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Medicinal uses of *Holarrhena antidycenterica* on Pharmacological basis

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ABSTRACT: Since ancient times, there have been thousands of medicinal plants with rich sources of ingredients for the purpose of illnesses and diseases. The efficiency, affordability, and less side effects of the drugs made from medicinal plants are causing a rising level of interest. The plant *Holarrhena antidysentrica* linn of family *Apocynaceae,* commonly known as kurchi or kutaj is praised for its medicinal uses of stem, bark, leaves and seeds in ayurvedic texts. This little deciduous tree with white blossoms is abundantly found in India. It is frequently used in conventional treatments of a range of medical conditions such as diarrhoea, diabetes and various types of infections. In this review, all pharmacological and toxicological aspects are discussed. Some recent studies have revealed many new properties such as Angiotensin-converting-enzyme inhibitory, acetylcholinesterase inhibitory activity and neuroprotective activity. This review is an attempt to reveal some pharmacological effects of various parts of plants and their therapeutic uses for various diseases.

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INTRODUCTION:

Medicinal plants are utilized traditionally all over the world. These are essential in the prevention as well as treatment of many diseases. Medicinal plants have gained popularity in developed nations due to their safety, efficacy, accessibility and minimum side effects [1]. Although medicinal plants have been around for a long time, their value as a supply of essential medicines wasn't recognised until the rise of human civilizations. Thus, classical medicinal writings like the Ayurvedic texts Sushruta Samhita and the Rig Veda were developed [2]. One such therapeutic plant called *Holarrhena antidysentrica* Linn of family Apocynaceae is also known as "Indrayava," "Coneru " in English, and "Vatsaka" in Sanskrit. It is a flowering shrub that is

found all over India up to an elevation of 4,000 ft. The plant has got favourable reviews in traditional Indian medicine for the dealing of dysentery, diarrhoea, and intestinal worms [3]. The plant is well known for its numerous therapeutic benefits. Its seeds, leaves, and bark have been employed in Ayurvedic formulations. Traditional Ayurvedic medicine uses stem and bark of the tree, known as "kurchi" on the Indian subcontinent and "conessi bark" in Europe, to cure diarrhoea, particularly amoebic dysentery. The plant bark is also used as an antimicrobial, anti-inflammatory, and analgesic in the Ayurvedic system of medicine [4]. Leaves of the plant also have antidiabetic and hepatoprotective activity.

SCIENTIFIC CLASSIFICATION [5]:

Kingdom	: Plantae.
Subkingdom	: Tracheobionta.
Super division	: Spermatophyta.
Division	: Mangoliophyta.
Class	: Mangoliopsida.
Subclass	: Asteridae.
Order	: Gentianales.
Family	: *Apocynaceae.*
Genus	: Holarrhena.
Species	: *Holarrhena antidysentrica.*

VERNACULAR NAME [5]:

English	: Tellicherry Bark
Hindi	: KarvaIndrajau, Kutaja, Kurchi
Odia	: kure
Sanskrit	: Indrayava, Kutaja, Sakraparyaaya,
Tamil	: Kirimllikai, Kutaca-P-Palai,
Telugu	: Girimallika, Kodisepala, Kolamukku,
Punjabi	: Keor, Kewar
Gujarati	: KadavoIndrajav

ORIGIN AND DISTRIBUTION:

The plant is found all over India, particularly in the Himalayan mountain regions. In India, it possesses cultural and folkloric values. During the Nabanna or “Nuakhai” festival in the Indian state of Odisha, people use the leaves of the plant as a rice eating plate [6]. The seeds of the plant are 1 to 2 cm long and concave. These are light brown in colour and marked with linear lines [7]. The plant is accessible in Asia, Africa, and subtropical and tropical climates. The tree grows from May to July. It is also available in Africa, Pakistan, Sri Lanka, Burma, and Nepal. It is widespread in India, but it is most common as tropical Himalayan deciduous woods at altitudes between 900 and 1250 m [8].

Fig 1. The plant *Holarrhena antidysentrica* (Leaf, seed, bark, and leaf).

CHEMICAL CONSTITUENTS:

Holarrhena antidysentrica chemical components were primarily identified in the different parts of the tree. The main phytoconstituents are tannins, triterpenoids, ergosterol, flavonoids, phenolic acids, resin, saponins, steroidal alkaloids, and coumarins.

Several steroidal alkaloids, including conanines, 3-aminoconanines, 20-aminoconanines, 3-aminopregnans, 3, 20-diaminopregnae, and their derivatives, are found in the plant's seeds. Holadysenterine, a brand-new steroidal alkaloid, was discovered and studied [9]. Similarly the stem bark contains conessine ($C_{24}H_{40}N_2$), isoconessine ($C_{24}H_{40}N_2$), conessimine/ isoconessimine ($C_{23}H_{38}N_2$), conarrhimine ($C_{21}H_{34}N_2$). Bark contains 2 % of alkaloids. Conessine, conkurchine ($C_{21}H_{32}N_9$), kurchine ($C_{23}H_{40}CL_2N_2$), holarrhemine, holarrhenine, kurchicine, and conkurchinine are among them [10].

Yang, *et al*. studied the acetyl cholinesterase inhibitory activity of an alcoholic extract of seeds, with an IC_{50} of 6.1 g/ml. Specifically, five steroidal alkaloids called conessine, iso-conessine, connesimin, corarchimin, and conimin, were discovered using chromatographic fractionation. All other compounds, with the exception of isoconnesimin, displayed an IC_{50} value of 4 to 20 g/ml, the IC_{50} value for connesimin was 4 g/ml. Connesimin's IC_{50} value was 4 g/ml, while the IC_{50} values for the other substances ranged from 4 to 20 g/ml for isoconnesimin. The leaf of plant contain Holantosine-A($C_{22}H_{47}NO_6$), Holantosine-B($C_{38}H_{45}NO_5$), Holantosine-C($C_{28}H_{47}NO_6$), Holarosine-A, Holarosine-B, Holarricine, Kurchiphyllamine, Kurchaline [11].

ETHNOMEDICINAL USES:

The plant *H. antidysenterica*, also known as Kutaj, and its seeds, known as Indrajava, are native to tropical and

subtropical parts of Asia and Africa. It is very common in the Himalayan mountains of India. It has cultural and folkloric values in India. During the "Nabanna"or “Nuakhai” festival of Odisha, people take rice on this plant's leaves making it as a plate. In Uttar Pradesh, particularly in the districts of Varanas and Mirzapur, its bark is employed to treat stomach issues [12]. The bark of the plant is also used by the Asur and Santhal tribes in the Netarhat plateau in Bihar. The stem and bark of the plant are used to treat skin conditions by the tribes of Nallamala area of Andhra Pradesh. This herb is also utilised as traditional medicine by the Assamese Bodo people. Some classic Ayurveda formulas that incorporate this plant are Kutajarishta, Kutajavleha, and Kutajghanvati, Mahamanjishtadi Kashayam, Stanyashodhana Kashaya, and Patoladi Choornam. Disorder like blood or blood-related ailments, skin disorder called Kustha, Pravahika (amebiasis), Atisara (diarrhoea) and secondary diarrhoea are some of the conditions for which the plant is traditionally known for treatment. Nine different medications together known as bhunimbadi churna are prepared to cure diabetes, anaemia, jaundice, and fever, according to the Brihat Bhaishajya Ratnakar [13].

Ethnomedicinal use of different parts of plant:

Therapeutic indication(s)	: Part used
Dysentery	: Leaves
Diarrhoea	: Seeds, Bark and Fruit
Wound healing	: Leaves and Latex of Plant
Worm infestation	: Bark
Diabetes	: Seeds, leaves, bark
Cancer	: Leaves and bark
Malaria	: Root and bark
Hepatic Disorders	: Leaves and bark
Inflammation	: Leaf and bark
Rheumatism	: Stem bark
Urinary tract infection	: Seeds
Convulsion	: Seeds
Hypertension	: Seeds

PHARMACOLOGICAL ACTIVITY:

Anti-amoebiasis and diuretic activity

The aqueous seed extract of *Holarrhena antidysenterica* (HA) has diuretic activity at doses between 30 to 100 mg/kg. The urine production was greatly increased in wistar rats. The quantity of Na and K ions discharged through the urine of rats (treated) likewise showed a significant rise [14] .Individuals with amoebiasis were totally healed after taking the powder of bark daily for two weeks. Another research experiment also examined the effectiveness of Amoebin cap, an amoebiasis medication that includes *Holarrhena antidysenterica* as its ingredients [15].

Anti-diarrhoeal activity:

The ethanolic extract of seed when given to rats with castor oil and E coli-induced diarrhoea, a rise in the density of their dry stools and a decrease of defecation drops occurred [16] .The potential of bark extracts to withstand entero invasive *E. coli* (EIEC), Salmonella enteritidis, *Shigella boydii*, *Shigella flexneri* was well recognised [17]. A commercially available formulation of *Holarrhena antidysenterica* is effective against diarrhoea. *Kutajaparpati vati* exhibited a significant decrease in watery diarrhoea and small intestine content motility. Moreover, it demonstrated notable 67.55 % protection against castor oil [18].

Anti-bacterial activity and anti-haemorrhoidal action:

The plants extracted from the bark seeds show promise antibacterial activity against Salmonella, E. coli, and Staphylococcus [19]. Also, the plant prevented enteropathogenic E. coli from adhering to host epithelial cells [20] . An Ayurvedic formulation of stem bark extract called "Kutajatvak Churna" showed therapeutic properties in bleeding piles [21].

Antihypertensive and antimutagenic activity:

In an investigation of anti-mutagenic activity of *H. antidysenterica*, the methanolic extract of the bark showed anti-mutagenic potential against strains of *Salmonella typhimurium* that had been subjected to methyl methane sulfonate and sodium azide induced mutagenicity [22]. The capacity of shrubs with antihypertensive activity to prevent the production of angiotensin, which causes vasoconstriction and raises blood pressure, is being studied. Angiotensin-converting enzyme (ACE) inhibition by ethanolic extracts of seed was 24 %, which was excellent [23].

Antidiabetic efficacy:

A recent study found that doses of 300 and 600 mg/kg of an ethanolic seed extract resulted in considerable recovery in diabetic rats. The weight of rats significantly increased in each 7 days of treatment while the range of

blood sugar, serum cholesterol, triglycerides, aspartate, and uric acid transaminase, alanine transaminase, alkaline transferase, urea, creatinine significantly decreased [24]. Similar outcomes were also seen in rats treated with methanolic seed extracts that had been streptozotocin-induced diabetes [25]. When normoglycemic rats received hydro-methanolic seed extract of Holarrhena antidysenterica, glucosidase turned out to be inhibited. This enzyme facilitates the absorption of glucose by the intestines and can thus be very important in controlling postprandial diabetes [26]. In a different investigation, it was found that the hydro-methanolic seed extract doesn't increase glutamate oxaloacetate transaminase (GPT) [27].

Acetylcholinesterase inhibitory:

In a microplate experiment for AChE, the alkaloid extract from the *Holarrhena antidysenterica* seeds was testified to have a 91 % inhibition of AChE. Three fractions were produced by column chromatography with the alkaloidal extract over an MCIGEL with the alkaloidal extract utilising a gradient solvent system of MeOH-H2O (50, 60, 70, 80, and 90 %, v/v). Ellman's approach was used to examine the five compounds' ability to inhibit AChE in 96-well microplates [28,29]. The total alkaloidal seed extract of Holarrhena antidysenterica substantially inhibited the enzyme with an IC_{50} value of 6.1 g/ml [30].

Neuroprotective effect:

Considering the HbA1C level to be an important marker of AGEs, in an investigation, Methanolic extract of HA considerably reduced this high HbA1c level. Comparatively to the diabetic control group, Methanolic extract of HA significantly lowers the elevated levels of plasma cholesterol and blood glucose. Comparing MEHA-treated rats to their unaffected peers revealed improved locomotor activity, showing that diabetic neuropathy can be avoided with the treatment of plant [31].

It is preferable to inhibit acetylcholinesterase while treating neurological conditions like Alzheimer's disease. In a research study, certain alkaloids from *H. antidysenterica* were examined for comparable activities because alkaloids present in some plants have been shown to block AChE. With an IC_{50} range of 4 mM, the separated alkaloids conessimine, isoconessimine, conessimine, conarrhimine, and conimine showed the greatest effects. Conferring to the findings of the study, these alkaloids may be used in medications for healing of neurological illnesses. The CNS-stimulating effects of methanolic extract of bark on Swiss albino mice were examined in a different investigation. The results demonstrated that it considerably reduced and relaxed the muscles ability to grip independent of dosage, along with the spontaneous locomotor activity, indicating a depressant activity on the central nervous system [32].

Wound healing activity:

Significant wound healing activity of leaf extract of the plant *H. antidysenterica* was observed. In comparison to the control group, the wound contraction was better in the rats treated with the 5 % gel made from the ethanolic leaf extract of the plant [33].

Hepatoprotective activity:

Hepatoprotective effect was dose-dependent in leaves and bark extracts. Refampicin, paracetamol, CCl_4 cause liver damage in Wister rats resulting in an increase in enzymes such as SGPT, SGOT, ALP, and total Bilirubin. In the extracted rats, the hepatic cells, central vein, and sinusoids were almost normal, based on the liver's histology evaluation. It indicates that the extract reduces the strictness of liver damage, prevents the development of fibrous septa, and limits liver weight loss brought on by paracetamol, CCl_4, and Rifampicin [34,35].

Anti- Inflammatory activity and analgesic activity:

In male albino wistar rats that had 2,4-Dinitrobenzene sulfonic acid-induced colitis, methanolic extract of *H. Antidysenterica* bark showed decreased nitric oxide and malondialdehyde levels and increased levels of glutathione and superoxide dismutase. Nitric oxide levels have fallen, signifying that the anti-inflammatory effects may be owing to a drop in iNOS production. Treatment with *H. antidysenterica* also reduced goblet cell rupture, inflammatory cellular infiltration, and inflammation in mucosal layer. Rat paw edema caused by carrageenan was inhibited by extract of *H. antidysenterica* leaf in methanol. Moreover, the extract of *H. antidysenterica* in methanol reduced tail flick latency, demonstrating the activity of analgesic by suppressing the writhing caused by acetic acid response in a dose-dependent manner. A *H. antidysenterica* ethanol extract had analgesic effects by preventing albino mice from writhing.

Anti-microbial activity and Anthelmintics activity:

Ethanolic and aqueous extracts of bark of *H. antidysenterica* produced notable outcomes on the

earthworm Pheretima posthuma in in-vitro study. Regions of inhibition by ethanolic extracts of seed against EPEC (Enteropathogenic *E coli*) bacteria-containing bacterial cultures were concentration-dependent. The extract is regarded as a potential antimicrobial agent because EPEC is resilient to a number of drugs. According to study, a bark extract in petroleum ether had MIC (minimum inhibitory concentration) of 50 mg/ml and inhibited *E. coli* at that level, although extracts in chloroform and methanol had greater MIC values [36].

CONCLUSION:

Diseases are always associated with human beings. Thousands of medicinal plants and formulations remain hidden for years. The current article reviewed *H. antidysenterica* as a potential medicinal plant with a range of pharmacological activities. The plant parts such as seeds, leaves, and bark can be employed in a number of medical conditions due to its effectiveness and safety. *H. antidysenterica* is used traditionally to treat diseases like diarrhoea, dysentery, anti-inflammatory, anti-oxidant, and antimalarial activities. It also has Anti-amoebiasis and diuretic activities. The plant has been also employed in Ayurvedic formulations such as *Bhunimbadi churna* to cure diabetes, anaemia, jaundice, and fever, according to the Brihat Bhaishajya Ratnakar. With the advanced technology, the investigation discovers more pharmacological properties of the plants such as neuroprotective activities. This plant contains many chemical constituents' tannins, triterpenoids, ergosterol, flavonoids, phenolic acids, resin, saponins, steroidal alkaloids, and coumarins that are useful for pharmacists to synthesize and formulate novel drugs for various enteric, skin diseases and diabetes.

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