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Review

A review on *Justicia adhatoda:* A potential source of natural medicine

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It has been established that up to 25% of the drugs prescribed in conventional medicines are allied directly or indirectly to natural substances mostly of plant origin. Hence, during the last few decades there has been an increasing interest in the study of medicinal plants and their long-established use in different countries. However, today it is compulsory to afford scientific testimony as to whether it is reasonable to use a plant or its active principles. As far as contemporary drugs are concerned they must be further characterized after their pharmacological screening by studying the pharmacokinetic and pharmacodynamic properties, including toxicity. Therefore the present communication constitutes a review on the medicinal properties, ethnomedicinal uses, phytochemistry, pharmacological activities, pharmacokinetic and toxicity of an Indian medicinal plant, *Justicia adhatoda.* A wide range of phytochemical constituents have been isolated from *J. adhatoda* which possesses activities like antitussive, abortifacient, antimicrobial, cardiovascular protection, anticholinesterase, anti-inflammatory and other important activities. Although the medicinal values of this plant is due to the presence of small doses of active compounds which produce physiological actions in the human and animal body. Some important bioactive compounds have been reported in various part of *J. adhatoda* are essential oil and quinazoline alkaloids. Hence, extract of *J.adhatoda* could form one of the best options for developing novel natural medicine.

Key words: *Justicia adhatoda,* pharmacological activities, pharmacokinetic, phytochemistry, toxicity.

INTRODUCTION

Plants have played a critical role in maintaining human health and civilizing the quality of human life for thousands of years. The use of plants as Medicines is as old as human civilization itself and out of about 258,650 species of higher plants reported from the world; more than 10% are used to cure ailing communities (Shinwari, 2010). Many of the existing medicinal system such as Ayurveda, Unani, Homeopathy, Naturopathy, Sidha and other alternative medicinal system have been utilizing plants as effective medicines to cure many harmful diseases (Prasad et al., 2011). The world health organization (WHO) has estimated that 80% of the earth's inhabitant relied on traditional medicine for their primary health care needs and most of these therapies involved the use of plant extract or their active compounds (Bruneton, 1995). *Justicia adhatoda* (L.) Nees (family Acanthaceae) is a shrub widespread throughout the tropical regions of Southeast Asia (Chakrabarty and Brantner, 2001). The name *J. adhatoda* (L.) Nees and *Adhatoda zeylanica* Medic are used synonymously. It is commonly known as Vasaka or Malabar nut. It is a perennial, evergreen and highly branched shrub (1.0 m to 2.5 mm height) with unpleasant smell and bitter taste (Patel and Venkata-Krishna- Bhatt 1984). It has opposite ascending branches with white, pink or purple flowers (Patel and Venkata-Krishna- Bhatt, 1984). It is a highly valuable Ayurvedic medicinal plant used to treat cold, cough, asthma and tuberculosis (Sharma et al., 1992). Its main action is expectorant and antispasmodic (bronchodilator) (Karthikeyan et al., 2009). Moreover the importance of Vasaka plant in the treatment of respiratory disorders can be understood from the

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ancient Indian saying, “No man suffering from phthisis need despair as long as the Vasaka plant exists” (Dymock et al., 1893). Thus the frequent use of *J. adhatoda* has resulted in its inclusion in the WHO manual “The Use of Traditional Medicine in Primary Health Care” which is intended for health workers in south-east Asia to keep them informed of the restorative utility of their surrounding flora (WHO, 1990). The major alkaloids of the plant, vasicine and vasicinone, have been found to be biologically active and are the area under discussion of many chemical compounds and pharmacological studies.

MEDICINAL PROPERTIES

J. adhatoda is a well known plant drug in Ayurvedic and Unani medicines (Claeson et al., 2000). It is used by Ayurvedic physicians and possesses some medicinal properties. It has been used for the treatment of various diseases and disorders, particularly for the respiratory tract ailments. Therefore, it is a primary herb of the Ayurvedic system used in the treatment of cough, bronchitis, asthma and symptoms of common cold (Karthikeyan et al., 2009). The source of the drug ‘Vasaka’ is well known in the indigenous system of medicine for its beneficial effects, particularly in bronchitis (Kumar et al., 2005). Similarly Bisolven, a branded drug containing Vasaka as an ingredient is used to clear the airways by decreasing the mucus secretions and opening the passages (Racle, 1976). There are various herbal formulations accessible for the treatment of various kinds of respiratory disorders (Table 1). Such as, Kanjang, an oral solution with a fixed combination of standardized extracts of *Echinacea purpurea*, *J. adhatoda* and *Eleutherococcus senticosus* has been used in the relief of symptoms allied with the common cold (coughing and irritability of the throat), with a well established medical use comprising 50 million human daily doses (Narimanian et al., 2005). The major efficacy of this solution is mainly due to the presence of Vasaka. Other constituents of Kanjang have been exposed to have anti-stress effects, which might be occasioned partly by an endocrine and partly by an immunomodulatory mechanism of action. This plant is a source of Vitamin C and has medicinal uses, mainly antispasmodic, fever reducer, anti-inflammatory, anti-bleeding, bronchodilator, anti-diabetic, disinfectant, anti-jaundice and oxytocic (Maurya and Singh, 2010). It is antiperiodic, astringent, diuretic, purgative and is also used as an expectorant in addition to liquefy sputum (Salalamp et al., 1996). The leaves, flowers and roots of this plant used in herbal drugs against tubercular activities (Barry et al., 1955), cancer (Pandey, 2002) and possessed anti-helmintic properties (Ayyanar and Ignacimuthu, 2008). The leaf juice is stated to cure diarrhea, dysentery and glandular tumor (Ayyanar and Ignacimuthu, 2008). Similarly in Homeopathy, the plant has been used in the treatment of cold, cough, pneumonia, fever, jaundice, catarrh, whooping cough and asthma (Asolkar et al., 1992).

Ethnomedicinal uses

All the parts of *J. adhatoda* has been used for their curative effects from ancient times (Atal, 1980). It has been used in Ayurvedic system of medicine for the treatment of various ailments of respiratory tract in both children and adults. Various parts of the plant are used in Indian traditional medicine for the treatment of asthma, joint pain, lumber pain, sprains, cold, cough, eczema, malaria, rheumatism, swelling and venereal diseases (Jain, 1991). *J. adhatoda* has also been used by the European medical practitioners. The fluid extract and tincture were used in England as an Antispasmodic, Expectorant and febrifuge. It was said to be beneficial in intermittent, typhus fever and Diphtheria (Wren, 1932). In Germany, the leaves are used as an expectorant and spasmolytic agent (Madaus, 1938). In Sweden *J. adhatoda* is classified as a natural remendy and some preparations against cough containing an extract of Vasaka are accessible (Farnlof, 1998). The ethnomedicinal uses of various parts of *J. adhatoda* are along these lines.

Whole plant

The whole plant is used as an ingredient of numerous popular formulations including cough syrup used in combination with Ginger (*Zingiber officinale*) and Tulsi (*Ocimum sanctum*) where it exerts its action as an expectorant and antispasmodic (Atal, 1980). The plant is used for treatment of excessive phlegm and menorrhagia in Sri Lanka (Kirtikar and Basu, 1975). It is also used for the treatment of bleeding piles (Ahmad et al., 2009), impotence and sexual disorders (Pushpangadan et al., 1995).

Leaves

A yogic practice is to chew the leaf buds alone or with a little ginger root, to clear the respiratory passages in preparation for the vigorous breathing exercises. The various preparation of leaves are used for curing bleeding, haemorrahge, skin diseases, wounds, head-ache and leprosy in Southeast Asia (Adnan et al., 2010; Atta-Ur-Rahman et al., 1986; Roberts, 1931). The bruised fresh leaves are used for snake-bites in India and Sri Lanka (Roberts, 1931). Usually, yellow leaves are exploited for cough (Lal and Yadav, 1983) and smoke from leaves is used for asthma (Shah and Joshi, 1971). The plant leaves are used for checking postpartum haemorrhage and urinary trouble (Pushpangadan et al.,

Table 1. Some herbal preparation containing *J. adhatoda.*

S. No.	Name of preparation	Indication	Country	Reference
1.	Kada	Asthma	India	Iyengar et al. (1994)
2.	Fermiforte	Leucorrhoea	India	Shete (1993)
3.	Salus Tuss	Dry cough, bronchitis, cold, smoker's cough	Germany	Rote (1997)
4.	Kan Jang	Alleviation of symptoms of cold, antitussive, mucolytic, occasional irritation of the respiratory tract	Sweden	Farnlof (1998)
5.	Spirote	Alleviation of the symptoms (in the nose and throat) of colds, occasional cough (mucolytic, dry cough, Antitussive)	Sweden	Farnlof (1998)

1995). It is found that 70% of the pregnant women in the Gora village of Lucknow (Uttar Pradesh, India) use the leaves of *J. adhatoda* to induce abortion (Nath et al., 1997). Moreover, it is observed that the Neterhat people in Bihar (India) used a decoction of the leaves to stimulate and heal before and after delivery (Jain et al., 1994). The leaf powder boiled in sesame oil is used to stop bleeding, earaches as well as pus from ears (Reddy et al., 1989) and jaundice (Reddy et al., 1988). Decoction and ash of leaves are used for bronchial complaints such as asthma, tuberculosis (Jain and Puri, 1984), antipyretic (Jain, 1965) and relieve acidity. The leaves are toxic to 'all forms of lower life' and have insecticidal effects (Agrawal et al., 1986). It was also used for stomach catarrh with constipation, gout, urinary stone (Madaus, 1938) and warmed leaves used externally for rheumatic pains and dislocation of joint (Rao and Jamir, 1982). Moreover, the preparation of leaves in spirit is used for curing the wealthy persons suffering from certain humours in Myanmar (Kirtikar and Basu, 1975).

Root

The extract of roots of *J. adhatoda* is commonly used by rural population against diabetes, cough and certain liver disorders (Bhat et al., 1978). The paste, powder and decoction of root is used for curing tuberculosis, diphtheria, malarial fever, leucorrhoea and eye diseases in Southeast Asia (Dymock et al., 1890; Kirtikar and Basu, 1975). The paste of roots mixed with sugar and used for treatment of acute nightfall in Sitapur District, Uttar Pradesh, India (Siddiqui and Hussain, 1993). Moreover, the macerated roots of *J. adhatoda* are applied on the pubic region and vagina to help parturition (Pathak, 1970) and it facilitates the expulsion of foetus (Iyengar, 1994). The root decoction is also used for gonorrhea (Siddiqui and Hussain, 1993).

Flower

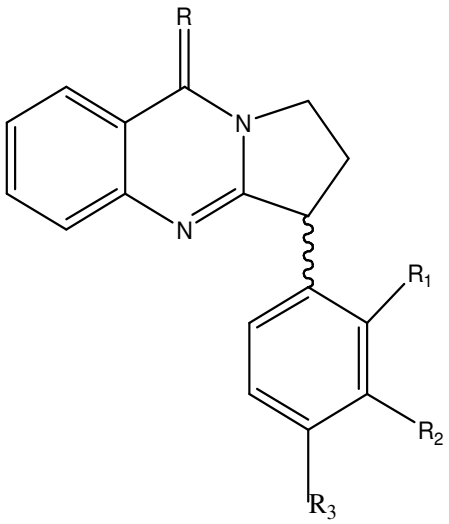
The fresh flowers are used for opthalmia and various preparations of flowers are used for treatment of cold, phthisis, asthma, bronchitis, cough, antispasmodic, fever and gonorrhea in South-East Asia (Dymock et al., 1890; Kirtikar and Basu, 1975; Atta-Ur-Rahman et al., 1986). The flowers are also used as antiseptic to improve blood circulation and hectic heet of blood (Kirtikar and Basu, 1975; Atta-Ur-Rahman et al., 1986; Dymock et al., 1890).

Fruit

The fruit of *J. adhatoda* are used for curing cold, antispasmodic, bronchitis, Jaundice (Kirtikar and Basu, 1975), Diarrhea, Dysentery, Fever and as laxative (Roberts, 1931; Kirtikar and Basu, 1975; Atta-Ur-Rahman et al., 1986).

Phytochemistry

The chemical compounds found in *J. adhatoda* plant includes essential oils, fats, resins, sugar, gum, amino acids, proteins and vitamins 'C' etc (Bhat et al., 1978). The phytochemical analysis show that phenols, tannins, alkaloids, anthraquinone, saponins, flavonoids and reducing sugars were found in the leaves of *J. adhatoda* (Pathak, 1970). But the pharmacologically most studied chemical component in *J. adhatoda* is a bitter quinazoline alkaloid, vasicine (1, 2, 3, 9-tetrahydropyrrole [2, 1-b] quinozolin-3-ol, $C_{11}H_{12}N_2O$) (Figure 1) which is present in the leaves, roots and flowers. It can be synthesized by addition of 2-aminobenzylamine to the vicinyl vicinal trycarbonyl reagent which leads to the short synthesis of Vasicine (Wasserman and Kuo, 1991). Besides vasicine, the leaves contain several alkaloids (Vasicinone, Vasicinol, Adhatodine, Adhatonine, Adhvasinone, Anisotine and Hydroxypeganine), betaine, steroids and alkanes (Lahiri and Prahdan, 1964; Chowdhury and Bhattacharyya, 1987). Vasicine is metabolized to vasicinone and analysis of *J. adhatoda* leaf extract showed that it contained 0.85% vasicine and 0.027% vasicinone. The absolute stereochemistry of (-)-Vasicine and (-) –Vasicinone have been shown the 3S

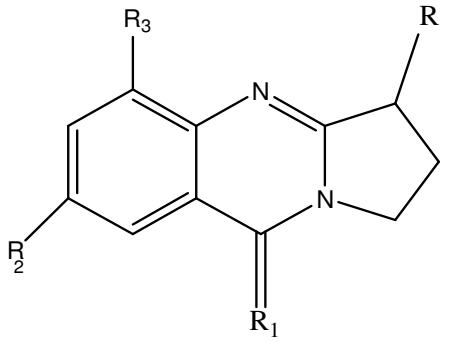


(1) Adhatodine (Johne et al.,1971)
R=H,H, R_1=H, R_2= $COOCH_3$, R_3=$NHCH_3$

(2) Anisotine(Johne et al.,1971)
R=O, R_1=H, R_2=$COOCH_3$, R_3=$NHCH_3$

(3) Vasicoline (Johne et al.,1971)
R=H,H, R_1=$N(CH_3)_2$ R_2= H, R_3=H

(4) Vasicolinone (Johne et al.,1971)
R=O, R_1=$N(CH_3)_2$ R_2= H R_3=H



(5) Vasicine (Atal, 1980)
R= OH, R_1= H,H, R_2=H, R_3=H

(6) Vasicinone (Amin and Metha, 1959)
R= OH, R_1= O, R_2=H, R_3=H

(7) Adhavasinone (Chowdhury and Bhattacharyya, 1987)
R= OH, R_1= O, R_2=H, R_3=OCH_3

(8) Vasicinolone (Karthikeyan et al., 2009)
R= OH, R_1= O, R_2= OH, R_3=H

(9) Hydroxypeganine (Karthikeyan et al., 2009)
R= OH, R_1= H,H, R_2=OH, R_3=H

(10) Adhavasine (Karthikeyan et al., 2009)
R= OH, R_1= H,H, R_2=H, R_3=OCH_3

Figure 1. Some bioactive compounds isolated from *J. adhatoda*.

configuration on the basis of X-ray analysis of the alkaloid hydrobromides. Similarly, Vasicinol and Vascinolone which have been interrelated should also have the 3S configuration (Joshi et al., 1996). The novel alkaloid isolated leaves and characterized as 1, 2, 3, 9-tetrahydro-5-methoxypyrrol [2, 1-b] quinazolin-3-ol (Chowdhury and Bhattacharyya, 1987). The roots also contain alkaloids (vasicinal, vasicinolone, vasicinone and adhatonine), a steroid (daucosterol), carbohydrates and alkanes [54]. In the flowers triterpenes (α-amyrin), flavonoids (Apigenin, Astragalin, Kaempferol, Quercetin, Vitexin) and alkanes have been found (Haq et al., 1967).

Pharmacology

The major phytochemical active compounds like vasicine and vasicinone which are isolated from water and alcoholic extracts of vasaka exert effective pharmacological actions. Various activities reported as:

Antitussive

The extracts of *J. adhatoda* were shown to comprise a good antitussive activity in anaesthetized rabbits and

guinea pigs as well as in unanaesthetized guinea pigs. Because Vasicine showed the bronchodilatory activity both *in vitro* and *in vivo*. Although, Vasicinone the main metabolite of Vasicine, which is also present in *J. adhatoda* extracts, showed bronchoconstriction *in vivo*. The two alkaloids in combination showed a bronchodilatory activity both *in vitro* and *in vivo* (Atal, 1980). It may be due to the presence of the specific site of action of Vasicinone and Vasicine (major alkaloids) which suppress coughing by its action on its neuronal system in the medulla (Dhuley, 1999). Intravenously, it was (1/20 -1/40) as active as codeine on mechanically and electrically induced coughing in rabbits and guinea pigs.

Abortifacient

Vasicine was found to have uterotonic activity in different species including human beings. It was shown that the effect was influenced by the priming degree of the uterus by estrogens. Vasicine initiated rhythmic contractions of human myometrial strips from both non-pregnant and pregnant uteri with the effect which was comparable with that of oxytocin and mathergin (Atal, 1980). In a study conducted on rats, rabbits, hamsters and guinea pigs; it was found that vasicine has uterotonic and abortifacient effects possibly by enhancing the synthesis and release of prostaglandins. In this study dose dependent effect was observed with effective doses ranging between 2.5 to 10 mg/kg. However, administration of estradiol dipropionate potentiated the abortifacient effect in guinea pigs whereas treatment with aspirin inhibited the abortifacient activity due to inhibition of release of prostaglandins (Chandhoke, 1982).

Antimicrobial

The water extract was shown to be active against microbial flora isolated from patients with gingivitis (Patel and Venkata-Krishna-Bhatt, 1984). The alcoholic extract of leaves and roots showed antibacterial activity against *Staphylococcus aureus* and *Escherichia coli,* whereas water extract showed activity against *S. aureus* only (George et al., 1947). The crude ethanolic extract of the leaves exhibited antimicrobial activity against *Staphylococcus epidermidis, Bacillus subtilis, Proteus vulgaris* and *Candida albicans* (Karthikeyan et al., 2009). Moreover the methanolic extract of *J. adhatoda* exhibited positive antimicrobial activity for *P. aeruginosa, S. aureus* and *B. subtilis* while *E. coli* was not effectively inhibited by extracts of tested plant (Shinwari et al., 2009). While the extract of plant showed minimum inhibition in the growth of fungi, *Microsporum gypseum, Chrysosporium tropicum* and *Trichophyton terrestre* (Quershi et al., 1997). Growth of mycobacterium tuberculosis was found to be inhibited by benzyl amine, ambroxol, bromhexine (semi synthetic derivatives of vasicine) due to their mucolytic action. As these compounds are concentrated in macrophages they might exerts a clinically useful effects on intracellular tuberle bacilli by enhancement of lysozyme level in bronchial secretions and levels of rifampicin in lung tissue and sputum. Therefore these compounds are being active as adjunctive for therapy of tuberculosis (John and Snell, 1996).

Cardioprotective

In combination of vasicine and vasicinone significant reduction in cardial depressant effects was observed. No effect was shown by vasicinone (Dl-form), however L-form was found to be weakly effective stimulating cardiac muscles (Atal, 1980).

Anticholinesterase

Vasicinone obtained from the roots, produced transient hypotension in cats, contraction of isolated intestine and depression of isolated heart in guinea pigs, thus showing good anticholinesterase activity (Lahiri and Prahdan, 1964).

Anti-inflammatory

The methanolic extract of *J. adhatoda* was evaluated for anti-inflammatory activity by the modified hen's egg chrioallantoic membrane test. The alkaloid fraction showed potent activity at a dose of 50 µg/pellet (Chakrabarty and Brantner, 2001).

Other activities

The essential oil from the leaves of *J. adhatoda* showed smooth muscle relaxant activity in the isolated guinea-pig tracheal chain (Cruz et al., 1979). Methanolic extract from the plant has been shown to possess anti-allergic activity in guinea pig at doses of 6 mg per animal (Muller et al., 1993). The ethanolic extracts from the leaves showed hypoglycaemic activity after oral administration in rats and rabbits (Modak and Rao, 1966; Dhar et al., 1966). Leaf showed significant hepatoprotective effect at doses of 50 to 100 mg/Kg on liver damage induced by D-galactosamine in rats (Bhattacharyya et al., 2005). The radiomodulatory influence of ethanolic extract of leaves was studied against radiation-induced hematological alterations in peripheral blood of swiss albino mice. A significant increase in serum alkaline phosphatase activity and decrease in acid phosphatase activity was observed in irradiated animals during the entire period of

study (Kumar et al., 2005). It exerts antioxidant effect against lipid peroxide and xanthine oxidase induced oxidation (Jahangir et al., 2006). Leaf powder of this plant showed considerable antiulcer activity in experimental rats in ethanol induced ulceration model (Shrivastava et al., 2006). The rate of healing was found to be higher in the plant extract treated wounds in buffaloes as compared to pancreatic tissue extracts (Zama et al., 1991). The decoction of leaves activated the trypsin enzyme hence stimulated the digestion process (Vijaya and Vasudevan, 1994).

Pharmacokinetics

The studies on absorption and distribution of vasicine in mice after intravenous, intramuscular and subcutaneous administration show similar results as these reported in rats (Zutschi et al., 1980). Vasicine (20 mg/kg) given intramuscularly was well absorbed reaching a maximum concentration of about 56 µg/ml in blood in both pregnant and non-pregnant rats and about 10 µg/ml in amniotic fluid (Atal, 1980). After intravenous injection in rats and mice high concentration of vasicine were found in the uterus within 5 min and the peak level was achieved after 10 min. The half-life was after intravenous, 5 to 7 min, 1.5 and 2 h intramuscular and subcutaneous administration respectively. It is reported that vasicine and its metabolites are mainly excreted in the urine. On intravenous and intramuscular administration about 55% of excreted product in the first 18 and 22 h respectively, was vasicine, while an oral administration about 18% of the excreted product was vasicine during the first 24 h (Atal, 1980). After oral administration, very low concentration was found in the uterus. Vasicine is metabolized in the liver to vasicinone and other metabolites which contribute to the first pass effects and which is an important way of elimination of Vasicine.

Toxicity

In a screening study of anti-fertility activity of *J. adhatoda,* after administration of extract of leaves either in mice or in rats, no effects on the pregnancy were recorded (Bhaduri et al., 1968). But the animals treated with about 100 mg/kg of different *J. adhatoda* extracts did not show any implantation sites (Prakash et al., 1985). The effect of *J. adhatoda* spissum leaf extract on early gestation was studied. There was no effect on the maternal body weight or any other parameter recorded in the form of statistically significant differences between the treated and control animals. Analysis of *J. adhatoda* leaf extract showed that it contained the vasicine ranges from 0.0541 to 1.105% (Bhaduri et al., 1968). So the toxicology study of vasicine has been performed separately. No remarkable adverse effects were recorded in any species (Atal, 1980). The general toxicity after repeated oral administration of vasicine daily for 6 month has been studied in rats and monkeys (Pahwa et al., 1987). Clinical observations, clinical chemistry and histopathology of the major organs were performed in both the species. Moreover, autopsy and histopathological examination of major organs did not reveal any abnormalities. In rats vasicine (5 and 10 mg/kg body weight) was administered intraperitoneally to groups of ten animals at various interval of pregnancy. On 1 to 7 days pregnancy, no anti-implantation effect but an abortifacient effect was observed after 7 days pregnancy (Atal, 1980). The teratogenic studies on vasicine were performed in rats and rabbits (Atal, 1980). Except for occasional pregnancy wastage seen at a dose of 2.5 mg/Kg but partial wastage at higher doses of vasicine did not exhibit any teratogenic effects or any other adverse effects in any of pups of the first or second germination (Atal, 1980).

Vasicine has been tried in a preliminary human study being conducted for interruption of mid-trimester pregnancy by intraamniotic instillation of the drug. Doses above 60 mg were given in 12 cases and all of them aborted after about 48 h (Wakhloo et al., 1979). Furthermore, in other studies it has been shown that vasicine is a very effective oxytocic agent in human beings and stopping post-partum haemorrhage (Atal, 1980).

CONCLUSION

The literature survey revealed that *J. adhatoda* has been widely studied for its pharmacological activities and regarded as Universal Panacea in Ayurvedic medicines and finds its position as a versatile plant having a wide spectrum of medicinal activities. It can be concluded that *J. adhatoda* is an important source of many pharmacologically and medicinally important chemicals such as Vasicine, Vasicinone, Vasicoline and other various useful minor alkaloids. There is not sufficient scientifically valid evidence to state that *J. adhatoda* extract could be potentially harmful to human beings. As the global scenario is now changing towards the use of non toxic plant products, development of modern drugs from vasaka should be emphasized. It is also clear that much needs to be discovered, both as to the active ingredients and their biological effects. Furthermore, the information summarized here is intended to serve as a reference tool to researchers in the field of ethnopharmacology of *J. adhatoda.*

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