

JUSTICIA ADHATODA HAVING MULTIFUNCTIONAL PHARMACOLOGICAL PROPERTIES CAN PREVENT COVID-19 DISEASE**Dr. Subha Bose Banerjee and Kuntal Gupta***

Department of Physiology, Hooghly Mohsin College, Chinsurah, Hooghly, WB, India.

***Corresponding Author: Kuntal Gupta**

Department of Physiology, Hooghly Mohsin College, Chinsurah, Hooghly, WB, India.

Article Received on 26/05/2021

Article Revised on 15/06/2021

Article Accepted on 05/07/2021

ABSTRACT

Novel coronavirus disease (COVID-19) is the major health crisis in the world. World Health Organisation has declared COVID-19 as a global pandemic. There are no effective drugs to treat COVID-19 infection. Till date include remdesivir, umifenovir, favipiravir, lopinavir/ritonavir, ribavirin, hydroxychloroquine, etc are used to treat this disease. There is an urgent need for public health measures to implement preventive approaches to control severe COVID-19 disease. In this situation people are searching for safe herbal extracts and pharmacologically active molecules having numerous therapeutic properties. *J. adhatoda* is a well-known plant drug in Ayurvedic and Unani medicines. It has been used for the treatment of cough, bronchitis, asthma and symptoms of common cold. 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. The alkaloids from leaf extracts of *Justicia adhatoda* have also been reported to possess anti-viral activity. The main protease (Mpro), key component for the cleavage of the viral polyprotein, is considered to be one of the important drug targets for treating COVID-19. Various phytochemicals, including polyphenols and alkaloids, have been proposed as potent inhibitors of Mpro. It has been observed that anisotine and vasicoline of *Justicia adhatoda* and Pemirolast are very good inhibitors. Hence, extract of *J. adhatoda* could form one of the best options for developing novel natural medicine against COVID-19.

KEYWORDS: *Justicia adhatoda*, Pharmacological activities, COVID-19, Anti-viral, Anti-inflammatory.**INTRODUCTION**

Justicia adhatoda (L.) Nees (family Acanthaceae) is a shrub widespread throughout the tropical regions of Southeast Asia.^[1] 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 m height) with unpleasant smell and bitter taste.^[2] It has opposite ascending branches with white, pink or purple flowers.^[2] It is a highly valuable Ayurvedic medicinal plant used to treat cold, cough, asthma and tuberculosis.^[3] Its main action is expectorant and antispasmodic (bronchodilator). 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.^[4]

The phytochemical analysis show that phenols, tannins, alkaloids, anthraquinone, saponins, flavonoids and reducing sugars were found in the leaves of *J. adhatoda*. But the pharmacologically most studied chemical component in *J. adhatoda* is a bitter quinazoline alkaloid, vasicine which is present in the leaves, roots

and flowers. The chemical compounds found in *J. adhatoda* plant includes essential oils, fats, resins, sugar, gum, amino acids, proteins and vitamins 'C' etc.^[5] Besides vasicine, the leaves contain several alkaloids (Vasicinone, Vasicinol, Adhatodine, Adhatonine, Adhvasinone, Anisotine and Hydroxypeganine), betaine, steroids and alkanes.^[6] The major phytochemical active compounds like vasicine and vasicinone which are isolated from water and alcoholic extracts of vasaka exert effective pharmacological actions.

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. It has been used for the treatment of cough, bronchitis, asthma and symptoms of common cold.^[7] 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. The alkaloids from leaf extracts of *Justicia adhatoda* have also been reported to possess anti-viral activity. The main protease (Mpro), key

component for the cleavage of the viral polyprotein, is considered to be one of the important drug targets for treating COVID-19. Various phytochemicals, including polyphenols and alkaloids, have been proposed as potent inhibitors of Mpro.^[8] Anisotine and vasicoline of *Justicia adhatoda* and Pemirolast are very good inhibitors.^[9] Hence, extract of *J.adhatoda* could be one of the best options for developing novel natural medicine for COVID-19.

Pharmacological Properties of *Justicia adhatoda*

A wide range of phytochemical constituents have been isolated from *J. adhatoda* which possesses activities like antitussive, abortifacient, antimicrobial, cardiovascular protection, anti-cholinesterase, anti-inflammatory and other important activities. 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. It has been used for the treatment of cough, bronchitis, asthma and symptoms of common cold.^[7] Vasicine, an alkaloid, is one of the major components of the plant and is responsible for most of its activities, including its antioxidant, anti-inflammatory, and bronchodilatory qualities.

Antitussive activity

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*.^[10] 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.^[11] It has been proven for its antitussive activity as effective as codeine in irritant aerosols and citric acid-induced cough models. The leaves, roots, flowers, and bark of this plant have been used in the treatments of cough, colds, asthma, to liquefy sputum, as a bronchodilator, bronchial catarrh, bronchitis, and tuberculosis. A number of parts of the plant are commonly used in the forms of decoctions or powders. The juice from the leaves is also frequently used.^[12]

Antimicrobial activity

The water extract was shown to be active against microbial flora isolated from patients with gingivitis.^[2] 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.^[13] The crude ethanolic extract of the leaves exhibited antimicrobial activity against *Staphylococcus epidermidis*, *Bacillus subtilis*, *Proteus vulgaris* and *Candida albicans*.^[7] 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.^[14] While the extract of plant showed minimum inhibition in the growth of fungi, *Microsporum gypseum*, *Chrysosporium tropicum* and *Trichophyton terrestre*.^[15] 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 exert a clinically useful effects on intracellular tubercle 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.^[16]

Anti-viral activity

The alkaloids from leaf extracts of *Justicia adhatoda* have also been reported to possess anti-viral activity.^[8] The main protease (Mpro), key component for the cleavage of the viral polyprotein, is considered to be one of the important drug targets for treating COVID-19. Various phytochemicals, including polyphenols and alkaloids, have been proposed as potent inhibitors of Mpro. But whether these alkaloids exhibit any inhibitory effect on SARS CoV-2 Mpro is far from clear. Efficacy of primary active alkaloid vasicine against coronavirus infectious symptoms, evaluated by an *in Silico* screening studies on virus proteins ACE 2 Receptor, 3CL protease and Spike protein SARS HR1 motif using PyRx tool and AutoDoc 1.5.6. Based on PyRx results, Vasicine with ACE 2 Receptor showed higher docking affinity score - 7.1 K/cal respectively when compared to other virus proteins. AutoDoc 1.5.6 screening study report showed that vasicine promotes good inhibitory constant 486.54 mM on 3CL protease more than others. Results reveal that the vasicine could be a potential target for the treatment of COVID 19.^[17] *Justicia adhatoda* alkaloids possessing proper drug-likeness properties and two anti-HIV drugs (lopinavir and darunavir; having binding affinity -7.3 to -7.4 kcal/mol) were docked against SARS CoV-2 Mpro to study their binding properties. Only one alkaloid (anisotine) had interaction with both the catalytic residues (His41 and Cys145) of Mpro and exhibited good binding affinity (-7.9 kcal/mol). Molecular dynamic simulations (100 ns) revealed that Mpro-anisotine complex is more stable, conformationally less fluctuated; slightly less compact and marginally expanded than Mpro-darunavir/lopinavir complex.^[8] Few common drug-molecules are tested as protease inhibitor and replicase inhibitor of COVID-19 virus using COVID-19 Docking Server. It is observed that anisotine and vasicoline of *Justicia adhatoda* and Pemirolast are very good inhibitors. As all these three compounds are market available drugs, immediate clinical trial is plausible which may lead to the golden success against the present pandemic. It has been suggested that anisotine is a more potent Mpro inhibitor than the two previously recommended antiviral drugs (lopinavir and darunavir) and may evolve as a promising anti-COVID-

19 drug if proven in animal experiments and on patients.^[9]

Anti-inflammatory activity

It has an anti-inflammatory action on the respiratory tract and is effective in respiratory tract infection.^[12] The methanolic extract of *J. adhatoda* was evaluated for anti-inflammatory activity by the modified hen's egg chorioallantoic membrane test. The alkaloid fraction showed potent activity at a dose of 50 µg/pellet.^[11]

Antioxidant activity

It exerts antioxidant effect against lipid peroxide and xanthine oxidase induced oxidation (Jahangir et al., 2006).^[18] Vasicine, an alkaloid, is one of the major components of the plant and is responsible for most of its activities, including its antioxidant properties. *Justicia adhatoda* could enhance mitochondrial ROS generation and increase the permeability of mitochondrial membrane, thereby inducing megakaryocytic maturation.^[19]

Antiallergic activity

Methanolic extract from the plant has been shown to possess anti-allergic activity in guinea pig at doses of 6 mg per animal.^[20] Bromhexine, a derivative of vasicine, has been shown to possess mucus-liquefying/expectorant activity. Ambroxol, a widely used secretolytic agent developed from vasicine, was shown to inhibit IgE-dependent mediator secretion from human MCs and basophils—the principal effectors of allergic inflammation. Ambroxol, a widely used secretolytic agent developed from vasicine, was shown to inhibit IgE-dependent mediator secretion from human MCs and basophils—the principal effectors of allergic inflammation. As compared to vasicine, ambroxol showed a greater effect in lowering basophil IL-4 and IL-13 secretions. It was also reported to reduce IgE-dependent p38 mitogen-activated protein kinase (MAPK) phosphorylation in basophils.^[21] The alkaloids vasicinone and vasicine have potent bronchodilator and antiallergic activity. Owing to these activities, AV is effective in acute asthma conditions.

Hypoglycemic activity

The ethanolic extracts from the leaves showed hypoglycaemic activity after oral administration in rats and rabbits.^{[22][23]}

Hepatoprotective activity

Leaf showed significant hepatoprotective effect at doses of 50 to 100 mg/Kg on liver damage induced by Dgalactosamine in rats (Bhattacharyya et al., 2005).^[24]

Cardioprotective activity

In combination of vasicine and vasicinone significant reduction in cardiac depressant effects was observed. No effect was shown by vasicinone (DI-form), however L form was found to be weakly effective stimulating cardiac muscles (Atal, 1980).^[10]

Anticholinesterase activity

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).^[25]

Abortifacient activity

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).^[10] 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. 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.^[26]

Anti-radiation activity

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.^[27]

Anti-ulcer activity

Leaf powder of this plant showed considerable antiulcer activity in experimental rats in ethanol induced ulceration model.^[28]

Wound healing activity

The rate of healing was found to be higher in the plant extract treated wounds in buffaloes as compared to pancreatic tissue extracts.^[29]

Digestive activity

The decoction of leaves activated the trypsin enzyme hence stimulated the digestion process.^[30]

CONCLUSION

COVID-19 is the major health crisis in the world. There are no effective drugs to treat this infection. Remdesivir, umifenovir, favipiravir, lopinavir/ritonavir, ribavirin, hydroxychloroquine, etc are used to treat this disease. In this situation people are searching for safe herbal extracts and pharmacologically active molecules having numerous therapeutic properties. *J. adhatoda* is a well known plant drug in Ayurvedic and Unani medicines. It has been used for the treatment of cough, bronchitis, asthma and symptoms of common cold. 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. The alkaloids from leaf extracts of *Justicia adhatoda* have also been reported to possess anti-viral activity. The main protease (Mpro), key component for the cleavage of the viral polyprotein, is considered to be one of the important drug targets for treating COVID-19. Vasicine could be a potential target for the treatment of COVID 19. Various phytochemicals, including polyphenols and alkaloids, have been proposed as potent inhibitors of Mpro. Anisotine and vasicoline of *Justicia adhatoda* and Pemirolast are very good inhibitors. Hence, extract of *J.adhatoda* could be one of the best options for developing novel natural medicine for COVID-19.

REFERENCES

- Chakrabarty A, Brantner AH. Study of alkaloids from *Adhatoda vasica* Nees on their anti-inflammatory activity. *Phytother Res*, 2001; 15:532-534.
- Patel VK, Venkata-Krishna- Bhatt H. In vitro study of antimicrobial activity of *Adhatoda vasica* (L) (Leaf extract) on gingival inflammation- A preliminary report. *Ind J Med Sci*, 1984; 38: 70-72.
- Sharma MP, Ahmad J, Hussain A, Khan S. Folklore medicinal plants of Mewat (Gurgaon district), Haryana, India. *Int J Pharmacogn*, 1992; 30: 129-134.
- Maurya S, Singh D. Quantitative analysis of total phenolic content in *Adhatoda vasica* Nees extracts. *Int J Pharm Tech Res*, 2010; 2: 2403-2406.
- Bhat VS, Nasavatl DD, Mardikar BR. *Adhatoda vasica*-an Ayurvedic plant. *Indian Drugs*, 1978; 15: 62-66.
- Chowdhury BK, Bhattacharyya P. Adhavasine: A new quinazolinone alkaloid from *Adhatoda vasica* Nees. *Chem Ind (London)*, 1987; 1: 35-36.
- Karthikeyan A, Shanthi V, Nagasathya A. Preliminary Phytochemical and antibacterial screening of crude extract of the leaf of *Adhatoda vasica* (L). *Int J Green Pharm*, 2009; 3: 78-80.
- Ghosh R, Chakraborty A, Biswas A, Chowdhuri S. Identification of alkaloids from *Justicia adhatoda* as potent SARS CoV-2 main protease inhibitors: An *in silico* perspective. *J Mol Struct*. 2021; 1229:129489.
- Bag A, Bag A. Treatment of COVID-19 patients: *Justicia adhatoda* leaves extract is a strong remedy for COVID-19 – Case report analysis and docking based study. *ChemRxiv*. Cambridge: Cambridge Open Engage; 2020; This content is a preprint and has not been peer-reviewed.
- Atal CK. Chemistry and Pharmacology of vasicine: A new oxytocin and abortifacient. *Indian Drugs*, 1980; 15: 15-18.
- Dhuley JN. Antitussive effect of *Adhatoda vasica* extract on mechanical or chemical stimulation – induced coughing in animals. *J Ethnopharmacol*, 1999; 67: 361-365.
- Claeson UP, Malmfors T, Wikman G, Bruhn JG. *Adhatoda vasica*: a critical review of ethnopharmacological and toxicological data. *J Ethnopharmacol*. 2000; 72(1-2): 1-20.
- Dhankhar S, Kaur R, Ruhil S, Balhara M, Dhankhar S and Chhillar AK. A review on *Justicia adhatoda*: A potential source of natural medicine. *Afr J Plant Sci*, 2011; 5(11): 620-627.
- Shinwari ZK, Khan I, Naz S, Hussain A. Assessment of antibacterial activity of three plants used in Pakistan to cure respiratory diseases. *Afr J Biotechnol*, 2009; 8: 7082-7086.
- Quershi S, Rai MK, Agrawal SC. In vitro evaluation of inhibitory nature of extracts of 18-plant species of Chhindwara against 3-keratinophilic fungi. *Hindus Antibiot Bull*, 1997; 39: 56-60.
- John M, Snell JC. Activity of bromhexine and ambroxol, semisynthetic derivatives of vasicine from the Indian shrub *Adhatoda vasica*, against *Mycobacterium tuberculosis* in vitro. *J Ethnopharmacol*, 1996; 50: 49-53.
- Thangaraju P, Sudha Ty S, Pasala PK, Hari Ty S, Venkatesan S, Thangaraju E. The Role of *Justicia Adhatoda* as prophylaxis for COVID-19 - Analysis based on docking study. *Infect Disord Drug Targets*. 2021 Jan 19. doi: 10.2174/1871526521666210119120643.
- Jahangir T, Khan TH, Prasad L, Sultana S. Reversal of cadmium chloride –induced oxidative stress and genotoxicity by *Adhatoda vasica* extract in Swiss albino mice. *Biol Trace Elem Res*, 2006; 111(1-3): 217-228.
- Gutti U, Komati JK, Kotipalli A, Saladi RGV, Gutti RK. *Justicia adhatoda* induces megakaryocyte differentiation through mitochondrial ROS generation. *Phytomedicine*. 2018; 43: 135-139.
- Muller A, Antus S, Bittinger M, Kaas A, Kreher B, Neszmelyi A, Stuppner H, Wagner H. Chemistry and pharmacology of antiasthma *Galphimia glauca*, *Adhatoda vasica* and *Picrorhiza kurrooa*. *Planta Medica*, 1993; 59: 586-587.
- Basu R, Pant S, Kumar M, Priyanka M and Sonam S. Review & Future Perspectives of Using Vasicine, and Related Compounds. *Indo glob j pharm*, 2011; 1(1): 85-98
- Modak AT, Rao MRR. Hypoglycemic activity of a non nitrogenous principle from the leaves of *Adhatoda vasica* Nees. *Ind J Pharm*, 1966; 28: 105-106.
- Dhar ML, Dhar MM, Dhawan BN, Mehrotra BN, Ray C. Screening of Indian plants for biological activity. *Indian J Exp Biol*, 1966; 6: 232-247.
- Bhattacharyya D, Pandit S, Jana U, Sur TK. Hepatoprotective activity of *Adhatoda vasica* aqueous leaf extract on D-galactosamine-induced liver damage in rats. *Fitoterapia*, 2005; 76: 223-225.
- Lahiri PK, Prahdan SN. Pharmacological investigation of Vasicinol- an alkaloid from *Adhatoda vasica* Nees. *Indian J Exp Biol*, 1964; 2: 219-223.

26. Chandhoke N. Vasicine, the alkaloid of *Adhatoda vasica*. *Indian Drugs*, 1982; 24: 425-426.
27. Kumar A, Ram J, Samarth RM, Kumar M. Modulatory influence of *adhatoda vasica* Nees leaf extract against gamma irradiation in Swiss albino mice. *Phytomedicine*, 2005; 12: 285-293.
28. Shrivastava N, Shrivastava A, Banarjee A, Nivsarkar M. Antiulcer activity of *Adhatoda vasica* Nees. *J Herb Pharmacother*, 2006; 2: 43-49.
29. Zama MMS, Singh HP, Kumar A. Comparative studies on *Adhatoda vasica* and pancreatic tissue extract on wound healings in buffaloes. *Ind Vet J*, 1991; 68: 864-866.
30. Vijaya S, Vasudevan TN. The effect of some medicinal plants activity of digestive enzyme. *Ind Drugs*, 1994; 31: 215-217.