REVIEW ARTICLE

Adhatoda vasica: A critical review

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Abstract

Natural products are the most important source for discovery of new and effective drug molecules. The emergence of drug-resistant pathogens and the increase in diseases affecting the immune system have greatly intensified the need to investigate new bioactive metabolites for potential pharmaceutical and industrial applications. Ayurvedic classics have a unique wealth of medicinal plants and vast traditional knowledge of herbal medicine for the cure of various diseases. *Adhatoda vasica* (Nees) (AV) of family Acanthaceae, is a shrub growing throughout the Indian peninsula. The frequent use of AV has resulted in its inclusion in the WHO manual – The Use of Traditional Medicine in Primary Health Care. Thus, extensive research work has been conducted on the AV. The present article is an endeavor to review the ethanopharmacological evidence of therapeutic uses of AV in nutshell.

Key words: *Adhatoda vasica*, vasicinone, vasicol, vasicine

INTRODUCTION

Nature acts as a major reservoir for new and novel therapeutics. The emergence of drug-resistant pathogens and the increase in diseases affecting the immune system have greatly intensified the need to investigate new bioactive metabolites for potential pharmaceutical and industrial applications.[1,2] Ayurvedic classics have a unique wealth of medicinal plants and vast traditional knowledge of herbal medicine for cure of various diseases.

Indian flora encompasses nearly 49,000 - plant species[3] and 8000 - species of these, are known to have medicinal potential.[4] Indian System of Medicine - Ayurveda quotes around 2500 - plant species for the purpose of treatment belonging to more than 1000 - genera.[5]

Adhatoda vasica (Nees) (AV) of family *Acanthaceae*, known commonly as Malabar nut tree, is a shrub growing throughout the Indian peninsula. The names *Adhatoda zeylanica* Medic. and *Justicia adhatoda* L. are used synonymously. AV is a well-known expectorant in both Ayurvedic and Unani Systems of Medicine.[6,7] In Ayurvedic preparations, *Vasaka* leaf juice (*Vasa swarasa*) is incorporated in more than 20 formulations.[8] The frequent use of AV has resulted in its inclusion in the WHO manual – The Use of Traditional Medicine in Primary Health Care.[9] In the 1980s, the WHO included AV in The Special Programme of Research in Human Reproduction as a worthy plant for fertility regulation study.[10] Thus, extensive research work has been conducted on the chemical components of AV.

The present article is an endeavor to review the ethanopharmacological evidence of therapeutic uses of AV in nut shell.

METHODS

The data available in various databases have been collected from May 2015 to June 2016 which was further critically reviewed. The compiled information has been systematically studied and categorized in different headings and commented.

RESULTS

Ethnological Relevance

Various survey conducted in different region of world proved that AV poses high ethnomedicinal status. The

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survey conducted in region like Garhwal Himalaya,[11] lesser Himalaya of the Pakistan,[12] Kani tribes in Thodu hills of Kerala, South India,[13] North district of Tripura, and North East India,[14] revealed that AV is the most common species found in tropical and subtropical region and is used by traditional healer. It is identified with local name Bhekker and found to be most cited species (43%) and is one of the species having the highest cultural index values as well. It has been also used in the veterinary conditions such as stomach disorder, fever, dehydration, and dysentery.[12] In the eastern region of Shimoga District, Karnataka, India, Adhatoda, was assigned with high degree of fidelity level (100%) analysis value.[15] Moreover, four ethano-medicinal recipes prepared from AV are found to be used in Southeast Asian countries against diabetes.[16]

Chemical Constituents and Evaluation of Analytical Methods

Many studies have been reported to evaluate various chemical contents present in AV. The most studied chemical component is a bitter quinazoline alkaloid, vasicine, which is present in the leaves, roots, and flowers.[17-20] Apart from vasicine, important chemical constituents identified in the leaf are vasicol, adhatonine, vasicinone, vasicinol, and vasicinolone.[21,22] The other alkaloids discovered in the plant are adhatonine, adhavasicinone, anisotine, and peganine, betaine, steroids, and alkanes.[17-20] It also contains vitamin C, saponins, flavonoids as well as steroids and fatty acids.[23] Essential oils of the leaves of AV are also known to contain ketone, terpene, and phenolic ether.

For the isolation and identification of the active principles, different chromatographic methods like high-performance liquid chromatography, medium-pressure liquid chromatography, elementary analysis, ultraviolet, mass, 1H- and 13C-nuclear magnetic resonance spectroscopy have been used. A new analytical method using capillary electrophoresis which separates, the two alkaloids, namely, vasicine and vasicinone from AV within 11 min with good repeatability has been reported. The method has been applied for the quantitative determination of vasicine and vasicinone and validated in terms of reproducibility, linearity, and accuracy.[24] An analytical study has also been developed by Das *et al.* to determine these two alkaloids simultaneously using a simple high-performance thin-layer chromatographic method.[25] The distribution pattern of the alkaloids of AV has also been studied with change of season.[22]

Apart from above analytical methods, a study was conducted to identify a method which extracts similar quality of total alkaloid obtained by the traditional method.[26] In this experiment, the juice was prepared by four methods. First, traditional bolus method (modified *Put Pak Vidhi*)[27] was used, whereas the second method employed was steaming of leaves. In the third method, AV Swarasa was prepared by manual way and in fourth method using a grinder. The study revealed that the juice (*swarasa*) prepared by traditional *Putapak vidhi* method contained the highest amount of total alkaloids 5.93 mg/ml and vasicine 5.64 mg/ml of juice. In the modified method, total alkaloid content was 4.05 mg/ml and vasicine content 3.46 mg/ml little less than that of the traditional method. The experiment concluded that traditional method is superior to the modified method.

Respiratory Disorders

AV has been used for thousands of years in various traditions for inflammatory conditions of respiratory tract without any adverse effect. In a critical review, AV has been acknowledged as a mainstream natural agent used for the inflammatory condition of the respiratory tract.[28] It has been also proven for activities such as bronchodilatation, antitussive, antihistaminic, relief in chronic disorders like asthma.

Bronchodilator

In 1959, a first study was reported to claim bronchodilatation activity of vasicinone, alkaloid of AV.[29] Along with vasicinone, hitherto, a unknown alkaloids from AV showed pronounced protection against allergen-induced bronchial obstruction in guinea pigs.[30] Vasicine is also claimed to have bronchodilator activity. A study was conducted to assess a mode of action of a bronchodilator obtained by the chemical modification in the molecule of alkaloid vasicine named 6, 7, 8, 9, 10, 12-hexahydro-azepino-[2, 1-b]-quinazoline-12-one (RLX). The oral administration of RLX (10 and 20 mg/kg) inhibited antigen-induced mast cell degranulation and histamine secretion from target tissues. These results suggested that RLX could be acting such as disodium cromoglycate and aminophylline with additional attributes of oral efficacy and long duration of action.[31]

Antitussive

AV has been also identified for its antitussive activity. It has been proved as effective as codeine on mechanically or electrically and irritant aerosols induced coughing, respectively, in rabbits and guinea pig.[32] In another experiment, pharmacodynamics characteristics of arabinogalactan samples extracted from AV have been investigated for antitussive activity. In a citric acid-induced cough model test drug was administered orally in guinea pigs. There was 67% cough suppression with AV which was comparable with codeine (62%).[33]

Asthma

A clinical study was conducted to assess the effect of syrup prepared from AV (*vasa avaleha*) with two different types of dose of AV, namely, aqueous extract (*swaras*) and heated extract (*kwath*). The parameters of assessment used were subjective relief in symptoms of asthma observed in patients and certain hematological parameters. Both the formulations showed significant reduction. But more significant relief

in the symptoms of patients and insignificant decrease in hematological parameters treated with vasa syrup prepared with aqueous extract (*Swarasa*) were noted.[34] An experimental study reported antioxidant and thereby anti-asthmatic effect of herbal compound formulation Pentapala-04, wherein AV was one of the ingredient. Lung damage was induced by ova albumin and aluminum hydroxide in rats.[23] Pentapala-04 supplementation was potentially effective in blunting lipid peroxidation (LPO), suggesting that it possibly has antioxidant property to reduce ova albumin and aluminum hydroxide-induced membrane LPO, and thereby to preserve membrane structure. Thus, "Pentapala-04" prevents lung injury and inflammatory changes proving the antiasthmatic activity.[35] Two more studies demonstrated the antiasthmatic activity of AV.[36] Furthermore, Sharma and Atal have proved the efficacy of AV against allergen-induced bronchial obstruction.[37]

Acute Upper Respiratory Tract (URT) Infection

In a randomized controlled trial efficacy of AV was assessed in a combination of other medicinal herbs in acute URT infection. A fixed combination of extract of three herbals containing AV, *Echinacea purpurea,* and *Eleutherococcus senticosus* was compared with the combined extracts of *E. purpurea* and *E. senticosus* alone (echinacea mixture), whereas Bromhexine, a standard drug was used as a standard control. The patients treated with AV in combination with other herbs showed significantly greater improvement compared with those receiving the standard treatment. The addition of extract of AV in the Echinacea mixture claimed to enhance the efficacy.[38]

Antitubercular Activity

Aqueous extracts of leaves of, AV, was tested *in vitro* for their activity against two multidrug-resistance (MDR) isolates (DKU-156 and JAL-1236). The reference susceptible strain used was *Mycobacterium tuberculosis* H37Rv as well as rapid grower mycobacterial pathogen *Mycobacterium fortuitum* (TMC-1529). Extracts of AV exhibited anti-tuberculosis activity in L-J medium. The proportion of inhibition is 32% for MDR isolate DKU-156 and 86% for another MDR isolate JAL-1236, whereas for sensitive *M. tuberculosis* H37Rv inhibition was found to be 70%. There was no inhibition against rapid grower *M. fortuitum*.[39] In another experiment the benzylamines, bromhexine and ambroxol, semi-synthetic derivatives of vasicine from AV, have a pH-dependent growth-inhibitory effect on *M. tuberculosis*. These compounds found to be concentrated in macrophages. In the *in vitro* study, along with this effect enhancement of lysozyme levels in bronchial secretions and possibly clearance of bacilli-laden mucus from cavities and bronchi, have been observed suggesting a potentially useful adjuvant effect in the therapy of tuberculosis.[40] Few molecular study have also been supported the antitubercular potential of AV. The unique structural features and universal occurrence in *M. tuberculosis* is enzyme β-ketoacyl-acyl-carrier protein synthase III that catalyzes the initial step of fatty acid biosynthesis (FabH) through a type II fatty acid synthase (mtFabH). Thus, it was considered as a target for designing of anti-tuberculosis compounds. The natural alkaloids derived from AV have inhibitory activity against mtFabH, thereby preventing the initial step of FabH and can be effective against *M. tuberculosis*.[41] Another molecular study have revealed the probable molecular interactions of vasicine and two of its close natural derivatives-vasicinone and deoxyvasicine, with certain biological targets in *M. tuberculosis*. Subsequent comparative molecular docking to identify the best ligand-target interactions revealed antigen 85C of M. tuberculosis as the most potent biological target of vasicine on the basis of optimum molecular docking values.[42] Ignacimuthu and Shanmugam have reported that two compounds extracted from AV, vasicine acetate and 2-acetyl benzylamines found to be highly effective against *M. tuberculosis* reference strain, MDR, and sensitive strains. Vasicine acetate was more effective than 2-acetyl benzylamine at all concentrations.[43] In support of above studies, Barry *et al.*[44] and Gupta and Chopra[45] have also reported the antitubercular potential of AV.

Anti-Oxidative and Radical Scavenging Activity

AV has been identified to pose an antioxidant and radical scavenging activity. The related reports have been compiled here. The antioxidant activity of AV has been demonstrated by the significant increase in the activities of acid soluble sulfhydryl (-SH) content, cytochrome P450, nicotinamide adenine dinucleotide phosphate-cytochrome P450, reductase, cytochrome b5, NADH-cytochrome b5 reductase, glutathione S-transferase, DT-diaphorase, superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase. The findings were observed in the liver at two dose levels of treatments with AV. Significant inhibition was noted in the cytosolic protein at both the dose levels of treatment indicating the possibility of its involvement in the inhibition of protein synthesis.[46] Jahagir *et al.* have reported antioxidant activity of AV against two agents cadmium and ferric nitrilotriacetate (Fe-NTA). Prophylactic pretreatment of AV extract in cadmium-intoxicated Swiss albino mice showed marked inhibition of LPO and xanthine oxidase activity. The findings support the antimutagenic efficacy of AV attributing to its restoring effects on antioxidant status and suppression of malondialdehyde level formation.[47] The another experiment exhibited the antioxidative, and thereby, chemopreventive effects against Fe-NTA-induced renal oxidative stress, hyperproliferative response, and two-stage renal carcinogenesis.[48]

In an experiment, crude extracts fractions of three plants (AV, *Capparis aphylla*, and *Aegle marmelos*) was tested for antioxidant potential. Results indicated that petroleum ether fraction of AV possesses the admirable antioxidant

abilities with high total phenolic content. The results of this study imply that 2,6,10,14,18,22-tetracosahexaene, 2,6,10,15,19,23-hexamethyl is an antioxidant ingredient in AV.[49] In another experiment, water, ethanol, and chloroform extracts of few selected plants were evaluated for antioxidant activity along with rat lens aldose reductase inhibitory potential and anti-cataract activity. AV was one of these selected herbs. The extracts of the tested plant showed significant free-radical scavenging activities and inhibited the activity of enzyme polyphenol oxidase, a model oxidizing enzyme.[50] It has been also reported that the vasicine, isolated from AV exhibited significant DPPH inhibition activity indicating antioxidant activity. A dose-dependent behavior of vasicine, was indicated in the ferric reducing antioxidant power antioxidant assay.[51] AV has been also exhibited antioxidant potential using DOOH assay.[52] A study conducted by Duraipandiyan *et al.* also concluded the antioxidant activity of vasicine. Cytotoxic studies against lung adenocarcinoma cancer cell line revealed that vasicine acetate had anticytotoxic efficacy and the claimed mechanism is antioxidant potential of AV.[53]

Anti-inflammatory Activity

Few studies have been reported the anti-inflammatory activity of AV. The anti-inflammatory activity of phytochemicals of AV tested using carrageenan and CFA-model induced paw edema. The results revealed that vasicine showed most potent anti-inflammatory effects (59.51%) at the dose of 20.0 mg/kg at 6 h after carrageenan injection.[54] In another experiment, the modified hen's egg chorioallantoic membrane test was used to evaluate anti-inflammatory activity of the methanol extract of AV. The alkaloid fraction showed potent activity at a dose of 50 µg/pellet equivalent to that of hydrocortisone.[55]

Antimicrobial Activity

Duraipandiyan *et al.* reported that vasicine acetate obtained by acetylation of vasicine exhibited good zone of inhibition against bacteria: *Enterobacter aerogenes*, *Staphylococcus epidermidis*, and *Pseudomonas aeruginosa*.[53] Furthermore, strong antibacterial activity was exhibited by vasicine against *Escherichia coli* at 20 µg/ml dose and also demonstrated maximum antifungal activity against *Candida albicans* at the dose of >55 µg/ml.[56] Methanolic extract of AV have showed antibacterial activity against Gram-positive strain, namely, *Staphylococcus aureus*, *Micrococcus luteus*, and Gram-negative *Pseudomonas aeruginosa.* Four different concentrations were tested in dimethyl sulfoxide using agar well diffusion method.[56] Bose and Chatterjee have reported the green synthesized silver nanoparticles, using AV leaf extract, have a potential to inhibit the growth of bacteria. The process was cost-effective and eco-friendly as well as reducing capping agent. The antibacterial activity of these nanoparticles against *P. aeruginosa* MTCC 741 has been measured by disc diffusion method, agar cup assay, and serial dilution turbidity measurement assay. The nanoparticles are well shaped and the average particle size is 20 nm in the range of 5–50 nm.[57] Karthikeyan *et al*. have also supported the above findings and demonstrated the antimicrobial activity of AV leaf extracts against *S. aureus*, *S. epidermidis*, *Bacillus subtilis*, *Proteus vulgaris*, and *C. albicans*.[58] A moderate antibacterial activity and significant DPPH inhibition activity was exhibited by vasicine.[51] Bacterial quorum sensing activity by disturbing the bacterial communication system causes attenuation of microbial pathogenicity. Quorum sensing allows bacteria to control all essential processes and could be considered as a promising and novel target for anti-pathogenic drugs, especially in combating bacterial infections caused by resistant strains. To overcome MDR, research efforts have focused recently on developing antipathogenic agents to control bacterial diseases by inhibiting the communication between bacteria. *Adhatoda* leaves extract was assessed for the anti-quorum sensing activity against *Chromobacterium violaceum* strain and found to be effective.[59]

Effect on Reproductive System

AV has been traditionally used as an antifertility drug in combination of few other medicinal herbs. A survey organized in Lucknow and Farrukhabad, two towns of Uttar Pradesh, India, from March 1987 to July 1987 reveled that AV was one of the common herb used by women for its anti-reproductive potential. In support of the survey, an experimental study was conducted. Aqueous and 90% ethanol extracts of AV was administered orally for 10 days after insemination to note effects on fetal development. Leaf extracts of AV were found to be 100% abortive at doses equivalent to 175 mg/kg.[60] In another experiment various extracts of one hundred and eight medicinal plants were screened for their anti-implantation activity in female albino rats. Out of these, ethanolic extract of AV showed 60–70% anti-implantation activity.[61] Gupta *et al.* also had reported promising uterotonic abortifacient activity of AV.[62] Although AV has been claimed to pose abortifacient activity one controversial study has been reported in this context. Burgos *et al.* administered the extract of AV leaf between day 1 and 9 of pregnancy but did not produce abortion.[63]

Effect on Gastrointestinal Tract

Amin *et al.* provide a scientific support toward the traditional uses of AV in stomach-related diseases. The extract of AV was tested against *Helicobacter pylori* and exhibited appreciable antiurease activity.[64] An investigation was carried out to study the antiulcer activity of AV leaves using two ulcer models, Ethanol-induced and Pylorus ligation plus aspirin-induced models. The highest degree of activity (80%) was observed in the ethanol-induced ulceration model.[65] In a clinical study, to assess effect of AV on non-ulcer dyspepsia (*Amlapitta*) a 60 ml syrup of dry leaves of AV was given to patient in 4 divided doses for 6 weeks. Significant effect was observed in the symptoms of pyrosis and burning sensation

in abdomen. Furthermore, the symptoms such as loss of appetite, flatulence, and constipation, a noteworthy reduction was observed along with the markedly decreases in level of free HCl. Thus, *Vasa* syrup produces total beneficial effect on the patients suffering from non-ulcer dyspepsia.[66]

Hepatoprotective Activity

A hepatoprotective activity of vasicinone has been reported in CCl_4-induced acute hepatotoxicity model in mice. Pretreatment with vasicinone significantly decreased the liver enzyme levels and normal hepatic architecture when compared to silymarin suggesting pronounced recovery from CCl_4-induced liver damage.[67] In another experiment, AV leaf showed significant hepatoprotective effect at doses of 50–100 mg/kg on liver damage induced by D-galactosamine in rats.[68]

Radioprotection Activity

In an experimental study, mice pretreated with ethanolic leaf extract of AV for 15 consecutive days and then exposed to 8 gyradiations. Death of AV pretreated irradiated mice was reduced to 70% at 30 days when compared with non-treated animals. The non-treated mice showed radiation-induced sickness including marked changes in histology of testis and chromosomal aberrations in bone marrow cells with 100% mortality within 22 days. The study suggests, AV pretreatment significantly prevented radiation-induced chromosomal damage in bone marrow cells and has radioprotective effects on testis.[69] Furthermore, Kumar *et al* reported the restoration of hematological changes caused by irradiation in Swiss albino mice by AV.[70]

Thrombolytic Activity

Prasad *et al*.[71] and Ratnasooriya *et al*.[72] reported the thrombolytic potential of crude extract of roots of AV using *in vitro* clot lysis model. In another experiment, at 5 mg/ml concentration of root extract of AV showed 19.63% clot lysis activity which was highly significant comparing with negative control, normal saline.[73]

Antidiabetic Activity

Adhatoda vasica has been also proved for its anti-glucosidal activity. In screening experiment, 40 traditional herbs were tested for rat intestinal α-glucosidase. The methanolic extract from the leaves of AV showed the highest sucrose inhibitory activity.[74]

Antigingival Activity

An experiment was conducted to investigate the oral hygiene and gingival health benefits of toothpaste formulated with a mixture of the herbs of which AV was one. One milliliter of resting saliva was collected to ascertain anaerobic and aerobic bacterial counts, plaque index, percentage sites with bleeding on probing and pocket depth at 6 sites/tooth were recorded at baseline. Home use of the allocated toothpaste (test or placebo) twice a day for 12 weeks was fallowed. Significant reduction was noted in test sample treated group indicating the beneficial effects of this herbal toothpaste containing AV on oral hygiene and gingival health variables.[75]

Anti-Alzheimer Activity

In a study conducted by Shereen *et al*. showed extracts of AV has inhibitory effect on acetylcholinesterase, and this effect on enzyme is reversible. Researcher claimed that the herbal drug AV may be used in the treatment of Alzheimer.[76]

Along with above-said beneficial health effects, the AV also showed few other activities which have indirect effect on human health conservation, namely, antifungal,[77,78] larvicidal,[79-81] anticestodal,[82] and acaricidal.[83]

Although AV has been used as a medicine from long back and claimed to be safe for the use as medicine[78] still few adverse effects have also been reported like cytotoxicity,[84] adverse reaction in the form of urticaria, exanthema, and contact dermatitis in Sweden population.[85]

DISCUSSION

AV, a medicinal herb have habitat in tropical and subtropical region of world. AV has been always in main stream herbal entity in Indian and Unani system of medicine. It has high ethnological relevance with high cultural index values. The important chemical constituents identified in AV are vasicine, vasicol, adhatonine, vasicinone, vasicinol, vasicinolone, adhavasicinone, and anisotine. Various analytical methods have been adopted for identification and isolation of chemical constituents. Although traditional method of *Putapak vidhi* require more human efforts and time duration but it is superior to any other method to extract the total alkaloids.

Numerous *in vitro*, *vivo,* and clinical studies acknowledged AV as an important natural agent for many medical illnesses. AV has anti-inflammatory action on the respiratory tract and is effective in respiratory tract infection. The alkaloid vasicinone and vasicine have potent bronchodilator and anti-allergent activity. Owing to these activities AV is effective in acute conditions of Asthma. AV has been proved for antitussive activity as effective as codeine in irritant aerosols and citric acid-induced cough model. AV is effective in acute URT infection as well. Aqueous extract of AV is found to be effective in inhibition of *M. tuberculosis*, even in MDR isolates. The researcher claimed the possible reason is the inhibitory activity against mtFabH preventing the initial step of FabH. Researcher has revealed the antigen 85C of *M. tuberculosis* as the most potent biological target

of vasicine. Both these findings can help to develop new therapeutic drug to control global threat tuberculosis.

Many more studies have proved the antioxidant and free-radical scavenging potential of AV. Owing to antioxidant activity AV is effective in conditions such as two-stage renal carcinogenesis, anti-cataract activity, anti-cytotoxic activity, anti-mutagenic activity.

AV showed anti-inflammatory action equivalent to that of hydrocortisone in carrageenan and CFA - model induced paw edema and in modified hen's egg chorioallantoic membrane test.

Various *in vitro*, *in vivo*, and clinical studies have proved the antimicrobial activity of leaf extract of AV against *E. aerogenes*, *S. epidermidis*, *P. aeruginosa*, and *E. coli*. AV also showed efficacy against Gram-positive strain, namely, *S. aureus*, *Micrococcus luteus*. AV extract also showed anti-quorum sensing activity against *C. violaceum* strain.

Traditionally, Av has been used for the anti-reproductive potential. Ethanolic extract of AV showed anti-implantation and uterotonic abortifacient activity in female albino rats. However, one controversial study has also been reported.

The traditional use of AV in GIT has been supported by the scientific study. AV exhibited anti-urease activity against *H. pylori* and anti-ulcer activity in aspirin and ethanol-induced model. It is also found to be effective in non-ulcer dyspepsia because of markedly decrease in HCl level.

AV had shown hepatoprotective effect against CCl_4 and D-galactosamine. It provides protection against 8 gyradiations with prevention of chromosomal damage in bone marrow and has radioprotective effect on testis. In clot lysis model, the thrombolytic activity of AV has been noted. Along with these activities it has shown anti-diabetic, anti-gingival, and anti-Alzheimer activity.

Few adverse effects have also been reported like cytotoxicity, adverse reaction in the form of urticarial, exanthema and contact dermatitis.

CONCLUSION

AV is a novel medicinal herb used in the Indian and Unani system medicine and may be used as an important source for the discovery of new and potential drug molecules.

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