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A COMPREHENSIVE REVIEW: *BERGENIA LIGULATA* WALL - A CONTROVERSIAL CLINICAL CANDIDATE

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ABSTRACT: *Bergenia ligulata* Wall is considered amongst the high valued medicinal herbs and one of the important examples of controversial drugs which is popularly known as 'Paashanbheda' (meaning 'to dissolve the stone') in Indian systems of medicine. 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. ligulata* show 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. 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 *Bergenia ligulata*) 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 ScienceDirect) and literature available from 1962 to 2013, which will guide in proper identification and authentication of *B. ligulata* and will contribute towards further exploration of this potential clinical candidate.

INTRODUCTION: 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.

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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.

Bergenia ligulata 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.

Though drug has been listed in the *Charak Samhita*, *Sushruta Samhita* 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.

TABLE-1: PLANTS USED AS PAASHANBHEDA

Sr. No.	Botanical name	Family	Parts used	Phytochemicals
1.	<i>Aerva lanata</i> Juss.	Amaranthaceae	Roots	α -amyrin and β -sitosterol
2.	<i>Bergenia ligulata</i> Wall.	Saxifragaceae	Roots, Rhizomes	Coumarin (bergenin), gallic acid, tannic acid, minerals and wax
3.	<i>Bridelia crenulata</i> Roxb.	Euphorbiaceae	Stem, Bark	friedelin, epifriedelinol, n -octacosanol, a-amyrin, β -sitosterol, β -sitosterol-3- β -D-glucopyranoside and luteofolol
4.	<i>Bryophyllum calycinum</i> Salisb.	Crassulaceae	Leaves	Citric acid, malic acid and flavonoids
5.	<i>Coleus amboinicus</i> Lour.	Lamiaceae	Leaves	Essential oil (contains carvacrol)
6.	<i>Decalepis arayalpathra</i>	Periplocaceae	Roots	2-hydroxy, 4-methoxy benzaldehyde
7.	<i>Homonoia riporia</i> Lour.	Euphorbiaceae	Rhizomes	Isoflavonoids
8.	<i>Rotula aquatica</i> Lour.	Boraginaceae	Whole plant	Tannins
9.	<i>Didymocarpus pedicallata</i>	Gesneriaceae	Whole plant	Chalcones, polyterpenes, flavonoid, dicarboxylic acid, essential oil

Present review is an attempt towards further exploration of this 'high value' medicinal plant by highlighting the research work carried out till date in the direction of its pharmacognosy, phytochemistry, pharmacological and clinical studies.

PLANT PROFILE

Bergenia ligulata Wall belonging to family Saxifragaceae is popularly known as a 'stone flower/stone breaker'. It is also known as *Saxifraga ligulata* Wall.

Classification ⁶

Kingdom : Plantae- Plants

Subkingdom : Tracheobionta-Vascular plants
 Superdivison : Spermatophyta- Seed plants
 Division : Magnoliphyta Flowering plants
 Class : Magnoliopsida- Dicotyledons
 Subclass : Rosidae
 Order : Rosales
 Family : Saxifragaceae- Saxifrage family
 Genus : *Bergenia* Moench- elephant ear
 Species : *Bergenia ligulata* (Wall.)

Synonyms: *Bergenia ciliata* (Haw.) Sternb., *Megasea ciliata* (Haw.), *Saxifraga ciliata* (Haw.)

Royle., *Saxifraga ligulata* Wall., *Saxifraga thysanodes* Lindl.^{5,6}.

Vernacular names⁷

Assamese	: Patharkuchi
Bengali	: Himasagara, Patharchuri, Patrankur
Gujarati	: Pakhanbheda, Pashanbheda
Hindi	: Dakachru, Pakhanabhed, PakhanabhedaPatharcua, Silparo, Silpbheda
Kannada	: Alepgaya, Hittaga, Hittulaka, Pahanbhedi, Pasanberu
Kashmiri	: Pashanbhed
Malayalam	: Kallurvanchi, Kallurvanni, Kallorvanchi
Marathi	: Pashanbheda
Mizoram	: Khamdamdawi, Pandamdawi
Oriya	: Pasanbhedi, Pashanabheda
Punjabi	: Batpia, Dharposh, Kachalu, Pashanbhed
Sanskrit	: Ashmabheda, Nagbhita, Pashaanbheda, Silabheda
Tamil	: Sirupilai
Telugu	: Kondapindi, Telanurupindi
Urdu	: Kachalu, Pakhanabheda

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 2000-2700 m and very common in Pakistan, Central and East Asia^{9,10}.

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)^{11,7,12}.



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^{13,14}.

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 (CaC_2O_4) 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 parenchyma. Centre is occupied by large pith composed of circular to oval parenchymatous cells containing starch grains with CaC_2O_4 crystals similar to those found in cortical region. Vessels with simple pits have perforation plates on one end or at both ends and tracheids have helical thickenings^{11,13,14,15}.

TRADITIONAL USES AND ETHNOMEDICAL CLAIMS:

The plant *B. ligulata* is employed in several Indian languages with local variations and indicates that the plants grow between rocks appearing to break them or that they possess lithotriptic property. The ethno-botanical and ethno-medicinal literature states that in *Ayurveda* and *Unani* medicines, the roots of *B. ligulata* possess cooling, laxative, analgesic, abortifacient, aphrodisiac properties and used in treatment of vesicular calculi, urinary discharges, excessive uterine haemorrhage, diseases of the bladder, dysentery, menorrhagia, splenic enlargement and heart diseases⁷. It is also considered absorbent and given in dysentery. In Sind (Pakistan), the root is rubbed down and given with honey to children when teething. In Indo-China the leaves are ground in a mortar and the juice is used for earaches¹⁶.

Hot water extract of whole dried plant of *B. ligulata* has been employed orally for renal or urinary calculi¹⁷. In Nepal, about 10 g of rhizome paste or juice of *B. ligulata* has been taken orally by human adults with the molasses, twice a day for 3-4 days as an anthelmintic for the expulsion of roundworms and also for the treatment of cold^{18, 19}. In India dried roots of *B. ligulata* have been used externally for cuts, boils, wounds and burns; its oral infusion for the treatment of dysentery while its rootstock has also been used as masticator by

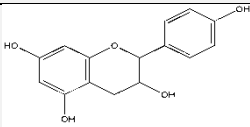
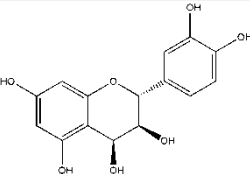
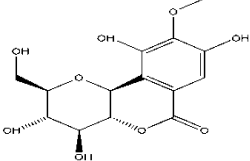
human adults²⁰. Decoction of fresh roots of *B. ligulata* is taken orally by human adults to treat urinary disorders, stomach disorders and urogenital complaints^{21, 22}. It is further mentioned that its hot water extract has been applied externally for boils and also used topically for the treatment of ophthalmia^{8, 23}.

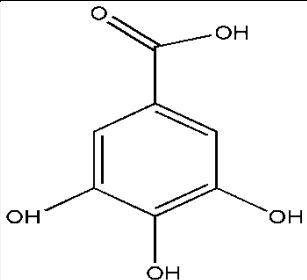
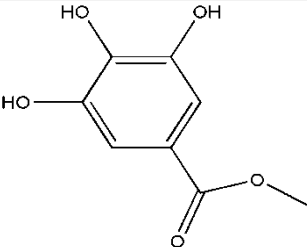
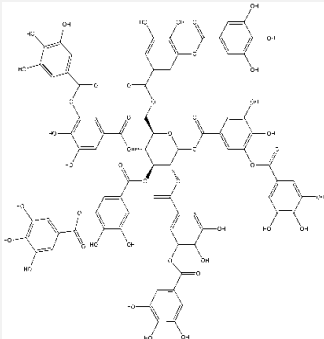
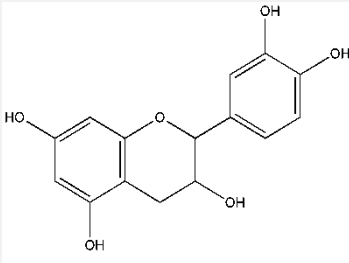
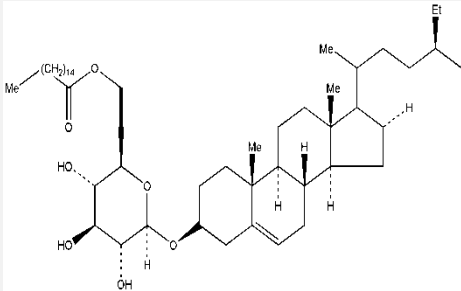
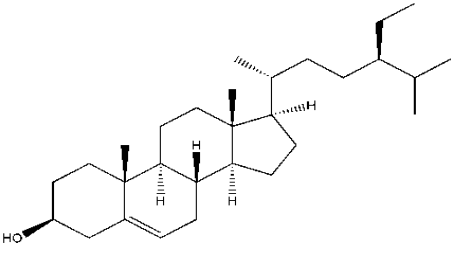
PHYTOCHEMISTRY:

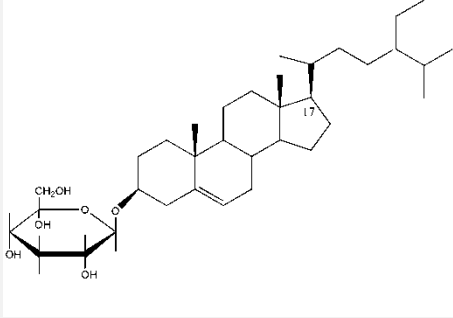
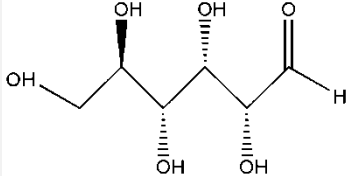
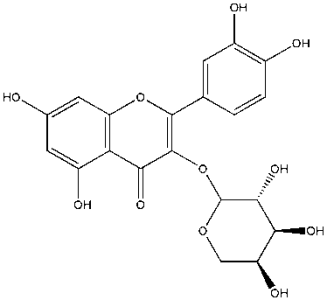
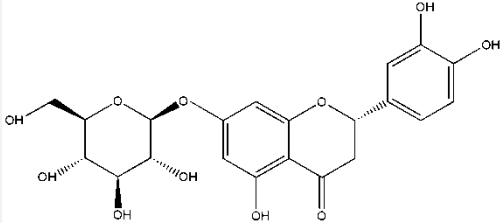
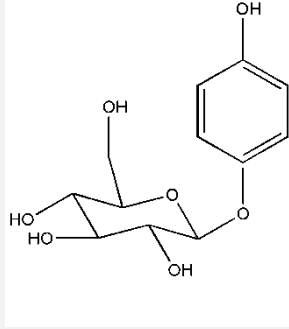
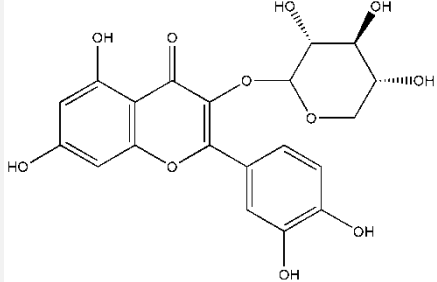
It consists of major phenolic compound 'bergenin' (nearly 0.9 %) and other phenolic compounds in minor amount^{24, 25, 26, 27, 28}. Phenolic compounds includes (+)- afzelechin, [29] leucocyanidin, gallic acid, tannic acid, methyl gallate³⁰, (+)-catechin, (+)-catechin -7-O-β-D-glucopyranoside, 11-O-galloyl bergenin²⁸; a lactone- Paashaanolactone³¹. It also contains sterols viz., sitoindoside I, β-sitosterol and β-sitosterol-D-glucoside, glucose (5.6 %), tannin (14.2-16.3 %), mucilage and wax²⁸.

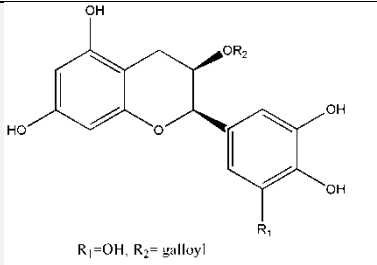
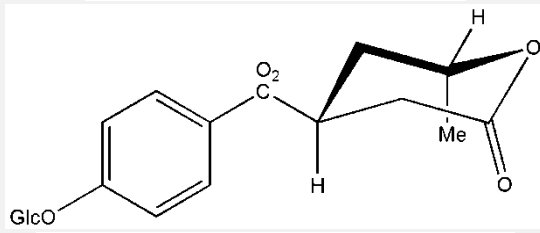
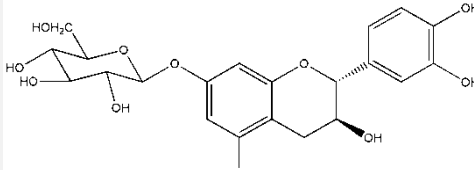
Rhizomes of *B. ligulata* showed a presence of different chemical entities like; **Coumarins:** bergenin, 11-O-galloyl bergenin, 11-O-P-hydroxy-benzoyl bergenin; 11-O-brotocatechuoyl bergenin, 4-O-galloyl bergenin; **Flavonoids:** (+) afzelechin, avicularin, catechin, eriodictyol-7-O-β-D-glucopyranoside, reynoutrin; **Benzenoids:** arbutin, 6-O-P-hydroxy-benzoyl arbutin, 6-O-protocatechuoyl arbutin; 4-hydroxy benzoic acid; **Lactone:** Idehexan-5-olide, 3-(6'-O-P-hydroxy)^{31, 32} (Table 2).

TABLE-2: SECONDARY METABOLITES FROM *B. LIGULATA*

Compound name (Molecular Formula)	Chemical Structure	Plant part	Reference No.
Afzelechin (C ₁₅ H ₁₄ O ₅)		Rhizome	29
Leucocyanidin (C ₁₅ H ₁₄ O ₇)		Rhizome	30
Bergenin (C ₁₄ H ₁₆ O ₉)		Root, Rhizome	27

Gallic acid ($C_7H_6O_5$)		Rhizome	30
Methyl gallate ($C_8H_8O_5$)		Rhizome	30
Tannic acid ($C_{76}H_{52}O_{46}$)		Rhizome	30
Catechin ($C_{15}H_{14}O_6$)		Rhizome	28
Sitoinoside I ($C_{51}H_{90}O_7$)		Rhizome	25, 26
β -Sitosterol ($C_{29}H_{50}O$)		Root	26, 28

β -Sitosterol-D-Glucoside ($C_{35}H_{60}O_6$)	 <p>The structure shows a steroid nucleus with a glucose molecule attached to the C-3 position via a beta-glycosidic bond. The steroid has a hydroxyl group at C-3, a double bond at C-5, and a side chain at C-17.</p>	Root	26, 28
Glucose ($C_6H_{12}O_6$)	 <p>The structure shows the open-chain form of D-glucose, a six-carbon aldehyde with hydroxyl groups on carbons 2, 3, 4, and 5.</p>	Rhizome	28
Avicularin ($C_{20}H_{18}O_{11}$)	 <p>The structure shows a flavonoid core with a glucose molecule attached to the C-7 position via a glycosidic bond. The flavonoid has hydroxyl groups at C-5, C-7, and C-8.</p>	Rhizome	32
Eriodictyol-7- β -D-glucopyranoside ($C_{21}H_{22}O_{11}$)	 <p>The structure shows a flavonoid core with a glucose molecule attached to the C-7 position via a beta-glycosidic bond. The flavonoid has hydroxyl groups at C-5, C-7, and C-8.</p>	Rhizome	32
Arbutin ($C_{12}H_{16}O_7$)	 <p>The structure shows a glucose molecule attached to a hydroquinone ring at the C-4 position via a glycosidic bond.</p>	Rhizome	32
Reynoutrin ($C_{20}H_{18}O_{11}$)	 <p>The structure shows a flavonoid core with a glucose molecule attached to the C-7 position via a glycosidic bond. The flavonoid has hydroxyl groups at C-5, C-7, and C-8.</p>	Rhizome	31, 32

11-O-galloyl bergenin (C ₂₁ H ₂₀ O ₁₃)		Rhizome	28
Pashaanolactone (C ₁₉ H ₂₄ O ₁₀)		Rhizome	31
Catechin-7-O-β-D-glucopyranoside (C ₂₁ H ₂₄ O ₁₁)		Rhizome	28

BIOLOGICAL ACTIVITIES:

Antiuro lithic activity

The traditional use of *B. ligulata* for kidney disorders is also supported by the experimental studies^{33, 34, 35}. The methanolic extract of rhizomes of *B. ligulata* and the isolated constituents like bergenin were compared for urolithiatic activity in albino rats.

B. ligulata rhizomes inhibited CaC₂O₄ crystal formation as well as crystal aggregation and exhibited antioxidant effect against 1, 1-diphenyl-2-picrylhydrazyl free radical and lipid peroxidation in *in-vitro* conditions. In a modified animal model (male wistar rats) of urolithiasis which developed by addition of 0.75% ethylene glycol in drinking water, methanolic extract (5–10 mg/kg) of *B. ligulata* rhizomes prevented CaC₂O₄ crystal deposition in the renal tubules. Polyuria, weight loss, impairment of renal function and oxidative stress, due to the lithogenic treatment were also prevented by *B. ligulata* extract. Unlike the untreated animals, ethylene glycol intake did not cause excessive hyperoxaluria and hypocalciuria in *B. ligulata* treated groups and there was a significant increase in the urinary Mg²⁺. These data indicated the antiuro lithic activity of *B. ligulata* mediated possibly through CaC₂O₄ crystal

inhibition, diuretic, hypermagneseuric and antioxidant effects which rationalizes its medicinal use in urolithiasis.^[36] Methanolic extract of *B. ligulata* and bergenin exhibited marked dissolution of urinary calculi both in kidney and urine constituents³⁷.

In-vitro antilithiatic / anticalcification activities of various extracts of *B. ligulata* and *Dolichos biflorus* individually and in combination were tested by the homogeneous precipitation method. The extracts were compared with an aqueous extract of 'Cystone' (Formulation of Himalaya Company, India) for their activities. Extracts of *D. biflorus* showed activity almost equivalent to 'Cystone' while *B. ligulata* showed less activity and the combination was not as active as the individual extracts. After this study, it was concluded that the active constituent/s seem to be non-protein, non-tannin molecule/s which may act through inhibition of calcium and phosphate accumulation³⁸. Low doses of *B. ligulata* extract (0.5 mg/kg of alcoholic extract) promote diuresis in rats, but higher doses of 100 mg/kg reduce the urine output and the diuresis produced by urea³⁹.

In comparative study, the aqueous extracts of *B. ligulata* produced maximum inhibition of the growth of Calcium oxalate monohydrate (COM)

crystals than *Tribulus terrestris*⁴⁰. From this study it was hypothesized that the biomacromolecules from *B. ligulata* seem to play an important role in the inhibition of COM crystals.

Antiviral activity

In ethno-pharmacological screenings, plants used in Nepalese traditional medicine along with *B. ligulata* were evaluated for antiviral activity^{41, 42}. Methanolic and hydromethanolic extracts were assayed by *in-vitro* viral systems viz. influenza virus/MDCK cells and herpes simplex virus/vero cells and showed the highest antiinfluenza-viral activity with ID₅₀ at 10 µg/ml^{43, 44}.

Free radical scavenging activity

Methanolic extract of *B. ligulata* exhibited free radical scavenging activity with IC₅₀ value of 50 µg/ml by DPPH assay⁴⁵. It was further fractionated between n-butanol and water. The fractions obtained were screened for *in-vitro* free radical scavenging activity using DPPH radical scavenging assay and nitric oxide scavenging assay⁴⁶. IC₅₀ value of n-butanol fraction was found to be 4.5 µg/ml whereas aqueous fraction showed an IC₅₀ value of 30 µg/ml.

Antidiabetic activity

The alcoholic extract (250 mg/kg body weight) of roots of *B. ligulata* exhibited hypoglycemic activity^{47, 48}. It reduced the elevated blood sugar in diabetic rats. It was concluded that the antidiabetic effect may be due to the stimulation of cells of pancreatic islets or mediated through stimulation of insulin release resembling the oral hypoglycemic sulphonylureas. The (+)- afzelechin isolated from rhizomes of *B. ligulata* was found to be an inhibitory compound of alpha-glucosidase activity with ID₅₀ value 0.13mM⁴⁹. These studies revealed antidiabetic potential of *B. ligulata* and could be helpful to develop medicinal preparations or nutraceutical and functional foods for diabetes and related symptoms.

Hepatoprotective activity

The assessment of hepatoprotective activity was carried out on male albino rats of wistar strain⁵⁰. The 'Liv 52' syrup was used as standard manufactured by Himalaya Drug Company,

Bangalore and carbon tetrachloride (CCl₄) was used to induce hepatotoxicity. Animals treated with alcoholic extract (500 mg/kg body weight) of roots of *B. ligulata* showed significant decrease in the levels of Serum glutamic oxaloacetic transaminase (SGOT), Serum glutamic pyruvic transaminase (SGPT), Alkaline phosphatase (ALP) and total bilirubin as compared to control and confirmed the hepatoprotective action of the same. However, hepatoprotective mechanism is still unclear.

Diuretic activity

Diuretic activity of *B. ligulata* was assessed by the method described by Lipschitz, using Furosemide tablet (Aventis Pharma Limited, GIDC estate Ankleshwar) as standard⁵⁰. Alcoholic extract (500 mg/kg body weight) of roots of *B. ligulata* was found to be effective in increasing urinary electrolyte concentration of Na⁺, K⁺ and Cl⁻ which indicates its significant diuretic activity. It was concluded that the active principles like flavonoids and saponins present in alcoholic extract of roots of *B. ligulata* might be responsible for diuretic activity.

Antipyretic activity

The assessment of antipyretic activity was carried out using Brewer's Yeast induced pyrexia method in wistar rats⁵⁰. 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 methods⁵¹. Consequently it was inferred that the extract was devoid of analgesic activity.

Antioxaluria activity

Pendse et al. have carried out an antioxaluria evaluation on Indian human adults⁵². They prepared tablets each containing *Didymocarpus pedicellata* (65 mg), *B. ligulata* (16mg), *Rubia*

cordifolia (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/ml⁵³.

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 activity⁵³. 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, 39}.

Acute 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 weight⁴⁸.

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 properties²⁹.

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 *Entamoeba histolytica*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 synthesis⁵⁷.

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 balance⁶⁰. 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.

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 F₂₅₄⁶¹. 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 compounds⁶².

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) techniques⁶³. 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(1*H*, 3*H*)-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 plasma⁶⁵. 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 bergenin concentration in human plasma after therapeutic oral doses and has been first and successfully used for its pharmacokinetic studies in healthy Chinese volunteers.

Limits for quality parameters

Quality parameters for *B. ligulata* are mentioned in Indian Herbal Pharmacopoeia¹¹;

Foreign matter	: Not More Than 2.0%
Total ash	: Not More Than 17.0%
Acid insoluble ash	: Not More Than 2.0%
Alcohol soluble extractive	: Not Less Than 10.0%
Water soluble extractive	: Not Less Than 20.0%

Patents

Mitra has filed a patent of a novel herbal composition for maintaining or caring the skin around the eyes comprising extracts of *B. ligulata*, *Cipadessa baccifera*, *Embllica officinalis* and cosmeceutically acceptable excipients. Lee and Martin have also filed patents of cosmetic composition comprising *B. ligulata* as an active ingredient for artificial tanning of human skin and remedying skin wrinkles^{66, 67, 68}.

Agarwal and Kumar have patented an improved process for isolation of bergenin from *Bergenia* species⁶⁹.

Dosage Forms and Safety Profile

B. ligulata is an established ingredient of many formulations used for kidney ailments e.g. Cystone and Nephrolex (Himalaya Herbal Healthcare, Bangalore). The acetone extract of the rhizomes is reported to be cardiotoxic in higher doses and has depressant action on the central nervous system⁷⁰.

Cardiotoxic, antidiuretic and CNS depressant action of *B. ligulata* on experimental models has been reported with large doses. It is unlikely that these effects will be encountered with the doses in clinical use. In rats, the LD₅₀ of the aqueous extract was 650 mg/kg intraperitoneally³⁹.

Dosage:

Powered rhizomes	: 1-3 gm b.i.d. ^{71, 39}
For decoction	: 20-30 gm rhizomes ⁷²

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 drugs⁷³.

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 criteria⁷⁴. 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 micropropagation 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.

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