerted antihepatotoxicity against CCl4-induced cytotoxicity through glutathione-mediated detoxification as well as free radical suppressing activity.

Bergenin isolated from rhizomes of B. ligulata and its O-demethylated derivative norbergenin are reported to show anti-arthritic activity through possible modulation of Th1/Th2 cytokine balance 60. Flow cytometric study showed that the oral administration of these compounds at doses of 5, 10, 20, 40 and 80 mg/kg per oral dose inhibit the production of proinflammatory Th1 cytokines (IL-2, IFN-γ and TNF-α) whereas potentiate anti-inflammatory Th2 cytokines (IL-4 and IL-5) in the peripheral blood of adjuvant-induced arthritic mice. The oral LD50 for the compounds was more than 2000 mg/kg body weight of the mice.

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Estimation of Bergenin

A simple TLC method has been developed for the simultaneous quantification of bergenin, catechin and gallic acid from different parts of B. ligulata using HPTLC plate precoated with silica gel 60 F254 61. The method was developed in toluene: ethyl acetate: formic acid (4:6:1 v/v) and validated in terms of precision, repeatability, and accuracy. The linearity range for bergenin, catechin and gallic acid were found to be 160-800, 160-480 and 160-560 ng/spot respectively with correlation coefficients of 0.999, 0.999 and 0.999 respectively, which were indicative of good linear dependence of peak area on concentration. This method permits reliable quantification and showed good resolution and separation from other constituents of extract. Accuracy of the method was checked by conducting recovery studies at three different levels for all the three marker compounds and the average percentage recoveries were found to 99.29%, 98.66% and 99.23%, respectively. The rhizomes were found to contain higher concentration of bergenin, catechin and gallic acid than other parts of the plants. This reported method is simple, precise, specific, sensitive and accurate. It can be used for routine quality control of herbal material and formulations containing B. ligulata.

Bergenin and gallic acid are the most important bioactive constituents of B. ligulata. A simple and highly precise RP-HPLC method coupled with photodiode-array detection has been developed and validated for simultaneous determination of these compounds 62.

Pharmacokinetics of bergenin

The interaction between bergenin and human serum albumin (HSA) in isooctane/water microemulsions was studied by fluorescence quenching technique in combination with UV absorption spectroscopy, circular dichroism (CD) spectroscopy and dynamic light scattering (DLS) techniques 63. The binding of bergenin with HSA in microemulsions was stronger than that in buffer solution. The alterations of protein secondary structure in the microemulsions in the absence and presence of bergenin compared with the free form of HSA in buffer were qualitatively and quantitatively analyzed by the evidence from CD spectra. The results indicated that bergenin bound to HSA mainly by a hydrophobic interaction in microemulsions which was in agreement with the result of the molecular modeling study. The DLS data suggested that HSA may locate at the interface of the microemulsion and bergenin could interact with them.

A study reported the development and validation of an assay for quantitation of bergenin in human plasma using liquid chromatography/tandem mass spectrometry (LC-MS/MS) 64. Bergenin and the internal standard, 5-bromo-2, 4(1H, 3H)-pyrimidinedione (5-BrU), were separated by reversed phase HPLC and quantitated by MS/MS using electrospray ionization (ESI) and multiple reaction monitoring (MRM) in the negative ion mode. The method was linear in the range 3–1000 ng/mL with intra and inter-day precision of 3.94–5.96 and 1.62–8.31% respectively and accuracy was < 2.33%. The assay was successfully applied to a pharmacokinetic study in healthy volunteers after administration of a single 250 mg/kg oral dose.

Wang et al. have also developed a highly sensitive, simple and selective high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) method and applied to the determination of bergenin concentration in human plasma 65. Bergenin and the internal standard (IS) thiamphenicol in plasma were extracted with ethyl acetate and separated on a C18 reversed-phase column. Further subjected for elution with mobile phase of acetonitrile-water and detected in the multi-reaction monitoring mode using precursor product ions of m/z 327.1 --> 192 for bergenin and 354 --> 185.1 for the IS, respectively. The linear range of the calibration curve for bergenin was 0.25-60 ng/mL, with the lowest limit of quantification of 0.25 ng/mL and the intra/inter-day relative standard deviation (RSD) was less than 10%. It was concluded that the method is suitable for the determination of low bergeninconcentration

IV. CONCLUSION

Due to lack of scientific names in the original texts, under one name different plants are known in different parts of the country as per the description, which makes the drug controversial. Pashanabheda, Sariva, Brahmi, Vidari, Daruharidra, are some examples of controversial drugs 73.

Pashaanbheda i.e. B. ligulata is considered amongst the high valued temperate medicinal herbs. Many plants are known with the same name in different regions. Therefore proper identification and standardization should be done to achieve desired therapeutic effect as well as minimized adulteration. It is listed as a threatened or endangered and vulnerable medicinal plant using new IUCN criteria 74. Regular use of these plants may lead to rapid depletion of their population. Over exploitation of them will result in their extinction from natural habitats. Therefore strategic aspects about judicial use and conservation, preservation measures and appropriate agro-techniques are urgently needed. Establishment of protocols for in-vitro culture and micropropogation of this endangered but clinically potential candidate is the need of hour.Total lack of standardization including authentic identification of the plant species is prevalent today. The only way is to depend upon the modern scientific parameters like taxonomical, pharmacognostical and phytochemical properties. Such studies will not only provide accurate scientific details for solving the identification of controversial drugs but also help in laying down proper standardization parameters of the drug, which is the utmost need of time.

According to botanical, pharmacognostic, phytochemical and pharmacological data, the present review will be helpful in proper identification and authentication of B. ligulata and will contribute towards further exploration of this potential clinical candidate.In human plasma after therapeutic oral doses and has been first and successfully used for its pharmacokinetic studies in healthy Chinese volunteers.

Important Formulations containing Pashanbheda
Pashanbheda(Bergenialigulata) plant is used in preparation of many Ayurvedic medicines. Some of them are Ashmariharkashay for kidney stone, MutravirechanKashay, Himalaya Herbal Healthcare's Cystone to disolves kidney stone, Nephrolex and Liv 52, BaidyanathPathrina, Charak Pharmaceuticals Bombay, Calcury etc.

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