Aristolochia indica L.: A Review

1Abhijit Dey and 2Jitendra Nath De
1Department of Botany, Presidency College, 86/1, College Street, Kolkata-700073, West Bengal, India
2Department of Botany, Charuchandra College, Kolkata, India

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 antispermatic 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 Ishamul (Bengali and Hindi) is a shrub with long twining 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, 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 (Rueker 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. rodriguezii (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 fructing 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 stenomatal development in 3 Species of Aristolochia was discussed by Philip (1983). Nair and Nanayanan (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
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 (Coultts et al., 1959). Some novel derivatives of AA from A. indica were isolated and elucidated structurally by Kutchan and Merianos (1968). Total Ishwarone a novel tetra cyclic sesquiterpenes was reported by Ganganul et al. (1969). Two sesquiterpene hydrocarbons (Ishwarone 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 Govindachar and Parthasarathy (1971). Kelly et al. (1972) have reported total synthesis of Racemic Ishwarone, 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). Pakrashri et al. (1977) have reported new phanenathrene derivatives from the plant which included aristolochic acid, isoisaristolochic acid, allatonicin 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-Isociswaran-12-ol, a new type of sesquiterpene was reported by Pakrashi et al. (1980). Aristololactam N-(β-2-deoxy (a phanenathrene derivative) and 3β-hydroxy-stigmaster-5-en-7-one and 6β-hydroxy-stigmaster-4-en-3-one (two steroids) were isolated from A. indica by Achari et al. (1981). The roots of A. indica contains aristolindiquinone, aristololide, 2-hydroxy-1-methoxy-4H dibenzo-4,5(6H)-dione, cephradione, aristolactam IIa, β-sitosterol-β-D-glucoside aristolactam glycoside I, stigmastenones II and III, methylaristolactate, ishwarol, Ishwarone and aristolochene (Achari et al., 1982, 1983). The Aristolochic acids and Aristolactams were reported by Mix et al. (1982). Aristolindiquinone, a new naphtthoquinone 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 Belzani, 1988) have been reported from Aristolochia species. Methyl ester of 12-nonenacosenoic 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%), α-pine (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 Kutchan and Dskoch (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 aristolactate 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. Foreestomach 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). Antipyrretic activity of this species collected from Tirumala hills, Andhra Pradesh, India has also been reported (Vedavathy and Rao, 1991). Vannedweghem (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 caryophyllene and a-humulene from the plant was reported by Shafi et al. (2002). Aristolochic Acid Nephropathy (AAN) and urothelial cancer are associated with A (Arif 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 mutative 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 Aristolochiaceaeae 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 Pierylhydrazyl (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 (Singhramasampandan 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.

**ETHNOMICROBOTANY**

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 venomous (Prashanthkumar and Vidyasagar, 2006; Rahmatullah et al., 2010a; Rahmatullah et al., 2010b). Its use against snakebite with another traditional anti snakebite plant Rauwolfia 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 Cheritya 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: Eshwari) 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 sure treated by the tribes of Sahar Mandal in Vizianagaram district, Andhra Pradesh, India by using this plant species (Valhuru 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: Eswaramoolgam) is taken orally in skin disease and scorpion sting by Kurumba Tribals in Penagaram 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, antisepic, 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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