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A Review on Pharmacological Aspects of *Holarrhena antidysenterica*

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Review Article

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Abstract: Medicinal plants have been known for millennia and are highly esteemed all over the world as a rich source of therapeutic agents for the prevention of diseases and ailments. *Holarrhena antidysenterica* commonly known as kurci, kurchi or kutaj is being used from ancient time. *Holarrhena antidysenterica* (syn. *H. pubescens*) belonging to the family Apocynaceae, is commended for the medicinal applications of its stem bark, leaves and seeds in Ayurveda. From the past years, various phytochemical has been isolated from the plant and shown the traditional pharmacological activities such as analgesic, antibacterial, anti-diarrhoeal, anti-diabteic, anti-oxidant, anti-urolithic and anti-inflammatory activities. Moreover, recent studies have shown the new activities viz. Angiotensin-converting-enzyme inhibitory, acetylcholinesterase inhibitory activity, Anti-amnesic activity and neuroprotective activity. This review is a step to open insight for therapeutic uses for various diseases.
Keywords: *Holarrhena antidysenterica*, Conessine, Anti-amnesic, Neuroprotective.

INTRODUCTION

Medicinal plants have been known for millennia and are highly esteemed all over the world as a rich source of therapeutic agents for the prevention of diseases and ailments. The demand for plant based medicines, health products, pharmaceuticals, food supplement, cosmetics etc are increasing in both developing and developed countries, due to the growing recognition that the natural products are non-toxic, have less side effects and easily available at affordable prices.

Holarrhena antidysenterica Linn (Family Apocynaceae) is one such plant, popularly known as "Indrajav," "Coneru" in English and "Vatsaka" in Sanskrit is a shrub, distributed throughout India upto an altitude of 4,000 ft. In Indian traditional medicine, the plant has been considered a popular remedy for the treatment of dysentery, diarrhea, and intestinal worms [1]. This tree is popular for its numerous medicinal properties and seeds and bark of this tree have been used in Ayurveda since long time. The stem bark which is commonly known as "kurchi" in the Indian subcontinent and as 'conessi bark' in Europe is used in traditional ayurvedic medicine to treat dysentery, especially amoebic dysentery. Bark of *Holarrhena antidysenterica* Linn is used in Ayurveda as an anti-microbial, anti-inflammatory and analgesics [2]. Other useful parts used as medicine are root and leaf. The bark and the roots have been found to be an excellent remedy for both acute and chronic dysentery especially in cases where there is excessive blood with mucus and colic pain associated with stools. In addition the plant has been reported to possess antihelminthic, appetizing, antidiarrhoel and astringent properties. *Holarrhena antidysenterica* has been reported to be used as an immunodulating agent, larval growth inhibitor and against malaria and vaginities [3].

Scientific Classification [4]

Kingdom	:	Plantae
Subkingdom	:	Tracheobionta
Superdivision	:	Spermatophyta
Division	:	Magnoliophyta
Class	:	Magnoliopsida
Subclass	:	Asteridae
Order	:	Gentianales
Family	:	Apocynaceae
Genus	:	Holarrhena
Species	:	Holarrhena antidysenterica

Vernacular Name [5]

English	:	Tellicherry Bark
Hindi	:	Karva Indrajau, Kutaja, Kurchi
Sanskrit	:	Indrayava, Kutaja, Sakraparyaaya, Sakraasana, Vatsaka
Tamil	:	Kirimllikai, Kutaca-P-Palai, Mlaimllikai
Telugu	:	Girimallika, Kodisepala, Kolamukku, Kondamalle, Kutajamu
Punjabi	:	Keor, Kewar
Gujarati	:	Kadavo Indrajav

Plant Description

H. antidysenterica Linn a deciduous 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, and arched; its petioles are up to 1.5 cm; and its cymes are 3–6 cm in diameter [6]. Its seed are 1-2cm long, linear or oblong concave with a long coma, light brown, marked with linear lines and are bitter in taste [7].

Origin and distribution

The plant 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 [6]. The plant is found in tropical and subtropical regions of Asia and Africa. The tree found in Burma, Srilanka, Pakistan, Nepal and Africa and flowers in the months of May-July. In India, it can be found throughout the country, especially in deciduous forests of tropical Himalayas, at altitudes ranging from 900 to 1250 m [8].

Chemical Constituents

Stem bark and seeds of the plant are reported to contain a number of steroidal alkaloids, such as conanines, 3-aminoconanines, 20-aminoconanines, 3-aminopregnans, 3,20-diaminopregnanes and their derivatives. A new steroidal alkaloid was isolated and characterized, designated as holadysenterine. Corresponded to the molecular formula $C_{23}H_{38}N_2O_3$ [9]. The stem bark of *Holarrhena antidysenterica* also contains conessine ($C_{24}H_{40}N_2$), isoconessine ($C_{24}H_{40}N2$), conessimine/ isoconessimine ($C_{23}H_{38}N_2$), conarrhimine ($C_{21}H_{34}N_2$) [10].

Pharmacological Activities

Anti-amnesic activity

Administration of ethanolic extract of *Holarrhena antidysenterica* seeds for 28 days to the separate groups of STZ significantly decrease the level of AChE as compared to the diseased group, prevented the rise in MDA levels and GSH depletion in a dose dependent manners [11]**.** Cholinergic dysfunction was assessed by acetyl cholinesterase activity. Decreased level of AChE, prevented levels of MDA and Glutathione showed anti amensic property of *Holarrhena antidysenterica*.

Neuroprotective activity

Treatment with MEHA significantly prevented fall in body weight as compared to the diabetic control group, the elevated levels of blood glucose and plasma cholesterol levels were significantly depleted, HbA1C level was considered as a key indicator of AGEs and in the present investigation treatment with MEHA significantly inhibited this elevated level of HbA1c. MEHA treated rats showed improvement in locomotor activity as compared to their non-treated counterparts indicate the prevention of diabetic neuropathy [12].

Acetylcholinesterase inhibitory

The alkaloidal extract of *Holarrhena antidysenterica* seeds was subjected to microplate assay for AChE and found to have 91% inhibition of AChE. The alkaloidal extract was subjected to column chromatography over a MCI-GEL using a gradient solvent system MeOH–H2O (50%, 60%, 70%, 80%, 90%) (v/v) to afford three fractions (Fr. 1 to Fr. 3). The five compounds were tested for AChE inhibiting activity by the Ellman's method in 96-well microplates [13,14]. The total alkaloidal extract from the seeds of H. antidysenterica strongly inhibited the AChE with an IC_{50} value of 6.1 μg/mL while huperzine A showed AChE inhibiting activity with an IC_{50} value of 0.015 μg/mL [10].

Antidiabetic activity

Ethanolic extract of HA significantly reduced plasma glucose levels ½ hr after administration of glucose in euglycemic rats. Diabetic rats showed a decrease in body weight during the experimental period. H. antidysenterica and glibenclamide treated diabetic group rat showed significant increase in weight. The decrease in blood glucose level in EHA treated group decreased the total cholesterol, triglyceride, AST, ALT, urea and serum creatinine [15]. Methanolic

extract of *Holarrhena antidysenterica* showed same results in diabetic rats [16]. These parameters are an indication of its better metabolic control and potent antidiabetic property.

Hepatic glucose-6-phosphatase is an important enzyme in glucose homeostasis [17] and it is regulated by insulin in negative way [18]. After administration of the aqueous extract, significant recovery was noted in these biosensors which may be due to insulin recovery [19].

Inhibition in the activity of intestinal α-glucosidase is an important strategy to control postprandial hyperglycemia in diabetes. The blood glucose level was significantly lower in acarbose or different doses of hydro-methanolic extract treated groups with respect to the control group. Phenolic compounds and flavonoids of the extract are responsible for the inhibition in α-glucosidase activity and thereby inhibit glucose absorption in connection with the management of postprandial hyperglycemia [20].

Antiurolithic activity

Crude extract of HA in *in vitro* study showed inhibition of DPPH (2,2-Diphenyl-1-Picrylhydrazyl) free radical for antioxidant effect and inhibited lipid peroxidation, induced in rat kidney homogenate. Ha. Cr had no toxic effect on MDCK (kidney epithelial cell lines) cells. In *in vivo* experiment Ha.Cr had no significant effect on the CaOx crystalluria. The body weight was reduced in stone forming group as compared to the normal saline group. The co-administration of Ha.Cr prevented the loss in body weight. A co-treatment with Ha.Cr reduced polyurea and water intake compared to stone forming group. Oxalate excretion was increased in stone forming animals, whereas Ca^{++} excretion was decreased. In histological study Ha.Cr treated groups, less number of CaOx crystal deposits [21]. Through this article it can be speculated that the inhibitory effect of the plant extract on CaOx crystal deposition in renal tubules is possibly caused by its antioxidant activity. Thus, these data suggest that the preventive effect of Holarrhena antidysenterica in urolithiasis is mediated through multiple pathways. Few articles are also studied for ulcerative colitis and bleeding piles [22, 23].

Antibacterial activity

For antibacterial activity the study was done by studiesd zone of inhibition (in mm) was observed on three bacteria (Staphylococcus aureus, Salmonella typhimurium and Escherchia coli). From bark extract 10.05 mm inhibition zone was observed showing highest antibacterial activity against Staphylococcus whereas in case of Salmonella and E. coli it was only 6.65mm and 2.7mm respectively. Holarrhena antidysenterica seed extract with 100% concentration also showed antibacterial activity against Staphylococcus. Callus extracts with 100% concentration showed 4 mm inhibitory zone against Staphylococcus and its least activity was observed in E. coli with 3.1mm inhibition zone even in 100% concentration. Results obtained in the present study revealed that three types of extracts of Holarrhena antidysenterica possess potential antibacterial activity against Staphylococcus, Salmonella and E. coli [3]. Various workers have already shown that plants extracts has antibacterial activity in many aspects [24, 25, 1].

Anti-inflammatory and Analgesic Activity

Methanolic leaf extract of *Holarrhena antidysenterica* revealed inhibition of rat paw edema induced by carrageenan. Furthermore, Methanolic extract of *Holarrhena antidysenterica* suppressed acetic acid induced writhing response in dose dependent manner and demonstrated the analgesic effect by improving tail flick latency [26]. Ethanolic extract of *H. antidysenterica* exhibited analgesic effect by suppressing writhing response in albino mice [27].

Methanolic bark extract of *H. antidysenterica* exhibited the decreased levels of nitric oxide and malondialdehyde levels and showed increase levels of superoxide dismutase and glutathione in 2,4-Dinitrobenzene sulfonic acid induced colitis in male albino wistar rats. The decreased level of nitric oxide thus suggesting that reduction iNOS generation may be responsible for anti-inflammatory effect. *H. antidysenterica* treatment also prevented rupture of goblet cells, inflammatory cellular infiltration and inflammation in muscosal layer [27].

Anti-malarial activity

Conessine isolated from stem bark of *H. antidysenterica* exhibited the greatest anti-plasmodial activity, with reproducible IC_{50} value 1.3 µg/ml in *in-vitro* experiment and 88.95% suppression of parasitaemia in vivo experiment when administered at 10 mg/kg. Furthermore, liver function tests were observed due to conessine cytotoxic nature. liver is the mostly affected organ in the early stage of malaria leading to significant alterations in the host hepatocyte physiology and morphology. Elevated levels of Alkaline phospahatse (ALP) and bilirubin are an indication of hepatocyte damage due to malarial infection. The elevated levels of ALP and bilirubin were significantly depleted at dose of 30mg/k [29].

Bark extracts of *H. antidysenterica* significant results in *in-vitro* and *in-vivo* anti-malarial activity against *P. falciparum* and *P. berghei* infected albino mice. Chloroform extract revealed the anti-plasmodial activity with IC_{50} value

of 5.7 mg/ml in the *in-vitro* experiment and showed suppression of parasitaemia at dose 30 mg/ml in *in-vivo* experiment [30].

Anti-diarrhoeal activity

Ethanolic seed extracts of *H. antidysenterica* shown a significant increase in the dry weight of their faeces and reduction in defecation drops in castor oil and *E coli* induced diarrhoea in rats [31]. Aqueous and alcoholic bark extracts are known to act against enteroinvasive E. coli (EIEC), Salmonella enteritidis, Shigella boydii and Shigella flexneri [32]. *H. antidysenterica* marketed preparation kutaja parpati vati shown significant reduction in watery diarrhea and motility of small intestine content in castor oil induced diarrhea in rats. Furthermore, it shown significant 67.55% protection against castor oil induced enteropooling [33].

Antimutagenic and Antihypertensive Acitivity

Methanolic bark extract of *H. antidysenterica* exihibited anti-mutagenic potency in methyl methane sulphonate and sodium azide induced mutagenicity in *Salmonella typhimurium* strains [24].

Plants with anti-hypertensive activity are investigated on their ability to inhibit the secretion of angiotensin and anginotesin converting enzyme, which causes vasoconstriction leading to increased blood pressure. Ethanolic seed extracts of *H. antidysenterica* revealed a satisfactory 24% angiotensin-converting enzyme (ACE) inhibition [35]. For antihypertensive activity, Endophytes were obtained from the fungal extract of *H. antidysenterica* and dissolved in 20% methanol. Endophytes exhibited 60% angiotensin-converting enzyme (ACE) inhibition [36].

CONCLUSION

Diseases have been associated with humans since their existence. There are tremendous amount of herbal medicines that are remain hidden for the decades. This paper reviewed *Holarrhena antidysenterica* as promising medicinal plant with wide range of pharmacological activities which could be utilized in several medical applications because of its effectiveness and safety. *H. antidysenterica* has been traditionally used to treat diseases like diarrhoea, dysentery, anti-inflammatory, anti-oxidant and anti-malarial activities. But with evolution in technology, experimental studies made it possible to discover more pharmacological properties of the plants such as Anti-amnesic and neuroprotective activities. This plant contains unknown chemical constituents that are useful for pharmacists to synthesize and formulate novel drugs for various other diseases.

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