

***Tylophora asthmatica* Wight & Arn. - Review**

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Received:21.11.2010; Revised: 29.12.2010; Accepted:01.01.2010; Published:15.01.2011.

Abstract

Tylophora asthmatica is used in the treatment of respiratory diseases. In Ayurveda. Animal studies have demonstrated antiasthmatic, anti-allergic, cytotoxic, hepatoprotective and immunomodulator activities of *T.asthmatica*. Several clinical trials have been carried out in case of bronchial asthma; however, design of most of these studies is convoluted. The monograph analyses chemistry, pharmacology and toxicology of *T. asthmatica*.

Keywords: *Tylophora asthmatica*; alkaloids; tylophorine; pharmacology; toxicology

Introduction

Tylophora asthmatica Wight & Arn. syn *Tylophora indica* Merr., is a perennial plant native to south and east India. It belongs to family Asclepidaceae and is commonly known as Indian Ipecacuanha (Bhavan,1992). In Ayurveda, *T. asthmatica* is known as *arkaparni* or *antamool* [which is based on morphology of the roots]. The drug is official in Bengal pharmacopoeia (Nadkarni, 1976).

Chemical composition

T. asthmatica contains 0.2-0.3 % of alkaloids having phenanthroindalizidine and furoquinoline framework (Karnick,1976; Etherington, Herbert and Jackson,1977). Tylophorine (1) and tylophornine are important alkaloids encountered and the percentage is not affected by seasonal variations [Govindachari *et al.*, 1961].

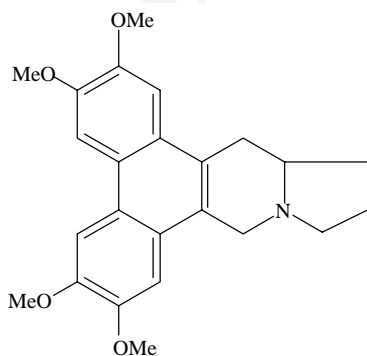


Fig .1: Structure of tylophorine

The phenolic alkaloid tylophorinidine (2), isolated from *T. asthmatica*, along with minor alkaloids, *d*-septicine (3) and *d*-isotylocrebrine have been isolated from the plant (Govindachari, Viswanathan and Radhakrishnan, 1973).

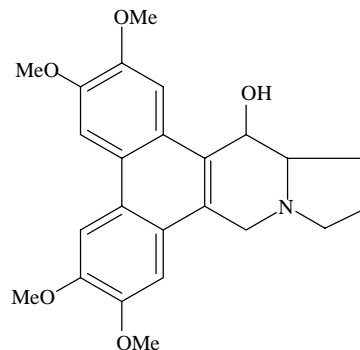


Fig .2: Structure of tylophorinidine

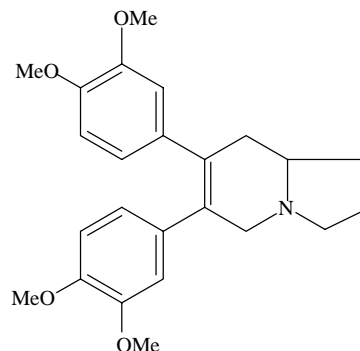


Fig.3: Structure of septicine

Tylophorinicine, a minor alkaloid isolated from the roots of *T. asthmatica* has been characterized as 14-hydroxytylophorine (Mulchandani and Venkatachalam, 1984). New alkaloids, desmethyl - tylophorine, and desmethyltylophorinine have been reported (Rao *et al.*, 2006). Other alkaloids including, tyloindane (4), and tyloindicine A-G (5,6), have been characterized from the plant.

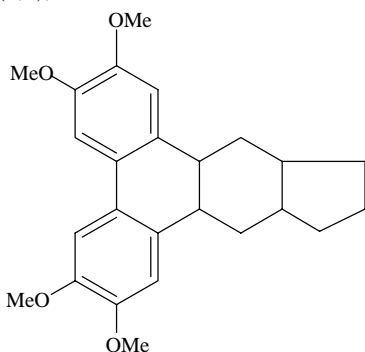


Fig. 4: Structure of tyloindane

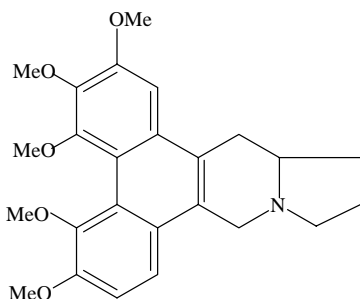


Fig. 5: Structure of tyloindicine A

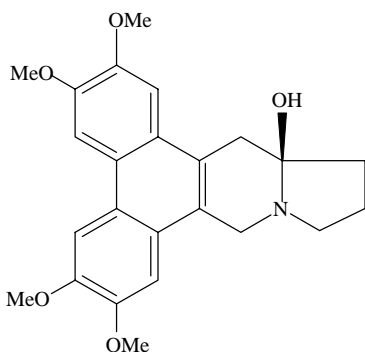


Fig. 6: Structure of tyloindicine G

T. asthmatica The extract of marketed by pharmaceutical companies is standardized to contain 0.1% of the total alkaloids

Pharmacology

Anti asthmatic and anti allergic

The total alkaloids of *T. asthmatica* were tested for mast cell stabilizing effect in comparison with disodium cromoglycate by challenging against three different mast cell degranulators, diazoxide, carbachol and polymixin B, *in vitro*. Both tylophora alkaloids and disodium cromoglycate prevented in similar concentrations, the mast cell degranulation occurring with diazoxide alone. Tylophora alkaloids may have similar mechanism of action as disodium cromoglycate through cyclic AMP (Geetha *et al.*, 1981).

The effect of the alcoholic extract of *T. asthmatica* on weight of the adrenal glands and its functional activities and pituitary adrenal axis was studied on normal, unilaterally adrenalectomised, dexamethasone treated and hypophysectomised male albino rats. The extracts showed stimulation of adrenals as indicated by increase in weight and decrease in cholesterol and vitamin C. It was concluded that probably, *T. asthmatica* acts by direct stimulation of adrenal cortex (Udupa *et al.*, 1991).

Cytotoxic

A study reported cytotoxicity of alkaloids derived from *T. asthmatica* (Ali *et al.*, 2001). Tylophora alkaloids induced apoptosis in K562 cells with characteristic apoptotic features like nuclear condensation, apoptotic body formation, flipping of membrane phosphatidylserine, activation of caspase 3 and release of mitochondrial cytochrome c. These studies suggest that the tylophora alkaloids, in addition to their antiproliferative effects also induce apoptosis in erythroleukemic cells. These observations imply that Tylophora alkaloids could be useful molecules for their antiproliferative activity and for induction of apoptosis in tumor cells (Ganguly and Khar, 2002).

Four tylophorine analogs, designated DCB-3500, DCB-3501, DCB-3502, and DCB-3503. All four tylophorine analogs exerted potent growth-inhibitory effects against HepG2, a human hepatocellular carcinoma cell line, and KB, a human nasopharyngeal carcinoma cell line. HepG2 cells. Unlike conventional antitumor drugs, 3 micro M DCB-3503 did not cause DNA breaks or apoptosis in HepG2 cells. Tylophorine analogs had an inhibitory effect on cyclic AMP response elements, activator protein-1 sites, or



nuclear factor-kappa B binding site-mediated transcriptions (Gao *et al.*, 2004).

Hepatoprotective

The methanolic extract of *T. asthmatica* leaves was screened for hepatoprotective activity in carbon tetrachloride induced hepatotoxicity in albino rats. Hepatoprotective activity of methanolic extract at a dose of 200 mg/kg and 300 mg/kg body weight, i.p., was compared with Silymarin (25 mg/kg, i.p.) treated animals. *Tylophora indica* leaves (200 and 300mg/kg) exhibited significant reduction in serum hepatic enzymes when compared to rats treated with carbon tetrachloride alone. Furthermore, histopathological studies were also done to support the study (Mujeeb *et al.*, 2009).

Immunosuppressive

Crude extract of the leaves of *T. asthmatica* inhibited delayed hypersensitivity reaction to sheep red blood cells in rats when the alkaloid mixture was administered before and after immunization with these cells. The alkaloid mixture also inhibited contact sensitivity to dinitro-fluorobenzene in mice when given prior to or after contact sensitization. Lymphocytes taken from contact sensitized mice, when treated with tylophora alkaloid *in vitro* and transferred into naive syngeneic hosts, could suppress the transfer of delayed type hypersensitivity (DTH) response (Ganguly, 20010).

Immunomodulator

Concanavalin A induced proliferation of splenocytes was used as a model system to study the effect of the alkaloids on cellular immune responses. The alkaloid mixture was found to inhibit proliferation of splenocytes at higher concentrations and augment the same at lower concentrations. Both macrophages and T cells were found to be vulnerable to tylophora alkaloids. Inhibition of proliferation at higher concentrations of the alkaloid is due to inhibition of IL-2 production and activation of macrophages, which have a cytostatic effect (Ganguly *et al.*, 2001)

Clinical trials

One such study randomly assigned 110 bronchial asthma patients to receive one *Tylophora asthmatica* leaf (150 mg of the leaf by weight) or comparable placebo to be chewed and swallowed daily in the early morning for six days. At the end of one week, 62% of the patients consuming the tylophora reported experiencing moderate to complete relief of their asthma symptoms compared to 28% in the placebo group. In a follow-up study, the alcoholic extract of crude tylophora leaves in 1 gram of glucose

had comparable effects to that of chewing the crude leaf, with 56% of the patients reporting moderate to complete improvement in asthmatic symptoms compared to 32% in the placebo group (Shivpuri *et al.*, 1972).

In a double-blind placebo-controlled crossover study of 195 individuals with asthma, participants showed significant improvement when given 40 mg of a *T. asthmatica* alcohol extract daily for 6 days as compared to placebo. Surprisingly, the difference was even more marked months after use of the herb was stopped. Similar long-lasting results were seen in two double-blind placebo-controlled studies involving over 200 individuals with asthma (Mathew and Shivpuri, 1974).

In another clinical trial, 30 patients with a diagnosis of bronchial asthma for at least two years were assigned at random to one of two treatment groups consisting of 15 individuals each. One group received either 350 mg of tylophora leaf powder or placebo daily in the first week. In comparison, a second group of asthmatics were given a similar amount of the leaf for seven days followed by an anti-asthmatic drug combination. Overall, results of the study showed the amount of oxygen in the lung increased in those using the leaf but decreased in those using the placebo. (Thiruvengadam *et al.*, 1978).

However, the designs of most of these studies are a bit convoluted, and various pieces of information are missing from the reports, making it difficult to evaluate the validity of these trials. A higher quality double-blind study that enrolled 135 individuals found no benefit from *T. asthmatica* in asthma (Gupta *et al.*, 1979). In another double-blind placebo-controlled study, *Tylophora asthmatica* produced a significant reduction in sneezing and nasal obstruction, and the improvement noted in ventilatory capacity lasted for nearly 10 days (Gore *et al.*, 1980).

Toxicology

One report described dermatitis as toxic effect of the alkaloids from *T. asthmatica*. The alkaloids tylophorine and tylophorinine, are described as vesicant but no formal skin testing appears to have been reported in the literature (Govindachari *et al.*, 1961). Administration of pure alkaloid of *T. asthmatica*, suspended in peanut oil and given in single doses (12-100 mg/kg) by gavage, to male rats caused inactivity, respiratory distress, salivation, nasal discharge and diarrhoea. The oral LD50 value of the alkaloid was 35.32 mg/kg (Dikshith *et al.*, 1990).



Traditional uses

In Traditional Indian Medicine (Ayurveda), *T. asthmatica* is used in treatment of asthma, dermatitis and rheumatism. The plant has been described as bronchodilator, emetic, expectorant and diaphoretic.

Dose: The dosage of *T. asthmatica* leaf in dried or capsule form is 200 mg twice daily or 400 mg total in 2 doses.

Conclusion

T. asthmatica is used as bronchodilator in Traditional Indian Medicine (Ayurveda). Animal studies have demonstrated antiasthmatic and antiallergic activities of *T. asthmatica* extracts, justifying traditional use. Cytostatic and anti-proliferative activities of tylophorine and its analogs are noteworthy findings. Clinical studies in case of bronchial asthma are a bit convoluted thus demanding large scale clinical trials.

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