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BERGENIA LIGULATA WALL: ITS CHEMICAL CHARACTERIZATION AND PHARMACOLOGICAL POTENTIAL – A REVIEW

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ABSTRACT
Bergenia ligulata Wall also known as Paashanbheda (which means 'to dissolve stones') is a very important medicinal herb and is considered as an example of controversial drug in the Indian System of Medicine. On phytochemical screening, it shows presence of various chemical constituents or secondary metabolites like, coumarins, flavonoids, benzenoids, lactones, etc. It shows a wide range of pharmacological activities with the main ones being, antiurolithic, antiviral, free radical scavenging, antidiabetic, hepatoprotective, diuretic, anti-inflammatory, cardioprotective and antipyretic. This review provides a detailed description of and throws insight on the pharmacognosy, phytochemistry, phytochemical standards, characterization of phytoconstituents, pharmacological activities and marketed formulations that are available in the market of *Bergenia ligulata*. It contains information collected from scientific journals, books and reports by visiting a library and electronic search (Science Direct, Google Scholar, etc.). This review will be helpful in the further investigation of *Bergenia ligulata*.

INTRODUCTION
*Bergenia ligulata*Wall is considered among the high valued, endangered temperate medicinal herbs and one of the principal examples of controversial drugs. It is popularly known as 'Paashanbheda' (which means 'to dissolve stones') in Indian systems of medicine as the rhizomes of *B. ligulata* have been used for centuries in herbal formulations for the dissolution of kidney and bladder stones.[1]

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 in length. The 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.[1,2]

Bergenia species possess several biological activities such as diuretic, antidiabetic, antitussive, insecticidal, anti-inflammatory, antipyretic, anti-bradykinin, antiviral, antibacterial, antimalarial, hepatoprotective, antiulcer, anticancer, antioxidant, antiobesity, and adaptogenic.[3]

The rhizomes, especially of *Bergenia ligulata* are used as main ingredients in various Ayurvedic and Unani formulations for the treatment of urolithiasis, haemorrhoids, stomach disorders, ophthalmia, heart diseases, chronic venereal diseases, boils and blisters, leucorrhoea, arthritis, epilepsy and pulmonary infections.[4]

It consists about 30 genera and 580 species worldwide. It is found in Afghanistan, South Tibet and Bhutan. It is found throughout temperate Himalayas from Kashmir to Bhutan at an altitude of 900-3000m.[5]

B. ligulata shows the presence of different chemical entities like; Coumarins: bergenin, 11-O-galloyl bergenin, 11-O-P-hydroxybenzoyl bergenin; 11-O-brotocatechuoyl bergenin, 4-0-galloyl bergenin; Flavonoids: (+) afzelechin, avicularin, catechin, eriodictyol-7-O-β-Dglucopyranoside, reynoutrin; Benzenoids: arbutin, 6-O-P-hydroxy-benzoyl arbutin, 6-O-protocatechuoyl arbutin; 4-hydroxy benzoic acid; Lactone: Idehcxan-5-olide, 3-(6'-O-P-hydroxy)[1]

Fig. 1: *Bergenia ligulata* Wall (Paashanbheda).

PLANT DETAILS

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

COMMAN NAMES: *Bergenia ciliate (Haw.) Sternb., Megasea ciliate, Saxifraga ciliate.*

VERNACULAR NAMES ACROSS THE WORLD[6]

Sanskrit- Amabhedaka,
English- Hairy bergenia, Stone breaker
Gujrati- Pashanbheda, Pakhanbheda
Hindi- Pakhanabheda, Silphara, Pakhanabhed, Silpbheda, Sadpottar, Dhoklumbo, Patharchat, Pandamdawi, Laoo-patra
Kannada- Alepgaya, Pahanbhedi, Hittaga, Pasanaberu, Hittulaka Khasi La Khowang
Kashmiri- Pashanbhed, Batweyaa
Marathi- Pashanbheda

TAXONOMICAL CLASSIFICATION[1]

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.)

CHEMICAL CONSTITUENTS

Chemical constituents present in the plant parts of *Bergenia ligulata* are as mentioned below.

ROOTS AND RHIZOME

It Contain 4(4′-β-D-glucopyranosyloxy-1′-benzoyloxy)-6-methyltetrahydropyran-2-one named as paashaanolactone[7], bergenin, phenolic compounds leucocyanidin, gallic acid, methyl gallate, catechin and polymeric tannin.[8]

Quercetin 3-oβ-D xylopyranoside – $C_{20}H_{18}O_{11}$ Flavonoid, Quercetin 3-oα-L arbinofuranoxide.[6]

SEED

It containcoumarin (bergenin), tannic acid, gallic acid, minerals and wax.[9]

AERIAL PARTS

Bergenin, p-hydroxybenzoylbergenin, 11-O-galloylbergenin and methyl gallate Present in aerial Parts.[10]

PHYSICOCHEMICAL PARAMETERS FOR *BERGENIA LIGULATA* AS MENTIONED IN INDIAN HERBAL PHARMACOPOEIA[11]

Table 1: Physicochemical Parameters for Bergenia ligulataAs Mentioned in Indian Herbal Pharmacopoeia.

Physicochemical parameter% w/w	Accepted values
Foreign matter	Not More Than 2.0%
Total ash	Not More Than 17.0%
Acid insoluble ash	Not More Than 2.0%
Water soluble extractives	Not Less Than 20.0%
Alcohol soluble extractives	Not Less Than 10.0%

QUANTITATIVE TESTS

Table 2: Quantitative tests.

Quantitative test	Result
% of Tannin	9.86
Total phenol content %	4.03

PHYTOCHEMICAL SCREENING OF DIFFERENT ROOT EXTRACTS OF *BERGENIA LIGULATA*[12]

Table 3: Phytochemical Screening of Different Root Extracts of *Bergenia ligulata.*

Sr No.	Extract	Phyto-constituents Present
1	Petroleum Ether	Fats, Steroids, Terpenoids
2	Diethyl Ether	Steroids
3	Chloroform	Alkaloids, Tannins, Glycosides

4	Acetone	Flavonoids, Tannins, Glycosides, Saponins
5	Ethanol	Alkaloids, Glycosides, Flavonoids, Carbohydrates

CHARACTERIZATION OF CHEMICAL CONSTITUENTS

Table 4: Characterization of Chemical Constituents.

Chemical constituent	Method	Specifications	Result	References
Bergenin	TLC densitometric method using silica gel HPTLC	Methanolic extract of bergenin was used. Solvent system for HPTLC toluene:ethylacetate:formic acid (4:6:1)	R_f = 0.29	[13]
	Reverse phase HPLC	reverse-phase column with water:acetonitrile as the mobile phase.	Capacity factor (k') = 2.3 R_t = 10.1 min	[9]
Catechin	TLC densitometric method using silica gel HPTLC	Methanolic extract of Catechin was used. Solvent system for HPTLC toluene:ethylacetate:formic acid (4:6:1)	R_f = 0.54	[13]
Gallic acid	TLC densitometric method using silica gel HPTLC	Methanolic extract of Gallic acid was used. Solvent system for HPTLC toluene:ethylacetate:formic acid (4:6:1)	R_f = 0.60	[13]
Alfzelechin	Reverse phase HPLC	reverse-phase column with water:acetonitrile as the mobile phase.	Capacity factor (k') = 3.9 R_t = 14.8 min	[9]

MARKETED FORMULATIONS

Table 5: Marketed Formulations.

PLANT NAME	TYPE OF THE FORMULATION	MANUFACTURE COMPANY	MARKETED NAME
Pashanbheda(*Bergenia ligulata*)	Liquid/syrup	Shree Balaji Ayurveda	Ashmariharakashaya
Saxifraga ligulata	Tablets	Himalaya	UriCare
Pashanabheda	Churna	Charak Samhita Sutrasthana	Mutravirechaniya Kashayam
Pashanbhed *Bergenia ligulata*	Tablet 200 mg	Sanify Ayurveda	Albestone Capsules

PHARMACOLOGICAL ACTIVITIES

Antiurolithic activity

The **methanolic extract of rhizomesof *B. ligulata*** and the isolated constituents like bergenin were compared for urolithiatic activity in albino rats. *B. ligulata* rhizomes inhibited CaC_2O_4 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 CaC_2O_4 crystal deposition in their renal tubules. Polyuria, weight loss, impairment of renal function and oxidative stress, caused 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 Mg^{2+}. These data indicated the antiurolithic activity of *B. ligulata* mediated possibly through CaC_2O_4 crystal inhibition, diuretic, hypermagneseuric and antioxidant effects which justifies its medicinal use in urolithiasis. Methanolic extract of *B. ligulata* and bergenin exhibited marked dissolution of urinary calculi both in kidney and urine constituents.

In comparative study, the aqueous extracts of *B. ligulata* produced maximum inhibition of the growth of Calcium oxalate monohydrate (COM) crystals than *Tribulus terrestris.* From this study it was hypothesized that the biomacromolecules from *B. ligulata* played an important role in the inhibition of COM crystals.[1]

Antiviral activity

Hydro-methanolic extract from rhizomes of *B. ligulata* inhibited the replication of influenza virus *in vitro* in a dose dependent manner and did not show virucidal activity at effective concentration. Pretreatment of cells with *B. ligulata* extract was shown to be most effective to prevent cell destruction. The extract inhibited viral

RNA synthesis and reduced viral peptide synthesis at 10 mg/ml. The inhibitory effect on the virus is related to the presence of condensed tannins in the extract.[14]

Free radical scavenging activity

Methanolic extract of *B. ligulata* exhibited free radical scavenging activity with IC_{50} value of 50 µg/ml by DPPH assay. 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 assay. IC_{50} value of n-butanol fraction was found to be 4.5 µg/ml whereas aqueous fraction showed an IC_{50} value of 30 µg/ml.[15]

Antidiabetic activity

The alcoholic extract (250 mg/kg body weight) of the roots of *B. ligulata* exhibited hypoglycemic activity.[16]It decreased 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 also found to be an inhibitory compound of alpha-glucosidase activity with ID_{50} value 0.13mM . The studies revealed antidiabetic activity of *B. ligulata* and could be helpful to develop medicinal preparations or nutraceutical and functional foods for diabetes and related symptoms.[17]

Hepatoprotective activity

Ethanolic extract of the root of *Bergenia ligulata* were assessed for its hepatoprotective activity in albino rats that was compared with standard drugs. Acute toxicity studies were carried out for ethanolic extract of *B. ligulata* root on healthy Swiss albino mice of body weight 25- 35g by using Up and Down or the Stair-case method. Assessment of the hepatoprotective activity was done by measuring the levels of serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transminase (SGOT), serum alkaline phosphatase and total bilirubin levels. The ethanolic extract of the roots of *Bergenia ligulata* was found to produce significant activity.[18]

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 standard. **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 substantial diuretic activity. It was therefore concluded that the active principles like flavonoids and saponins present in alcoholic extract of roots of *B. ligulata* might be responsible for diuretic activity.[19]

Anti-inflammatory activity

Paashanolactone, a key component isolated from *Bergenia ligulata* rhizomes, has been shown to possess anti-inflammatory properties.[18]

Expression analysis for oxidative stress and inflammatory biomarkers in NRK-52E cells revealed up-regulation of Mitogen activated protein kinase (MAPK), Osteopontin (OPN) and Nuclear factor- κB (NF-κB), in response to calcium oxalate insult; which was drastically reduced in the presence of *B. ligulata* extract.[20]

Polyphenol-rich fraction of *Bergenia ligulata* (PFBL), is also used for its anti-inflammatory and antineoplastic properties.[21]

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 dog models resulted into positive hypotensive activity.

On frog's heart, the extract induced a positive chronotropic and inotropic effect.

On continuous heart perfusion in rabbits, 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 it did not modify the response of 5-HT and acetylcholine on isolated guinea pig ileum.[1]

Antipyretic activity

The evaluation of antipyretic activity was carried out using Brewer's Yeast induced pyrexia method in wistar rats. The outcomes revealed that the **alcoholic extract of roots of *B. ligulata*** shows 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.[19]

Other activities

Phenolic and flavonoid contents in **leaf extracts of *Bergenia ligulata*** have been examined for their contribution in **antimicrobial and antioxidant activities**.[22]

11-O-galloylbergenin was found to be very active in *invitro* antioxidant assay as compared to bergenin, which was found to be almost inactive. in the total antioxidant phosphomolybdate assay, 11-O-galloylbergenin was found more potent as compared to α-tocopherol.[23]

CONSTITUENTS RESPONSIBLE FOR PHARMACOLOGICAL ACTIVITY

Table 6: Constituents Responsible for Phrmacological Activity.

Constituents	Pharmacological Activity	References
1. Bergenin	antihepatotoxic, antiulcerogenic, anti-HIV, antifungal, hepatoprotective, antiarrhythmic, neuroprotective, antiinflammatory, immunomodulatory and burn wound healing activity.	[24]
2. Gallic Acid	antioxidant, anticancer, antimicrobial, gastrointestinal-, cardiovascular-, metabolic -, neuropsychological-, and miscellaneous- diseases. anti-inflammatory, and antineoplastic activity.	[25]
3. Quercetin	antioxidant mechanism and the broad-spectrum antibacterial and antiparasite activity. antioncology and cardiovascular protection and anti-immunosuppression treatment. antioxidant, antiviral, anticancer, antimicrobial, anti-inflammatory activity.	[26]

CONCLUSION

From this review it is quite evident that *Bergenia ligulata* Wall is an important herb of medicinal value. It consists of a large amount of chemical constituents that that possess essential pharmacological activites. Majorly its roots and rhizomes are used in traditional medicine. This review summarizes the pharmacognosy, phytochemistry, chemical characterization and pharmacological activities of *Bergenia ligulata*. This review will be helpful in further developmental work and investigation to bring the potential medicinal candidate, *Bergenia ligulata* into mainstream medicine.

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CONFLICT OF INTEREST

There are no conflicts of interest.

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