Review Article

POLYPHARMACOLOGICAL ACTIVITIES OF *BERGENIA* SPECIES

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ABSTRACT

Bergenia species are evergreen herb belonging to the family *saxifragaceae*. The rhizomes of these plants are used in the indigenous system of medicines. There are three species of Bergenia, namely *B. ligulata, B. ciliata and B. stracheyi.* The rhizome and other parts of *B. ligulata* is used in urinary bladder stone, antilithic activity diuretic activity, anti-bradykinin activity, antiviral activity, antipyretic activity, antibacterial, anti inflammatory, hepatoprotective activity, insecticidal activity, α-glucosidase activity and all these activities of the plant is due to presence of its constituents like; β-Sitosterol, Tannic acid, Stigmesterol, Gallic acid, Bergenin, (+)- Afzelechin, (+)-afzelechin, (+)-afzelechin tetraccetate, (+)-5,7,4'-trimethoxyafzelechin, (+)-tetramethoxyazelechin, (+)-3-acetyl-5,7,4'-trimethoxyafzelechin. The second species is *B ciliata,* have antitussive, antiulcer, antioxidant, antibacterial, hypoglycemic, toxicological activity. The plant contains Tannic acid, Gallic acid, Glucose, Metarbin, Albumen, Bergenin, (+)-Catechin, Gallicin and Gallic acid *B. stracheyi* is third species shows DPPH radical scavenging activity, antimicrobial and xanthine oxidase inhibitory activities. It also used in arthritis. The main chemical constituent of the species is Bergenin.

Keywords: *Bergenia* species, *B. ligulata, B ciliata, B. stracheyi, Pharmacological activity.*

INTRODUCTION

Nature is an extremely rich source of highly diverse and innovative chemical structures.[1] The relationship existing between plants and humans is as old as mankind, dating back to the origin of human civilization.[2] Humans have relied on plants for food, clothing, shelter, fuel and medicine.[3] Therapeutic plant use can be a herbal tea, a crude extract, a phytopharmaceutical or herbal mixture or isolated compounds.[2,4] Harbalism is a traditional medicinal or folk practice based on the use of plants and plant extracts.[5] The World Health Organization has recently defined traditional medicine (including herbal drugs) as comprising therapeutic practices that have been existence, often for hundreds of years, before the development and spread of modern medicine and still use in today.[6] Herbal drug constitute only those traditional medicines which primarily use medicinal plant preparation for therapy. The earliest recorded evidence of their use in Indian, Chinese, Egyptian, Greek, Roman and Syrian text dates back to about 5000 years. The classical Indian texts dates include Rigveda, Atherveda, Charak Samhita and Sushruta Samhita. The herbal medicines/traditional medicaments have, therefore, been derived from rich traditions of ancient civilization and scientific hertage.[7]

Saxifragaceae is a family of herbs or shrubs, rarely trees or vines. The family includes about 80 genera and 1250 species worldwide. Most members of the saxifragaceae family are herbs, and usually have a flower cluster held well above the basal whorl of leaves. Many of its members grow in rocky places. The fruit is a capsule with a lot of seeds. In term of economically importance, the family has *Saxifrage, Heuchera*, and *Bergenia.*[8]

Genus *Bergenia* is a small group of hardy perennials growing wild plant found from Afghanistan to southeast Tibet and the Himalayas. These plant form clumps of large, evergreen leaves, which have leathery texture, and clusters of small flowers. The flower colors range from the palest pink to ruby red or dark purple. They grow from 1 to 2 feet high and spread 20 to 24 inches. They are good cover plant. Plant can tolerate full sun, but grow best in a sit that receives afternoon shade and has a moisture retentive soil.[9] There are three species of *Bergenia* found in India. *Bergenia ligulata, Bergenia ciliata, Bergenia stracheyi, Bergenia ligulata*s are evergreen herb belonging to the family *saxifragaceae*. The rhizomes of these plants are used in the indigenous system of medicines.[10]

Bergenia ligulata syn. Saxifraga ligulata is being widely accepted under this name. the use of various names attributed to it, viz., *Pashanbheda*[11], *Pashana, Zakhmehayat*[12], *Asmaribheda*, *Ashmabhid*, *Ashmabhed*, *Nagabhid*, *Upalbhedak*, *Parwatbhed* and *Shilabhed* (dissolving or piercing stones or slabs) etc.[13] It belongs to family saxifragaceae. Its medicinally used part is rhizome. The plant *Bergenia ligulata* is chief botanical source of pashanbheda drug used in indigenous system of medicine and incorporated in medical texts and material media.[14]

It is a perennial, climbing plant that grows well in moist and shady areas, especially in the foothills of the Himalayas and the Khasi hills Assam. The stems show thick, ovate and bright red leaves seasonally. The flowers are white, pink or purple.[12]

Figure 1: *Bergenia ligulata* whole plant

An attempt has been made during the last decade to study the identity, chemistry, pharmacology and clinical investigations of Pashanbheda plants.[15] The whole plant, rhizome and root of *Bergenia ligulata* is used for kidney and bladder stones,[16-23] urinary problems.[24] Rhizome is the official part, is light, cool, bitter, used in cough and cold[25] flowers are boiled and pickled.[17] With honey *Bergenia ligulata* is applied to gums in teething of children to allay irritation.[17] *Bergenia ligulata* has been reported to exhibit various biological activities and thus has several traditional uses. It is used as an antidiabetic (alpha-glucosidase inhibitor),[26] antipyretic,[27,17,28] and as a tonic.[19,29,30] Ethanobotanical study of upper siran velly in Pakistan show that *Bergenia ligulata* (*but pewa*) used as diuretic,[17,31-33] hepatoprotective,[17] alcoholic extracts of *Bergenia ligulata* showed anticancer,[34,15] antiprotozoal, diuretic, cardiovascular, antiscorbutic, antilithiatic,[35] litholytic property,[33] anti-inflammatory,[15,33] activity in dose dependent manner in rats.[38,39] A novel herbal composition is being formulated using with *Saxifraga ligulata (Bergenia ligulata)* extract for maintaining/caring the skin around the eyes.[37,77] The efforts done by asian scientists in the period 2000-2008 to isolate natural antiviral agents from asian plants *Bergenia ligulata* for influenza virus.[38] *Bergenia ligulata* is main ingredient of *Pashanbhed* churna manufacturer by dave Ayurved Bhavan, panvel, Mumbai, is used for diuretic, diarrhea, cough, pulmonary infection and fever.[39]

The plant *Bergenia ligulata* showed in vitro, in vivo animals study that the crystal (calcium oxalate monohydrate) growth inhibition, decreases calcium phosphate nucleation, calcium oxalate, crystalyzation inhibition, diuretic, hypermagneseuric and antioxidant effect.[40,89,12]

Antilithic activity

The antilithic property of the crude extract has been investigated that the alcoholic extract had no effect in preventing stone formation in rats (after the method of Lyon) but was of significant help in dissolving preformed stones. Low doses of *Pashanabheda* extract (0.5 mg/kg of alcoholic extract) promote diuresis in rats, but higher dose 100 mg/kg reduce the urine output and also reduce the diuresis produced by urea.[41, 39]

The crude aqueous-methanolic extract of *Bergenia ligulata* rhizome (BLR) was studied using *in-vitro* and *in-vivo* methods. The result was that BLR inhibited calcium oxalate (CaC_2O_4) crystal aggregation as well as crystal formation in the metastable solutions and exhibited antioxidant effect against 1,1-diphenyl-2-picrylhydrazyl free radical and lipid peroxidation in the *in vitro*. BLR caused diuresis in rats accompanied by a saluretic effect. In an animal model of urolithiasis, developed in male wistar rats by adding 0.75% ethylene glycol (EG) in drinking water, BLR (5-10 mg/kg) prevented CaC_2O_4 crystal deposition in the renal tubules. The lithogenic treatment caused polyuria, weight loss, impairment of renal function and oxidative stress, manifested as increased malondialdehyde and protein carbonyl contents, depleted reduced glutathione and decreased antioxidant enzyme activities of the kidneys, which were prevented by BLR. Unlike the untreated animals, EG intake did not cause excessive hyperoxalurea and hypocalciurea in BLR treated groups and there was a significant increase in the urinary Mg^{2+}, instead of a slight decrease. These data indicate the antiurolithic activity in *Bergenia ligulata* mediated possibly through CaC_2O_4 crystal inhibition, diuretic, hypermagneseuric and antioxidant effects and this study rationalizes its medicinal use in urolithiasis.[25,22,20] Garimella *et.al* studied urine or cell culture in vivo on *Bergenia ligulata* and the result was that the plant decreases calcium phosphate precipitation.[42]

Diuretic activity

The ethanolic extracts of root of *Bergenia ligulata* were assessed for diuretic activity in albino rats that was compared with standard drugs. For evaluation of the diuretic activity Lipschits method, was used.[43-45] It was done by measuring the volume of urine collected at the end of 5 hrs and Na^+, K^+ and Cl^- concentration in urine. The ethanolic extract of the roots of *Bergenia ligulata* was found to produce significant activity.[17]

The extracts of *Bergenia ligulata* root were studied in the presence of artificial reference urine (ARU) and human urine (HU) the growth behaviors of CHPD crystals grew within the rings. The addition of aqueous extract of *B.ligulata* to the calcium chloride in the supernatant solution modified the diffusion process and hence the periodic precipitation and the number of liesegang rings. The maximum length of the crystals was reduced due to inhibition produced by the addition of aqueous extract of *B.ligulata* the HU aqueous extract (AE) of *B.ligulata* contained a large number of salts and organic molecule. And their complex formation may have promoted the effect on growth of CHPD crystals. But when they are added separately to $CaCl_2$ they inhibit the growth of crystals. This suggests that these solutions separately inhibit the growth of crystals in in–vitro condition. But mixing with HU (humane urine) changes their behaviour

markedly. The diuretic nature of AE/*B.ligulata* seems to be important in the remedy rather than their inhibitive nature.[46]

Anti-bradykinin activity

The alcoholic extract of *Bergenia ligulata* rhizome displays marked anti-bradykinin activity. Although it does not affect the action of 5-HT and acetylcholine on isolated guinea pig ileum. It has been shown to potentiate the action of adrenaline on guinea-pig trachea and ileum muscle. Its cardiotoxic, antidiuretic and CNS depressant action on experimental models have been reported with large doses.[6] It is unlikely that these effects will be encountered with the doses in clinical use. In rats, the LD_{50} of the aqueous extract was 650 mg/kg intraperitoneally. It is widely used in the treatment of dysuria and renal failure, cystitis and crystalluria. Its anti-inflammatory property finds a use in the treatment of abscesses and cutaneous infections. It is also used in the treatment of dysentery and diarrhoea.[39]

Antiviral activity

Methanol-water extract from rhizomes of *Bergenia ligulata* inhibited in vitro the replication of influenza virus in a dose dependent manner and did not show virucidal activity at effective concentration.[47] 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 µg/ml. The principal chemical compound was condensed tannins in the extract.[48,49]

Antipyretic activity

The ethanolic (95%) extracted of roots, rhizomes and leaves and aqueous extract of whole plant of *Bergenia ligulata Wall* in yeast induced fever in albino rats of wistar strain were assessed for antipyretic activity.[55] The yield of semisolid mass (w/w) was obtained as ethanol extract of roots (13.36%), ethanol extract of rhizomes (15.12%), ethanol extract of leaves (11.02%) and aqueous extract of whole plant (09.21%). Acute toxicity studies were carried out for all the extracts of *Bergenia ligulata Wall* on healthy swiss albino mice of body weight 25-35g by using Up and Down or Stair case method.[50] The suspension of all the extracts of *Bergenia ligulata Wall* was prepared in 5% gum acacia and employed for assessment of antipyretic activity at the dose of (300 and 500mg/kg-body weight).[36] The standard drug used was paracetamol (200mg/kg p.o).[51] Rectal temperature of experimental animals was recorded at a time interval of 1hr, 2hr, 3hr, 4hr and 5 hr after drug administration for evaluation of antipyretic activity. The ethanolic extract of roots and rhizomes of *Bergenia ligulata Wall* at a dose of 500mg/kg p.o decreased the yeast induced fever in experimental animals.[27]

The ethanolic extracts of root of *Bergenia ligulata* were assessed for antipyretic activities in albino rats that were compared with standard drug. The assessment of Antipyretic activity was carried out using Brewer's Yeast induced pyrexia method in wistar rats.[52] Rectal temperature was recorded at a time interval of 0, 30 min, 1 hr, 2 hr, 3 hr after drug administration for evaluation of antipyretic activity the ethanolic extract of the roots of *Bergenia ligulata* was found to produce significant antipyretic activity.[17]

Antibacterial activity

The antibacterial activity was tested using the diffusion method.[53] The activity measured by fixed volume of plant extract (10 mg/ml, 25mg/ml or 50 mg/ml). The zone of inhibition was calculated by measuring the minimum dimension of the zone of no microbial growth around the well. Aqueous, 50% ethanolic and methanolic extracts of *B. ligulata* rhizomes were tested for their ability to inhibit the growth of *E. coli*, *B. subtilis*, and *S. aureus* at the dose levels of 10, 25 or 50 mg/ml for each extract. At a dose level of 50 mg/ml, the antibacterial effect was most significant. Incidentally, the antibacterial effect of the extracts at this level was comparable to ciprofloxacin (25 mg/ml). The results clearly suggest that *B. ligulata* possesses a strong antibacterial activity.[54]

Antiinflammatory activity

Antiinflammatory activity of *B. ligulata* rhizome was determined according to the method described by Winter and colleagues.[56] Evaluation of the anti-inflammatory activity of aqueous and 50% ethanolic extracts of the rhizomes of *Bergenia ligulata* are reported to attenuate the inflammatory response as determined by pharmacological and biochemical measurements. The treatment significantly decreased the inflammation as can be seen in figure 1. The activity level of succinate dehydrogenase (SDH), which has been reported to rise in inflammation[55] decreased in rats receiving the extract treatment (Figure 2). In conclusion, this study reports the antiinflammatory and antibacterial activity of *B. ligulata* extracts. Besides these activities, the study reports the radical scavenging activity of the rhizomes of *B. ligulata*, and establishes the therapeutic rationale of using *B. ligulata* in India System of Medicine. [54]

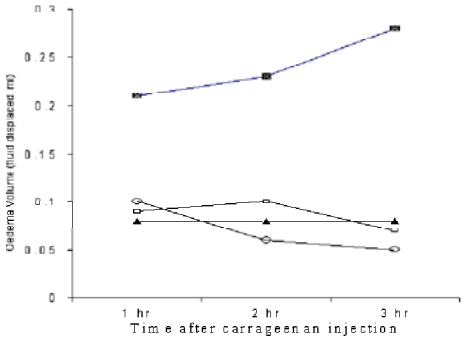


Figure 2: Effect of *Bergenia ligulata* on carrageenan induced oedema. □: Paw volume measured following the injection of carrageenan in rat hind paw; □: Paw volume in rats treated with the aqueous extract in inflammation model; □: Group treated with 50% ethanolic extract; and □: Rats treated with diclofenac. In all groups, the paw

volume was less in comparison to the carrageenan alone treated group.

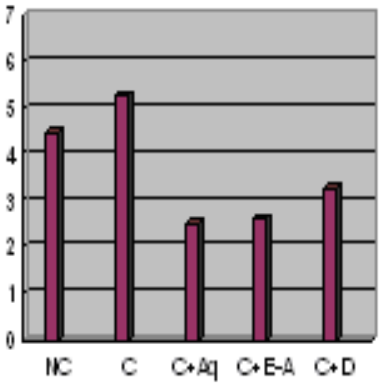


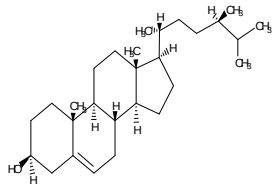
Figure 3: Succinate dehydrogenase in rats treated with *Bergenia ligulata* for treating inflammation. NC: normal control receiving the vehicle alone, C: animal group receiving carrageenan injection, C+Aq: treated with aqueous extract, C+E-A: treated with 50% ethanolic extract, and C+D: treated with diclofenac. Succinate dehydrogenase has been reported to increase in animal model of inflammation. Extract treatment could significantly bring down the increased value.

Hepatoprotective activity

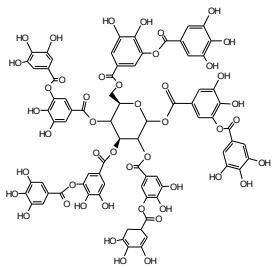
The ethanolic extracts of root of *Bergenia ligulata* were assessed for hepatoprotective activity in albino rats that was compared with standard drugs. Acute toxicity studies were carried out for ethanolic extract of *Bergenia ligulata* root on healthy Swiss albino mice of body weight 25- 35g by using Up and Down or Stair case method.[50] Evaluation 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.[56] The ethanolic extract of the roots of *Bergenia ligulata* was found to produce significant activity.[17]

Chemical constituents

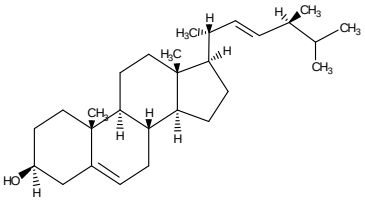
Bergenia has many bioactive compound in its rhizomes, including paashaanolactone[58] arbutin,[59] bergenin, catechin and gallic acid etc.[58,17,59] starch (19%), minerals, vitamins, albumin (7.75%), glucose (5.5%), mucilage, ash (mostly calcium oxalate).[17,59] Seeds of *Bergenia ligulata* contain coumarin (bergenin), tannic acid, gallic acid, minerals and wax.[60] The root of *Bergenia ligulata* was extracted with different organic solvent in increasing order of polarity (petroleum ether, diethyl ether, chloroform, acetone and ethanol). The result of the preliminary investigation revealed the presence of alkaloids, steroids, flavonoids, terpenoids, tannins, glycosides, carbohydrates and saponins the diethylether and acetone extract were studied. β-Sitosterol, stigmesterol, tannic acid and gallic acid were isolated by using thin layer and column chromatography. The chemical structures of the isolated compounds were established by spectroscopic techniques such as UV, IR and NMR spectroscopy. This was again confirmed by TLC with standard sample.[61] In fact, the whole plant of *Bergenia* can be used in medicine, but its active ingredients were mainly focused on polyphenols, among which bergenin is studied and applied most frequently.[62-65]



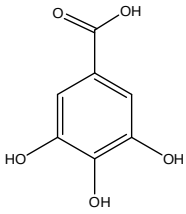
β-Sitosterol (1)



Tannic acid (2)



Stigmesterol (3)



Gallic acid (4)

According to the records of official Chinese Pharmacopoeia version 2005, bergenin can be used for relieving coughs and reducing sputum caused from the disease named chronic bronchitis. Recently, many studies demonstrated that bergenin have good effects in anti-virus, diminishing inflammation caused from bacteria, enhancing immunity and so on.[66, 67]

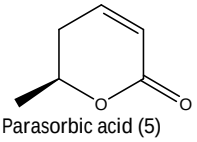
Rhizome, petiole and leaf (1gm each) were extracted with methanol and analysed by HPLC for the estimation of Bergenin and (+)-Afzelechin. Extraction of the rhizome material using three reflux periods (60, 90, 120 min.) showed that a 90 min reflux periods time gave the highest yield of the two active constituents, Bergenin and (+)-Afzelechin. Thus a procedure involving two cycle of refluxes (90 min each) with methanol (50 ml) was found to be suitable for the complete quantification of Bergenin and (+)-Afzelechin in all the test samples. Bergenin was found to be the major component of *B. ligulata yeo*. rhizomes with the concentration being about 7 times greater than that of (+)-Afzelechin while the latter was not detected in the aerial parts (petiole, leaf). The content of Bergenin in the petiole and leaf was found to be less than 8 times of that found in the rhizomes. Therefore rhizomes from the major source of bergenin and (+)- afzelechin.[68]

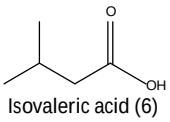
Specific compound activity

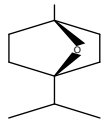
Natural insecidal activity

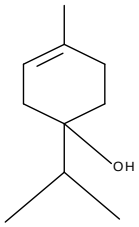
The volatile oil from roots of *Bergenia ligulata* was analyzed by GC-MS. A total of 97 compounds were identified. (+)-(6S)-parasorbic acid (5) 47.45%, isovalaric acid(6) 6.25%, 1,8-cineole(7) 4.24%,(Z)-asarone (9) 3.50%, and terpinen-4-ol (8) 2.96% were the most prominent constituents. The former one compound was isolated and characterized by spectroscopic data as (+)-(6S)-parasorbic acid (5). The volatile oil and the isolated compound were

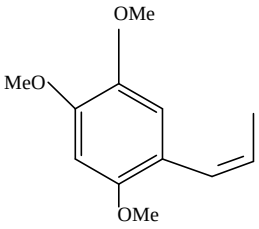
tested against Drosophila melanogaster. The results obtained showed that the volatile oil from roots could be considered as natural insecticidal effect agents.[28] From the rhizomes of *B. ligulata* only bergenin and β-sitosterol have been isolated.[41] This review presents a comprehensive literature search of different studies carried out on phytoconstituents like β-sitosterol, β-sitosterol-D-glucoside, afzelechin and Catechin. Further investigations may help in exploiting its properties.[69]


Parasorbic acid (5)

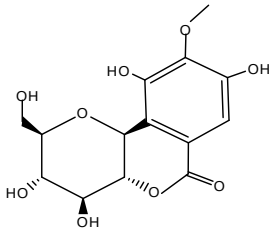

Isovaleric acid (6)

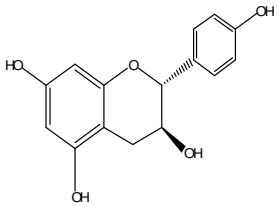

1,8-cineole (7)


Terpinen-4-ol (8)


(Z)-asarone (9)

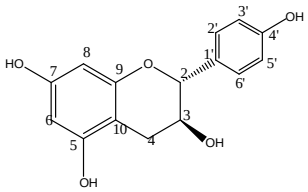
The dried and powdered raw material of *Bergenia ligulata* rhizomes (5kg) was sequentially extracted by cold percolation with petroleum ether, (60-80°C) chloroform and methanol and then phytochemical analysis was done respectiely and chracterised as (+)-afzelechin (11) and bergenin (10) respectively.[11]

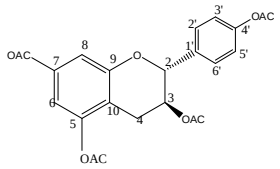

Bergenin (10)

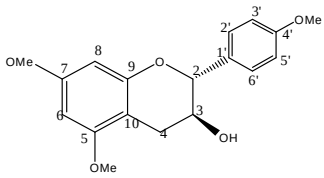

(+)- Afzelechin (11)

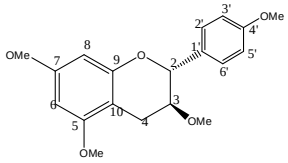
α-glucosidase activity

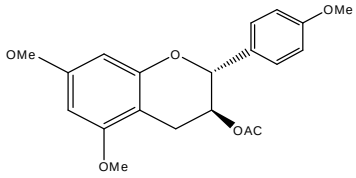
The 80% ethanolic extract of *B.ligulata* rhizome was fractionated to investigate for α-glucosidase. Sample solution were evaluated at dose levels of 5.0, 0.5, 0.05 mg/ml to obtain dose–response. The ethyl acetate extract exhibited an inhibitory effect of α-glucosidase activity. The α-glucosidase inhibitor was isolated by silica gel column chromatography with chloroform and methanol as eluents and identified as (+)-afzelechin (12) by EI-MS, IR, H^1 and C^{13} NMR spectroscopy. The inhibitory compound 12 was investigated in the inhibition of α-glucosidase activity at a concentration of 0.25 mm and the ID_{50} (50% Inhibition dose) value was 0.13 mm. For confirming the structure-activity relationship, compounds 13-16 were investigated in the inhibition of α-glucosidase activity test. Compound 13-16 inhibited 2.8%, 41.8%, 59.4% and 90.4% of α-glucosidase activity at a concentration of 0.25mm. The ID_{50} values of compound 15 and 16 were 0.14 and 0.05 mm respectively. Compound 16 had strongest inhibitory activity in these compounds and IC_{50} value of 16 was 2-fold higher than those of 12 and 15. Previously, α-glucosidase inhibitory activity of natural occurring flavan-3-ols has been reported.[71-73] IC_{50} value of (+)-catechin[71] and (-)-epicatechin[72] were 12.8 and 0.18 mm respectively. Compound 12, 15 and 16 showed more potent inhibitory activity than those of catechins. This research suggests that the α-glucosidase inhibitor in *B.ligulata* was primarily (+)-afzelechin.


(+)- afzelechin (12)


(+)-afzelechin tetraccetate (13)


(+)-5,7,4'-trimethoxyafzelechin (14)


(+)-tetramethoxyazelechin (15)


(+)-3-acetyl-5,7,4'-trimethoxyafzelechin (16)

Bergenia ciliata

Bergenia ciliata (haw.) sternb. is found throughout the temperate himalayas between elevations of 800-3000m.[74]

Figure 4: *Bergenia ciliata* whole plant

The efforts done by asian scientists in the period 2000 to 2008 to isolate natural antiviral agents from asian plants *Bergenia ciliata* for Herpes simplex virus.[75] *Bergenia ciliata* rhizome extracts is proved to have anti-bacterial and anti-tussive properties.[76,86] It is reported to be helpful in dissolving kidney-stones.[74] They are also reports on the anti-oxidant and the DNA protection abilities of the extracts.[78]

Anti-tussive activity

The methanol extract of the rhizome of *Bergenia ciliata Sternb. (Saxifragaceae*) has been evaluated for its

potential in a cough model induced by sulphur dioxide gas in mice. The extract exhibited significant anti-tussive activity in a dose-dependent manner, as compared with control. The antitussive activity of the extract was comparable to that of codeine phosphate (10 mg/kg body wt.), a standard anti-tussive agent. The extract at doses of 100, 200 and 300 mg/kg body wt. showed significant inhibition of cough reflex by 28.7, 33.9 and 44.2%, respectively, within 90 min of the experiment.[78]

The methanolic extract of *Bergenia ciliata* rhizome was screened for their antiviral activity against herpes simplex virus and influenza virus A by dye uptake assay. The methanolic extracts of *Bergenia ciliata* rhizome were found to be highly active against antiviral activity against HSV-1 (IC_{50} value 6.25µgml^{-1}) and influenza virus A (IC^{50} values from 8to 10µgml^{-1}).[79]

Antiulcer activity

Bergenia ciliata is used for the treatment of stomach disorders in the folk medicine of some areas of South East Asia. This study was designed to evaluate its gastroprotective effects on ethanol/HCl, indomethacin and pylorus ligation-induced gastric ulcers in rats. Doses of 15, 30 and 60 mg/kg between of the aqueous and methanol extracts of the rhizome were administered 1 h after ulcerogenic treatment. The animals were killed 3 h later, their stomachs removed and the mean area of ulcer lesion was determined. The weight of mucus and gastric acidity were also measured. The aqueous extract decreased the ulcer lesion ($p < 0.05$) in all models to a greater extent than the methanol extract, but at the higher doses the effect was reduced. In addition, the antiulcer activity appears to be mediated via cytoprotective effects conferred by enhancement of the mucosal barrier, rather than by prevention of gastric acid secretion or the lowering of pH and acidity.[80]

Anti-neoplastic activity

Methanolic and aqueous extract of *Bergenia ciliata* rhizome were found to have promising potential towards the development of drug that might be used to target tumours for chemoprevention/chemotherapy to check neoplastic growth and malignancy. Both extracts showed concentration-dependent cytotoxicity in each of the three cell lines. According to the American national cancer institute, the IC_{50} value to consider a crude extract promising for development of anticancer drugs is lower than a limit threshold (30µg/ml).[81] IC_{50} value of both the extracts falls well within this prescribed threshold in all cell lines (except the aqueous extract with higher IC_{50} in help 3B cell lines) *B.ciliata* bear potent anti-neoplastic activities that may have prospective clinical use as precursor for preventive medicine.[82]

Antioxidant activity

Methanolic and aqueous *B. ciliata* rhizome extracts were found to possess antioxidant activity, including reducing power, free radical scavenging activity and lipid peroxidation inhibition potential. The methanolic extract displayed greater potential in all antioxidant assays. It is, however, interesting to note that the aqueous extract demonstrated considerably higher DNA protection, albeit lagging behind its methanolic counterpart as an antioxidant.[82]

Antibacterial activity

The roots and leaves extract viz ethanol, hexane, ethyl acetate, chloroform, butanol and aqueous (5mg/ml) aliquots of *Bergenia ciliata* were used to test of antibacterial activity. *Bergenia ciliata* root extract was found to inhibit the growth of gram positive bacteria as compared to gram negative strain. Therefore in a way it can be inferred that *Bergenia ciliata* extracts exhibit rather a narrow spectrum antibacterial activity. The screening result of various leaves extract of *Bergenia ciliata* exhibited activity against the gram positive *staphylococcus auereus* (zone of inhibition 8-12 mm) whereas chloroform butanol and aqueous extracts were found active against *Bacillus subtilis, Bacillus megalerium and micrococcus*.(zone of inhibition 10-20). Consequently it can be suggested that the activity of root extract is much higher as compared to the leaves extract of *Bergenia ciliata.*[78]

Hypoglycemic activity

The roots and leaves extract viz., ethanol, hexane, ethyl acetate, chloroform, butanol and aqueous of *Bergenia ciliata* were used to test of hypoglycemic activity. All the extracts except chloroform extract of root and leaves of *Bergenia ciliata* were found to possess hypoglycemic activity in Streptozotocin (STZ) treated rats. Therefore the plant can be classified as hypoglycemic activity in experimental diabetes ranging from 40-70% of its onset to reduce blood glucose level.[69]

Toxicological investigation

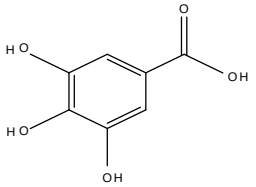
The toxicological investigations of *Bergenia ciliata* with particular reference to acute systematic toxicity and intracutaneous toxicity in experimental animals displayed that it elicit severe toxicity. The symptoms of toxicity in intracutaneous test showed erythema and edema whereas assessment of acute systemic toxicity frequently observed breathing problem and initiations of diarrhea with blood in stool of experimental model and caused gastero-intestinal syndrome. *Bergenia ciliata* can produce toxicity suggesting a role in certain diseases. It is therefore, premature to speculate about mechanism of effect until toxin is unequivocally identified.[69] The hemolysis test on the extract of *Bergenia ciliata* was almost devoid of activity.[69]

Chemical constituents

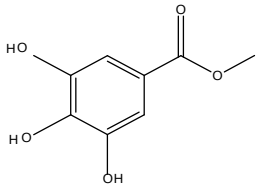
The plant contains tannic acid, gallic acid, glucose, mucilage, wax, metarbin, albumen and mineral Salts[99] Bergenin, (+)-Catechin, Gallicin and Gallic acid quantified by using solvent System of Toluene: Ethyl acetate: Formic acid (6: 6: 1, v/v/v) by HPTLC. Developed method permitted simultaneous quantification of Bergenin, (+)-

Catechin, Gallicin and Gallic acid, and showed good resolution and separation from other constituents of extract and was found to be simple, precise, specific, sensitive and accurate. It can be adopted for routine quality control of herbal material and formulations containing *Bergenia ciliata*.[82]

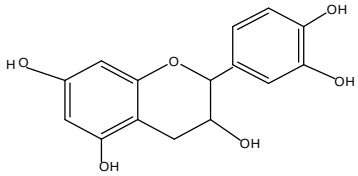
Tinctures were prepared by macerating the rhizomes of *B. ciliata* in different strengths of alcohol (30, 40, 50, 60, 70, 80, 90 and 100%, v/v) for 7, 14 and 21 days. After maceration, the pH, specific gravity and total solid matter, chemical contents were determined. The pH of the tinctures decreased with increase in alcohol strength, as well as with the number of days of maceration. Results showed that the tinctures prepared with 50% alcohol had the highest specific gravity of 0.9907 and yield (total solid content) of 9.11% (w/v) when macerated for 21 days. The chemical components of the tinctures irrespective of alcohol strengths were steroid, triterpenoid, flavonoid, tannins, carbohydrates and saponins.[12] The rhizome of *B.ciliata* yield gallolyted leucoanthocyanidin-4-(2-galloyl) glucoside as well.[41]



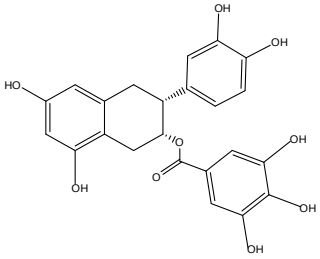
Gallic acid (17)



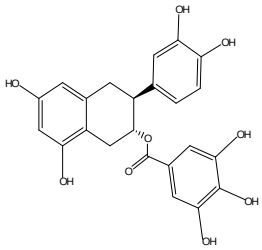
Gallicin (18)



(+)-catechin (19)



(-)-3-0-galloylepicatechin (20)



(-)-3-0-galloylcatechin(21)

Specific compound activity

α-glucosidase and α –amylase (antidiabetic) activity

50% aqueous–methanol extract of *Bergenia ciliata* rhizome lead to the isolation of two active compounds, (-)-3-O-galloylepicatechin and (-)-3-O-galloylcatechin. These isolated compounds demonstrated significant dose dependent enzyme inhibitory activities against rat intestinal α-glucosidase and porcine pancreatic α -amylase. IC_{50} value for sucrose, maltase and α-amylase were 560, 334 and 739 µM, respectively. For [(-)-3-O-galloylepicatechin] and 297, 150 and 401 µM, respectively for [(-)-3-O-galloylcatechin]. The anti-diabetic potential of *Pakhanbhed* could be helpful to develop medicinal preparations or nutraceutical and functional foods for diabetes and related symptoms.[84]

Bergenia stracheyi

Bergenia stracheyi (HK.) is a rhizometic herb species found in Afghanistan to Uttarakhand, between 3300-4500 m in alpine slopes.[85]

Figure 5: *Bergenia stracheyi* whole plant

Previous chemical and pharmacological studies on this species reported the occurrence of glycosides, gallic acid, tannic acid, mucilage, wax, albumens, starch etc. A K Goel et.al perform the antibacterial, antifungal, antiprotozoal, antiviral, antifertility cardiovascular, analgesia, and diuretic activity on plant excluding root of *Bergenia stracheyi* and the result was negative.[82]

Chemical constituents

Bergenia stracheyi have potential to act as broad spectrum antimicrobial agent because of the presence of phytochemicals showed positive result for free anthraquinone, ascorbic acid, carbohydrates, phenolics, saponins and steroids. The presence of phenolics, ascorbic acid, steroids in *Bergenia stracheyi* have potential to act as antioxidant, anticancer and antimicrobial agents.[87]

Specific compound activity

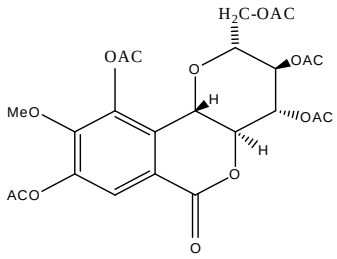
Anti-arthritic activity

Bergenin, a C-glycoside of 4-O-methylgallic acid, isolated from rhizomes of *Bergenia stracheyi* (Saxifragaceae) and its O-demethylated derivative norbergenin, prepared from bergenin, are reported to show anti -arthritic activity through possible modulation of Th1/Th2 cytokine balance. Flow cytometric study showed that the oral administration of bergenin and norbergenin at doses of 5, 10, 20, 40 and 80mg/kg per oral dose inhibit the production of proinflammatory Th1 cytokines (IL-2, IFN-gamma and TNF-alpha) while as potentiate anti-inflammatory Th2 cytokines (IL-4 and IL-5) in the peripheral blood of adjuvant-induced arthritic BALB/c mice. This shows the potential Th1/Th2 cytokine balancing activity of bergenin and norbergenin which is strongly correlated with their anti-arthritic activity. At similar dose levels, the effect of norbergenin was found to be more than that of bergenin. The oral LD (0) for

bergenin and norbergenin was more than 2000mg/kg body weight of the mice.[1]

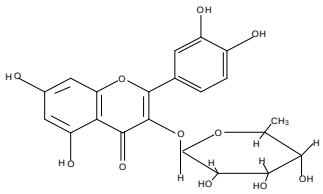
DPPH (diphenyl picrylhydrazyl) radical scavenging, antimicrobial and xanthine oxidase inhibitory activities

Bergenin pentacetate (22), a peracetate derivative of biologically active lead compound Bergenin isolated from methanol extract of *Bergenia stracheyi* rhizomes was subjected to lipase catalyzed regioselective alcoholysis to obtain 3,4,10,11-tetracetate of Bergenin. The free hydroxyl group of Bergenin-3, 4, 10, 11-tetraacetate was derivatised using higher carboxylic acids to obtain acyl derivatives (Hexanoate, Benzoate, Decanoate, Myristate). These compounds synthesized via chemoenzymatic route were characterized using H^1NMR, C^{13}NMR and mass spectral data and evaluated for DPPH radical scavenging, antimicrobial and xanthine oxidase inhibitory activities. The studies revealed that biological activity of Bergenin can be optimized by selective modification of its structure.[88]

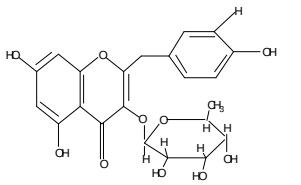


Bergenin pentacetate (22)

Quercetin-3-o-α-L-rhamnoside, kaempferol-3-o-α-L-rhamnoside and kaemferol-3-o-rhamnosyl (1-6) glucoside are flavanol glycosides. Among these three, first two gave promising antioxidative activity.[89]



Quercetin-3-0-α-L-rhamnoside (23)



Kaempferol-3-0-α-L-rhamnoside (24)

Phyto ecdysteroids are analogues of invertebrate steroids hormones. That occur in a wide variety of plant species.[90] A number of ecdysteroid conjugates have been isolated from plant sources.[91] Seed extracts of *Bergenia stracheyi* were assessed for the presence of ecdysteroid conjugates by incubation of the extract with a mixture of hydrolases from the gut juices of *H.pomatica*.[97] The roots of *B. stracheyi* contain a new derivative (+) catechin-3-gallate.[41]

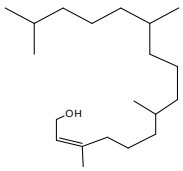
Combined plant extract

The fine powder of roots is made into paste mixed with the resin of pine tree and applied on fresh boils, enables them to ripen and brust.[92] Many extracts from *Bergenia* have high medicinal values, take methanol extract as an example, the results obtained[92] showed that it had a wide spectrum of concentration dependent antibacterial activity, in addition, it was demonstrated anti-inflammatory potentiality.[93]

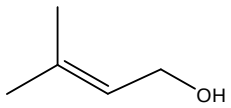
A simple TLC method has been developed for the simultaneous quantification of bergenin, catechin and gallic acid from different parts of *Bergenia ligulata* and *Bergenia ciliata* using HPTLC plate precoated with silica gel 60 F250. The method was developed in toluene: ethyl acetate: formic acid (4:6:1,v/v). The linearity range for bergenin, catechin and gallic acid were found to be 160-800, 160-480 and 160-56 ng/spot respectively. The rhizomes were found to contain higher concentration of bergenin, catechin and gallic acid than other parts of the plants.[94] The rhizome of *Bergenia ciliata* and *Bergenia stracheyi* contain gallic acid, tannic acid, mucilage, wax, glycosides, albumens, starch, etc. The rhizome used, wounds cure septic, act as astringent etc.[95] The seeds of *Dolichos biflorus* and rhizomes of *Bergenia ligulata* were tested for their in vitro antilithiatic and anticalcification activity by the homogenous precipitation method. The extracts were compared with an aqueous extract of cystone (a marketed preparation) for their activities. Also a combination of the extracts of the two plants was tested. Extracts of *Dolichus biflorus* showed activity almost equivalent to cystone while *Bergenia ligulata* showed less activity and the combination was not as active as the individual extracts.[96]

Effectiveness of *Bergenia ligulata, Nigella sativa* and their combination on rats rendered nephrolithiasis by administration EG.[16]

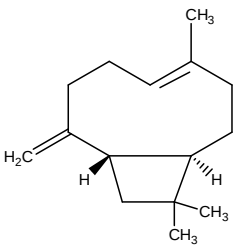
Volatiles were distilled from leaves of three *Bergenia* species collected from Yunnan, Xinjiang and Tibet in western China and analyzed using GC/MS instrumentation. The contents of extractable volatiles varied substantially among the three species with *B. crassifolia* having approximately 0.05% dry wt (v/w), *B. purpurascens* 0.01% (v/w) and *B. stracheyi* 0.13% (v/w), respectively. In *B. stracheyi*, 3-methyl-2-buten-1-ol was the dominant sort of volatile (52.71%), whereas detected major constituents included β-eudesmol (7.44%), damascenone (3.22%), caryophyllene (2.75%) and phytol (2.57%).[89]



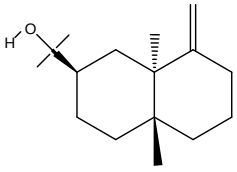
Phytol (25)



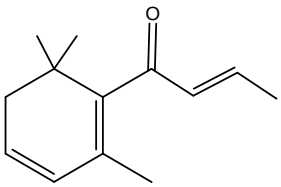
3-Methyl-2-buten-1-ol (26)



Caryphyllene (27)



β-eudesmol (28)



Damascenone (29)

Flavonoids are also found in other species of *Bergenia* as glycosides.[100] Flavonoids has widely been associated with various biological activities such as antimicrobial, antioxidant, anti-inflammation and anticancerogenic.[100] Antioxidant play a role in maintenance of the pro/antioxidant balance by neutralizing the radicular oxygen and nitrogen species which are responsible for deleterious processes in biological system.[100]

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