RESEARCH ARTICLE OPEN ACCESS

An Overview of the Phytochemical, Pharmacologicaland Clinical Activities of Holarrhena Antidysenterica (L.)

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ABSTRACT :
Holarrhena antidysenterica, an invaluable medicinal plant, has been extensively studied for its diverse pharmacological properties and therapeutic applications. Its stem bark, leaves, and seeds have been utilized for various ailments. Phytochemical studies have revealed compounds with analgesic Holarrhena antidysenterica, a member of the Apocynaceae family. This comprehensive review synthesizes the current knowledge on the phytochemistry, pharmacology, and clinical efficacy of Holarrhena antidysenterica. Through meticulous phytochemical analyses, numerous bioactive compounds including alkaloids, flavonoids, and terpenoids have been identified, contributing to its pharmacological versatility. Pharmacological investigations have revealed its profound anti-inflammatory, antimicrobial, antidiarrheal, antidiabetic, and anticancer activities, among others. Additionally, traditional medicinal uses of Holarrhena antidysenterica in treating dysentery, diarrhoea, malaria, and diabetes are corroborated by scientific evidence. Importantly, safety assessments highlight its favourable toxicological profile, further affirming its potential as a therapeutic agent. This review consolidates the existing knowledge base, emphasizing the need for continued exploration of Holarrhena antidysenterica to harness its full therapeutic potential for the benefit of global healthcare.

Keywords : Neuroprotective, Hypoglycaemia, Indrajav, Holarrhena antidysenterina, Conessine.

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INTRODUCTION
Holarrhena antidysenterica, commonly known as Kutaj, is a medicinal plant abundant in India, particularly in the Himalayan regions. Its traditional uses are documented in classical Ayurvedic texts and folklore across various Indian states, including Odisha, Uttar Pradesh, Bihar, Andhra Pradesh, and Assam. The plant holds economic significance, with its products like seed powder, bark powder, kutajakwatha, Kutaja Prapati Vati, and herbal dietary supplements being exported. In Odisha, the leaves of HA are offered during the Nabanna festival, while in Uttar Pradesh's Mirzapur and Varanasi districts, the bark is utilized for gastric issues. HA and its seeds, known as Indrajava, are prevalent in tropical and subtropical regions of Asia and Africa, further emphasizing their cultural and medicinal importance in traditional Indian practices.

The holistic use of Holarrhena antidysenterica extends to various indigenous communities across India. The Asur and Santhal communities in Bihar's Netarhat plateau utilize the bark, while tribes in Andhra Pradesh's Nallamala district apply it for skin diseases. Similarly, the Bodo tribe in Assam relies on this plant for traditional medicine. In Ayurveda, it features prominently in formulations such as Kutajarishta, Kutajavleha, and Kutajghanvati, addressing ailments like amebiasis, diarrhea, secondary diarrhea, blood disorders, skin issues, and thirst. Additionally, Bhunimbadichurna, comprising nine drugs, finds mention in ancient texts for treating fever, jaundice, anemia, and diabetes. These diverse applications underscore the plant's significance in indigenous healthcare systems and its potential for modern pharmacological exploration. Holarrhena antidysenterica, commonly known as Kutaj, and its seeds, Indrajava, are prevalent in tropical and subtropical regions of Asia and Africa, notably abundant in India, particularly in the Himalayan ranges. The plant holds

traditional and folklore significance in India, with practices like offering its leaves during the Nabanna festival in Odisha. Additionally, the bark of Holarrhena antidysenterica is utilized for gastric problems in the Mirzapur and Varanasi districts of Uttar Pradesh. These cultural practices underscore the plant's importance in indigenous healthcare systems and highlight its long-standing use in addressing various ailments. Such traditions contribute to the plant's recognition and utilization in traditional medicine, emphasizing its significancein local communities and its potential for further exploration in modern pharmacology.

Indrajav, known scientifically as Holarrhena antidysenterica, is a medicinal plant widely utilized in pharmacognosy for its diverse therapeutic properties. Native to the Indian subcontinent, it has been an integral part of traditional medicine systems like Ayurveda and Unani for centuries.The plant contains a rich array of bioactive compounds, including alkaloids such as conessine, conarrhimine, and kurchine, which contribute to its medicinal efficacy. These compounds exhibit various pharmacological activities, including antidiabetic, anti-inflammatory, antimicrobial, antidiarrheal, and antimalarial properties.

In pharmacognosy, Indrajav is valued for its role in treating gastrointestinal disorders, such as diarrhoea and dysentery, due to its antidiarrheal and anti-inflammatory effects. Additionally, its antimicrobial properties make it effective against a range of bacterial and fungal infections.Furthermore, research suggests that Indrajav possesses potential antimalarial activity, making it a subject of interest in the development of new treatments for malaria. Its traditional uses and pharmacological properties make Indrajav a promising candidate for further study and utilization in modern medicine, highlighting its significance in pharmacognosy.

Table 1: Medicinal Properties of *Holarrhena antidysenterica*

Sr. No.	Disease	Medicinal Properties
1	Diabetes	Regulates blood sugar
2	Indigestion	Appetizer, stomachic , treatment of constipation, colic and diarrhea
3	Blood related disorders	Anaemia, blood infection, blood purifier, haemorrhage, nose bleeding
4	Body pain	Pain reliever for rheumatoid arthritis, knee pain, headaches, and body aches
5	Brain related disorders	Improves depression and other nervous disorders, acts as memory enhancer
6	Skin disorders	Action against warts, dermatitis, leukoderma, pimples, ringworm, scabies, skin allergies, abscesses, boils, bruises, and other skin conditions
7	Gastrointestinal disorders	Active against colic problems, intestinal ulcers, stomach aches, dyspepsia, flatulence, cholera, diarrhoea, and dysentery as well as food poisoning, gastroenteritis, and indigestion
8	Piles	Active against piles, fissures, fistula, haemorrhoids
9	Intestinal parasites	Antihelmintic for internal worms such as threadworms, tapeworms, and Guinea worms
10	Cancer	Inhibit growth of tumorous cells

Table 2: Botanical Classification of *Holarrhena antidysenterica*

Sr. No.	Taxonomical Level	Classification
1	Kingdom	Plantae
2	Superdivision	Spermatophyta
3	Division	Magnoliophyta
4	Class	Magnoliopsida
5	Subclass	Asteridae
6	Order	Gentianales
7	Family	Apocynaceae
8	Genus	Holarrhena
9	Species	Holarrhena antidysenterica

Vernacular Name

English KarvaIndrajau, Kutaja, Kurchi
Hindi Indrajab, Karwainderjau, Kauriya, Kuda, Kura, Kurchi, Tita-indrajao (seeds)
Sanskrit Bhadrayava, Girimallika, Indrayava (seeds), Kutaj, Kutaja, Kalinga (tree)
Punjabi Keor, Kewar

Plant Description

Biological source:

Holarrhena antidysenterica is a bark or seed of the Holarrhena antidysenterica tree also known as Kutaja or Conessi tree belonging to family Apocynaceae.

Origin and Distribution

Holarrhena antidysenterica is native to India and is particularly abundant in the Himalayan ranges. It holds significant traditional and folklore value in Indian culture, as evidenced by its use during festivals such as "Nabanna" in the Odisha state, where people offer its leaves along with rice.

Beyond India, the plant is also found in tropical and subtropical regions of Asia and Africa. It can be spotted in countries like Burma, Sri Lanka, Pakistan, Nepal, and various parts of Africa. Flowering typically occurs between the months of May to July.

In India, Holarrhena antidysenterica is widespread and can be found throughout the country, especially in deciduous forests of the tropical Himalayas. Its habitat ranges from altitudes of 900 to 1250 meters above sea level.

Holarrhena antidysenterica, a deciduous shrub or small tree, can reach heights of up to 13 meters with a girth of 1.1 meters and a clear bole of 3–7 meters. Its leaves, measuring 15–30 cm × 4–12 cm, have obtuse or acute bases and feature 10–14 pairs of opposite, sessile, elliptic or ovate nerves. The leaves are oblong, membranous, strong, and arched, with petioles up to 1.5 cm long. The plant produces seeds that are 1-2 cm long, linear or oblong, concave, and light brown, with linear markings, and have a bitter taste. Additionally, its cymes are 3–6 cm in diameter. These botanical characteristics contribute to its identification and utilization in traditional medicine practices across various cultures, emphasizing its importance as a therapeutic resource.

(a)Flower

(b) Seed

(c) Fruits

(d) Leaves

Fig 1:*Holarrhena antidysenterica*(a)Flower, (b) Seed, (c) Fruits, (d) Leaves

Table 3: Morphology of *Holarrhena antidysenterica*

Sr. No.	Features	Description
1	Leaves shape	Oblong or ovate, with a pointed tip and smooth margins
2	Leaf size	10-20 cm long and 5-10cm wide
3	Leaf surface texture	Velvet-like pubescence
4	Flower colour	Creamy–white to yellowish–brown
5	Flower shape	Tubular, with 5 petals and a 5 – lobed corolla
6	Fruit type	Capsule, 10-15 cm long, with numerous seeds
7	Bark colour and texture	Greyish brown with vertical fissures and corky texture when mature
8	Root	Thick,fibrous roots release a bitter , yellowish – white latex

Cultivation of Plant :

Holarrhena antidysenterica, commonly known as connessi or kutaja, is cultivated for its medicinal properties, particularly in treating dysentery and other gastrointestinal ailments. To cultivate this plant, suitable tropical or subtropical climates with well-drained sandy loam soil are preferred. Propagation can be achieved through seeds or stem cuttings, with seeds typically sown during the rainy season. After 4-6 months, seedlings are ready for transplantation, with a recommended spacing of 4-5 meters between plants. Adequate watering, especially during the initial growth stages, along with organic fertilization, promotes healthy plant development. Pruning helps in shaping and branching, while regular pest and disease monitoring ensures plant health. Harvesting of bark and seeds, the parts used for medicinal purposes, should be conducted carefully to avoid damaging the tree. Proper post-harvest handling, including drying and storage in airtight containers, preserves the medicinal properties. Sustainable cultivation practices, such as selective harvesting and reforestation efforts, are crucial for long-term plant population viability.

Collection of Plant Material

Holarrhena antidysenterica is abundant in most parts of the Gondia district, typically flowering from April to July and fruiting from May to August. It exhibits both bushy and tree forms in different locations. Various parts of the plant, including leaves, stems, fresh flowers, and fruits, were collected from forest areas. Dried flowers were crushed into a powder and stored in an airtight container, while other plant parts were preserved in 4% formalin for further analysis. Identification was done using botanical references, and herbarium specimens were deposited for documentation. Freshly collected stems and leaves were utilized for anatomical and stomatal studies, while flowers were dried naturally at room temperature under shade. This systematic approach facilitates botanical research and contributes to understanding the plant's properties and potential applications in traditional medicine.

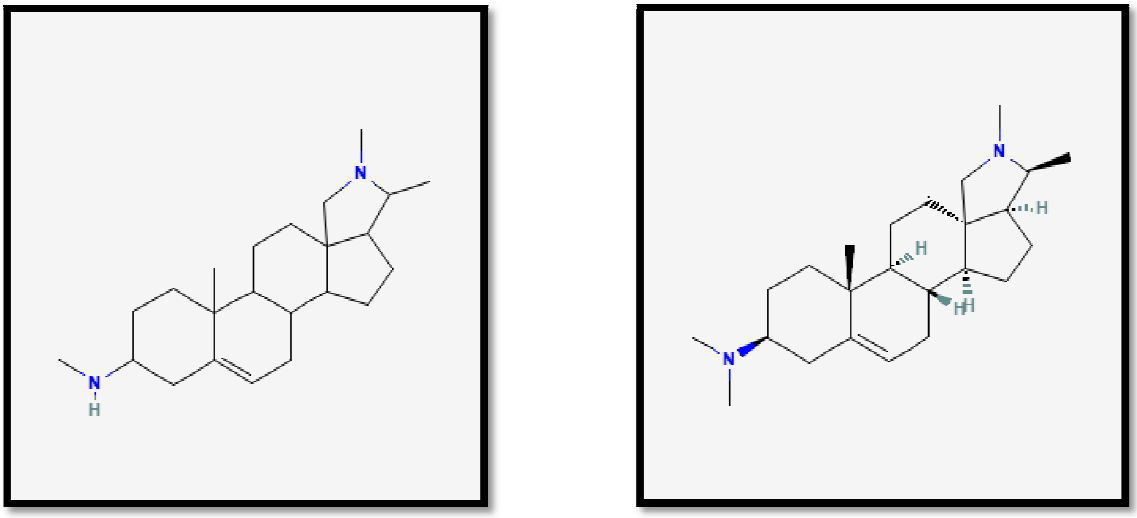
Chemical Constituents of Kutaja

The constituents of Kutaja encompass a diverse array of compounds, including steroidal alkaloids, resin, flavonoids, phenolic acids, triterpenoids, tannins, coumarins, saponins, and ergosterol. Notably, the bark contains alkaloids like conessine, kurchine, holarrhimine, conkurchine, holarrhenine, kurchicine, and conkurchinine, while the stem bark and seeds are rich in steroidal alkaloids such as conanines, 3-aminoconanines, 20-aminoconanines, 3-aminopregnans, and their derivatives. A newly identified steroidal alkaloid, holadysenterine, has been characterized with the molecular formula C23H38N2O3. Additionally, the stem bark contains conessine, isoconessine, conessimine/isoconessimine, and conarrhimine. These chemical constituents contribute to the pharmacological activities attributed to Holarrhena antidysenterica and highlight its potential in traditional and modern medicine for various therapeutic purposes.

The seeds of Holarrhena antidysenterica (formerly known as Holarrhenapubescens) contain various chemical constituents, primarily alkaloids, which contribute to its medicinal properties. Some of the notable alkaloids found in the seeds include:

1. **Conessine:** Conessine is one of the major alkaloids present in the seeds of Holarrhena antidysenterica. It exhibits antispasmodic, anti-inflammatory, and antiplasmodial activities.
2. **Conarrhimine:**Another significant alkaloid found in the seeds, conarrhimine, has been studied for its potential antimalarial and antiamoebic properties.
3. **Kurchine:** Kurchine is another alkaloid present in the seeds, which has shown antimicrobial and anti-inflammatory effects.

4. **Holarrhenine:**This alkaloid has been reported to possess antiamoebic and antispasmodic activities.
5. **Isoholarrhenine:**Isoholarrhenine is a structural isomer of holarrhenine and shares similar pharmacological properties.



(a) (b)

Fig 2: Chemical Structures of the major Phytochemicals (a) Kurchine, (b) Conessine

In addition to alkaloids, the seeds may also contain other secondary metabolites such as flavonoids, tannins, saponins, and steroids, which can contribute to the overall medicinal efficacy of Holarrhena antidysenterica. These chemical constituents collectively impart various pharmacological activities to the plant, making it valuable in traditional medicine systems for treating conditions such as diarrhoea, dysentery, malaria, and gastrointestinal disorders.

Microscopic characteristics :

Holarrhena antidysenterica, commonly known as Kutaja, is a medicinal plant widely used in traditional Ayurvedic medicine for its therapeutic properties, particularly in treating dysentery and diarrhoea. Microscopic examination of its various parts, especially the stem bark, reveals distinct features that aid in its identification and authentication.

1**. Cork Cells:**Rectangular to polygonal in shape.Walls are suberized, providing protection and waterproofing.

2.Parenchyma Cells: Found abundantly and filled with starch grains and calcium oxalate crystals.Provide storage and support functions.

3. Fibers: Elongated cells with thick walls, imparting strength and flexibility to the tissue.
Often arranged in bundles.

4. Vessels: Present in radial multiples.Conduct water and nutrients throughout the plant.

METHOD OF EXTRACTION:

One common method for extracting bioactive compounds from Indrajav seeds in pharmacognosy involves solvent extraction. Here's a step-by-step outline of the process:

1. **Preparation:**Start by collecting and drying the Indrajav seeds to remove excess moisture. This helps preserve the integrity of the bioactive compounds.
2. **Size Reduction:**Once dried, the seeds may be ground or crushed into smaller particles to increase the surface area for extraction, aiding in the release of the desired compounds

3. **Selection of Solvent:**Choose a suitable solvent based on the polarity of the compounds to be extracted. Common solvents include ethanol, methanol, or a mixture of water and organic solvents.
4. **Extraction:** Place the ground or crushed seeds in a container and cover them completely with the selected solvent. Stir or shake the mixture to facilitate the extraction process, ensuring good contact between the solvent and the seed material.
5. **Time and Temperature:**Allow the extraction to proceed for a specific duration, which can range from several hours to overnight, depending on factors such as the solvent used and the desired concentration of the extract. The extraction can be carried out at room temperature or slightly elevated temperatures, as appropriate.
6. **Filtration:**After the extraction period, filter the mixture to separate the solvent containing the dissolved bioactive compounds from the solid seed residue. This can be done using filter paper or other suitable filtration methods.
7. **Concentration:**Concentrate the solvent extract by evaporating it under reduced pressure or through other means, such as rotary evaporation, to remove the solvent and obtain a concentrated extract.
8. **Purification:** Depending on the desired purity of the extract, additional purification steps such as column chromatography or crystallization may be employed to isolate specific compounds or remove impurities.
9. **Analysis:** Finally, analyze the purified extract using various analytical techniques to determineits chemical composition, concentration of bioactive compounds, and potential pharmacological properties.

This solvent extraction method is commonly used in pharmacognosy to extract bioactive compounds from Indrajav seeds for further study and potential medicinal applications.

Pharmacological Actions :

Anti-amnesic activity :

Administration of ethanolic extract of Holarrhena antidysenterica seeds for 28 days in separate groups of STZ significantly reduced acetylcholinesterase (AChE) levels compared to the diseased group. It also prevented the increase in malondialdehyde (MDA) levels and depletion of glutathione (GSH) in a dose-dependent manner. This indicates the anti-amnesic property of Holarrhena antidysenterica, as cholinergic dysfunction was assessed by AChE activity. The observed decrease in AChE levels and prevention of MDA and GSH depletion highlight the potential of Holarrhena antidysenterica in ameliorating cognitive dysfunction. These findings suggest a promising therapeutic role for Holarrhena antidysenterica in conditions associated with cholinergic dysfunction and oxidative stress.

Antidiabetic activity:

The ethanolic extract of Holarrhena antidysenterica (HA) demonstrated a significant reduction in plasma glucose levels in euglycemic rats shortly after glucose administration. Diabetic rats treated with HA or glibenclamide showed significant weight gain compared to untreated diabetic rats, alongside decreased blood glucose levels and improved metabolic parameters such as total cholesterol, triglycerides, AST, ALT, urea, and serum creatinine. Additionally, the methanolic extract exhibited similar antidiabetic effects in diabetic rats. Administration of the aqueous extract led to a significant recovery in hepatic glucose-6-phosphatase activity, possibly due to insulin recovery. Inhibition of intestinal α-glucosidase activity by the hydro-methanolic extract resulted in significantly lower blood glucose levels, attributed to phenolic compounds and flavonoids present in the extract. These findings underscore the potent antidiabetic properties of Holarrhena antidysenterica, offering promising avenues for managing postprandial hyperglycemia and improving overall metabolic control in diabetes.

Anti-inflammatory and Analgesic Activity:

The methanolic leaf extract of Holarrhena antidysenterica demonstrated inhibition of rat paw oedema induced by carrageenan and suppressed acetic acid-induced writhing response, indicating its anti-inflammatory and analgesic properties. Additionally, it exhibited analgesic effects by improving tail-flick latency. The ethanolic extract showed similar analgesic effects by suppressing the writhing response in albino mice. Furthermore, the methanolic bark extract decreased nitric oxide and malondialdehyde levels while increasing superoxide dismutase and glutathione levels in 2,4-Dinitrobenzene sulfonic acid-induced colitis in male albino Wistar rats. This suggests an anti-inflammatory effect, possibly attributed to reduced NOS generation. Holarrhena antidysenterica treatment also prevented goblet cell rupture, inflammatory cellular infiltration, and inflammation in the mucosal layer. These findings highlight the plant's potential as a therapeutic agent for inflammatory conditions and pain relief.

Anti-diarrhoeal property:

Ethanolic seed extracts of Holarrhena antidysenterica demonstrated effectiveness against castor oil-induced diarrhoea in rats, leading to a significant increase in faecal dry weight and reduction in defecation drops. Aqueous and alcoholic bark extracts exhibited activity against enteroinvasive E. coli (EIEC), Shigella flexneri, Shigella boydii, and Salmonella enteritidis. Additionally, aqueous and methanolic leaf extracts inhibited the growth of diarrheal pathogens including Salmonella typhimurium, Vibrio cholerae, Vibrio alginolyticus, Vibrio cholera 0139, E. coli 0157:H7, and Salmonella typhi. These findings highlight the potential of various extracts of Holarrhena antidysenterica in combating diarrheal diseases caused by a range of pathogens, suggesting its utility as a natural remedy for gastrointestinal infections.

Inhibition of acetylcholinesterase and CNS-stimulant activity:

A study investigated the potential of alkaloids from Holarrhena antidysenterica to inhibit acetylcholinesterase (AChE), a desirable trait for treating neurological conditions like Alzheimer's disease. Results showed promising inhibitory effects, particularly with conessimine exhibiting significant activity. Another study explored the central nervous system (CNS)--stimulating activity of methanolic bark extract in Swiss albino mice, revealing a depressive effect on CNS function. The extract decreased muscle gripping capabilities and spontaneous locomotive activity regardless of dosage. Notably, out of the five isolated alkaloids (conessine, isoconessimine, conessimine, conarrhimine, and conimine), conessimine demonstrated the most profound effects, suggesting its potential in drug development for neurological disorders. These findings highlight the therapeutic potential of Holarrhena antidysenterica alkaloids in managing neurological conditions by inhibiting AChE activity and modulating CNS function.

Anti-mutagenic and anti-hypertensive activity :

The investigation into plants with anti-hypertensive activity often focuses on their ability to inhibit the secretion of angiotensin, which can lead to vasoconstriction and increased blood pressure. Ethanolic seed extracts of Holarrhena antidysenterica exhibited a satisfactory 24% inhibition of angiotensin-converting enzyme (ACE), suggesting potential as an anti-hypertensive agent. Additionally, a study explored the anti-mutagenic activity of H. antidysenterica, particularly its methanolic bark extract. This extract demonstrated anti-mutagenic potency against mutagenicity induced by sodium azide and methyl methane sulphonate in Salmonella typhimurium strains. These findings highlight the multifaceted therapeutic potential of Holarrhena antidysenterica, not only in managing hypertension but also in combating mutagenic processes, suggesting its utility in promoting overall health and well-being.

AVAILABLE DOSAGE FORM:

(a) **(b)** **(c)**

Fig 3: Marketed dosage forms of Indrajav(a) Powder, (b) Tablet, (c) Churna

Precautions to Take WithKutaja: Kutaja is known to possess anti-diabetic activity. Hence, Kutaja should be used with caution in diabetic patients on anti-diabetic drugs.

Interaction With Other Drugs: Kutaja may interact with anti-diabetic drugs and cause hypoglycaemia.

CONCLUSION

The paper highlights Holarrhena antidysenterica as a promising medicinal plant with a wide range of pharmacological activities, suggesting its potential for various medical applications due to its effectiveness and safety. Traditionally used to treat ailments like diarrhoea, dysentery, and inflammation, recent experimental studies have unveiled additional properties such as anti-amnesic and neuroprotective activities. The plant's diverse activities are attributed to its numerous active principles, with 68 alkaloids identified through a literature survey. While significant progress has been made in understanding its pharmacological properties, further research is needed to elucidate the specific active compounds responsible for each activity. This underscores the importance of continued investigation into Holarrhena antidysenterica's therapeutic potential and its possible role in developing novel drugs for a range of diseases.

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