International Journal of Pharmacy and Biological Sciences-IJPBS™ (2021) 11 (2): 125-134
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Review Article | Biological Sciences | OA Journal | MCI Approved | Index Copernicus

Holarrhena antidysenterica (Wall.) Kutaja: Medicinal Plant with High Steroidal Alkaloid Profile

Isha Kumari, Gitika Chaudhary and Hemlata Kaurav*
Shuddhi Ayurveda, Jeena Sikho Life care Pvt. Ltd. Zirakpur 140603, Punjab, India.

Received: 16 Jan 2021 / Accepted: 14 March 2021 / Published online: 01 April 2021
***Corresponding Author Email:** shuddhi.research@jeenasikho.co.in

Abstract
Herbal remedies have been therapeutically used for centuries for their effective actions in the living system. There are many herbal plants that exist in nature. *Holarrhena antidysenterica* commonly called Tellicherry bark in English and Kutaja in Hindi, is a therapeutically important plant. It belongs to the family *Apocynaceae*. It is commonly used in folk remedies to treat a variety of human ailments like amoebic dysentery, diarrhea, asthma, skin diseases, bronchitis, hematuria, spermatorrhoea, epilepsy, asthma, piles, leprosy, stomachic, diabetes mellitus, eczema, diarrhea, fevers. It mainly grows in the areas near the mountain ranges. The characteristic feature of *Holarrhena antidysenterica* is its steroidal alkaloid profile. It is associated with therapeutic properties like anti-diabetic, analgesic, anti-oxidant, hepatoprotective, anti-malarial, anti-amnesic, diuretic and anti-urolithiasis. In this review article, the Ayurvedic and modern therapeutic value of *Holarrhena antidysenterica* have been summarized along with its utilization in the Folklore medicinal system.

Keywords
Kutaja, Rasapanchak, Conessine, Anti-diarrhoeal, Anti-diabetic.

*****

INTRODUCTION:
As per WHO, in developing nations, almost 4000 million people strongly believed in the effective actions of herbal remedies and they use them on daily basis [1]. The active ingredients i.e. secondary metabolites especially terpenoids extracted from the medicinal plants are served as the raw material for the manufacturing of various drugs. These are associated with many important therapeutic properties like anti-inflammatory, anticancer, anti-malarial, anti-viral and anti-bacterial activities etc. Drugs like laxatives and blood thinners have the presence of plant contents in them [2,3]. There are numerous medicinal plants in nature that are therapeutically important, for example, *Holarrhena antidysenteric*a L. (Figure 1). It is an important typical Indian medicinal plant that belongs to the family *Apocynaceae* and known as Conessi bark and Bitter oleander in English, Kutaja and Inderjo tulkh in Sanskrit and Kura or Kurchi in Hindi [4-9]. The Apocynaceae family is considered as one of the largest families of kingdom Plantae. Initially, Asclepiads were placed under *Apocineae* but Robert Brown (1810) decided to separate *Asclepediaceae* from *Apocynaceae* for some practical reasons [10,11]. As per the updated classification of the Apocynaceae family by Endress et al., there are almost 424 genera and more than 4,600 different plant species in the Apocynaceae family which are categorized into five subfamilies viz. *Rauvolfioideae, Apocynoideae, Periplocoideae, Secamonoideae* and *Asclepiadoideae* [12]. Holarrhena antidysenterica usually grows in mountain areas [13]. Each part of the plant is medically important. It is well-recognized

plant for its antidiabetic potential [14,15]. It holds a significant place in the Unani and Ayurvedic systems of medicine where it is used to cure infections mainly caused by micro-organisms like helminths, Staphylococcus aureus, Entamoeba histolytica, and Escherichia coli. In Ayurveda, it is used in a formulation to treat AIDS [16,17]. Holarrhena antidysenterica is a plant of great market potential due to its effective actions to treat many diseases like amoebic dysentery, diarrhea, asthma, skin diseases and many other diseases. [18-23]. It is a popular drug in Tibetian culture that is known to have cholagogic, analgesic, antidiarrheal, and alexipharmic activities, and is used to treat diseases hepatic diseases and diarrhea [24]. This important medicinal plant is primarily known for its high amount of steroidal alkaloids. It also contains flavonoids, triterpenoids, phenolic acids, tannin, resin, coumarins, saponins, and ergosterol. The principal phytochemical conessine is responsible for anti-diarrhoea and anti-plasmodial activities [25,26]. This plant is associated with many important therapeutic properties such as anti-diabetic, analgesic, anti-oxidant, hepatoprotective, anti-malarial, anti-amnesic, diuretic and anti-urolithiasis. But, its over-exploitation due to factors like pharmaceutical industry requirements, limited cultivation and negligible steps for its reforestation, has led to the depletion of this important medicinal plant. Also, it is a species with a very slow multiplication rate and bears seeds during the onset of the monsoon rains only. So, there is an immediate requirement to take some preventive steps so that our future generations can also enjoy the benefits of this important medicinal plant [27,28]. Vernacular names and taxonomic classification of Holarrhena antidysenterica are given in table no. 1 and 2.

Figure 1. *Holarrhena antidysenterica* Plant

Table 1. Vernacular names of *Holarrhena antidysenterica* [29]

English	Ester Tree, Kurchi, Conessi, Tellicherry bark
Hindi	Kutaja, Dhudi, Hat, Karchi, Kari, Kaura, Kura, Kora
Sanskrit	Girimallika, Indra, Indradu, Indrayava, Indrayavaphala, Kahi, Kalinga
Gujrati	Kari, Kaura, Kadvoindarjou, Kuda, Indrajwnunjad
Assamese	Dudcori
Telugu	Amkudu, Chedukodise, Girimalika, Kodaga
Punjabi	Kewar, Kogar, Kiam, Koeva
Persian	Zabanekunjashketalkh, Indarjavetalkh, Tukhmeahharetalkh
Arabic	Lasanulassafirulmurr, Tivraja

Table 2. Taxonomy of *Holarrhena antidysenterica* [30]

Taxonomic Rank	Taxon
Kingdom	Plantae
Subkingdom	Tracheobionta
Superdivision	Spermatophyta
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Asteridae
Order	Gentianales
Family	Apocynaceae
Genus	*Holarrhena*
Species	*antidysenterica*

MORPHOLOGY:

Holarrhena antidysenterica is an evergreen woody, aromatic, deciduous, and lactiferous small shrub or tree having greyish-brown and rough stem bark. The stem of the plant is whitish soft. It has 10- 20 cm long leaves which are simple and ovate to elliptical in shape and are obtusely acuminate. Flowers are small and white in color and present in terminal corymbose cymes having a diameter of 7.5- 15 cm. The corolla tube is about 4-13cm long whose base is slightly inflated. The lobs are almost of equal length as of corolla tube and having a rounded apex. The follicles are almost 20-38 cm in length giving the appearance of two slender pencils that come from an anode which have white spots over it. The fruits are small. Numerous flat, 1-2cm long seeds are released from the brown hair when the dried fruit opens up in a split manner. The seeds are light brownish and linear/oblong concave with a long coma-like structure having linear lines over them. The seeds have a bitter taste [31-34].

GEOGRAPHICAL DISTRIBUTION:

Holarrhena antidysenterica is an indigenous plant of the tropical Himalayas. It is mainly found in tropical India, Burma, Sri Lanka, Pakistan, Nepal, and Africa. In India, it is found growing in Assam, Uttar Pradesh, down to Travancore [35].

PHYTOCHEMISTRY:

Holarrhena antidysenterica stem, bark, leaves and seeds as well contain many phytochemical constituents. The plant primarily contains steroidal alkaloids in high amounts whereas it also contains flavonoids, triterpenoids, phenolic acids, tannin, resin, coumarins, saponins and ergostenol. The phytochemical analysis of leaf and callus extract done by Nahak et al., revealed that proteins, amino acids, phenolic compound, flavonoids and anthraquinone glycosides are present in both the extracts while chemicals like alkaloids, gums mucilage, tanins, steroids, flavones are only present in leaf extract [36]. *Holarrhena antidysenterica* stem bark, leaves and seeds consists of steroidal alkaloids such as conessine, isoconessine, conessidine, regholarrhenine, kurchine, kurchicine, holarrhimine, conarrhimine, conaine, conessimine, iso-conessimine, conimine, holacetin, conkurchin, holadysenterine, isoconessimine and kurchessine, holarrifine, kurchamide, kurcholessine, trimethylconkurchine, (3),-n-methylholarrhimine, (20),-n-methylholarrhimine, holarrhidine, kurchenine, holarrhessimine, holarrhine, kurchamine, 7a-hydroxyconessine, kurchilidine, neoconessine, lettocine, kurchimine, holarrhenine, holacine, holafrine, holadysone, holacetine, 3a-aminoconan-5-ene, dihydroisoconessimine, conamine, conkurchine, pubadysone, puboestrene, pubamide, holadiene, kurchinidine, kurchinine, pubescine, norholadiene, pubescimine, holonamine, regholarrhenine A, regholarrhenine B, regholarrhenine C, 4 regholarrhenine D, regholarrhenine E, regholarrhenine F, holantosine-A, holantosine-B, holantosine-C, holantosine-D, holantosine-E, holantosine-F, holarosine A, holarosine B, holarricine, kurchiphyllamine, kurchaline, and kurchiphylline. Among all steroidal alkaloids, conessine amount is quite high. Kumar et al., discovered a novel steroidal alkaloid called antidysentericine from *Holarrhena antidysenterica* seeds and characterized it as 3β-dimethylaminocon-5-enin-18-one (**1**) [37-43]. As per Rajalakshmi et al., the ethanolic extract of *Holarrhena antidysenterica* bark contains N-2-carbamoyloxy ethyl carbamic acid, 3-dimethyl amino benzene methanol, trimethoquinol, 9-butyl-9,10-dihydro acridine, 2,7 dimethyl carbazole, 2-phenyl -3-pyridinol, pirlindole, silanamine1,1,1-trimethyl –N(4-trime, 10,13-eicosadienoic acid methyl ester, 2-[2-(4-chlorophenyl)-3-morpholin-4yl-3], 1-[2-(4-bromophenoxy)ethyl] pyrrolidine, 9,10-diphenyl anthracene, 3,18 bis acetyloxy pregn-16-en-20-one, 4-imino-1,5,5-triphenyl-2-imidazolidinon, 1-triethyl siloxyheptadeccane, 5,9,10 -2H,6h-pyrano[3,2-b] xanthen-6-one, dl-alpha-toccopherol succinate, desmosterol, campesterol, cholesta-22,24-dien-5-ol, methyltribenzocentrotriquinanol and lanosta-8,24-dien-3-one [44].

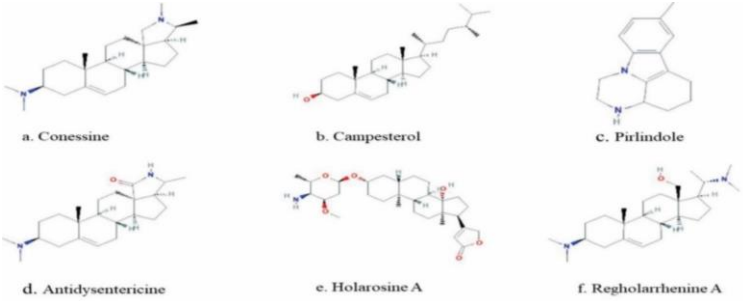

Figure 2. Phytochemical Structures of Some of Phytochemical Constituents of *Holarrhena antidysenterica*

TRADITIONAL AND MODERN VIEW:

Ayurvedic view

Ayurveda, the science of life is the oldest traditional system of medicine in India. It promotes good health and longevity. Ayurveda maintains body harmony by balancing the three body components/doshas of the body i.e. Kapha (water and earth), pitta (fire), and Vata (space and air)

Medicinal plants play a vital role in the Ayurvedic treatment practices [45-48]. One such important medicinal plant of great significance in Ayurveda is, *Holarrhena antidysenterica* commonly known as 'Indrayava/ Indrajav' in Ayurvedic classics [49]. It balances the Kapha and Pitta Doshas of the body. The fresh bark and seeds of *Holarrhena antidysenterica* are recommended by *Bhavaprakasha* against diabetes [50]. Its seeds are used in many Ayurvedic polyherbal formulations for flatulence, jaundice, piles, cancer, chronic fever, and worms [51-54]. It helps in enhancing appetite [55]. Rasapanchak of *Holarrhena antidysenterica* is given in Table No. 3.

Table 3. Rasapanchak as per Ayurveda [56]

Sanskrit/English	Sanskrit/English
Virya/Potency	Sheeta/Cold
Vipak/Metabolic property	Katu/Pungent
Guna/Physical property	Laghu/Light, Ruksha/Dry
Rasa/Taste	Tikta/Bitter, Katu/Pungent Kashay/Astringent

Actions and Properties as per Ayurveda [57,58]

Sansthanik karam waha: Its decoction is used in the wound healing.

Abhyantar pachan sansthan: It is used as an appetizer, anti-fibrinolytic, anti-helminthic agent and used to treat amoebic dysentery, diarrhoea, piles and abdominal pain.

Rakat wah sansthan: It is used as a blood purifier to treat gout and other skin problems.

Taapkram: It is used as an anti-pyretic to treat malaria.

Saatmikaran: It helps in the nourishment of tissues and used to treat obesity.

Ayurvedic formulations of *Holarrhena antidysenterica*

Holarrhena antidysenterica is used in several Ayurvedic formulations like Kutaja Kwatha, Kutaja Prapati Vati, Kutajarishta, Kutajavleha and Kutajghan Vati, Mahamanjishtadi Kashayam, Stanyashodhana Kashaya, Patoladi Choornam and Chandra Kalka [59,60]. Uses of some of the Ayurvedic formulations are discussed below:

Kutajarista: The description of this plolyherbal formulation is found in Bhaisajyaratnavali and Atisaradhikara. It is a famous anti-diarrheal polyherbal formulation. It is used to treat diarrhea, dysentery and other gastrointestinal tract problems [61-63].

Laghulai Churna: It is an important polyherbal formulation that is made up of many medicinal plants. *Holarrhena antidysenterica* is one of its main ingredient. It is used in the treatment of mal absorption syndrome (grahani), diarrhoea (atisara), pain (sula) and distension of abdomen due to urine and stool passage obstruction (anaha) [64].

Lagugangadhar Churna: It is a popular Ayurvedic polyherbal formulation used for the treatment of diarrhea and dysentery [65].

Ayuartis capsule: It is a polyherbal Ayurvedic formulation. As per Mundhe et al., clinical study, ayuartis capsule is an effective treatment measure of osteoarthritis (OA) [66].

Kutaja tvak churna: It is useful in the treatment of shonitarsha (Bleeding piles). A successful clinical trial of kutaja tvak churna on 20 patients suffering from bleeding piles, suggested that this herbal formulation can be used as a treatment for bleeding piles [67].

Folk View

Holarrhena antidysenterica is a plant of rich ethnobotanical significance. It is used in many folk cultures to treat various diseases. For instance, in Nagpur city, it is used in the treatment of anemia [68]. Rabha people of Assam, traditionally use its bark in bone setting practices [69]. In Barisal, Bangladesh, people use its leaves against dysentery and stem bark to treat impotency as well as dysentery [70]. In Mirzapur and Varanasi districts of Uttar Pradesh, people use the bark of *Holarrhena antidysenterica* to get relief from gastric problems [71]. The tribal people of Nallamala district, Andhra Pradesh, use the stem bark to treat skin diseases [72]. The rural population of Garhwal Himalaya, uses the bark of this plant to treat dysentery and leaf and seeds as febrifuge [73]. In Kachin State, Northern Myanmar, people use roots, barks and seeds traditionally to treat dysentery, analgesic and anti-inflammatory [74]. The seed powder and bark decoction of this plant is used as a preventive measure to diabetes by some ethnic communities of Unakoti, Tripura [75]. People in the Barisal area of Bangladesh, administer leaf juice as a remedy to

dysentery [76]. *Holarrhena antidysenterica* is used to treat skin diseases like eczema and puses in some areas of West Bengal [77]. The tribal people of Japali Hanuman Theertham, use this plant to treat ulcers traditionally [78]. People in Wayanad district, Kerala, use its stem and bark powder to treat stomach-related problems [79].

Modern View

There are a lot of issues in the standardization of herbal products. Insufficient guidelines of regulation of herbal product manufacturing are directly related to quality degradation [80]. Adulteration is the most common malpractice of quality degradation of herbal products. Adulteration can be unintentional or intentional [81]. From the earlier documented reports, it is clear that many of the herbal products in the International as well as domestic markets are adulterated [82,83]. For instance, *Wrightia tinctoria* R. Br. plant belongs to the same family as that of *Holarrhena antidysenterica* (*Apocynaceae* family), is the most common adulterant plant species used in *Holarrhena antidysenterica* derived products. This may happen due to the morphological similarity between the two species. Kurchi Bismuth Iodide is a formulation prepared from *Holarrhena antidysenterica* is adulterated with *W. tinctoria* [84-87]. Techniques such as chemotaxonomy, chromatography and microscopy were used in the earlier times to detect adulteration. But these techniques were not so successful in detecting species adulteration due to complex chemistry, unavailability of unique compounds, environmental influence, plant age, and geographical variations [88]. But with the advancement in technology, a reliable method known as DNA barcoding has been discovered to detect adulteration. It is a rapid method of identifying almost 10 million species. In this technique, short DNA sequences are used for the identification [89]. It also works on assembling a precise and standard reference library. Thus, it highly relies on traditional and inexpensive protocols for extraction, amplification and sequencing of DNA [90].

THERAPEUTIC PROPERTIES:

Holarrhena antidysenterica exhibits many important therapeutic properties. Some of its reported studies on therapeutic actions are summarized below:

Anti-diarrhoeal

Munshi et al., performed an *in-vivo* study to test the anti-diarrhoeal activity of a polyherbal formulation LQ14, in rat models in which diarrhoea was induced artificially by castor oil. *Holarrhena antidysenterica* is the major ingredient of this formulation. The study revealed that polyherbal formulation LQ14 exhibited a significant anti-diarrhoeal activity by reducing the number of diarrhoea stools. It caused a delay in gastrointestinal propulsion and showed inhibitory actions against the accumulation of fluid in the intestinal tract of models [91]. Kavitha et al., also investigated the anti-diarrhoeal activity of *Holarrhena antidysenterica* in an *in-vivo* study on castor oil-induced diarrhoeal rat models. The alkaloids from the ethanolic extract were found to be very effective against diarrhoea. A decrease in the wet feces number was noticed on administration of alkaloid at the dosage of 200-800 mg/kg [92]. Sharma et al., also reported the anti-diarrhoeal activity of *Holarrhena antidysenterica.* They performed an *in-vivo* test on castor oil and *Escherichia coli* induced diarrhoeal rat models. Ethanolic seed extract at the dosage of 200 mg/kg and 400 mg/kg body wt. were found to be very effective in prevention of diarrhoea [93].

Anti-diabetic and Antihyperlipidemic

Holarrhena antidysenterica is a plant that is widely known for its anti-diabetic property. Various studies have supported the anti-diabetic potential of this plant. For instance, Ali et al., suggested the use of *Holarrhena antidysenterica* in the management of diabetes and hyperlipidemia. They carried out an *in-vivo* study on streptozotocin (STZ) induced diabetic rat models. The administration of aqueous extract of seed, significantly restored all the changes induced by STZ such as glucose-6-phosphatase, glucose-6-phosphate dehydrogenase and hexokinase activities in liver along with quantification of liver and skeletal muscle glycogen and serum levels of total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDLc), very low density lipoprotein cholesterol (VLDLc) and high density lipoprotein cholesterol (HDLc) [94]. Mana et al., also suggested that *Holarrhena antidysenterica* is associated with anti-diabetic and antihyperlipidemic activities. They tested the methanolic extract of the plant against streptozotocin (STZ) induced diabetic Wistar rat models. The administration of the methanolic extract at the dosage of 250 mg/kg orally for 18 days continuously, decreased the blood glucose level effectively. It also caused a marked decrease in serum total cholesterol, triglyceride levels whereas liver glycogen levels were increased [95]. Hegde et al., carried out an *in vivo* study on alloxan and streptozotocin-induced diabetic rat models to check the anti-diabetic activity of ethanolic extract of *Holarrhena antidysenterica* leaves. The findings of the study revealed that leaf extract in the dose dependent manner exhibited significant anti-diabetic activity in the models [96].

Anti-urolithic

Khan et al., studied the anti-urolithic property of *Holarrhena antidysenterica* in *in-vitro* as well as *in-vivo* tests. For the *in-vivo* test, male Wistar rat models were used which were administered with drinking water containing 0.75% ethylene glycol (EG) along with 1% ammonium chloride (AC) for 21 days. It was observed that crude aqueous-methanolic extract (Ha.Cr) caused prevention of toxic changes induced by EG and AC. Whereas in the *in-vitro* test, Ha.Cr caused inhibitory actions on the aggregation slope in a dose-dependent manner. A decrease in crystal size as well as transformation of calcium oxalate monohydrate (COM) into calcium oxalate dehydrate (COD) crystals was observed [97].

Anti-oxidant

Ganpathy et al., conducted an *in-vitro* study to evaluate the anti-oxidant potential of *Holarrhena antidysenterica* by using hydroxyl radical, superoxide anion scavenging and reducing power assays. The methanolic leaf extract of the plant strongly exhibitted anti-oxidant activity in concentration-dependent manner. Noticeable scavenging of reactive oxygen species (ROS) in all the assays was observed [98]. Ali et al., reported that ethyl acetate fraction of hydro-methanolic (2:3) extract of seeds exhibitS anti-oxidant activity. It showed effective actions in hydroxyl radical scavenging, hydrogen peroxide scavenging, nitric oxide scavenging and lipid peroxidation inhibition [99].

Analgesic

Bhyuyan et al., investigated the analgesic potential of *Holarrhena antidysenterica* in swiss albino mice pain models. For evaluating peripheral analgesic activity, they used acetic acid-induced writhing test and for central anti-nociceptive, they used heat-induced pain models. Whereas formalin induced licking test used to evaluate both peripheral and central anti-nociceptive activity. Ethanol extract of seeds in a dose dependent manner proved to be a good analgesic agent [100].

Hepatoprotective

Verma et al., studied the hepatoprotective nature of *Holarrhena antidysenterica* in paracetamol-induced hepatic damage in male Wistar rat models. The administration of *Holarrhena antidysenterica* extract caused a significant decrease in serum glutamate pyruvate transaminase (SGPT), Serum glutamic oxaloacetic transaminase (SGOT), Alkaline phosphatase (ALP) and Total bilirubin (TB). It also worked on inhibition of liver weight loss which was induced by PCM and reduction of fibrous septa formation. Many other preventive changes were observed [101].

Diuretic

Khan et al., studied the diuretic property of *Holarrhena antidysenterica* in an *in-vivo* test performed on Wistar rat models which were on fasting mode for 24 hours with water ad labium. The administration of crude extract of seeds (Ha.Cr) caused a significant increase in urine output and urine contents of Na+ and K+ and aqueous (Ha.Aq) extract also caused an increase in urine output. Whereas n-butanol fraction of crude extract was mildly associated with diuretic actions. [102].

Anti-malarial

Verma et al., investigated the anti-malarial activity of *Holarrhena antidysenterica* in *in-vitro* and *in-vivo* tests. A schizont maturation and parasite lactate dehydrogenase (pLDH) assay was used to perform the *in-vitro* test whereas *Plasmodium berghei* NK65 infected Swiss albino mice models were used for the *in-vivo* test. It was observed that chloroform extract of the plant had effective actions in both the tests i.e. *in-vitro* and *in-vivo* [103]. Dua et al., performed *in-vitro* as well as *in-vivo* tests which showed that conessine is strongly associated with anti-malarial activity. [104].

Larvicidal

Kumar et al., suggested that silver nanoparticles (AgNPs) synthesized using aqueous bark extract of *Holarrhena antidysenterica* are strongly associated with larvicidal activity. They tested AgNPs against larvae of *A. aegypti* and *C. quinquefasciatus* which resulted in expressive mortality rate [105].

Anti-amnesic

Singh et al., studied the anti-amnesic behavior of *Holarrhena antidysenterica* in intracerebroventricular-streptozotocin (STZ-ICV) induced dementia rat models. Ethanol extract administration in the models at the dosage of 200 and 300 mg/kg showed a marked enhancement in glutathione (GSH) level and it also decreased brain acetylcholinesterase (AChE) and thiobarbituric acid reactive substances (TBARS) levels [106].

CONCLUSION:

Holarrhena antidysenterica is a very common medicinal plant that is well recognized for its anti-diabetic and anti-diarrhoeal potential. It is used in many folklore cultures to treat variety of human ailments and in number of polyherbal Ayurvedic formulations as a main ingredient. It is the only species of the *Apocynaceae* family that contains maximum number of steroidal alkaloids. The main objective of the present review was to explore each aspect of *Holarrhena antidysenterica* i.e. its photochemistry, traditional utilization and therapeutic significance. It is quite evident from the

study that it is a plant of high medicinal value which exhibits many important therapeutic properties. However, more scientific studies and research on this plant may discover many more aspects of *Holarrhena antidysenterica.* Also, this promising medicinal plant needs immediate conservation plans as it is depleted at a very fast rate due to its increasing demand in the pharmaceutical industry.

ACKNOWLEDGMENT:
Authors are thankful to the Department of Research and Development of Jeena Sikho Pvt. Ltd. Zirakpur Punjab for giving us the opportunity to explore this ancient medicinal fruit plant.

CONFLICT OF INTEREST:
None

REFERENCES:

1. Rai LK, Prasad P, Sharma E., Conservation threats to some important medicinal plants of the Sikkim Himalaya. Biological conservation, 93(1):27-33, (2000)
2. Rasool Hassan BA., Medicinal plants (importance and uses). Pharmaceut Anal Acta, 3(10):2153-435, (2012)
3. Mahato SB, Sen S., Advances in triterpenoid research, 1990–1994. Phytochemistry, 44(7):1185-236, (1997)
4. Prajapati S, Singh S, Sharma M, Kumar A, Verma D, Gupta P, Arya R, Dwivedi B, Arya BS., Morphological Characterization of Homeopathic Medicinal Plants and Evaluation of their Biological Effect Against the Microsporum canis. Alcohol. International Journal of Pharmacognosy and Phytochemical Research, 90(7.0):1-6, (2019)
5. Mallikarjuna K, Rajendrudu G., High frequency in vitro propagation of Holarrhena antidysenterica from nodal buds of mature tree. Biologia plantarum, 51(3):525-9, (2007)
6. Bhadekar RK, Jadhav AB. Radhika. M. Khandelwal., An Experimental Study of Antagonistic Effects of Homoeopathic Medicines Against Pseudomonas aeruginosa. Global Journal for Research analysis, 9(3):1-4, (2020)
7. Mishra R, Kumar M, Dwivedi B, Arya BS, Arya R, Khurana A, Manchanda RK., Chemoprofiling of Homoeopathic drug Holarrhena antidysenterica L. Indian Journal of Research in Homoeopathy, 1;12(4):212, (2018)
8. Aqil F, Zahin M, Ahmad I. Antimutagenic activity of methanolic extracts of four ayurvedic medicinal plants. Indian Journal of Experimental Biology, 46:668-672, (2008)
9. Gilani AH, Khan A, Khan AU, Bashir S, Rehman NU, Mandukhail SU., Pharmacological basis for the medicinal use of Holarrhena antidysenterica in gut motility disorders. Pharmaceutical biology, 48(11):1240-6, (2010)
10. Endress ME, Liede-Schumann S, Meve U., An updated classification for Apocynaceae. Phytotaxa, 159(3):175-94, (2014)
11. Endress ME, Bruyns PV., A revised classification of the Apocynaceae sl. The Botanical Review, 66(1):1-56, (2000)
12. Endress, ME., Meve, U., Middleton, DJ., Liede-Schumann S., Apocynaceae. InFlowering Plants, Eudicots 2018
13. Sharma DK, Gupta VK, Kumar S, Joshi V, Mandal RS, Prakash AB, Singh M., Evaluation of antidiarrheal activity of ethanolic extract of Holarrhena antidysenterica seeds in rats. Veterinary world, 8(12):1392, (2015)
14. Ali KM, Chatterjee K, De D, Jana K, Bera TK, Ghosh D., Inhibitory effect of hydro-methanolic extract of seed of Holarrhena antidysenterica on alpha-glucosidase activity and postprandial blood glucose level in normoglycemic rat. Journal of ethnopharmacology, 135(1):194-6, (2011)
15. Patel DK, Kumar R, Laloo D, Hemalatha S., Natural medicines from plant source used for therapy of diabetes mellitus: An overview of its pharmacological aspects. Asian Pacific Journal of Tropical Disease, 2(3):239-50, (2012)
16. Usmanghani K, Akhtar N, Asif H.M, Akram M, Ahmed K, Shaheen G, Rehman R, Ahmad A, Sumreen L., Monograph of *Holarrhena antidysenterica* (Linn.). wall. *Int. J. Phytomed,* 2(4):345–348, (2011)
17. Sharma V, Hussain S, Bakshi M, Bhat N, Saxena AK., In vitro cytotoxic activity of leaves extracts of Holarrhena antidysenterica against some human cancer cell lines. Indian Journal of Biochemistry and Biophysics, 51:46-51, (2014)
18. Sharma A, Shanker C, Tyagi LK, Singh M, Rao CV., Herbal medicine for market potential in India: an overview. Acad J Plant Sci, 1(2):26-36, (2008)
19. Ahmad I, Mehmood Z, Mohammad F., Screening of some Indian medicinal plants for their antimicrobial properties. Journal of ethnopharmacology, 62(2):183-93, (1998)
20. Bhattacharjee, SK., Handbook of medicinal plants, Jaipur 2004.
21. Sensarma, P., Pal, DC., A Lexicon of Medicinal Plants in India, Naya Prokash 2001.
22. Nahar UJ, Bhuiyan MM, Samsudduzah AN, Uddin MR, Maryam Z., Phytochemical screening, cytotoxic and CNS depressant activities of Holarrhena antidysenterica leaves and seeds. International Journal of Pharmaceutical Sciences and Research, 6(2):620, (2015)
23. Zahin M, Aqil F, Khan MS, Ahmad I., Ethnomedicinal plants derived antibacterials and their prospects. Ethnomedicine: a source of complementary therapeutics. 2010:149-78.
24. Yang ZD, Duan DZ, Xue WW, Yao XJ, Li S., Steroidal alkaloids from Holarrhena antidysenterica as acetylcholinesterase inhibitors and the investigation for structure–activity relationships. Life sciences, 90(23-24):929-33, (2012)
25. Siriyong T, Srimanote P, Chusri S, Yingyongnarongkul BE, Suaisom C, Tipmanee V, Voravuthikunchai SP.,

Conessine as a novel inhibitor of multidrug efflux pump systems in Pseudomonas aeruginosa. BMC complementary and alternative medicine, 17(1):1-7, (2017)
26. Kaith BS, Dhiman J, Bhatia JK., Preparation and application of grafted Holarrhena antidycentrica fiber as cation exchanger for adsorption of dye from aqueous solution. Journal of Environmental Chemical Engineering, 3(2):1038-46, (2015)
27. Kumar R, Sharma K, Agrawal V., In vitro clonal propagation of Holarrhena antidysenterica (L.) Wall. through nodal explants from mature trees. In Vitro Cellular & Developmental Biology-Plant, 41(2):137-44, (2015)
28. Raha S, Roy SC., In vitro plant regeneration in Holarrhena antidysenterica wall., through high-frequency axillary shoot prolieferation. In Vitro Cellular & Developmental Biology-Plant, 37(2):232-6, (2001)
29. Shilpy G, Vijendra K., Pharmacological Evaluation of Palashbeejadi Yoga Against Worms Infestation. World Journal of Pharmaceutical Research, 7(7):1962-1974, (2018)
30. Mrinal NS., A Review on Pharmacological Aspects of Holarrhena antidysenterica. Scholars Academic Journal of Pharmacy, 7(12):488-92, (2018)
31. Shwetha C, Latha KP, Asha KA., Study on analgesic activity of Holarrhena antidysenterica leaves. J Herb Med, 2:14-6, (2014).
32. Patra JM, Panda SS, Banani Pattanayakand Nabin KD., Validations of Tribal Claims On Vanda Tessellate (Roxb.) Hook. Ex G. Don., Vitex Negundo L. And Holarrhena Antidysenterica Wall. Ex. A. Dc. Through Phytochemical Screening and Antibacterial Activity. Int. J. Pharm. Biol. Sci, 6(8):593-9, (2015).
33. Rahman AM, Akter M., Taxonomy and traditional medicinal uses of Apocynaceae (Dogbane) family of Rajshahi district, Bangladesh. Res. Rev. J. Bot. Sci, 4:1-2, (2015).
34. Shah SA, Usmanghani K, Akhtar N, Asif HM, Akram M, Ahmed K, Shaheen G, Shamim T, Rehman R, Ahmad A, Sumreen L., Monograph of Holarrhena antidysenterica (linn.) Wall. International Journal of Phytomedicine, 2(4), (2010)
35. Mahato S, Mehta A, Roy S., Studies on antibacterial effects of bark, seed and callus extracts of Holarrhena antidysenterica Wall. The Bioscan, 8(2):717-21, (2013)
36. Nahak G, Kanungo S, Sahu RK., Comparative Antioxidant Activity and Phytochemical Contents of Callus and Leaf Extracts of Holarrhena anti dysenterica (L.). Int. J Pharm. Sci. Rev. Res, 26:159-64, (2014)
37. Bhadane BS, Patil MP, Maheshwari VL, Patil RH., Ethnopharmacology, phytochemistry and bio technological advances of family Apocynaceae: A review. Phytotherapy Research, 32(7):1181-210, (2018)
38. Kumar N, Singh B, Bhandari P, Gupta AP, Kaul VK., Steroidal Alkaloids from Holarrhena antidysenterica (L.) W ALL. Chemical and pharmaceutical bulletin, 55(6):912-4, (2007)
39. Kumar D, Kumar G, Das R, Kumar R, Agrawal V., In vitro elicitation, isolation, and characterization of conessine biomolecule from Holarrhena antidysenterica (L.) Wall. callus and its larvicidal activity against malaria vector, Anopheles stephensi Liston. Environmental Science and Pollution Research, 25(7):6783-96, (2018)
40. Kumar A, Ali M., A new steroidal alkaloid from the seeds of Holarrhena antidysenterica. Fitoterapia, 71(2):101-4, (2000)
41. Sinha S, Sharma A, Reddy PH, Rathi B, Prasad NV, Vashishtha A., Evaluation of phytochemical and pharmacological aspects of Holarrhena anti dysenterica (Wall.): A comprehensive review. Journal of pharmacy research, 6(4):488-92, (2013)
42. Amrinder K, Deepak K., Pharmacognostic, Pharmacological and Toxicological Review of Seeds of Holarrhena antidysenterica (Apocynaceae). Plant Archives, 21(1):2636-40 (2021)
43. Bhutani KK, Ali M, Sharma SR, Vaid RM, Gupta DK., Three new steroidal alkaloids from the bark of Holarrhena antidysenterica. Phytochemistry, 27(3): 925-8, (1988)
44. Rajalakshmi C., GC MS analysis of the bark of Holarrhena antidysenterica. Journal of Pharmacognosy and Phytochemistry, 7(4):797-800, (2018)
45. Garodia P, Ichikawa H, Malani N, Sethi G, Aggarwal BB., From ancient medicine to modern medicine: ayurvedic concepts of health and their role in inflammation and cancer. J Soc Integr Oncol, 5(1):25-37, (2007)
46. Samy RP, Pushparaj PN, Gopalakrishnakone P., A compilation of bioactive compounds from Ayurveda. Bioinformation, 3(3):100, (2008)
47. Hankey A., CAM modalities can stimulate advances in theoretical biology. Evidence - Based Complementary and Alternative Medicine, 2(1):5-12, (2005)
48. Lad, V., The human constitution. Ayurveda: The Science of Self-Healing, Wilmot 1985
49. Niranjan K, Ravishankara MN, Padh H, Rajani M., A new spectrophotometric method for the estimation of total alkaloids in the stem bark and seed of Holarrhena antidysenterica (Linn.) Wall. and in the Ayurvedic formulation, Kutajarishta. Journal of Natural Remedies, 2(2):168-72, (2002)
50. Sheikh Y, Manral MS, Kathait V, Prasar B, Kumar R, Sahu RK., Computation of in vivo antidiabetic activity of Holarrhena antidysenterica seeds extracts in Streptozotocin-induced diabetic rats. Iranian Journal of Pharmacology and Therapeutics, 14(2):22-27, (2016)
51. Keshri UP., antidiabetic efficacy of ethanolic extract of holarrhena antidysenterica seeds in streptozotocin induced diabetic rats and its influence on certain biochemical parameters. Journal of drug Delivery and Therapeutics, 2(4):159-162, (2012)
52. Pandey MM, Rastogi S, Rawat AK., Indian traditional Ayurvedic system of medicine and nutritional supplementation. Evidence-Based Complementary and Alternative Medicine, 2013:1-12, (2013)

53. Samy RP, Pushparaj PN, Gopalakrishnakone P., A compilation of bioactive compounds from Ayurveda. Bioinformation, 3(3):100, (2008)
54. Shah S., Ayurveda: The conventional Indian medicine system and its global practice. International Journal of Innovative Science and Technology, 26:13-33, (2019)
55. Pooja BA, Bhatted S., Ayurvedic management of Pravahika–A case report. Ayu, 36(4):410, (2015)
56. S G., Study of physicochemical properties of Indrayava (Holarrhena antidysenterica wall.) and its antibacterial effect on Enteropathogenic e-coli (EPEC) (in vitro). International Journal of Ayurvedic Medicine, 4(2):113-121, (2013)
57. Muddgal, D., Dravyagun Vijnana, Jaipur, Rajasthan 2019.
58. Sharma, PV., Dravyagun Vigyan, Varanasi, India 2019.
59. Jamadagni PS, Pawar SD, Jamadagni SB, Chougule S, Gaidhani SN, Murthy SN., Review of Holarrhena antidysenterica(L.) Wall. ex A. DC.: Pharmacognostic, pharmacological, and toxicological perspective. Pharmacognosy reviews, 11(22):141, (2017)
60. Chamara AM, Kuganesan A, Dolawatta KD, Amarathunga IM, Wickramasinghe WY, Madushani YM, Thiripuranathar G., Evaluation of bioactivities of two polyherbal formulations found in Sri Lankan Ayurvedic treatments. Int J Pharm Sci Res, 9(5):2073-9, (2018)
61. Raj SP, ES MK., Effectiveness of Musta-Takra Basti in the Management of Ulcerative Colitis (Pittaja grahani)–A Case Report. An International Journal of Research in AYUSH and Allied Systems, 7(5):2940-2944, (2020)
62. Premnath Shenoy KR, Yoganarasimhan SN. Evaluation of antidiarrhoeal activity of Kutajarista-a classical Ayurvedic preparation. Indian Journal of Traditional Knowledge, 7(4):557-559, (2008)
63. KR PS, SN Y., Antibacterial activity of Kutajarista-An ayurvedic preparation. Indian Journal of Traditional Knowledge, 8(9):270-271, (2009)
64. Tripathi M, Sikarwar RL, Tiwari A, Dwivedi N., Pharmacognostical identification of ingredients in Laghulai curna: An Ayurvedic compound formulation, 14(4):531-536, (2015)
65. Rathi A, Rai V, Khatoon S, Rastogi S, Rawat AK, Mehrotra S, Pandey MM., Evaluation of Ayurvedic compound formulations III-Laghugangadhar Churna. Indian Journal of Traditional Knowledge, 9(3):576-580, (2010)
66. Mundhe NB, Tamoli SM, Pande SP, Kulkarni SA, Patil VG, Mahadik SB., An open-label, prospective, multicenter, clinical study to evaluate efficacy of Ayuartis capsules in patients suffering from osteoarthritis of the knee (s). Ayu, 40(1):16, (2019)
67. Pal A, Sharma PP, Mukherjee PK., A clinical study of Kutaja (Holarrhena antidysenterica Wall) on Shonitarsha. AYU (An international quarterly journal of research in Ayurveda), 30(4):369, (2009)
68. Maurya R, Dongarwar N., Studies on the medicinal uses of wild trees of Nagpur district. Int J Life Sci Pharma Res, 2(1):21-5, (2012)
69. Dutta T., Traditional Bone Setting Practice of Rabha People of Assam. Asian J Pharm Clin Res, 12(1):81-3, (2019)
70. Hossain U, Rahman MO., Ethnobotanical uses and informant consensus factor of medicinal plants in Barisal district, Bangladesh. Bangladesh Journal of Plant Taxonomy, 25(2):241-55, (2018)
71. Singh KK, Maheshwari JK., Traditional phytotherapy amongst the tribals of Varanasi district, Uttar Pradesh. Journal of economic and taxonomic botany, 4(3):829-838, (1983)
72. Jeevan Ram AA, Raju VR., Certain potential crude drugs used by tribals of Nallamalai, Andhra Pradesh for skin disease. *Ethnobotany,* 13(1):110–5, (2011)
73. Kumar M, Bussmann RW, Mukesh J, Kumar P., Ethnomedicinal uses of plants close to rural habitation in Garhwal Himalaya, India. Journal of Medicinal Plants Research, 5(11):2252-60, (2011)
74. Aung HT, Sein MM, Aye MM, Thu ZM., A review of traditional medicinal plants from Kachin State, Northern Myanmar. Natural product communication s, 11(3):353-364, (2016)
75. Tarafdar RG, Nath S, Talukdar AD, Choudhury MD., Antidiabetic plants used among the ethnic communities of Unakoti district of Tripura, India. Journal of ethnopharmacology, 160:219-26, (2015)
76. Hossain U, Rahman MO., Ethnobotanical uses and informant consensus factor of medicinal plants in Barisal district, Bangladesh. Bangladesh Journal of Plant Taxonomy, 25(2):241-55, (2018)
77. Saha MR, Kar P, Sen A, De Sarker D., Ethnobotany of Chanchal Block of Malda District of West Bengal (India): plants used in local healthcare. Pleione, 8(2):381-90, (2014)
78. Savithramma N, Yugandhar P, Rao ML., Ethnobotanical Studies on Japali Hanuman Theertham-A Sacred Grove of Tirumala hills, Andhra Pradesh, India. Journal of Pharmaceutical Sciences and Research, 1;6(2):83, (2014).
79. Prasad AD, Shyma TB, Raghavendra MP., Plants used by the tribes for the treatment of digestive system disorders in Wayanad district, Kerala. Journal of Applied Pharmaceutical Science, 3(8):171, (2013)
80. Sahoo N, Manchikanti P., Herbal drug regulation and commercialization: an Indian industry perspective. The Journal of Alternative and Complementary Medicine, 19(12):957-63, (2013)
81. Menthe S, Menthe R., Substitution and Adulteration-Past and Present. Ayushdhara, 4(2):1118-1124, (2017)
82. Morris CA, Avorn J., Internet marketing of herbal products. Jama, 290(11):1505-9, (2003)
83. Shanmughanandhan D, Ragupathy S, Newmaster SG, Mohanasundaram S, Sathishkumar R., Estimating herbal product authentication and adulteration in India using a vouchered, DNA-based biological reference material library. Drug safety, 39(12):1211-27, (2016)
84. Srivastava R., A review on phytochemical, pharmacological, and pharmacognostical profile of Wrightia tinctoria: Adulterant of kurchi. Pharmacognosy reviews, 8(15):36, (2014)

85. Jolly CI, Mechery NR., Comparative Pharmacognostical, Physicochemical And Antibacterial Studies On Seeds Of Holarrhena Antidysenterica Wall And Wrightia Tinctoria R. Br. Indian journal of pharmaceutical sciences, 58(2):51, (1996)
86. Anil ZR, Shrikanth P, Kumar KS, Ravikrishna S, Bairy TS., Comparative pharmacognosy atlas of Pum Kutaja (Holarrhena antidysenterica Wall. Ex A. Dc.) And Stree Kutaja (Wrightia tinctoria (Roxb.) R. Br.). Journal of Pharmacognosy and Phytochemistry, 1;5(3):160, (2016).
87. Atal CK, Sethi PD., Wrightia Tinctoria Bark, an Adulterant of Kurchi. Journal of Pharmacy and Pharmacology, 14(1):41-5, (1962).
88. Techen N, Parveen I, Pan Z, Khan IA., DNA barcoding of medicinal plant material for identification. Current Opinion in Biotechnology, 1;25:103-10, (2014)
89. Savolainen V, Cowan RS, Vogler AP, Roderick GK, Lane R., Towards writing the encyclopaedia of life: an introduction to DNA barcoding. Philosophical Transactions of the Royal Society B: Biological Sciences, 360(1462):1805-11, (2005)
90. Frézal L, Leblois R., Four years of DNA barcoding: current advances and prospects. Infection, Genetics and Evolution, 8(5):727-36, (2008)
91. Munshi S., A study on the evaluation of anti-diarrhoeal efficacy of a polyherbal formulation versus loperamide in rat models. IJPR, 6(11):343, (2016)
92. Kavitha D, Shilpa PN, Devaraj SN., Antibacterial and antidiarrhoeal effects of alkaloids of Holarrhena antidysenterica WALL. Indian Journal of Experimental Biology, 42:589-594, (2004)
93. Sharma DK, Gupta VK, Kumar S, Joshi V, Mandal RS, Prakash AB, Singh M., Evaluation of antidiarrheal activity of ethanolic extract of Holarrhena antidysenterica seeds in rats. Veterinary world, 8(12) :1392, (2015)
94. Ali KM, Chatterjee K, De D BT, 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, 2(3):13-21, (2009)
95. Supriya M, Sachin S, Sharma NK, Dharmendra S., Hypoglycemic effect of Holarrhena antidysenterica seeds on streptozotocin induced diabetic rats. International Journal of PharmTech Research, 2(2):1325-9, (2010)
96. Hegde K, Jaisal KK., Anti-diabetic potential of ethanolic extract of Holarrhena antidysenterica Linn Leaves. Int J Pharma Sci Res, 5:429-35, (2014)
97. Khan A, Khan SR, Gilani AH., Studies on the in vitro and in vivo antiurolithic activity of Holarrhena antidysenterica. Urological research, 40(6):671-81, (2012)
98. Ganapathy PS, Ramachandra YL, Rai SP., In vitro antioxidant activity of Holarrhena antidysenterica Wall. methanolic leaf extract. Journal of basic and clinical pharmacy, 2(4):175, (2011)
99. Ali KM, Chatterjee K, De D, Maiti S, Pathak TK, Ghosh D., Evaluation of antioxidant activity of seed of Holarrhena antidysenterica: An approach through different in vitro models. Journal of Natural Pharmaceuticals, 2(2):115-118, (2011)
100. Bhuiyan MM, Bhuiya NM, Hasan MN, Nahar UJ., In vivo and in silico evaluation of antinociceptive activities of seed extract from the Holarrhena antidysenterica plant. Heliyon, 6(5):e03962, (2020)
101. Verma P, Srivastava S, Rao CV., Hepatoprotective effect of Ethanolic Extract of Holarrhena antidysenterica against Paracetamol Induced Toxicity in Wistar Rats. Research Journal of Pharmacy and Technology, 11(4):1633-9, (2018)
102. Khan A, Bashir S, Gilani AH., An in vivo study on the diuretic activity of Holarrhena antidysenterica. African Journal of Pharmacy and Pharmacology, 6(7):454, (2012)
103. 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. Malaria Journal, 10(1):1-5, (2011)
104. 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. Malaria journal, 12(1):1-6, (2013)
105. Kumar D, Kumar G, Agrawal V., Green synthesis of silver nanoparticles using Holarrhena anti dysenterica (L.) Wall. bark extract and their larvicidal activity against dengue and filariasis vectors. Parasitology research, 117(2):377-89, (2018)
106. Mrinal NS, Bansal N., Antiamnesic Activity of Holarrhena antidysenterica Extract in Streptozotocin -Induced Memory Deficient Rats. Scholars Academic Journal Pharmacy, 5(8):317-25, (2016)