



## A systematic ethnobotanical review of *Adhatoda vasica* (L.), Nees.

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### ABSTRACT

*Adhatoda vasica* (L.), Nees belonging to the family Acanthaceae is a shrub with opposite ascending branches. The plant has been used in the indigenous system of medicine in India for near about 2500 years. It is a well-known plant as a drug in Ayurvedic and Unani medicines. Traditionally it was used for the treatment of various acute and chronic diseases and showed strong pharmacological activity particularly for bronchial infections, cough, bacterial infections, reproductive disorders, cardiac diseases and many more. Various phytochemicals like alkaloids, flavonoids, tannins, etc. were obtained from *Adhatoda vasica* (*A. vasica*). The active constituent of the plant is vasicine, l-vasicinone, deoxyvasicine, maiontone, vasicinolone and vasicinol etc. This review consists of updated information on the phyto-constituents isolated from *A. vasica* and their potential role in the treatment of various ailments traditionally and medically. Based on the critical review it was concluded that there is not sufficient scientifically strong evidence to explain that *A. vasica* extract, could be harmful to human beings especially in pregnant women. Major data on traditional uses as well as toxicological studies, evaluated various correctness, relevance, importance, and reliability for the overall evaluation of *A. vasica* safety. Numerous clinical trials are conducted around the globe on the herbal formulations of vasaka. This review includes strong data about phytochemical and ethnopharmacological studies that indicate that *A. vasica* is a versatile native plant of the Indian subcontinent having a commercial reputation and thus can be encouraged for diversified applications like medicinal and other potential uses.

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### Introduction

*Adhatoda vasica* Nees. (*Justicia adhatoda* L.) belongs to the family *Acanthaceae* is commonly known as Malabar nut, adhatoda, and adalsa/adosa, etc. This is a vital plant and a native of Asia that is widely spread in the area of the Indian subcontinent viz. Punjab, Bengal, Nepal, Assam, and Sri Lanka. Along with that, it covers the plains of India and ranges of Himalayan at an altitude of 1300 m above sea level (1). It is also found in Malaysia, Ceylon, Singapore and many more countries around the globe (2). For several decades it was used as a medicine for the treatment of various ailments and due to its versatile nature has a unique place in a different system of medicines like Ayurveda, Siddha, Homeopathy, and Unani (3). As per the Ayurvedic system of medicine it is used for the prevention and management of various diseases (4). In the Indian system of medicine, it is well known by its name "vasaka". And widely used for the treatment of various respiratory diseases especially asthma and

bronchitis (5). *Adhatoda vasica* (*A. vasica*) is included in the manual of the World Health Organization (WHO) for its traditional use in primary health care (6). Though in present Indian health care delivery system vasaka consists of both traditional and modern systems of medicines, both organized traditional systems of medicines like Ayurveda, Siddha and Unani and unorganized system of medicine viz. folk medicine.

*A. vasica* is a 2 m tall evergreen herb with long opposing branches and huge lance-shaped leaves exstipulate with a dark green to a yellowish tint. The pedunculate flowers are white or purple (7). This study updates information on phyto-constituents extracted from *A. vasica* and their potential involvement in traditional and medical therapy of various diseases. The literature says it can cure cough, bacterial infections, reproductive issues, heart issues, and more. (8). We also conclude that this herb's therapeutic benefits should be further investigated. Traditional and ethnomedical uses of adosa highlight

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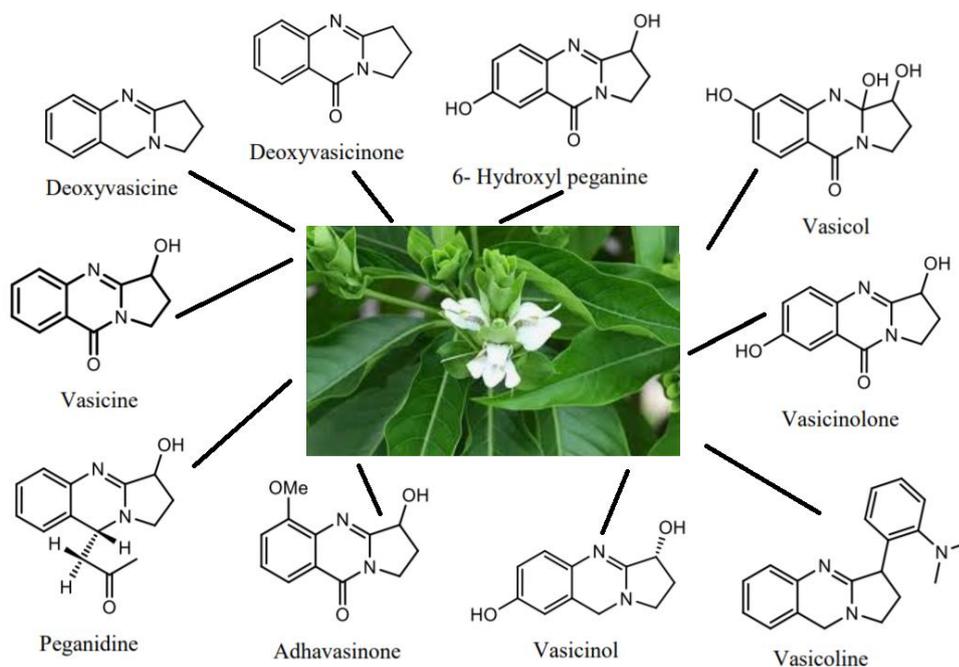
its value and inspire us to research more about herbal items for a better therapy to treat mankind with minimal toxicity. Numerous therapeutic trials on vasaka herbal preparations are being conducted globally (6).

### Phytochemistry

Ayurveda uses *A. vasica* for its mucolytic and expectorant properties. According to Charaka Samhita, these activities are caused by bioactive components. *A. vasica* contains phytochemicals such as alkaloids, glycosides, sterols, and phenolic acid. Alkaloids (quinazoline) (vasicine, vasicinone, 7-hydroxyvasicine, vasicinolone, 3-deoxyvasicine, vasicolinone, vasicol, vasicoline) betaine, steroidcarbohydrate and alkanes are the most common constituents (9). The major pharmacological actions are due to the presence of alkaloidal content specially vasicine (7.5%) in the plant (10). Besides

vasicine, the leaves include alkaloids (Vasicinone, Adhatodine, Vasicinol, Adhvasinone, Anisotine Adhatonine, and Hydroxypeganine), betaine, steroids, alkanes, kaempferol and quercetin (Fig. 1) (11).

The leaves are high in vitamin C and carotene, making this plant a potential essential oil source (12). In addition, it contains amino acids and proteins. Triterpenes and flavonoids are abundant in flowers. Apigenin, astragaline, kaempferol, quercetin, and vitexin are flavonoids (13). The majority contain potassium, sodium, calcium, and magnesium, while zinc, copper, nickel, cadmium, manganese, and iron are negligible. The seeds contain 25.8% deep yellow oil consisting of glycerides of be-henic 11.2 percent, arachidic 3.1 percent, cerotic 5 percent, lignoceric 10.7 percent, linoleic 12.3 percent, oleic 49.9 percent, and -sitosterol (2:6 %). *A. vasica* contains significant (Ca, K, Na, and Mg) and trace (Zn, Cu, Cr, Ni, Co, Cd, Pb, Mn, and Fe) elements (5).



**Figure 1.** Chemical bioactive compounds obtained from *Adhatoda vasica*.

### Pharmacological activities of the different components present in *Adhatoda vasica*

The wide range of pharmacological activities of vasaka is attributed to the presence of various chemical elements in the plant. The main alkaloid is quinazoline, which is widely isolated from the leaves

and other sections of the plant. Vasicine is a significant alkaloid with various activities on the human body and can be employed as a therapeutic source. Alkaloids such as 1-vasicinone, deoxyvasicine, maiontone, vasicinolone, etc. Below Table 1 provides a quick description.

**Table 1.** Pharmacological activities in reference to the constituents and phytochemical categories

S. No.	Chemical constituents	Part used	Pharmacological activity	References
1.	Vasicine (1, 2, 3, 9-tetrahydro-5-methoxypyrrol [2,1-b] quinazolin3-ol)	Leaves Roots flowers	Bronchodilator, Respiratory stimulant, Thrombopoietic, Uterine stimulant, Hypotensive, Antibacterial, Abortifacient, Anti-inflammatory, Antioxidant, HIV-protease inhibitor, Hepatoprotective and Wound healing activity.	(5, 14, 15)
2.	Vasicinone	Leaves Root	Antitussive, Bronchodilator, Anti-allergic, Hepatoprotective, Cardioprotective, Anti-cancer, Wound healing and Uterine activity.	(10, 14)
3.	B-sitosterol	Roots	Anti-diabetic, Hepatoprotective, Antimicrobial, Anti-inflammatory, Anticancer, Antifertility, Angiogenic, Antioxidant, Immunomodulatory, and Antinociceptive activity.	(15, 16)
4.	Bglucoside-galactose	Roots	Anti-diabetic and Hepatoprotective activity.	(16)
5.	Deoxyvasicine	Roots	Acetylcholinesterase Inhibitor and Butyryl cholinesterase Inhibitor.	(17)
6.	2'-4-dihydroxychalcone - 4-glucoside	Flowers	Anti-inflammatory, Antioxidant, Antileishmanial, Antimalarial, Anti-tuberculosis, and Antiviral activity.	(15, 16)
7.	Kaempferol	Flowers	Hepatoprotective, Antitumor, Antioxidant and Anti-inflammatory activity.	(7)
8.	Quercetin	Flowers	Cardioprotective, Anti-inflammatory, Neuroprotective, Anti-Cancer, Anti-Ulcer, Antibacterial, Antiviral and Anti-allergy activity.	(7)
9.	Epitaraxerol	Roots	Antimitotic, Ecboic and Antithyroid activity.	(7, 18)
10.	Adhatodine	Leaves	Anti-tubercular, Anti-allergic, Hepatic and Cardioprotective activity.	(7, 19)
11.	Carotene	Whole plant	Antioxidant and Cardioprotective activity.	(20)
12.	Crystalline acid	Seeds	Muscle relaxant, Antioxidant, Anticarcinogenic and Hepatoprotective activity.	(6)
13.	Arachidic acid	Seeds	Muscle relaxant, Insecticidal, Hepatoprotective, Synthesis of prostaglandins 6 and leukotrienes C7 corticosteroids and thus inhibit phospholipase A2 activity.	(6)
14.	Be- henic acid	Seeds	Muscle relaxant, Antimicrobial activity, Hepatoprotective and Insecticidal activity.	(6)
15.	Linoleic acid	Seeds	Muscle relaxant, Insecticidal, Hepatoprotective, Cardioprotective, Anti-cancer, Neuroprotective, Anti-osteoporotic, Anti-inflammatory and Antioxidative activity.	(6)
16.	Oleic acid	Seeds	Anti-inflammatory, Analgesic and Gastroprotective activity.	(6)

### Traditional utilization

Traditional medicine has utilized *A. vasica* for centuries to treat various ailments. In Ayurveda, *vasaka* has *tikta*, *kashaya*, *laghu*, *sheeta*, and *virya* properties. So, it may help treat heart disease and respiratory diseases. Traditional usage of plant components and their pharmacological action (Table 2) (21).

It was initially used to treat respiratory diseases, but its use has grown steadily over time (22). It is used

to treat asthma, arthritis, sprains, colds, coughs, eczema, malaria, rheumatism, swelling, and sexual disorders in the Indian System of Medicine (23). Leaves are used traditionally for the betterment of cough, asthma, hepato-protective, bronchitis, tuberculosis, and as a uterine tonic (24). The fluid extract was used in Europe to treat spasms, typhus fever, coughs, and as a febrifuge (25). It was an expectorant and antispasmodic in Germany. Sweden people used to treat cough. The whole plant is used in

Sri Lanka for phlegm, menorrhagia, and piles. The leaves are smoked to cure asthma (26) In another investigation, ethanolic leaf extract was employed to suppress pathogenic organisms (27). It is also used as an herbal remedy for allergen-induced obstruction of the respiratory system along with that it also possesses hepatoprotective activity. The Naga tribes use the decoction of the leaves to get rid of intestinal worm infections (28). It is commonly utilized in South East Asian indigenous and folk medicine (6). It is also used as a natural treatment for allergic bronchospasms and has hepatoprotective properties. The Naga tribes utilize a leaf concoction to treat intestinal worms and also as an anti-bacterial agent (28, 29).

Our findings suggest that *A. vasica* is a wonder plant, as it is utilized to heal various ailments. Traditional use around the world confirms the folklore claims and encourages researchers to investigate. The scientist discovered that the traditional assertion that *A. vasica* can be used to cure different conditions is true, especially in the case of respiratory diseases.

**Table 2.** Different parts of *A. vasica* and their traditional uses

Part of the plant	Disease / Disorder
Roots	Gonorrhea
Flowers	Jaundice and eye disorder
Leaves	Respiratory disease (bronchitis, expectoran anti-tussive, asthma), Diarrhea/ dysentery, Antiseptic, anthelmintics etc.

### Pharmacological Properties

The plant's abundant pharmacological actions are related to its primary metabolite composition, especially its alkaloid concentration (26). The main pharmacological activities of *A. vasica* are attributed to an alkaloid (vasicine) and its derivatives. The following are the pharmacological activities of the vasaka plant, attributable to whole-plant extracts, sections utilized for extraction, or chemical constituents:

#### Antibacterial activity

The petroleum ether and ethanolic extracts from leaves show potent antibacterial activity determined by the disc diffusion method against numerous bacteria viz. *Bacillus subtilis*, and *Vibrio cholera* etc. (30). The effect is the same whether the method is paper disc or dilution. Another study suggests using

leaf extracts from different solvents against bacteria like *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Bacillus subtilis*, *Enterococcus faecalis*, *Escherichia coli*, *Pseudomonas eugeniae*, *Klebsiella pneumoniae* and *Candida albicans* has potent antibacterial activity by inhibiting bacterial multiplication (27). Bi-metal (silver and gold) doping can increase the biological properties of zinc oxide nanoparticles and reveals its promising role as an anti-bacterial (31). *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Serratia marcescens* and *Methicillin resistant S. aureus* are significantly affected by the plant's alcoholic extracts (32). Due to the presence of alkaloids in the plant, *A. vasica* leaf extract has antibacterial and cytotoxic properties. The plant component vasicine was isolated and acetylated to generate vasicine acetate that is used to inhibit *Enterobacter aerogenes*, *Staphylococcus epidermidis*, and *Pseudomonas aerogenes*. It also shows a minimum inhibitory concentration for bacteria: *E. aerogenes*, *S. epidermidis*, and *P. aeruginosa* (17, 33). The disc diffusion assay was used to test the silver and gold nanoparticles produced from *A. vasica* leaves extract and loaded with cerium oxide. This investigation found it to have the highest zone of inhibition against *E. coli* and *S. aureus* strains (34, 35). Another study group submitted identical findings but manufactured the silver nanoparticles in a different way (36).

#### Anti-asthmatic activity

The leaf and root extracts are used to treat bronchitis, cough, and upper respiratory infections. It also acts as an expectorant by loosening phlegm. In guinea pigs, acetylcholine and histamine aerosol produced bronchial constriction (37). Singh et al. 2014 (38) propose that vasaka exerts anti-asthmatic action by directly stabilizing mast cells, blocking the enzyme lipoxygenase/cyclooxygenase, or by decreasing platelet-activating factor (5). As a bronchodilator, the plant source has been utilized for centuries to treat asthma. Vasicine and vasicinone, both alkaloid renowned for their therapeutic effect on the respiratory system, contribute to this function (39, 40) but among both vasicinone (an oxidized product of vasicine) is a more potent bronchodilator than other (41). Azepino (2, 1b) quinazolones is a synthetic

analogue of vasicine that is known for its anti-asthmatic activity (42).

*A. vasica* is also a major element in numerous polyherbal formulations used to treat various ailments. Kanak asava is one of those that fight ovalbumin-induced asthma (43). A novel polyherbal formulation comprises 0.25 percent w/w vasicine, which reduces the mortality rate of rats by stabilizing the mast cells in a dosage-dependent way. (43). The preclinical study on the animals shows a positive result against asthma (44). The vasaka patent for treating asthma is US 6746694. As indicated above, numerous herbal formulations containing this active ingredient demonstrate a considerable decrease in asthma, making it a promising constituent for the future (45).

### **Anti-diabetic activity**

Several studies suggested that *A. vasica* also has a potent anti-diabetic property (46). It has an antihyperglycemic effect in the Streptozotocin-produced hyperglycemic model in rats (100, 200, 400 mg/kg/day). Another study indicated that the plant's methanolic leaf extract had great efficacy against diabetes. The alkaloid has the same action with IC50 values of 125 and 250  $\mu$ M for vasicine and vasicinol (47). In a mouse model of diabetes caused by alloxan, *A. vasica* leaf extract was found to be a potent target for diabetes treatment. It not only lowers blood glucose levels but also reverses diabetes-related depression when compared to escitalopram. (48). Vasaka can be employed as anti-diabetic either as a plant source, the active constituent, herbal formulation, or most importantly, nanoformulation. These nanoformulations are made using green synthesis and a plant alcoholic extract as a capping medicament. The aforesaid synthesized particle has a considerable anti-diabetic and anti-pathogen effect. (49).

### **Anticancer activity**

The people of Chhattisgarh (India) use the vasaka plant for the prevention of cancer because of its antioxidant property (50). The same action is observed in the animal model too that shows a significant decline in hyperproliferative responses and carcinogenic activity against the ferric nitrilotriacetate induced renal oxidative stress and renal carcinogenesis (51). The alkaloid vassicine was

isolated from *A. vasica* ethanolic extract and acetylated to yield vassicine acetate (17). This chemical has been shown to be cytotoxic to the A549 lung adenocarcinoma cell line. It is also worth noting that additional metabolic components from the plant's leaves have been shown to protect against cervical cancer in an in vitro study using human cervical cancer (HeLa) cells (52). Adenocarcinoma was studied in vitro utilizing the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay. The presence of alkaloids in the plant was determined by gas chromatography-mass spectrometry (GC-MS) experiments (49).

The anticancer efficacy of *A. vasica* leaf extract nanoparticles loaded with Argentinum and gold and doped with cerium oxide is substantial (34). Another study found metal and metal oxide nanoparticles to be anticancer in the same HeLa cell line model (31). So bi-metal doping can improve biological qualities and may be linked to cancer. *A. vasica* alkaloids inhibit the growth of oxidative stress-driven lung cancer cells in A549 cells. Reduced cell viability, DNA fragmentation, mitochondrial potential disturbance, and cell wound repair activity may be the mechanism. It is mediated by Bcl-2 associated agonists of cell death (BAD) and Fas death receptors (50). Methanol extract of *Justicia adhatoda* was also an anticancer in MCF-7 cells (25).

### **Insecticidal activity**

*A. vasica* is an insecticide commonly used in India and globally (10). Egypt uses this plant's insecticidal properties against *Culex pipiens* (53). A number of studies mentioned that this plant can be used as an insecticide (54). The leaf methanolic extract is anti-feedant to *Spodoptera littoralis* larvae. A twenty-six-day treatment of fresh leaves or fake food containing leaves results in 100% mortality of larvae and harmful effects on larvae (55). Few investigations explored *A. vasica* L.'s anti-feedant effectiveness against *Spodoptera litura* larvae. *A. vasica* is a biopesticide with excellent anti-feedant efficacy against this insect (56). The acetone extract of the leaves shows a significant insecticidal activity (mortality 86.66%) against *Callosobruchus maculatus* in beetles due to the presence of terpenoids (57). Methanolic fraction of vasaka leaf extract showed larvicidal activity against *Bancroftian filariasis* vector *Culex quinquefasciatus*

and *Aedes aegypti*. The data reveal significant larvicidal activity at 100-250 ppm (58). Aside from its diverse pharmacological properties, it can be utilized as a natural larvicidal agent. The essential oils were tested against four stored-grain insects: *Bruchus chinensis*, *Sitophilus oryzae*, *Rhizopertha dominica* and *Stegobium paniceum* (59). Against *Plutella xylostella*, the alkaloidal ingredient of vasaka (vasicine acetate) is larvicidal (antifeedant). The highest inhibitory/antifeedant activity against larvae and pupae was identified in vasicine (98 percent at 1000 ppm) (60). Vasicine is also a good insect repellent (61). Surprisingly, a Baghdad researcher found that vasicine (an alkaloid from vasaka) inhibited more than 92 percent of insects when treated with less than one ml (62). Based on the research, the plant has insecticidal properties and can be utilized as an insecticide (15).

#### **Thrombolytic and cardioprotective activity**

The thrombolytic and cardioprotective medicines are inseparable. A natural substance with thrombolytic activity may also have cardioprotective properties. The plant's alkaloids and terpenoids are known to have a thrombolytic effect (63).

The methanolic fraction of *Adhatoda vasica* leaf extract has the highest thrombolytic activity (53.23 percent) when compared to conventional streptokinase (7, 64). The results of a methanolic fraction of stem and root show thrombolytic activity with clot lysis values of 36.420.16% and 42.630.28% for stem extractives and 40.340.25% and 46.480.28% for root extractives compared to 63.520.86% for conventional streptokinase. The thrombolytic capability of *A. vasica* root crude extract in vitro clot lysis model. Another study found that at 5 mg/ml, vasaka root extract demonstrated 19.63 percent clot lysis activity, compared to the negative control, normal saline (64).

The plant contains full of alkaloids, flavonoids, sterols, and glycosides. It has a wide range of therapeutic properties, with cardioprotection being the most important (6, 62). Combining vasicine and vasicinone reduced cardiac depressive effects (66) and suggest that the plant's component may have a cardiac effect (67). The racemic vasicinone mixture had no impact, whereas the Levo form has a minor effect on the heart muscle, causing contraction (19).

#### **Antitussives**

*Adhatoda* extract has antitussive action in an animal model of guinea pigs and rabbits. A recent study found vasicine to be bronchodilatory in vitro and in vivo (10). It has a stronger antitussive impact than codeine (68). One study found that the plant's chemical constituents including vasicine and kaempferol can act as expectorants. Kan Jang oral solution is the commercial preparation. Placebo-controlled research found this plant to be effective in treating upper respiratory infections (65). Nepali et al. 2013 (70) found dihydro deoxyvasicinone, 2, 4-dibromo-7, 8, 9, 10-tetrahydroazepino [2, 1-b] quinazolin-12 as an antitussive and more potent than codeine (10 mg/kg). This alkaloid (vasicinone and vasicine) has been shown to have antitussive effects in mice using sulphur dioxide gas as a model (66). Dhuley 1999 (72) tested its antitussive action on rabbits and guinea pigs and found it to be bronchodilatory. According to Dey et al. 2018 (50), the plant's bronchodilator function is attributable due to vasicinone. The quinazoline alkaloids ( $\pm$ )-vasicine, deoxyvasicine, and ( $\pm$ )-vasicinone have antitussive, expectorant, and bronchodilator properties (73).

#### **Anti-tuberculosis activity**

The antitubercular medicines have drawbacks due to multidrug-resistant *Mycobacterium tuberculosis* (67). The anti-tubercular efficacy of vasaka leaf aqueous extract was evaluated in vitro against multidrug-resistant isolates (68). In Ayurveda, various herbal remedies are used against tubercular bacteria, one of which is made from vasaka (gulkand) flowers. Using essential oil (2-20 g/ml) effectively inhibits *Mycoplasma tuberculosis* growth in vitro (22). A coupon (MB105) was presented to Garhwal (Uttarakhand, India). Using the disk diffusion approach, vasaka has substantial anti-tuberculosis efficacy (69). Barry et al. discovered *A. vasica*'s significant growth inhibitory effect against *Mycobacterium tuberculosis* in 1955 (70). This action is due to the presence of vasicine (71) by increasing the level of lysozyme and rifampicin indirectly in the bronchioles (72). Valasicoline, vasicolinone, vasicinone, vasicine, triterpenes and anisotine are the main antitubercular alkaloid constituents of the plant. The beta-ketoacyl-(acyl-carrier-protein) synthase III enzyme has an impact on the unique structural feature

and incidence in tubercular bacteria (73). When used at a dose of 100g/ml, various vasaka extracts exhibit a dramatic reduction in microbial colony-forming unit ability. The most active components were vasicine acetate and 2-acetyl benzylamine, which were tested against the multidrug-resistant strain (74). The alkaloids from vasaka are docked with the -ketoacyl-acyl-carrier protein synthase III enzyme. Anti-tubercular medications target these protein molecules. The study's findings imply this is a viable alternative to costly animal testing (19).

### **Analgesic activity**

In acetic acid-induced writhing response, hot plate analgesiometer and warm water tail immersion test, *A. vasica* showed substantial analgesic and anti-inflammatory activity in albino rats. Maharasnadhi quathar is an ayurvedic polyherbal remedy for arthritis. This investigation found that the formulation had powerful anti-inflammatory and analgesic activity dosage-dependent (75).

### **Uterine Activity**

Oral administration of *A. vasica* leaf hydroalcoholic extract (175 mg/kg) for 10 days, causes positive abortion (10) and has significant uterine tonic and abortifacient effect due to vasicine. The dual effect stimulates uterine contractions, which aids in childbirth (5). The scientists discovered that it operates similarly to oxytocin and ergometrine in animals (7). In an *in vitro* investigation, vasicine and its derivatives were discovered to release prostaglandin production dose-dependently. Vasicine has been shown to stimulate the uterus and myometrium layer (76). The action and dose are concerned with the stage of pregnancy. Vasicine had stronger effects when estrogens were utilized as priming agents; this suggests it acts via prostaglandin release (77). An alkaloid from *A. vasica*, vasicinol, has been demonstrated to reduce fertility in insects by blocking the oviduct (54).

### **Hepatoprotective Activity**

The plant shows extremely protective action against the liver toxicity. Ethyl acetate extract of the plant at a dose of 100 and 200 mg/kg; shows highly significant protective action against the carbon tetrachloride-induced liver toxicity in albino rats. It elevates the

liver marker enzymes which were reduced due to the injury in the liver (78). The same results were also reproduced by another research by using whole plant powder drug, these records for its hepatoprotective activity and various liver disorders (79). The aqueous extract of leaves shows significant hepatoprotective activity induced by d-galactosamine in rats at a dose less than 100 mg/kg per oral (24). Another researcher works on the same at a dose of 250 mg/kg body weight, by using the carbon tetrachloride induce model (9, 80). The ethanolic extract of the plant vasaka, restore the significantly elevated biochemical levels to that of a normal range which was changed due to the liver toxicity induced by perchloroethylene(81).

The possible activity is due to the presence of the chemical constituent vasicinone. It was reported by Sarkar et al. 2014 (82) that the pretreatment of vasicinone with silymarin at a dose of 25 mg/kg/day shows a potent hepatoprotective activity by decreasing the level of hepatic enzymes. The ethanolic extract of leaves from vasaka (100 – 200 mg/kg p.o.) shows significant protective action on hepatic cells in a carbon tetrachloride (CCl<sub>4</sub>) induced model (83).

The extracts of the plant were prepared by using various solvent (alcohol, chloroform and ether) shows its potent hepatoprotective action against the CCl<sub>4</sub> inducing liver damage in the rat model. Amongst all the alcoholic extract showed a significant ( $p < 0.05$ ) protective effect on liver as compared with others. It acts by reducing the different biochemical levels due to the presence of its biologically active constituents like alkaloids, flavonoids, tannins in the plant (84). Pingale 2009 (85) reported the hepato-suppression activity of vasaka against CCl<sub>4</sub> induced liver toxicity in rats. The investigation was done on the powder of the whole plant and its activity against liver damage in the rat model. Saroj and Mishra 2012 (86) selected a polyherbal formulation having vasaka as a constituent and reported its protective action on the liver against paracetamol-induced hepatotoxicity.

### **Anti-inflammatory**

The anti-inflammatory effect of carrageenan and formalin was assessed in rat paws using an ethanolic extract of vasaka (200-400 mg/kg/per oral). This study found a strong anti-inflammatory effect. Vasicine is the main active element in alkaloids that has anti-

inflammatory properties. The modified hen's egg chorioallantoic membrane test revealed that the methanolic extract has substantial anti-inflammatory activity due to saponins and alkaloids (87).

The possible anti-inflammatory actions were estimated by a research group by using the aqueous and butanol fraction against the metabolites of arachidonic acid. The result of this study proves that the aqueous fraction of the plant source inhibits the arachidonic acid pathway by either working on the cyclo-oxygenase, thromboxxygenase or platelet-activating factor. Hence, they prove the hidden mechanism behind its anti-inflammatory action (78). The plant extract (aqueous fraction) shows its inhibitory activity by showing strong action against the arachidonic acid via the cyclo-oxygenase pathway whereas the butanol fraction shows inhibitory action against the collagen induce aggregation factor and platelet-activating factor (78).

The anti-inflammatory activity is due to the presence of numerous bioactive constituents in *vasaka* viz., vasicine, vasicinone, vasicine acetate, 2-acetyl benzyl amine and vasicinolone. Singh and Sharma 2013 (88) reported that the chloroform fraction possesses a high anti-inflammatory activity than other fractions against the carrageenan paw edema and complete Freund's adjuvant model induced paw edema in rats. Another research found that *Adhatoda vasica* shows anti-inflammatory activity that is due to the encephalopathy from diabetic in the rat model. The change in behavioral and biochemical parameters proves the scientific evidences of its role as anti-inflammatory (44). Water and alcoholic extract of the plant show a significant anti-inflammatory action as compared to the standard drug diclofenac. The responses and pharmacological activity were significant at a specific dose (89).

### Antioxidant activity

Antioxidants are the products that are generated from free radicals in the different mechanisms of chain reaction (33). The leaves are a rich source of natural antioxidants. The methanolic extract of *A. vasica* was estimated for the anti-oxidant activity by 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH), and reducing power potential and iron chelating activity (90). The antioxidant property of the plant is due to the presence of high levels of polyphenols basically

flavonoids and phenolic acids (3). The anti-oxidant activity was also estimated by another method of estimation by the means of oxidative parameters like reduce glutathione, lipid peroxidase enzyme in liver and DPPH, (2, 2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid)) ABTS assay as a measure of free radical scavenging activity. Another research suggests that the aqueous leaf extract of the plant shows DPPH radical scavenging activity, hydroxyl radical-scavenging activity in Fe<sup>3+</sup>/ascorbate/EDTA/H<sub>2</sub>O<sub>2</sub> system, inhibition of lipid peroxidation induced by FeSO<sub>4</sub> in egg yolk and metal chelating activity by *in vitro* estimation (91). The tissue culture of *A. vasica* suggests that the isolated compounds vasicine and vasicinone both showed utmost free radical-scavenging (DPPH radicals) activity in the water extracts (67). Shahwar et al. 2012 (33) reported that in their study the antioxidant property is due to vasicine that shows significant free radicals scavenging activity in DPPH assay and a concentration-dependent increase in reduced ferric ion in Ferric Reducing Ability of Plasma assay.

### Radio modulatory activity

The ethanolic extract of the leaves from plant *A. vasica* shows a potent radio modulatory activity against the radiation-induced changes in the blood parameters. This irradiation study was carried out on the Swiss mice at a time interval between six hours to thirty days. The results show the pretreated group with extract shows a significant normal value of the blood parameters and gradual recovery of the animals was also noted (7).

Kumar et al. 2005 (9) found that rats exposed to radiation had illness conditions such as notable alterations in the histology of testis and chromosomal aberration in bone marrow cells, as well as 100% mortality after 22 days. The ethanolic extract of *A. vasica* leaf was given orally for 15 days at 800 mg/kg each mouse, then exposed to radiation, reducing death by 70% in 30 days. The plant extract greatly reduced radiation-induced chromosomal damage in bone marrow cells, indicating radioprotective effects on the testis.

### Immuno-modulatory activity

Different leaves extracts (methanolic, chloroform and diethyl ether) of *A. vasica* (400 mg/kg) are

validated for their immunomodulatory activity in the rat model. The plant is also used for its immunomodulatory activity because of the presence of a high amount of alkaloid in it. Oral administration of leaf extracts showed a significant increase in neutrophil percentage which get adhered on the fibers (7). The observation shows that at different doses it shows a significant effect as compared with control groups. The result of this study shows that the extract of the plant, *A. vasica* Linn positively modulates the immunity of the host (92).

The immunomodulatory properties of methanolic leaf extract of *A. vasica* (50, 100 and 200mg/kg body weight) was evaluated for the immune-modulatory activity by determining the antibody titer in serum, the plasma cells which produces the antibody, hypersensitivity reaction and cytokine level after treating it with sheep red blood cells. The anti-oxidant properties of the extract were assessed by determination of tissue glutathione (GSH), catalase and superoxide dismutase (SOD) enzyme activity and lipid peroxidation from different groups of mice. This shows that vasaka shows a positive action on the immune system positively by modulating the immunity of the host cell.

#### **Antimutagenic activity**

The anti-mutagenic activity of the plant vasaka was reported by a group against the cadmium chloride-induced renal oxidative stress and genotoxicity in the rat model. The pretreatment of the plant extract shows prophylaxis and a significant decline in the oxidative biomarker level (93). Another study shows that flavonoids and phenolic acids in vasaka fractions may act as anti-mutagenic agents. Among all fractions, hexane, chloroform, and water have the most potential for control. The outcome of this investigation supports its possible future role as a chemopreventive agent. (94, 95). In an unexpected result, vasicine displays a dose-dependent effect against the mutation produced by 2 aminofluorine. The data also reveal that the chemical triggers apoptosis in the PC 3 cancer cell (94).

#### **Anti-Alzheimer Activity**

The chemical ingredient of *A. vasica* (alcoholic extract) inhibited the acetylcholine esterase enzyme reversibly. Among the active ingredients are vasicine,

vasicinone, vasicole, anisotine. Because of its competitive inhibitory action on AChE, the study concluded that vasicine could be used to treat Alzheimer's disease. Most isolated alkaloids had no or modest inhibitory effects on cholinesterase (96). The results from the docking show that vasicine having same action as that of tacrine and galantamine in the catalytic site due to its binding similarity (97).

#### **Anthelmintic activity**

Shaibani et al. (2008) used *A. vasica* as an anthelmintic activity in vitro against gastrointestinal nematodes in sheep. Egg hatching and larval development assays were used to evaluate the plant's aqueous and ethanolic extracts (98). The ethanolic extract outperformed the other. The plant extract has anthelmintic or anticestodal action at 800mg/kg. With regard to the young worms, the extract exhibits a considerable drop in recovery rate. The anthelmintic property of *Adhatoda vesica* was evaluated in vitro and in vivo against the conventional medication levamisole. In vitro, the aqueous and methanolic extracts have substantial inhibitory activity, but the root powder has the best effects. Both models have anthelmintic action against nematodes (99).

#### **Wound healing activity**

The methanolic extract of *A. vasica* has been found to be valuable for the management of wounds in the rat model (84). This study was supported with another research when the wound was created beside the vertebral columns of calves and afterward, they are treated with the alcoholic and chloroform extract of the *A. vasica*. The result of this study suggests that alcoholic extract shows a significant improvement in the wound healing process than other extracts (100). A different research group works on the different extracts of vasaka prepared from the leaves extract against the wound healing property in mice model induced by excision. The result was remarkable that the ointment (1%) prepared by using methanolic extract shows potent wound healing activity (101).

#### **Anti-Ulcer activity**

Ethanolic extract of *A. vasica* leaves shows a potent action on the gastric ulcer induced by the pylorus ligation, ethanol and aspirin. But the better results were gained from the ethanol-induced gastric ulcer

model in rats. The other research on the syrup prepared from the plant extract shows that it has a potent anti-ulcerogenic activity along with that it can be used for the treatment of dyspepsia (102).

### Antiviral activity

The aqueous and methanolic extract of the plant shows significant antiviral activity against the influenza virus by inhibiting attachment of virus at host surface and/or replication cycle of the virus. Thus, we can say that it can be used as prophylaxis for the treatment of viral infection (103).

### Anti-allergic activity

Vasicinol and vasicine are the active constituent of the plant and possess anti-allergic activity by inhibiting the ovalbumin-induced allergic reactions in the animal model of mice, rats and guinea pig. The patents consisting *Adhatoda vasica* are used for treating allergy US 6746694 (45).

### Anticholinesterase activity

Vasicinone is an alkaloid obtained from the roots of *A. vasica* that produces hypotension in cat model and also a contraction of isolated intestine along with that it causes depression in isolated frog heart in a guinea pig model (73).

### Antifungal activity

Ramachandran and Sankaranarayanan 2013 (104) reported that the phytochemical constituents of the plant were found to inhibit the growth of human pathogenic fungus (*Aspergillus ruber* and *Trichophyton rubrum*).

### Cholagogue activity

The plant *A. vasica* has a potent action on the liver and causes an increase in bilirubin secretion (more than forty percent) in animal models at a dose of 5 mg/kg intravenous (10).

### Safety Profile of *Adhatoda vasica*

When we concern regarding the safety profile of *A. vasaka* we did not find any record as such regarding its severe adverse effects or mortality. Some minor effects are there like diarrhea and vomiting but they occur when they are taken in higher doses than prescribed. Apart from the viable and toxic effect, the

leaves of the plant show a prominent action on the uterus that leads to increased contraction of the uterus and may be a possible cause of abortion (77). All the studies that are reported under the banner toxicity are related to the reproductive toxicity either it is due to the administration of the plant as a whole or from the active constituents *i.e.*, vasicine. Therefore, we can conclude this plant is nontoxic in a dose-dependent manner (5, 105, 106). The acute toxicity studies were done for vasicine after a single administration of it then subsequently observation till fourteen days then LD<sub>50</sub> was calculated for different individuals are mentioned in Table 3.

**Table 2.** Toxic dose of vasicine in different animal groups

Route	Oral Route	Intraperitoneal	Subcutaneous	Intravenous
Rats	640	115	335	-
Mice	290	125	200	79

### Global Perspectives and Future Approaches

From the above details, it is clear that the plant *Adhatoda vasica* is widely used for the treatment of various diseases that are well documented and mentioned in traditional and pharmacological uses. The different parts of the plant and their chemical constituents are also mentioned in the table for biological use. In conclusion, it can be used as a treatment strategy and for the development of a novel drug delivery system. For its use in multiple aspects screening and bioassay are must along with that we have to collect sufficient knowledge of the chemical constituents and their structure-activity relationship studies are needed to explore its further actions. The current details will provide a backbone for the development of a new natural product having the least or minimal side effects than the synthetic or chemical compound. It also promotes the researcher in agro-industries that basically work on herbal products. The future perspective involves better resolution with the different bioactive compounds isolated from the *A. vasica*.

### Concluding Remarks

The detailed discussion was thoroughly done after a deep literature survey that revealed the beneficial effects of *A. vasica* plant extracts, its phytoconstituents and its pharmacological actions.

Due to the high chances of side effects due to chemical compounds in the form of drugs, there is an unmet need to develop a herbal drug or their preparation to reduce the chances of adverse effects or resistance in the case of antibiotics. Apart from different pharmacological uses such as antibacterial, antitussive, anti-inflammatory, antiviral and protection on heart, liver and other organs. It never allows to confine at these only but further explorations are still envisaged due to an extensive high range of diverse phytochemical potential of this miraculous plant.

### Declaration of Competing Interest

The author declares that she has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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### Conflicts of interest

No conflict of interest.

### Ethical approval

Not required.

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