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Review Article

# SECONDARY METABOLITES FOUND IN *BERGENIA* SPECIES: A COMPENDIOUS REVIEW

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**ABSTRACT**

Secondary metabolites are chemical found in plants. These have no role in plant growth but these are important for human because it have many pharmacological activity. *Bergenia* species such as *Bergenia stracheyi, Bergenia ligulata* And *Bergenia ligulata* etc. have many secondary metabolites such as 1. Bergenin 2. Tannic acid 3. Gallic acid 4. Stigmesterol 5. β-Sitosterol 6. catechin 7. (+)-Afzelechin 8. 1,8-cineole 9. Isovalaric acid 10. (+)-(6S)-parasorbic acid 11. Arbutin 12. Phytol 13. Caryophyllene 14. Damascenone 15. β-eudesmol 16. 3-methyl-2-buten-1-ol 17. (Z)-asarone 18. Terpinen-4-ol 19. Paashaanolactone which are medicinally important.

**Keywords:** Secondary metabolites, Pharmacological uses, *Bergenia* species, *Bergenia ligulata*, *Bergenia stracheyi*, *Bergenia ciliata, Bergenin.*

## INTRODUCTION

Metabolites are essential for plants growth, development specific function such as pollinator attraction or defense against herbivory. Basically metabolites have two type first is primary metabolites and second one is secondary metabolites. [1]

### Primary Metabolites

Primary metabolites made up of many different organic compounds, such as carbohydrates, lipids, proteins and nucleic acids. They are found in the plants because they have the products of fundamental metabolic pathways such as the Krebs cycle, glycolysis and Calvin cycle. [2-6]

**Primary metabolites are divided into different category such as**

**Energy rich fuel molecules**: Sucrose and starch

**Structural components:** Cellulose

**Informational molecules:** Deoxyribonucleic acid and ribonucleic acid

**Pigments:** Chlorophyll

These primary metabolites play a very important role for growth and development of plant. Primary metabolites are also use to precursors for the synthesis of secondary metabolites. [2-6]

### Secondary metabolites

Secondary metabolites are chemicals produced by plants. Secondary metabolites have no role in growth, reproduction, photosynthesis or we can say that this have no role in primary function. Secondary metabolites divided into three classes

**1) Alkaloids**

**2) Terpenoids**

**3) Phenols**

Secondary metabolites are important use by humans found in plant. Most pharmaceuticals are based on plant chemical structures and secondary metabolites. **S**econdary metabolites have been isolated from plants which give Pharmacological effects in humans so that is used as medicines. [2-6]

***Bergenia* species have the following secondary metabolite**

1. Bergenin
2. Tannic acid
3. Gallic acid
4. Stigmesterol
5. β-Sitosterol
6. Catechin
7. (+)-Afzelechin
8. 1,8-cineole
9. Isovalaric acid
10. (+)-(6S)-parasorbic acid
11. Arbutin
12. Phytol
13. Caryophyllene
14. Damascenone
15. β-eudesmol
16. 3-methyl-2-buten-1-ol
17. (Z)-asarone
18. Terpinen-4-ol
19. Paashaanolactone

The secondary metabolites of ***Bergenia*** species has been described in present article one by one**.**

### 1. BERGENIN

Bergenin is most abundant in the genera of saxifragaceae, euphorbeaceae and myrsinaceae. [7] It is also known as Cuscutin a C-glucoside of 4-0-methyl gallic acid characterized by polyphenol. It is found in colorless crystal form isolated from *Bergenia* species such as *Bergenia ligulata*, *Bergenia ciliata*, *Bergenia stracheyi*, *Bergenia crassifolia* etc. [8-9] Its IUPAC name is 4-methoxy-2-[(1S,2R,3S,4S,5R)-3,4,5,6-tetrahydro-3,4,5-trihydroxy-6-(hydroxymethyl)-2H-pyran-2-yl] -α-resorcylic acid δ lacto ne monohydrate. Its chemical formula is $C_{14}H_{16}O_9.H_2O$ and molecular weight 346.3 grams per mole. It has two analogues (norbergenin and acetylbergenin) with additional pharmacological effects.

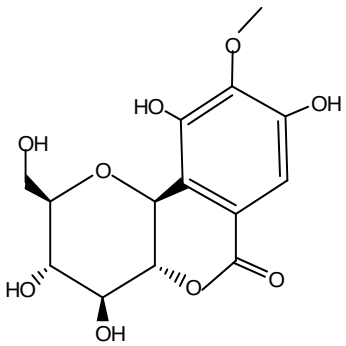


**Fig. 1: Bergenin**

### USES OF BERGENIN

### Influence on Arrhythmia

Bergenin containing herbs have been used in arrhythmia. In several animal models arrhythmias have been countered

effectively with varying dosages. It is hypothesized that bergenin increase the parasympathetic component of the autonomic nervous system. [15-17]

**Inhibits Reactions Promoted By Oxygen or Peroxides**

Bergenin inhibit reaction promoted by oxygen and decreases lipid peroxidation of cell membranes. It has antioxidant activity more than vitamin C and protects against ascorbic acid depletion in several different body tissues. [15-17]

**Germicide Activity**

Bergenin has demonstrated Germicide activity against species *E. coli* and *Pseudomonas aeruginosa*. It is also effective against many types of fungus by blocking a crucial enzyme called yeast alcohol dehydrogenase which is required for fermentation reactions. [15-17]

**Anti-hepatitis activity**

Bergenin has demonstrated anti-hepatitis C virus (HCV) activity and weak anti-HIV activity *in vitro*. It is *not* effective at attacking HIV-I reverse transcriptase and HIV integrase. [15-17]

**Liver-Protective Properties**

Bergenin have protective effect on the liver against damaging environmental poisons. When bergenin have given to animal and then challenged with toxins like carbon tetrachloride their livers experience less damage and secrete less of the indicators like aspartate aminotransferase and alanine aminotransferase. Part of the mechanism for this appears to be replenishment and protection of the crucial glutothione antioxidant system in liver cells burdened with the tasks of neutralizing or eliminating environmental toxins. [15-17]

**Anarchic effect**

Bergenin effects anarchic or inflammation by balancing secretion of cellular messengers (cytokines) from pro-inflammatory and inhibitory cells of the immune system. It inhibits the release of inflammatory cytokines like Interleukin-2 (IL-2), gamma interferon (IFN-gamma), and Tumor Necrosis Factor-alpha (TNF-alpha). It also promotes the release of anti-inflammatory messengers like Interleukin-4 and Interleukin-5. It also stimulates the release of protective prostaglandins. [15-17]

**Chubbiness and Insulin**

Bergenin also plays a role in the breakdown of fat. It is becoming a popular component of thermogenic fat-burning dietary supplements. It does not directly stimulate lipolysis but appears to enhance the activity of lipolytic adrenergic hormones like norepinephrine. It also opposes the lipogenic activities of insulin. The mechanism appears to be through the enhancement of norepinephrine to phospholipids of adipose cells. It is also play moderate activity against an enzyme called protein tyrosine phospatase 1B. This enzyme negatively regulates insulin and leptin signaling and some of the positive effects of insulin and leptin may be enhanced by its inhibition. [15-17]

**Toxicity**

Bergenin has no toxicity. It is used for long time. This has no adverse effects have been observed, even with very large dosages. [15-17]

**2. TANNIC ACID**

Tannic acid found in seed of *Bergenia ligulata***.** Tannic acid is a form of tannins which is a type of polyphenol. It is also known as acidum tannicum, gallotannic acid, digallic acid, gallotannin, tannimum, quercitannin, oak bark tannin, quercotannic acid, querci-tannic acid and querco-tannic acid. It has a weak acidity because it has many phenol groups in their structure. The chemical formula for commercial tannic acid is $C_{76}H_{52}O_{46}$, which corresponds with decagalloyl glucose, but in fact it is a mixture of polygalloyl glucoses or polygalloyl quinic acid esters with the number of galloyl moieties per molecule ranging from 2 up to 12 depending on the plant source used to extract the tannic acid. [18,19]

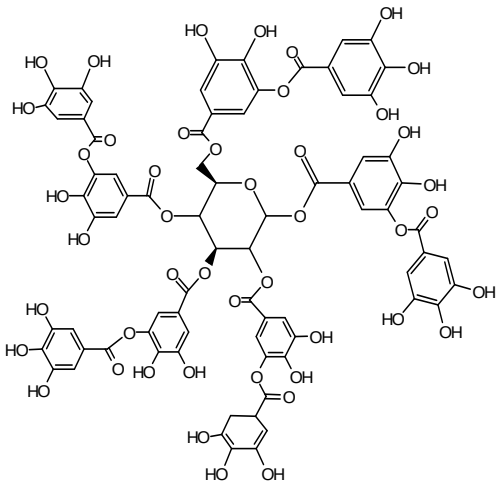

**Fig. 2: Tannic acid**

**USES OF TANNIC ACID**

Tannic acid is commonly used in dyeing process for cellulose fibers such as cotton, often combined with iron. The tannin mordant should be done first as metal mordants combine well with the fiber-tannin complex. Tannic acid also be used as an after treatment to improve wash fastness properties of acid dyed polyamide. It is also an alternative for fluorocarbon after treatments to impart anti-staining properties to polyamide yarn. It is also use in textile auxiliary as an agent to improve chlorine fastness. Tannic acid is used in the conservation of ferrous metal objects to passivate and inhibit corrosion and it is also prevent corrosion. Tannic acid is also found in commercially available iron/steel corrosion treatments such as Hammerite Kurust. It is used also in food applications. It is used as process aids in beer clarification, aroma compound in soft drinks and juices and equally important in the wine industry, where it finds use as a natural clarifying agent, color stabilizer and taste enhancer. Tannic acid was also used as a treatment for many toxic substances, such as strychnine, mushroom, and ptomaine poisonings in the late 19th and early 20th centuries. [20]

Tannic acid is also used for treatment in burn injuries which significantly reduced mortality rates. [21,22] Now a days tannic acid is still used in pharmaceutical applications to produce albumin tannate which is used as an anti-diarrhea drug, anti-histamins and anti-tussives to impart increased stability or slow release properties to the active pharmaceutical ingredient.

**Tannins have many physiological effects for example [23-25]**

1. To accelerate blood clotting 2. Reduce blood pressure 3. Decrease the serum lipid level

4. Produce liver necrosis 5. Modulate immunoresponses. 6. Prevent blisters, foot odor, rough and dry feet. 7. A popular home remedy to stop the bleeding after wisdom tooth extraction is applying tea bags in the back of the jaws and biting down, given that the tannic acid in tea helps to clot blood.

**3. GALLIC ACID**

Gallic acid is found in seed of *Bergenia ligulta* and *Bergenia ciliate* [26] Gallic acid also known as 3,4,5-Trihydroxybenzoic acid. [27] It is a type of Phenolics has chemical formula $C_6H_2(OH)_3COOH$. Gallates are the salts and esters form of gallic acid. [28]

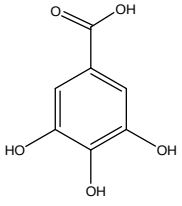

**Fig. 3: Gallic acid**

**USES OF GALLIC ACID**

It is used as a standard for determining the phenol content by the Folin-Ciocalteau assay, results are reported in gallic acid equivalents. [29] Gallic acid seems to have anti-fungal and anti-viral, diabetes, cytotoxicity against cancer cell and antioxidant activity which helps to protect human cells against oxidative damage. Gallic acid also have astringent effect in cases of internal haemorrhage. It is used as ingredients in some ointments to treat psoriasis and external hemorrhoids contain gallic acid. [27] It is a weak carbonic anhydrase inhibitor. [30]

**4. STIGMESTEROL**

It is found in *Bergenia ligulata* rhizome. [31] Stigmasterol is one of a group of plant sterols, or phytosterols, that include β-sitosterol, campesterol, ergosterol, brassicasterol, delta-7-stigmasterol and delta-7-avenasterol, Stigmesterol are chemically similar to animal cholesterol.

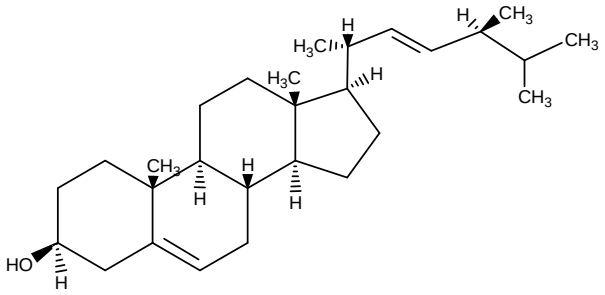


**Fig. 4: Stigmesterol**

Phytosterols are insoluble in water but soluble in most organic solvents and contain one alcohol functional group. [32,33] Stigmesterol is an unsaturated plant sterol used as a precursor in the manufacture of semisynthetic progesterone, [34-36] progesterone is a human hormone that plays an important role in the regulatory and tissue rebuilding mechanisms related to estrogen effects and It act as an intermediate in the biosynthesis of androgens, estrogens, and corticoids. It is also used as the precursor of vitamin $D_3$. [37] Research has indicated that stigmasterol may be useful in prevention of certain cancers, including ovarian, prostate, breast, and colon cancers. It inhibits several pro-inflammatory and matrix degradation mediators typically involved in osteoarthritis-induced cartilage degradation. It also possesses potent antioxidant, hypoglycemic and thyroid inhibiting properties. [38,39] Stigmesterol is a steroid so it is used as a precursor of anabolic steroid boldenone is commonly used in veterinary medicine to induce growth in cattle, but it is also one of the most commonly abused anabolic steroids in sports. [40-42]

**5. β-SITOSTEROL**

It is found in *Bergenia ligulata*. [26] β-Sitosterol is a phytosterols with chemical structures similar to cholesterol. It is also known as 22, 23-Dihydrostigmasterol, Stigmast-5-en-3-ol, and β-Sitosterin. Its molecular weight is $C_{29}H_{50}O$. β-Sitosterol is white, waxy powders with a characteristic odor, hydrophobic in nature and soluble in alcohols. [43-45]

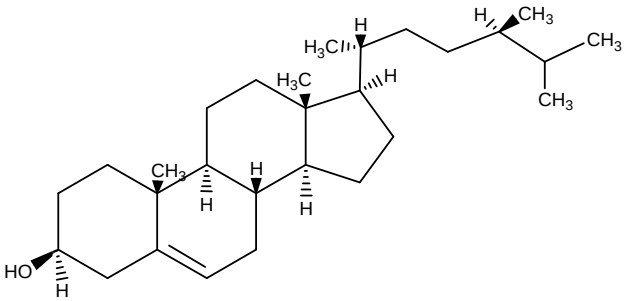


**Fig. 5: β-Sitosterols**

**USES OF β-SITOSTEROL**

β-Sitosterol reduces blood levels of cholesterol, alone and in combination of similar structure. Sometimes it is used in treating hypercholesterolemia. It inhibits cholesterol absorption in the intestine. [43-45] β-Sitosterol takes the place of dietary and biliary cholesterol in micelles produced in the intestinal lumen. This causes less cholesterol absorption in the body. [46,47] β-Sitosterol is used in the treatment of benign prostatic hyperplasia in herbal therapy. [48,49] It is used in the treatment of prostatic carcinoma. [50] Its effect are not enough known on unborn and newborn baby so this should be avoided during pregnancy and breast-feeding. β-Sitosterol is also not recommended for individuals with sitosterolemia, a rare inherited fat storage disease. Because people with this condition have too much β-sitosterol and related fats in their system, taking β-sitosterol will only worsen this condition. High levels of β-sitosterol concentrations in blood have been correlated with increased severity of heart disease in men having previously suffered from heart attacks. [51,52]

**6. CATECHIN**

Catechin is found in *Bergenia ciliata*. [26] It is a flavan-3-ol, a type of natural phenol. It is a secondary metabolite of plant belongs to the group of flavan-3-ols or simply flavanols. [53] It is associated with (+)-catechin or (-)-epicatechin. It is described as not exactly astringent and also not exactly bitter. [54] Catechin is also known as Cianidanol, Cyanidanol,(+)-catechin, D-Catechin, Catechinic acid, Catechuic acid, Cianidol, Dexcyanidanol, (2R,3S)-Catechin,2,3-trans-catechin., 3,3',4',5,7–flavanpentol and molecular formula is $C_{15}H_{14}O_6$. [55] It is envisaged to encapsulate catechin in cyclodextrins to mask its taste to use it as an additive. [56]

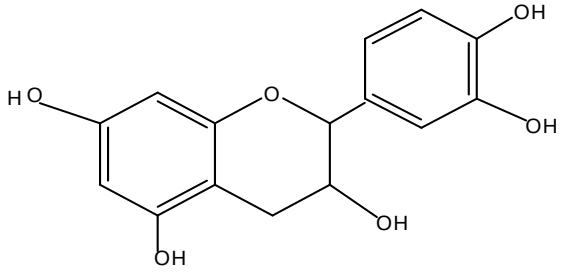


**Fig. 6: Catechin**

**USES OF CATECHIN**

Catechin prevents mouse brain after a stroke at various doses for different time. [57] (+)-catechin is a histidine decarboxylase inhibitor. Thus, it inhibits the conversion of histidine to histamine so it is beneficial through reduction of potentially damaging, histamine-related local immune responses. [58] According to an article in 2011, (–) epicatechin enhances fatigue resistance and oxidative capacity in mouse muscle. [59] The catechin family of compounds are strong therapeutic candidates for protection against the cognitive decline caused by HIV. Epicatechin, epigallocatechin gallate and other catechin flavonoids may protect against neurotoxic oxidative stress and caused by the HIV-Tat protein. Epicatechin is able to cross the blood-brain barrier more efficiently than resveratrol. It activates brain derived neurotrophic factor pathways. [60] (+)-Catechin and (-)-epicatechin are also selective monoamine oxidase inhibitors. They had also property to treat Parkinson's and Alzheimer's disease. [61]

**7. (+)-AFZELECHIN**

It is found in *Bergenia ligulata* rhizome which conformed by EI-MS, IR, $H^1$ and $C^{13}$ NMR spectroscopy. Afzelechin is a flavan-3ol, a type of flavonoids It has α-glucosidase inhibitor activity. [62-64] Afzelechin-3-O-β-D-xylopyranoside and afzelechin-3-O-β-D-glucopyranoside are afzelechin glycosides isolated from the roots of *Arthromeris mairei*. [65] (+)-afzelechin-O-β-4'-D-glucopyranoside has isolated from the rhizomes of *Selliguea feei*.[66] Afzelechin have the synthetic derivative which structure is given below.

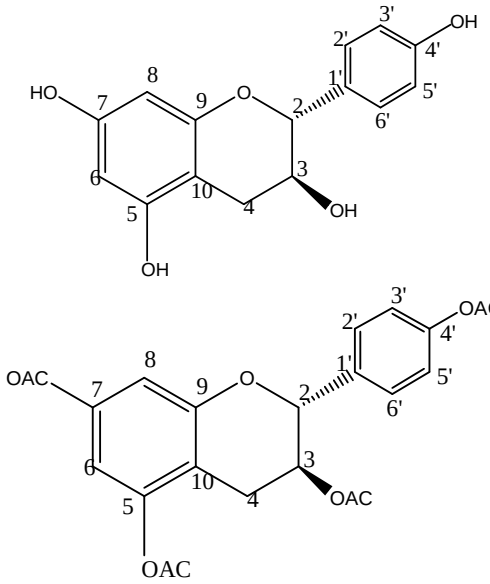

**Fig. 7: (+)- afzelechinFig. 8:(+)-afzelechin tetraccetate**

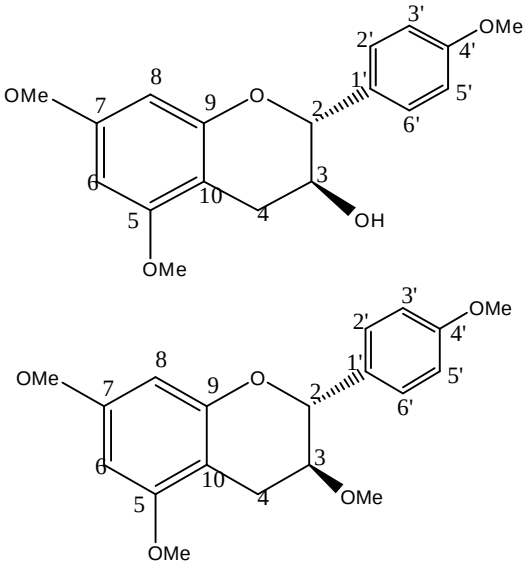

**Fig. 9: (+)-5,7,4'-trimethoxyafzelechin Fig. 10: (+)-tetramethoxyazelechin**

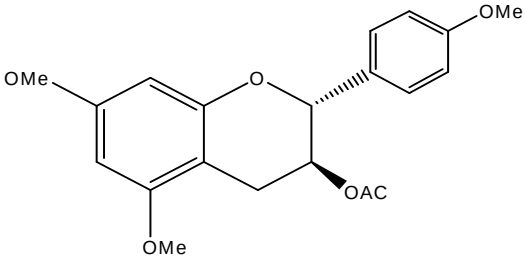

**Fig. 11: (+)-3-acetyl-5,7,4'-trimethoxyafzelechin**

**8. 1, 8-CINEOLE**

It is found in volatile oil of *Bergenia ligulata* root. 1,8-cineole is also known as by a variety of synonyms such as 1,8-cineol, eucalyptol, limonene oxide, cajeputol, 1,8-epoxy-p-menthane, 1,8-oxido-p-menthane, eucalyptol, eucalyptole, 1,3,3-trimethyl-2-oxabicyclo [2,2,2] octane, cineol, cineole. It is a natural organic compound which is a colorless liquid, cyclic ether and a monoterpenoid has a fresh camphor-like smell and a spicy, cooling taste. It is insoluble in water, but soluble in ether, ethanol and chloroform. The boiling point is 176 °C and the flash point is 49 °C. 1, 8-cineole forms crystalline adducts with halogen acids, o-cresol, resorcinol, and phosphoric acid. [67,68]

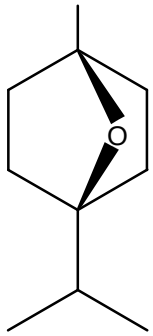

**Fig. 12: 1, 8-cineole**

**USES OF 1, 8-CINEOLE**

It is used as an insecticide and insect repellent inhibit cytokine production in cultured human lymphocytes and monocytes. [69] 1,8-cineole was found to control airway mucus hyper secretion and asthma, suppress arachidonic acid metabolism and cytokine production in human monocytes. [70,71] 1, 8-cineole was found to be an effective treatment for nonpurulent rhinosinusitis. Treated subjects experienced less headache on bending, frontal headache, sensitivity of pressure points of trigeminal nerve, impairment of general condition, nasal obstruction, and rhinological secretion. It has no side effect. [72] Because of its pleasant spicy aroma and taste. 1, 8-cineole is used in flavorings, fragrances, and cosmetics. [73] In higher doses It is hazardous via ingestion, skin contact or inhalation. It can have acute health effects on behaviour, respiratory tract and nervous system. The acute oral $LD_{50}$ is 2480 mg/kg (rat). [74]

**9. ISOVALARIC ACID**

It is also found in root of *Bergenia ligulata* in the form of volatile oil. [75] It is also known as 3-Methylbutanoic acid, delphinic acid, 3-methylbutyric acid, isopentanoic acid a natural fatty acid found in a wide variety of plants and essential oils. Isovaleric acid is clear colorless liquid that is sparingly soluble in water, but extremely soluble in most common organic solvents.

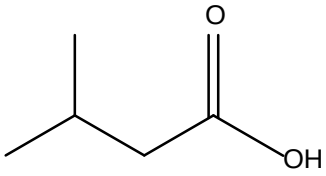

**Fig. 13: Isovalaric acid**

**USES OF ISOVALARIC ACID**

Isovaleric acid has a strong cheesy or sweaty smell, but its volatile esters have pleasing scents and are used widely in perfumery. It has been proposed that it is the anticonvulsant agent in valerian. [76]

**10. (+)-(6S)-PARASORBIC ACID**

It is a consitutents of *Bergenia ligulata* root. [75] Its synonyms are 5-hydroxy-2-hexenoic acid lactone, 2-hexen-5, 1-olide and sorbic oil. Its molecular formula is $C_6H_8O_2$ and molecular weight is 112.13. It is oily liquid, sweet aromatic odor soluble in water, freely soluble in alcohol and ether. [77]

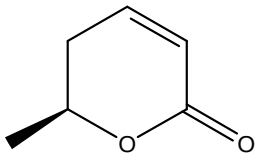

**Fig. 14: (+)-(6S)-parasorbic acid**

**USES OF (+)-(6S)-PARASORBIC ACID**

Parasorbic acid administered by subcutaneous injection to rats produced local sarcomas. Feeding experiments in rats where parasorbic acid was given in combination with sorbic acid cannot be evaluated because of the relatively low dose of parasorbic acid administered. A further oral study in rats was considered inadequate due to the small number of surviving animals. [78]

**11. ARBUTIN**

It is also know as Arbutoside hydroquinone β-D-glucopyranoside. Its molecular formula is $C_{12}H_{16}O_7$. Arbutin are found both form an ether and also a glycoside.

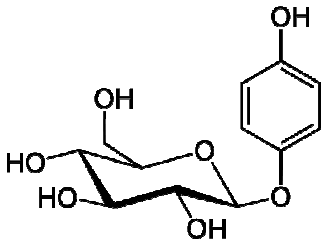


**Fig. 15: Arbutin**

**USES OF ARBUTIN**

A glycosylated hydroquinone extracted from bearberry plant in the genus *Arctostaphylos*. It inhibits tyrosinase enzyme and thus it prevents the formation of melanin. Arbutin is also used as a skin-lightening agent. Arbutin is found in wheat, and is concentrated in pear skins. It is also found in *Bergenia crassifolia Bergenia ligulata* and *Bergenia ciliata*. [79] Bearberry, which contains arbutin, is a traditional treatment for urinary tract infections. [80]

**12. PHYTOL**

The volatile oil of *Bergenia stracheyi* contain phytol. It is an acyclic diterpene alcohol that can be used as a precursor for the manufacture of synthetic forms of vitamin E [81] and vitamin K. [82] In ruminants, the gut fermentation of ingested plant materials liberates phytol, a constituent of chlorophyll, which is then converted to phytanic acid and stored in fats. [83,84]

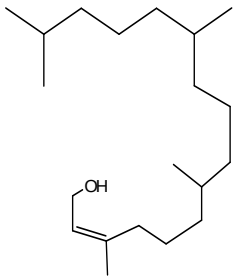


**Fig. 16: Phytol**

**13. CARYOPHYLLENE**

It is found in volatile oil of *Bergenia stracheyi*. caryophyllene, is a natural bicyclic sesquiterpene that is a constituent of many essential oils. [85,86]

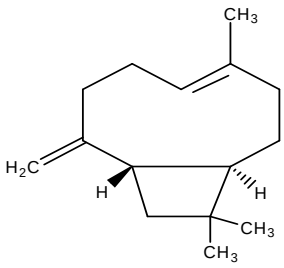


**Fig. 17: Caryphyllene**

**14. DAMASCENONE**

It is also a major chemical consitutents of volatile oil of *Bergenia stracheyi*. [84] Damascenones are a series of closely related chemical compounds that are components of a variety of essential oils. It is an important fragrance chemical used in perfumery. [85] The damascenones are derived from the degradation of carotenoids. [87]

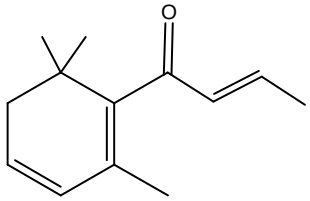


**Fig. 18: Damascenone**

**15. B-EUDESMOL**

It is also a composition of volatile oil of *Bergenia stracheyi.* [84] It is a sesquiterpenoid have effects on nervous system. It is also know as 2-[(2R,4aR,8aS)-4a-methyl-8-methylidene-1,2,3,4,5,6,7,8a-octahyd ronaphthalen-2-yl] propan-2-ol, (2R,4aR,8aS)-decahydro-8-methylene-a,a,4 a-trim ethyl-2-naphthyl methanol, eudesm-4(14)-en-11-ol, 4(15)-eudesmen-11-ol, 2- [(2R,4aR,8aS)-4a-methyl-8-methylidene-1,2,3,4,5,6,7,8a-octahyd ronaphthalen-2-yl] propan-2-ol and beta-selinenol. It is soluble in alcohol and insoluble in water. [84,88]

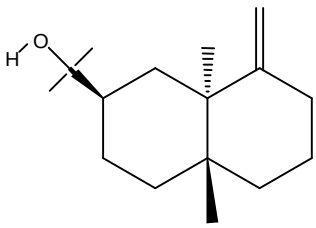


**Fig. 19: β-eudesmol**

**16. 3-METHYL-2-BUTEN-1-OL**

It is also the part of volatile oil of *Bergenia stracheyi*. It is known as prenol and 3,3-dimethylallyl alcohol is a natural alcohol. It is one of the simplest terpenes. It is clear colorless oil that is reasonably soluble in water and miscible with most common organic solvents. It has a fruity odor and is used occasionally in perfumery. Its molecular formula is $C_5H_{10}O$. [89]

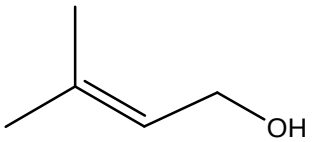


**Fig. 20: 3-methyl-2-buten-1-ol**

**17. TERPINEN-4-OL**

It is a chemical constituents which is found in root of *Bergenia ligulata***.** It is a terpene with a molecular weight of 154.249. [90,91]

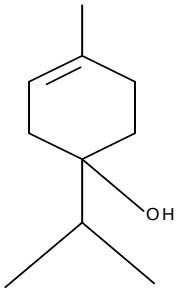


**Fig. 21: Terpinen-4-ol**

**18. (Z)-ASARONE**

It is also found in root of *Bergenia ligulata*. It is also known as **(**Z)-1,2,4-Trimethoxy-5-propenylbenzene, cis-asarone and cis-isoasarone. The molecular formula of this is $C_{12}H_{16}O_3$ and molecular weight is 208.25 and density boiling point and flash point is 1.028, 296 ºC and 108 ºC [91,92]

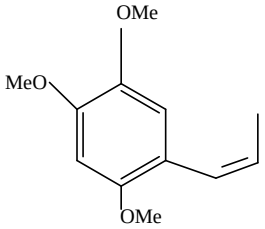


**Fig. 22**: **(Z)-asarone**

**19. PAASHAANLACTONE**

Paashaanolactone also known as 4(4'-ß-D-glucopyranosyloxy-1'-benzoyloxy) - 6-methyltetrahydropyran-2-one. It is identified first time in *Bergenia ligulata* rhizome which is commonly known as Paashaanbhed. [93]

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