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Review Article

Holarrhena antidysenterica in Inflammatory Bowel Disease: a potential review

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Abstract

Holarrhena antidysenterica belongs to the Apocynaceae family and is generally known as kurchi in Hindi. It is a small deciduous tree found in arid woods throughout the world including India. *H. Antidysenterica* is commonly used in Indian traditional medicine to treat Inflammatory Bowel disease, dysentery, diarrhoea and worms in the intestines. Plant parts like bark are useful in antimicrobial, anti-inflammatory and analgesic treatments, amoebiasis, chronic bronchitis, boils, and ulcers. The Phytoconstituents found in the plant ergosterol, flavonoids, phenolic acids, resins, saponins, steroidal alkaloids, coumarins, tannins and triterpenoids. Anti-amnesic, anti-diabetic, antibacterial action, anti-inflammatory, anti-diarrhoeal, antioxidant/free radical activity , radical scavenging, diuretic, anti-amoebic, anthelmintic and anti-microbial effects are found as pharmacological properties of *Holarrhena antidysenterica*. *H. antidysenterica* bark contains alkaloids the most important of which is the steroidal alkaloid conessine which is the major therapeutic constituent. Conarrhimine, Conimine, Conamine, Conessidine, Isoconessimine, Dimethyl Conkurchine and Holarrhimine are among the various alkaloids studied. The bark also includes gum, resin, tannin, lupeol and the digitenol glycoside Holadysone in addition to alkaloids. Bark of *Holarrhena antidysenterica* is used to treat malaria, chest infections, asthma, bronchopneumonia, stomach disorders, dyspepsia, diarrhoea and dysentery.

Keywords: HA- *Holarrhena antidysenterica,* IBD- Inflammatory Bowel Disease, Collitus

1 Introduction:

Holarrhena antidysenterica (Family - Apocynaceae, Common Name: Kutaza, Bitter Oleander, Kurchi) is a large tree, 9-10 feet tall, abundant in sub Himalayan tract and mountainous areas. The seeds are linear or oblong concave with a long coma shape, light brown in color and showing epigeal germination. The Unani and Ayurvedic medicine system uses this excellent drug against many infectious diseases caused by helminthes, Staphylococcus aureus, Entamoeba histolytica, and Escherichia coli infections. The bark and seeds of HA used in diarrehoea, ashthma,piles , amoebic dysentery [1] . *H. antidysenterica* produces gastrointestinal tract activation by activating histamine receptors and relaxes the gastrointestinal tract by blocking the Ca ++ channel, which provides a basic reason for its usefulness in gastrointestinal disorders such as constipation and diarrhea [2]. Alkaloids are the major elements in HA and are responsible for a variety of actions. Alkaloids are usually insoluble in water however the HA plant contains conessine an alkaloid that is soluble in water and has a variety of therapeutic effects. Other alkaloids that are found in nature and have a variety of pharmacological effects [3].

According to Charaka, the pods have stanyasodhana (a lactodepurant), the indrayava (seed) contains ama and asthapanopaga (includes enema) and the plant contains vamaka and arsoghna, which have symptoms of bleeding and anti-haemorrhoidal respectively. For no Ayurveda, a plant recommended for the treatment of obesity, asthma, bronchopneumonia, hepatosplenomegaly and rheumatism. *H. antidysenterica* is a major ingredient in a few Ayurvedic remedies arrangements such as Kutajghan Vati, Kutajarista and Kutaja churna, used to treat diarrhea, diarrhea, fever and bacterial infections. This plant is mentioned in Susruta Samhita as antiseptic, vermifuge, febrifuge, detoxicant[4]. In Indian Ayurvedic medicine *H. antidysenterica* is used to cure Atisara (diarrhoea and dysentery). The pods include stanyasodhana (a lactodepurant) the indrayava (seeds) contain ama and asthapanopaga (enema adjuncts) and the plant contains vamaka and arsoghna which have emetic and anti-haemorrhoidal qualities respectively according to Charaka. Susruta attributes diuretic properties of seeds and sukrasodhana to the plant in general (sperm-purifier). The herbs is characterized as antiseptic, vermifuge, febrifuge and detoxicant in the Susruta Samhita and is thought to cure malignant ulcers, leprosy, diarrhoea and other severe skin illnesses. The herb is used to treat obesity, asthma, bronchopneumonia, hepatosplenomegaly and rheumatism in modern Ayurveda[4].The administration of an aqueous extract of *H. antidysenterica* seed to diabetic mice resulted in a considerable increase in antioxidant enzyme activity as well as a reduction in free radical levels. The results of the above stated biomarkers showed that extract of *H. antidysenterica* seed reduces oxidative stress in diabetic animals by inhibiting ROS formation and reducing high blood glucose levels [5].

***Holarrhena Antidysenterica* plant**	Seeds

Figure 1 HA Bark, flower and Seeds

Taxonomic classification:

Kingdome : Plantae
Subkingdome : Tracheobionta
Superdivision : Spermatophyta
Division : Magnoliophyta
Class : Magnoliopsida
Subclass : Asteridae
Order : Genteanales
Family : Apocynaceae
Genus : Holarrhena
Species : Antidysenterica

2 Active constituents:

Most of the active constituents are found in the stem, leaves, bark and seeds of the *Holarrhena Antidysenterica*. The major constituents are steroidal, alkaloidal, flavonoids, terpenoids, Tannins, resins, coumarins, saponins etc. [6]

Table 1 Active constituents of *Holarrhena antidysenterica*

s.no.	Plant parts	Active constituents
1.	Stem bark	Conessine, Holarrifine ($C_{24}H_{38}N_2O_2$), Kurchamide, Kurcholessine, Trimethylconkurchine($C_{24}H_{38}N_2$),(3),-NMethylholarrhimine ($C_{22}H_{38}N_2O$), (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 ($C_{24}H_{40}N_2O$), Kurchilidine ($C_{22}H_{31}NO$), Neoconessine (isomer of conessine) ($C_{24}H_{40}N_2$), Holadysenterine ($C_{23}H_{38}N_2O_3$), Kurchessine ($C_{25}H_{44}N_2$), 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 ($C_{23}H_{40}N_2$), Conamine ($C_{22}H_{36}N_2$), Conkurchine ($C_{20}H_{32}N_2$),Pubadysone ($C_{21}H_{26}O_3$), Puboestrene ($C_{20}H_{24}O_3$), Pubamide ($C_{21}H_{27}NO_3$),Holadiene ($C_{22}H_{31}NO$), Kurchinidine ($C_{21}H_{29}NO_2$), Kurchinine ($C_{19}H_{24}O_3$),Pubescine ($C_{22}H_{26}N_2O_4$), Norholadiene ($C_{21}H_{29}NO$), Pubescimine ($C_{24}H_{40}N_2O$), Holonamine, Regholarrhenine A ($C_{22}H_{31}NO_2$), Regholarrhenine B ($C_{21}H_{29}NO_2$), Regholarrhenine C ($C_{22}H_{34}N_2$), Regholarrhenine D ($C_{23}H_{38}N_2O$), Regholarrhenine E ($C_{25}H_{44}N_2O_2$), Regholarrhenine F ($C_{25}H_{44}N_2O$).
2.	Leaf	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 ($C_{21}H_{32}N_2O_3$), Kurchiphyllamine, Kurchaline, Kurchiphylline ($C_{23}H_{47}NO_2$), Holarrifine ($C_{24}H_{38}N_2O_2$), Kurchamide, Kurcholessine, Trimethylconkurchine ($C_{24}H_{38}N$
3.	Seed	Conimine ($C_{22}H_{36}N_2$), Antidysentericine ($C_{23}H_{36}N_2O$).

Conessine as major compound:

Around 25 alkaloids (1.5-3%) predominantly from the bark have been isolated from the plant. They are steroidal alkaloids having C21 group. Tewj's main alkaloid is conessine has a yield of up to 0.4 % and is a stenol with a structure similar to 7-ergosten-3-ol and Y-Stigmasterol. Conessine is a pharmacological drug that is used to treat dysentery and helminthic disorders. *H. antidysenterica* barks contain alkaloids mainly the steroidal alkaloid conessine which is the main therapeutic constituent [7]. The alkaloid fraction has substantial antibacterial activity against *S. aureus, S. epidermidis* and *S. faecalis* with inhibition zones up to 18 mm in diameter including a 9 mm disc diameter and MIC with a range of 95 to 170 mg/ml. Alkaloids that are identified to be less effective against B. subtilis, E. coli and other bacteria having MIC values range from 420 to 600 mg/ml [8].

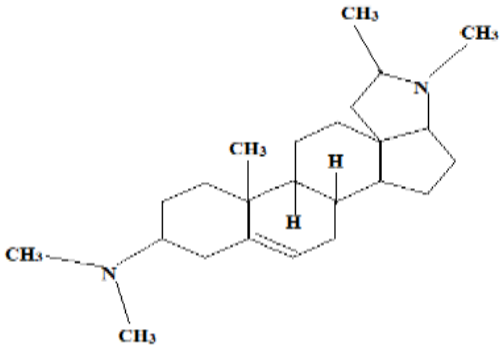

Figure 2 Structure of Conessine

3 Macroscopy of *H. Antidysenterica*:

Size and Shape various sizes and thicknesses of little re-curved pieces. Various sizes and thicknesses of little re-curved pieces. The exterior surface rough buff to brownish. Wood often adheres to the inner bark. Taste is bitter and No odour. Smoothed Surface Transverse Wide Phelloderm having stone cells and wide phloem with medullary ray and tangentially organized stone cells are shown on the outer cork. The drug show short and granular fracture.

Microscopy of *H. antidysenterica*:

Periderm: It has a cork and readily elongated cells having yellowish color. **Phellogen** no color with two rectangular cells. Phelloderm is composed of 5-10 layers of thin-walled rectangular cells that are sometimes arranged readily. Rhomboidal crystals and a few starch grains can be found in the parenchymatous cells. **Cortex** They are wide with groups of lignified, pitted stone cells of varied shapes (rectangular to elongate) and sizes interleaved. Rhomboidal crystals can be found in both the cortical parenchyma surrounding the stone cells and the stone cells themselves. Cortical parenchyma contains starch granules. The cortex has one or two clusters of non-lignified pericyclic fibers. **Secondary phloem** is made up of phloem parenchyma, medullary rays and tangential rows of stone cells separated by medullary rays. A coating of parenchyma containing rhomboidal calcium oxalate crystals surrounds the stone cells in the secondary phloem. **Medullary rays** They are 1-3 seriate with thin walled radially elongated parenchymatous cells that are broad towards the outside. Starch granules can be found in the phloem parenchyma and medullary ray cells (In figure 3) [9].

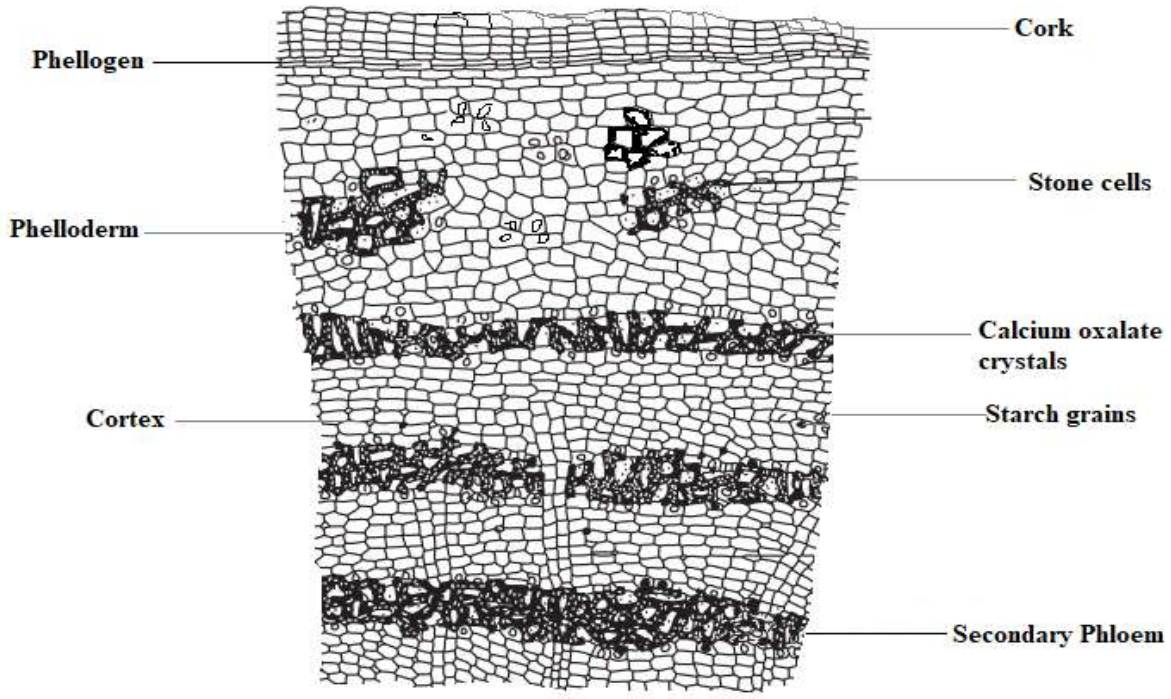

Figure 3 TS of Kurchi Bark

4 Mechanism of action:

- The extract of *Holarrhena antidysenterica* will produce the gastrointestinal stimulation by activation of histamine receptor and relaxes the gastrointestinal by blocking Ca^{2+} ion channel which results in decreasement in diarrhea [1]. The ethanolic extracts of seeds will results in the density dry feaces increment and decreasement in defecation drops. [6]
- Antioxidant property: the antioxidant properties of *H. antidysenterica* Methanolic leaf extracts were found to be scavenge superoxide ions and hydroxyl ions and reduced ability to convert Fe^3 Fe^2 [10]

5 Pharmacological actions of *H. antidysenterica*:

5.1 Antidiarrheol activity:

On a culture of HEPr, the Antidiarrheol activity of HA root bark decoction was tested on three strains of Escherichia coli: EPEC-B170, ETECTX1 (078: H 12), and ETEC B 831-2. HA reduces the virulence of enterotoxigenic (ETEC) strains by inhibiting stable toxin synthesis and preventing its intestinal secretions. As a result, it can be stated that HA protects against a variety of phases of diarrehoea[11]. At a dosage of 200 mg/ml, alcoholic and aqueous extracts of the HA stem bark were found to have antibacterial activity against 10 enteric pathogens in another investigation. S. aureus, Vibrio cholerae 01, Vibrio cholerae 0139, enteroinvasive E. coli, enteropathogenic E. coli, Salmonella typhimurium, Salmonella enteritidis, Shigella flexneri, Shigella boydii, and Pseudomonas aeruginosa were the 10 enteric pathogens employed in the investigation[12]. In another study Data suggest that *Holarrhena antidysenterica* has spasmogenic and spasmolytic actions, which are mediated via histaminergic receptor activation and Ca++ antagonist pathways, respectively, however other processes cannot be ruled out [13]. Plants Antidiarrheol activity is related to phytochemicals such as saponins, steroids, alkaloids, tannins and flavonoids. Alkaloids and flavonoids found in H. pubescens seeds extract are estimated to be associated for this activity. Extracts in aqueous and methanol of H. pubescens leaves were reported to be efficacious against Salmonella typhimurium a diarrheal pathogen, Vibrio cholerae, Vibrio alginolyticus and Salmonella typhi [14].

5.2 Anti convulsant activity:

Swiss albino mice were used to test the anticonvulsant effect of an ethanolic extract of HA. The maximum electroshock seizure (MES) test, pentylenetetrazol (PTZ), and bicuculine (BC) tests were used to examine the anticonvulsant activity of ethanolic extract of HA seeds (250 and 500 mg/kg, p.o.) in mice. The duration of seizures generated by maximum electroshock was greatly reduced by an ethanolic extract of HA (MES). The mice were given ethanol extract in dosages of 250 and 500 mg/kg, which provided protection (17 and 50%, respectively). The same doses also protected mice from Pentylenetetrazol-induced tonic seizures and greatly delayed the start of Pentylenetetrazol-induced tonic seizures. Bicuculine-induced seizures were unaffected by the extract. PTZ-induced convulsions were decreased by an ethanolic extract of *H. antidysenterica* (EEHA) [6].

5.3 Anti diuretic effects:

HA show their activity by saluritic effect. The HA inhibits the tubular reabsorption at the dose of 30-300 mg/kg[15]. These findings suggest that *Holarrhena antidysenterica* has antiurolithic activity which may be mediated through CaOx crystal aggregation inhibition, antioxidant and renal epithelial cell protection and may serve as a foundation for future research to determine its efficacy and safety for clinical use.

5.4 Anti-oxidant property:

In doses of 100 and 200 mg/kg a Methanolic extract of *H. antidysenterica* inhibited paw edema in a dose-dependent manner. The acetic acid-induced writhing response was greatly decreased by the Methanolic leaf extract of *H. antidysenterica* (100 and 200 mg/kg) in a dose-dependent manner [10]. The antioxidant and phytochemical activity of the water and ethanol extracts of the seeds were investigated using appropriate methods. The DPPH technique was used to determine the free radical scavenging activity. Total polyphenol, flavonoids, tannin, and ascorbic acid were among the phytochemical investigated. For all of the metrics, the ethanol extracts of the seeds yielded better results. Both the water and the ethanol extract contained low levels of ascorbic acid. *Holarrhena antidysenterica* seeds have significant antioxidant effects and can thus be utilized to treat diabetes Mellitus and a variety of other disorders. Many researches have also been conducted to demonstrate the plant's ability to treat such ailments [16]. Methanolic leaf extracts were found to be scavenging superoxide ions and hydroxyl ions and reduced ability to convert Fe^3 to Fe^2.

5.5 Anti urolithic property:

The Methanolic extract of seeds of Holarrhena antidysenterica reduce the size of calcium oxalate crystals and converts them into calcium oxalate dehydrate from calcium oxalate monohydrate[2].

5.6 Anti-bacterial or anti-inflammatory:

When examined for antimicrobial activity the seed and bark of *Holarrhena antidysenterica* showed varying degrees of antibacterial activity against an organism that has been tested. As a result it has been discovered to be beneficial against all microorganisms evaluated with inhibition zones ranging from 18 to 25 mm [6]. The in-silico test could be a useful tool for discovering new anti-nociceptive and anti-inflammatory drugs. Because of the presence of bioactive chemicals in its seeds. The ethanolic seed extract of *H. antidysenterica* shows a great potential for central analgesic activity and moderate peripheral analgesic activity. The enzymes cyclooxygenase-1 and cyclooxygenase-2 were thus computationally evaluated against *H antidysenterica* [17].

5.7 Anti diabetic property:

In this study treatment with methanol, petroleum ether and an aqueous extract of *Holarrhena antidysenterica* (seed) had a beneficial effect on blood glucose levels, liver glycogen, serum lipids and body weight. This revealed the potential of *Holarrhena antidysenterica* seed as an anti-diabetic drug as well as a treatment for diabetic complications. The ethanolic extract of H. antidysenterica seed exhibits antihyperglycemic activity as it decreases serum glucose levels and improves glucose tolerance in diabetic albino rats. It inhibits weight loss in diabetic rats and restores normal biochemical markers such as serum cholesterol, triglycerides, aspartate transaminase, alanine transaminase, alkaline transferase, total protein, urea, creatinine, and uric acid [18].

5.8 Inhibition of Acetyl cholinesterase:

When treating neurological issues like Alzheimer's disease, acetylcholinesterase inhibition is effective. Because alkaloids from several plants have been shown to suppress AChE a study examined the effects of alkaloids from *H. antidysenterica* comparable action. Conessine, Isoconessimine, conessimine, Conarrhimine and Conimine are five isolated alkaloids With an IC50 of 0, conessimine had the most significant effects. A concentration of 4 mM alkaloids can be the Drugs to treat neurological problems [19].

5.9 Anti hypertensive and ant mutagenic activity:

A study examined the anti-mutagenic activity of *H. antidysenterica* and found that the plant's methanolic bark extract inhibited sodium azide and methyl methane sulphonate-induced mutagenicity in Salmonella typhimurium strains [20]. The ability of 25 plants with anti-hypertensive activity to block the release of angiotensin which causes vasoconstriction and elevated blood pressure is examined. Angiotensin-converting enzyme (ACE) inhibition was found to be 24 percent in ethanolic seed extracts [4].

6 Medicinal properties of *H. antidysenterica*:

In Indian medicine it is commonly used to treat ailments such as diarrhoea, amoebic dysentery, liver disorders, irritable bowel syndrome and bleeding piles. The plant's flavor is astringent and bitter. It's used as a conventional method to treat various ailments [12].

Table 2 Medicinal Properties of *H. antidysenterica* [21]

Disease	Medicinal properties
Gastrointestinal disorders	Gastroenteritis, Colic problems, IBD, energetic against hyperacidity, Cholera, Diarrehoea, Dysentery, Constipation, food poisoning, Stomach disorders, flatulence
Diabetes	Treat complications of diabetes
Fever	Antipyretic, Pyrexia
Dermatological problem	Effective against cyst, dermatitis, leukoderma, acne, skin allergy, bruises, active against ringworms
Dental problems	Act as a analgesic
Throat and cod related diseases	Act as expectorant in throat and cold problems
Body pain	Act as a analgesic for body ache, knee ache, backache, Rheumatoid arthritis
Intestinal parasites	Inhibits growth of Tapeworm, Threadworm, Guinea worm other intestinal worms
Animal bites	Act as a antidote for snack bite, dog bite, other animal bite
Indigestion	Hyperphagia, stomachic
Brain disorders	Memory enhancer, ameliorate depression
Liver infection	Improves excessive excretion of bile, treat Jaundice
Respiratory disorders	Active against Bronchitis, Asthma
Urinary disorders	Treat urinary tract infection, cystitis, diuresis, urination problems treat

7 Uses of *H. antidysenterica:*

Ayurveda and traditional Chinese medicine both use *H. antidysenterica*. Its seeds are used to treat worms. Its bark has Antidiarrheol properties [22]. It is used to treat anemia, jaundice, dysentery, stomach aches, diarrhoea, epilepsy and cholera in Ayurvedic medicine. It is frequently used to treat Asra (blood or blood-related ailments), Atisara (diarrhoea), Kustha (leprosy), Pravahika (amoebiasis) and Jwaratisara (secondary diarrhoea).

Bark: Its bark is widely used in Ayurvedic medicine for the treatment of piles, diarrhoea, leprosy, biliousness and spleen illnesses. Bark is used to cure heavy menstrual flow, piles and headaches. In Unani medicine its bark is used to treat malaria, chest infections, asthma, bronchopneumonia, stomach disorders, dyspepsia, diarrhoea and dysentery [21]. Conessine a steroidal alkaloid derived from the bark of *H. antidysenterica* had significant anti-malarial efficacy and being minimally cytotoxic [23]. In vitro anti-malarial activity of *H. antidysenterica* was found with an IC50 value of 5.5 g/ml against chloroquine-resistant P. falciparum. Its bark is helpful to detoxify the blood.

Figure 4: Traditional uses of *H. antidysenterica* bark

Seeds: The seeds are used as an anthelmintic and astringent in Ayurvedic medicine to treat dysentery, biliousness, leprosy, tiredness, skin problems, bleeding piles, and hallucinations. Seeds are employed as a carminative, aphrodisiac, astringent and lithotriptic in Unani medicine [24]. They are also used to treat diuresis, chronic chest infections, asthma, malaria and vaginitis, diabetes, arthritis, hematuria, epilepsy, bronchitis, diarrhoea, dermatitis and jaundice in other regions of the world [25]. The ethanolic extract of *H. antidysenterica* seed exhibits antihyperglycemic activity as it decreases serum glucose levels and improves glucose tolerance in diabetic albino rats. It reduces weight loss in diabetic rats and restores normal biochemical markers such as serum cholesterol, triglycerides, aspartate transaminase, alanine transaminase, alkaline transferase, total protein, urea, creatinine and uric acid [18]. *H.antidysenterica* has been used to treat a variety of ailments, including indigestion, diarrhoea, anti-oxidant and anti-diabetic activities. This plant has unknown chemical compounds that pharmacists can use to synthesize and formulate innovative medications for a variety of infections [6].

Leaf: The extract of leafs of *H.antidysenterica* inhibits alpha glucosidase activity which decrease carbohydrate absorption from intestinal system [12]. Also used in liver infections, chronic bronchitis.

Conclusion:

Holarrhena antidysenterica is a promising medicinal plant with a wide variety of pharmacological activity that could be used in a few therapeutic applications due to its effectiveness and protection. *H. antidysenterica* has been used to treat a variety of ailments, including indigestion, diarrhoea, anti-oxidant and anti-diabetic activity. Unidentified chemical components in this plant are useful in the synthesis of various drugs. It's possible that this plant could be used to treat IBD patients with Collitus and Chrons disease. The active ingredient of *H. antidysenterica* conessine has biological characteristics. Holarrhimine, Conkurchine, Kurchicine, Holarrhenine, kurchine and Conkurchinine are some of the other important bioactive components. The seeds of this plant are used to treat worms. It contains Antidiarrheal effects in its bark. The alpha glucosidase activity of HA leaves is inhibited.

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