

ADHATODA VASICA: VASAKA

Adhatoda vasica is a well-known plant drug in Ayurvedic and Unani medicine. Adhatoda leaves have been used extensively in Ayurvedic Medicine primarily for respiratory disorders. The medicinal properties of Adhatoda vasica, called Vasa or Vasaka in Sanskrit have been known in India and several other countries for thousands of years.

DESCRIPTION

Macroscopic-Leaves, 10-30 cm long and 3-10 cm broad, lanceolate to ovate-lanceolate, slightly acuminate, base tapering, petiolate; petioles 2-8 cm long, exstipulate, glabrescent, 8-10 pairs of lateral vein bearing few hairs; dried leaves dull brown above, light greyish brown below; odour, characteristic; taste, bitter.

Microscopic-Transverse section of leaf shows, dorsiventral surface with 2 layers of palisade cells; in surface with 2 layers of palisade cells; in surface view, epidermal cells sinuous with anomocytic stomata on both surfaces, more numerous on the lower; clothing trichomes few, 1-3 rarely upto 5 celled, thin-walled, uniseriate, upto 500 μ and glandular trichomes with unicellular stalk and 4 celled head measuring, 25-36 μ in diameter in surface view; cystoliths in mesophyll 1 years, elongated and cigar shaped; acicular and prismatic forms of calcium oxalate crystals present in mesophyll; palisade ratio, 5-6, 5-8.5; stomatal index, 10.8-14.2-18.1 for lower surface.

ORIGIN AND DISTRIBUTION

The plant is distributed all over the plains of India & in lower Himalayan ranges, ascending to a height of 1,500 m.

TRADITIONAL MEDICINAL USES

Adhatoda vasica Nees (Vasaka) is used in various chest affections and enjoys wide reputation as an expectorant in the indigenous system of medicine. It was used also by traditional midwives at the time of delivery. The leaves, the roots and flowers of Adhatoda vasica are extensively used in indigenous medicine as remedy for cold, cough, bronchitis and asthma. Both the decoctions and powder from constituents of many preparations use in the Ayurvedic medicine for various affections of the respiratory tract. In chronic bronchitis and asthma it is said to be very useful. The medicine was considered so useful in tuberculosis that it was said that no man suffering from this disease need despair as long a vasica plant exists in this world. The juice of the leaves is used in diarrhoea and dysentery and powdered leaves in malaria in southern India.

Adhatoda vasica is traditionally used in many of the following ways:

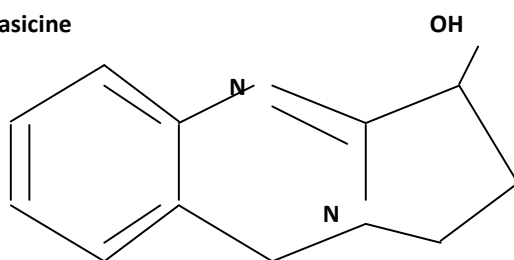
- Juice from the leaves and the decoction of the leaves and roots are helpful in asthma, bronchitis and chronic coughs and breathlessness.
- Used for bleeding due to idiopathic thrombocytopenic purpura, local bleeding due to peptic ulcer, piles, menorrhagia.
- Relief in pyorrhoea and for bleeding gums by locally application.
- Relieves or eases muscular spasms, cramps or convulsions
- Stimulates contraction of the uterine muscle, facilitating or speeding up childbirth
- Lowers blood pressure

Adhatoda is said to be non-poisonous to mammals, but to kill fish, insects, and lower organisms.

CHEMICAL CONSTITUENTS

The leaves of the plant contain an essential oil and alkaloids vasicine, N-oxides of vasicine, vasicinone, deoxyvasicine and maiontone. The roots are known to contain vasicinolone, vasicol, peganine and 2' - hydroxy - 4 - glucosyl -oxychalcone. The flowers contain β -sitosterol-D-glucoside, kaempferol, its glycosides and quereetin.

Vasicine



PHARMACOLOGICAL ACTIVITIES AND CLINICAL TRIALS

Abortifacient activity

A survey programme was organised in Lucknow and Farrukhabad, two towns of Uttar Pradesh, from March 1987 to July 1987. During the survey, the common folk medicine plants used by women were recorded and Ayurvedic and Unani drug encyclopedias were consulted for the antireproductive potential of these plants. Aqueous or 90% ethanol extracts of the plants of interest were studied in rats orally dosed for 10 days after insemination with special reference to effects on fetal development. Leaf extracts of *Moringa oleifera* and *Adhatoda vasica* were 100% abortive at doses equivalent to 175 mg/kg of starting dry material.

Anti-allergic activity

A methanolic extract from the entire plant has been shown to possess anti-allergic activities in the guinea-pig after inhalation or intragastric administration at doses of 6 mg per animal or 2.5 gm/kg, respectively.

Compound 73/602 (AA) is a structural analogue of vasicinone, an alkaloid present in the leaves and roots of *Adhatoda vasica* (Acanthaceae). It possesses potent antiallergic activity in mice, rats and guinea pigs. The pK (a) of AA was determined to be 2.87 +/- 0.19 by UV spectrophotometry. The absorption kinetics of this compound was studied in-situ using a rat gut technique at pH 2.6 and 7.4. The rate of absorption at pH 2.6 (0.0288 +/- 0.004 min⁻¹). This characteristic behavior was attributed to the low pK (a) of AA, weakly basic compounds, where nearly 35% of the compound remained in the unionized form at pH 2.6. Also, the return of compound into the mucosal lumen from the blood capillaries over a period of 2 h after administering a 2 mg dose in tail vein was less than 0.3%. Hence it was concluded that entero-enteric circulation of AA did not contribute significantly to the in-situ absorption rates. Pharmacokinetic parameters of AA were determined in male rats after administering a single 10 mg/kg intravenous dose (i.v.) and 50 mg/kg oral bolus dose. Following i.v. administration the initial decline in serum concentration was rapid with half-life of 20.2 min. after a single oral dose the concentration-time data of AA in rats was 50.6 min, indicating absorption rate limiting disposition at the high dose given. Comparison of ACU of oral and i.v. data indicates that only about 60% of the oral dose reaches the systemic circulation.

Structure-activity relationships obtained from in vitro screening results obviously indicate that the highest inhibition effects on cyclooxygenase and 5-lipoxygenase are found amongst the class of phenolic compounds (flavonoids, polyphenols, coumestans, phenol carboxylic acids) and arachidonic acid

analogous (alkylamides, retinoids, arylheptanoids, thiosulfonates, sulfinyl disulfides). The antiinflammatory activities of some triterpenic acids, sesquiterpene lactones and polysaccharides may be due to their immunomodulating activities on the complement and/or T-lymphocyte populations, respectively. In the search for potential anti-allergic and anti-asthmatic compounds, the thiosulfonates of onion were found to be active principles of the drug. The mechanism of action of some other anti-allergic plant drugs (i.e. *Tylophora asthmatica*, *Adhatoda vasica*, etc.) has not yet been clarified.

Anti-asthmatic activity

A methanolic extract from the entire plant has been shown to possess anti-asthmatic activities in the guinea-pig after inhalation or intragastric administration at doses of 6 mg per animal or 2.5 gm/kg, respectively.

Hitherto unknown alkaloids from *Adhatoda vasica* showed pronounced activity against allergen-induced bronchial obstruction in guinea pigs (10 mg/ml aerosol). Androsin from *Picrohiza kurroa* prevented allergen- and PAF-induced bronchial obstruction (10 mg/kg orally; 0.5 mg inhalative). Histamine release in vitro was inhibited by other compounds of the plant extract yet to be identified. Pharmacological effects of plant extracts and pure compounds in man are under investigation.

Anti-inflammatory activity

Adhatoda vasica Nees is a shrub widespread throughout the tropical regions of Southeast Asia. It possesses a wide spectrum of medicinal properties including positive effects on inflammatory diseases. The anti-inflammatory activity of the methanol extract, the non-alkaloid fraction, the saponins and the alkaloids was evaluated by the modified hen's egg chorioallantoic membrane test. The alkaloid fraction showed potent activity at a dose of 50 microg/pellet equivalent to that of hydrocortisone while the MeOH extract and the other fractions showed less activity.

Anti-microbial activity

The present report deals with the preliminary experiments designed to evaluate the in vitro effects of *Adhatoda vasica* (ARDUSI) leaf (AVL) extract on micro-organisms of inflamed gingiva by employing antibiotic sensitivity test by disc diffusion method. In vitro sensitivity test with AVL extract of micro-organism of inflamed gingiva showed significant antimicrobial activity.

Anti-tubercular activity

The oil obtained from leaves, flowers and roots of *vasica* plant possesses significantly high activity against tubercle bacilli. The growth of *M.tuberculosis* B 19-4 (human) is inhibited in a concentration of 2 µg.; that of B 19-3 (bovine) partially in a concentration of 2 µg./c.c., and completely in a concentration of 5 µg; while of B19-1 (avian) strain is inhibited completely in a concentration of 5 µg. The anti-tubercular activity of the active principle from leaves is twice less than that of streptomycin. The action of the active principle is specific for tubercle bacillus. The growth of non-acidfast bacteria is not inhibited in a concentration of 500 µg./c.c. The drug in a dose of 2.3g/kilo body-weight when injected subcutaneously to mice does not produce any toxic symptoms. Five hundred mg./kilo injected subcutaneously in guinea-pig does not produce any toxic symptoms. The oil has low toxicity for paramecia. 1/5,000 dilution of the oil does not kill these in one hour.

Anti-tussive activity

The antitussive activity of *Adhatoda vasica* (AV) extract was evaluated in anaesthetized guinea pigs and rabbits and in unanaesthetized guinea pigs. AV was shown to have a good antitussive activity. Intravenously, it was 1/20-1/40 as active as codeine on mechanically and electrically induced coughing in rabbits and guinea-pigs. After oral administration to the guinea-pig the antitussive activity of AV was similar to codeine against coughing induced by irritant aerosols.

Bronchodilatory activity

The pharmacological actions of vasicinone on the bronchial musculature were studied on the guinea pig tracheal chain, on perfused guinea-pig lung and by the overflow method in intact guinea pigs. Vasicinone had a definite bronchodilator action on the normal lungs and a powerful bronchodilator action against the

histamine-induced bronchoconstriction; but its action was weaker than adrenaline. Laevo-vasieinone was however, stronger in action than its DL-form. Vasicinone showed a slight and transient fall in the blood pressure of a dog. On isolated perfused hearts of guinea pig and rabbit vasicinone had a positive inotropic action and increased the flow in the coronary vessels. Both L-and DL-forms of vasicine displayed a bronchoconstrictor action, had a negative inotropic action on the heart and also reduced the flow in the coronary vessels.

Chemopreventive efficacy

The effect of two different doses (50 and 100 mg/kg body wt/day for 14 days) of 80% ethanolic extract of the leaves of *Adhatoda vasica* were examined on drug metabolizing phase 1 and phase 11 enzymes, antioxidant enzymes, glutathione content, lactate dehydrogenase and lipid peroxidation in the liver of 8 weeks old Swiss albino mice. The modulatory effect of the extract was also examined on extra-hepatic organs viz. lung, kidney and forestomach for the activities of glutathione S-transferase, DT-diaphorase, superoxide dismutase and catalase. Significant increase in the activities of acid soluble sulfhydryl (-SH) content, cytochrome P450, NADPH-cytochrome P450 reductase, cytochrome b5, NADH-cytochrome b5 reductase, glutathione S-transferase (GST), DT-diaphorase (DTD), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase (GR) were observed in the liver at both dose levels of treatments. *Adhatoda vasica* acted as bifunctional inducer since it induce both phase 1 and phase 11 enzyme systems. Both the treated groups showed significant decrease in malondialdehyde (MDA) formation in liver, suggesting its role in protection against prooxidant induced membrane damage. The cytosolic protein was significantly inhibited at both the dose levels of treatment indicating the possibility of its involvement in the inhibition of protein synthesis. BHA has significantly induced the activities of GR and GSH in the present study. The extract was effective in the present study. The extract was effective in inducing GST and DTD in lung and forestomach and SOD and CAT in kidney. Thus, besides liver other organs viz., lung, kidney. Thus and forestomach were also stimulated by *Adhatoda*, to increase the potential of the machinery associated with the detoxification of xenobiotic compounds. But, liver and lung showed a more consistent induction. Since the study of induction of the phase 1 and phase 11 enzymes is considered to be a reliable marker for evaluating the chemopreventive efficacy of particular compound these findings are suggestive of the possible chemopreventive role played by *Adhatoda* leaf extract.

Hypoglycaemic activity

Ethanolic extracts from the leaves showed hypoglycaemic activity after oral administration in rats and rabbits.

Muscle relaxant activity

An essential oil from the leaves of *vasica* showed smooth muscle relaxant activity in the isolated guinea-pig tracheal chain.

Thrombopoietic activity

Repeated oral and intramuscular administration of vasicine (an alkaloid from *Adhatoda vasica*) resulted in an increase in platelet count in normal rats, mice, rabbits and dogs. This increase in platelets was also associated with significant hyperplasia of megakaryocytes in the bone marrow. No effects were observed on haemoglobin level and RBC or WBC counts and morphology. Bleeding and clotting times were not significantly altered nor was there any evidence of in vitro haemolysis. Vasicine did not influence platelet function. Results control of capillary haemorrhages and for correction of drug induced bone marrow depression.

Uterotonic activity

The uterotonic activity of vasicine was investigated in details on the uteri of different species of animals and in different hormonal states both in vitro and in vivo. Its uterotonic activity was found to be similar to that of oxytocin and methyl ergometrine. It was observed that the uterotonic activity of vasicine was

influenced by the degree of priming of the uterus by oestrogens (known to enhance the synthesis of prostaglandins in the uterus) and it was markedly reduced after pretreatment of the uterus with aspirin and indomethacin. This indicated that the uterotonic effect of vasicine was at least partly mediated through the release of prostaglandins.

PHARMACOKINETICS

Vasicine, 20 mg/kg body weight, given intramuscularly was well absorbed reaching a maximum concentration of about 50 µg/ml in blood in both pregnant and non-pregnant rats and about 10 µg/ml in amniotic fluid. After intravenous injection in rats and mice high concentrations of vasicine were found in the uterus within 5 min and the peak level was achieved after 10 min. The half-life was 5-7 min, 1.5 and 2 h after intravenous, intramuscular and subcutaneous administration, respectively. The studies on absorption and distribution of vasicine in mice after intravenous, intramuscular and subcutaneous administration show similar results as those reported in rats. After oral administration very low concentrations were found in the uterus. Vasicine is metabolized in the liver to vasicinone and other metabolites which contribute to the first pass effect and which is an important way of elimination of vasicine.

It is reported that vasicine and its metabolites are mainly excreted in the urine. On intravenous and intramuscular administration about 55% of the excreted product in the first 18 to 22 h, respectively, was vasicine, while on oral administration about 18% of the excreted product was vasicine during the first 24 h.

TOXICOLOGY

All studies on the effects of *A. vasica* extract and vasicine on the reproduction system and function are reviewed under reproduction toxicity even though they were not always assigned as toxicity studies.

General toxicology

The acute toxicity of vasicine after single administration is moderate. A similar degree of acute toxicity has been found by other investigators and in other species.

Vasicine was given daily for 2 weeks to groups of rats (six males and six females in each) subcutaneously, 10, 25 and 50 mg/kg body weight and orally, 20 and 100 mg/kg body weight. A control group was treated with normal saline. Groups of dogs (two males and two females in each) were treated subcutaneously, 3.5 and 17.5 mg/kg body weight and orally 35 mg/kg body weight. A fourth group served as control. Clinical observations, clinical chemistry and histopathological examination of major organs were performed on all the animals. No remarkable adverse effects were recorded in any species.

The general toxicity after repeated oral administration of vasicine daily for 6 months has been studied in rats and monkeys. Four groups of rats (ten males and ten females in each) were given 1, 2.5, 5 and 10 mg/kg body weight respectively. Clinical observations, clinical chemistry and histopathology of the major organs were performed in both the species. Mortality rate and body weight of the treated animals were comparable with the controls except the mortality rate in the treated male rats which was dose dependently increased. Haematological and biochemical determinations were within the normal physiological range. Autopsy and histopathological examination of major organs did not reveal any abnormalities.

Reproduction toxicity

The observation of the uterotonic action of vasicine prompted the testing of vasicine for its abortifacient activity. Mated female rats (ten in each group), were given vasicine, 5-15 mg/kg body weight intraperitoneally on day 8 or 16 of gestation. No effects on implantation or delivery were found. Pretreatment with estradiol did not change the outcome of the vasicine treatment. In guinea pigs vasicine, 30 mg/kg body weight given intraperitoneally caused abortion in four out of eight animals in late pregnancy. Pretreatment with estradiol increased the effect of vasicine.

In rats' vasicine, 5 and 10 mg/kg body weight was administered intraperitoneally to groups of ten animals at various intervals of pregnancy. No anti-implantation effect (no effect when given on day 1-7) but an abortifacient effect, pregnancy failure after day 7 which increased during pregnancy was found.

A pregnancy failure or abortifacient activity was also observed in hamsters (ten in each group) receiving vasicine 2.5 and 5 mg/kg body weight, intraperitoneally on day 7-9 and day 10-12 of pregnancy or in guinea pigs (in groups of three to ten animals) receiving vasicine 5 and 10 mg/kg body weight intraperitoneally for 3 days at different stages of pregnancy.

In rabbits, vasicine 2.5, 5 and 10 mg/kg body weight was administered intraperitoneally or intramuscularly, or 20 mg/kg body weight was administered orally day 10-12, day 17-19 or day 22-24 of pregnancy to groups of two to four animals. There were no control groups of two to four animals. There were no control groups. The animals were observed daily for any vaginal bleeding or expulsion of conceptuses. Abortifacient activity was observed in more than half of the animals after parenteral administration while no activity was observed after oral administration.

Teratogenic studies on vasicine were performed in rats and rabbits. Groups of mated rats were given vasicine, 2.5, 5 and 10 mg/kg body weight intraperitoneally day

1-7, 8-15 and 18-22 of gestation. Pups delivered at full term were kept under observation till maturity when they were randomly mated. Pregnant animals were given vasicine, 2.5 mg/kg body weight intraperitoneally from day 1 to day 20 of gestation. All the pups were recorded and examined closely for any grossly abnormal fetuses. Except for occasional pregnancy wastage seen at 2.5 mg/kg and a dose related but partial wastage at higher doses vasicine did not exhibit any teratogenic effects or any other adverse effects in any of pups of the first or second generation.

Groups of mated rabbits were given vasicine, 1.25, 2.5 and 5 mg/kg body weight intraperitoneally day 9-16, 16-23 and 23-30 of pregnancy. Control groups were given saline. Some animals in the two highest dose groups aborted while the rest of the animals delivered normally on the due date. The pups did not show any gross abnormalities. They were observed till they reached adult age and then they reproduced normally. No abnormality was detected in the second generation of the treated animals.

Reproduction toxicity

In a screening study of antifertility activity of a number of medicinal plants, an extract of *A. vasica* leaves was included. Various doses of the extract were fed to albino mice 7 days before and 14 days during cohabitation and to female rats on the day spermatozoa were detected in the vaginal smear and then for 4 more days. No effects on the pregnancy were recorded after administration of *A. vasica* leaves extract either in mice or in rats.

In an anti-implantation study, aqueous, benzene and 50% ethanol extracts of *A. vasica* leaves and acetone and methanol extracts of bark and root were fed to mated rats (five to ten animals per group), on day 1-7 of pregnancy. About half of the animals treated with about 100 mg/kg of different *A. vasica* extracts did not show any implantation sites.

A. vasica aqueous extract was included and the results were separately published. The extract at 175 mg/kg was given orally during day 5-10 or 0-9 of gestation to seven mated females. All the animals were delivered by caesarian section on day 20. There was no foetus observed in the treated animals but 104 resorptions. 104 implantations and 104 corpora lutea. Corresponding numbers in the controls were eight resorptions, 98 implantations and 98 corpora lutea. The time of exposure differs between the two publications despite it being obvious from all other data that the two publications deal with one and the same publications.

The effects of *A. vasica* spissum leaf extract on early gestation were studied in two experiments in rats given the extract orally day 1-9 of gestation. In the first experiment one group of five mated females was given 325 mg/kg body weight of *A. vasica* dissolved in saline by a gastric cannula. Another group of five animals served as control and was given saline. The animals were sacrificed on day 18 of gestation and the outcome of the gestation recorded. 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 the control animals.

Studies in human beings

Vasicine has been tried in a preliminary human study being conducted for interruption of mid-trimester pregnancy by intraamniotic instillation of the drug. Doses above 60 mg were given in 12 cases and all of them aborted. In another preliminary report, which might include the cases reported in the above study, 62 cases with intraamniotic instillation of the drugs are reported. All cases given more than 60 mg aborted after about 48h. Furthermore, in other studies it has been shown that vasicine is a very effective oxytocic agent in human beings stopping post-partum hemorrhage. Clinical studies in which intravenous and intramuscular administrations were shown to be less effective than intraamniotic administration.

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