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Review Article

Evaluation of phytochemical and pharmacological aspects of *Holarrhena antidysenterica* (Wall.): A comprehensive review

Snehadri Sinha [a], *Aishwarye Sharma* [b], *P. Hemalatha Reddy* [c], *Brijesh Rathi* [d], *N.V.S.R.K. Prasad* [b], *Amit Vashishtha* [e,*]

[a] *Department of Biological Sciences, Sri Venkateswara College, University of Delhi (South Campus), Dhaula Kuan, New Delhi 110021, India*
[b] *Department of Botany, Sri Venkateswara College, University of Delhi (South Campus), Dhaula Kuan, New Delhi 110021, India*
[c] *Department of Biochemistry, Sri Venkateswara College, University of Delhi (South Campus), Dhaula Kuan, New Delhi 110021, India*
[d] *Department of Chemistry, Sri Venkateswara College, University of Delhi (South Campus), Dhaula Kuan, New Delhi 110021, India*
[e] *Assistant Professor, Department of Botany, Sri Venkateswara College, University of Delhi (South Campus), Dhaula Kuan, New Delhi 110021, India*

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ABSTRACT

Medicinal plants are generating an ever-increasing amount of interest due to the effectiveness, low cost and minimal side-effects associated with drugs derived from them. *Holarrhena antidysenterica* (syn. *H. pubescens*) WALL., belonging to the family Apocynaceae, is commended for the medicinal applications of its stem bark, leaves and seeds in Ayurveda. During the past century, studies on the phytochemical and pharmacological nature of the plant have yielded important results regarding the chemical constituents present and have also verified the traditionally claimed properties associated with the plant viz. analgesic, antibacterial, anti-diarrhoeal, anti-amoebic, anti-inflammatory and anti-haemorrhoidal activities. Moreover, recently some other properties have also been discovered viz. anti-malarial, anti-diabetic, anti-oxidant, anti-urolithic, anti-mutagenic, CNS-stimulating, Angiotensin-converting-enzyme inhibitory and acetylcholinesterase inhibitory activity. This review discusses the findings of studies on the aforementioned properties of the plant in detail and 68 alkaloids isolated from various parts of plant to justify its widespread use in the treatment of a variety of diseases and suggests future lines of research.

1. Introduction

Medicinal plants have been known to exist since centuries, but their importance as a source of vital drugs remained unknown until the establishment of human civilisations. This was followed by the development of ancient medical literature such as the *Rig Veda* and *Sushruta Samhita* in Ayurveda, Dioscorides' *De Materia Medica*, the *Ebers Papyrus* of ancient Egyptians, and the *Pen Tsao* of the Chinese. In India, Ayurveda is the predominant source of traditional medicinal knowledge, in which the central idea is the presence of three "*doshas*", or body systems, named *kapha*, *pitta* and *vata*. The Unani and Siddha systems of medicine also find some importance in certain regions of India, according to which, certain elements

* *Corresponding author*. Tel.: +91 8860302550 (mobile).
E-mail addresses: vashishtha24@gmail.com, amitvashishtha24@gmail.com (A. Vashishtha).
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when present in a balanced state lead to proper health while their imbalance leads to various forms of diseases.[1]

Holarrhena antidysenterica (Roxb. ex Fleming) Wall. (Syn. *Holarrhena pubescens* (Buch.Ham.) Wallrch ex. Don) is commonly known as Tellicherry Bark (English) and Kurchi (Hindi), and belongs to family Apocynaceae. The plant is found in tropical and subtropical regions of Asia and Africa. In India, it can be found throughout the country, especially in deciduous forests of tropical Himalayas, at altitudes ranging from 900 to 1250 m.[2]

H. antidysenterica is being used in Indian ayurvedic medicine system to treat *atisaara* (diarrhoea and dysentery). According to Charaka, the pods have *stanyasodhana* (a lactodepurant), the *indrayava* (seeds) have *ama* and *asthapanopaga* (adjuncts to enema) and the plant contains *vamaka* and *arsoghna*, which have emetic and anti-haemorrhoidal properties respectively. *Susruta* attributes the seeds with having diuretic properties and the plant in general as *sukrasodhana* (sperm-purifier). In the *Susruta Samhita* the plant is described as antiseptic, vermifuge, febrifuge, detoxicant and is believed to cure malignant ulcers, leprosy, diarrhoea and other virulent skin diseases. In modern Ayurveda, the plant is suggested for treating obesity, asthma, bronchopneumonia, hepatosplenomegaly and rheumatism.[3] *H. antidysenterica* is a major ingredient in several Ayurvedic preparations such as *Kutajghan Vati*, *Kutajarista* and *Kutaja churna*, which are used to treat dysentery, diarrhoea, fever and bacterial infections.[4–6] Recently, a number of studies have been done on isolation and characterization of phytochemicals, as well as on several pharmacological properties of *H. antidysenterica* based on experimental trials on animals.

2. Pharmacological properties

2.1. Anti-diabetic efficacy

A recent study reported significant recovery in diabetic rats when they were orally administered with doses of 300 mg/kg and 600 mg/kg of ethanolic extract of seeds. Each week of treatment showed significant decrease in levels of blood glucose, serum cholesterol, triglyceride, aspartate transaminase, alanine transaminase, alkaline transferase, urea, creatinine and uric acid while the weight of the rats increased substantially.[7] Methanolic seed extracts have also shown similar results in streptozotocin-induced rats.[8] Inhibition of α-glucosidase was observed in normoglycemic rats when administered with hydro-methanolic seed extract of *H. antidysenterica*. This enzyme helps in absorption of glucose from intestines and therefore, can play a major role in regulating postprandial diabetes.[9] In another study, no metabolic toxicity of the hydro-methanolic seed extract was reported by glutamate oxaloacetate transaminase (GOT) and glutamate pyruvate transaminase (GPT) activities in the liver and kidneys.[10]

2.2. Anti-diarrhoeal property

Ethanolic seed extracts of *H. antidysenterica* in castor oil-induced diarrhoea in rats *in vivo* have shown a significant increase in the dry weight of their faeces and reduction in defecation drops. Aqueous and alcoholic bark extracts are also known to act against enteroinvasive *E. coli* (EIEC), *Shigella flexneri*, *Shigella boydii* and *Salmonella enteritidis*.[2] Aqueous and methanolic leaf extracts of *H. antidysenterica* were found to inhibit the growth of diarrhoeal pathogens *Salmonella typhimurium*, *Vibrio cholerae*, *Vibrio alginolyticus*, *Vibrio cholera* 0139, *E. coli* 0157:H7 and *Salmonella typhi*.[11]

2.3. Anti-inflammatory and analgesic property

Methanolic bark extract of *H. antidysenterica* demonstrated decreased nitric oxide and malondialdehyde levels and increased levels of superoxide dismutase and glutathione levels in 2,4-Dinitrobenzene sulfonic acid induced colitis in male albino wistar rats. The rats also resisted rupture of goblet cells, inflammation in mucosal layers and inflammatory cellular infiltration.[12] Furthermore, methanolic leaf extracts demonstrated inhibition of rat paw oedema in carrageenan-induced paw oedema in Swiss albino mice.[13]

H. antidysenterica has been mentioned in Ayurveda to have analgesic effects. Methanol bark extract on Swiss albino mice and wistar rats showed analgesic effects.[14]

2.4. Antioxidant/free radical scavenging property

It has been established that the application of free radical scavenging compounds have healing effect and property of protecting tissue from oxidative damage. Recently in a study that investigated antioxidant property of *H. antidysenterica*, methanolic leaf extracts were found to scavenge superoxide ions and hydroxyl ions as well as reduced capability of converting $Fe^{3+} \rightarrow Fe^{2+}$. Further, the efficiency of these effects was found to be proportional to the concentration of the extract.[15] Hydro-methanolic seed extracts of the plant also showed inhibition of deoxyribose degradation by OH^- ions, inhibition of nitrite formation by competing with O_2, degradation of H_2O_2 and inhibition of lipid peroxidation, all from the ethyl acetate fraction.[16]

2.5. Anti-urolithic property and anti-haemorrhoidal action

Crude aqueous methanolic seed extracts of *H. antidysenterica* significantly decrease the size of calcium oxalate crystals and convert them from calcium oxalate monohydrates (COM) to calcium oxalate dehydrate (COD) *in vitro*. The extract suppresses cell toxicity (induced by COM) and production of lactate dehydrogenase. The extract was tested *in vivo* in male wistar rats, which showed substantial decrease in polyurea, water intake, Ca^{++} excretion and crystal formation.[17]

Stem bark extract of *H. antidysenterica* in the form of "Kutaja tvak churna" showed healing activity in patients suffering from bleeding piles.[18]

2.6. Diuretic property and anti-amoebiasis

Aqueous seed extract of *H. antidysenterica* showed a significant increase in urine output of wistar rats at dosage range of 30–100 mg/kg. A substantial increase was also observed in the amount of Na^+ and K^+ ions excreted through urine of treated rats.[19]

A daily intake of the bark powder for 15 days completely cured patients suffering from amoebiasis. Another clinical trial investigated the therapeutic efficacy of "Amoebin cap", a medicine for amoebiasis containing *H. antidysenterica* as one of its constituents.[20]

2.7. Inhibition of acetylcholinesterase and CNS-stimulant activity

Inhibition of acetylcholinesterase is desirable when treating neurological problems such as Alzheimer's disease. Since alkaloids from some plants have already been known to inhibit AChE, a study tested some alkaloids of *H. antidysenterica* for similar action. Out of five isolated alkaloids (conessine, isoconessimine, conessimine, conarrhimine and conimine), conessimine exhibited the most profound effects, with an IC_{50} value of 4 μM. The study concluded that these alkaloids can be potentially used in drugs for treating neurological disorders.[21]

A separate study investigated the CNS-stimulating activity of methanolic bark extract on Swiss albino mice. The results showed that regardless of the dosage, the extract significantly decreased and relaxed the gripping capabilities of the muscles and also the spontaneous locomotive activity, thus indicating a depressing effect on the CNS.[22]

2.8. Anthelminthic and anti-microbial activity

In-vitro activity of aqueous and ethanolic extracts bark on *Pheretima posthuma* (earthworm) showed significant results.[23] Ethanolic seed extracts showed concentration-dependent zones of inhibition against bacterial cultures of EPEC bacteria. Since EPEC is resistant to many antibiotics, the ethanolic extract is considered as a promising antibacterial agent.[2] In one study, petroleum ether extract of bark inhibited *E. coli* at 50 μg/ml with a minimum inhibitory concentration (MIC) of 50 μg/ml while methanol and chloroform extracts did so at higher concentrations, thus having higher MIC values. Yet, compared to other plants, *H. antidysenterica* showed moderate activity.[24]

2.9. Anti-mutagenic and anti-hypertensive activity

A study investigated anti-mutagenic activity of *H. antidysenterica*, where methanolic bark extract of the plant demonstrated anti-mutagenic potency in sodium azide and methyl methane sulphonate induced mutagenicity in *Salmonella typhimurium* strains.[25]

Plants with anti-hypertensive activity are investigated on their ability to inhibit the secretion of angiotensin, which causes vasoconstriction leading to increased blood pressure. Ethanolic seed extracts showed a satisfactory 24% angiotensin-converting enzyme (ACE) inhibition.[26]

2.10. Anti-malarial activity

Bark extracts tested for *in vitro* and *in vivo* anti-malarial activity against *Plasmodium falciparum* isolates and *P. berghei* infected Swiss mice respectively, showed significant results.[27] Chloroform bark extract demonstrated the greatest anti-plasmodial activity, with an average IC_{50} value of 5.7 μg/ml in the *in vitro* experiment and 70% suppression of parasitaemia in the *in vivo* experiment when administered at 30 mg/kg.[27]

3. Chemical constituents

Most of the known chemical constituents in *H. antidysenterica* have been found in the stem, bark, leaves and a few in the seeds as well. The major constituents are steroidal alkaloids, flavonoids, triterpenoids, phenolic acids, tannin, resin, coumarins, saponins and ergostenol.[3,28,29] The 68 alkaloids which have been discovered from various parts of *H. antidysenterica* to date are listed below.

3.1. From both stem bark and seeds

Conessine ($C_{24}H_{40}N_2$), Isoconessine ($C_{24}H_{40}N_2$), Conessimine/Isoconessimine ($C_{23}H_{38}N_2$), Conarrhimine ($C_{21}H_{34}N_2$)[21]

3.2. From stem bark

Holarrifine ($C_{24}H_{38}N_2O_2$), Kurchamide, Kurcholessine,[7] Trimethylconkurchine ($C_{24}H_{38}N_2$), (3),-N-Methylholarrhimine ($C_{22}H_{38}N_2O$), (20),-N-Methylholarrhimine ($C_{22}H_{38}N_2O$), NNN'N′-Tetramethylholarrhimine ($C_{25}H_{44}N_2O$), Conessidine ($C_{21}H_{32}N_2$), Holarrhidine ($C_{21}H_{36}N_2O$), Kurchenine ($C_{21}H_{32}N_2O_2$), Holarrhessimine ($C_{22}H_{36}N_2O$), Holarrhine ($C_{20}H_{38}N_2O_3$), Conkurchinine ($C_{25}H_{36}N_2$), Kurchamine ($C_{22}H_{36}N_2$), 7α-Hydroxyconessine ($C_{24}H_{40}N_2O$),[28]Kurchilidine ($C_{22}H_{31}NO$),[29] Neoconessine (isomer of conessine) ($C_{24}H_{40}N_2$),[30] Holadysenterine ($C_{23}H_{38}N_2O_3$), Kurchessine ($C_{25}H_{44}N_2$),[31] Lettocine ($C_{17}H_{25}NO_2$), Kurchimine ($C_{22}H_{36}N_2$), Holarrhenine ($C_{24}H_{40}N_2O$), Holarrhimine/Kurchicine ($C_{21}H_{36}N_2O$), Holacine ($C_{26}H_{44}N_2O_2$),Holafrine ($C_{29}H_{46}N_2O_2$), Holadysone ($C_{21}H_{28}O_4$), Holacetine ($C_{21}H_{32}N_2O_3$), 3α-Aminoconan-5-ene ($C_{22}H_{36}N_2$), Dihydroisoconessimine($C_{23}H_{40}N_2$),[32] Conamine ($C_{22}H_{36}N_2$), Conkurchine ($C_{20}H_{32}N_2$),[33] Pubadysone ($C_{21}H_{26}O_3$), Puboestrene ($C_{20}H_{24}O_3$), Pubamide ($C_{21}H_{27}NO_3$),[34] Holadiene ($C_{22}H_{31}NO$), Kurchinidine ($C_{21}H_{29}NO_2$), Kurchinine ($C_{19}H_{24}O_3$),[34] Pubescine ($C_{22}H_{26}N_2O_4$), Norholadiene ($C_{21}H_{29}NO$), Pubescimine ($C_{24}H_{40}N_2O$),[34] Holonamine, Regholarrhenine A ($C_{22}H_{31}NO_2$), Regholarrhenine B ($C_{21}H_{29}NO_2$), Regholarrhenine C ($C_{22}H_{34}N_2$),[4] Regholarrhenine D ($C_{23}H_{38}N_2O$), Regholarrhenine E ($C_{25}H_{44}N_2O_2$), Regholarrhenine F ($C_{25}H_{44}N_2O$).[31]

3.3. From leaves

Holantosine-A ($C_{28}H_{47}NO_6$), Holantosine-B ($C_{28}H_{45}NO_5$), Holantosine-C ($C_{28}H_{47}NO_6$), Holantosine-D ($C_{28}H_{45}NO_5$), Holantosine-E ($C_{28}H_{47}NO_6$), Holantosine-F ($C_{28}H_{45}NO_5$), Holarosine A ($C_{30}H_{47}NO_6$), Holarosine B ($C_{30}H_{47}NO_6$), Holarricine ($C_{21}H_{32}N_2O_3$),[3] Kurchiphyllamine, Kurchaline,[11]Kurchiphylline ($C_{23}H_{47}NO_2$).[32]

3.4. From seeds

Conimine ($C_{22}H_{36}N_2$),[27] Antidysentericine ($C_{23}H_{36}N_2O$).[31]

4. Conclusion

Diseases have been associated with humans since their existence. They reduce the health of human beings and in severe

cases even lead to death. Just as a negative charge is stabilized by a positive charge in an atom, likewise, nature has provided medicinal plants as the source of remedies for these diseases. *H. antidysenterica* has been traditionally used to treat diseases like diarrhoea, dysentery, and helminthic disorders. But with emergence of new methods in the last few years, experimental studies made it possible to discover more pharmacological properties of the plants such as anti-inflammatory, anti-oxidant and anti-malarial activities. The multiple activities exhibited by the plant can be attributed to the large number of active principles it possesses. After an extensive literature survey, 68 alkaloids have been reported in this review. While appreciable results have been reported regarding the various activities discussed in the review, there is still a need to carry out further research to determine the active principle involved in each activity. This will allow pharmacists to synthesize novel drugs composed of the specific alkaloid(s) along with other compounds.

Conflicts of interest

All authors have none to declare.

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