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REVIEW ARTICLE

Unravelling the therapeutic spectrum of *Holarrhena antidysenterica* (G.Don) Wall. ex A.DC.: Mechanistic insights of its bioactive potential in human health

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Abstract

The Ayurvedic and Siddha medicine, *Holarrhena antidysenterica* (G.Don) Wall. ex A.DC., a medicinal plant belonging to the family Apocynaceae, has a rich history in the treatment of skin, inflammatory and gastrointestinal diseases. Recent research indicates that it can also safeguard the liver and the nervous system. A wide variety of chemical compounds are found in this medicinal plant, including flavonoids, iridoids, triterpenoids, steroids and glycosides; conessine, holarrhenine and quercetin are the important ones. The antioxidant activity of methanolic extract of leaves is strong with DPPH scavenging (IC_{50} = 46.3 ug/mL) and superoxide scavenging (IC_{50} = 58.7 ug/mL) comparable to ascorbic acid. The plant lessens the damage through enhancing antioxidant enzyme synthesis and decreasing inflammation in animal models of liver injury induced by alcohol, paracetamol and chloroform. Mechanistic analyses indicate that the nuclear factor erythroid 2-related factor 2/antioxidant response element pathway is activated, NF-kB signalling is inhibited, transforming growth factor-beta and alpha smooth muscle actin are downregulated and there is a reinstatement of superoxide dismutase, catalase and glutathione. The neuroprotective effects involve acetylcholinesterase inhibition, anxiolytic, antidepressant and anti-seizure effects, that probably acting via reduced oxidative stress and altering the microglial inflammatory mediators. This evidence highlights the need for standardised extraction, dose optimisation and human studies. *Holarrhena antidysenterica* shows potential for further research on its liver and nervous system benefits and may serve as a basis for future phytotherapy development.

Keywords: *Holarrhena antidysenterica*; hepatoprotection; inflammation; neuroprotection; oxidative stress; pharmacology; phytochemistry

Abbreviations : AChE: Acetylcholinesterase; ADME: Absorption, distribution, metabolism and excretion; ALP: Alkaline phosphatase; α-SMA: Alpha smooth muscle actin; ACE: Angiotensin converting enzyme; BAX: Bcl-2-associated X protein; BAK: Bcl-2 homologous antagonist; BW: Body weight; CAT: Catalase; CNS: Central nervous system; COX: Cyclooxygenase; CYP: Cytochrome P450; DAMP: Damage-associated molecular pattern; ECG: Electrocardiogram; GLP: Good laboratory practice; GCLC: Glutamate-cysteine ligase catalytic subunit; GSH: Glutathione; GPx: Glutathione peroxidase; HO-1: Heme Ooxygenase-1; HSCs: Hepatic stellate cells; OH-: Hydroxide; iNOS: Inducible nitric oxide Ssynthase; IL: Interleukin; IC_{50}: Half maximal inhibitory concentration; LD_{50}: Lethal dose; LOX: Lipoxygenase; MDA: Malondialdehyde; MIC: Minimum inhibitory concentration; Nrf2: Nuclear factor erythroid 2-related factor 2; NAFLD: Non-alcoholic fatty liver disease; NF-κB: Nuclear factor kappa B; NQO1: NAD(P)H quinone dehydrogenase 1; ROS: Reactive oxygen species; SGOT: Serum glutamic-oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; SAR: Structure-Aactivity relationship; SOD: Superoxide dismutase; STZ: Streptozotocin; TGF-β: Transforming growth factor beta; TNF-α: Tumour necrosis factor alpha; UPLC-MS: Ultra performance liquid chromatography-mass spectrometry.

Introduction

Since ancient times, medicinal plants have formed the basis of traditional medical systems worldwide. In India, ayurvedic medicine has long utilised botanicals to address neurological, gastrointestinal, metabolic, respiratory, dermatological and hepatic disorders. Ancient texts such as the Rig Veda, Sushruta Samhita, De Materia Medica, the Ebers Papyrus and the Pen Tsao highlight early recognition of medicinal plants. Among the medicinal plant families, Apocynaceae is recognised for its healing properties (1), largely due to its indoline and steroidal alkaloids. This family includes numerous tropical trees, shrubs and vines that typically produce milky sap and have traditionally been used to treat digestive issues, fever, malaria, pain, diabetes-related skin conditions and parasitic diseases. Some species also serve as timber sources or ornamental plants (2).

Holarrhena antidysenterica (G.Don) Wall. ex A.DC. is known as Kutaja or kurchi, is a key Apocynaceae member listed in the World Flora Online database as Numer. List no. 1672 (1829) (3). Ancient

Ayurvedic literature documents its use against intestinal parasites, liver diseases, gastrointestinal issues, diarrhea and dysentery. As a traditional ethnomedical remedy with growing pharmacological evidence, its therapeutic potential especially in hepato-pathology and neurology warrants close examination. The plant grows in dry forests and scrub areas across tropical and subtropical India and its bark, seeds and leaves are used in tribal and Ayurvedic practices (1, 4).

Phytochemical and pharmacognostic studies show that *H. antidysenterica* contains steroidal alkaloids (conessine, isoconessimine, conessimin, conarrhimine, conimin), flavonoids, phenolic acids, saponins, triterpenoids and tannins. Steroidal alkaloids are of particular interest due to their biological activity. The plant exhibits anti-inflammatory, hepatoprotective, antioxidant and antidiabetic effects and as its species name suggests, it is well known for treating dysentery. Consequently, researchers have explored its antidiarrheal, antimicrobial, anti-inflammatory, antioxidant, antidiabetic and hepatoprotective properties (2, 5). Hydro-ethanolic extracts exhibit two effects, spasmogenic and spasmolytic at different dosages, suggesting that they have both a complex effect on gut motility by blocking the calcium-channel and histamine-receptor. These results indicate its conventional application in colitis, constipation and diarrhea. Since there is an increased prevalence of liver and neurological diseases, its therapeutic scope should also include gastrointestinal conditions.

Liver inflammation, chronic liver failure, non-alcoholic fatty liver disease (NAFLD) and hepatotoxicity by xenobiotics are life-threatening diseases. There is preliminary evidence indicating that the hepatoprotective effects of the ethanolic leaf and bark extracts of *H. antidysenterica* alleviated liver damage in chloroform- or paracetamol-induced rat models without affecting hepatocyte integrity (6). Such preliminary results are encouraging and should be reviewed further. Similarly, the prevalence of other neurological diseases like strokes, neuropathies, Parkinson's disease, Alzheimer's disease and metabolic cognitive impairment are also on the rise. Some of these conditions are associated with excitotoxicity, cholinergic dysfunction, neuroinflammation and oxidative stress. Steroidal alkaloids of the seeds inhibit acetylcholinesterase, indicating neuroprotective and anti-amnesic activity, but the neurological usage has not been studied as extensively.

Holarrhena antidysenterica traditionally has been used gastrointestinally but is currently being researched with an extended use in non-communicable diseases. Its alkaloids can regulate cholinergic signaling and its phenolic and flavonoid (7) can mitigate oxidative stress which provides mechanistic rationale of its hepatoprotective and neuroprotective actions (8). Generally, this introduction will provide a comprehensive analysis of the ethnobotany, phytochemistry, pharmacology, mechanisms of action and translational potential of the plant especially its hepatoprotective and neurotherapy applications. Ayurveda is a system of vata, kapha and pitta and it is still the centre whereas Unani and Siddha play a limited role in the region where such a plant is not fully used (1). This review will assess its contribution to liver disease and neurological disorders, including conventional applications, phytochemistry, mechanisms, pre-clinical evidence, gaps in the research and translational opportunities.

Methodology

The literature search was done to review the phytochemistry, pharmacological activities and therapeutic potential of *H. antidysenterica* as applied in the liver and neurological diseases. Several electronic databases, such as PubMed, Scopus, Web of Science, Science Direct, Springer Link and Google Scholar, were searched. Only peer-reviewed studies (in English) on *H. antidysenterica* were considered, provided they reported phytochemical constituents or pharmacological activities such as hepatoprotective and neuroprotective effects. Research covering liver and neurological disorders, using any plant part and any experimental design, qualified for inclusion.

Studies lacking plant-specific phytochemical or pharmacological findings were left out, along with inaccessible full texts, non-English articles, abstracts, editorials and unpublished theses. Duplicate reports, works focused solely on related *Holarrhena* species and methodologically weak studies were similarly dropped. Database searching identified 250 records and then 30 more records were obtained via manual search and reference lists. With the elimination of duplicate records, 240 unique records were obtained. Screening of these studies was done according to titles and abstracts, resulting in 110 records being eliminated due to their irrelevance. A total of 130 full text articles were evaluated in terms of eligibility. Out of all full-text, 77 articles were eliminated due to lack of phytochemical or pharmacological data, unavailability of full texts, or inadequate experimental information. Out of these, 53 full text articles were selected for the current study. Variables that were extracted: parts of plants used, extract types, active compounds, experimental models (*in vivo* or *in vitro*), dosage, administration routes, pharmacological outcomes, mechanisms of action and safety or toxicity evaluation. The focus was made on hepatoprotective and neuroprotective functions (9). The PRISMA diagram (Fig. 1) summarises the selection process and flow of the study.

Taxonomy and morphology

The detailed taxonomic hierarchy and key morphological characteristics of the species are tabulated in Table 1 and illustrated in Fig. 2 (10, 11).

Pharmacognostic characterisation of *Holarrhena antidysenterica*

The microscopic features of *H. antidysenterica* are very important in the pharmacognostic characterisation of the plant, especially the crystalline inclusions and starch-rich parenchyma. These locations are useful anatomical features in normalising raw plant material (11). Transverse section reveals that the parenchymatous area surrounding medullary rays includes many grains of starch and the outer cortex does not include prismatic calcium oxalate crystals (12, 13). The cortex in the bark is wide and is made up of polygonal parenchymatous cells, which contain starch granules, prismatic crystals and scattered stone cells (14, 15).

Phytochemicals identified in *Holarrhena antidysenterica*

The extraction of *H. antidysenterica* bark was done by taking ethanol as a solvent by. After this, Gas Chromatography-Mass Spectrometry an Agilent 8890 GC system and a 5977 MSD was employed to reveal the presence of 15 different bioactive substances that fall into the 4 main groups of phytochemicals: volatile metabolites, phenolic acids, sterols and fatty acids. An ideal temperature programme (75 to 300 °C; 53.5 min) was used for the analysis to match spectra with the

Table 1. Morphology and taxonomic features of *Holarrhena antidysenterica*

Category	Details
Synonyms	*Holarrhena febrifuga* (Roxb. ex-Fleming) K. Schum.; *Holarrhena antidysenterica* (L.) R. Br. (syn. in older texts) *Holarrhena pubescens* Wall. ex G. Don;
Common names	Kurchi, Tellicherry bark, Conessi bark, Ivory wood and Fever pod
Vernacular names	Sanskrit: Kutaja, Indrayava • Hindi: Kurchi, Indrajau • Tamil: Vettupaalai • Telugu: Kodisapala • Malayalam: Karingotta • Kannada: Kodasige • Bengali: Kurchi • Marathi: Indrajav • Gujarati: Kuda
Native region	Native to tropical and subtropical regions of the Indian subcontinent
Geographical locations	Vastly located in all over India, Sri Lanka, Nepal, Bangladesh and Myanmar; also found in Southeast Asia (Thailand, Cambodia, Vietnam) and occasionally in Africa
Habitat	Common in dry deciduous forests, open woodlands, scrub jungles and hill slopes; prefers well-drained loamy or sandy soils; altitudinal range: up to 1200 m
Propagation	Naturally propagated by seeds; also propagated vegetatively by stem cuttings or root suckers; seeds require light for germination and moderate moisture
Habit	Small deciduous tree or large shrub, 4–10 m tall, with milky white latex exudate; bark rough, pale grey to yellowish-grey
Flowering	February to June (may vary regionally); profuse flowering occurs before leaf emergence
Flower longevity	Individual flowers last 2–4 days; inflorescences remain in bloom for 2–3 weeks
Stem	Cylindrical, woody; young branches pubescent; bark corky, pale grey with transverse cracks and lenticels; exudes white latex when cut
Leaves	Simple, opposite, short-petioled, elliptic to oblong (8–20 cm × 3–8 cm), glabrous above, slightly pubescent beneath; pinnate venation with 10–15 pairs of lateral veins; apex acute and base rounded
Inflorescence	Terminal or axillary corymbose cymes; many-flowered; peduncles pubescent; flowers fragrant and white
Calyx	Small, 5-lobed, persistent; lobes ovate-lanceolate, pubescent, green; 2–3 mm long
Corolla	Salverform, white; tube long (1–1.5 cm), slender, with five spreading lobes; fragrant; aestivation twisted
Androecium	Anthers are sagittate and connivant around the stigma, forming a cone; stamens 5 are epipetalous and placed close to the base of the corolla tube.
Gynoecium	Bicarpellary, syncarpous at base, ovaries free above; superior ovary with two follicles; style slender; stigma head-shaped; ovules numerous on parietal placentation

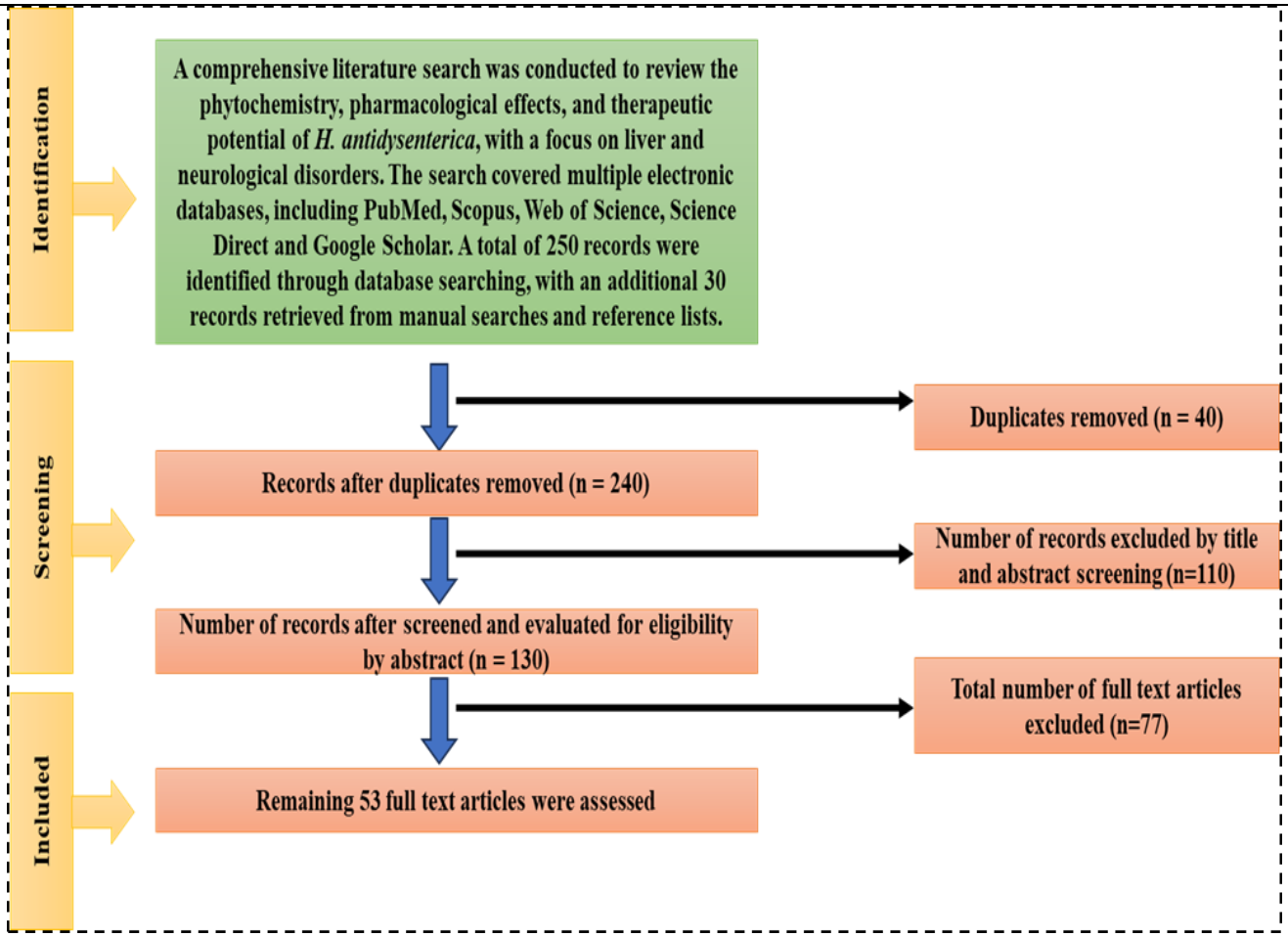


Fig. 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram depicting the process of selection of the studies included in the review.

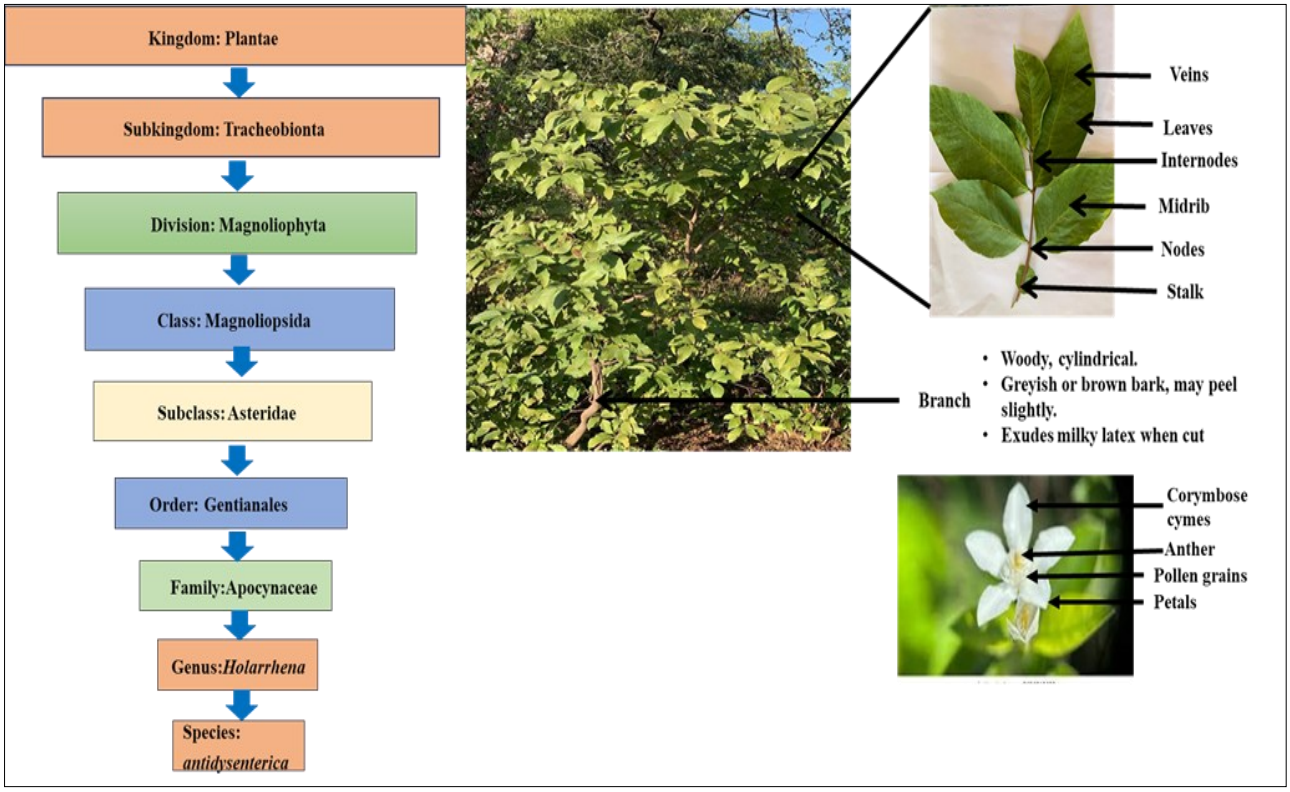


Fig. 2. Pictorial representation of the taxonomic hierarchy and morphological features of *Holarrhena antidysenterica*. The left panel illustrates the complete taxonomic classification, ranging from Kingdom Plantae, Subkingdom Tracheobionta, Division Magnoliophyta, Class Magnoliopsida, Subclass Asteridae, Order Gentianales, Family Apocynaceae, Genus *Holarrhena*, to Species *H. antidysenterica*. The central panel shows the natural habitat of the plant. The upper right panel depicts leaf morphology, highlighting characteristic venation patterns, while the lower right panel presents the white flower with clearly visible petals and reproductive structures.

NIST17 library and identify compounds. The chromatogram revealed a phenolic-acid chemical profile with notable concentrations of vanillic acid (29.33 %), apocynin (18.23 %) and trans-cinnamic acid (17.52 %). g-sitosterol, conjugated linoleic acid, n -hexadecanoic acid, cis- vaccenic acid, P-coumaric acid and 4-acetoxy-3-methoxycinnamic acid were additional significant constituents. Many pharmacological effects, such as lipid-lowering, neuroprotective, cardioprotective, anti-inflammatory, antioxidant and antimicrobial properties, are linked to these metabolites. The traditional medicinal uses of the plant are supported by these effects (15–18). Among other unique findings not previously documented in prior GC-MS investigations of *H. antidysenterica*, the bark extracts identification of apocynin and 9,12-octadecadienoic acid ethyl ester may offer new pharmaceutical discoveries (19, 20). The phytochemical complexity of *H. antidysenterica* is highlighted by the thorough GC-MS profile, which offers a scientific foundation for its various therapeutic applications in treating oxidative stress, inflammation, metabolic problems and microbial infections (21, 22). About 68 steroidal alkaloids have been discovered and extracted from *H. antidysentrica*. Conessine, Isoconessine, Conessimine / Isoconessimine and Conarrhimine are obtained from stem bark and seeds. From the stem bark, Kurchamide, Kurcholessine and Holarrifine Trimethylconkurchin, N-Methylholarrhimine, N-Methylholarrhimine, N′-Tetamethylholarrhimine, Conessidine, Holarrhidine, Kurchenine, Holarrhessimine, Holarrhine, Conkurchinine, Kurchamine, 7-α-Hydroxyconessine, Kurchilidine, Neoconessine (isomer of conessine), Holadysenterine, Kurchessine, Lettocine, Kurchimine, Holarrhenine, Holarrhimine/Kurchicine, Holacine, Holafrine, Holadysone, Holacetine, 3α-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 and Regholarrhenine F. From foliage, holantosine-A, holantosine-B, holantosine-C, holantosine-D, holantosine-E, holantosine-F, holarricine, 3 Kurchiphyllamine, kurchaline and kurchiphylline. Conimine and antidysentericine originate from seeds (23–25).

Pharmacological roles of *Holarrhena antidysenterica*

Anti-psoriatic property

Holarrhena antidysenterica exhibits anti-psoriatic activity through its anti-inflammatory, wound-healing and anti-itch properties, as demonstrated in Suryapaki Taila (sesame oil-based) formulations used in Ayurvedic practice (26).

Anti-diabetic property

Ethanolic seed extracts from *H. antidysenterica* seeds have been shown in multiple studies to reduce the symptoms of diabetes at a dose of 300 mg/kg body weight (BW). Additionally, seed extracts at 250 mg/kg BW in water, petroleum ether and methanol showed antihyperglycemic and anti-hyperlipidemic effects. Quercetin-rich methanolic seed extract provided some protection against diabetes brought on by streptozotocin. Like acarbose, a hydro-methanolic seed extract reduced post-meal blood sugar and carbohydrate absorption by inhibiting α-glucosidase. Furthermore, in diabetic rats, ethanolic leaf extracts at 400 mg/kg BW decreased blood sugar in a manner comparable to glibenclamide (27, 28).

Anti-hypertensive property

Holarrhena antidysenterica is positive in the suppression of the blood pressure within the arteries by inhibiting angiotensin converting enzyme or ACE. It is the primary rennin angiotensin aldosterone system blockade. The ethanolic seed extracts of *H. antidysenterica* inhibited 24 % of the AChE' enzyme activity (*in*

vitro), which further indicates its moderate antihypertensive activity (28). The steroidal alkaloids might also contribute to the identified activity and need to be confirmed by similar findings reported *in vivo*.

Anti-microbial property

Recent research suggests that by focusing on bacterial efflux pumps, the alkaloid conessine from *H. antidysenterica* may improve the effectiveness of antibiotics. Like the MexAB-OprM system in *Pseudomonas aeruginosa*, conessine inhibits the AdeIJK pump in *Acinetobacter baumannii* and restores antibiotic sensitivity in strains of resistant *Pseudomonas aeruginosa*. Thus, steroidal substances like conessine may enhance the effectiveness of traditional antibiotics against bacteria that are resistant to multiple drugs. The antibacterial effects of ethanolic seed and bark extracts are concentration-dependent; the bark ethanolic extract is more effective than methanol or chloroform extracts with higher minimum inhibitory concentration (MIC) values, inhibiting *Escherichia coli* at 50 mg/mL (28).

Anti-malarial property

With an average IC_{50} of 5.7 mg/mL and roughly 70 % inhibition of parasitaemia at a dose of 30 µg/kg, chloroform extracts of the bark showed the strongest anti-plasmodial activity (28). Using *Plasmodium falciparum* isolates and *Plasmodium berghei*-infected Swiss mice, these effects were assessed in both *in vitro* and *in vivo* experiments. It is tabulated in Table 2 and illustrated in Fig. 3.

Anti-mutagenic property

Bacterial mutagenicity assays show that *H. antidysenterica* bark methanolic extract protects *Salmonella typhimurium* DNA from mutagen-induced damage. The extract reduces revertant formation, indicating protective rather than direct anti-mutagenic action. Flavonoids and steroidal alkaloids likely prevent oxidative DNA injury, supporting its potential role in chemoprevention and genetic stability (29).

Anti-inflammatory and analgesic properties

Methanolic extracts of *H. antidysenterica* bark reduced malondialdehyde and nitric oxide while increasing glutathione and superoxide dismutase in Wistar rats with 2,4-Dinitrobenzene sulfonic acid-induced colitis, without signs of inflammation or tissue damage. Leaf extracts prevented carrageenan-induced paw oedema in Swiss albino mice. Both bark and leaf extracts demonstrated analgesic effects in writhing and tail-flick tests, suggesting modulation of prostaglandin pathways and supraspinal mechanisms. The extract's

Table. 2. Tabular representation on the pharmacological profile of *Holarrhena antidysenterica* extracts

Sl. No.	Type of extract or formulation	Disease/pharmacological activity	Dosage	Experimental/clinical model	References
1.	Stem bark powder (Kutaja Tvak Churna)	Anti-haemorrhoidal (management of bleeding piles)	Oral administration (dose as per Ayurvedic formulation)	Human patients with bleeding haemorrhoids	(4)
2.	Ethanolic seed extract	Anti-diarrhoeal property	200, 400 mg/kg p.o.	Diarrhea induced in rats via castor oil	(4, 31)
3.	Alcoholic seed extract	Acetylcholinesterase inhibition / Neuroprotective	IC50 = 6.1 µg/mL (extract); 4–20 µg/mL (fractions); connesimin = 4 µg/mL	*In vitro* enzyme inhibition assay	(7)
4.	Methanolic leaf & ethyl-acetate seed extracts	Antioxidant/Free radical scavenging	—	*In vitro* antioxidant assays	(8, 13)
5.	Kutaja Suryapaki Taila (Tilataila + Kutaja)	Psoriasis (Dermatological disorder)	Topical application	Human application (Ayurvedic formulation)	(26)
6.	Ethanolic, aqueous, petroleum ether, methanolic, hydro-methanolic (2:3), & ethanolic leaf extract	Antidiabetic, antihyperglycemic, anti-hyperlipidemic and glucosidase inhibition	300, 250, 300, 400 mg/ kg BW	a) Streptozotocin-induced diabetic rats b) Rat model c) Starch-loaded rats d) Alloxan + Streptozotocin-induced diabetic rats	(27), (30), (31)
7.	Aqueous as well as alcoholic extract	Anti-microbial property	200 mg/mL	S. aureus, Vibrio cholerae O1, V. cholerae O139, enteroinvasive *E. coli*, enteropathogenic *E. coli*, *S. typhimurium*, *S. enteritidis*, *Shigella flexneri*, *Shigella boydii* and *Pseudomonas aeruginosa*	(28)
8.	Chloroform bark extract	Anti-malarial	30 mg/kg	*P. falciparum* (*in vitro*), *P. berghei*-infected mice (*in vivo*)	(28)
9.	Methanolic bark extract	CNS depressant / Stimulant activity	Dose-dependent	Swiss albino mice; behavioral assays (open field, rotarod and locomotor activity)	(28)
10.	Ethanolic seed extract	Anti-hypertensive (ACE inhibition)	24 % ACE inhibition (*in vitro*)	In vitro	(28)
11.	Methanolic bark extract	Analgesic	—	Acetic acid induced in Wistar rats	(29)
12.	Methanolic bark extract	Anti-mutagenic	Not specified	*Salmonella typhimurium* strains (Ames assay)	(29)
13.	Ethanolic bark extracts	Anthelmintic	1.0, 2.0, 5.0 and 10.0 mg/mL	*Raillietina* spp.	(30)
14.	Bark powder/ Amoebin cap formulation	Anti-amoebic	15 days oral course	Human patients with amoebiasis	(30)
15.	Crude aqueous-methanolic extract	Anti-urolithic	30, 50 and 100 mg/kg	Male Wistar rats rendered hyperoxaluric + 0.75 % ethylene glycol (EG) in drinking water for 21 days + 1 % ammonium chloride (AC) for initial 3 days	(35, 36)
16.	Methanolic bark extract	Anti-inflammatory (Colitis protection)	-	2,4-Dinitrobenzene sulfonic acid-induced colitis in Wistar rats	(41, 42)

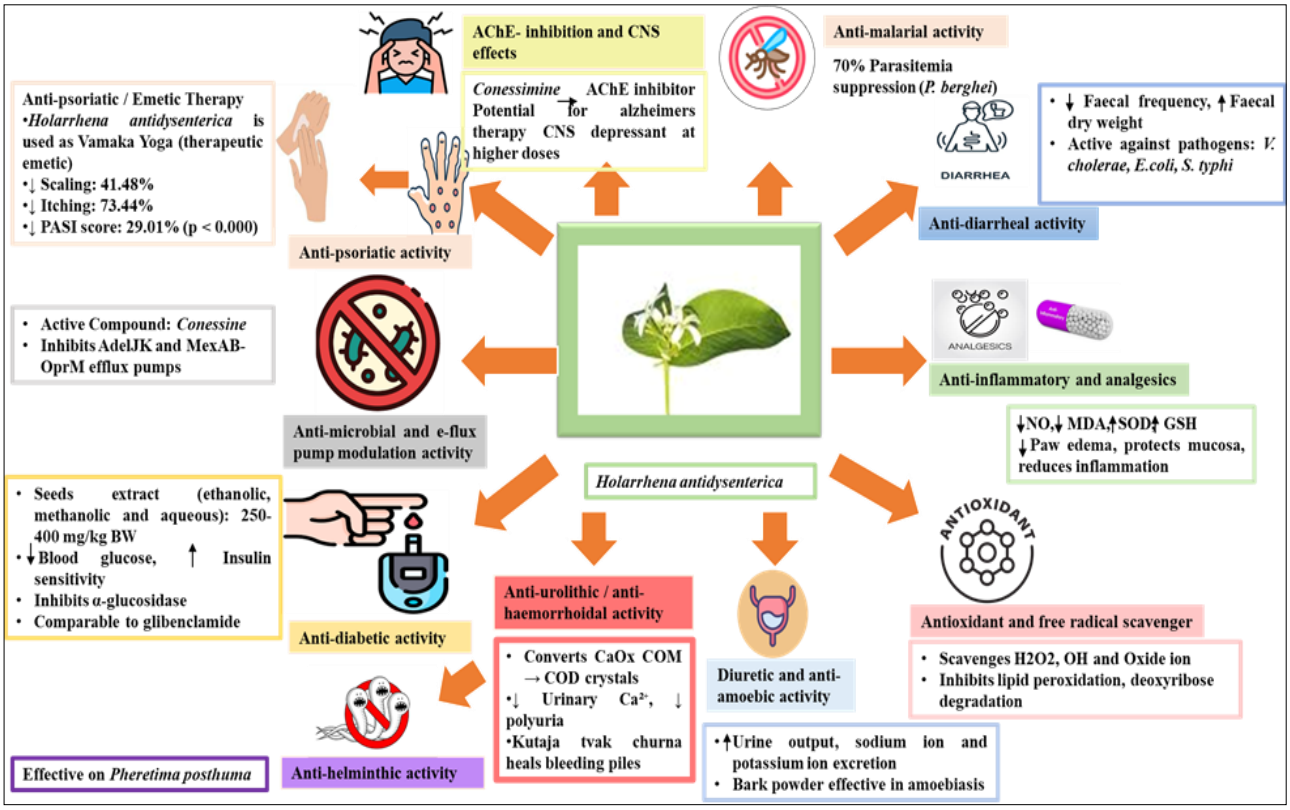


Fig. 3. Pharmacological roles of *Holarrhena antidysenterica*. The central panel depicts *H. antidysenterica*, from which arrows radiate outward to illustrate its wide spectrum of reported biological activities. These include acetylcholinesterase (AChE) inhibition and central nervous system effects, antimalarial, antidiarrheal, anti-inflammatory and analgesic, antioxidant and free radical scavenging, diuretic and antiamoebic, antiurolithic and antihaemorrhoidal, antihelminthic, antidiabetic, antimicrobial with efflux pump modulation, and antipsoriatic activities. Each activity is represented by a corresponding illustrative icon for enhanced visual clarity.Note: AChE- Acetylcholinesterase, CaO-Calcium oxide, COD- Calcium Oxalate Dihydrate, CNS-Central nervous system, GSH- Reduced glutathione, NO-Nitric oxide, SOD-Superoxide Dismutase.

effects on peripheral and central pain pathways, consistent with previous findings, indicate multimodal analgesic potential for *H. antidysenterica* (29).

Neuroprotective property

Neurodegenerative diseases involve oxidative stress, inflammation and neurotransmitter dysfunction. *H. antidysenterica* contains steroidal alkaloids and other phytochemicals with cholinergic, antioxidant and anti-inflammatory effects (7). It inhibits acetylcholinesterase (AChE), activates the nuclear factor erythroid 2-related factor 2/antioxidant response element (Nrf2/ARE) pathway, reduces pro-inflammatory cytokines and improves memory in Streptozotocin (STZ)-induced dementia rats, though further pharmacokinetic and toxicity studies are needed (28).

Diuretic and anti-amoebiasis properties

Wistar rat's urine production was found to be considerably increased by aqueous extracts of *H. antidysenterica* seeds at doses ranging from 30 to 100 mg/kg BW. Additionally, it was discovered that the treated rats' urine had noticeably greater concentrations of K^+ and Na^+ ions. After taking the bark powder daily for 15 days, the amoebiasis patients were fully cured. The therapeutic effects of the amoebin cap, a remedy for amoebiasis that contained *H. antidysenterica*, were examined in a separate clinical trial (29, 30).

Anti-helminthic property

Holarrhena antidysenterica shows strong anti-helminthic activity. Ethanolic and ethyl acetate extracts cause dose-dependent worm paralysis and death, with tegumental damage seen in scanning electron microscope and transmission electron microscope. Enzyme activity decreases (alkaline phosphatase or ALP, ATPase, 5'-nucleotidase), impairing nutrient uptake and metabolism. These findings support its tegument-targeting anti-helminthic action (30).

Anti-diarrheal property

Significant increase in the dry weight of feces and a decrease in defecation drops after using ethanolic seed extracts of *H. antidysenterica* on castor oil-induced diarrhea in rats. Aqueous and alcoholic extracts from the bark of *H. antidysenterica* were also found to inhibit the growth of diarrheal pathogens, such as *Salmonella typhimurium*, *Vibrio cholerae*, *Vibrio alginolyticus*, *Vibrio cholera* (0139), *E. coli* (0157:H7) and *S. typhi* (31).

Antioxidant property

Chemicals that scavenge free radicals can repair an organ and shield it from oxidative damage. According to the studies on the antioxidant qualities of *H. antidysenterica*, methanolic leaf extracts efficiently scavenged hydroxyl and superoxide ions. It also showed the capacity to convert Fe^{3+} to Fe^{2+} (28, 32). Moreover, by competing with O_2, H_2O_2 and deoxyribose breakdown by hydroxide (OH^-) ions, the concentration-corresponding ethyl acetate fraction of the plant also inhibited lipid peroxidation and nitrite production (33, 34). Hydro-methanolic seed extracts also showed promise in preventing lipid peroxidation, reducing the breakdown of H_2O_2, inhibiting the production of nitrite by competing with O_2 and preventing OH^- ions from degrading deoxyribose (30).

Anti-urolithic and anti-haemorrhoidal properties

Both *in vitro* and *in vivo* studies highlight the potential of *H. antidysenterica* seeds in preventing and treating urolithiasis. An aqueous methanolic seed extract protected male Wistar rats from calcium oxalate-induced kidney stones, reducing serum urea, creatinine and urine oxalate levels at 30–100 mg/kg BW over 21 days. Histopathology confirmed decreased crystal deposition, likely due to antioxidant and membrane-protective effects that prevent oxidative stress and crystal adherence. Additionally, stem bark extract (Kutaja tvak churna) promoted healing in patients with bleeding hemorrhoids (35, 36).

Liver-protective property

Leaf extracts show hepatoprotective and cytotoxic effects. In paracetamol-injured rats, they reduced bilirubin, ALP, serum glutamic pyruvic transaminase (SGPT) and serum glutamic-oxaloacetic transaminase (SGOT) and prevented fibrosis. *In vitro*, 95 % ethanol extracts strongly inhibited HepG2 and HEP-2 cells, with chloroform fractions most active, indicating anticancer and hepatoprotective potential (37).

Mechanistic pathways involved in hepato- and neuroprotection

Liver protective pathways

i. Antioxidant defence (Nrf2/ARE pathway)

Oxidative stress drives hepatocellular injury through reactive oxygen species (ROS)-mediated DNA, protein and lipid damage, marked by elevated malondialdehyde (MDA) and reduced superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione (GSH). The Nrf2/ARE pathway counters this by inducing heme oxygenase-1 (HO-1), NAD(P)H quinone dehydrogenase 1 (NQO1) and GST enzymes (37, 38). *Holarrhena antidysenterica* phytochemicals activate Nrf2, reduce MDA, enhance antioxidant enzymes, stabilise mitochondria and prevent ROS-induced apoptosis. Organic extracts show greater efficacy, improving biochemical and histological outcomes in liver toxicity models (39, 40).

ii. Anti-inflammatory signalling (NF-κB / TNF-α / IL-6 suppression)

In liver injury, damage-associated molecular pattern (DAMP)-activated immune cells elevate tumour necrosis factor-alpha (TNF-α) and interleukins (IL-1βand IL-6) through nuclear factor-kappa B (NF-κB), worsening damage and fibrosis. *Holarrhena antidysenterica* extracts show anti-inflammatory activity, enhancing SOD or CAT and lowering MDA via Nrf2 activation (41). Flavonoids and glycosides scavenge ROS, stabilize mitochondria and upregulate HO-1 and glutamate-cysteine ligase catalytic subunit (GCLC). Organic extracts are more effective, while triterpenoids modulate peroxisome proliferator-activated receptor and glucocorticoid pathways, suppressing NF-κB and improving hepatic biomarkers (42).

iii. Anti-fibrotic modulation - TGF-β/α-SMA axis

Fibrogenesis involves hepatic stellate cells (HSCs) activation, extracellular matrix deposition and transforming growth factor-beta (TGF-β) upregulation, disrupting liver architecture. *Holarrhena antidysenterica* phytochemicals such as phenolics, flavonoids and triterpenoids mediate TGF-b/Smad signalling, suppressing HSC activation, alpha smooth muscle actin (α-SMA) and collagen deposition. Extracts also lower oxidative stress and inflammatory cytokines. Lipophilic fractions penetrate HSCs, polar glycosides modulate the paracrine environment, enabling multi-target antifibrotic effects by simultaneously inhibiting TGF-β/α-SMA signalling and upstream triggers (43).

iv. Anti-apoptotic regulation–BAX/Bcl-2 balance

Toxin-induced hepatocyte apoptosis involves Bcl-2- associated X protein (BAX)/Bcl-2 homologous antagonist (BAK)-mediated cytochrome c release, countered by Bcl-2/Bcl-xL. The *H. antidysenterica* extracts increase Bcl-2, decrease BAX and inhibit caspase-3, reducing apoptosis (44). Flavonoids and glycosides stabilise mitochondria, prevent cytochrome c release and reduce caspase-9/3 activation. Chloroform fractions selectively target malignant cells (45). Extracts also activate phosphatidylinositol 3-kinase protein kinase B signaling pathway, modulate Nrf2/NF-κB pathways and improve hepatocyte survival and liver recovery, as shown in Fig. 4 (46).

Neuroprotective pathways

i. Inhibition of cholinesterase enzyme

Cholinesterase inhibition is a key approach for neurodegenerative diseases, where impaired cholinergic signalling causes cognitive deficits (47). The AChE hydrolyses acetylcholine, reducing synaptic transmission, while its inhibition enhances cholinergic function. The *H. antidysenterica* seeds contain steroidal alkaloids; conessine, isoconessimine, conessimin, conarrhimin, conimine; which are potent AChE inhibitors (half maximal inhibitory concentration or IC_{50} 4-28 uM; conessimin 4 uM) (48). Non-competitive, reversible non-classical AChE inhibition is demonstrated by mechanism studies. Molecular docking emphasises the hydrogen and hydrophobic binding in the aromatic gorge of AChE, where C-3 alterations allowed an increase in binding (3). Structure-activity relationship (SAR) research has shown that methyl, dimethyl amino, OH^- or methoxy fission will enhance potency and stereochemistry will alter the inhibition. Ethanol seed extracts prevent the memory impairments in STZ induced dementia models through a reduction in AChE activity, lipid peroxidation and improvement in GSH. The steroidal backbone could facilitate penetration by the blood-brain barrier. Although the *in vitro* evidence is promising, pharmacokinetics, brain bioavailability, systemic toxicity and *in vivo* efficacy of *H. antidysenterica* alkaloids are not well studied, which makes them likely neuroprotective agents (3,7).

ii. Decrease of reactive oxygen species and lipid peroxidation

Neurodegeneration is caused by oxidative stress because of disproportionate accumulation of endogenous antioxidants and ROS. *Holarrhena antidysenterica* extracts have strong antioxidant power to suppress ROS and lipid peroxidation. Methanolic leaf extracts are antioxidants that help in the protection of cellular machinery. Ethanolic seed extracts reduced MDA, CAT and SOD enhancing cognitive ability in streptozotocin-induced dementia models. The hippocampal tissues regained the antioxidant enzyme activity with the help of the bark's extracts minimising oxidative damages. These effects suggest that *H. antidysenterica* seeds and bark prevent the accumulation of ROS, boost endogenous antioxidant defense mechanisms, lower lipid peroxidation and protect neuronal integrity and these effects indicate their neuroprotective properties (48).

iii. Antioxidant genes of the Nrf2/ARE

The Nrf2 signalling pathway mediates the transcription of genes encoding detoxifying and antioxidant enzymes because it is a vital controller of the antioxidant defenses of the cell through the ARE. The pathway may be disrupted and lead to increased oxidative stress and neurodegeneration (49). *Holarrhena antidysenterica* has been shown to enhance the body's innate antioxidant defences by activating the Nrf2/ARE pathway. Preclinical studies indicate that *H. antidysenterica* extracts upregulate the expression of Nrf2 and its

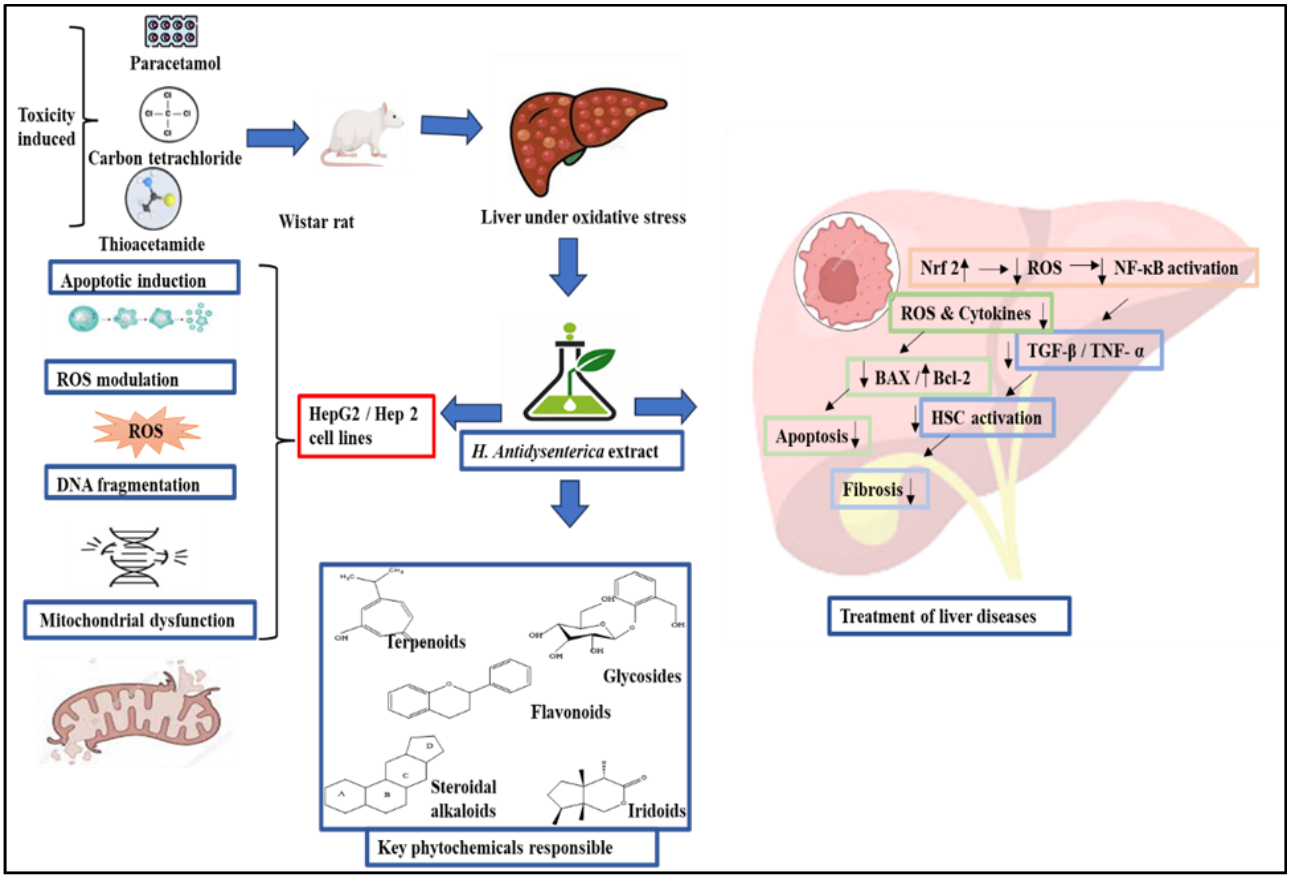


Fig. 4. Mechanistic pathways involved in the treatment of liver diseases. Hepatotoxic agents administered to rat models induce oxidative stress, reactive oxygen species (ROS) generation, apoptosis, and DNA damage. *Holarrhena antidysenterica* extract counteracts these effects by activating nuclear factor erythroid 2-related factor 2 (Nrf2), suppressing nuclear factor kappa B (NF-κB), reducing transforming growth factor-β (TGF-β) and tumour necrosis factor-α (TNF-α), inhibiting hepatic stellate cell (HSC) activation, and modulating apoptotic regulators by downregulating BAX and upregulating Bcl-2. These actions collectively attenuate apoptosis and fibrosis and help restore hepatic architecture. Note: BAX: Bcl-2-associated X protein, HSC: Hematopoietic stem cells, Nrf2: Nuclear factor related erythroid 2-related factor 2, NF- κB: Nuclear factor kappa-light-chain-enhancer of activated B cells, ROS: Reactive oxygen species, TGF-β: Tumour growth factor β and TNF-α: Tumour necrosis factor-α.

downstream targets, including haem oxygenase-1 (HO-1), glutathione (GSH), glutathione peroxidase (GPx), catalase (CAT) and superoxide dismutase (SOD). These enzymes prevent cells against the effects of oxidative damage by inhibiting the process of lipid peroxidation and reducing the levels of ROS (50).

iv. Pro-inflammatory enzyme and cytokine inhibition

The role of neuroinflammation in the development of neurodegenerative diseases is important. Microglia and astrocytes activation liberates pro-inflammatory mediators such as cytokines and chemokines, which cause oxidative stress, mitochondrial dysfunction and neuronal death. The continued stimulation of cyclooxygenase (COX), lipoxygenase (LOX) and inducible nitric oxide synthase (iNOS) enhances the damage through reactive oxygen and nitrogen species (2, 7). *Holarrhena antidysenterica*, one of the Ayurvedic medicinal plants, has been shown to possess neuroprotective and anti-inflammatory properties in preclinical studies. Its extracts inhibit cyclooxygenase (COX) and inducible nitric oxide synthase (iNOS), thereby reducing the production of prostaglandins and nitric oxide. In addition, steroidal alkaloids present in the plant suppress pro-inflammatory cytokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) (48). These mechanisms help reduce neuronal damage, maintain synaptic functionality and support cognitive performance. The antioxidant properties of the plant further enhance its anti-inflammatory effects by neutralising oxidative stress, a key contributor to chronic neurodegeneration. Collectively, *H. antidysenterica* modulates neuroinflammatory cascades, thereby alleviating acute neuronal injury and slowing chronic neurodegenerative processes, supporting its traditional use in the management of cognitive and neurological disorders (49, 51).

v. Neurotransmitter systems modification to ensure neuronal homeostasis

Neuronal homeostasis and synaptic activity play a vital role in cognition, memory and neuronal health. Dysregulation of cholinergic, dopaminergic and serotonergic pathways contributes to impaired cognition in neurodegenerative disorders. *Holarrhena antidysenterica* provides neuroprotection through its antioxidant, anti-inflammatory and neurotransmitter-modulating properties. Its steroidal alkaloids inhibit acetylcholinesterase (AChE), leading to increased acetylcholine levels and improved memory function (7, 51). The plant also modulates dopaminergic and serotonergic signaling, thereby enhancing synaptic plasticity and neuronal resilience (49). In addition, its antioxidant and anti-inflammatory activities protect synaptic proteins and neurons from oxidative stress and inflammatory damage (50, 51). By restoring neurotransmitter balance and supporting neuronal homeostasis, *H. antidysenterica* demonstrates therapeutic potential in neurodegenerative diseases, as illustrated in Fig. 5.

Toxicology and safety profiles

Specific safety evaluations are required to make translations on the

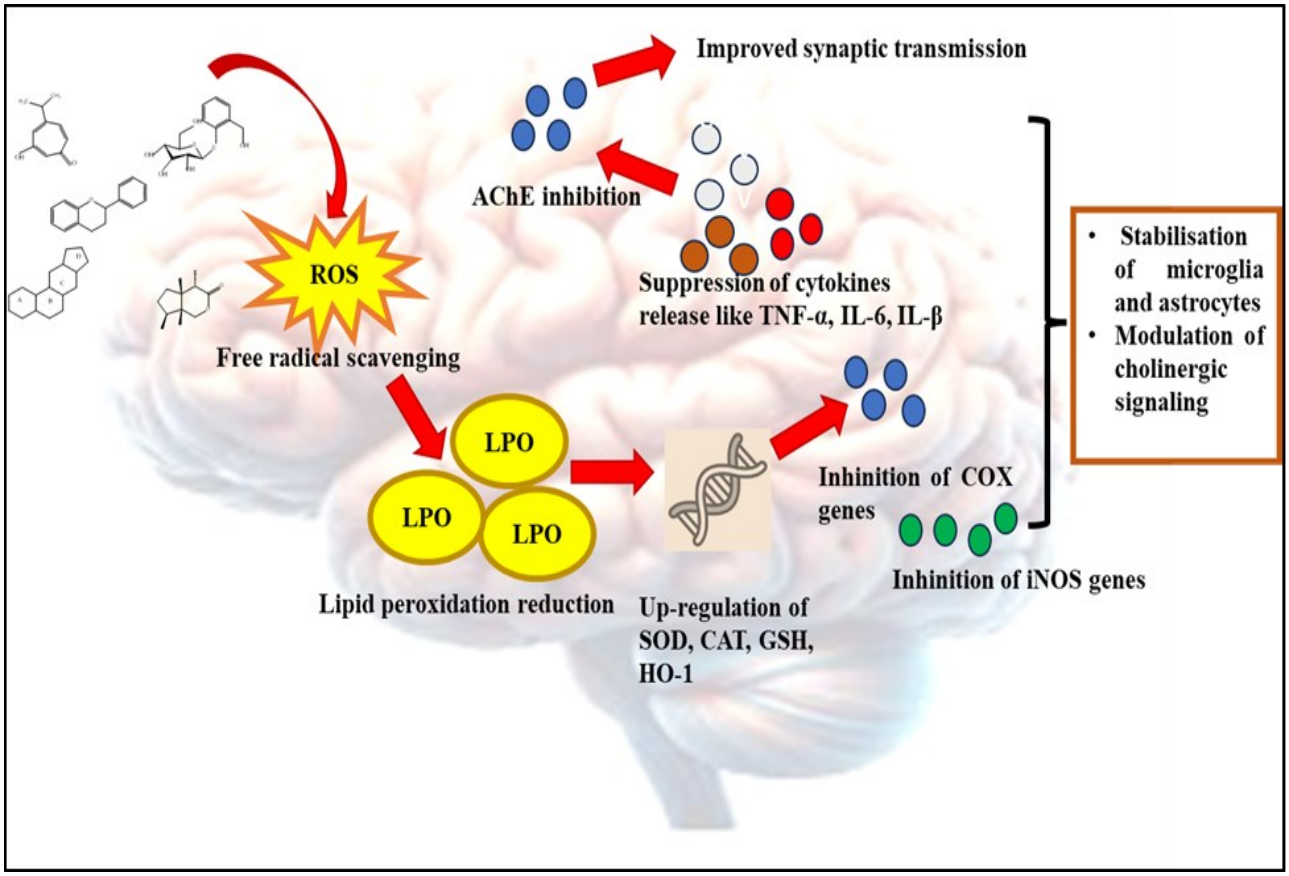


Fig. 5. Role of *Holarrhena antidysenterica* extract in the management of neurodegenerative diseases. Bioactive compounds present in the extract scavenge reactive oxygen species (ROS), reduce lipid peroxidation (LPO), and enhance antioxidant defence by upregulating enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), and haem oxygenase-1 (HO-1). Additionally, acetylcholinesterase (AChE) inhibition improves synaptic transmission, while suppression of pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β) mitigates neuroinflammation. Inhibition of cyclooxygenase (COX) and inducible nitric oxide synthase (iNOS) further stabilises microglia and astrocytes, collectively contributing to the modulation of cholinergic signalling and neuroprotection. Note: AChE: Acetylcholinesterase; COX: Cyclooxygenase; HO-1: Heme oxygenase-1; iNOS: Inducible nitric oxide synthase; IL-6: Interleukin-6; IL-β: Interleukin-β; LPO: Lipid Peroxidation; LOX: Lipoxygenase; ROS: Reactive oxygen species; TNF-α: Tumour necrosis factor-α.

effects of *Holarrhena* plant extract between the preclinical and clinical studies.

i. Acute toxicity studies

Acute toxicity tests estimate immediate adverse effects and lethal dose (LD_{50}). Crude extracts and alkaloid fractions of *H. antidysenterica*, particularly lipid-soluble steroidal alkaloids such as conessine and conessimine, exhibit pharmacological activity at low doses but may affect gastrointestinal and autonomic systems at higher doses (7, 51). In rodent studies, reported effects include tremors, salivation, altered respiration and, in rare cases, mortality. Methanolic or aqueous extracts (200–2000 mg/kg BW) are generally safe, while concentrated alkaloid fractions require careful evaluation (52).

ii. Sub-acute and sub-chronic toxicity studies

Sub-acute (14–28 days) and sub-chronic (28–90 days) studies show organ-specific and cumulative toxicity. High or repeated doses of non-standardised *H. antidysenterica* extracts cause minor, dose-dependent changes in liver enzymes, body weight and histology, with variable haematological and renal effects due to extract differences (44). Long-term studies should assess hepatic enzymes, oxidative stress markers, bile parameters and early fibrosis, with good laboratory practice (GLP)-compliant, multi-species toxicology needed for translational development.

iii. Dose tolerance

Traditional *H. antidysenterica* preparations are generally well tolerated, but pharmacokinetic and animal data are needed to establish safe human doses. Lipophilic and alkaloid-rich extracts are more potent yet higher risk. Steroid alkaloids require caution in GI disorders, ulcers or with cholinergic/AChE inhibitors. Monitor potential cytochrome P450 or P-glycoprotein interactions. Special care is needed in pregnancy, lactation, pediatric and geriatric populations due to placental transfer (47).

iv. Requirement of human safety validation and suggested pathways

Advancing *H. antidysenterica* to clinical use requires structured safety evaluation. Marker compounds like conessine, flavonoids, glycosides should be standardised via high performance liquid chromatography/ultra performance liquid chromatography-mass spectrometry. The GLP-compliant toxicology, including acute, sub-chronic, reproductive, genotoxicity and clinical pathology, must assess liver, cholestasis and neurological endpoints. Pharmacokinetics, ADME (absorption, distribution, metabolism and excretion) and central nervous system (CNS) penetration are needed. Phase I trials should monitor electrocardiogram (ECG), hepatic/renal function and neurological status, with cautious dosing for alkaloid-rich seed fractions (52, 53).

Conclusion and Future perspectives

Holarrhena antidysenterica has been widely used in ayurveda and

has several ethnomedicinal uses, recent research have shown its extensive pharmacological role. Its bioactive constituents-including steroidal alkaloids such as conessine, kurchine, holarrhenine, flavonoids, tannins and phenolic compounds exhibit antioxidant, anti-inflammatory, hepatoprotective and neuroprotective activities.

Experiments show that by lowering oxidative stress, boosting endogenous antioxidant enzyme activity, preserving cellular membrane integrity and modifying pro-inflammatory mediators, *H. antidysenterica* promotes liver health and preserves hepatic architecture and function. It also shows neuroprotective benefits by enhancing cholinergic signaling, reducing oxidative neuronal damage and preventing neuroinflammation, indicating potential importance in neurodegenerative diseases like Parkinson's and Alzheimer's diseases.

Despite these promising preclinical findings, research has largely been limited to *in vitro* and animal studies. Clinical research is critically needed to establish safety, optimal dosage, pharmacokinetics and long-term efficacy in humans. Standardising plant extracts and identifying bioactive markers are crucial for ensuring therapeutic consistency and repeatability. Future research should focus on elucidating molecular pathways to develop novel therapeutic candidates derived from plants.

Integrating traditional knowledge with contemporary pharmacology could accelerate the translation of *H. antidysenterica* into safe, effective and affordable therapeutic options. Cross-disciplinary collaboration will be essential to transform this traditional remedy into a scientifically validated and clinically applicable treatment strategy.

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Authors' contributions

AS carried out the research activities, data compilation and drafting of the original manuscript. MS contributed to the conceptualisation of the study, preparation of the original draft, editing and data curation. DK assisted with conceptualisation, preparation of the original draft, review, editing and visualisation. AKB contributed to editorial support, review and visualisation. DS participated in the editing, review, investigation, visualisation, conceptualisation and supervision of the study. PJ contributed to the editing, review, investigation, visualisation, conceptualisation and supervision. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest: Authors do not have any conflict of interests to declare.

Ethical issues: None

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