



A Comprehensive Abridged Description on Phytopharmacological Constituents and Intrinsic worth of Dutchman's Pipe (*Aristolochia tagala* L.)

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Abstract

Species of *Aristolochia* are widely distributed in all parts of the world and were utilized traditionally for their various medicinal uses. *Aristolochia indica* is credited with innumerable medicinal activities. Several phytoconstituents like aristolochic acid, ceryl alcohol, β - sitosterol, stigmast-4-en-3-one, friedelin, cycloeucalenol and rutin have been isolated from different parts of the plant. *Aristolochia tagala* L. (*Aristolochiaceae*) has long been used in Indian subcontinent in the traditional system of medicine to treat cholera, fever, bowel troubles, ulcers, leprosy, skin diseases, menstrual problems and snakebites. The plant is also used as emmenagogue, abortifacient, antineoplastic, antiseptic, anti-inflammatory, antimicrobial, antipyretic, antifertility and antispermatogenic agent. Aristolochic acid, a major active constituent of the plant is reported to cause cancer, nephropathy, and is a potent abortifacient. This study was carried out to compile the review form on *A. tagala* concerning to the traditional uses, pharmacology and phytochemistry.

Keywords: Magnoflorine, Anti-inflammatory, Abortifacient, Diaphoretic, Pharmacology, Phytochemistry

Introduction

Aristolochia tagala (Aristolochiaceae), a member of the bitter and poisonous Aristolochias is a rare medicinal herb reported to be used against snakebites and bowel complaints. The plant is commonly known as Oval leaf Dutchman's pipe (Fig. 1 & 2) and is distributed in the northeast and southern parts of India, China, South-East Asian countries and Australia. They may grow as climbing vines, as short creeping herbs and a few are shrub-like. *Aristolochia* species are herbaceous perennials, undershrubs or shrubs, often scandent, scrambling, twining, sometimes lianas, usually with prostrate or tuberous rhizomes or rootstocks, and alternate, pinnate, polymorphic or lobed leaves bearing essential oils. Species of *Aristolochia* were widely distributed in tropical, subtropical and temperate regions of the world. They are known to occur in Asia, Africa, North and South America and Australia but there is a wide distribution across tropical Asia. [1,2]



Fig. 1 & 2 *Aristolochia tagala* Plants

Various species of *Aristolochia* have been used in the folk and traditional medicines as medicaments and tonics. The major negative aspect of some of the aristolochic acids found in the members of Aristolochiaceae is nephro-toxicity which restricts its use. A significant enormousness of research have been reported involving different species of *Aristolochia* viz. *A. indica*, *A. elegans*, *A. cucurbitifolia*, *A. pubescens*, *A. anguicida*, *A. cymbifera*, *A. chamissonis*, *A. fimbriata*, *A. paucinervis*, *A. bracteolata*[etc. This review compiles different aspect of the plant species emphasizing on its pharmacological and ethnomedicobotanical aspects. Medicinal importance *Aristolochia tagala* is extensively used in traditional medicine. Roots of the plant are mainly used to treat different ailments. Apart from roots. Leaves, flowers, fruits and whole plant is used for the preparation of different medicines. *A. tagala* has been for the treatment of various diseases, and the presence of compounds such as isocorydine, kaempferol, and beta-sitosterol must have contributed to their biological property. Although there are reports of the anticancer property of aristolochic acid

previously and there are also reports of its nephrotoxicity, the use of *A. tagala* in its crude form is still a concern. The Virginia snakeroot is attracting increasing interest for its medicinal virtues and as a result is becoming uncommon in the wild. It merits consideration for cultivation in forest areas. It is used in a number of proprietary medicines for treating skin, circulatory and kidney disorders. The plant contains aristolochic acid (Sodium; 8-methoxy-6-nitronaphtho[2,1-g][1,3]benzodioxole-5-carboxylic acid) [Fig. 3] which, whilst stimulating white blood cell activity and speeding the healing of wounds, is also carcinogenic and damaging to the kidneys. [2-5]

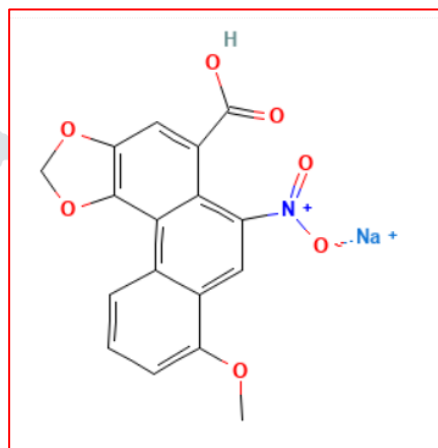


Fig Sodium;8-methoxy-6-nitronaphtho[2,1-g][1,3]benzodioxole-5-carboxylic acid

The root is harvested in the autumn and dried for later use. The root is antidote, anti-inflammatory, bitter tonic, diaphoretic, diuretic and stimulant. Traditionally it was chewed in minute doses or used as a weak tea to promote sweating, stimulate the appetite and promote expectoration. The native North Americans considered it to have analgesic properties and used an infusion internally to treat rheumatism, pain - but especially sharp pains in the breast, and as a wash for headaches. The bruised root is placed in hollow teeth for treating toothache. An extract of the root can be drunk to relieve stomach pains. The boiled root, or a decoction of the whole plant, can be used to treat fevers. The chewed root or crushed leaves was applied to snakebites. This species was the most popular snakebite remedy in N. America. It has also been applied externally to slow-healing wounds and in the treatment of pleurisy. Aristolochia species plants are used in all parts of the world for various ailments based on their anecdotal reports. In this review our main objective is to systematically access the widespread local and traditional uses of Aristolochia species. [4-7]

Chemical Constituents and Pharmacology of Aristolochia tagala

The therapeutic value of *A. indica* has been recognized in different system of traditional medicine for the treatment of different ailments of human beings. The plant possesses emmenagogue, abortifacient, anti-spermatogenic, anti-fertility, anti-arthritic, anti-inflammatory, antiperiodic, diuretic, and anti-bilious properties. The leaves of the plant are applied externally in skin diseases. The plant contain aromatic oil (0.5%), coloring material, and an alkaloid (aristolochine 0.05-0.07%). Aristolochic acid (0.06-0.07%), glycosides, and

steroids are present in rhizome. Aristolochic acids are a family of carcinogenic, mutagenic, and nephrotoxic compounds commonly found in the birthwort family of the plants. It functions as a phospholipase A2 inhibitor, antiseptic, anti-inflammatory, and bactericidal agent. Aristolochic acid [1:1 mixture of two forms, Aristolochic acid I, and Aristolochic acid II] (Fig. 4). This review of literature including phytochemical and pharmacological investigations on *Aristolochia* species have covered 164 compounds belonged to the classes of aristolochic acids and esters, aristolactams, aporphines, protoberberines, isoquinolines, benzyloisoquinolines, amides, flavonoids, lignans, biphenyl ethers, coumarins, tetralones, terpenoids, benzenoids, steroids, and others with extensive physiological activities. [8-11, 16,22,23-25]

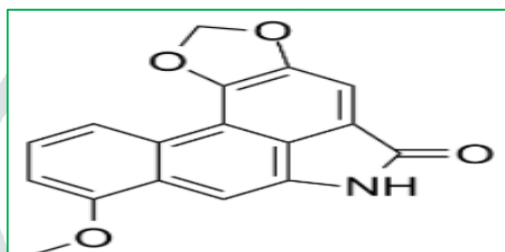


Fig. 4 Chemical Structure of Aristolochic acid I and Aristolochic acid II

Aristolochic acid has been reported to have antitumor and anticancer effects. It also causes nephrotoxic effect. The antimicrobial potency of *A. tagala* is believed to be due to steroids, phenolic compounds, and flavonoids. Magnoflorine found to have anti-inflammatory activity, apigenin dimethyl ether, reported to have potential antidiabetic and anti-obesity. Phytochemical screening of different extracts of *A. tagala* revealed the presence of steroids, phenolic groups and flavonoids. The ethanolic, acetone and chloroform extracts of *A. tagala* showed antibacterial activity. Aristololactam (Fig. 5) is the main metabolite of aristolochic acid I (AA-I), participates in the processes that lead to renal damage.

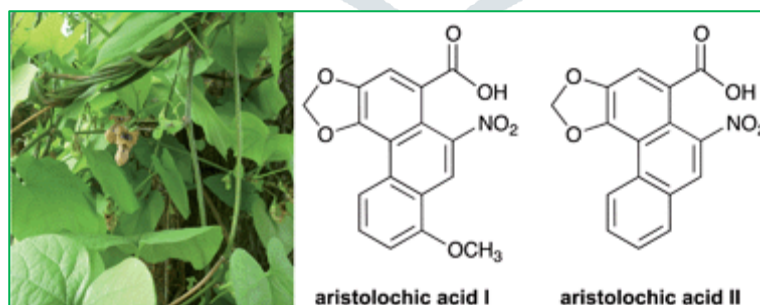


Fig. 5 Chemical Structure of Aristololactam

The secondary metabolites from *Aristolochia* species cover 16 major groups classified by their chemical structures, including

- aristolochic acids and esters,

- aristolactams, aporphines, protoberberines, isoquinolines, benzylisoquinolines, amides, flavonoids, lignans, biphenyl ethers, coumarins, tetralones, terpenoids, benzenoids, steroids, and others.
- The aristolochic acids were host of phenanthrene derived metabolites in which the aristolactams also possessed the similar skeleton. The identified terpenoids can further be divided into three subgroups: mono-, sesqui-, and diterpenoids.

Aristolochic acids and esters

The constituents from the *Aristolochia* genus became the interesting topic for the phytochemical and pharmaceutical researchers since the discovery of aristolochic acid derivatives. The naturally occurring aristolochic acids possessed the 3,4-methylenedioxy-10-nitro-phenanthrenic-1-acid skeleton are typical constituents of the *Aristolochia* species and claimed to be responsible for the various biological activity of *Aristolochia* species [Fig. 6]. Aristolochic acid I (1) is the most abundant aristolochic acid found in almost all species of *Aristolochia* studied with few exceptions. Recently health food supplements containing aristolochic acids have been prohibited for use in weight reduction with complete scientific results supported. In addition, seven methyl esters of aristolochic acid were reported from the *Aristolochia* species and among these only ariskanin A (52) did not possess the 3,4-methylenedioxy substitution pattern. Only few cases of aristolochic acid esters, including aristolochic acid methyl ester (151) and 6-methoxyaristolochic acid methyl ester (152), do not possess the nitro group at the C-10 position. The majority of these denitroaristolochic acids were reported from the Formosan *A. manshuriensis*.



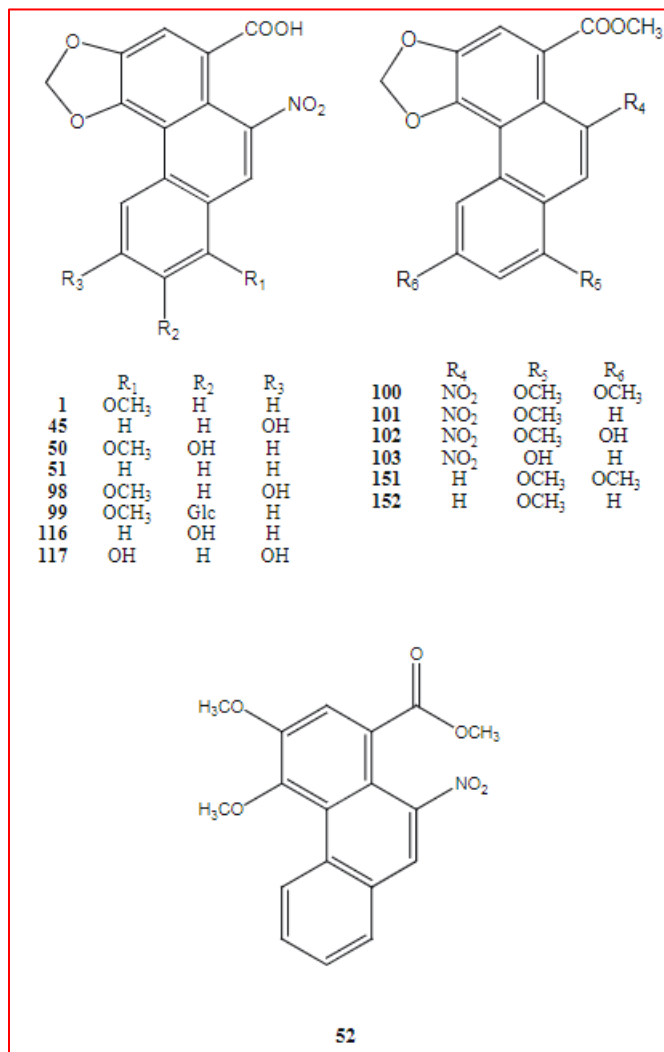


Fig. 6. Aristolochic acids and esters from the Aristolochia species

Aristolactams

Aristolactams are regarded as biogenetic intermediates in the biosynthetic pathway of aristolochic acids. They are usually supposed to originate from the cyclization condensation reaction of the reduction products of aristolochic acids. From Fig2, it is evident that twelve aristolactams have been reported from Aristolochia species and among them there were also six compounds having the 3,4-methylenedioxy substitution groups. Aristolactam I (15), aristolactam AII (36), and aristolactam Ia N -β-D-glucoside (122) were the frequently encountered aristolactams in the Aristolochia species. Aristolactam II (36) found in several species of Aristolochia is a simple aristolactam without any substitutions on rings B and C. The 9-oxygenated aristolactams are rare in Aristolochia with only compounds 68 and 125 being reported. Compound 125 was one example of 9-oxygenated aristolactam with the substitution of diglucoside.

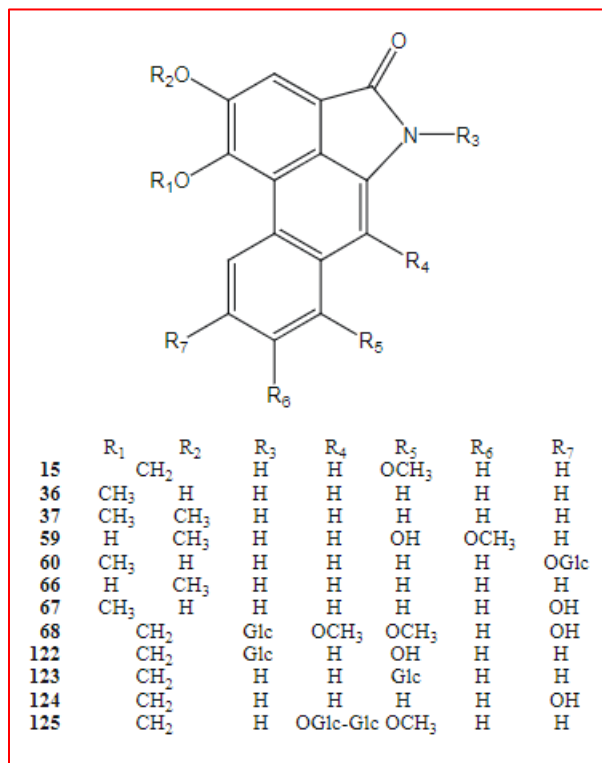


Fig. 7. Aristolactams from the Aristolochia species

Aporphines

Seventeen aporphine alkaloids have been characterized from *Aristolochia* species (Fig8). Aporphines with N -formyl substitution, 6 α ,7-dehydro-N - formylnornantenine (11) and N-formylnornantenine (12), were reported from *A. brevipes*. The polar quaternary aporphine magnoflorine (104) was found in *A. elegans* and *A. gigantea*. The 4,5-dioxoaporphine is a small group of aporphine alkaloid found mostly among the *Aristolochia* ceae family and usually considered as possible intermediates of the precursors of aristolactams and aristolochic acids in plants. Only 4,5-dioxodehydro- asimilobine (107) was reported from *A. elegans*. Most of the aporphines found in *Aristolochia* species possess 4,5-tetrahydro basic skeleton. Lagesianines B-D (140-142) were the dimeric aporphine alkaloids linked through the substituent on nitrogen, oxygenated functions, and substituent on the phenanthrene ring, respectively. These dimeric aporphines were only reported from the leaves of *A. ligesiana*.

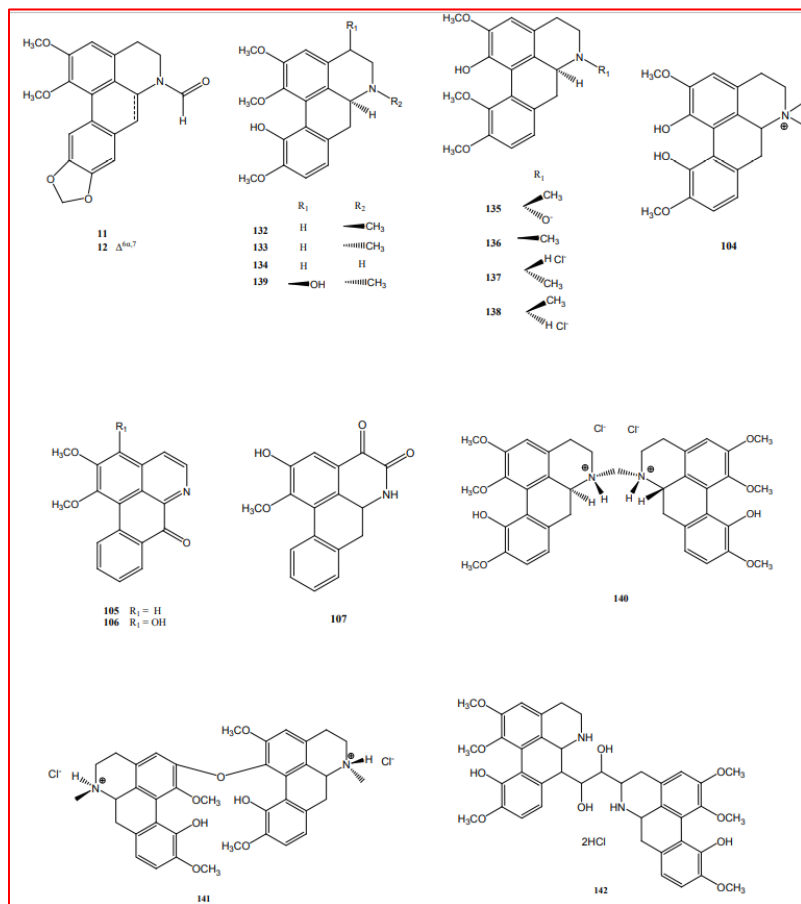


Fig. 8. Aporphines from the Aristolochia species

Protoberberines

Occurrence of protoberberine alkaloids (Fig9) was rare in *Aristolochia*, and they were only reported from *A. constricta*. 8-Benzyltetrahydroprotoberberine type alkaloid, 23, had been obtained by introduction of a benzyl group at C-8 of berberine to result in this unusual carbon skeleton. Isoquinolines The presence of isoquinoline alkaloids 78-82 in the genus *Aristolochia* is limited to *A. elegans*. Purified compounds of this class were listed in the Fig5. All of these alkaloids reported possessed the tetrahydroisoquinolone basic skeleton. Isoquinoline alkaloids were usually considered as biogenetic intermediates in the catabolic process of bisbenzyltetrahydroisoquinoline alkaloids.

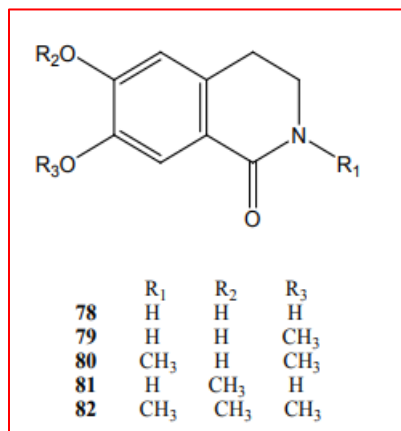


Fig. 9. Isoquinolines from the Aristolochia species

Benzylisoquinolines

The occurrence of benzylisoquinoline type alkaloids, aristoquinolines A-C (61-63) constitute the first report of N-oxide benzoyl benzyltetrahydroisoquinoline ether alkaloids from Aristolochia species (Fig10). These provided the natural evidence for the catabolic process of structurally interesting bisbenzyltetrahydroisoquinolines. The isoquinolones, benzylisoquinolines, biphenyl ethers, and N-oxide benzoyl benzyltetrahydroisoquinoline ether alkaloids were derived biogenetically from bisbenzylisoquinolines, common metabolites of Aristolochia species, in general alkaloid catabolic process.

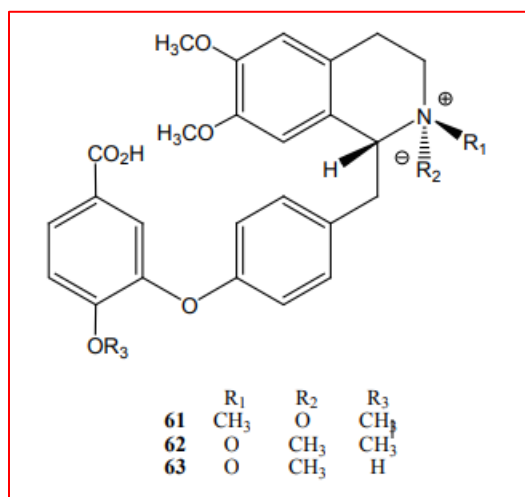


Fig. 10. Benzylisoquinolines from the Aristolochia species

Amides

The amides are another type of compounds isolated from several Aristolochia plants (Fig 11). One class of the amides from Aristolochia species, on structural investigation were found to contain a tyramine unit connected to phenolic acids like cis- or trans- coumaric

and ferulic acids. Aristolamide (149) and aristolamide II isolated from *A. manshuriensis* contain $-\text{CONH}_2$ group at C-1 which possessed the phenanthrene basic skeleton was another class of amide reported from *Aristolochia* species.

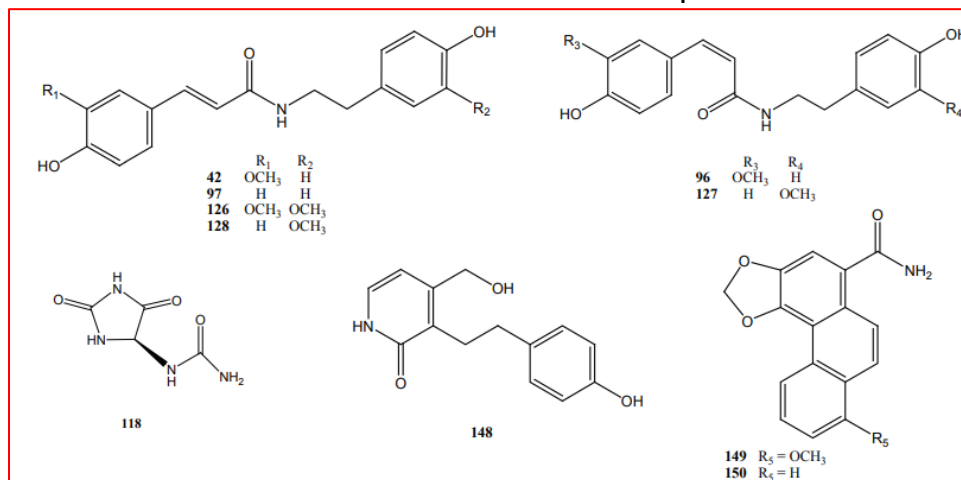


Fig. 11. Lignans from the *Aristolochia* species

Flavonoids

Flavonoids continue to attract the researchers' interests due to their structural diversity, biological and ecological significance. They affect plant interactions with microsymbionts, insect predators and pollinators, and also function in pigmentation and act as protectants against UV irradiation. Virtually almost all higher plants produce flavonoids, however, some of them are fairly unique, in which many specific compounds are accumulated during plant growth and development. Six bisflavones, one unusual chalconeflavone dimer and two tetramers were characterized from *A. ridicula*. (Fig 12). These reports constitute the presence of biand tetraflavonoids in the family Aristolochiaceae. In addition, there was also simple flavone reported from *Aristolochia* species, like kaempferol (161) from *A. tagala*.

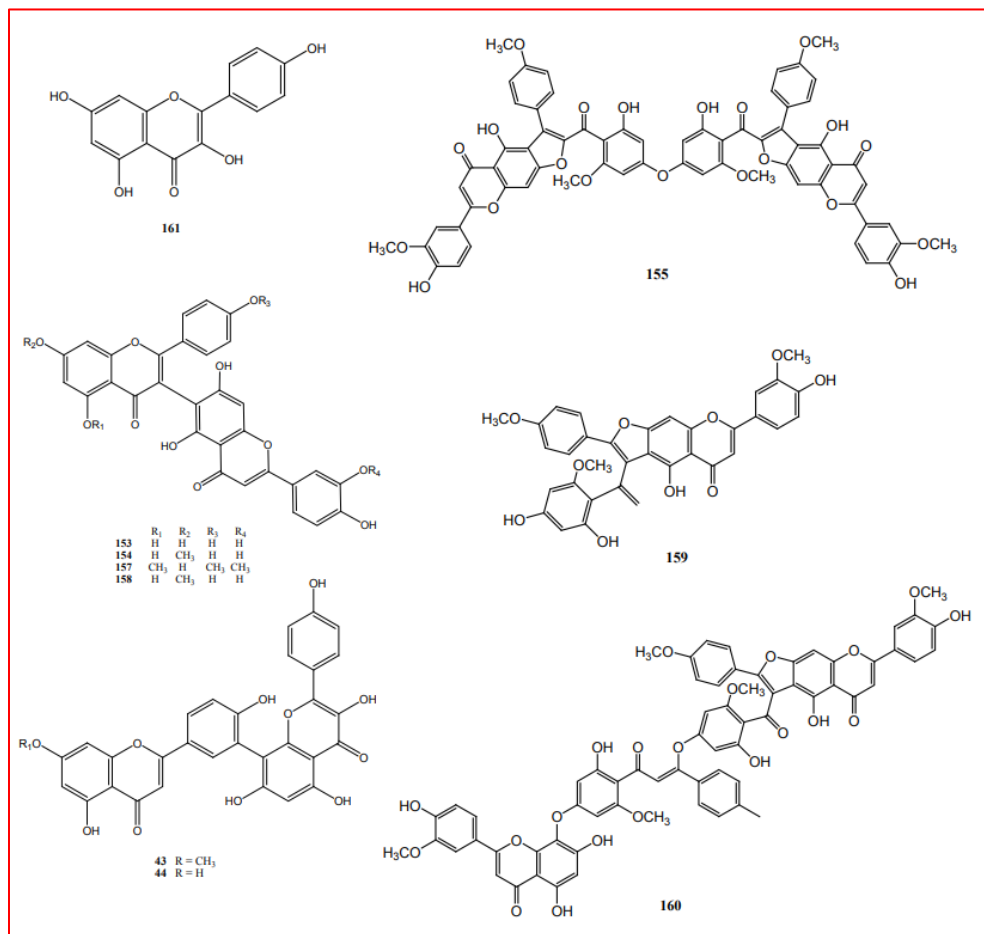


Fig. 12. Flavonoids from the Aristolochia species

Lignans

Lignans were another important type of metabolites found in several species of *Aristolochia*. There are five basic skeletons of neolignans and lignans with structural diversity reported from *Aristolochia* genus (Fig. 13), including diaryldimethyltetrahydrofurans, dibenzylbutanoids, benzofurans, and bisepoxylignans. The 2,5-diaryl-3,4-dimethyl-tetrahydrofurans 3-9 were all characterized from the roots of *A. arcuata*. Occurrence of the dibenzylbutane type lignans is the most common in *Aristolochia* genus. These lignans could be further divided into dibenzyltetrahydrofurans, dibenzylbutyrolactones, and dibenzylbutane diol depending on their oxidation states. Licarin A (162), licarin B (163), and eupomatenoid-7 (164) were benzofuran type lignans only reported from *A. taliscana*. The other type of lignans frequently encountered in *Aristolochia* species were the bisepoxylignans which were exemplified in Fig. 13, reported from *A. cymbifera*, *A. elegans*, *A. gigantea*, and *A. malmeana*, respectively. In addition, there was also one dimeric lignan (8R, 8'R, 8''R, 8'''R, 9R, 9''S)-bicubebin A (131) linked through the oxygen atom.

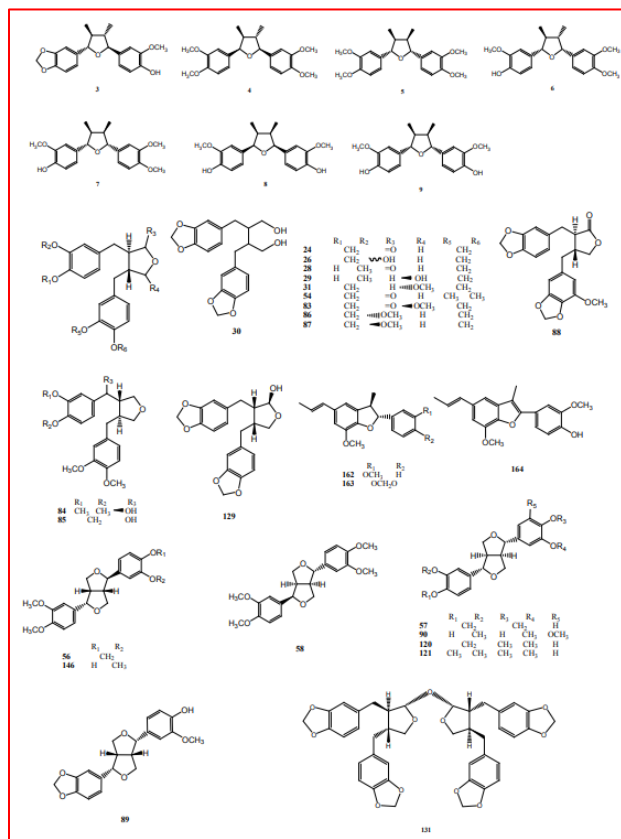


Fig. 13. Lignans from the Aristolochia species

Biphenyl ethers

Seven biphenyl ethers had been reported, including aristogins A-E (69-73), F (64), and 4-methoxy-3,4-oxydibenzoic acid (74) (Fig. 14). All these compounds have only been reported from *A. elegans* and they are usually considered as one of the end products in the catabolic process of bisbenzylisoquinoline alkaloids.

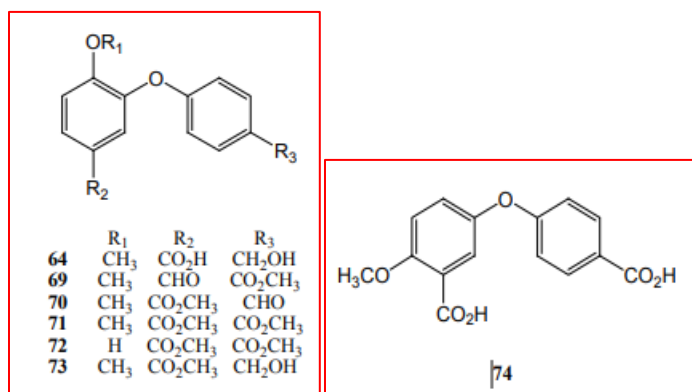


Fig. 14. Biphenyl ethers from the Aristolochia species

Coumarins

Although there were only two coumarins, 7,9-dimethoxytariacuripyronone (13) and 9-methoxytariacuripyronone (14), characterized from the roots of *A. brevipes* (Fig. 15), these constituents also displayed significant physiological activity.

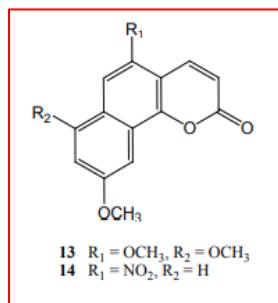


Fig. 15. Coumarins from the Aristolochia species

Tetralones

Among five tetralones reported from Aristolochia species so far (Fig. 16), four tetralones, aristelegones A-D (38, 75-77) have been characterized in the stems and roots of *A. elegans* collected in Taiwan). Aristelegone A (38) and (+)-4,7-dimethyl-6-methoxy-1-tetralone (39) were reported from the stems of *A. constricta*. Most of these identified tetralones possessed a keto substituent at C-1 except that aristelegone D (77) had 1,2-diol functionalities.

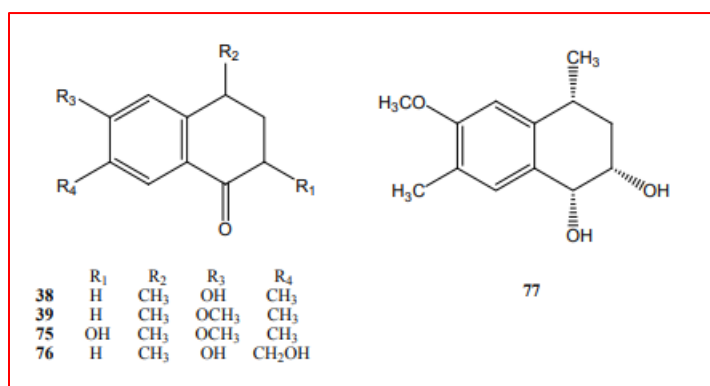


Fig. 16. Tetralones from the Aristolochia species

Terpenoids

Although there were so many terpenoids characterized from Aristolochia species in our previous review, the number of terpenoids reported in the period between 2004 and 2011 was comparatively limited (Fig. 17). Only one monoterpene, 3-hydroxy α -terpineol (17), was identified from the roots of *A. brevipes*. Three sesquiterpenoids, cadalene (40), aristololide (95), and E-nerolidol (119), belonged to the cadinane, bourbonanes, and farnesane basic skeleton, respectively, were also characterized from the Aristolochia species. The diterpenoids with three types of C₂₀ carbon skeletons constitute the largest group of terpenoid metabolites in Aristolochia. First type of diterpenoid is the clerodane basic skeleton. 2-Oxo-populifolic acid (53) was reported from *A. cymbifera* and (-)-kolavenic acid (144) and (-)-2-oxokolavenic acid (147) were purified from *A. malmeana*, respectively. A furanolactone diterpene belonged to the clerodane type was isolated from the rhizomes of *A. albida* and identified as columbin (2). Second type is labdanes in which only (-)-copalic acid (55) and (-)-ent-6- β -hydroxycopalic acid (145) possessed this basic skeleton that were

only a little different from the clerodane type diterpenoids. From the reports up to date, it revealed that *Aristolochia* species were rich sources of ent-kaurane diterpenoids. In our reviewing period, totally eight ent-kaurane diterpenoids were reported from *A. constricta*, *A. elegans*, and *A. pubescens*. In addition, one ent-kaurane lignan 9-O-[(–)-kaur15-en-17-oxyl]cubebin (25), and one ent-kaurane diterpenoid ester of aristolochic acid aristolin (91) were also characterized from *A. constricta* and *A. elegans*, respectively. Aristolin (91) is the first example of an ester composed of aristolochic acid and a diterpenoid, in which C-16 hydroxy group of ent-kauran-16- β , 17-diol involves in the ester linkage with C-11 carboxylic acid group of aristolochic acid.

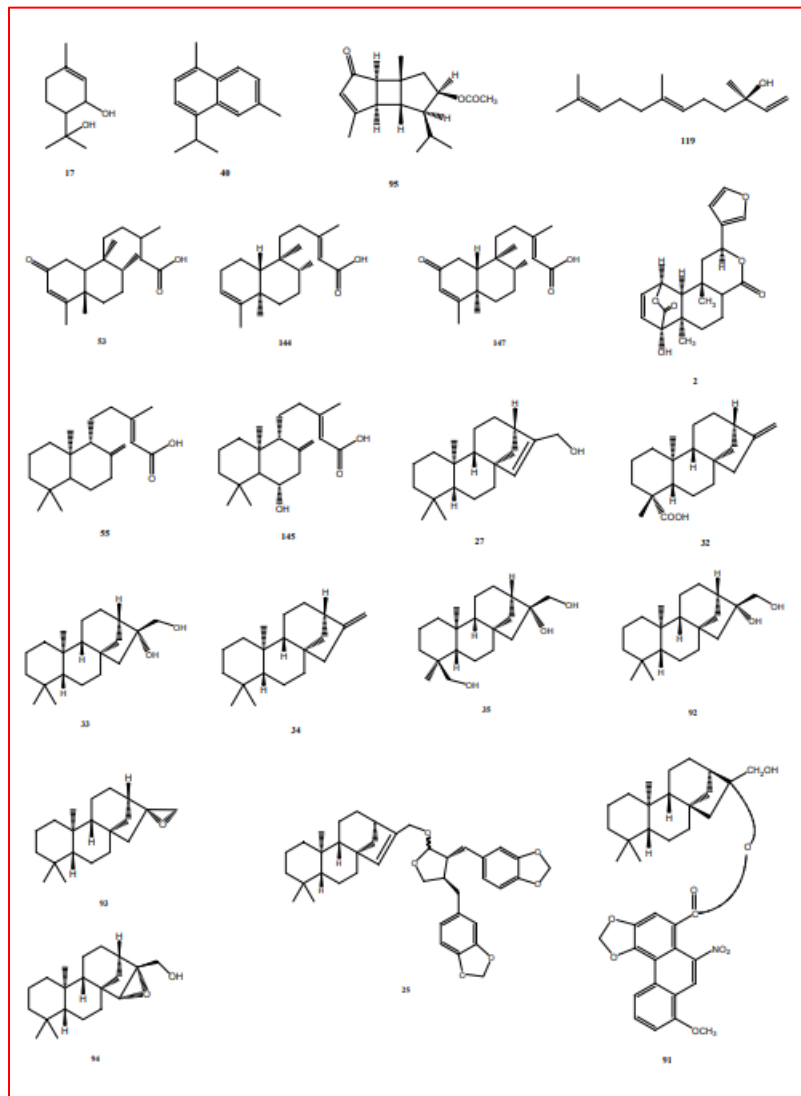


Fig. 13. Terpenoids from the *Aristolochia* species

Benzenoids

A number of benzenoid derivatives were isolated from different *Aristolochia* species, which include phenylmethanoids and phenylpropanoids (Fig. 18). Four simple benzenoid derivatives 108-111 were isolated from the stems and roots of *A. elegans*. Eight phenylpropanoids, including aglycones 112-115 from *A. elegans* and glycosides 46-49 from

A. cretica, respectively, were reported and most of them are ferulic, cinnamic, p-coumaric, and caffeic acids derivatives.

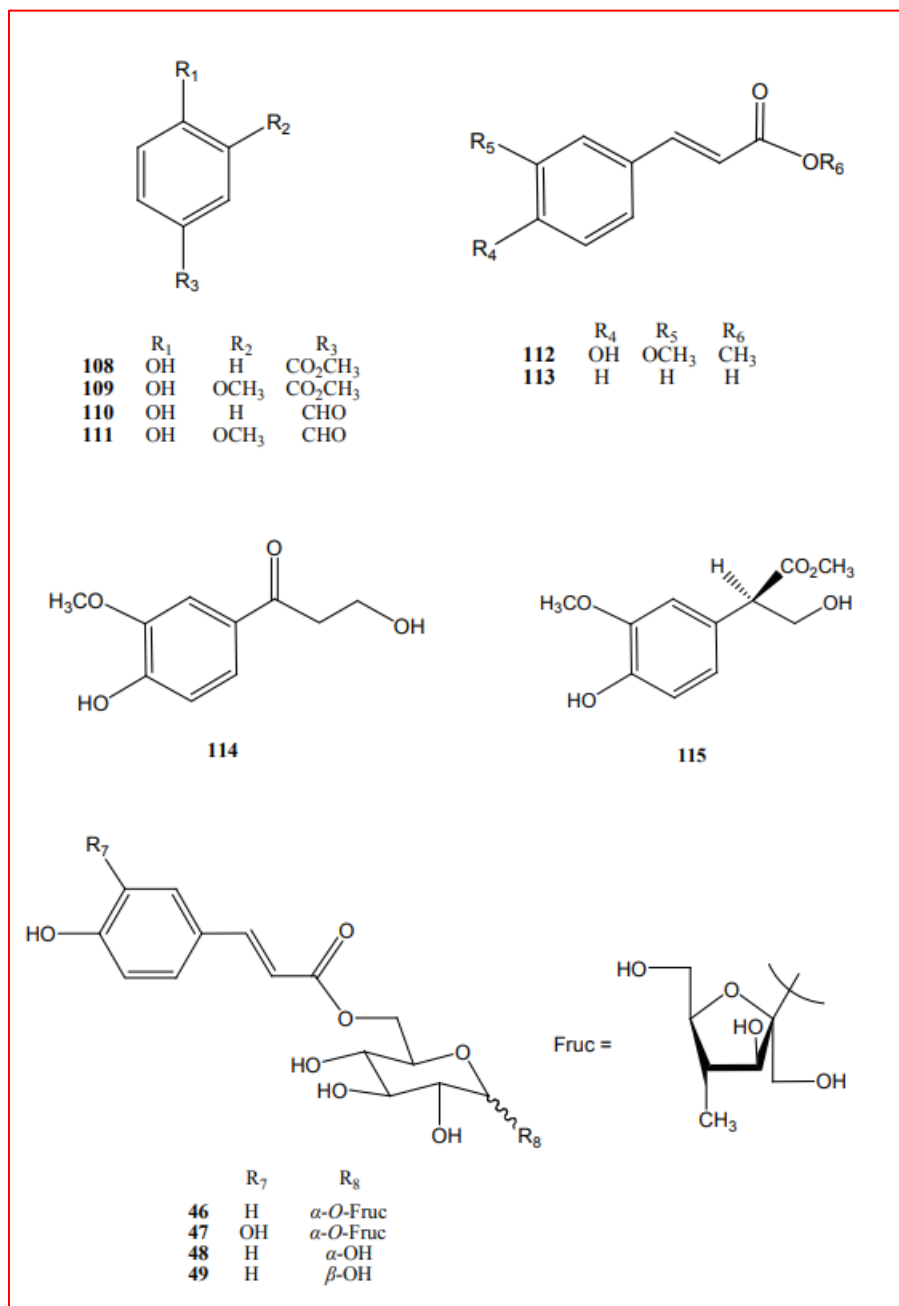


Fig. 18. Benzenoids from the Aristolochia species

Steroids and others

Steroids are usually encountered in natural sources, and those presented in Aristolochia species are mostly derivatives of β -sitosterol and stigmasterol. Among these steroids, β -sitosterol (10) and β -sitosteryl glucoside (41) were frequently found in several Aristolochia species (Figure 19). In addition, some miscellaneous compounds including glycerol (143) and proto-quercitol (156) were also reported from Aristolochia species.

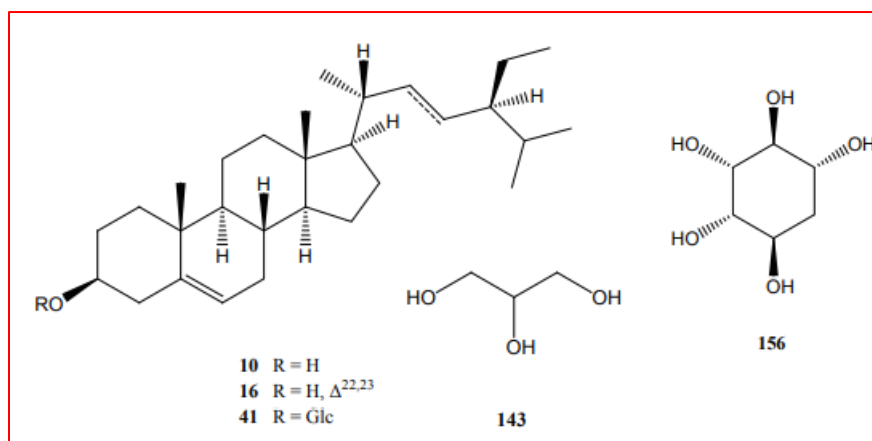


Fig. 19. Steroids and others from the Aristolochia species

Classical therapeutic applications of *A. tagala* for wellbeing

In Ayurveda, the root bark of the plant are used as antidote for all types of poisons (snake poison, spider poison, scorpion stings, etc.) The tribal people are using this plant from ancient times to treat cobra poison, and scorpion stings. The bruised roots are applied to bites of centipedes, and scorpion stings. 1.5 inch root is smashed, and placed under the tongue for the neutralization of snake venom. In one study, ethanolic extract of the plant exhibited protective effect against the red scorpion venom, and showed 50% survival benefits in mice. The plant is administered in low doses to treat low appetite, menstrual disorders, and to remove toxins from blood. The powdered root with honey is given for dropsy, leukoderma, tonsillitis, and chronic dyspepsia. For fever, indigestion, and digestive disorders, one pinch of root powder (Fig. 20 & 21) is taken with warm water. The fresh leaves ground with water are applied in acute, and chronic rheumatism. For swelling, the seed paste is applied externally. For headaches, the paste of leaves is mixed with turmeric, and applied on forehead, twice a day. [12-14]



Fig. 20 & 21 Root powder of Aristolochia tagala

For leucoderma, skin diseases, wounds, and swelling the paste of leaves is applied topically on the affected areas. The birthwort plant has astringent property. It remove the fluids in abscesses and wounds and help increase the speed of healing. It is best had in the form of decoctions and infusions. The infusion shows some antiseptic property. Apply it on the wounds and cuts to help the healing process. They give the decoction of the birthwort plant to help induce labour. It prevents infections and induces menstruation. So, you must take care as it might induce a miscarriage. Use only a mild decoction of the plant. The anti-inflammatory property of the birthwort is useful for controlling inflammation of the tissues in the bone joints. It reduces the pain and helps the patients get relief. : The infusion of the *Aristolochia* spp. is useful for curing the ulcers. It soothes the stomach and helps the ulcers to heal fast. It removes the blockages and helps to soothe the airways. helps make the functioning of the digestive system normal. Tea made from birthwort to get relief from flatulence. It will help improve the bowel movement and remove the gas from the intestine. Roots In many of the tribal settlements, the fresh root of *A. tagala* is used against poisonous bites from snakes and scorpions. Root decoction is consumed as tonic, carminative and emmenagogue. [15-18] It is also used to treat high blood pressure, Beri Beri and swollen feet. In Andhra Pradesh, roots are used to increase the production of breastmilk. The rheumatic area is massaged with the paste of the roots by tribal of Meghalaya. Root decoction is used for treating Stomach pain, chest pain, fever, poultice in abdomen, skin disease, snake bite, malaria, dyspepsia and flatulent in Andaman and Nicobar. The root extract of the *Aristolochia tagala* used as female antifertility medicine. The various gynaecological disorders can cause much pain for women. The use of birthwort infusion helps relieve the pain and make the disorder alright again. For women who have late periods, having birthwort decoction will help to speed up the menstrual cycle. Have a cup of birthwort tea, and this will make the woman menstruate. In some regions of the world, people use the *Aristolochia* as a contraceptive as it induces a miscarriage. Strong infusion of the *Aristolochia* induces the menstruation. The birthwort helps open the airways and clear any phlegm. The birthwort helps stimulate the action of the WBC (white blood corpuscles). This is the primary defender against germs, bacteria, and viruses. By augmenting this action, our immune system gets activated, and we remain protected from foreign invasions. When colic forms in the gastrointestinal tract due to allergies, it can be overcome by the action of the birthwort. Colic can form in the GI tract and in the gallbladder. [19-23,25]

Conclusion

This project report of literature including phytochemical and pharmacological investigations on *Aristolochia* species have covered 164 compounds belonged to the classes of aristolochic acids and esters, aristolactams, aporphines, protoberberines, isoquinolines, benzylisoquinolines, amides, flavonoids, lignans, biphenyl ethers, coumarins, tetralones, terpenoids, benzenoids, steroids, and others with extensive physiological activities. This project report will help researchers and scientists in locating the detailed information on *Aristolochia* species and address the continuous development in the phytochemistry and the therapeutic application of the *Aristolochia* species. The active compounds of birthwort plant are Aristolochic acids, tannins, and volatile oils. Aristolochic acids have been reported

to have antibacterial, antiviral, antifungal, and antitumor effects and in more recent times, have been used in conventional pharmaceuticals. Herbal remedies containing aristolochic acids have been used for different illnesses such as hepatitis, urinary tract infection, vaginitis, oral ulcer, upper respiratory tract infection, eczema, headache, dysmenorrhea, arthralgia, neuralgia, hypertension, cerebrovascular accident, bronchitis, pneumonia, heart failure and edema. It has been recommended for the treatment of dry cough, joints pain, inflammation, biliousness, dysphoea of children, snake bite and also used as abortifacient. Most importantly, the studies have shown that the plant exhibited significant antimicrobial activity.

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