



Ethno-pharmacology of *Holarrhena antidysenterica* wall. ex g. don. (*Tewāj*) in light of unani system of medicine

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Abstract

Medicinal plants (millennia) are highly esteemed all over the world due to the effectiveness, low cost and minimal side-effects associated with drugs derived from them. *Holarrhena antidysenterica* Wall. Ex G. Don. (Syn: *Holarrhena pubescens* Wall. Ex G. Don.) is an important medicinal plant belonging to the family Apocynaceae. It is a shrub or a small tree commonly found in all part of the country. It is commended for the medicinal applications of its Bark, Seeds, and leaves in Unani System of Medicine. It is most widely used medicine in Unani for the treatment of dysentery and diarrhoea. It is known by different vernaculars in different parts of the country such as Kadvo-indarjou in Gujrati, Keor in Kashmir, Tita-indarjou in Bengali, Amkudu in Telgu, Erukalaipalai in Tamil, and in English it is called Conesse bark or Tellicherry bark. Various phytochemical constituents have been isolated from *Holarrhena antidysenterica* in which coumarins, steroidal alkaloids, flavonoids, ergosterol, phenolic acids, resins, tannins, saponins, and triterpenoids are primary phytoconstituents. Conessine is the principal alkaloid of *Tewāj*, used as a therapeutic drug for the treatment of dysentery, and helminthic disorders. The plant also possesses various traditional pharmacological activities such as Antioxidant, Antibacterial, Antidiarrheal, Antidiabetic, Hepatoprotective, Antifertility, Analgesic, anti-urolithic, wound healing and acetylcholinesterase inhibitory activity. This review explores the complete profile of *Tewāj* (*Holarrhena antidysenterica*) with the reference of Unani medicine.

Keywords: unani, *Tewāj*, *Holarrhena antidysenterica*, conessine, dysentery

Introduction

It is a deciduous shrub or a small tree, which belongs to Apocynaceae family. The family "Apocynaceae" is one of the largest families in the plant kingdom [1]. *Holarrhena antidysenterica* Wall. Ex G. Don. (Syn: *Holarrhena pubescens* Wall. Ex G. Don.) is also known as "Conesse bark", "Tellicherry bark" in English, and "Vatsaka" in Sanskrit. It is distributed throughout India up to an altitude of 4,000 feet. [2] It has been used in British Materia Medica for a long time and is also mentioned in some Persian and Urdu Unani Materia medica books. The tree forms a part of several indigenous systems of medicine, where has been used in the treatment of diarrhoea and dysentery. The various parts of *H. antidysenterica* such as bark, root, stem, and seeds are used as medicine and reported in many traditional systems including Unani and Ayurveda [3]. A number of pharmacological properties of *H. antidysenterica* have been verified and proved on experimental trials on animals, as well as several studies have been done on isolation and characterization of phytochemicals. The tree is having lots of pharmacological activities such as antibacterial, antimicrobial, antidiarrheal, anti-diabetic, antioxidant, Anthelmintic activity, hepatoprotective, anti-urolithic, etc. [4]

Historical background

This tree is popular for its numerous medicinal properties considered to be the most popular valuable medicinal product. The tree is fabled to have sprung from the drops of amrita which fell on the ground from the bodies of Rama's monkey, which were restored to life by Indra. The bark of the tree is one of the most important parts which is described as bitter, astringent, cold, and digestive in the Nighantas. It was also described by Sushruta as an expectorant, an antidote to poison. According to Charaka and Sushruta, every part of the plant except the flower is used as a snakebite remedy and some Unani authors have also disputed this property. The seeds of the tree were also described by Arabic and Persian writers as carminative and astringent under the name of Lisan-ul-asafir-ul-murr and Zanban-i-gungishk-i-talkh (bitter sparrow's tongue). The Conessi bark was also described by Portuguese physicians under the name of Codagapala and Corte-de-pala, who stated that the bark is applied as a lep (plaster) in rheumatism and the hot decoction of its bark is used in toothache. The plant is widely cited in the literature for various medicinal preparations especially dysentery-related matters which signify from its species name also i.e. antidysenterica [5, 6].

Habitat and geographical distribution

The tree is found in tropical and subtropical regions of Asia and Africa. It is abundant in India and distributed throughout India up to an altitude of 4000 feet especially in deciduous forests of the tropical Himalayas and open wastelands. This tree also has traditional and folklore value in India and people offer leaves of this tree along with rice in Odisha during the festival of "Nabanna". The tree is also found in Burma, Sri Lanka, Pakistan, Nepal, and Africa. It is also cultivated as an ornamental plant for its beautiful flowers which appear before the appearance of the leaves and are often produced in the month of September-November [7, 8, 9].

Table 1: Taxonomical classification [10]

Kingdom	Plantae
Subkingdom	Tracheobionta
Superdivision	Spermatophyta
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Asteridae
Order	Gentianales
Family	Apocynaceae
Genus	Holarrhena
Species	<i>Holarrhena antidysenterica</i>

Vernacular names [11, 12, 13, 14]

Arabic: Lisan-ul-Asafir, Lasanulasafirmurr, Tivreja

English: Conesse bark, Tellicherry bark, Kuruchi

Urdu: Inderjao Talkh

Persian: Indarjvetalkh, Tukhmeaharetalkh, Zabanejunjashketalkh

Hindi: Dhudi, Karchi, Kari, Karra, Kaura, Kaureya, Kora, Kura, Karvaindarjau

Sanskrit: Kutaja, Pandura, Girimallika, Indra, Indradu, Indrayavaphala, Kalinga, Katuka, Kauta

French: Conessie

Kashmiri: Keor, Kewar, Kor

Bengali: Kurchi, Tita-indarjou

Assamese: Dudcory

Gujrati: Kadvo-indarjou, Kuda, Dhowda, Hath, Hathbaha, Indra-jwanunjad

Marathi: Kadu-indrajau, Brdaki, Kodaga, Kuda, Kurra, Pandharakurra, Pandharakuda

Telugu: Amkudu, Girimalika, Kalingamu, Kodaga, Kodise, Kodisepala, Manupala, Palabarra

Kannada: Kodasige

Tamil: Erukkalaipalai, Indrabam, Kasappuveppalai, Kalingam, Kirimalligai, Kudasam

Malyalum: Kaippakkotakappala, Kotakappala, Pala, Palapatta, Panialai, Venpala

Uriya: Kherwa, Krya, Patrukurwan, Pitakorwa, Pittakrya, Potrokrya

Nepal: Karingi, Kirra, Kurra

Portuguese: Coru, Herva du Malabar, Kudo

Ethnobotanical description of *Holarrhena antidysenterica* (Tewāj)

Holarrhena antidysenterica is a deciduous shrub or a small tree, which attains a height up to 30-40 feet and a girth of 4 feet with a clear bole of 10-20 feet and produce milky white and less profuse latex. The stem bark of the tree is greyish-brown, rough, and peeling off in irregular flakes with a bitter taste. The bark of the root is the same as the old stem

but is more of a rusty brown in colour. Its leaves are simple, ovate, large, smooth, or hairy, arranged opposite to each other and about 4-12 inches × 2-5 inches in size.

The base of the leaves is obtuse, often rounded or acute. The nerves of leaves are in 10-14 pairs, opposite and sessile. Its petioles are 1.5 cm in length and cymes are 3-6 cm in diameter. [7, 8] The flowers of the tree are white, small, and arranged in a cluster which looks like a flattened top. The petals are disc-shaped and overlap towards the right side. Corolla is 3-4 times longer than calyx and anther is present inside the corolla tube. Its seeds are 0.3-0.5-inch-long, linear, or oblong concave with a long coma or boat-shaped which is light brown in colour marked with linear lines and shows epigeal germination. The taste of the seeds is bitter and hairs are present at the apex of the seeds. The fruits have long follicles about 6-18 inches in length and 0.2-0.4 inches in diameter, which looks like two slender pencils arising from a node and these follicles have white warty spots on the surface. The dried fruits when busted it releases numerous flat seeds with brown hairs. The hairs are short-lived [3, 7, 15, 16].

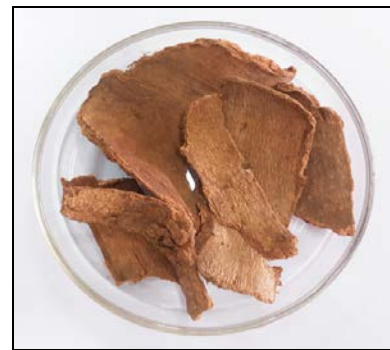


Fig 1: Bark of *Holarrhena*



Fig 2: Seeds of *Holarrhena antidysenterica* (Tewāj)



Fig 3: Leaves of *Holarrhena antidysenterica* (Tewāj)

Description of *Holarrhena antidysenterica* (Tewāj) in unani system of medicine

This is a small to medium sized tree, about 8-10 feet in height and gives white milky latex. Bark, Seeds, and leaves are the parts (*Hissa-i-Musta'mela*) which used as medicine in Unani System of Medicine. [12, 17, 18] The bark of tree is brown in colour and resemble to the bark of "Chunar" tree. According to some physician, it is a "Talisfer" externally, and some said that this is a bark of "Kadwa Wialyati" that's why ancient Unani physician called it *Kadwa Wilayati*. It keeps origin from "Khataa" that's why also called it *Tewāj-e-Khatai*. It is bitter in taste, found mostly on Himalayas regions. The flowers are white, shiny, arranged in cluster form and the seeds of the plant are like Barley, which is bitter in taste [19, 20, 21]. There are three mode of treatment in Unani System of Medicine such as Ilaj bil tadbeer wa ghiza, Ilaj bil dawa and Ilaj bil yad, and *Tewāj* is used as Ilaj bil dawa [22].

The *Mizāj* (temperament) of *Tewāj* is Har 2 Yabis 2 (Hot 2 & Dry 2) as suggested by the majority of the Unani physicians and some said Barid 2 Yabis 2 (Cold 2 & Dry 2). It is described *Muzir* (harmful) for hot temperament people. The *Muṣleh* (corrective drugs) used for its harmful effects are *Katīra*, *Isapgol*, *Roghan-i-Badām* (Almond oil), and *Bazur Qutuna*. The *Badal* (substitute) of *Tewāj* is *Anjbār* and *Dam-ul Akhwain* but it is strongly recommended to use original drug as far as possible. The *Miqdār-i Khurak* (dose) is 2-3 gm or masha and it may be used up to 4.5 gm or maasha as per classical unani literature [18-21, 23].

In Unani System of Medicine, *Tewāj* has been used as a single drug or as a compound formulation (*Murakkabāt*) for the management of various diseases. *Jawārish Zarūnī ba nuskhā kalān*, *Mājūn Sa'lab*, *Safūf Tiryāq*, *Mājūn Chobchini*, *Hab Hind*, etc. some are the common formulation which has been used from thousands of the years of clinical experience of Unani physicians in which *Tewāj* is an ingredient of it. These formulations are named on the basis of their chief ingredient or the disease condition in which it has to be used [18].

Afa'al (Pharmacological actions) of *Holarrhena antidysenterica* (Tewāj) in unani [13, 18, 19, 20, 23]

Qābiḍ (Astringent), *Hābis al-Dam* (Haemostatic), *Ḥabis-Ishāl* (*Antidiarrheal*), *Kasir-i-Riyāh/Muḥallil-i-Riyāh* (Carminative), *Muqawwiye-i-Bah/Muḥiyiye-i-Bah* (Aphrodisiac), *Muqawwiye-i asab* (Nervine tonic), *Mudirr-i-Bawl* (Diuretic), *Muḥallil-i-Waram* (Anti-inflammatory), *Mufattit-i-Ḥaṣāh* (Lithotriptic), *Mushtahī* (Appetizer), *Dāf 'i-Bukhār* (Febrifuge), *Mugharrī* (Stimulant), *Muwallid-i-Manī* (Spermatogenic), *Qātil-i-Dīdān-i-Am 'ā'* (Antihelminthic)

Mawāq-i-Istemāl (Therapeutic Uses) of *Holarrhena antidysenterica* (Tewāj) in unani [13, 18, 19, 20, 23]

Ishāl Muzmin (Chronic Diarrhoea), *Zahīr Muzmin* (Chronic dysentery), *Bawāsīr* (Haemorrhoids), *Waram al-Litha* (Gingivitis), Toothache, *Nazla* (Cold), *Zukām* (Catarrh), *Sailan al-Raḥem*, *Sudā'* (headache), *Nakseer* (Epistaxis), *Ṭā'ūn* (Plague), *Shuqāq al-Maq'ad* (Anal Fissure), *Judhām* (Leprosy), *Ḥummā* (Fever), *Iḥtibās al-Bawl* (Retention of urine), *Dīdān al-Am 'ā'* (Worms infestation), Burning sensation, also used in many other skin diseases, good in erysipelas, hallucinations, and chronic bronchitis.

Table 2: Ethnomedicinal use of different parts of *Holarrhena antidysenterica* (Tewāj)

Therapeutic indication(s)	Part used
Dysentery	Leaves [24]
Diarrhoea	Seeds [25], Bark [26] and Fruit [27]
Wound healing	Leaves [28] and Latex of Plant [27]
Worm infestation	Bark [29]
Diabetes	Seeds, leaves and bark [30]
Cancer	Leaves [31] and bark [32]
Malaria	Root [33] and bark [34]
Hepatic Disorders	Leaves [35] and bark [36]
Inflammation	Leaf [37] and bark [38]
Rheumatism	Stem bark [27]
Urinary tract infection	Seed [39]
Convulsion	Seeds [40]
Hypertension	Seeds [41]
Pediatric care	Seeds [27]
Gynecological complaints	Bark [42]

Phytochemical constituents of *Holarrhena antidysenterica* (Tewāj)

Stem, bark, leaves, and seeds of the plant are reported to contain a number of chemical constituents in which coumarins, steroidal alkaloids, flavonoids, ergosterol, phenolic acids, resins, tannins, saponins, and triterpenoids are primary phytoconstituents [15]. Around 25 alkaloids (1.5-3%) have been isolated from the plant, mostly from the bark. They are C21 group steroidal alkaloids [43]. The bark of this tree contains steroidal alkaloids (up to 2.5%). Conessine, 7-a-hydroxy conessine, holonamine, dihydroisoconessimine, 3-aminoconan-5-ene and kurcholessine are the steroidal alkaloids isolated from the bark of this plant. Conessine is the principal alkaloid of *Tewāj*, yield up to 0.4%, which is a stenol and structure resemble with 7-ergosten-3-ol and Y-stigmastanol. [7] The Conessine is used as a therapeutic drug for the treatment of dysentery and helminthic disorders. Other alkaloids such as regholarrhenine A-F, pubescine, norholadiene, pubescimine, kurchinin, kurchinine, holarrifine, holadiene, etc are also reported to be found in the bark of this plant. [11, 44] New steroidal alkaloids, named holadysenterine (C23H38N2O3) and antidysentericine, have been isolated from the plant of *Holarrhena antidysenterica*. [45, 46] Leaves contain kurchiphylline, kurchiphyllamine, kurchaline, holadysine, and holadysamine. The root bark of this plant has been reported to be the occupants of steroidal alkaloid that is holacetine. In addition to the alkaloids, *Tewāj* also contain gum (9.5%), resin (0.2%), and tannin (1.14%). Lupeol and β-sitosterol (triterpene alcohol) have been isolated from the unsaponifiable matter of the bark. The seeds of the plant contain many of the alkaloids present in the bark but in a lower concentration up to 1.82%. The seeds yield 19-30% of a greenish-yellow oil drying with penetrating odour and a mild taste. The components of the fatty acids of the oil are linolenic acid, linoleic acid, oleic acid, palmitic acid, stearic acid, and lignoceric acid. [47] Few other bio-organic components such as isoconessine (C24H40N2), conessimine/ isoconessimine (C23H38N2), conarrhimine (C21H34N2), norconessine, dioxyconessine, conkurchine, conessidine, lettocine, N3- Methyl hollarhimine were isolated from the plant. A small amount of calcium, potassium, glycosides, steroids, carbohydrates, crude fibers and crude proteins are also present [12, 14, 43, 45].

Pharmacological activities of *Holarrhena antidysenterica* (*Tewāj*)

Antibacterial activity

Tewāj was assessed for its antibacterial activity using Agar well diffusion method, which demonstrated good antimicrobial activity against microbial strains such as *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella species*, *Proteus species*, *Pseudomonas species*, *Salmonella species*, and *Vibrio cholera* [48].

Anti-diarrhoeal activity

Seed extract exhibited significant antidiarrheal activity in castor oil and *E. coli* induced diarrhoea in Wistar rats as it showed a significant increase in the dry weight of their faeces and reduction in defecation drops [25].

Wound healing activity

A significant wound healing activity was observed, the wound contraction was better in the animals (Wistar Albino rats) treated with 5% gel prepared with the ethanolic extract of leaves of *Holarrhena antidysenterica* as compared to the control group [28].

Antioxidant activity

Among the various extracts, methanolic extract of leaves and methanolic and aqueous extract of bark showed the highest free radical scavenging activity in a concentration-dependent manner with inhibition of more than 90% DPPH free radicals at 0.1 mg/mL whereas hexane extract showed weak DPPH radical scavenging activity [30, 49].

Anthelmintic activity

The bark extracts showed significant dose-dependent anthelmintic activity, as paralysis, as well as the death of the earthworms, was observed. The most potent activity was observed with the alcoholic extract at the dose of 40mg/ml. [29].

Antidiabetic activity

It reduced the blood sugar level ($P < 0.05$) in alloxan and streptozotocin-induced diabetic rats and possesses significant dose-dependent anti-diabetic activity [50-54].

The stem bark exhibited significant ($p < 0.05$) hypoglycaemic activity in the fasted normal mice and maximum activity was observed with the methanolic extract at the dose of 500 mg/kg b.w. with a reduced percentage of blood glucose of 39.7% during 1-2 h of treatment [30].

Anti-Amnesic activity

The seed extract significantly decreased the level of AChE (acetylcholinesterase), prevented the rise in TBARS (thiobarbituric acid reactive substances) levels, and GSH (glutathione) depletion in a dose dependent manner in Streptozotocin-induced Memory Deficient Rats [55].

Anti-Cancer activity

The leaf extract (95% and 50%) showed significant cytotoxic activity against seven human cancer cell lines OVCAR-5 (ovary), HT-29 (colon), SK-N-MC (neuroblastoma), HEP-2 (liver), COLO-205 (colon), NIH-OVCAR-3 (ovary) and A-549 (lung) [31].

The bark extract of *H. antidysenterica* inhibited cell viability and BrdU incorporation and induced apoptotic cell death in Ca9-22 gingival and HSC-3 tongue SCC cells and

act as a safe anticancer agent against OSCC growth and OSCC-mediated bone resorption [32].

Antimalarial activity

It exhibited potent antimalarial activity against *Plasmodium falciparum* K1 strain and *Plasmodium berghei* NK65 strain [33, 34, 56].

Hepatoprotective activity

Leaves and bark extracts showed dose-dependent hepatoprotective activity in carbon tetrachloride (CCl_4) and paracetamol (PCM) induced hepatic damage in rats by lowering the levels of enzyme-like SGPT, SGOT, ALP, and total bilirubin. The histopathological examination of the liver revealed that the hepatic cells, central vein, and sinusoids are almost normal, it reduced the severity of liver damage, formation of fibrous septa and also restricts the liver weight loss induce by PCM and CCl_4 [35, 36].

Anti-Inflammatory activity

The leaf extract showed dose-dependent anti-inflammatory activity in Carrageenan-induced rat paw edema in Swiss-albino mice. The bark extract exhibited an anti-inflammatory effect by decreasing the levels of nitric oxide and malondialdehyde, and increased levels of superoxide dismutase and glutathione in 2, 4-Dinitrobenzene sulfonic acid-induced colitis in male albino Wistar rats [37, 38].

Analgesic activity

The leaf extract showed dose-dependent analgesic activity in tail-flick test (centrally acting analgesics) and acetic acid-induced writhing method (peripherally acting analgesics) in an experimental animal model [37].

Anti-Urolithic activity

It significantly reduced the size of crystals and transformed the calcium oxalate monohydrate (COM) to calcium oxalate dehydrate (COD) crystals *in vitro* and thereby reduced the cell toxicity and production of lactate dehydrogenase. Along with there is a reduction in polyurea, water consumption, calcium ions excretion, and crystal formation [39].

Anti-Convulsant activity

The seed extract exhibited dose-dependent anticonvulsant activity in swiss-albino mice that significantly reduced the duration of seizures induced by maximal electroshock (MES) and significantly delayed the onset of tonic seizures in pentylenetetrazol (PTZ) induced experimental model [40].

Acetylcholinesterase inhibitory activity

The seed and bark extracts showed potent AChE inhibitory activity with an IC_{50} value of 6.1 $\mu\text{g/mL}$ (Ellman's method in 96-well microplates assay) and 1.44 to 23.22 μM (bioautographic assay), respectively [45].

Antihypertensive activity

The seed extract exhibited anti-hypertensive activity on the basis of its ability to inhibit the secretion of angiotensin and angiotensin-converting enzyme, which causes vasoconstriction and leading to increased blood pressure. Among them, ethanolic extract revealed adequate 24% angiotensin-converting enzyme (ACE) inhibition [41].

Antimutagenic activity

The bark extract exhibited dose-dependent anti-mutagenic activity in methyl methane sulphonate (MMS) and sodium azide (NaN₃) induced mutagenicity in *Salmonella typhimurium* strains (TA 97a, TA 100, TA 102 and TA 104)^[57].

Diuretic activity

The seed extract exhibited dose-dependent diuretic activity in Wistar rats and showed a significant increase in urine output at the dosage range of 30-100 mg/kg. In addition, a substantial increase was also observed in the amount of Na⁺ and K⁺ ions excreted through urine of tested rats^[58].

CNS depressant activity

It exhibited dose-dependent CNS depressant activity by adopting open field test, hole cross test, Rota rod and actophotometer in Swiss-albino mice, as the extract significantly decreased the locomotor activity as well as spontaneous motor activity and decreased in grip by rota-rod^[59, 60].

Radioprotective effect

The root extract exhibited radioprotective effect under *in vitro*, *ex vivo* and *in vivo* conditions of radiation exposure as the extract protects cellular DNA from deleterious effects of radiation and hence it may be useful to prevent genomic insults from radiation^[61].

Antifertility activity

The seeds of *Holarrhena antidysenterica* have also been reported to have antifertility activity^[62].

Conclusion

Holarrhena antidysenterica have been reported as various traditional healers to treat various diseases of mankind. Diseases have been associated with humans since their very existence. They reduce the health of humans and even lead to death in severe cases. *Holarrhena antidysenterica* as promising very potent and effective drug which has been using as single and compound formulation in Unani System of Medicine for several medical applications because of its effectiveness and safety. It is reported that, it is very useful drug for dysentery and diarrhoea and it has been proved by many studies of antimicrobial activity against various microbes. Traditionally, it has been used to treat diarrhoea, dysentery, and helminthic disorders. But in the past few years, experimental studies have made it possible to discover more pharmacological properties of the plants such as anti-inflammatory, anti-oxidant, anti-malarial, analgesic, Anti-amnesic and Hepatoprotective activities. A number of biologically active compounds isolated from various parts of *Holarrhena antidysenterica* which belongs to various chemical groups. The isolated components belong to coumarins, alkaloids, flavonoids, ergosterol, phenolic acids, resins, tannins, saponins, terpenoids, Fatty acids, Essential oils and some other miscellaneous compounds. In last it can be concluded that it is an important plant origin drug of Unani System of Medicine which can be used frequently by physicians according to its vast pharmacological actions. Though, *Holarrhena antidysenterica* has various medicinal applications, but there is need to explore more medicinal values at molecular level.

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