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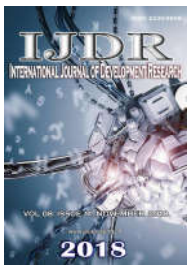

REVIEW ARTICLE OPEN ACCESS

A REVIEW ARTICLE ON *ADHATODA VASICA* NEES: A POTENTIAL SOURCE OF BIOACTIVE COMPOUNDS

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ABSTRACT

Herbal medicine is still the mainstay of about 75–80% of the world population, mainly in the developing countries, for primary health care because of better cultural acceptability, better compatibility with the human body and lesser side effects. However, the last few years have seen a major increase in their use in the developed world. 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 plant Adhatodavasica. A wide range of phytochemical constituents have been isolated from this plant having activities like antitussive, abortifacient, antimicrobial, insecticidal, hepatic protection, cardiovascular protection, anticholinesterase, antioxidant, antiinflammatory and other important activities. Some important bioactive compounds have been reported in various part of Adhatodavasicaare essential oils and quinazoline alkaloids. Sothis plant can form one of the best options for developing novel compounds having medicinal value.

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INTRODUCTION

The World Health Organization (WHO) has defined traditional medicine (including herbal drugs) as comprising therapeutic practices that have been in existence, often for hundreds of years, before the development and spread of modern medicine and are still in use today (Gansser, 1964). 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). *Adhatoda vasica* is popularly known as Basak in Bangla, Malabar Nut in English, Adosa in Hindi and Vasaka in Sanskrit (Aslam*et al.,* 2013). It has been used in preparation of herbal medicines for the past 2000 years. It is a medicinal plant native to Asia, widely used in Siddha Medicine, Ayurvedic and Unani system of medicine. The plant's range includes Sri Lanka, Nepal, India, Pakistan, Indonesia, Malaysia, and China, as well as Panama where it is thought to have been introduced This evergreen perennial shrub has leathery leaves. The flowers are dense and large having large bracts and whitish pink/purple colored. The herb is often grown as a hedge and its leaves and twigs are utilized as green-manure. The whole plant or its roots, leaves, bark and flowers are used in various herbal preparations. They are oppositely arranged, smooth-edged, and borne on short petioles (Kumar *et al.,* 2013).

Medicinal property: *Adhatoda vasica* has been used for the treatment of various diseases and disorders. It is a primary medicinal plant for the respiratory tract ailments in the

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treatment of cough, bronchitis, asthma and symptoms of common cold (Karthikeyan *et al.,* 2009). Constituents of the plant have been exposed to have antistress 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 cancer and possessed anti-helmintic properties (Ayyanar and Ignacimuthu, 2008).

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 antitussive activity of *Adhatoda vasica* extract was evaluated in anaesthetized guinea pigs and rabbits and in unanaesthetized guinea pigs. The plant was shown to have a good antitussive activity as vasicine showed the bronchodilatory activity both in vitro and in vivo (Dhuley and Jayant, 1999). Although, Vasicinone the main metabolite of Vasicine, which is also present in *Adhatoda vasica* 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 and Jayant, 1999).

Abortifacient: The plant was found to have uterotonic activity in different species including human beings due to vesicine. 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.

Antimicrobial: The ethanolic extract of plant root was analysed against the standard and clinical isolates of five microbial strains viz. *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Salmonella typhimurium and Pseudomonas aeruginosa* (RachnaVerma *et al*, 2016). The plant root extract showed maximum inhibition against clinical isolate of *Salmonella typhimurium* (13.3±0.5) at 200µg/ml concentration. The maximum antioxidant activity (38.55 ± 0.22) of root extract of plant was observed at 75µg/ml concentration and minimum (13.47±0.47) at 15µg/ml concentration. Standard analysis of phytochemicals in the root extract of plant showed presence of terpenoids, flavonoids, tannins, cardiac glycosides, alkaloids, reducing sugars and saponins. In GC-MS profiling the plant root extract showed presence of important compounds possessing antimicrobial, antitumour, anti-inflammatory, anticancer and antidiabetic properties. The antimicrobial activity (MIC) of *Adhatoda vasica* was assessed against clinical pathogen solvents like methanol, ethanol, acetone, chloroform, diethyl ether and water were used for the preparation of plant extracts in various concentrations by disc diffusion method the antimicrobial activity (MIC) was measured. From this, solvents showed higher activity in the order of diethyl ether > methanol > ethanol > acetone > Chloroform > water. The plant extract of Adhatoda vasica showed higher activity for different clinical pathogens in the order of *Klebsiella pneumonia> Staphylococcus aureus > Proteus valgaris > Pseudomonas aeruginosa > Streptococcus pyogens* (Josephin Sheeba and Selva Mohan, 2012). Two natural compounds, vasicine acetate and 2-acetyl benzylamine, were isolated from the plant. They were bioassayed against Mycobacterium tuberculosis. The two compounds showed strong antimycobacterial activity. Vasicine acetate and 2-acetyl benzylamine isolated from hexane extract of *A. vasica* leaves, significantly inhibited M. tuberculosis and one multi-drug-resistant (MDR) strain and one sensitive strain at 200 and 50 µg/ml, respectively (Ignacimuthu and Shanmugam, 2010).

Antioxidant property: The leaf samples of *Adhatoda vasica* was subjected to phytochemical analysis. The plant contained antioxidant phytochemicals such as alkaloids, tannin, saponins, phenolics and flavonoids. The methanolic extracts of the plants were also analyzed for antioxidant and reducing power potentiality. The plant showed strong antioxidant and reducing power ability. The strong antioxidant and reducing power ability of the plant underlines their use as antioxidant supplement against diseases such as typhoid during which antioxidant system fails; cardiovascular diseases which are caused due to accumulation of Reactive oxygen species; ageing related diseases, Alzheimer disease, Parkinson's disease, Amytrophic lateral sclerosis, cataractogenesis and other diseases(Manoj Kumar *et al.,* 2013). Extracts of this plant was irradiated in Co-60 irradiator (gamma chamber 900) at dose of 1, 2, 3, 5 and 10 kGy at ambient temperature. The effect of radiation on the methanol extract was investigated by different assays. In case of DPPH assay, at the dose of 5 kGy, the samples showed good scavenging activity (31.41%). Similarly in case of reducing power and FRAP assays values increased up to 38.68 mg equi of Fe^{+3}/g of dw and 25.90 mg equi of Fe^{+3}(Nilima*et al.,* 2012). Environmental and occupational exposure with cadmium affects the renal system adversely. Cadmium is an established genotoxic agent. Oral administration of *A. vasica* at two doses (50 and 100 mg/kg BW) for seven consecutive days showed significant ($p<0.001$) suppression of mutagenic effects of $CdCl_2$ in plant-pretreated groups (Jahangir *et al*. 2006). To study the mechanism by which *Adhatoda vasica* exerts its anti-mutagenic potential, enzymes involved in metabolism and detoxification were also estimated. Cadmium intoxication altered the antioxidant levels and enhanced MDA formation significantly ($p<0.001$). *A. vasica* showed significant ($p<0.001$) recovery in antioxidant status, viz., GSH content, its dependent enzymes, and catalase activity (Jahangir *et al.,* 2007).

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).

Hepatoprotective: *Adhatoda vasica* leaf showed significant hepatoprotective effect at doses of 50-100 mg/kg, p.o., on liver

damage induced by D-galactosamine in rats (Bhattacharyya *et al.,* 2005).

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

Antiulcer property: *Adhatoda vasica* leaf powder showed a considerable degree of anti-ulcer activity in experimental rats when compared with a control. The highest degree of activity (80%) was observed in the ethanol-induced ulceration model (Shrivastava *et al.,* 2006). Results of the study suggest that in addition to its classically established pharmacological activities, the plant also has immense potential as an antiulcer agent of great therapeutic relevance.

Wound healing effect: Methanolic, chloroform and diethyl ether extracts of *Adhatoda vasica* were evaluated for its wound healing activity in the form of Ointment dosage form in excision wound model in albino rats. The methanolic extract ointment of *Adhatoda vasica* showed a significant effect in excision wound model as comparable to standard drug and other two extracts of ointment, by calculating the parameters, percentage closure of excision wound model (G.Vinothapooshan and K. Sunder, 2010).

Insecticidal effect: Feeding on fresh leaves resulted in 100% mortality of larvae after 26 days of unsubstantial growth. The extract exhibited strong antifeedant and toxic activity against the larvae when applied either on leaf discs or incorporated into artificial diet (Sadek and Medhat, 2003).

Other activities

The anticestodal efficacy of *Adhatoda vasica* leaf extract was evaluated using Hymenolepisdiminuta-rat experimental model. The study shows that the leaf extract of *Adhatoda vasica* possesses significant anticestodal efficacy and supports its use in the folk medicine (Yadav *et al.,* 2008). The efficacy of 3 fungicides and 5 phyto-extracts against A. alternata were evaluated in vitro and in vivo in Adusa (*Adhatoda vasica* Nees). Mancozeb was found to be the most effective fungicide in checking the mycelial growth and conidial germination of A. alternate (Sing *et al.,* 2010). The radiomodulatory influence of ethanolic extract of *Adhatoda vasica* Nees leaf extract against radiation-induced hematological alterations in peripheral blood of Swiss albino mice was studied at various post-irradiation intervals between 6 h to 30 days. Oral administration of the leaf extract (800 mg/kg body weight) prior to whole body irradiation showed a significant protection in terms of survival percentage and hematological parameters (Kumar *et al.,* 2005). The growth promoting potential of *Piriformosporaindica*, which is a newly discovered arbuscularmycorrhizalikefungus is studied. It is a facultative symbiont and unlike arbuscularmycorrhizal fungi, it can be cultured in vitro. *Adhatoda vasica* is a medicinal plant. Rapid proliferation of roots was recorded in *Adhatoda vasica* with an important root colonization estimated to 95percent after 6 months. *P. indica* improved growth of *Adhatoda vasica*. This association forms a new host-symbiont combination (Rai *et al.,* 2005). The methanolic extract from the leaves of *Adhatoda vasica*showed the highest sucrase inhibitory activity with sucrose as a substrate (Gao *et al.,* 2008). Enzyme assay-guided fractionation of this extract afforded vasicine and vasicinol), and the structures of these compounds were elucidated on the basis of MS and NMR analysis. These compounds showed a high sucrase inhibitory activity, and the IC_{50} values were 125 µm and 250 µm, respectively. Ethanolic extract of *Adhatoda vasica* (100 mg/kg, 150 mg/kg and 200 mg/kg) significantly reduced the duration of seizures induced by maximal electroshock (MES) as well as protected animals from pentylenetetrazole induced tonic seizures. The results suggest that the ethanolic extract of the leaves of *Adhatoda vasica*may produce its anticonvulsant effects via non-specific mechanisms since it reduced the duration of seizures produced by maximal electroshock as well as delayed the latency of seizures produced by pentylenetetrazole (Ganga Rju*et al.,* 2011).

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.

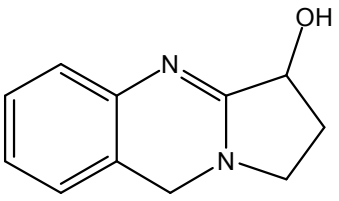
TOXICITY

Anti-fertility activity of *Adhatoda vasica*, 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 *Adhatoda vasica* extracts did not show any implantation sites (Prakash *et al*., 1985). The effect of *Adhatoda vasica* 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 *Adhatoda vasica leaf* extract showed that it contained the vasicine ranges from 0.0541 to 1.105% (Bhaduri *et al.,* 1968).

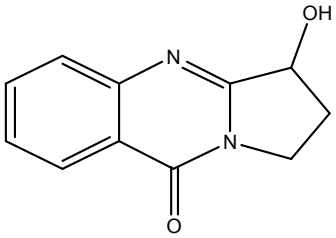
PHYTOCHEMISTRY

*Adhatoda vasica*is an Indian herbal plant, which due to its quinazolin alkaloids, is traditionally used for treating

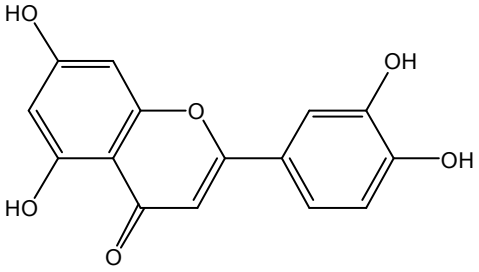
respiratory diseases (Herrmann, *et al*. 2006). Despite the fact that the herbal drug is still widely used in Indian local medicine and is rated by WHO as safe with local manufacturability, its use in European medicine for the therapy of respiratory diseases has drastically reduced. In contrast, the nasal application of Adhatoda extracts for allergic rhinitis has been increasing on the German market. The following monograph reviews the respective literature on phytochemical, pharmacological and clinical data of *Adhatoda vasica.* Two new aliphatic hydroxyketones, isolated from the aerial parts of *Adhatoda vasica* have been characterized as 37-hydroxyhexatetracont-1-en-15-one and 37-hydroxyhentetracont an-19-one, respectively, on the basis of spectral data and chemical studies (Singh *et al.,* 1991). 2',4-Dihydroxychalcone 4-glucoside has been identified in the flowers of *Adhatoda vasica* (Bhartiya and Gupta, 1982). A novel alkaloid and a galactoside isolated from the roots of *Adhatoda vasica* have been characterized as 9-acetamido-3,4-dihydropyrido-(3,4-b)-indole and O-ethyl-α-D- galactoside respectively by chemical and spectroscopic methods. In addition sitosterol β-D-glucoside, D-galactose and deoxyvasicin one have also been isolated from the roots of this plant (Jain*et al.,* 1980). Two new pyrroloquinazoline alkaloids, viz. 1,2,3,9- tetrahydropyrrolo (2,1-b)-quinazolin-9-one-3R-hydroxy-3(2'-dimethylamino phenyl (desmethoxyaniflorine) and 7-methoxy-3R-hydroxy-1,2,3,9- tetrahydropyrrolo-[2,1-b]-quinazolin-9-one (7-methoxyvasicinone), together with several known compounds were isolated from the leaves of *Adhatoda vasica*. Their structures were established by spectroscopic and X-ray diffraction analyses (Thappa *et al.,* 1996).



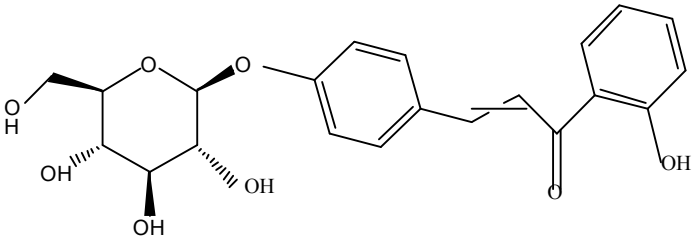
Vasicine



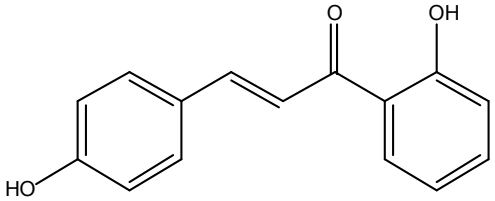
Vasicinone



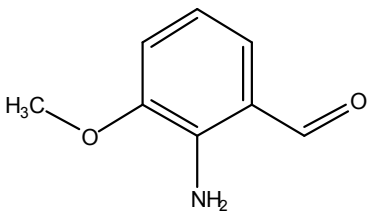
2-(3,4-Dihydroxy-phenyl)-5,7-dihydroxy-chromen-4-on



2',4-dihydroxychalcone 4-O-ß-glucopyranoside



2',4-dihydroxychalcone



2-amino-3-methoxy-benzaldehyde

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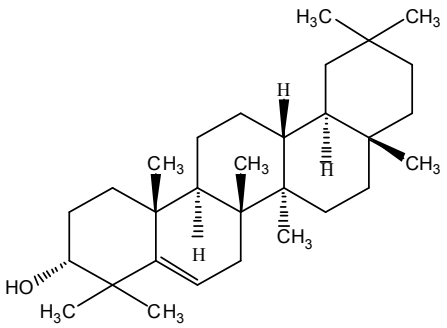
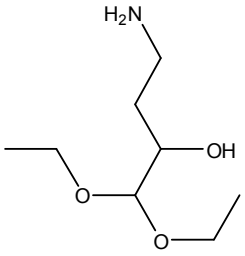
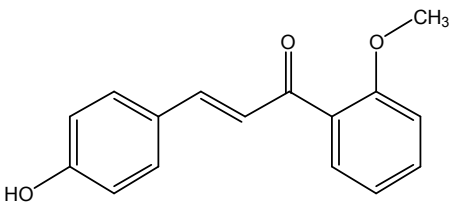


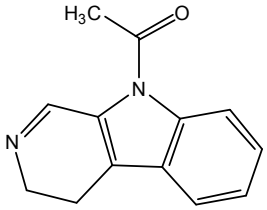
3a-hydroxy-oleanane-5-ene



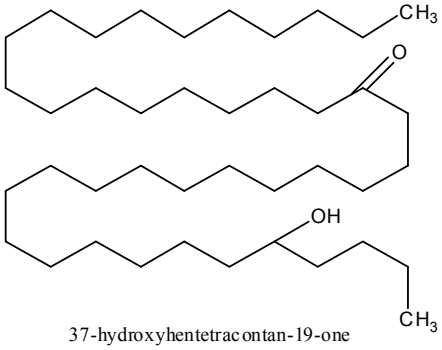
4-amino-2-hydroxy-butyraldehyde diethyl acetal



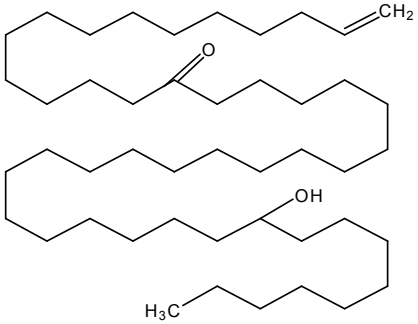
4-hydroxy-2'-O-methoxychalcone



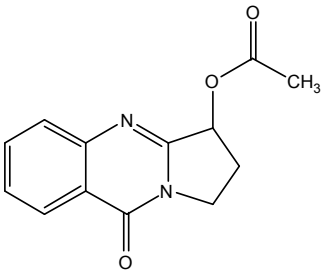
9-acetamido-3,4-dihydropyrido-(3,4-b)-indole



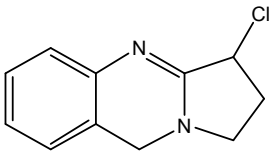
37-hydroxyhentetracontan-19-one



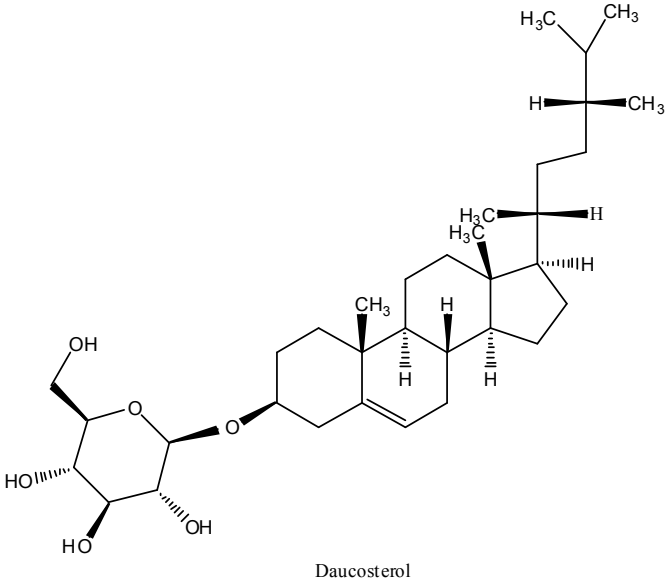
37-hydroxyhexatetracont-1-en-15-one



Acetylvasicinone



Chlorodesoxy vasicine



Daucosterol

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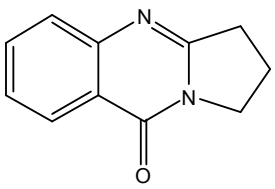
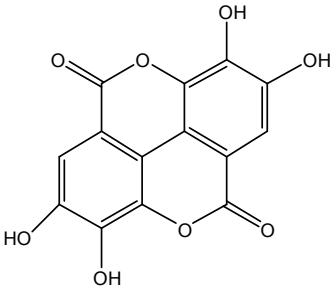
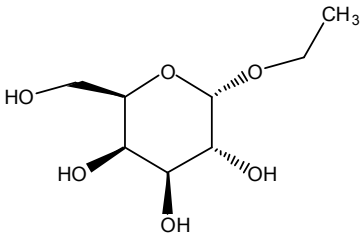


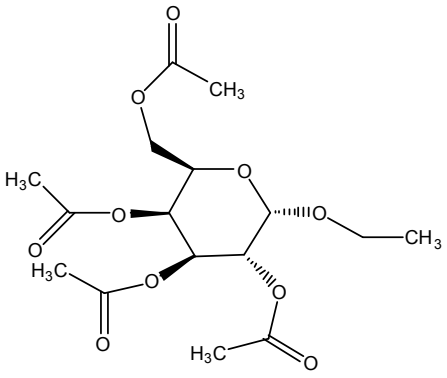
Deoxyvasicinone



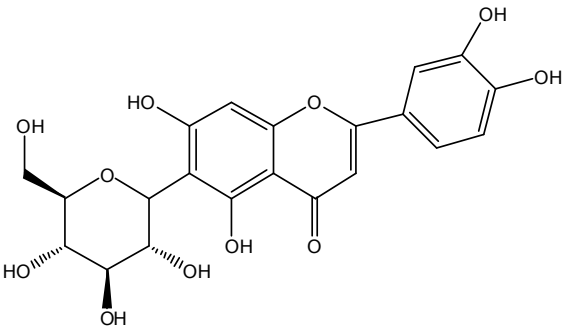
Ellagic acid



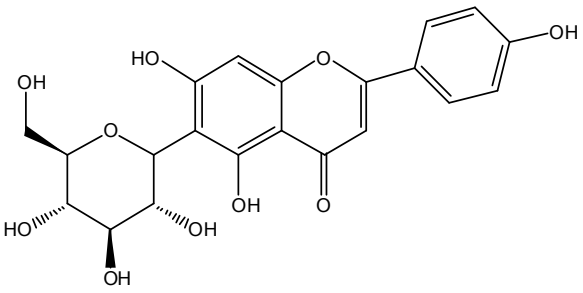
Ethylgalactoside



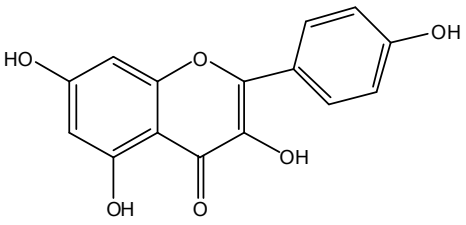
Ethyl-(tetra-O-acetyl-a-D-galactopyranoside)



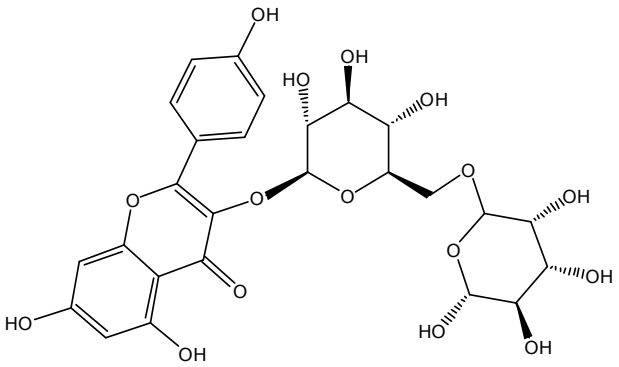
Isoorientin



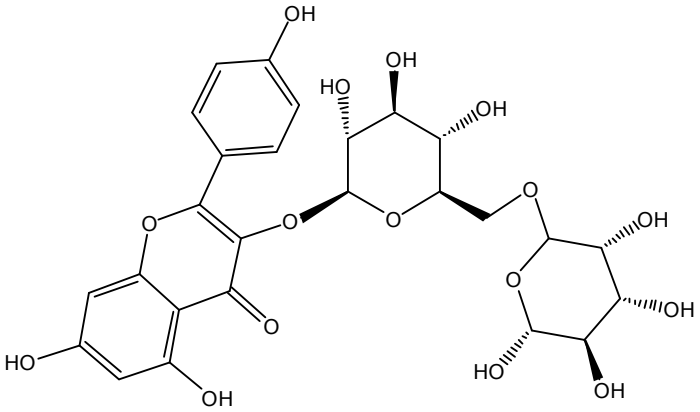
Isovitexin



Kaempferol

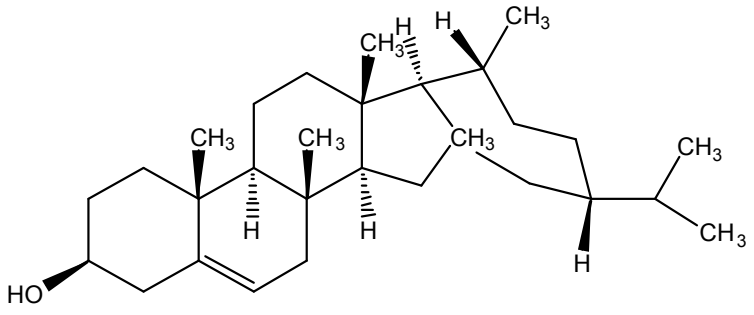


Kaempferol-3-rutinoside



Kaempferol-3-rutinoside

Continue…….



ß-sitosterol

Figure 1. Structure of few compounds isolated from *Adhatodavasica* Nees

Reinvestigation of the aerial parts of *Adhatoda vasica* led to the isolation of a new triterpenoid, 3α-hydroxy-oleanane-5ene. The structure of this compound was elucidated and identified by spectral studies (Sultana*et al.,* 2005). A new dihydroxy alcohol has been isolated from the aerial part of the *Adhatoda vasica*. The compound was identified as 2,4- dihydroxynonane on the basis of spectral land chemical studies (Sinha *et al.,* 2010). Tricyclic quinazoline alkaloids are found to be the most abundant in these plants which are responsible for broad-spectrum medicinal properties. A method was developed to elucidate the main fragmentation pathways of tricyclic quinazoline alkaloids in positive ion mode using high-performance liquid chromatography coupled with electrospray ionization quadrupole time-of-flight tandem mass spectrometry (HPLC/ESI-QTOF-MS/MS). It has been successfully used to identify 23 tricyclic quinazoline alkaloids in the alkaloidal fraction of *Adhatoda vasica* (Sing *et al.,* 2015).

QUANTITATIVE DETERMINATION OF COMPOUNDS

A new method of capillary electrophoresis was developed for the quantitative determination of vasicine and vasicinone from *Adhatoda vasica* Nees. The electrophoretic separation was performed using a 47 cm x 50 µm ID (38.5 cm effective length) fused silica capillary. The method was validated in terms of reproducibility, linearity, accuracy and applied for the quantitative determination of vasicine and vasicinone in *A. vasica*plant samples/extracts. Parameters affecting the resolution such as pH, temperature, organic modifier, buffer concentration and capillary dimensions were reported (Avula*et al.,* 2008). The juice samples were evaluated for the total alkaloid content by spectrophotometric method and vasicine content by thin layer chromatography densitometric method using high performance thin layer chromatography. The high performance thin layer chromatography method was validated for precision, repeatability and accuracy. The total alkaloid content varied from 0.3 mg/ml to 5.93 mg/ml and that of vasicine content varied from 0.2 mg/ml to 5.64 mg/ml in the juice samples prepared by different methods. The present study revealed that steaming of fresh leaves under 15 lb pressure yielded same quantity of juice as the traditional bolus method (25 ml/100 g leaf) and its total alkaloid content and vasicine content (4.05±0.12 and 3.46±0.06 mg/ml, respectively) were very high when compared to the other methods (Soni*et al.,* 2008). A simple high-performance thin-layer chromatographic (HPTLC) method has been developed for the simultaneous determination of the pharmacologically important quinazoline alkaloids vasicine and vasicinone in *Adhatoda vasica*.

The assay combines the separation and quantification of the analytes on silica gel 60 GF254 HPTLC plates with visualisation under UV and scanning at 270 and 281 nm. Using this technique, the alkaloidal content of differentparts of the title plant have been determined (Das *et al.,* 2005).

CONCLUSION

The literature survey has revealed that *Adhatoda vasica* Nees has been widely studied for its pharmacological activities. It is agood source of many medicinally important chemicals such as Vasicine, Vasicinone, Vasicoline and other various useful minor alkaloids. Asresearchers adopt on the global scenario for drug discovery from plant sources, development of therapeutically active compound from *Adhatoda vasica* should be emphasized.

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