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Aristolochia indica L.: A Review

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Abstract: *Aristolochia indica* 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, sister chromatid exchange and is a potent abortifacient. The present review deals with the different scientific studies and reports available in different aspects of this plant in the areas of Morpho-taxonomy, Phytochemistry, Pharmacology, Medicoethnobotany, Tissue culture and Chromosomal study.

Key words: *Aristolochia indica*, aristolochic acid, phytochemistry, pharmacology, ethnomedicobotany

INTRODUCTION

Aristolochia indica, one of the 500 species of the family Aristolochiaceae is distributed throughout the tropical, subtropical and Mediterranean countries. In Indian subcontinent, the plant is found in low hills and plains of India from Nepal and lower Bengal to Chittagong in Bangladesh and Coromondal Coast (Murugan *et al*., 2006; Kanjilal *et al*., 2009). This endangered medicinal plant, locally known as Isharmul (Bengali and Hindi) is a shrub with long twinning stem. Since the Graeco-Roman period, aristolochic acid, a constituent of *Aristolochia* species, has been used for medicinal purposes (Pezzuto *et al*., 1988). The plant is used to treat cholera, fever, bowel troubles, ulcers, leprosy, poisonous bites (Krishnaraju *et al*., 2005; Kanjilal *et al*., 2009). It is also used as emmenagogue, abortifacient, antineoplastic, antiseptic, anti-inflammatory, antibacterial and phospholipase A_2 inhibitor (Achari *et al*., 1981; Das *et al*., 2010). Several investigations have carried out on different species of the genus viz. *A. elegans* (Lopes *et al*., 1990b; Wu *et al*., 2000a; Wu *et al*., 2002; Shi *et al*., 2004), *A. albida* (Lajide *et al*., 1993; Choudhury *et al*., 1997), *A. papillaris* (Lemos *et al*., 1993), *A. mollissima* (Yu *et al*., 2007), *A. triangularis* (Rucker *et al*., 1981; Lopes *et al*., 1990a), *A. fangchi* (Martinez *et al*., 2002), *A. constricta* (Rastrelli *et al*., 1997), *A. cucurbitifolia* (Wu *et al*., 2000b), *A. heterophylla* (Wu *et al*., 1999), *A. rodriguesii* (Correa *et al*., 1998), *A. pubescens* (Nascimento and Lopes, 2003), *A. anguicida* (Gaitan *et al*., 2002; Fraga, 2004), *A. malmeana* (Messiano *et al*., 2008), *A. cymbifera* (Leitao *et al*., 1992), *A. chamissonis* (Bomm *et al*., 1999) and *A. ringens* (Larrahondo and Acevedo, 1990). The present review deals with a compilation of different reports on *A. indica* and one of its major component Aristolochic acid (from different *Aristolochia* sp.).

HABIT, HABITAT AND MORPHO-TAXONOMY

The plant is a shrubby or herbaceous vine with a woody root stock (Kanjilal *et al*., 2009). Flowering and fruiting of this climbing herb are found from December to February (Neelima *et al*., 2011). The leaves are glabrous, very variable, usually obovate-oblong to sub-pandurate entire with undulate margins, cordate acuminate. Flowers are few, in axillary racemes with a perianth up to 4 cm long having a glabrum pale green inflated (Das *et al*., 2010). Morphology of roots of *A. indica* was described by Bal and Gupta (1956). Sivarajan and Pradeep (1989) had noted co-evolution of *A. Indica* and Papilionid Butterflies. Foliar stomatal development in 3 Species of *Aristolochia* was discussed by Philip (1983). Nair and Narayanan (1962) had performed a study on the Nodal and floral anatomy of the family Aristolochiaceae. Wanke *et al*. (2006) had investigated the relationships within subfamily Aristolochioideae (Aristolochiaceae) combining morphological and molecular characters. Perianth development and systematics of *Aristolochia* were discussed by Gonzalez and Stevenson (2000). Phylogeny

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of Aristolochiaceae based on parsimony, likelihood and Bayesian analyses of *trnL-trnF* sequences was reported by Neinhuis *et al*. (2005).

PHYTOCHEMISTRY

Essential oil from the roots of the plant was reported by Rao *et al*. (1935). Preliminary studies on the essential oil were carried out by Rao and Mulhara (1955). Acidic and basic constituents of *A. indica* were reported while discussing the chemistry of the *Aristolochia* species (Coutts *et al*., 1959). Some novel derivatives of AA from *A. indica* were isolated and elucidated structurally by Kupchan and Merianos (1968). Total Ishwarone a novel tetra cyclic sesquiterpene was reported by Ganguly *et al*. (1969). Two sesquiterpene hydrocarbons (Ishwarane and aristolochene) from the roots of the plant have been isolated (Govindachari *et al*., 1970). Ishwarol, a new tetracyclic sesquiterpene alcohol from the plant species was reported by Govindachari and Parthasarathy (1971). Kelly *et al*. (1972) have reported total synthesis of Racemic Ishwarane a tetracyclic sesqui terpenoid. 5βH,7β,10α-Selina-4 (14), II-diene, a new sesquiterpene hydrocarbon from *A. indica* was discovered (Govindachari *et al*., 1973). Pakrashi *et al*. (1977) have reported new phenanthrene derivatives from the plant which included aristolochine alkaline, isoaristolochic acid, allatonin etc. A short synthesis of ishwarone was reported by Cory *et al*. (1979). Synthesis of tetra cyclic sesqui terpenoids racemic ishwarone was reported by Piers and Hall (1980). (12S)-7, 12-Secoishwaran-12-ol, a new type of sesquiterpene was reported by Pakrashi *et al*. (1980). Aristololactam N-β- D-glucoside (a phenanthrene derivative) and 3β-hydroxy-stigmast-5-en-7-one and 6β-hydroxy-stigmast-4-en-3-one (two steroids) have been isolated from *A. indica* by Achari *et al*. (1981). The roots of *A. indica* contains aristolindiquinone, aristololide, 2-hydroxy-1-methoxy-4Hdibenzo quinoline-4,5-(6H)-dione, Cephradione, aristolactam IIa, β-sitosterol-β-D-glucoside aristolactam glycoside I, stigmastenones II and III, methylaristolate, ishwarol, ishwarone and aristolochene (Achari *et al*., 1982, 1983). The Aristolochic acids and Aristolactams were reported by Mix *et al*. (1982). Aristolindiquinone, a new naphthoquinone from *A. indica* was reported by Che *et al*. (1983). Fertility-regulation activity of the roots was analyzed by Che *et al*. (1984). Clerodane diterpenes (Lopes *et al*., 1987) and Lignans and diterpenes (Lopes and Bolzani, 1988) have been reported from *Aristolochia* species. Methyl ester of 12-nonacosenoic acid from *A. indica* was reported Mahesh and Bhaumik (1987). Leitao and Kaplan (1992) had demonstrated the Chemistry of the genus *Aristolochia*. Aristolochic acid I and II were quantitatively analyzed by High Performance Liquid Chromatography (HPLC) (Hashimoto *et al*., 1999). Essential oil of the aerial parts was analyzed by Jirovetz *et al*. (2000). Preliminary phytochemical analysis of the plant has revealed the presence of alkaloids, tannins, cardiac glycosides, steroids, flavonoids and saponins (Vaghasiya and Chanda, 2007). Chemical composition of stem oil of the plant was investigated by gas chromatography and gas chromatography/mass spectroscopy. Among the total 15 compound identified, the major constituents of oil were trans-pinocarveol (24.2%), a-pinene (16.4%) and pinocarvone (14.2%) (Kanjilal *et al*., 2009). C-NMR Data of Diterpenes Isolated from *Aristolochia* Species were enumerated by Pacheco *et al*. (2009).

PHARMACOLOGY

Aristolochic acid (AA) (3,4-methylenedioxy-8-methoxy-10-nitrophenanthrene-1-carboxylic acid) is the major active constituent found in the plant. AA from *A. indica* has been reported as a tumor inhibitor by Kupchan and Doskotch (1962). The roots of *A. indica* extracted in petroleum ether, chloroform and alcohol showed 100% interceptive activity in mature female mice at the single dose of 100 mg kg^{-1} body wt (Pakrashi *et al*., 1976). Antispermatogenic effect of the extract of *A. indica* on male mice was noted by Pakrashi and Pakrasi (1977). A sesquiterpene from the roots of *A. indica* was found to exert anti-implantation and anti-oestrogenic activity. 100% interceptive activity and 91.7% anti-implantation activity in mice at a single oral dose of 100 mg kg^{-1} b. wt without any toxic effect at the dose levels used (Pakrashi and Shaha, 1977). Biological profile of p-coumaric acid isolated from *A. indica* was investigated (Pakrashi and Pakrasi, 1978). AA's effect on the fertility of female mice has been studied with Methyl ester of AA. The compound isolated from the roots was found to be a potent abortifacient (Pakrashi and Shaha, 1978). Anti-oestrogenic and anti-implantation effect of AA from *A. indica* was examined (Pakrashi and Chakrabarty, 1978a). Antifertility effect of AA from *A. indica* in female albino rabbits was reported by Pakrashi and Chakrabarty (1978b). Anti-fertility efficacy of the plant on mouse was also reported (Pakrashi and Pakrasi, 1979). Short term toxicity with methyl ester of AA from *A. indica* in mice was studied (Pakrashi and Shaha, 1979a). Effect of methyl aristolate from *A. indica* on implantation in mice was studied (Pakrashi and Shaha, 1979b). Changes in uterine phosphatase levels treated with AA during early pregnancy in mice were reported by Pakrashi and

Ganguly (1982). Carcinogenic action of AA in rats (Mengs *et al*., 1982) and acute toxicity of the same in rodents (Mengs, 1987) were also reported. Forestomach carcinoma in rats was reported to be caused by AA (Mengs, 1983). Chaudhury and Haq (1980) had mentioned this plant having antifertility activity. Kamboj and Dhawan (1982) in their study on plants for fertility regulation in India had mentioned *A. indica*. Farnsworth and Waller (1982) had reviewed plant-derived agents that prevent sperm production and included this species as one of them. The plants were containing some known or partially known sperm-agglutinating compounds contributed to their semen coagulating properties. Sister chromatid exchange and chromosomal aberrations in human lymphocytes *in vitro* are caused by it (Abel and Schimmer, 1983). Pregnancy was found to be disrupted in mouse by AA from *A. indica*. It disrupted nidation in mice when administered on Day 1 of pregnancy (Ganguly *et al*., 1986). Mutagenic and cytostatic potential of AA and several of its derivatives were evaluated by Pezzuto *et al*. (1988). AA binds covalently to the exocyclic amino group of purine nucleotides in DNA (Pfau *et al*., 1990). Antipyretic activity of this species collected from Tirumala hills, Andhra Pradesh, India has also been reported (Vedavathy and Rao, 1991). Vanherweghem (1997) has indicated relation between chronic interstitial nephropathies in Indians and *Aristolochia* sp. Progressive interstitial renal fibrosis has been reported to be associated with AA (Sekita *et al*., 1998). *Aristolochia* was reported to produce interstitial nephritis due to the occurrence of AA during chronic use in the treatment of rheumatism, diuretic and analgesic (Hashimoto *et al*., 1999). Whole plant extract has been reported to have antineoplastic effect against Ehrlich Ascites Carcinoma (EAC) in mice (Rana and Khanam, 2002). Moderate antibacterial activity of the essential oil containing β-caryophyllene and α-humulene from the plant was reported by Shafi *et al*. (2002). Aristolochic Acid Nephropathy (AAN) and urothelial cancer are associated with A (Arlt *et al*., 2002). Detection of genotoxicity of AA was performed by Zhang *et al*. (2004). Butanolic extract of the plant collected from South West coast of India, showed maximum inhibitory activity against the cattle pathogen *Listeria monocytogen* (Ravikumar *et al*., 2005). Krishnaraju *et al*. (2005) have mentioned the plant in the assessment of bioactivity of Indian medicinal plants using brine shrimp (*Artemia salina*) lethality assay. Kumar *et al*. (2006) had explored the antibacterial and antifungal properties of crude extracts of *A. indica* explaining its vast ethnomedicinal use. Genotoxic effect and nitrative DNA damage were observed in cells exposed to AA. Cheng *et al*. (2006) have reported high sensitivity of chronic renal failure rats to AAs. The compound could exert genotoxicity probably via Nitric Oxide and its derivatives at higher concentrations (Wu *et al*., 2007). Extracts of the plant were tested against different microbes for their antimicrobial potential. The plant was found to be effective against Gram-Positive, Gram-Negative bacteria and fungi. Leaf and stem of the plant were found to be used therapeutically in venomous insect bites and in intermittent fevers, blood complaints (Vaghasiya and Chanda, 2007). AAN, a progressive renal interstitial fibrosis frequently associated with urothelial malignancies has been reported from different parts of the world (Debelle *et al*., 2008). Antioxidant property of some Aristolochiaceae members including *A. indica* has been reported. The phenolics like terpenoids are the important components present in the family members. Petroleum ether, chloroform and ethyl acetate were used as extraction solvents and ammonium thiocyanate assay, 2, 2-Diphenyl Picrylhydrazyl (DPPH) radical scavenging activity, reducing power activity and total poly phenol estimation were performed. From the results it was found that antioxidant activity may be affected by DPPH free radicals scavenging activity, reducing power and amount of phenolic compounds. The antioxidant activity was mainly contributed by phenolic compounds present in the plants (Thirugnanasampandan *et al*., 2008). The active fractions of *A. indica* was found to neutralize rattle snake venom actions (Samy *et al*., 2008). Meenatchisundaram *et al*. (2009) have applied *in vivo* and *in vitro* methods to assay this plant's extracts against *Daboia russelli* venom. Anti-inflammatory activity of antidote *A. indica* to the venom of *Heteropneustes fossilis* in rats was studied. The dried plant extract is used as anti-inflammatory, anti-pyretic and analgesic activity against *H. fossilis* venom extract present in the glandular cell (poison gland) at the base of pectoral spine (Das *et al*., 2010). Adulticidal, repellent and larvicidal activity of crude hexane, ethyl acetate and methanol extracts of *A. indica* against mosquito was tested by Kamaraj *et al*. (2010). Products containing AA were withdrawn from the market in the early 1980s because AA was found to be a potent carcinogen (Pezzuto *et al*., 1988; Zhang *et al*., 2004). Risk of using *A. indica* along with some other *Aristolochia* species was assessed by Heinrich *et al*. (2009). Use of AA against snake envenomation has been mentioned by Gomes *et al*. (2010) in their review on herbs and herbal constituents active against snakebite.

ETHNOMEDICOBOTANY

Ethnobotany, the interaction between plants and people involves traditional use of medicinal plants by

indigenous communities and management of plant diversity by the aboriginals (Ishtiaq *et al*., 2007). Culture and traditions of the local people have been influenced by plants (Ishtiaq *et al*., 2006). Ethnobotany of *Aristolochia* was reported by Reddy *et al*. (1995). Several ethnobotanical reports indicate the plant as a potent anti snake venoumous (Prashantkumar and Vidyasagar, 2006; Rahmatullah *et al*., 2010a; Rahmatullah *et al*., 2010b). Its use against snakebite with another traditional anti snakebite plant *Rauvolfia serpentina* has been reported in a review (Dey and De, 2010a) indicating certain plants' increased effectiveness when administered in combination (Dey and De, 2010b). In several surveys conducted in the tribal belt of Purulia district, India (De, 1965, 1967, 1979, 1980; Jain and De, 1964) many anti venomous plants have been reported by the author (Jain and De, 1966) and use of *A. indica* as an antidote to snake venom from the same region was reported by Chakraborty and Bhattacharjee (2006). Nair *et al*. (1971) had cited this plant while studying some of the South Indian market samples of Ayurvedic drugs. Rajashekharan *et al*. (1989) had performed Ethno-medico-botanical studies of *Cheriya arayan* and *Valiya arayan* (*Aristolochia indica* Linn.; *Aristolochia tagala* Cham.). Nair *et al*. (1984) had mentioned the plant as a part of the Medico-botany of Andaman and Nicobar Islands, India. The plant is used in abortion by *Irulars* of Coimbatore district, Tamil Nadu, India (Balakrishnan *et al*., 2005). Roots of the plant (local name: Eeshwari) are boiled in coconut oil with seed of *Centrantherum anthelminticum* and externally applied in scabies by the people of Uttara Kannada District in Karnataka, India. In skin allergies, the paste is applied whereas leaf juice is applied to warts (Harsha *et al*., 2003). In Southern part of Tamilnadu, India, this plant has been confirmed to be effective against snakebite (Samy *et al*., 2008). Traditional people of Seshachalam hills, Andhra Pradesh, India use this plant with pepper and garlic against snakebite (Reddy *et al*., 2009). Menstrual disorder sare treated by the tribes of Salur Mandal in Vizianagaram district, Andhra Pradesh, India by using this plant species (Valluru and Mani, 2009). Roots of the species (local name: *Zarawand*) are used as tonic, stimulant and to stop excess menstruation and are given in fever as an Arab folk medicine in Makkah Al-Mukarramah area (Bajrai, 2010). The plant is used as a decoction in snakebite (Gomes *et al*., 2010). Leaf juice of the plant (local name: *Eswaramooligai*) is taken orally in skin disease and scorpion sting by *Kurumba* Tribals in Pennagaram Region, Dharmapuri District of Tamil Nadu, India (Alagesaboopathi, 2011). 10-20 g root paste is externally applied in scabies by the ethnic people of Rapur forest division, Nellore district, Andhra Pradesh, India (Neelima *et al*., 2011).

TISSUE CULTURE

In vitro plant regeneration of *A. indica* through axillary shoot multiplication and organogenesis was reported by Manjula *et al*. (1997). *In vitro* organogenesis was reported by Remashree *et al*. (1997). Plant regeneration from nodal segment derived callus was reported by Siddique *et al*. (2002). Rapid *in vitro* propagation of the plant from axillary shoots has been reported. Development of callus, advent of roots from the callus, shoot regeneration and hardening of tissue culture raised plants were performed in different concentrations and combinations of plant growth regulators (Siddique *et al*., 2006a). Callus induction, callus regeneration and root induction in MS medium supplemented with different concentrations and combinations of growth regulators were reported by Siddique *et al*. (2006b). In a report on *in vitro* propagation of *A. indica*, multiple shoots from shoot tip and nodal explants, shoot differentiation from leaf bases and internodes, regeneration from callus and rooting of elongated shoots were observed on Murashige and Skoog (MS) medium supplemented with different growth regulators in various concentrations (Soniya and Sujitha, 2006).

CHROMOSOMAL STUDY

Somatic chromosomes of five species of *Aristolochia* including *A. indica* were investigated. *A. indica*, having the lowest number of diploid chromosome (2n = 12) with only one pair of chromosomes with secondary constrictions, probably represents the most primitive species of the five studied (Sharma and Varma, 1959).

CONCLUSION

Despite being a potential carcinogen, the plant is still used in some herbal remedies. It has been documented as emmenagogue, abortifacient, antineoplastic, antiseptic, anti-inflammatory, antimicrobial and antipyretic at one hand and on the other it has been reported to be a potent nephrotoxic, antifertility and antispermatogenic agent. Aristolochic acid, one of the major constituents of the plant is being extensively investigated for its pharmacological properties. Most of the mentioned dangers associated with the plant may be contributed by aristolochic acid which is reflected in the cited literature. Folklore use of the plant as a popular abortifacient and antivenom should be restricted considering its harmful effects.

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