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REVIEW ARTICLE

Review of *Holarrhena antidysenterica* (L.) Wall. ex A. DC.: Pharmacognostic, Pharmacological, and Toxicological Perspective

Pallavi Shrirang Jamadagni, Sharad D. Pawar, Shrirang B. Jamadagni[1], Shridhar Chougule, Sudesh N. Gaidhani[2], S. N. Murthy[3]

Department of Pharmacology, Regional Ayurveda Institute of Fundamental Research, [1]Department of Animal and Experimental Pathology, Regional Ayurveda Institute of Fundamental Research, [2]Department of Pharmacology, Headquarters, Central Council of Research in Ayurvedic Sciences, New Delhi, [3]Department of Ayurveda and In-charge, Regional Ayurveda Research Institute, Gwaliar Road, Jhansi, Uttar Pradesh, India

ABSTRACT

Holarrhena antidysenterica (L.) Wall. ex A. DC. is a medicinal plant abundantly found in India. Its uses are mentioned in the classical Ayurvedic literature and by many folklore claims. The plant is also of extreme economic importance. Its seeds are mainly used as an antidiabetic remedy. All pharmacological and toxicological aspects of this plant are discussed in this review.

Key words: Antidiabetic, *Holarrhena antidyscentrica*, pharmacology

INTRODUCTION

Holarrhena antidysenterica (L.) Wall. ex A. DC. (HA) is a medicinal plant abundantly found in India especially in Himalayan ranges. Its uses are mentioned in the classical Ayurvedic literature and by many folklore claims. References on its use in states of Odisha, Uttar Pradesh, Bihar, Andhra Pradesh and Assam are reported and are compiled in this review. The plant is also of extreme economic importance. It is exported in the form seed powder, bark powder, kutaja kwatha, Kutaja Prapati Vati and as herbal dietary supplement. Seeds of HA are mainly used as an anti-diabetic remedy. Various reviews have been published on different medicinal uses of this plant hence this review will emphasize studies on anti-diabetic properties of this plant.

ETHNOMEDICINE

The plant *Holarrhena antidysenterica* (HA), which is commonly known as Kutaj, and its seeds, which are known as Indrajava, are found in tropical and subtropical regions of Asia and Africa. It is abundant in India, especially in the Himalayan ranges. HA has got traditional and folklore values in India. In the Odisha state of India, during the festival of "Nabanna," people offer leaves of this plant along with rice. The HA bark is used in the Mirzapur and Varanasi districts of Uttar Pradesh for gastric problems.[1] Asur and Santhal communities of Netarhat plateau of Bihar also use the HA bark.[2] Tribes of Nallamala district of Andhra Pradesh use the stem bark of this plant for skin diseases.[3] The Bodo tribe of Assam also uses this plant as a traditional medicine.[4]

In Ayurveda, this plant is used in classical formulations, namely, Kutajarishta, Kutajavleha and Kutajghan vati, Mahamanjishtadi Kashayam, Stanyashodhana Kashaya, and Patoladi Choornam. It is classically known for curing Pravahika (amebiasis), Atisara (diarrhea), Jwaratisara (secondary diarrhea), Asra (blood or blood-related disorders), Kustha (skin disorder), and Trsna (thirst).[5] Bhunimbadi churna is a group of nine drugs, which has been mentioned in the Brihat Bhaishajya Ratnakar for its use in treating fever, jaundice, anemia, and diabetes.[6]

PHARMACOGNOSY

HA is categorized as a deciduous, laticiferous shrub or a small tree, which attains a height up to 13 m and a girth of 1.1 m with a clear bole of 3–7 m. Its leaves span 15–30 cm × 4–12 cm; its base is obtuse, often rounded or acute; its nerves are in 10–14 pairs, opposite, sessile, elliptic or ovate; it is oblong in shape, membranous, strong, arched; its petioles are up to 1.5 cm; and its cymes are 3–6 cm in diameter. Corymbose are terminal and sessile; bracts are small and ciliate; and pedicels are slender. Flowers are inodorous and white in color and are in terminal corymbose cyme. The calyx lobe is 2.5–3 mm long, oblong-lanceolate, acute, and ciliate. Corolla puberulous outside; tube 8–13 mm long, slightly inflated near the base over the stamens,[7] mouth not closed with ring of hair; throat hair inside; lobes about equaling the tube, oblong, rounded at the apex, and more or less pubescent. Follicle divaricated, cylindrical, 15–45 cm long and 5–10 mm in diameter, parallel, terete, corecious,

Correspondence:
Dr. Pallavi Shrirang Jamadagni,
Research Officer (Pharmacology), Department of Pharmacology, Regional Ayurveda Institute of Fundamental Research, Nehru Garden, Gandhi Bhavan Road, Kothrud, Pune - 411 038, Maharashtra, India.
E-mail: pallavideshmukh7@gmail.com

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and obscurely lonelose, usually with dotted white spots. Seeds are 8 mm long or more, linear oblong, tipped with spreading deciduous coma of brown hair, 2–2.5 cm long, light brown, 8–12 mm long, 900–1000 seeds weighing one ounce (Oz.), 25–30 in a follicle: coma brownish, spreading 2.5–10 cm long.[7]

The *Wrightia tinctoria* bark is used as an adulterant for HA. The pharmacognostic characteristics of both can be used to enable the identification of this herbal drug.[8] However, both differ in their medicinal properties as well as their physical and chemical characteristics. The bitter value of HA seeds is 11000 [Figure 1].[9]

ECONOMIC IMPORTANCE

The United States is the largest buyer of Kutaja, accounting for exports worth USD 1644 followed by Canada and Singapore which imported Kutaja worth USD 961 and USD 360, respectively, during the years 2014–2016. India exported Kutaja worth USD 3382 during this period.[10]

EXPERIMENTAL PHARMACOLOGY

In vivo pharmacology

HA has been widely studied for its antidiabetic activity which is mainly found in seed extract,[11-14] and mostly the ethanolic extract of seeds at the dosage of 300 mg/kg has been proved beneficial.[12,13]

Aqueous, petroleum ether, and methanolic extracts of HA seeds are known to have anti-hyperglycemic and anti-hyperlipidemic activities at the dosage of 250 mg/kg body weight (BW) in rats.[14]

In another study, the methanolic extract of HA seeds moderately protected against streptozotocin-induced diabetes at the dose of 300 mg/kg BW in rats. Its antidiabetic property was attributed to quercetin, which is used as a marker compound for HA.[12]

Figure 1: Photographs depicting the difference in stem, leaves, and pods of *Holarrhena antidyscentrica* (left) and *Wrightia tinctoria* (right)

The effect of hydromethanolic (2:3) extract of seeds of HA on alpha-glycosidase activity in starch-loaded rats was studied where the extract exhibited the inhibition of alpha glycosidase activity, thus decreasing carbohydrate absorption from the intestine, which in turn prevents postprandial hyperglycemia comparable to acarbose (a modern medicine).[15]

Apart from seeds, the ethanolic extract of HA leaves also have antidiabetic property when administered for 21 consecutive days in diabetic rats (diabetes induced with 100 mg/kg BW alloxan and 50 mg/kg BW streptozotocin), when administered at the dose of 400 mg/kg BW.[16] This effect was comparable to glibenclamide at a dose rate of 5 mg/kg BW given orally.

OTHER PHARMACOLOGICAL ACTIVITIES

Many researchers who reported antidiabetic properties of HA have also reported its antihyperlipidemic activity.[11,14] Jain has suggested that HA may be beneficial for the treatment of leukoderma.[17]

In vitro pharmacology

The *in vitro* cytotoxic activity of ethanolic, hydroalcoholic, and aqueous extracts of HA leaves against 14 human cancer cell lines, namely, A 549, COLO-205, DU-145, HeLa, HEP-2, IMR-32, KB, MCF-7, NCI-H23, OVACAR-5, SiHa, Sk-N-MC, SW-620, and ZR-75-1, from nine different tissues, namely, breast, colon, cervix, central nervous system, lung, liver, oral, ovary, and prostate, was studied. The ethanolic extract was found beneficial against lung, colon, liver, oral, ovarian, cervical, and neural cancer cell lines. Hydro-alcoholic extract also showed similar results except on ovarian cancer cell line. The aqueous extract showed more than 50% growth inhibition in lung and colon cancer cell lines. Further fractions of the extract were studied, and it was observed that, chloroform-soluble fraction showed the highest anticancer potential against human cancer cell lines.[18]

The *in vitro* antiplasmodial activity of HA whole plant extracts (chloroform and petroleum ether) using parasite lactate dehydrogenase (LDH) assay was studied. The extracts significantly reduced parasitemia in *Plasmodium berghei*-infected mice as compared to chloroquine with ED_{50} value at 18.29 mg/kg BW where the chloroform extract showed a significant activity with IC_{50} value at 16 µg/ml. The cytotoxic effect on rat skeletal muscle myoblast cells (L6 cells) was studied, and no cytotoxicity was observed up to 16 µg/ml.[19]

A similar study was performed by Dua *et al.* on conessine, an alkaloid isolated from the HA bark.[20] The study reports antiplasmodial activity, with IC_{50} value at 1.9 µg/ml using schizont maturation and 1.3 µg/ml using parasitic LDH assay. The alkaloid showed cytotoxicity with its IC_{50} value at 14 µg/ml, against L6 cells of rat skeletal muscle myoblast.

The antidiarrheal activity of HA root bark decoction was studied on three strains of *Escherichia coli,* i.e., EPEC-B170, ETECTX1 (078: H 12), and ETEC B 831-2, on a culture of HEPr. HA inhibits the stable toxin production and prevents its intestinal secretions, which leads to a decrease in the virulence of enterotoxigenic (ETEC) strains. Thus, it can be concluded that HA gives protection against multiple stages of diarrhea.[21]

Srivastava and Saxena studied the *in vitro* activity of the aqueous extract of HA seeds against *E. coli*, *Shigella, Staphylococcus aureus,* and *Salmonella typhi* organisms and found it highly effective against these pathogens responsible for diarrhea.[22]

In another study, alcoholic and aqueous extracts of the HA stem bark were reported to have an antibacterial activity against 10 enteric pathogens at the dosage of 200 mg/ml.[23] The ten enteric pathogens used for the study were *S. aureus, Vibrio cholerae* 01, *V. cholerae* 0139, enteroinvasive *E. coli,* enteropathogenic *E. coli*, *S. typhimurium, S. enteritidis, Shigella flexneri, Sh. boydii,* and *Pseudomonas aeruginosa*.

Khan *et al.* studied the antiurolithic activity of hydro-alcoholic extract of HA seeds *in vitro* by the determination of antioxidant activity, calcium oxalate crystallization, and cytotoxicity and LDH release by Madin–Darby canine kidney cell lines. They have reported a proliferation concentration of 300 μg/ml and an inhibition concentration of 1000 μg/ml. Moreover, inhibition of 2,2-diphenyl-1-picrylhydrazyl free radicals at a concentration of 14 μg/ml was obtained.[24]

The *in vitro* antioxidant activity of HA leaves (methanolic extract) using hydroxyl radical, superoxide anion scavenging, and reducing power assays was studied, and it was found to contain high radical scavenging activity and phenolic contents.[25]

DRUG CHARACTERIZATION

The bark contains 2% of alkaloids, namely, conessine, conkurchine, kurchine, holarrhemine, holarrhenine, kurchicine, and conkurchinine [Figure 2: structure of steroidal alkaloids conessine isolated from the bark of HA].[20]

Thappa *et al.* described the growth inhibitor, sterilant, and antifeedant activity of conessine in *Aedes aegypti, Dysdercus koenigii, Spodoptera litura, and Pieris brassicae*.[26]

Yang *et al.* studied the acetylcholinesterase inhibitor activity of alcoholic extract of HA seeds with IC_{50} of 6.1 μg/ml. Chromatographic fractionation was carried out and five steroidal alkaloids were identified, namely, conessine, iso-conessine, connesimin, corarchimin, and conimin. Except isoconnesimin, all other compounds showed an IC_{50} value of 4–20 μg/ml and connesimin showed an IC_{50} value of 4 μg/ml.[27]

PHARMACODYNAMICS

Gilani *et al.* studied the crude hydro-alcoholic extract of HA and its fractions on isolated Guinea pig ileum.[28] They described the presence of both gut stimulant and relaxant activities in the extract. They concluded that these gut stimulant and relaxant activities are possibly mediated through the activation of histamine receptors and Ca (++) channel blockade, respectively. Using activity-directed fractionation, it was revealed that the spasmogenic component was present in the aqueous fraction, while the spasmolytic component was found in the organic fraction.

Ali *et al.* reported the inhibition of alpha glycosidase and thereby reduced the absorption of carbohydrates as possible mechanism of action of HA seed extract.[15]

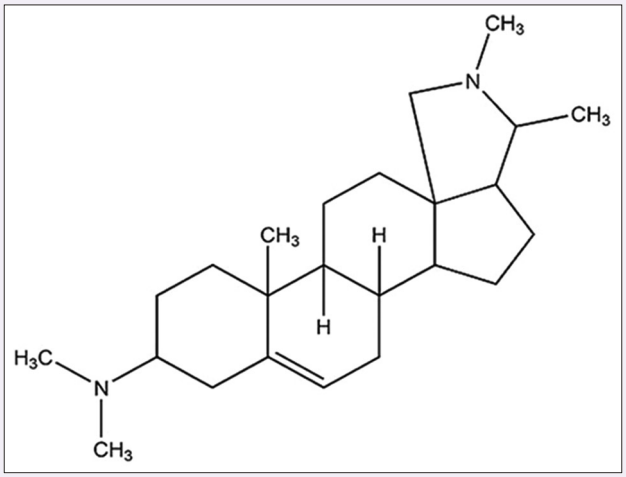

Figure 2: Structure of conessine

SAFETY AND TOXICITY STUDIES

Sheikh *et al.* and Pathak *et al.* studied the acute oral toxicity and found that all types of extracts (aqueous, ethanolic, hydro-alcoholic, etc.) of HA seeds are safe up to 2000 mg/kg BW in rats.[13,14] Hegde and Jaisal reported that the ethanolic extract of HA leaves is safe up to 2000 mg/kg single oral dose in rats.[16] It is reported that the ethanolic extract is safe up to 3000 mg/kg BW.[12,29]

HA seed ethanolic extract prevents streptozotocin-induced BW loss and hyperglycemia when administered for 28 consecutive days.[29]

Subchronic toxicity of ethanolic extract of HA complexes with polyvinylpyrrolidone at the dose of 270 and 530 mg/kg BW/day (which is 10 and 20 times less than the dosage used for humans), causes hepatotoxicity in rats when given for 3 consecutive months.[30] Hence, it was suggested that overdoses and prolonged use should be avoided so as to prevent hepatotoxic effects.

CLINICAL PHARMACOLOGY STUDIES

Singh (1985) reported the clinical efficacy of HA stem bark extract in forty patients of clinical amebiasis and giardiasis. The extract was found to improve 70% of clinical symptoms (symptoms such as loose motions, constipation, flatulence, abdominal cramping, diminished appetite, and mucus in stools related to these infections) when given at 4 g/day per adult in three divided doses for 15 consecutive days.[1]

Chaturvedi and Singh reported various side effects observed in four clinical individuals given 4 g powder of HA bark in three divided doses for 15 consecutive days. The symptoms were sensation of heat in abdomen and head, nausea, flatulence, constipation, agitation, nervousness and insomnia, vertigo, syncope, weakness and emptiness, xerostomia, and lightness of body. One patient reported a decrease in body temperature.[31]

Pal *et al.* also observed that the HA stem bark powder administered to patients with bleeding piles at a dose of 4 g twice a day for 2 weeks each showed significant efficacy.[32]

Panda *et al.* reported a reduction in glycosylated hemoglobin after administration of ethanolic extract of HA seeds to a 65-year-old woman for 48 consecutive days, suggesting that HA seeds have a promising action against mild-to-moderate type II diabetes mellitus.[33]

CONCLUSION

The plant HA has the potential to develop drug against various enteric, skin diseases and diabetes.

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Conflicts of interest

There are no conflicts of interest.

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