



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

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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 antidysenterica* 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 *Asclepodiaceae* 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 Tibetan 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	<i>Holarrhena</i>
Species	<i>antidysenterica</i>

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 lobes 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 ergosterol. 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, isoconessimine, conimine, holacetin, konkurchin, holadysenterine, isoconessimine and kurchessine, holarrifine, kurchamide, kurcholessine, trimethylkonkurchine, (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, konkurchine, 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 3 β -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-icosadienoic 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 siloxyheptadecane, 5,9,10 -2H,6h-pyrano[3,2-b] xanthen-6-one, dl-alpha-tocopherol succinate, desmosterol, campesterol, cholesta-22,24-dien-5-ol, methyltribenzocentrotriquinanol and lanosta-8,24-dien-3-one [44].

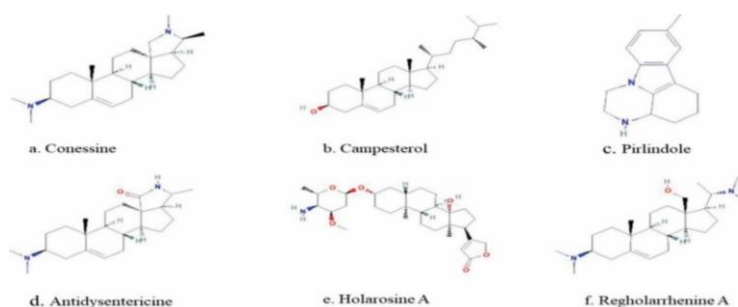


Figure 2. Phytochemical Structures of Some of Phytochemical Constituents of *Holarrhena antidysenterica*

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 Chooranam and Chandra Kalka [59,60]. Uses of some of the Ayurvedic formulations are discussed below:

Kutajarista: The description of this polyherbal 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 exhibited 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 libitum. 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.

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CONFLICT OF INTEREST:

None

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