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BIOMEDICAL APPLICATIONS OF *HOLARRHENA ANTIDYSENTERICA*: AN UPDATED REVIEW

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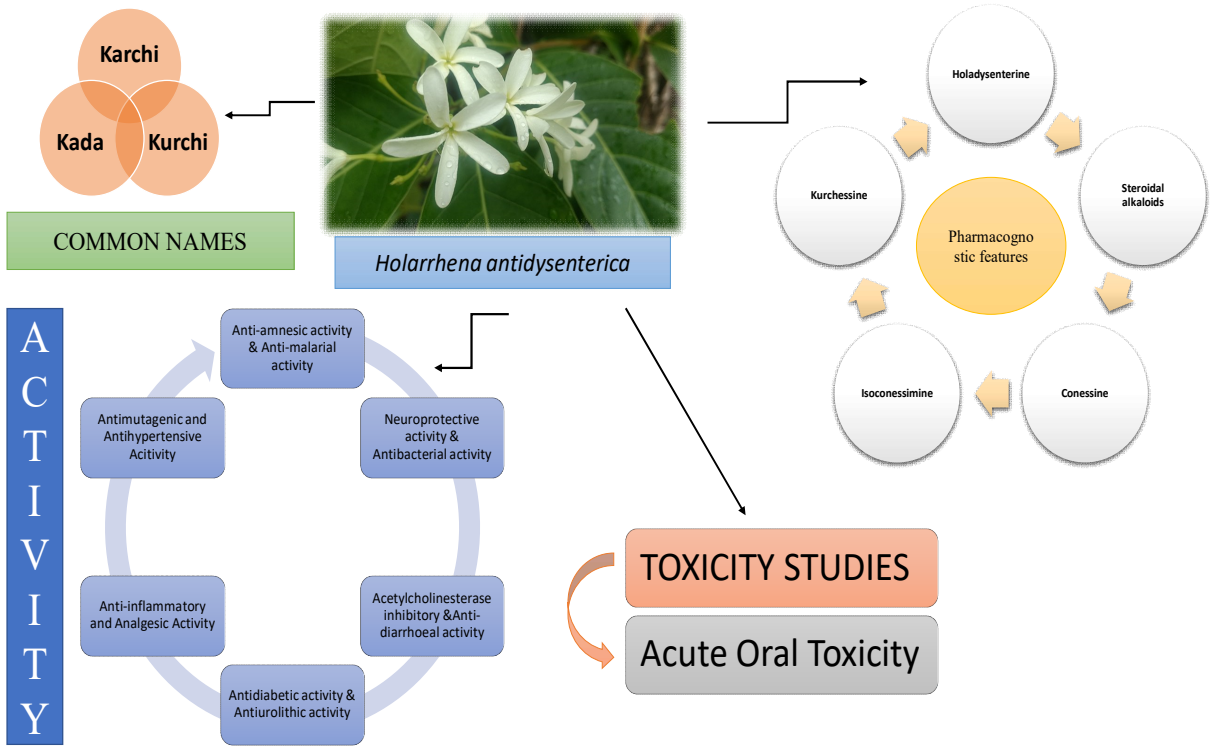
ABSTRACT

Background: Holarrhena antidysenterica is an herbal plant which found to be effective against several diseased conditions like anti-diabetic, anti-diarrhea, analgesic activity, anti-microbial, antihypertensive activity, anti-inflammatory, and anti-malarial, the whole plant of Holarrhena antidysenterica contains medicinal value like seeds, callus, stem, leaf and bark. It originates from the family Apocynaceae. It is used from ancient time and their traditional name was kada, kurchi or kutaj. Objectives: The goal of this study is to precise all pharmacological activities with therapeutic uses. Material and Methods: A bibliographic investigation from recognized scientific databases PubMed, ScienceDirect, Google scholar, etc. Clinical databases were also included in previous research papers from 1980 - 2022. Result: In this review, paper explores the knowledge about novtheel use of Holarrhena antidysenterica which relates to their new pharmacological action and, harmacognostic studies (about stem, bark, leave, flower & root) including their toxicity studies. Conclusion: Holarrhena Antidysenterica is one the important plant for the treatment of various diseases like malaria, constipation, pile, diabetes, dysentery and other disease. This medicinal plant found very effect against worms from ancient time.

Graphical Abstract



INTRODUCTION

A little evergreen tree having white blooms, *Holarrhena antidysenterica* is indeed a member of the Family Apiaceae and is sometimes referred to as Kurchi in Hindi or Tellicherry bark also in English. This species is widespread throughout the tropical & subtropical zones of the world, and also in India, it is found in forests and at elevations of upwards of 4000 feet. [1,2] H. antidysentrica seems to be a common treatment for dysentery, diarrhea, and intestinal worms in Indian traditional medicine. [1] The bark is a plant component that is used to cure analgesics, anti-inflammatory, and antibacterial conditions. Amoebiasis, chronic bronchitis, boils locally, and ulcers [5] A bark infusion is applied on piles & bleeding heavily. [6] Cases involving profuse bleeding accompanying mucus and abdominal discomfort with feces, roots, and bark have been shown to be an exemplary performance for chronic and acute diarrhea. [7] Ayurveda utilizes seeds extensively to cure parasites, piles, hepatitis, & flatulence. [5] Hydro-alcoholic seed extracts have been shown to exhibit anti-urolithic activity in both in-vitro as well as in approaches, and they also stop the formation of calcium oxalate crystals. [8] The natives of Andhra Pradesh used stem bark to treat skin conditions. [9] It was discovered that a methanolic preparation of stem bark was useful in treating inflammatory bowel illness. [6] This plant's leaves were believed to treat scabies. [10]. The plant also often reportedly has anti-diarrheal, anti-helminthic, appetizing, bronchitis, astringent, eczema, seizure disorders, pyrexia, jaundice, leprosy, piles, and steatorrhea properties. [11, 12] It has an immune-modulating agent, larval growth inhibitor property, & acts against malaria and vaginitis.[7] It includes gut-stimulating & inhibiting constituents. [9]

Taxonomical Classification of *Holarrhena Antidysenterica* [13]

Kingdom	Plantae
Subkingdom	Tracheobionta
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Asteridae
Order	Gentianales
Family	Apocynaceae
Subfamily	Apocynoideae
Genius	*Holarrhena*
Species	*Antidysenterica*

Botanical name and Varieties [13]

S. No.	Varieties
1	Holarrhena antidysenterica (Linn.) Wall.exA.DC.
2	Wrightia antidysenterica (Linn.) R.Br.,
3	H. pubescens (Buch.-Ham.) Wall.ex DC Wrightia tinctoria R.Br.
4	Wrightia tomentosa Roem. & Scult.

Regional names [14]

Languages	Names
Hindi	Kuraiya, Kadau
Marathi	Kuda, Kudaiyya
Guajarati	Kudo
Punjabi	Kewar, Kura
Tamil	Veppalei
Telugu	Kodaga
Kannad	Korchi
Malayalam	Kodagapal
English	Conessi, Kurchi
Bengali	Kurchi
Oriya	Kueri, Keruan
Urdu	Kherva
Sanskrit	Kalinga, Indravriksha

Figure 1: Traditional use of *Holarrhena Antidysenterica*

PHARMACOGNOSTIC STUDIES

HA is classified as being evergreen, multi-branched shrub or small tree which can grow up to 13 meters tall, 1.1 meters in diameter, and a transparent bole from 3 - 7 meters. Their leaflets were rectangular, membranous, robust, and arching; they measure 15–30 cm long by 4–12 cm wide; their bases are frequently rounded or acute; their nerves are all in 10–14 pairs; opposed, septate, elliptical, or oval; and their cotyledons can reach 1.5 cm in length. Corymbose is terminals and septate, with tiny, ciliate sepals and thin pedicels. Flowers are in an end corymbose cyme and are odorless and white in color The 2.5–3 mm long, oblong-lanceolate, acute, and bracts calyx lobe. Floral lobes are approximately equivalent to the tube length, rectangular, curved at the apex, and mostly pubescent. Tube 8-13 mm long, somewhat swollen located at the base above the pollen, mouth not sealed with a circle of hairs; throat hair within. Follicle divaricated, cylindrical, parallel, terete, rapacious, and obscurely lone lose, typically with dotted white patches, measuring 15–45 cm long & 5–10 mm in diameter. 900–1000 seeds weigh one ounce (Oz), are linear-oblong, at least 8 mm long, spreading terminal coma of brown hair, 2-2.5 cm long, and have 25–30 seeds per follicle. The coma is brownish and spans 2.5–10 cm. Bark from the Wrightia tinctorial plant is added to HA adulterants. This herbal medicine can be recognized using the pharmacognostic properties of both. [14] Both have different physical and chemical qualities in addition to having different therapeutic benefits. HA seeds have a bitterness value of 11,000 [Figure 1]. [15-17]

Leaf microscopy

Fresh leaf transverse sections through the midrib and lamina were placed in glycerin and examined with a compound microscope. Epithelial cells, stomata (type and dispersion), and epidermis hairs (type of rhizomes and distribution) were all observed to be present or absent (Anonymous 1986). [18] May saw the local collection of fresh plant material at Bhadra Wildlife Sanctuary in Karnataka (Southern India), including stem bark, leaves, and inflorescence. The sample was collected, dried in the shade, placed in a bag, and kept at room temperature until needed. [20,21,22] Petroleum ether, chloroform, and ethanol extracts underwent preliminary phytochemical examination using the techniques detailed in Harborne (1984) [23], Trease and Evans (1989) [24], Kokate et al. (1998) [25], and Khandelwal (1988] (2005). [26]

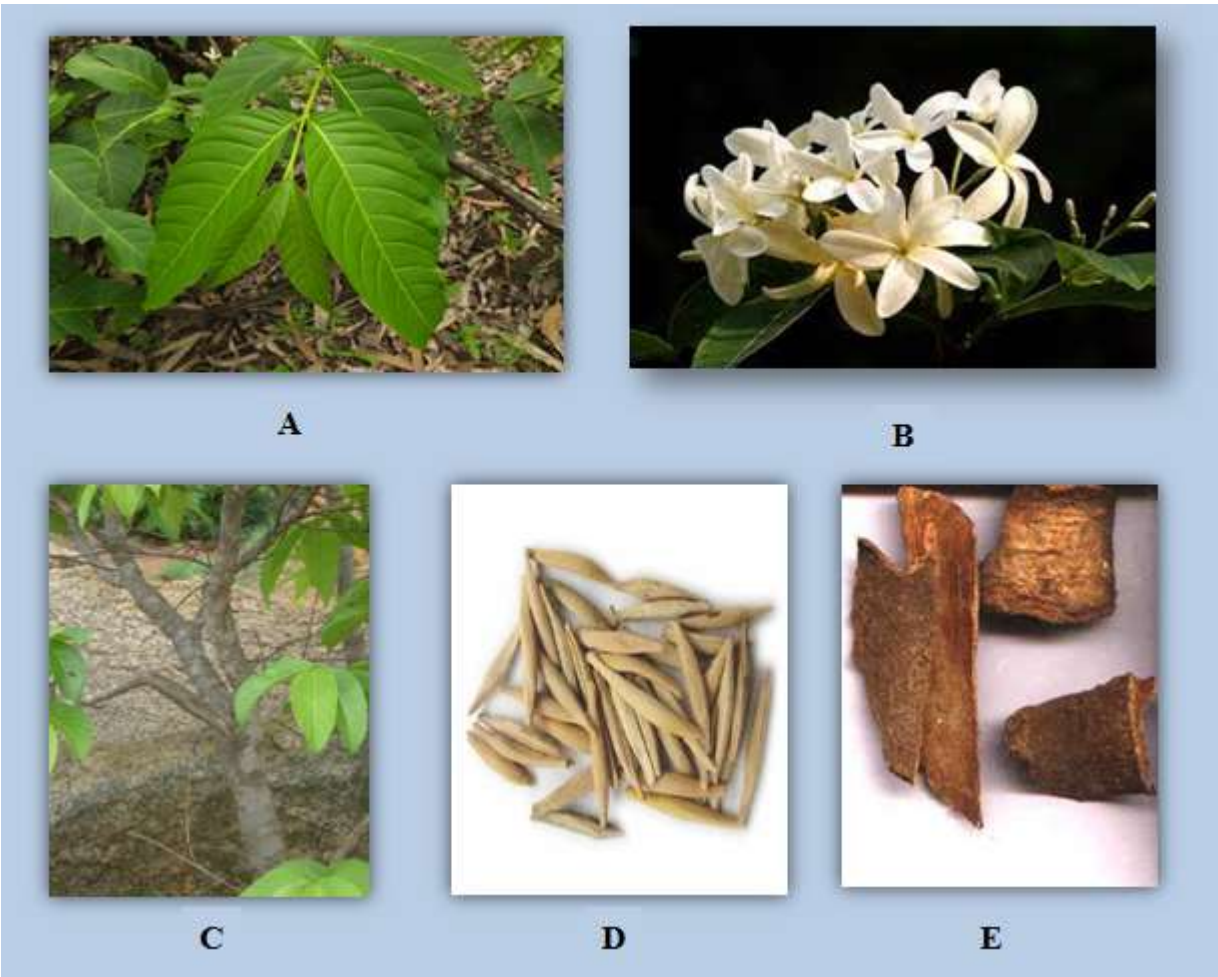


Figure 2: Plant part of Holarrhena Antidysenterica A) Leaves, B) Flower, C) Stem, D) Seeds, E) Bark Morphology [14]- Trees have yearly leaves and are 9 to 12 meters tall. The base of the bark is dry, smoky, and yellowish. Leaf: 4 to 8 cm by 9 to 18 cm. White flower with a strong scent that develops as an inflorescence. Fruit: 20 to 40 x 0.5 to 1 cm, white-spotted pods. Seed: Indrayava, named because it resembles lava, is a smoky, grain-like seed that is 1

cm long and contains 20 to 30 seeds in a cotton-covered pod. blooming from May to June, and bearing fruit in the winter.

Macroscopic Description [27]

The inner surface of the dried stem bark is brownish, rough, and scaly, with a short, granular fracture. The outer surface is beige to brownish horizontally wrinkled & bearing horizontal lenticels. Acrid and bitter to the palate.

Microscopic Description [27]

A transverse section of dried stem bark reveals that the cork is made up of 4–12 rows of tangentially elongated cells, while the cork cambium is made up of a row of thin-walled tangentially elongated cells. The secondary cortex is typically wide, parenchymatous, and interspersed with strands of stone cells. The stone cells are rectangular to oval and have numerous pits that are frequently filled with prismatic crystals of calcium oxalate, non-lignified pericyclic fibers up to 52 mm thick, present in bark, secondary phloem wide consisting of sieve-tubes, companion cells, phloem parenchyma, and stone cells. Stone cells are arranged in tangential rows in a concentric manner and are connected to a crystal sheath that contains calcium oxalate prisms. Medullary rays are typically bi- or triseriate but a few are uniseriate and become wider toward the outer part. These ray cells are made up of thin-walled, radially elongated parenchymatous cells, and they become sclerosed when they are close to the stone.

Chemical constituents

The stem, bark, leaves, and a few of the seeds of *H. antidysenterica* have been determined to contain the majority of the plant's chemical components. Steroid alkaloids, flavonoids, triterpenoids, phenolic acids, tannins, resin, coumarins, saponins, and ergosterol are the main components. [17,28,29]

68 alkaloids present in various parts of H. antidysenterica are listed below:

S. No.	Part of plant	
1	stem bark	Holarrifine (C24H38N2O2), Kurchamide, Kurcholessine,7 Trimethylconkurchine (C24H38N2), (3),-N-Methylholarrhimine (C22H38N2O), (20),-N-Methylholarrhimine (C22H38N2O), NNN'N0-Tetramethylholarrhimine (C25H44N2O), Conessidine (C21H32N2), Holarrhidine (C21H36N2O), Kurchenine (C21H32N2O2), Holarrhessimine (C22H36N2O), Holarrhine (C20H38N2O3), Conkurchi nine (C25H36N2), Kurchamine (C22H36N2), 7a-Hydroxyconessine (C24H40N2O),Kurchilidine (C22H31NO), Neoconessine (isomer of conessine) (C24H40N2), Holadysenterine (C23H38N2O3), Kurchessine (C25H44N2),[30] Lettocine (C17H25NO2), Kurchimine (C22H36N2), Holarrhenine

		(C24H40N2O), Holarrhimine/Kurchicine (C21H36N2O), Holacine (C26H44N2O2),Holafrine (C29H46N2O2), Holadysone (C21H28O4), Holacetine (C21H32N2O3), 3a-Aminoconan- 5-ene (C22H36N2), Dihydroisoconessimine(C23H40N2), Conamine (C22H36N2), Conkurchine (C20H32N2),[31] Pubadysone (C21H26O3), Puboestrene (C20H24O3), Pubamide (C21H27NO3),[32] Holadiene (C22H31NO), Kurchinidine (C21H29NO2), Kurchinine (C19H24O3),[32] Pubescine (C22H26N2O4), Norholadiene (C21H29NO), Pubescimine (C24H40N2O),[32] Holonamine, Regholarrhenine A (C22H31NO2), Regholarrhenine B (C21H29NO2), Regholarrhenine C (C22H34N2),4 Regholarrhenine D (C23H38N2O), Regholarrhenine E, Regholarrhenine F . [31,33]
2	Leaves	Holantosine-A (C28H47NO6), Holantosine-B (C28H45NO5), Holanto sine-C (C28H47NO6), Holantosine-D (C28H45NO5), Holantosine-E (C28H47NO6), Holantosine-F (C28H45NO5), Holarosine A (C30H47 NO6), Holarosine B (C30H47NO6), Holarricine (C21H32N2O3),3 Kurchiphyllamine, Kurchaline,11Kurchiphylline (C23H47NO2). [34]
3	Seeds	Conimine (C22H36N2),[31] Antidysentericine (C23H36N2O).
4	From both stem bark and seeds	20-Aminoconanines, 3-Aminoconanines, 3,20-Diaminopregnanes, 3-Aminopregnans, Conanines, Conarrhimine [C21H34N2], Conessimine/Isoconessimine [C23H38N2], Conessine [C24H40N2], Isoconessine [C24H40N2] and their derivatives. A new steroidal alkaloid was also extracted, characterized and named as holadysenterine corresponded to the molecular formula [C23H38N2O3]. [34,35]

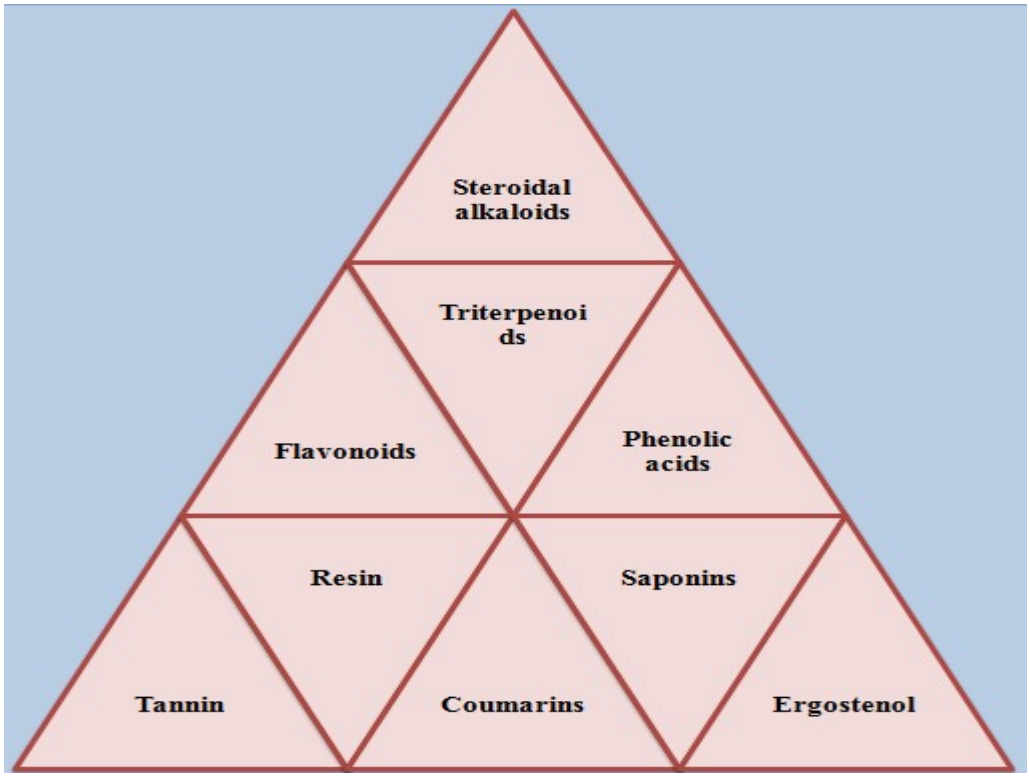


Figure 3: Major phytochemical present in *Holarrhena Antidysenterica*

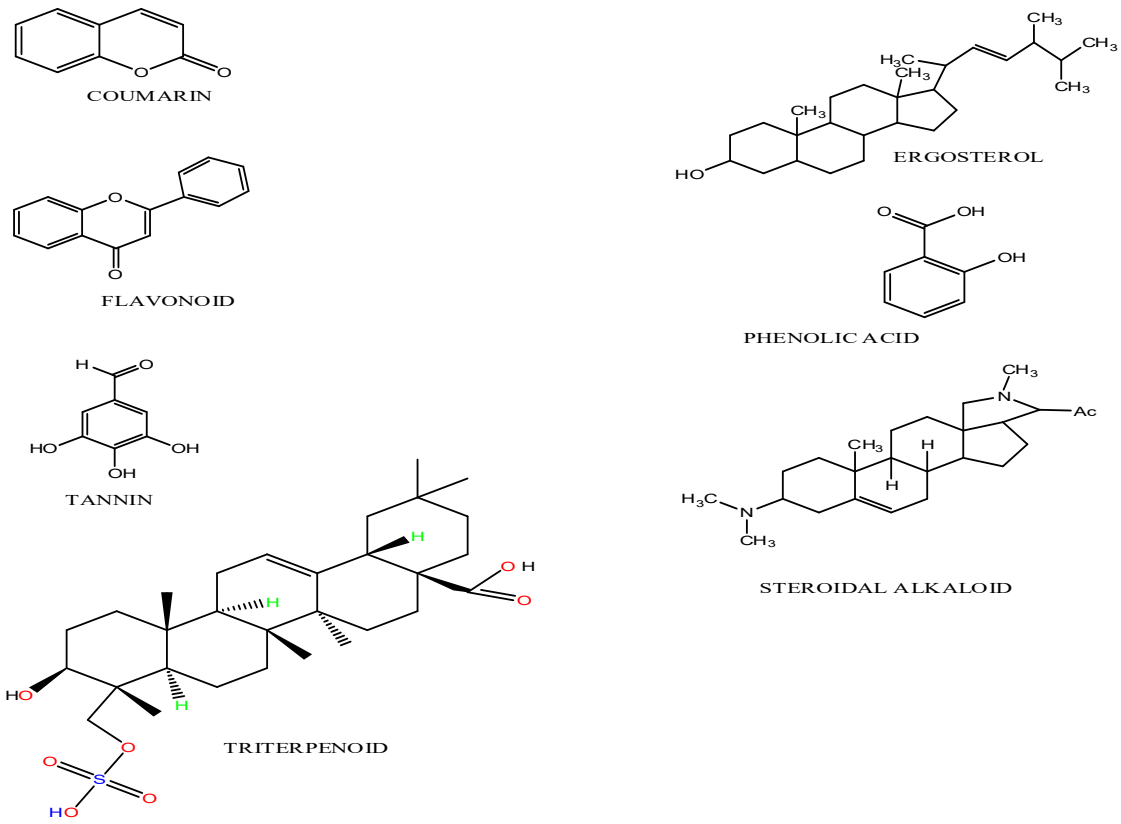


Figure 4: Structure of major phytochemical constituents

PHARMACOLOGICAL ACTIVITES

Anti-amnesic activity

As contrasted to the sick group, the independent STZ groups that received seed ethanol extract after 28 days saw a moderate decline in AChE levels. They also saw dose-dependent inhibition of elevated MDA levels and GSH depletion. Acetylcholinesterase activity corrected cholinergic dysfunction. The anti-amnesic property of Holarrhena antidysenterica was demonstrated by decreased levels of AChE, prevented the level of MDA, and increased glutathione. [36]

Neuroprotective activity

When compared to the diabetic control group, treatment with Methanolic Extract of Holarrhena antidysenterica (MEHA) moderately averted bodyweight loss, a rise in blood glucose, and a moderate depletion in plasma cholesterol. In the current investigation, treatment with MEHA reduced the elevated HbA1c level, which was investigated as a major indication of AGEs. When compared to the non-treated group, the MEHA-treated rats showed improvements in locomotion, indicating the prevention of diabetic neuropathy. [37]

Acetylcholinesterase inhibitory

Acetylcholine esterase was shown to be 91% inhibited by the alkaline extract of seed. [38, 39] Except for huperzine A, which exhibits inhibition at a dosage of 0.015 g/mL, the total alkaloid extraction from seed effectively inhibits acetylcholinesterase at a concentration of 6.1 g/mL. [40] It is preferable to inhibit acetylcholinesterase while treating neurological conditions like Alzheimer's disease. In a study, certain alkaloids from H. antidysenterica were examined for comparable activity because alkaloids from certain plants have been shown to block AChE. With an IC50 value of 4 mM, the separated alkaloids confessimine, isoconessimine, conessimine, conarrhimine, and coniine showed the most significant effects. According to the study's findings, these alkaloids may one day be used in medications for the treatment of neurological illnesses. [41]

Anti-diabetic activity

Plant extracts may have anti-diabetic properties. [42, 43] After 30 minutes of dosing to rats with normal blood sugar levels, a plant's ethanolic extract somewhat reduced plasma glucose levels. Both the ethanolic and the methanolic extract of the plant reduced the levels of blood glucose, total cholesterol, triglycerides, AST, ALT, urea, and serum creatinine. [4, 44] Those parameters indicate that plants possess improved metabolic regulation and effective anti-diabetic action. A critical enzyme for maintaining glucose homeostasis, hepatic glucose-6-phosphatase is negatively controlled by insulin. [45, 46] Following administration of the plant's aqueous extract, these biosensors recovered significantly due to inulin recovery. [47] When it comes to the management of postprandial hyperglycemia, phenolic chemicals and flavonoids found in plant extracts are what causes the resistance of -glucosidase action and subsequently, restrict glucose absorption. [48, 49] In a different investigation, the liver and kidneys' glutamate oxaloacetate transaminase (GOT) and

glutamate pyruvate transaminase (GPT) activities revealed no metabolic toxicity of the hydro-methanolic seed extract. [50]

Anti-urolithic activity

In vitro, calcium oxalate monohydrates (COM) increase cell toxicity and lactate dehydrogenase synthesis, however, hydro-methanolic extracts of seeds only slightly lessen the strength of calcium oxalate crystals and transform them into calcium oxalate dehydrate. In male Wistar rats, extract treatment results in a significant decrease in polyuria, water consumption, calcium ions excretion, and crystal formation. [7]

Anti-bacterial activity and anti-haemorrhoidal action

The plant's extracts from the bark, seeds, and calluses have potential antibacterial action against Staphylococcus, Salmonella, and E. coli. [6] Additionally, the plant prevented enteropathogenic E. coli from sticking to the host epithelial cells. [51, 52] An ayurvedic preparation of stem bark extract known as "Kutaja Tvak Churna" showed therapeutic properties in the case of bleeding piles. [53]

Analgesic Activity and Anti-inflammatory

The methanolic leaf extract of the plant prevented the swelling of the rat paws caused by carrageenan. H. glabra bark extract in methanol in colitis caused by 2,4-Dinitrobenzene sulfonic acid in male albino Wistar rats, antidysenterica showed decreased levels of nitric oxide and malondialdehyde and higher levels of superoxide dismutase and glutathione. Additionally, the rats were resistant to mucosal layer inflammation, goblet cell rupture, and inflammatory cellular infiltration. [54] In addition, it improved tail-flick latency and reduced the writhing response brought on by acetic acid in a dose-dependent manner, both of which showed the effectiveness of the analgesic.[55,56] In albino mice, ethanol plant extract reduced the writhing reflex, demonstrating its analgesic properties. [57,58] Treatment with H. antidysenterica also reduced inflammation in the mucosal layer, inflammatory cellular infiltration, and goblet cell rupture. [5] Ayurveda mentions the analgesic properties of H. antidysenterica. Swiss albino mice and Wistar rats both showed analgesic effects from a methanol bark extract. [59]

Anti-malarial property

When given at a dose of 10 mg/kg, conessine, which was isolated from the plant's stem bark, displayed an effective anti-plasmodial property, with a repeatable inhibitory concentration of 1.3 g/ml in vitro trials and an 88.95% suppression of parasitemia in vivo experiments. Bark extract showed noteworthy results in a laboratory trial and showed anti-malarial property resistance in albino mice that were infected with Plasmodium falciparum and Plasmodium berghei. Alkaline phosphatase (ALP) and bilirubin levels were elevated as a result of malarial infection, which is a sign of hepatocytic damage. [60,61]

Anti-diarrheal activity

When given with an ethanolic extract of the seed, rats with castor oil and E. coli-induced diarrhea showed an increase in the density of their dry stools and a decrease in defecation drops. [55] The resistance of bark extracts to enteroinvasive E. coli (EIEC), Salmonella enteritidis, Shigella boydii, and Shigella flexneri is widely established. [62] Castor oil, a commercially available preparation of *H. antidysenterica*, was used to produce diarrhea in rats. Kutaja parpati Vati exhibited a substantial reduction in watery diarrhea and small intestine motility. Additionally, it demonstrated a considerable 67.55% protection from enter polling brought on by castor oil. [63]

Anti-mutagenic and Anti-hypertensive Activity

Salmonella typhimurium strains subjected to mutagenicity were discovered to have anti-mutagenic efficacy in methanolic extracts of plant bark. [64] After administering ethanolic extracts of plant seeds, adequate 24% angiotensin-converting enzyme (ACE) inhibition was discovered. [65] Endophytes, which showed 60% angiotensin-converting enzyme (ACE) inhibition, were made from the fungal extract of H. antidysenterica and diluted in 20% methanol for antihypertensive action. [66]

Antioxidant/free radical scavenging property

Free radical scavenging substances repair and shield tissues from oxidative injury. An anti-oxidant feature that scavenges superoxide ions and OH ions with a reduced ability to convert ferric ions to ferrous ions was recently discovered in methanolic leaf extracts of plants. Furthermore, it was shown that these effects matched the extract's concentration. [67] An aqueous methanolic extract of the seed was found to prevent the oxidation of lipids, the deterioration of H2O2, the degradation of deoxyribose by OH ions, the degradation of H2O2, and the generation of nitrite when exposed to oxygen. [4]

Diuretic activity

Wistar rats exposed to aqueous seed extracts of the plant at doses ranging from 30 to 100 mg/kg developed excessive urine production. It was found that the amount of sodium and potassium ions discharged through urine had significantly increased. [68, 69]

Anti-amoebic activity

For two weeks, routine ingestion of the bark powder completely kept amoebic patients alive. One of the ingredients of "Amoebian cap," a treatment for amoebiasis, was investigated for its therapeutic impact against amoebiasis. [70 ,71]

Anthelminthic and anti-microbial activity

Anti-microbial and anthelminthic action, on earthworms, aqueous extract and ethanolic extracts of plant bark showed a significant amount of in-vitro activity. Depending on the extract concentration, ethanolic extracts of seeds displayed resistance to EPEC bacteria. The ethanolic extract is being looked into as a powerful antibacterial agent because EPEC showed resistance to a variety of medicines. [53, 72] In a further experiment, it was discovered that pets. ether bark extract

inhibited E. coli at a minimum inhibitory concentration (MIC) of 50 mg/ml while methanol and chloroform extracts were inhibited at greater doses. But when compared to other plants, *Holarrhena antidysenterica* showed a high amount of action. [73]

Anti-MRSA activity

Plant bark extract was discovered to have anti-methicillin-resistant Staphylococcus aureus (Anti-MRSA) properties when the minimum inhibitory concentration was between 0.3 and 3.25 mg/mL and the inhibition zone size ranged from 11 to 44 mm. [74]

Hepatoprotective effect and Anti-convulsant activity

A study revealed that treatment of plants is likely to reduce the severity of liver damage, and the formation of fibrous septa and also restricts liver weight loss induced by PCM. Therefore, the plant is considered a prevailing hepatoprotective agent. [75] Ethanolic extract of the plant exhibited anticonvulsant activity in mice and hence possesses promising anticonvulsant activity against MES and PTZ-induced seizures. [76]

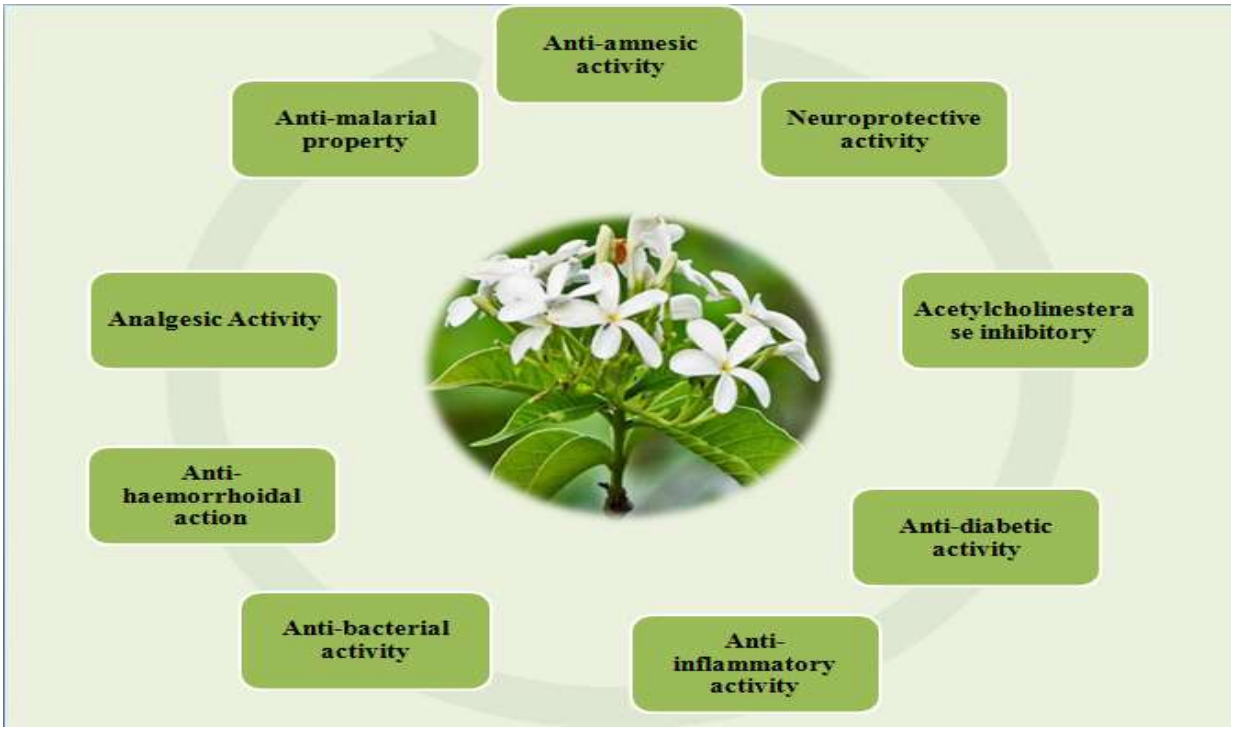


Figure 5: Shows pharmacological activities of *Holarrhena Antidysenterica*

THERAPEUTIC USES

Diarrhea/ Dysentry

Kutaj seed, also known as Indrajao, is well recognized in Ayurveda for treating severe diarrhea, amoebic dysentery, bacillary dysentery, giardiasis, parasite infection, and many other digestive

ailments by drying up the bowels and eliminating undesirable bacteria. [77, 78] It is used to control bowel movements and restore damaged cells in the intestinal wall, which helps to prevent inflammatory bowel diseases like Crohn's disease, colitis, and irritable bowel syndrome (IBD). Bleeding dysentery is treated using khat (decoction) made from H. antidysenterica and honey. Kutaj aids in the treatment of anorexia and agnideepan (activation of the digestive fire). [79]

Psoriasis – It is the most common skin condition worldwide. Kutaj contains a variety of photo materials, including lipids, saponins, tannins, alkaloids, phenols, steroids, flavonoids, and phenolic acids, which can be used to treat a variety of skin problems effectively. Excellent antipsoriatic properties of kutaj extracts encourage the skin's natural creation of collagen, which lessens the symptoms of psoriasis. [80] Kutaj powder is applied to psoriasis along with butter or coconut oil. [81]

Diabetes

The herb kutaj is beneficial for Madhumeha. It controls the body's insulin output and lowers elevated sugar levels. [82]

Hemorrhoids

Due to their astringent qualities, Kutaja Tvak Churna has the ability to stop bleeding, which allows it to treat Shonitarsha or bleeding piles. In Ayurveda, piles are referred to as Arsh and are caused by a faulty weight loss strategy and a sedentary lifestyle. An essential plant therapy for the treatment of bleeding piles is *H. antidysenterica*. [83]

Renal diseases

H. Antiurolithic properties exist in antidysenterica. It prevents the kidneys' calcium oxalate crystals from accumulating. Additionally, it possesses antioxidant properties that may help avoid kidney stones as well as effects that protect renal epithelial cells. It is also helpful for urinary issues that are accompanied by painful and burning urine. [84]

Inflammation

By reducing pain and inflammation, kutaj's antipyretic and anti-inflammatory properties aid to manage arthritis. Relieving cramping and stomach pain is also quite beneficial. [85]

Dementia

Dementia refers to memory, cognitive, and behavioral impairment that makes it difficult to carry out daily responsibilities. The results of studies suggest that the possible neuroprotective and antioxidant activities of the extract of *Holarrhena antidysentrica* may be helpful in the treatment of dementia. [82]

Malaria

Kutaj bark chloroform extracts showed significantly in vitro or in vivo anti-malarial efficacy. The roots of Holarrhena antidysentrica are particularly effective against P. falciparum which is resistant to artemisinin and chloroquine (K1, Dd2). [86]

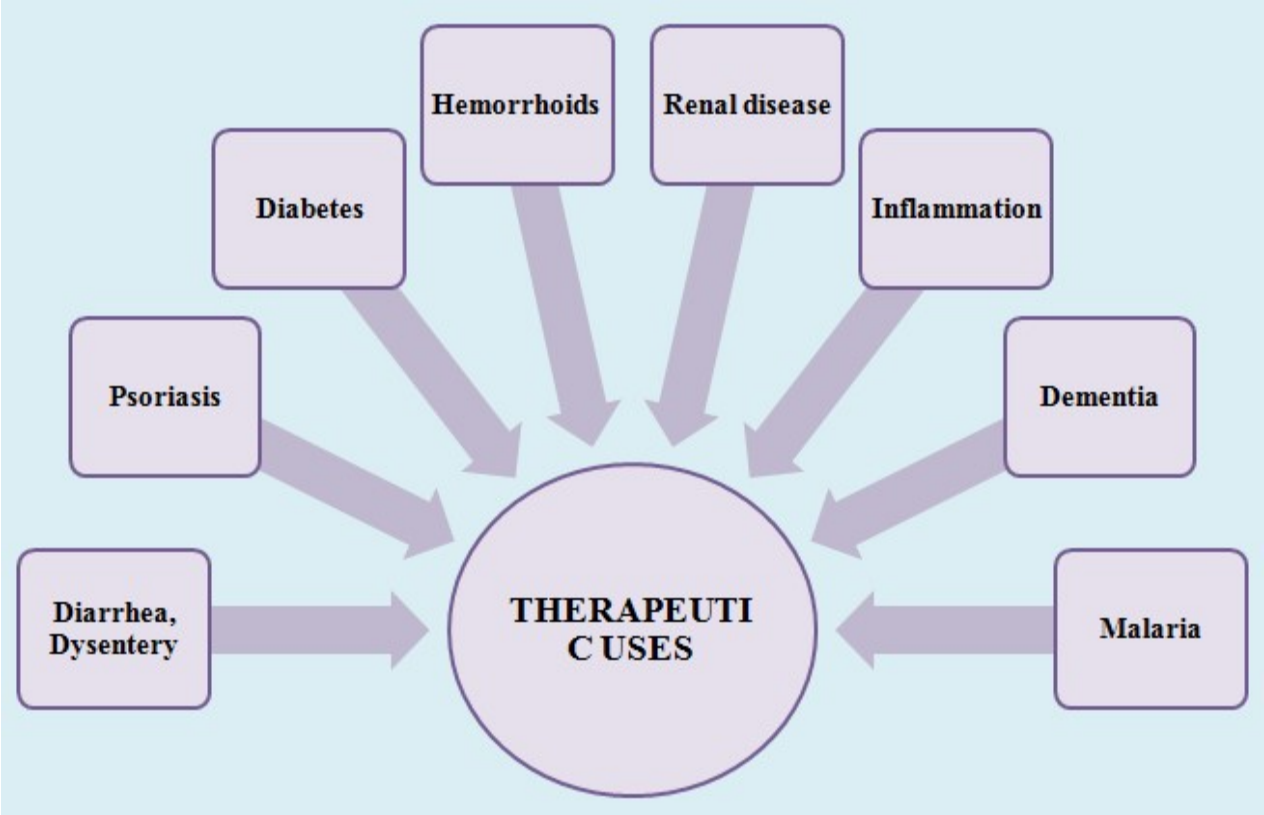


Figure 6: Shows therapeutic uses of *Holarrhena Antidysenterica*

CLINICAL PHARMACOLOGY STUDIES

Singh (1985) [87] reported the clinical efficacy of HA stem bark extract in forty patients with 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. Chaturvedi [88] 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 the sensation of heat in the abdomen and head, nausea, flatulence, constipation, agitation, nervousness and insomnia, vertigo, syncope, weakness and emptiness, xerostomia, and a lightness of the body. One patient reported a decrease in body temperature. Pal[89] *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. Panda[36] *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.

TOXICITY STUDIES

The two types of toxicity studies that were conducted on mice and rats include sub-acute toxicity studies on rats and acute toxicity studies on mice. The findings of the study showed that higher

drug intake during acute toxicity by histopathological testing on animals resulted in lower mortality rates in cases of acute toxicity. Investigations on sub-acute toxicity reveal normal results and no appreciable changes in the animal's blood hematology or other organ studies.

CONCLUSION

There are enormous ways of natural treatment that are used for decades. *Holarrhena antidysenterica* (HA) is one of the promising herbal plant with a wide range of pharmacological actions it is used as therapeutically in modern formulations due to its effective valve and safety. *Holarrhena antidysenterica* has been basically used to treat affliction like constipation, looseness of the bowels, colic, anti-oxidant activity, and against malarial activity. This plant contains obscure chemical constituents that are precious for the researcher to synthesize and formulates the novel medications from this plant against different infections.

REFERENCE

1. Kavitha D, Shilpa PN, Niranjali Devaraj S. Antibacterial and antidiarrhoeal effects of alkaloids of *holarrhena antidysenterica* wall. Indian J. Exp. Biol. 2004; 42: 589-594.
2. Gopal, Chauhen MG. *Holarrena antidysenterica*-A review Suppl to cultivation and utilization of medicinal plants, Ed Handa SS, Kaul MK, Jammu Tawi, Regional research laboratory; 1996:223-41.
3. Mrinal, Navjeet Singh. A Review on Pharmacological Aspects of *Holarrhena antidysenterica*. Sch. Acad. J. Pharm.2018; 7(12):488-492.
4. Warrier PK, Nambiar VP, Ramankutty C. Indian medicinal plant: A compendium of 500 species, Orient Longman, Delhi, 1994; 191- 194.
5. Sharma PC, Pyelne MB, Dennis TJ. Database on medicinal plants used in ayurveda, Central council for research in ayurveda and siddha, New Delhi, 2004; 2:550.
6. Umashanker KPD, Chandra S, Sharma J. Antidiabetic efficacy of ethanolic extract of *holarrhena antidysenterica* seeds in streptozotocin – induced diabetic rats and its influence on certain biochemical parameters. *J. drug deliv. ther*. 2012; 2(4): 159-162. https://doi.org/10.22270/jddt.v2i4.187.
7. Darji VC, Deshpande S, Bariya AH. Comparison between the effect of aqueous and methanolic extracts of *holarrhena antidysenterica* bark against experimentally induced inflammatory bowel disease. Int. Res. J. Pharm. 2013; 4(1): 131-134.
8. Mahato S, Mehta A and Roy S. Studies on antibacterial effects of bark, seed and callus extracts of *holarrhena antidysenterica* wall. *BioScan*. 2013; 8(2): 717-721.
9. Khan A, Khan S R, Gilani A.H, Studies on the *in vitro* and *in vivo* antiurolithic activity of holarrhena antidysenterica. Urol. Res. 2012; 40(6): 671-681.
10. Rajalakshmi C. GC-MS analysis of the bark of *holarrhena antidysenterica*. J. pharmacogn. phytochem. 2018; 7(4): 797-800.
11. Hasmah SN, Bhatt A, Keng CL. Micropropagation of Assam Karanda (Carissa carandas Linn). Pertanika J. Trop. Agric. Sci. 2013; 36(1): 89–98.

12. Bhattacharjee SK, Handbook of Medicinal Plants Jaipur, India: Pointer Publishers 2000;183.
13. Sanger R, Singh DC, Chaubey S, Kumar N. Identification of pum kutaja and stri kutaja mentioned in the Ayurvedic Literature. Int. J. Ayurveda Res. 2016; 4(10): 37-40.
14. Deshpande A.P., Ranade S. Dravyaguna Vigyan. Part 1&2. Pune: A.R. Nandurkar, Proficient Publishing House; Ju2010:476-479.
15. Akhtar P, Ali M, Sharma MP, Farooqi H, Mir SR, Khan HN. Development of quality standards of *holarrhena antidysenterica* (Linn.) bark. Recent Res Sci Technol 2010; 3: 73-80.
16. Srivastava R. A review on phytochemical, pharmacological, and pharmacognostic profile of Wrightia tinctoria: Adulterant of Kurchi. Pharmacognosy Rev. 2014; 8: 36-44. https://doi.org/10.4103%2F0973-7847.125528.
17. Jolly CI, Mechery NR. Comparative pharmacognostic, physicochemical, and antibacterial studies on seeds of Hola.
18. Anonymous. African Pharmacopoeia: General Methods for Analysis. OAU/STRC Scientific Publications, Lagos. 1986; 2: 1-5, 137-149, 223-237.
19. Chase CR, Pratt RJ. Fluorescence of powdered vegetable drugs with particular reference to the development of a system of identification. J. Am. Pharm. Assoc. 1949: 38, 324-331. https://doi.org/10.1002/jps.3030380612.
20. Kokoski J, Kokoski R, Salma FJ. Fluorescence of powdered vegetable drugs under ultraviolet radiation. J. Am. Pharm. Assoc.1959: 47, 75-78. https://doi.org/10.1002/jps.3030471010.
21. Anonymous. Indian Pharmacopoeia. New Delhi, Government of India Publication, 1966; (2): 367-370.
22. Anonymous. Official Methods of Analysis (AOAC). In Helrich K, Association of Official Analytical Chemists Inc.1984; (14): 1010-1039
23. Harborne JJ. Phytochemical methods: A guide to modern techniques of plant analysis. Chapman and Hall, New York.1984; (2): 85.
24. Trease GE, Evans WC. Pharmacognosy. ELBS Publication, Delhi. 1989; (13): 171.
25. Kokate CK, Purohit AP, Gokhale SB. Pharmacognosy. Nirali Prakashan, Pune. 1998; (23): 106-114.
26. Khandelwal KR. Practical Pharmacognosy: Techniques and Experiments. Nirali Prakashan, Pune. 2005; (13): 149-156.
27. Government of India, Ministry of Health and Family Welfare, Department of AYUSH. The Ayurvedic Pharmacopoeia of India. Delhi: The controller of Publications. 2001; (1).
28. Patel JD, Patel DK, Shrivastava A, Kumar V. Screening of plant extracts used in traditional antidiarrhoeal medicines against pathogenic Escherichia coli. Sci World. 2008; 6(6): 63-67. https://doi.org/10.3126/sw.v6i6.2636.
29. Verma G, Dua VK, Agarwal DD, Atul PK. Anti-malarial activity of Holarrhena

antidysenterica and Viola canescens, plants traditionally used against malaria in the Garhwal region of north-west Himalaya. Malar J. 2011; 10: 20.
30. Daniel M. Medicinal Plants: Chemistry and Properties. Enfield, NH: Science; 2006.
31. Usmani SB. Studies on the chemical constituents of Holarrhena antidysenterica L. and the b-carboline series of bases and their pharmacological activity. Thesis. Pakistan: H.E.J. Research Institute of Chemistry, University of Karachi; 1995.
32. Perez-Jimenez M, López-Soto M B, Cos-Terrer J. In vitro callus induction from adult tissues of peach (Prunus persica L. Batsch). In Vitro Cell. Dev. Biol. – Plant. 2013; 49(1): 79–84.
33. Alauddin M, Martin-Smith M. Biological activity in steroids possessing nitrogen atoms. J Pharm Pharmacol. 1962; 14: 469-495.
34. Kumar N, Singh B, Bhandari P, Gupta AP, Kaul VK. Steroidal alkaloids from *Holarrhena antidysenterica* (L.) wall. Chem Pharm Bull. 2007; 55(6): 912-914. https://doi.org/10.1248/cpb.55.912.
35. Yang ZD, Duan DZ, Xue WW, Yao XJ, Li S. Steroidal alkaloids from *Holarrhena antidysenterica* as acetylcholinesterase and the investigation for structure-activity relationships. Life Sci. 2012; 90: 929-933. https://doi.org/10.1016/j.lfs.2012.04.017.
36. Jamadagni PS, Pawar SD, Jamadagni SB, Chougule S, Gaidhani SN and Murthy SN. Review of *Holarrhena Antidysenterica* (L.) Wall. Ex A. DC. Pharmacognostic, Pharmacological, and Toxicological Perspective. Pharmacognosy Review. 2017; 11(22): 141–144. doi:10.4103/phrev.phrev_31_16.
37. Mrinal, Navjeet Singh, Nitin Bansal. Anti-amnesic activity of *Holarrhena Antidysenterica* extract in streptozotocin-induced memory deficient rats. Sch. Acad. J. Pharm. 2016; 5(8): 317-325. DOI: 10.21276/sajp.2016.5.8.2.
38. Bansal N, Singh N, Mrinal. *Holarrhena antidysenterica* extract promotes recovery of peripheral neuropathy in diabetic rats. *Am. j. PharmTech res*. 2016; 6(4): 2249- 338.
39. Ellman GL, Courtney KD, Andres V, Featherstone RM. A new and rapid colorimetric determination of acetylcholinesterase activity. Biochem. Pharmacol. 1961; 7(2): 88-95. https://doi.org/10.1016/0006-2952(61)90145-9.
40. Orhan I, Sener B, Choudhary MI, Khalid A. Acetylcholinesterase and butyrylcholinesterase inhibitory activity of some Turkish medicinal plants. J. Ethnopharmacol. 2004; 91(1): 57-60. https://doi.org/10.1016/j.jep.2003.11.016.
41. Daniel, M. Medicinal Plants: Chemistry and Properties; Science: Enfield, NH, USA, 2006.
42. Stephenson, R.P. The pharmacological properties of conessine, isoconessine, and neoconessine. Br. J. Pharmacol. 1948; 3: 237–245. doi:10.1111/j.1476-5381.1948.tb00381.x.
43. Kazi MA, Tushar KB, Suvra M, Bikash RB, Debidas G. Attenuation of diabetic disorders in experimentally induced diabetic rat by methanol extract of seed of Holarrhena antidysenterica. Int. J. Pharmtech Res. 2010; 1: 1205-1211.
44. Pradeep Sahu, Anindh Sharma, Tanushree Chatterjee. Natural Products with Potent

Hypoglycemic Activity. Research J. Pharm. and Tech. 2010; 3(3): 650-656.
45. Mana S, Singhal S, Sharma NK, Singh D. Hypoglycemic effect of *Holarrhena antidysenterica* seeds on streptozotocin induced diabetic rats. Int. J. Pharmtech Res. 2010; 2(2): 1325-1329.
46. Berg JM, Tymoczko JL, Stryer L. Glycolysis and gluconeogenesis. In: Biochemistry. Berg JM, Tymoczko JL, Stryer L. (Eds). W.H. Freeman: New York. 2001; 425-464. https://doi.org/10.2169/naika.99.3077.
47. Das D. Biochemistry. Kolkata, Academic Publishers. 2002; (11): 448.
48. Praparatana R, Maliyam P, Barrows LR, Puttarak P. Flavonoids and Phenols, the Potential Anti-Diabetic Compounds from Bauhinia strychnifolia Craib. Stem. Molecules. 2022;27(8):2393. doi:10.3390/molecules27082393.
49. Ali KM, Chatterjeea K, Dea D, Janaa K, Beraa TK, Ghosha D. Inhibitory effect of hydro-methanolic extract of seed of *Holarrhena antidysenterica* on alpha-glucosidase activity and postprandial blood glucose level in normoglycemic rats. J. Ethnopharmacol. 2011; 135: 194–196. https://doi.org/10.1016/j.jep.2011.02.034.
50. Ali KM, Chatterjee K, De D, Bera TK, Ghosh D. Efficacy of aqueous extract of seed of *Holarrhena antidysenterica* for the management of diabetes in experimental model rat: a correlative study with antihyperlipidemic activity. Int J Appl Res Nat Prod. 2009; 2(3): 13-21.
51. Monago Comfort C, Nwodo O. Fred C. Antidiabetic effects of crude flavanoid and alkaloid of Abrus precatorius Linn seed in alloxan diabetic rabbits. Research J. Pharmacognosy and Phytochemistry. 2010; 2(4): 331-335.
52. Kavitha D, Niranjali S. Inhibition of enteropathogenic Escherichia coli adhesion on host epithelial cells by *Holarrhena antidysenterica* (L.) wall. Phytother. Res. 2009; 23: 1229–1236. https://doi.org/10.1002/ptr.2520.
53. Premlata S, Krishan Kumar M, Padma K. Estimation of antibacterial efficacy in alkaloids of Anogeissus rotundifolia an indigenous medicinal plant against some pathogenic micro-organisms. Asian J. Research Chem. 2018; 11(2): 432-440. DOI: 10.5958/0974-4150.2018.00079.2.
54. Darji VC, Deshpande SS, Bariya AH. Effects of methanolic extract of *Holarrhena antidysenterica* bark against experimentally induced inflammatory bowel disease in rats. Int Res J Pharm. 2012; 3(9): 152-154.
55. Kumar N, Singh B, Bhandari P, Gupta AP, Kaul VK. Steroidal alkaloids from *Holarrhena antidysenterica* (L.) wall. Chem. Pharma. Bull. 2007; 55: 912–914. https://doi.org/10.1248/cpb.55.912.
56. Ganapathy PS, Ramachandra YL, Rai SP. In vitro antioxidant activity of *Holarrhena antidysenterica* Wall. Methanolic leaf extract. *J Basic Clin Physiol Pharmacol*. 2011; 2(4): 175-178. PMID: 24826020.
57. Pankaj R, Manju N, Sunil S, Milind P. Anti-inflammatory activity of petroleum ether extract of seeds of Ocimum Basilicum Linn. Research J. Pharm. and Tech. 2009; 2(3): 589-

591.
58. Shwetha C, Latha KP, Asha K. Study on analgesic activity of *Holarrhena antidysenterica* leaves. Int. J. Herb. Med. 2014; 2(3): 14-16.
59. Solanki R, Madat D, Chauhan K, Adeshara SP. Analgesic activity of *Holarrhena antidysenterica* (Apocynaceae) bark. Int J Pharma Phytochem Res. 2010; 2(4): 5-7. doi:10.5455/javar.2019.f379.
60. Manpreet K, Harinder K. Analgesic activity of roots of *Aralia racemosa*. Research J. Pharm. and Tech. 2011; 4(12): 1896-1897.
61. Dua VK, Verma G, Singh B, Rajan A, Bagai U, Agarwal DD, Gupta NC, Kumar S, Rastogi A. Anti-malarial property of steroidal alkaloid conessine isolated from the bark of Holarrhena antidysenterica. Malar. J. 2013; 12(1): 194. https://doi.org/10.1186/1475-2875-12-194.
62. Takate S.B, Pokharkar R.D, Chopade V.V. Gite V.N. Hepatoprotective activity of the water extract of Launaeaintybacea (Jacq)beauv in paracetamol induced hepatotoxicity in albino rats. Research J. Pharm. and Tech. 2010; 3(3): 815-817.
63. Dey A, De JN. Ethnobotanical Survey of Purulia district, West Bengal, India for medicinal plants used against gastrointestinal disorders. J. Ethnopharmacol. 2012; 143: 68-80. https://doi.org/10.1016/j.jep.2012.05.064.
64. Gupta K, Karale S, Warad V. Anti-diarrhoeal activity of a polyherbal formulation in various animal models of diarrhoea. Int. Res. J. Pharm. 2012; 3(8): 289-290. http://dx.doi.org/10.5958/0974-360X.2020.00362.5.
65. Lin J, Opoku AR, Geheeb-Keller M, Hutchings AD, Terblanche SE, Jager AK, Van Staden J. Preliminary screening of some traditional Zulu medicinal plants for anti-inflammatory and antimicrobial activities. J. Ethnopharmacol. 1999; 68: 267-274. https://doi.org/10.1016/S0378-8741(99)00130-0.
66. Somanadhan B, Varughese G, Palpu P, Sreedharan R, Gudiksen L, Smitt UW, Nyman U. An ethnopharmacological survey for potential angiotensin converting enzyme inhibitors from Indian medicinal plants. J. Ethnopharmacol. 1999; 65(2):103-112. https://doi.org/10.1016/S0378-8741(98)00201-3.
67. Guha Bakshi DN, P Sensarma and DC Pal A, Lexicon of Medicinal Plants in India. Calcutta, India: Naya Prokash Publishers. 2001; 2: 356-358.
68. Aqil F, Zahin M, Ahmad I. Antimutagenic activity of methanolic extracts of four ayurvedic medicinal plants. Indian J. Exp. Biol. 2008; 46(9): 668-672.
69. Khan A, Bashir S, Gilani AH. An in vivo study on the diuretic activity of *Holarrhena antidysenterica*. Afr. J. Pharmacy Pharmacol. 2012; 6(7): 454-458. DOI: 10.5897/AJPP11.395.
70. Sirisha N, Sreenivasulu M, Sangeeta K, Swarna Latha G, Lakshmi Devi A, Madhusudhana Chetty C. A review on herbal diuretics. Research J. Pharm. and Tech. March 2011; 4(3): 335-348.
71. Shahabuddin KU, Sarwar MS, Mohiuddin E. Clinical evaluation of some herbal medicine

for amoebiasis. Pak J Pharm Sci. 2006; 23(2): 9-12.
72. Bhattacharjee S, Guha N, Dutta G, Chakraborty M, Jana M, Paul S. Formulation and evaluation of sustained release matrix tablet of anti-amoebic drug by natural polymers. Research J. Pharm. and Tech. 2017; 10(7): 2041-2046. http://dx.doi.org/10.5958/0974-360X.2017.00356.0.
73. Patil R, Devkar S, Pawar P, Pattewar A. In-vitro anthelminthic activity of *Holarrhena antidysenterica* bark. Int. j. pharm. res. dev. 2012; 4(3): 147- 150.
74. Patel JD, Patel DK, Shrivastava A, Kumar V. Screening of plant extracts used in traditional antidiarrhoeal medicines against pathogenic Escherichia coli. *Sci. World J*. 2008; 6(6): 63-67. https://doi.org/10.3126/sw.v6i6.2636.
75. Farrukh A, Iqbal A, Mohd O. Evaluation of anti-methicillinresistant Staphylococcus aureus (MRSA) activity and synergy of some bioactive plant extracts. Biotechnol. J. 2006; 1:1093–1102. https://doi.org/10.1002/biot.200600130.
76. Verma P, Srivastava S, Rao VC. Hepatoprotective effect of ethanolic extract of *Holarrhena antidysenterica* against paracetamol induced toxicity in wistar rats. Research J. Pharm. and Tech. 2018; 11(4): 1633-1639. DOI: 10.5958/0974-360X.2018.00304.9.
77. Vandana K, Singh B, Kumar A, Singh G. Assessment of effect of Kutaja (*Holarrhena antidysenterica*, Wall) in different Doshika Atisara in infants: A clinical study. J Educ Res. Indian Medicine. 2017; 1. http://dx.doi.org/10.5455/JREIM.82-1501302642.
78. Danielle. Kutaja: An ayurvedic herb for dysentery, diarrhea, and parasitic infection svastha ayurveda. 2021.
79. Chauhan M. Indrajao (*Holarrhena antidysenterica*) - health benefits, uses, medicinal properties. Planet Ayurveda. 2020.
80. Singhal P, Sharma S. Anti-Psoriatic effect of Kutaja: A Review Study. *Int. j. appl. ayurved res.* 2018; 3(7): 1103-1106.
81. Shenoy S, Kumar A. Pharmaceutical and therapeutical study of Stree Kutaja Taila with special reference to autoimmune skin disorders. J. sci. innov. res. 2020; 9(1): 7-10.
82. Bansal N, Singh N. Antiamnesic activity of *Holarrhena antidysenterica* extract in streptozotocin induced memory deficient rats. Sch. Acad. J. Pharm. 2016; 5(8): 317-325. DOI: 10.21276/sajp.2016.5.8.2.
83. Pal A, Sharma P, Mukharjee P. A clinical study of Kutaja (*Holarrhena Antidysenterica* Wall) on shonitarsha. Ayu journal. 2009; 30(4): 369-372.
84. Siddiqui BS, Usmani SB, Ali ST, Begum S, Rizwan GH. Further constituents from the bark of H. pubescent. Phytochemistry. 2001; 58: 1199–1204. https://doi.org/10.1016/S0031-9422(01)00330-2.
85. Basu S. Kutaja Ghana Vati – benefits, uses, method, dosage and side effects. Netmeds. 2019.
86. Zahara K, Panda S, Swain s, Luyten W. Metabolic diversity and therapeutic potential of Holarrhena pubescens: An important ethnomedicinal plant. Biomolecules 2020. https://doi.org/10.3390/biom10091341.

87. Singh KK, Maheshwari JK. Traditional phytotherapy amongst the tribals of Varanasi district of UP. J Econ Taxon Bot. 1983; 4: 829.
88. Chaturvedi GN, Singh KP. Side effects of a traditional indigenous drug-Kutaja (*Holarrhena antidysenterica*). Indian J Physiol Pharmacol. 1983; 27: 255-6. PMID: 6668057.
89. Bhadane BS, Patil RH. Isolation, purification, and characterization of antioxidative steroid derivative from methanolic extract of Carissa carandas (L.) leaves. Biocatal. Agric. Biotechnol. 2017; 10: 216–223. https://doi.org/10.1016/j.bcab.2017.03.012.