

# Asian Journal of Research in Biological and Pharmaceutical Sciences

Journal home page: [www.ajrbps.com](http://www.ajrbps.com)



## A REVIEW ON PHARMACOGNOSY AND BIOLOGICAL ACTIVITIES OF *ARISTOLOCHIA*

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### ABSTRACT

*Aristolochia* is an important genus in the family of *Aristolochiaceae*. The genus *Aristolochia* consists of about 400 species of herbaceous perennials, under shrubs or shrubs bearing essential oils and is widespread across Tropical Asia, Africa and South America. *Aristolochia* species has been used extensively in the traditional Chinese medicine. Its diverse biological functions include hypertension relief, leukocyte enhancement, rheumatism relief, edema therapy, as well as analgesic and diuretic effects. Various *Aristolochia* species have been used in herbal medicines since antiquity in obstetrics and in treatment of snakebite, festering wounds, and tumors, and they remain in use particularly in Chinese herbal medicine.

### KEYWORDS

*Aristolochia*, Traditional Chinese Medicine and Biological Functions.

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### INTRODUCTION

*Aristolochia* belongs to the family *Aristolochiaceae*. In the indigenous system of medicine, the plant was used for the treatment of skin diseases, inflammation and purgative. Root extract was reported to have anti bacterial activity. A perennial climber shrub with woody base stocks. Leaves simple, alternate, entire, with undulate margins, acute; flowers greenish white, in auxiliary cymes; fruits rounded oblong, 6 chambered contain numerous winged compressed seeds<sup>1</sup>.

### Biological Source

*Aristolochia bracteolata* is a shrub distributed throughout India, belongs to the family *Aristolochiaceae*. The genus *Aristolochia* consists of

about 400 species of herbaceous perennials and shrubs.

### Synonyms

Greek name: Aristolochos  
English: Bracteated birthwort  
Gujarat: Midmari  
Hindi: Kitamari, Kalipaad, Hukka-bel  
Kanada: Kattackiru banagida  
Orissa: Paniri  
Sanskrit: Keetamari Dhoomrapatra, Nakuli, kitamari, visanika.  
Tamil: Aaduthinnapalai, atutinnapalai.  
Telugu: Gadida gadapa, gadidhagadapaaku, kadapara, Thella esshvari.  
Marathi: Gandhari, Gindhaan<sup>2</sup>.

### Scientific classification

Synonym: *Aristolochia bracteata*  
Kingdom: Plantae  
Order: Piperales  
Family: Aristolochiaceae  
Subfamily: Aristolochioideae  
Genus: *Aristolochia*  
Species: *Bracteolata*

### Species

Species of *Aristolochia* (Figure No.1).

*A. utriformis* S.M.Hwang, *A. watsonii* Woot. and Standl. (Watson's Dutchman's Pipe), *A. weddellii*, *A. westlandii* Hemsl, *A. wrightii* Seem, *A. yunnanensis* Franch<sup>3</sup>.

### Traditional uses

*Aristolochia bracteolata* is a shrub distributed throughout India, belongs to the family Aristolochiaceae. *A. bracteolata* commonly called as Worm killer in English and Aadutheendaapaalai in Tamil. It is used in traditional medicines as a gastric stimulant and in the treatment of cancer, lung inflammation, dysentery and snakebites. In the indigenous system of medicine, the plant was used as purgative, antipyretic & anti-inflammatory agents. The root part has antifungal and antibacterial activity and was used to treat syphilis, gonorrhoea, and skin diseases and also used during labours to increase uterine contraction. Its leaves are bitter and antihelmintic, antiulcer, antiplasmodial and are medicinally important. Almost every part of the

plant has medicinal usage. *A. bracteolata* is proved to have antioxidant property and insecticidal properties. The plant contain Aristolochic acid, has many medicinal properties in various disease condition. The Phytochemical screening revealed the presence of alkaloids, triterpenoids, steroids and sterols, flavonoids, tannins and phenolic compounds and cardio glycosides. The present review is an attempt to provide an up-to-date and detailed survey of literature of Pharmacognostical, ethno botanical and traditional uses as well as Phytochemical and Pharmacological reports on *A. bracteolata*<sup>4</sup>.

### Ethnomedical uses of different parts

#### Whole plant

Dermatitis, Allergic Disorder, Leprosy, Worms, Fever, Mosquito repellent, Anodyne, Purgative, Emmenagogue.

#### Leaves

Anti-Inflammatory, Dermatitis, Rashes, Skin Disease, For Scorpion Sting, Antipyretic, Snake Bite, Antiulcer, Amenorrhoea, Anthelmintic and Antiplasmodial.

#### Seeds

Antibacterial, Anti-Inflammatory and Analgesics and May Toxic to Goats.

#### Roots

Syphilis, Gonorrhoea, Skin Diseases and Eczema.

### Macroscopy

#### Leaf

Reniform, cordate or rounded, 3.8-7.5 cm long and as broad as long, obtuse, cordate at the base with a wide shallow sinus, entire, finely reticulately veined, tubescens beneath, glabrous above; petiole cylindrical, slightly grooved on upper surface 1.2-3.1cm long (Figure No.2). It has bitter taste with characteristic odour.

#### Fruits

Oblong or ellipsoid capsules and seeds compressed with cordate base<sup>5</sup>.

### Microscopy

Transverse section of leaf passing through midrib is strongly convex below, slightly elevated above, and shows a conjoint, collateral meristele embedded in its parenchymatous ground tissue located at the basal region of the two laminar extensions; 5-6 rows of

collenchymas lie under the upper epidermis, it being 2-3 in rows at lower side. Lamina dorsis ventral, shows a layer of palisade under the upper epidermis and 5-6 rows of spongy parenchyma traversed with obliquely cut vascular bundles both the epidermis are covered with this cuticle, traversed with stomata and bear simple, uniseriate, covering trichomes characterized by a straight or hook shaped terminal cell resting on a short rectangular cell with a balloon like extension<sup>6</sup>.

### **Propagation and cultivation**

It can be propagated by seeds which germinate in about two weeks. Seeds can be collected by bagging the fruits. The seeds are sown in June in well-mannered beds. Seedlings are transplanted after six weeks and trained on to bamboo platforms. The vines flower in September and fruit during February-March. They are allowed to grow for two years to yield roots of marketable size. The yield of roots is estimated at 4500-5600 kg/ha from two year old vines. The roots are collected in the autumn. The adhering earth is removed by minimum washing. The roots are dried in the sun or by gentle heat<sup>7</sup>.

### **Chemical constituents**

The roots of the plant from South India have been the subject of extensive investigation. The roots owe their odour to an essential oil, and their bitter taste to aristolochic acid. The essential oil had the pale yellow colour. The oil consists of sesquiterpenoids, which owing to their feeble volatility with steam, are best obtained by solvent extraction. The roots contain a small amount of fixed oil, which consists of glycerides of palmitic, stearic, lignoceric, cerotic, oleic and linoleic acids; non-saponifiables contain considerable amount of sitosterol, and a small quantity of a phytosterol glycoside which is probably of the type of ipuranol and on hydrolysis yields a phytosterol and a reducing sugar. Considerable amounts of reducing sugars in free form are present in the roots. The chief active principle of the drug is aristolochic acid, though aristolic and p-coumaric acids also appear to contribute to the activities of the drug. Aristolochic acid is 8-methoxy-3;4-methylenedioxy-10-nitrophenanthrene-1-carboxylic acid. It is intensely bitter and is optically inactive. It is the

same as isoaristolochic acid, aristolochia yellow, aristonic and aristolochic acids, but is different from aristolochine now identified as 1-curine. Isolation of the acid by column chromatography and crystallization from the mixture of dimethyl formamide and ethanol resulted in yellow-orange crystals with mp 275-78<sup>0</sup> C. Aristolochic acid can also be isolated by extracting the plant material with alcohol (95%) or ammonium hydroxide (5%) and chromatographing the extract. Aristolochic acid is found to occur in varying amounts in different samples of drug, ranging in yield from 0.06 to 0.7% on dry weight basis. This variation in the yield may be due to the varying amounts of the stems in different drug samples. Aristolochic acid acts as an anti-feedant and male sterilitant for some insects. It is toxic to houseflies; at 0.18% concentration, it caused 95% mortality in eight days. A study of chemosterilization effect three insects, viz. *Dysdercus koenigii* Fabr., *Aedes aegypti* Linn, and *Tribolium castaneum* (Herbst.) suggests that the acid brings a mitotic death or behaves as a dominant lethal mutant possibly due to the presence of –COOH group with methylenedioxy phenyl ring and NO<sub>2</sub> group in the acid<sup>8</sup>.

### **Phytochemistry**

The Phytochemical screening revealed the presence of alkaloids, triterpenoids, steroids and sterols, flavonoids, saponin, phytosterols, carbohydrates, proteins, phenolic compounds and cardio glycosides. Vaghasiya carried out the analysis of phytoconstituent of *A.bracteata* in different extracts (Figure No.3). The total phenolics content in the methanolic extract and acetone extract was found to be 59.22 ± 0.65 and 39.67 ± 0.92 respectively, were as the total content of flavonoids were 36.06 ± 0.17 and 130.93 ± 2.58 in the methanolic and acetone extract respectively<sup>9</sup>.

### *Lignoceric acid*

### **Reported Pharmacological Activity**

#### **Anti pyretic activity**

Petroleum ether and acetone extracts of *A.bracteolata* was investigated for their anti pyretic activity. Petroleum ether and acetone extracts of the plant *A. bracteolata* were prepared using Soxhlet

extraction. Pyrexia produced in rats by injecting 20ml/kg (s.c) of 20% aqueous suspension of brewer's yeast suspension. Extracts at 250 mg/kg exhibited significant anti pyretic activity. Aspirin (300mg/kg) was used as standard for which Pet. Ether extracts was found to be more effective than acetone extract<sup>10</sup>.

#### **Anti allergic activity**

Anti allergic activity of *A. bracteolata* was evaluated by using compound 48/80 induced anaphylaxis, dermatitis rhinitis and pruritis, as a preclinical model for acute phase of hypersensitivity reactions. The late phase hypersensitivity was evidenced by considering toluidine diisocyanate induced volume of broncho alveolar fluid secretion and its inhibition. The possible anti allergic mechanism was evaluated by using compound 48/80 induced mast cell activation and estimated serum nitric oxide (NO), rat peritoneal fluid NO, broncho alveolar fluid NO and blood histamine levels. It has been reported that the chloroform extract of *A.bracteolata* had potent and significant inhibitory effect on compound 48/80 induced pruritis and dermatitis activity in Swiss albino mice. It showed significant effect in toluidine diisocyanate induced rhinitis in Swiss albino mice. Mast cell membrane stabilization activity was also observed in compound 48/80 induced mast cell activation. A significant reduction was observed in serum nitrate levels, rat peritoneal fluid nitrate levels and BAL nitrate levels. The extract was also found to possess significant inhibitory effect on blood histamine levels. It could be concluded that the chloroform extract possesses potent anti allergic activity, possibly through mast cell membrane stabilization, inhibiting NO and histamine pathway<sup>11</sup>.

#### **Anti-inflammatory activity**

The ethanolic extract of the shade dried leaves of *A. bracteolata* was evaluated anti inflammatory activities in wistar rats by using the carrageenan induced left hind paw edema method. Significant reduction of edema volume was observed in the drug treated group when compared with the standard and untreated control. Antioxidant investigation of the ethanol extract along with its two successive fractions using nitric oxide and 1,1-diphenyl-2 picryl

hydrazyl (DPPH)-induced free radical assay methods showed good free radicals scavenging activity, thereby support in its anti-inflammatory properties.

#### **Anti-arthritis activity**

Anti-arthritic activity was demonstrated using Freund's complete adjuvant in rats. The results shows that, regular treatment of adjuvant induced arthritic rats with *A.bracteolata* extracts improves ESR, Hb value and also restores body weight. Significant (P<0.01) inhibitory effect was observed with *A. bracteolata* extract on Freund's complete adjuvant induced paw edema throughout the study (P<0.001). The latency to thermal stimuli and inhibitory effect on xylene induced ear edema was significantly (P<0.05) affected by oral treatment of *A.bracteolata*, irrespective of solvent used for extraction. Treatment of FCA induced rats with *A. bracteolata* extracts shown (P<0.05) increase in pain threshold, weight bearing ability, ambulation and also decline in scratching, defecation and urination, were observed as a sign of improvement in behavioral condition<sup>12</sup>.

#### **Antiulcer activity**

The aqueous extract of leaves of *A. bracteolata* exhibited antiulcer activity in rats. The antiulcer activity of *A. bracteolata* was evaluated against ethanol induced and pylorus ligation induced models, at two different dose levels of 400 and 800mg/kg/body wt/day. The activity was compared with standard drug Ranitidine. Pre-treatment with the extract resulted in a significant decrease of the ulcerated area. The volume and acidity of the gastric juice decreased in the pre-treated rats. Among the two doses assessed, 800mg/kg was found to have the significant activity than the lower dose.

#### **Antibacterial activity**

*A.bracteolata* leaves were subjected to antibacterial activity on disc diffusion method against bacillus subtilis, lactobacillus plantarum, Escherichia coli, staphylococcus aureus, streptococcus faecalis and pseudo monasaeruginosa. The leaves of *Aristolochia bracteolata* Retz were extracted with petroleum ether, chloroform and alcohol. Alcoholic extract showed significant anti bacterial activity as compared to that of other extracts. Negi PS *et al*

investigated the antibacterial activity of *Aristolochia bracteolata* root extracts. Powdered Roots of *A. bracteolata* were extracted with ethyl acetate, acetone, methanol, and water for 8 hours each using a Soxhlet extractor. Antibacterial activity of dried ex- tracts was evaluated by the pour-plate method against a few Gram-positive and Gram-negative bacteria. All the crude extracts showed a broad spectrum of antibacterial activity among which ethyl acetate extract was found to be the most effective. This study shows the potential for replacement of synthetic preservatives by the use of natural extracts. According to another study, the different extracts (Aqueous, methanol and chloroform) of this plant were effective against the bacterial strains *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, *Klebsiella pneumonia*, *Pseudomonas fluorescens*, *Shigella Flexner*, *Proteus vulgaris* and the fungal strains like *Aspergillus Niger*, *Aspergillus terries*, *Penicillium notatum* and *Rhizopus stolonifer*. Among the three extracts, methanol extract was found to have the significant activity followed by the chloroform extract against certain bacteria. Water extract did not have any activity against bacteria. Antifungal activity assessment indicated that the tested fungal strains are more susceptible to aqueous extract followed by methanol extract and chloroform extract<sup>13</sup>.

#### **Antifungal activity**

The ethanolic extracts of *A. bracteolata* was studied Antifungal activity using disc diffusion method and was found to have highest activity at minimum concentration. The study justify that the bioactive principles present in the extracts may be responsible in the treatment of ring worm infection. It was reported that Ethanolic extract effective against *Trichiophyton rubrum* and *Microsporium canis*.

#### **Antiplasmodial activity**

*In vitro* antiplasmodial activity against *Plasmodium falciparum* 3D7 (chloroquine sensitive) and Dd2 (chloroquine resistant and pyrimethamine sensitive) was investigated by Ramasubramania raja R *et al.* It was found that extract of *A.bracteolata* exerted activity on *P. falciparum* strain 3D7 with an IC50 less than 5µg/mL. Phytochemical analysis indicated

that the most active phase contained terpenoids and tannins and was devoid of alkaloids and saponins. The effect of plant extracts on lymphocyte proliferation showed low toxicity to the human cells. Another studies, shows that the plant extract of *A.bracteolata* has potent antimalarial activity (*in vitro*) against schizonts maturation of *Plasmodiumfalciparum*, the major human malaria parasite. The whole plant extracts of *Aristolochia bracteolata* produced 100% inhibition of the parasite growth at concentration  $\leq 50 \mu\text{g/ml}$ . The two most active plants showed the presence of sterols, alkaloids and tannins.

#### **Antioxidant properties**

*A.bracteolata* Retz was investigated and 2, 2-diphenyl picrylhydrazyl (DPPH) radical scavenging activities, reducing powers, and the amount of total phenolic compounds of the extracts were studied. The antioxidant activity was by ammonium thiocyanate assay. 2, 2-Diphenyl picrylhydrazyl (DPPH) free radicals scavenging activity was assessed according to Blois (1958), with a slight weight modification. Absorbance was measured at 700 nm. Ascorbic acid solution was used for comparison. Increased absorbance of the reaction mixture indicated increased reducing power. The antioxidative effect is mainly due to phenolic components, such as phenolic acids, and phenolic diterpenes. The antioxidant activity of phenolic compounds is mainly due to their redox properties, which can play an important role in absorbing and neutralizing free radicals, quenching singlet and triplet oxygen, or decomposing peroxides<sup>14</sup>.

#### **Antimicrobial activity**

The antimicrobial activity of *A.bracteolata* was investigated by Parekh *et al.* The antimicrobial assay was done by both the agar disc and agar well diffusion method against six medically important microorganisms viz. *Bacillus subtilis*, *Staphylococcus subfava*, *Alcaligenes fecalis*, *Proteus mirabilis*, *P. aeruginosa* and *Candida tropicalis*. According to the study, the methanol extract was found to be more effective than the aqueous extract. It has been found that the aristolochic acid from the root of *Aristolochia bracteolata* posses significant al

activity. Aristolochic acid I was isolated from the methanolic and ethyl extract extracts of *Aristolochia bracteolata* and conformed through IR, NMR and MS. The percentage purity of aristolochic acid I was determined by UV and HPLC method. Antibacterial activity of extracts of *A.bracteolata* and the isolated compound was determined by disc diffusion method. Microbial assay of isolated compound (Aristolochic acid) from ethyl acetate and ethanol extracts were shown good antimicrobial activity and the zone of inhibition of both at higher concentration 50µg/ml were similar with the standard aristolochic acid<sup>15</sup>.

#### **Wound healing activity**

The ethno botanical knowledge base for treatment of cuts and wounds which includes a usage of plants/plant extracts/decoctions or pastes, methods employed by tribals and folklore practices prevailing in India have been analysed. The ethanol extract of the leaves of *Aristolochia bracteolata* Lam. was studied for its effect on wound healing in rats, using incision, excision and deadspace wound models, at two different dose levels of 400 and 800 mg/kg/body wt /day. The plant showed a definite, positive effect on wound healing, with a significant increase of the level of two powerful antioxidant enzymes, super oxide dismutase and catalase, in the granuloma tissue<sup>16</sup>.

#### **Anti angiogenic activity**

Petroleum ether extract of *Aristolochia bracteolata* Lam (Aristolochiaceae) roots was screened for the activity against cutaneous melanoma using Chicken Chorioallantoic Membrane (CAM) Assay has been studied. Angiogenesis and melanoma cell survival were visualized and recorded using dissecting microscope and imaging system. Concentrations of the extracts ranging from 10mg to 50mg were screened. Chemical tests of the extract revealed the presence of alkaloids, triterpenes and steroids. It was observed that 30mg dose notably reduced the proliferation of blood vessels and reduced survival rate of melanoma cells in CAM. Cultured melanoma cell lines were obtained from cancer research centre, Hyderabad. It was concluded that the root extract of *Aristolochia bracteolate* possess inhibitory effect on proliferation of melanoma cells and its topical

application may be more advantageous to treat cutaneous melanoma, since topical treatments have advantages for rapid, effective and natural healing of cancers targeting the cancer site with much higher doses than could ever be achieved with oral treatments alone.

#### **Trypanosocidal effect**

*Aristolochia bracteolata* was evaluated for its *in vivo* activity against trypanosome evansi infection in the rats. Six groups of 10 rats each aged 5-7 weeks, average weight 150grams were used. Both the chloroformic and methanolic extract of the plant extract was administered orally at dose rates of 250 and 500mg/kgBW. The activity was compared to cymelarsan which was given at a dose rate of 2.5mg/kg BW subcutaneously. Results showed that plant extract gave a promising trypanosocidal effect. The chloroformic extract gave better result than that of the methanolic extract with both doses<sup>17</sup>.

#### **Anti implantation and abortifaciant activity**

Ethyl acetate soluble fraction of the ethanolic extract of *Aristolochia bracteolata* was tested for precoital and postcoital anti implantation test and abortifaciant activities in female albino rats. In the precoital study, the treatment at 20 and 40 mg/kg body weight showed significant and dose related anti implantation and abortifaciant properties. In the post coital study of 20, 30 and 40 mg/kg body weight doses similar results were observed. The total anti fertility activity of 40 mg/kg body weight was found to be comparable to the standard ethinyl oestradiol given for the similar period.

### **TOXICITY AND SIDE EFFECTS**

#### **In goats**

Diarrhea, dyspnea, tympany, arching of the back, loss of condition, and loss of hair from the back were the prominent signs when *Aristolochia bracteolata* was given orally to goats. The main lesions were hemorrhages in the lungs, heart, and kidneys, fatty change and congestion in the liver, mucoid abomasitis and enteritis and straw-colored fluid in serous cavities. An increase in aspartate amino transferase activity, ammonia and urea concentrations and a decrease in the concentrations

of total protein and magnesium were detected in the serum<sup>18</sup>.

#### Rats

Swiss albino rats were used to study the toxicological effect of methanolic and chloroformic extract of *Aristolochia bracteolata*. Methanolic and chloroformic extracts were given at doses of 250 and 500 mg/kg BW to Swiss albino rats. Oral administration of the extract caused symptoms such as depression, arching of the back and tremors. Serum analysis indicated increase in the activity of Aspartate amino transferase (AST), Alanine amino transferase (ALT) and alkaline phosphatase (ALP). The concentration of urea, creatinine, and ammonia were also increased and the concentration of total protein decreased. The main lesions found were haemorrhage in the kidney and congestion of the liver. It has been reported that chloroformic extract

at the rate of 500 mg/kg was more toxic than all the treatments.

#### In chicks

*A.bracteolata* is used in Sudanese folkloric medicine for the improvement of health by increasing body weight and treatment of various disorders. Bovans-type chicks were fed 10% *A.bracteolata* seed and 5% mixture of *A.bracteolata* and *Astragalus gummifer* of standard diet for two weeks. The given concentration mixture of the plants were toxic but not lethal to chicks and caused reduced body weight gain. Mild diarrhoea was observed in te chicks on the 5% mixture of two plants. Alteration of serum AST and ALT activities and total protein, albumin, globulin, cholesterol and uric acid were correlated with changes in haematology and pathological effects on vital organs<sup>19</sup>.



*A. acuminata* habitus drawing



*A. arborea* flowers



*A. lindneri*



*A. macrophylla*



*A. maxima* flowers



*A. pistolochia* flowers



*A. pontica* flower

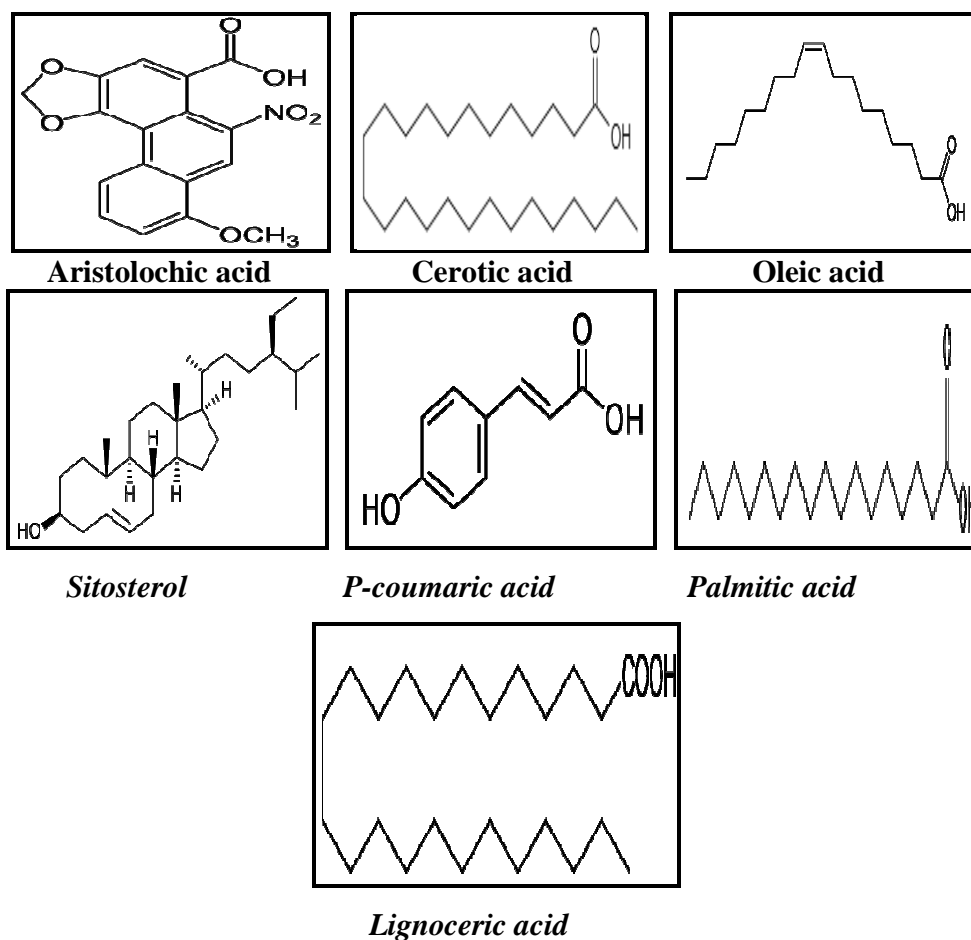


**Figure No.1: Species of *Aristolochia***



**Figure No.2: Leaf of *Aristolochia***





**Figure No.3: Phytoconstituents of *A.bracteata***

### CONCLUSION

The study was concluded that having many functions and phytochemical constituents. *Aristolochia* species have been used in herbal medicines since antiquity in obstetrics and in treatment of snakebite, festering wounds, and tumors, and they remain in use particularly in Chinese herbal medicine. The work has been used for further processing research work the same species.

### ACKNOWLEDGEMENT

Authors are thankful to Hon. Secretary, Khalsa College Charitable Society, Amritsar and Director-Principal, Khalsa college of Pharmacy, Amritsar for providing facilities to carry out this Review work.

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