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CRITICAL REVIEW OF ANIMAL STUDIES ON *HOLARRHENA ANTIDYSENTERICA* (KUTAJA)

[1]*Dr. Aishwarya Baste, [2]Dr. Pritam Pawale, [3]Dr. Parashuram Pawar, [4]Dr. Vrushali Dani

[1]PG Scholar, Dravyagun Vigyan Department Shree Saptashrungi Ayurved Mahavidyalaya and Hospital Nashik 422003.

[2]Guide and Professor, Dravyagun Vigyan Department, Shree Saptashrungi Ayurved Mahavidyalaya and Hospital Nashik.

[3]HOD and Professor Dravyagun Vigyan Department, Shree Saptashrungi Ayurved Mahavidyalaya and Hospital Nashik.

[4]Associate Professor Dravyagun Vigyan Department, Shree Saptashrungi Ayurved Mahavidyalaya and Hospital Nashik.

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***Corresponding Author**

Dr. Aishwarya Baste

PG Scholar, Dravyagun Vigyan Department Shree Saptashrungi Ayurved Mahavidyalaya and Hospital Nashik 422003.

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ABSTRACT

Holarrhena antidysenterica Wall. (Apocynaceae), traditionally known as Kutaja, is a pivotal medicinal plant in Ayurveda, primarily indicated for gastrointestinal disorders such as *Atisara* (diarrhoea) and *Pravahika* (dysentery). This article provides a systematic and critical appraisal of published preclinical research, examining the efficacy, experimental models, and pharmacological outcomes of Kutaja in animal subjects. Evidence from various rodent models supports its antidiarrheal, antimalarial, antidiabetic, and wound-healing properties. The alkaloid conessine emerges as a significant bioactive lead.

KEYWORDS: *Holarrhena antidysenterica*, Kutaja, Animal studies, Conessine, Antidiarrheal, Preclinical, Toxicology.

1. INTRODUCTION

Kutaja (*Holarrhena antidysenterica*) holds a prominent place in

the Ayurvedic Pharmacopoeia. Phytochemical investigations have identified several bioactive steroidal alkaloids, including conessine, kurchicine, and holarrhenine, which are believed to drive its therapeutic effects. Beyond its classical use in gastrointestinal conditions, modern researchers have evaluated its efficacy in malaria, wound healing, diabetes, and inflammatory disorders.[1,2]

Holarrhena antidysenterica (Kutaja)

Animal experiments serve as the bridge between traditional knowledge and clinical utility. While these studies provide valuable leads, their reliability depends on robust design, reproducibility, and safety validation. This article critically examines the compiled animal studies on *H. antidysenterica* to summarize current preclinical evidence.

Need of Study

Despite the extensive traditional use of Kutaja in Ayurveda, preclinical evidence remains fragmented. A critical appraisal is necessary to consolidate scattered animal study data, validate pharmacological claims, and identify research gaps in standardization and safety. This synthesis provides a scientific foundation for future clinical translation and evidence-based drug development.

2. MATERIALS AND METHODS

Databases including PubMed, Google Scholar, and ResearchGate were searched up to 2025 using keywords: *Holarrhena antidysenterica*, *Holarrhena pubescens*, Kutaja, Animal studies, Rats, Mice, and Conessine.

- **Inclusion Criteria:** *In vivo* animal studies testing pharmacological or toxicological activity.
- **Exclusion Criteria:** *In vitro*-only work, ethnobotanical surveys, or non-English reports.

3. RESULTS

Detailed Review of Animal Studies

3.1 Comprehensive Evaluation of Antidiarrheal and Antisecretory Efficacy

To scientifically validate the ethnomedical use of Kutaja in *Atisara* (diarrhoea), researchers conducted an extensive *in vivo* study using Wistar albino rats. The study employed three distinct experimental triggers: castor oil to induce diarrhoea (by releasing ricinoleic acid which irritates the mucosa), the charcoal meal test to observe intestinal transit, and an enteropooling assay to measure fluid accumulation. The intervention involved an ethanolic seed extract administered at 200 and 400 mg/kg. Findings revealed that the extract produced a dose-dependent inhibition of defecation frequency. Specifically, at 400 mg/kg, the extract significantly slowed the propulsion of the charcoal bolus through the gastrointestinal tract, demonstrating a potent antimotility effect. Furthermore, it reduced the volume of intestinal fluid accumulation, suggesting that Kutaja interferes with the prostaglandins or electrolyte secretions induced by castor oil. The pharmacological response of the higher dose was statistically comparable to Loperamide (5 mg/kg), confirming Kutaja as a potent antisecretory and antimotility agent.[1]

3.2 Spasmolytic Mechanisms via Calcium Channel Blockade

The physiological basis for Kutaja's ability to relieve abdominal griping was investigated using *ex vivo* smooth muscle preparations from isolated rabbit jejunum and guinea-pig ileum. When the crude methanolic extract of *H. antidysenterica* was applied to tissues exhibiting spontaneous rhythmic contractions, it induced a concentration-dependent relaxation. To determine the mechanism, researchers induced sustained contractions using high concentrations of Potassium (K+, 80 mM), which causes depolarization and opens voltage-dependent calcium channels. The extract's ability to relax these K+-induced contractions, coupled with a rightward shift in the Calcium Dose-Response Curves (similar to the action of Verapamil), indicates that Kutaja acts as a Calcium Channel Blocker (CCB). This mechanism explains its clinical efficacy in treating intestinal spasms and the hypermotility seen in dysentery.[2]

3.3 Antimalarial Potential of Chloroform Seed Extracts

The antimalarial efficacy of Kutaja seeds was appraised in Swiss albino mice infected with the *Plasmodium berghei* (NK65) strain, a standard model for human malaria. Using a chloroform-based extract at dosages of 300 and 600 mg/kg, researchers observed a significant chemosuppressive effect during a 4-day suppression test. Mice in the high-dose group (600 mg/kg) showed a 75-80% reduction in parasitemia levels compared to the untreated control. Crucially, the extract helped the mice maintain their body temperature and Packed Cell Volume (PCV), indicating protection against the hemolytic anemia usually caused by the parasite. The treated subjects showed a marked increase in mean survival time, suggesting that the lipophilic alkaloids in the seeds possess significant protozoicidal activity.[3]

3.4 Lead Compound Analysis: Antimalarial Activity of Conessine

Following the success of crude extracts, the major steroidal alkaloid, Conessine, was isolated and evaluated for targeted antimalarial activity in *P. berghei*-infected mice. Administered at doses of 10, 25, and 50 mg/kg, Conessine demonstrated potent inhibitory action against the parasite's erythrocytic stages. At the 50 mg/kg dose, Conessine exhibited a chemosuppression rate exceeding 85%, significantly outperforming the crude extract. Treated mice regained their physical vigor and body weight, surviving up to 25 days post-infection, whereas the control group succumbed within 8 days. This study positions Conessine as the primary bioactive lead responsible for the plant's antiplasmodial effects, potentially serving as a scaffold for new antimalarial drug development.[4]

3.5 Antidiabetic Activity and Oxidative Stress Mitigation

The metabolic influence of Kutaja was evaluated in Wistar rats where diabetes was induced via Streptozotocin (STZ), which selectively destroys pancreatic beta-cells. Oral administration of a methanolic seed extract (250 and 500 mg/kg) for 21 days resulted in a significant decline in fasting blood glucose and an improvement in the lipid profile, notably reducing LDL and VLDL cholesterol. Beyond glycemic control, the study focused on tissue-level protection; the extract restored the levels of endogenous antioxidants, including Superoxide Dismutase (SOD), Catalase, and reduced Glutathione (GSH) in the pancreas. This dual action—lowering blood sugar while simultaneously mitigating oxidative damage to pancreatic tissue—suggests that Kutaja may assist in the long-term management of diabetic complications.[5]

3.6 Accelerated Wound Healing and Angiogenesis

The tissue-repair potential of Kutaja leaf extract was examined using excision and incision wound models in albino rats. A formulated 10% w/w herbal gel was applied topically. In the excision model, the gel-treated group achieved 95% wound contraction by day 14, significantly faster than the 21 days required for the control. In the incision model, the "breaking strength" or tensile strength of the healed skin was significantly higher, indicating robust collagen cross-linking. Histopathological analysis showed an increase in fibroblast proliferation, enhanced angiogenesis (formation of new blood vessels), and a well-organized collagen matrix. These findings support the use of Kutaja in treating chronic wounds and inflammatory skin lesions through accelerated epithelialization and tissue remodelling.[6]

3.7 Anti-urolithiatic Activity and Renal Protection

The efficacy of Kutaja bark in treating urolithiasis was tested in Wistar rats induced with renal stones using 0.75% ethylene glycol. This chemical causes hyperoxaluria, leading to calcium oxalate crystal deposition in the kidneys. The intervention with a hydroalcoholic bark extract (200 mg/kg) resulted in a significant reduction in urinary levels of calcium, phosphate, and oxalate. Histopathological examination of the renal tissues showed a marked decrease in the size and density of crystals within the tubules, preventing the characteristic tissue damage and inflammation. The study concludes that Kutaja prevents the nucleation and growth of urinary calculi, acting as an effective lithotriptic and nephroprotective agent.[7]

3.8 Hepatoprotective Effects Against Chemical Insult

To evaluate liver protection, researchers used a Carbon Tetrachloride (CCl4) model in rats, which induces liver damage via free radical-mediated lipid peroxidation. Administration of an ethanolic bark extract (200 and 400 mg/kg) showed a significant hepatoprotective effect, as evidenced by the reversal of elevated serum markers such as SGOT, SGPT, and Alkaline Phosphatase (ALP). The extract also reduced total bilirubin levels. Histological sections of the liver from treated rats showed significant recovery, with reduced centrilobular necrosis and fatty changes. This protective effect is likely due to the antioxidant properties of the bark's alkaloids, which stabilize the hepatocyte membrane against oxidative triggers.[8]

3.9 Acute and Sub-acute Safety Profiling

Toxicological validation was performed following OECD guidelines to determine the safety margin of *H. antidysenterica*. In the acute phase, mice were given a single limit dose of 2000 mg/kg of the ethanolic seed extract. No mortality, tremors, or behavioral abnormalities were

noted over 14 days, establishing the LD50 as greater than 2000 mg/kg. In the sub-acute study (28 days), rats received daily doses of 200-400 mg/kg. Hematological analysis and biochemical assays for urea, creatinine, and liver enzymes showed no significant deviations from the normal range. Furthermore, gross pathological examination of internal organs revealed no signs of inflammation or toxicity, suggesting that Kutaja is remarkably safe for short-to-medium-term therapeutic use.[9]

3.10 Anti-inflammatory and Central Analgesic Properties

The anti-inflammatory potential of the alkaloid-rich fraction of Kutaja bark was investigated using carrageenan-induced paw edema, while analgesic activity was tested using the tail-flick method. The alkaloid fraction produced a 56% inhibition of paw swelling, which is significant as carrageenan-induced inflammation involves a complex release of histamine, serotonin, and prostaglandins. In the tail-flick model, which measures central pain response, the treated rats showed a significantly delayed reaction time to the thermal stimulus. This demonstrates that Kutaja possesses a dual-action profile: a peripheral anti-inflammatory effect and a central analgesic effect, making it highly effective for managing the pain and inflammation associated with infectious dysentery.[10]

4. DISCUSSION

The present critical appraisal of animal studies on *Holarrhena antidysenterica* (Kutaja) provides compelling preclinical evidence supporting its extensive traditional use described in Ayurvedic classics. The discussion synthesizes findings across diverse pharmacological domains, highlighting mechanistic plausibility, therapeutic breadth, and safety assurance, thereby strengthening the scientific justification for Kutaja as a clinically relevant medicinal plant.

Antidiarrheal and Antisecretory Activity: Validation of Classical Indications

The antidiarrheal study using castor oil–induced diarrhoea, charcoal meal transit, and enteropooling models offers robust validation of Kutaja's classical indication in *Atisara* and *Pravahika*. The observed dose-dependent reduction in defecation frequency, intestinal motility, and intraluminal fluid accumulation directly correlates with Ayurvedic descriptions of Kutaja as *Grahi*, *Stambhaka*, and *Atisaraghna*.

The equivalence of the higher extract dose (400 mg/kg) to loperamide, a standard synthetic antidiarrheal agent, is particularly significant. It indicates that Kutaja not only alleviates

symptoms but acts on fundamental pathophysiological mechanisms such as prostaglandin-mediated secretion and hypermotility. This study strongly supports Kutaja as a potent, natural alternative with multi-targeted antidiarrheal action rather than a single-pathway suppressant.

Spasmolytic Effect via Calcium Channel Blockade: Mechanistic Clarity

The spasmolytic activity demonstrated in isolated intestinal smooth muscle preparations provides a mechanistic explanation for Kutaja's efficacy in relieving abdominal cramps and tenesmus associated with dysentery. The extract's ability to inhibit potassium-induced contractions and shift calcium dose-response curves parallels the pharmacodynamics of standard calcium channel blockers like verapamil.

This finding is highly relevant clinically, as intestinal hypermotility and spasm are central to diarrhoeal disorders. By modulating calcium influx, Kutaja offers smooth muscle relaxation without complete gut paralysis, preserving physiological motility. Such balanced action supports its safe long-term use described in Ayurveda and explains its effectiveness in functional gastrointestinal disorders.

Antimalarial Activity: Expansion Beyond Gastrointestinal Indications

The antimalarial studies significantly broaden Kutaja's therapeutic scope. The substantial reduction in parasitemia, preservation of packed cell volume, and prolonged survival time in *Plasmodium berghei*-infected mice indicate genuine protozoicidal potential rather than nonspecific symptomatic relief.

The ability of the extract to prevent anemia and hypothermia suggests systemic protective effects beyond parasite suppression. This aligns with Ayurvedic descriptions of Kutaja as *Krimighna* and *Jwaraghna*. Importantly, the study reinforces the relevance of traditional knowledge in guiding modern drug discovery for neglected tropical diseases.

Conessine as a Lead Compound: Translational Significance

Isolation and evaluation of Conessine represent a critical advancement from crude extract studies to molecular pharmacology. The superior chemosuppression (>85%) achieved by Conessine compared to crude extracts confirms it as the principal antimalarial constituent.

The dose-dependent efficacy, restoration of body weight, and marked increase in survival duration establish Conessine as a promising lead compound. This positions Kutaja not merely

as a traditional remedy but as a source of novel antimalarial scaffolds, especially valuable in the context of increasing drug resistance.

Antidiabetic Activity and Antioxidant Restoration: Disease-Modifying Potential

The antidiabetic study demonstrates that Kutaja exerts both metabolic control and tissue protection. Reduction in fasting blood glucose, improvement in lipid profile, and restoration of pancreatic antioxidant enzymes suggest a disease-modifying effect rather than transient glycemic control.

Oxidative stress is a major contributor to diabetic complications, and Kutaja's ability to restore SOD, catalase, and glutathione levels highlights its cytoprotective role. This dual action supports its potential as an adjunct therapy in diabetes management, particularly for preventing long-term complications.

Wound Healing and Angiogenesis: Tissue-Level Regeneration

The wound healing studies provide strong histological and functional evidence of Kutaja's regenerative capacity. Accelerated wound contraction, increased tensile strength, enhanced angiogenesis, and organized collagen deposition reflect efficient tissue remodeling.

These findings validate Kutaja's classical *Ropana* and *Shothahara* properties. The topical gel formulation also demonstrates the feasibility of pharmaceutical development, bridging traditional herbal use with modern dosage forms suitable for chronic and non-healing wounds.

Anti-urolithiatic Activity: Renal Protection and Crystal Inhibition

The urolithiasis model illustrates Kutaja's ability to prevent stone formation at multiple stages—reducing crystal nucleation, growth, and tubular deposition. The normalization of urinary biochemical parameters and histological renal protection confirm its nephroprotective role.

Such findings are clinically relevant, as current lithotriptic therapies often address symptoms rather than recurrence prevention. Kutaja's multifaceted action suggests long-term utility in renal calculi management.

Hepatoprotective Effects: Antioxidant-Driven Organ Protection

The hepatoprotective study against carbon tetrachloride toxicity demonstrates Kutaja's capacity to stabilize hepatocyte membranes and reverse biochemical and structural liver damage. Restoration of liver enzymes and histological normalization indicate genuine hepatic regeneration.

This protective effect aligns with Kutaja's antioxidant alkaloid profile and supports its traditional use in systemic detoxification and metabolic disorders.

Anti-inflammatory and Analgesic Effects: Integrated Symptom Management

The dual peripheral anti-inflammatory and central analgesic actions observed reinforce Kutaja's suitability for inflammatory and infectious conditions involving pain. Inhibition of carrageenan-induced edema reflects modulation of inflammatory mediators, while delayed tail-flick response indicates central analgesic activity.

Such combined action is particularly advantageous in gastrointestinal infections, where inflammation and pain coexist.

Safety and Toxicological Assurance: Foundation for Clinical Translation

The acute and sub-acute toxicity studies provide strong reassurance regarding Kutaja's safety profile. Absence of mortality at high doses, normal hematological and biochemical parameters, and lack of organ pathology confirm a wide therapeutic margin.

This safety evidence supports traditional long-term use and strengthens the rationale for advancing Kutaja into controlled clinical trials.

Overall Interpretation of the Study

Collectively, the reviewed animal studies demonstrate that *Holarrhena antidysenterica* possesses **multidimensional pharmacological activity**, **mechanistic plausibility**, and **high safety margins**. While variability in extract standardization exists, the consistency of positive outcomes across independent models reinforces the therapeutic credibility of Kutaja.

The present review justifies the continued scientific exploration of Kutaja, supports its traditional claims with experimental evidence, and establishes a strong preclinical foundation for future **standardized formulations, chronic toxicity studies, and human clinical trials**.

5. CONCLUSION

The present review concludes that *Holarrhena antidysenterica* (Kutaja) exhibits significant and consistent pharmacological activities across multiple animal models, strongly validating its traditional Ayurvedic use, particularly in the management of *Atisara* and *Pravahika*. Preclinical evidence confirms its antidiarrheal, spasmolytic, antimalarial, antidiabetic, wound-healing, hepatoprotective, anti-urolithiatic, anti-inflammatory, and analgesic properties, with Conessine identified as a key bioactive constituent.

Moreover, toxicological studies demonstrate a wide margin of safety, supporting its long-standing therapeutic use. Overall, the reviewed animal studies provide a strong scientific foundation for Kutaja and justify further standardized formulation development and clinical evaluation for its integration into evidence-based practice.

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