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Review Article

A Comprehensive Review On *Caesalpinia Bonduc* (L.) Roxb. (Fevernut/Kakachoo): Taxonomy, Ethnopharmacology, Phytochemistry, Pharmacological Activities, And Future Perspectives

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ABSTRACT

Caesalpinia bonduc (L.) Roxb. [Syn. *Caesalpinia bonducella* (L.) Fleming; syn. *Guilandina bonduc* L.], commonly known as Fevernut or Kakachoo, is a thorny, perennial, climbing shrub of the family Fabaceae (sub-family Caesalpiniaceae). The plant enjoys a pantropical distribution and has been documented in the traditional medicinal systems of India—including Ayurveda, Siddha, Unani, and Homoeopathy—for centuries 1,2. Virtually all parts of the plant (roots, stem bark, leaves, seeds, flowers) are exploited medicinally. More than 97 phytoconstituents have been isolated to date, spanning cassane and norcassane diterpenoids, flavonoids, homoisoflavonoids, phenolic acids, steroids, alkaloids, saponins, fatty acids, and amino acids 3,4,5. Key bioactive compounds include bonducin, bonducellin, caesalpinin, and a suite of furanoditerpenes 1,3. Pre-clinical and in vitro studies have corroborated a broad spectrum of pharmacological activities: antidiabetic, anti-inflammatory, antipyretic, antimicrobial, antifungal, antioxidant, anticancer, hepatoprotective, immunomodulatory, anticonvulsant, analgesic, antifilarial, and antiestrogenic 5,6,7,8,9,10,11,12. The plant is also used in veterinary medicine and shows promising larvicidal properties. Despite this extensive pre-clinical evidence, validated clinical trials and detailed toxicological assessments remain limited, creating a significant gap between traditional use and modern pharmaceutical acceptance 2. This review consolidates existing knowledge on the taxonomy, geographical distribution, vernacular nomenclature, ethnopharmacology, pharmacognosy, phytochemistry, pharmacological activities, structure–activity relationships, toxicological profile, and future research directions of *C. bonduc*, with the aim of guiding researchers toward drug development from this remarkable medicinal plant.

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INTRODUCTION

Medicinal plants occupy a central position in global healthcare, supplying approximately 25% of all currently used pharmaceutical drugs¹³. The growing incidence of antimicrobial resistance, adverse effects of synthetic drugs, and escalating costs of modern therapeutics have intensified interest in plant-based medicine^{1,2}. Among the large pharmacopoeia of traditional medicinal plants, *Caesalpinia bonduc* (L.) Roxb.—popularly known in English as Feversnut, Nicker bean, or Physic nut, and in Hindi as Katkaranj or Kakachoo—stands out as a plant of exceptional medicinal versatility^{1,5}.

The genus *Caesalpinia* is vast, encompassing more than 500 species distributed across tropical and subtropical biomes worldwide². Within this genus, *C. bonduc* has attracted the most sustained scientific interest due to its prolific use across indigenous medicine systems of India, Africa, Southeast Asia, and Latin America^{1,2,5}. In Indian

traditional medicine, the plant has been described in classical Ayurvedic texts under the Sanskrit names *Latakaranja* and *Putikaranja* and has been used to treat intermittent fevers, diabetes mellitus, inflammation, worm infestations, skin diseases, hydrocele, and reproductive disorders^{1,2}.

Phytochemical investigations have revealed a rich repertoire of secondary metabolites, particularly cassane- and norcassane-type diterpenoids, which appear to be the principal bioactive scaffold^{3,4}. In vitro, ex vivo, and in vivo studies have validated numerous traditional claims^{6,7,8,9,10,14}. However, systematic reviews collating the full breadth of pharmacological data alongside taxonomy, pharmacognosy, and safety information remain relatively sparse, especially those incorporating literature published after 2020^{2,5}. This comprehensive review addresses that gap by synthesizing data from PubMed, Scopus, Web of Science, ScienceDirect, Google Scholar, and ResearchGate up to early 2025.



Figure 1: Spiny seed pods of *Caesalpinia bonduc* (L.) Roxb. on the branch, showing the characteristic prickly pericarp.

2. TAXONOMY AND NOMENCLATURE

The accepted scientific name of the plant according to current botanical classification is

Guilandina bonduc L. (World Flora Online, 2023)¹⁵; however, the names *Caesalpinia bonduc* (L.) Roxb. and *Caesalpinia bonducella* (L.) Fleming



remain widely used in the pharmacological literature and are treated here as synonyms ^{1,2}.

2.1 Taxonomic Classification

Table 1: Taxonomic classification of *Caesalpinia bonduc* [16, 19].

Rank	Classification
Kingdom	Plantae
Sub-kingdom	Tracheobionta
Super-division	Spermatophyta
Division	Magnoliophyta
Class	Magnoliopsida
Sub-class	Rosidae
Order	Fabales
Family	Fabaceae (Caesalpinaceae)
Sub-family	Caesalpinioideae
Genus	<i>Caesalpinia</i> / <i>Guilandina</i>
Species	<i>bonduc</i> (L.) Roxb.

2.2 Synonyms

Accepted synonyms include: *Caesalpinia bonducella* (L.) Fleming; *Caesalpinia crista* Linn.; *Guilandina bonduc* L.; *Bonduc majus* Medik.; *Guilandina bonducella* L.; *Guilandina gemina* Lour.; and *Caesalpinia jayabo* Maza, among others ^{2,15}.

2.3 Vernacular Names

C. bonduc is known by a wide range of common names across the languages and regions where it is traditionally used, including Fevernut, Nicker bean, and Physic nut in English; Katkaranj and Kakachoo in Hindi; Latakaranja in Sanskrit; and corresponding vernacular names in Bengali, Tamil, Telugu, Malayalam, Kannada, Oriya, Arabic, Persian, and French, among other languages ^{1,2}.

3. BOTANICAL DESCRIPTION AND MORPHOLOGY

Caesalpinia bonduc is a large, straggling, perennial, prickly shrub or woody climber that can

reach up to 10 m in height when supported ². The species name 'bonducella' is derived from the Arabic word *bonduce*, meaning 'little ball', an allusion to the globular shape of the seeds ⁵.

3.1 Stem and Branches

The stem is woody, green to grey, longitudinally striated, and heavily armed with recurved, hooked, and straight yellow-brown prickles approximately 0.3 cm long ². Young branches are densely grey-tomentose (finely downy). The thorns are present on both the rachis and branches, facilitating the plant's climbing habit ^{2,5}.

3.2 Leaves

Leaves are large, alternate, bipinnate, 30–90 cm long, with 3–8 pairs of pinnae ². Each pinna bears 3–4 pairs of opposite or sub-opposite leaflets. Leaflets are oblong to ovate, 2.5–5 cm × 1.5–3 cm, mucronate at apex, and slightly hairy on both surfaces. Stipules are subulate and caducous. The rachis itself is thorny ¹⁶.

3.3 Flowers



Flowers are bright yellow, bisexual, arranged in dense axillary or terminal racemes of 15–30 cm length². Each flower has 5 petals, the upper petal being smaller than the others with reddish streaks at the base. Sepals are 5, reddish-brown on the inner surface. Stamens are 10, free, with hairy filaments. Flowering season: primarily August to October⁵.

3.4 Fruits and Seeds

Fruits are oblong leguminous pods, 5–9 cm × 3.5–5 cm, covered with dense, stiff, yellowish prickles². Each pod contains 1–2 seeds. Seeds (the most medicinally prized part) are ovoid to globose, 1.5–2.5 cm in diameter, hard, lead-grey to dark grey in colour with a smooth, lustrous surface⁵. The seed coat is extremely hard and durable, enabling seeds to float in seawater for extended periods—an adaptation facilitating long-range ocean dispersal². Fruiting season: December to March.

3.5 Roots

Root system is well-developed and woody⁵. Root bark is thin, yellowish-grey, and bitter in taste. Roots are used medicinally in Ayurvedic preparations for fever and liver disorders^{1,2}.

4. GEOGRAPHICAL DISTRIBUTION AND ECOLOGY

Caesalpinia bonduc exhibits a pantropical distribution, occurring across tropical and subtropical regions of Asia, Africa, the Americas, and the Pacific Islands^{1,2,5}. In India, it is abundantly found in the Andaman and Nicobar Islands, Eastern Ghats, coastal Maharashtra, Goa, Kerala, Tamil Nadu, Karnataka, and Odisha. Beyond India, it is recorded in Sri Lanka, Bangladesh, Myanmar, Vietnam, China, Thailand, Indonesia, Australia, Caribbean islands, and parts of tropical Africa².

Ecologically, the plant thrives in moist deciduous forests, evergreen forests, scrub jungles, coastal thickets, and disturbed habitats⁵. It shows considerable tolerance to saline coastal environments and is frequently found on seashores, riverbanks, forest margins, and hedges². The plant grows best at altitudes below 1,000 m, in sandy to loamy soils with moderate rainfall (1,000–3,000 mm/year) and full to partial sunlight².

5. ETHNOPHARMACOLOGY AND TRADITIONAL USES

The ethnomedicinal use of *C. bonduc* spans centuries and multiple traditional medical systems^{1,2}. The earliest documented references appear in classical Ayurvedic texts including the Charaka Samhita and Sushruta Samhita, where the plant is described as a febrifuge, anthelmintic, and anti-inflammatory agent¹. Traditional documentation has been consistently reaffirmed by ethnobotanical surveys conducted across India and other tropical regions up to the present day^{2,5}.

5.1 Ayurveda

In Ayurveda, Latakaranja is classified as having tikta (bitter) and kashaya (astringent) rasa, laghu and ruksha properties, and ushna veerya (hot potency)¹. It is prescribed as a kaphavata pacifying drug. Traditional indications include jwara (fever), shwasa (asthma), kasa (cough), krimi (helminthiasis), udara (abdominal disorders), and arsha (haemorrhoids)^{1,2}. Formulations include Karanjadi churna and Latakaranjadi kwatha¹.

5.2 Siddha System

In Siddha medicine, practiced predominantly in Tamil Nadu, the plant is known as Kazharchi¹. Seed kernel preparations are used as kashayam



(decoctions) to treat recurring fevers, diabetes, and liver diseases ^{1,2}. The seeds are also roasted and administered as a general tonic ¹.

5.3 Unani System

In Unani medicine, the nuts and leaves are classified for their Muha'lil-e-waram (anti-inflammatory), Musakkin-e-alam (antipyretic),

Musaffi-i-Dam (blood-purifying), and Dafi-i-Tashannuj (anticonvulsant) properties ^{1,2}. Key conditions treated include Humma (seasonal fevers), Diq al-Nafas (bronchial asthma), Su'al-o-Surfa (bronchitis), Istisqa Ziqqi (ascites), Qarw Ma'i (hydrocele), and Dhat al-Janb (pleurisy) ¹.

5.4 Folk and Tribal Medicine

Table 2: Traditional uses of various parts of *Caesalpinia bonduc* [11, 15, 16].

Plant Part	Traditional Use	Preparation
Seeds (kernel)	Diabetes, fever, malaria, anthelmintic, hydrocele	Decoction, powder with milk
Leaves	Elephantiasis, smallpox, liver diseases, sore throat, intestinal worms	Juice, paste, gargle, poultice
Root bark	Fever, liver diseases, intermittent fevers	Decoction, extract
Stem bark	Anti-inflammatory, skin disorders, leprosy	Paste, decoction
Seed oil	Skin diseases, hair growth, rheumatism	Topical oil application
Flowers	Analgesic, anti-inflammatory	Infusion, powder
Seed coat	Antimalarial (traditionally chewed)	Direct use, powder
Whole plant	Snake bite (water-based extract), expectorant	With pepper and honey

6. PHARMACOGNOSTIC EVALUATION

6.1 Macroscopic Characters

Seeds: Ovoid to spherical, 1.5–2.5 cm diameter; surface smooth, glossy, lead-grey; extremely hard testa; cotyledons pale yellow, oily; distinct raphe visible ^{5,16}. Odour: faint, characteristic; taste: bitter and astringent. Leaves: Alternate, bipinnate; leaflets 2–5 cm, oblong, slightly hairy; mid-rib prominent; odour faint; taste slightly bitter ¹⁶.

6.2 Microscopic Characters

Seed transverse section reveals a thick, lignified testa composed of palisade-like macrosclereid cells (malpighian cells) forming the outermost layer, followed by a layer of hourglass cells (osteoscleroids) ^{5,16}. The cotyledonary parenchyma is filled with protein bodies and oil globules. Vascular bundles are collateral type. Calcium oxalate crystals (prism type) are present in the seed coat parenchyma. Leaf section shows dorsiventral lamina, anomocytic stomata, unicellular covering trichomes, and a prominent midrib with collateral vascular bundle ¹⁶.

6.3 Physicochemical Standards

Table 3: Physicochemical parameters for *C. bonduc* seed kernel and leaves [11, 17].

Parameter	Seed Kernel	Leaves
Loss on drying (% w/w)	≤ 9.0	≤ 10.0



Total ash (% w/w)	≤ 3.5	≤ 15.0
Acid-insoluble ash (% w/w)	≤ 0.5	≤ 4.0
Water-soluble extractive (% w/w)	≥ 12.0	≥ 20.0
Alcohol-soluble extractive (% w/w)	≥ 8.0	≥ 15.0
Crude fat (% w/w)	15–18	3–5
Crude protein (% w/w)	20–25	8–12
Swelling index	≥ 6	–

6.4 Phytochemical Screening

Preliminary phytochemical screening of various solvent extracts of *C. bonduc* seeds consistently reveals the presence of: alkaloids (Dragendorff's test +), flavonoids (alkaline reagent +), saponins (froth test +), tannins (FeCl₃ +), phytosterols (Liebermann–Burchard +), glycosides (Keller–Kiliani +), terpenoids (Salkowski +), phenolic compounds (+), fixed oils (+), proteins and amino acids (+)^{5,12,16,17}. Starch and reducing sugars are also detectable in some extracts¹².

7. PHYTOCHEMISTRY

More than 97 phytoconstituents have been isolated and structurally characterized from various parts of *C. bonduc*^{3,4,5}. The chemical diversity of this species is remarkable, spanning multiple biosynthetic classes. Seeds (particularly the kernel) are the most extensively studied plant part^{1,5}.

7.1 Cassane and Norcassane Diterpenoids

This class represents the chemotaxonomic marker of the genus and the primary bioactive scaffold³. Cassane diterpenoids isolated from seeds, stems, and roots include: caesalpinins A–P, caesalmins A–K, taepeenins A–L, neocaesalpins B, C, D, and H, and caesalpinianone^{3,4}. Norcassane diterpenoids include norcaesalpinins, nortaepeenins A and B, and related compounds⁴. These diterpenes feature a characteristic furanyl ring system (furanoditerpenes) that is linked to

their cytotoxic and anti-inflammatory properties^{3,5}.

7.2 Alkaloids

Alkaloids identified include bonducin (the principal bitter principle), bonducellin, and several uncharacterized minor alkaloids^{1,3}. Bonducin is a diterpene-related bitter substance responsible for significant antidiabetic and antipyretic activity^{7,12}.

7.3 Flavonoids and Homoisoflavonoids

The leaves and young twigs are particularly rich in flavonoids¹⁷. Isolated compounds include: apigenin, luteolin, quercetin, kaempferol, quercetin-3-methyl ether, and several isoflavone glycosides^{11,17}. Legumes (unripe pods) have yielded naringenin and kaempferol¹⁸.

7.4 Phenolic Acids

Leaves contain significant quantities of phenolic acids: caffeic acid, chlorogenic acid, p-coumaric acid, ferulic acid, and gallic acid^{11,17,19}. These contribute to antioxidant and anti-inflammatory activities^{11,19}.

7.5 Steroids and Phytosterols

β-sitosterol is the predominant phytosterol, along with stigmasterol, campesterol, and cholesterol in minor amounts^{3,5}. These compounds contribute to anti-inflammatory, anticancer, and hypocholesterolaemic activities^{1,5}.



7.6 Fatty Acids and Seed Oil

Fixed oil content of seed kernels ranges from 15–18% (w/w) ⁵. Major fatty acids include linoleic acid (C18:2), oleic acid (C18:1), palmitic acid (C16:0), and stearic acid (C18:0) ⁵. The seed oil has been evaluated for anti-inflammatory and antifungal properties ^{1,5}.

7.7 Other Constituents

Additional constituents isolated include: citrulline (an amino acid), homoisoflavonoid sphysterin, saponins (responsible for the frothy aqueous extract), tannins (gallotannins), polysaccharides from the seed gum, and fixed and volatile oils in minor proportions ^{3,4,5}.

Table 4: Major phytoconstituents isolated from various parts of *C. bonduc* [6, 7, 9, 10, 11, 12].

Class	Key Compounds	Plant Part
Cassane diterpenoids	Caesalpinins A–P, Caesalmins A–K, Taepeenins A–L, Neocaesalpins B/C/D/H	Seeds, stem, root
Norcassane diterpenoids	Norcaesalpinins, Nortaepeenins A & B	Seeds, stems, roots
Alkaloids	Bonducin, Bonducellin, Caesalpinin	Seeds, whole plant
Flavonoids	Apigenin, Luteolin, Quercetin, Kaempferol, Naringenin	Leaves, twigs, legumes
Phenolic acids	Caffeic, Chlorogenic, p-Coumaric, Ferulic, Gallic acid	Leaves
Sterols	β -Sitosterol, Stigmasterol, Campesterol	Seeds, leaves
Fatty acids	Linoleic, Oleic, Palmitic, Stearic acid	Seed oil
Amino acids	Citrulline, Glutamic acid, Alanine	Seeds
Tannins	Gallotannins, Ellagitannins	Bark, leaves
Saponins	Triterpenoid saponins	Seeds, roots

8. PHARMACOLOGICAL ACTIVITIES

The pharmacological profile of *C. bonduc* is exceptionally diverse, encompassing activities documented through in vitro assays, animal models, and limited human studies ^{1,2,5}. Each activity is discussed below with reference to the plant part, extract type, and study model employed.

8.1 Antidiabetic Activity

The antidiabetic potential of *C. bonduc* is among its best-documented properties ^{5,12}. Seed kernel extracts have demonstrated significant oral hypoglycaemic activity in alloxan-induced and streptozotocin-induced diabetic rodent models ¹². The petroleum ether extract of seeds reduced

blood glucose levels comparably to the reference drug glibenclamide ¹². Bonducellin and cassane diterpenoids are proposed as the primary active agents, acting through stimulation of insulin secretion from pancreatic beta-cells, inhibition of α -glucosidase and α -amylase enzymes, and enhancement of peripheral glucose uptake ¹². Antihyperlipidaemic effects have been concurrently observed, with normalization of total cholesterol, LDL, triglycerides, and elevation of HDL in diabetic animals ¹².

8.2 Anti-inflammatory and Antipyretic Activity

Archana et al. (2005) demonstrated significant antipyretic activity of *C. bonducella* seed kernel extract in Brewer's yeast-induced pyrexia in rats



(comparable to paracetamol) ⁷. Anti-inflammatory activity has been established in carrageenan-induced paw oedema, cotton pellet granuloma, and formalin-induced models, with methanol and ethanol seed/flower extracts showing dose-dependent inhibition ^{7,14}. The mechanism involves inhibition of prostaglandin synthesis (COX pathway) and reduction of pro-inflammatory cytokines (TNF- α , IL-6) ¹⁴. Arunadevi et al. (2008) validated the anti-inflammatory property of flower extract with HPTLC fingerprinting ¹⁴.

8.3 Antimalarial Activity

Traditional use as a malarial febrifuge is supported by experimental data ^{1,5}. Seed extracts have shown suppressive activity against *Plasmodium falciparum* (in vitro) and *Plasmodium berghei* (in vivo murine model) ^{5,8}. The cassane furanoditerpene fraction demonstrates the greatest antimalarial potency, with IC₅₀ values in the low micromolar range against chloroquine-sensitive strains ³. Mechanistically, the compounds appear to disrupt haem detoxification within the parasite, similar to chloroquine ⁵.

8.4 Antimicrobial and Antifungal Activity

Seed extracts prepared with different solvents (ethyl acetate, aqueous, petroleum ether) show broad-spectrum antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Salmonella typhi*, with MIC values ranging from 0.5–8.0 mg/mL ⁸. Antifungal activity has been established against *Aspergillus niger*, *Candida albicans*, *Fusarium oxysporum*, and *Alternaria solani* ¹⁰. A mechanistic study by Gowri et al. (2022) demonstrated that ethanolic extract of *C. bonduc* seeds (EECS) triggers metacaspase-dependent apoptosis in *C. albicans*, mediated by ROS generation, intracellular Ca²⁺ elevation, mitochondrial dysfunction, cytochrome c release,

and DNA fragmentation—confirming a unique antifungal mechanism of action ¹⁰.

8.5 Antioxidant Activity

Methanol and ethanol extracts of leaves, seeds, and young twigs demonstrate potent free radical scavenging activity in DPPH, ABTS, FRAP, and superoxide dismutase assays ^{11,19}. Total phenolic and flavonoid content correlates positively with antioxidant capacity ¹¹. Sembiring et al. (2018) characterized phenolic and flavonoid content across different plant parts using standardized extraction protocols ¹¹. The rich phenolic acid profile (gallic, caffeic, ferulic acids) is primarily responsible for antioxidant activity ^{11,19}.

8.6 Anticancer and Antiproliferative Activity

Cassane and norcassane diterpenoids, along with flavonoids from *C. bonduc*, have demonstrated cytotoxic activity against multiple cancer cell lines including MCF-7 (breast cancer), HeLa (cervical cancer), A549 (lung cancer), HepG2 (hepatocellular carcinoma), and HCT-116 (colorectal cancer) ^{3,5}. Proposed mechanisms include: (a) induction of apoptosis via caspase-3/7 activation; (b) cell cycle arrest at G₀/G₁ phase; (c) disruption of mitochondrial membrane potential; (d) modulation of BCL-2/BAX ratio; and (e) inhibition of topoisomerase II ^{3,5}. The IC₅₀ values of seed diterpenoid fractions range from 5–50 μ g/mL against sensitive cancer lines ³.

8.7 Hepatoprotective Activity

Seed and leaf extracts exhibit hepatoprotection against paracetamol- and CCl₄-induced hepatotoxicity in rats ^{1,5}. Treatment significantly reduces elevated serum transaminases (AST, ALT), alkaline phosphatase (ALP), total bilirubin, and restores hepatic antioxidant enzymes (catalase, SOD, glutathione) ⁵. Histopathological



studies confirm reduced centrilobular necrosis and hepatocyte vacuolation ^{1,5}. The protective mechanism is linked to membrane stabilization and antioxidant activity of flavonoids and phenolics ¹¹.

8.8 Immunomodulatory Activity

Seed extracts of *C. bonduc* demonstrate immunostimulant activity by enhancing phagocytic index of macrophages, stimulating delayed-type hypersensitivity (DTH) response, increasing antibody titre in SRBC-immunized mice, and promoting proliferation of splenocytes ^{1,5}. At higher doses, immunosuppressive effects have also been noted, suggesting a dose-dependent bidirectional immunomodulatory effect ⁵.

8.9 Analgesic Activity

Antipyretic and analgesic activities were simultaneously established by Archana et al. (2005) ⁷. Flower and seed kernel extracts exhibit central and peripheral analgesic properties in hot plate test and acetic acid-induced writhing models ^{7,9}. The mechanism is partly attributed to inhibition of prostaglandin synthesis and interaction with opioidergic pathways ⁹.

8.10 Anticonvulsant and Anxiolytic Activity

Seed extract of *C. bonducella* showed anticonvulsant effects in maximal electroshock seizure (MES) and pentylenetetrazole (PTZ)-induced convulsion models in rodents (Ali et al., 2009) ⁶. The anxiolytic effect has been documented in elevated plus-maze and open-field tests, with activity comparable to diazepam at therapeutic doses ⁶. The diterpenoid and flavonoid fractions likely interact with GABA-benzodiazepine receptors ⁶.

8.11 Antifilarial Activity

Seed extracts demonstrate in vitro microfilaricidal activity against *Brugia malayi* and *Setaria cervi* microfilariae ^{1,5}. Mortality rates comparable to diethylcarbamazine (DEC) were observed at concentrations of 200–400 µg/mL, suggesting potential in filariasis-endemic regions where the plant is readily available ⁵.

8.12 Antiestrogenic and Reproductive Effects

The plant's antiestrogenic and antiandrogenic potential is of growing interest for management of Polycystic Ovary Syndrome (PCOS) ^{2,5}. Seed extracts lower testosterone levels and reverse menstrual irregularities in PCOS animal models ⁵. Compounds act as selective estrogen receptor modulators (SERMs) ⁵. Anti-implantation and abortifacient effects at higher doses in rats necessitate caution in pregnancy ².

8.13 Larvicidal Activity

Leaf and seed oil extracts exhibit potent larvicidal properties against *Aedes aegypti*, *Anopheles stephensi*, and *Culex quinquefasciatus* at LC50 values of 50–200 ppm ^{2,5}. Silver nanoparticles biosynthesized using *C. bonducella* leaf extract (2024) have shown enhanced larvicidal activity, a potentially eco-friendly vector control strategy ².

8.14 Anti-diarrhoeal Activity

Anti-diarrhoeal activity is among the earliest pharmacologically validated traditional uses of *C. bonduc* and continues to be corroborated by more recent extract-based studies ^{20,21}. Iyengar and Pendse (1965) first reported that the nut (seed) of *C. bonducella* produced significant antidiarrhoeal activity in experimental rodent models, providing early pharmacological support for the plant's long-standing folk use against dysentery and gastrointestinal disorders ²¹.



More recent work by Rahman et al. evaluated the methanol extract of *C. bonducella* leaves and its ethyl acetate, chloroform, and petroleum ether fractions for antidiarrhoeal activity using the castor oil-induced diarrhoea model in mice ²⁰. Among the tested fractions, the ethyl acetate fraction produced the most pronounced antidiarrhoeal effect, significantly reducing both the frequency of defecation and the wet-stool count compared to castor oil-treated control animals, with efficacy comparable to the standard reference drug loperamide ²⁰.

The proposed mechanisms underlying this activity include: (a) inhibition of intestinal motility and peristalsis, thereby increasing gastrointestinal transit time; (b) reduction of prostaglandin-mediated intestinal fluid and electrolyte secretion; (c) an astringent action attributable to the tannin content of the extract, which precipitates mucosal

proteins and reduces intestinal secretions; and (d) a mild antimicrobial effect against enteropathogenic organisms, which may contribute to the resolution of infective diarrhoea ²⁰. Flavonoids, tannins, and saponins present in the leaf and seed extracts are considered the principal phytoconstituents responsible for this activity, acting synergistically to reduce both secretory and motility-driven components of diarrhoea ^{17,20}.

Collectively, these findings lend pharmacological credibility to the traditional use of *C. bonducella* preparations for diarrhoea and dysentery in Ayurvedic, Siddha, and folk medicine systems, and highlight the leaf and seed extracts as candidates for further isolation-guided studies to identify the specific active anti-diarrhoeal principle(s) ^{20,21}.

8.15 Summary of Pharmacological Activities

Table 5: Summary of pharmacological activities of *Caesalpinia bonduc*.

Activity	Plant Part/Extract	Model System	Active Compound(s)
Antidiabetic	Seed kernel (pet. ether, MeOH)	Alloxan/STZ rats	Bonducin, cassane diterpenes
Anti-inflammatory	Seeds, flowers (EtOH)	Carrageenan rat model	Flavonoids, phenolics
Antipyretic	Seed kernel (MeOH)	Yeast pyrexia in rats	Bonducin, bonducellin
Antimalarial	Seeds (various)	<i>P. berghei</i> mouse model	Furanoditerpenes
Antimicrobial	Seeds (EtOAc, aq.)	MIC assay, in vivo	Cassane diterpenes
Antifungal	Seeds (EtOH – EECS)	<i>C. albicans</i> apoptosis	Diterpenes, phenolics
Antioxidant	Leaves, seeds (MeOH)	DPPH, ABTS, FRAP	Phenolic acids, flavonoids
Anticancer	Seeds (various fractions)	MCF-7, A549, HeLa, HepG2	Cassane diterpenes
Hepatoprotective	Seeds, leaves (MeOH)	CCl ₄ /paracetamol rats	Flavonoids, phenolics
Immunomodulatory	Seeds (aq./EtOH)	SRBC immunized mice	Polysaccharides, flavonoids



Anticonvulsant	Seeds (EtOH)	MES/PTZ rat model	Diterpenes, flavonoids
Analgesic	Seeds, flowers	Hot plate, writhing test	Bonducellin, flavonoids
Antifilarial	Seeds (EtOH)	B. malayi (in vitro)	Cassane diterpenes
Antiestrogenic	Seeds (MeOH)	PCOS rat model	Diterpenoids
Larvicidal	Leaves, seed oil	Aedes, Anopheles larvae	Terpenoids, fatty acids
Anti-diarrhoeal	Leaves (MeOH, EtOAc fraction), seeds	Castor oil-induced diarrhoea in mice	Tannins, flavonoids, saponins

9. Structure–Activity Relationships (Sar)

The cassane diterpenoid scaffold of *C. bonduc* offers rich opportunities for SAR analysis ³. Key structural determinants of bioactivity are:

Furanoditerpene skeleton: The fused furan ring attached to the cassane diterpene backbone is critical for cytotoxic and antimalarial activity ^{3,5}. Removal or saturation of the furanyl moiety dramatically reduces potency. Hydroxylation at specific ring positions (C-7, C-11) enhances anti-inflammatory and antidiabetic activity ³.

Flavonoid hydroxylation pattern: The catechol B-ring (3',4'-dihydroxyl) present in luteolin and quercetin confers superior antioxidant and anti-inflammatory activity compared to monohydroxyl flavones like apigenin ¹¹. Glycosylation at C-3 modulates bioavailability and receptor binding ^{11,17}.

Phenolic acid conjugation: Ester-linked phenolic acids (chlorogenic acid = caffeoylquinic acid) demonstrate stronger antioxidant activity than their free acid counterparts, attributed to the synergistic effect of the quinic acid moiety enhancing electron delocalization ^{11,19}.

10. TOXICOLOGICAL PROFILE

Despite extensive pre-clinical pharmacological data, comprehensive, systematically conducted toxicological assessment of *C. bonduc* remains one of the principal gaps in the literature ².

10.1 Acute Toxicity

The LD₅₀ of seed extracts in mice via the oral route is generally reported as >2,000 mg/kg body weight (OECD 423 limit test), classifying the plant as Category 5 (low acute toxicity) by GHS classification ^{2,5}. Intraperitoneal administration yields lower LD₅₀ values (~800–1,200 mg/kg). No significant gross pathological changes were noted in surviving animals at sub-lethal doses ⁵.

10.2 Sub-chronic and Chronic Toxicity

28-day repeated dose studies in Wistar rats at doses of 250–1,000 mg/kg demonstrated no significant changes in haematological parameters, serum biochemistry (liver enzymes, creatinine, urea), organ weight ratios, or histopathology of liver, kidney, spleen, and testes at doses up to 500 mg/kg ^{2,5}. Mild hepatic changes were observed at 1,000 mg/kg in some studies, warranting caution at very high doses ².

10.3 Reproductive and Developmental Toxicity

Anti-implantation and abortifacient activity of *C. bonduc* seed extracts at higher doses has been



documented in rats, attributed to antiestrogenic activity ^{2,5}. This constitutes a significant safety concern: the plant is contraindicated in pregnancy and use during breastfeeding should be avoided pending further safety data ².

10.4 Genotoxicity

Limited Ames test data suggest absence of direct mutagenicity at sub-cytotoxic concentrations ². However, adequate in vivo genotoxicity studies (micronucleus test, comet assay) with characterized extracts are not yet available in peer-reviewed literature. This represents a regulatory gap for any clinical development pathway ².

11. MODERN FORMULATIONS AND NANO-FORMULATION APPROACHES

Beyond classical Ayurvedic formulations, recent research has explored modern delivery systems to improve the bioavailability and efficacy of *C. bonduc* phytoconstituents, which are limited by poor water solubility (diterpenoids) and rapid first-pass metabolism (flavonoids) ^{2,5}.

Nanoparticle formulations: Silver nanoparticles (AgNPs) green-synthesized using *C. bonduc* leaf extract demonstrate enhanced antimicrobial and larvicidal efficacy compared to the extract alone ². Polymeric nanoparticles (PLGA-based) encapsulating seed diterpenoid fractions show improved cytotoxicity and sustained release profiles in cancer cell line studies ⁵.

Phytosomes: Complexation of flavonoid fractions with phosphatidylcholine (phytosome technology) has been investigated to enhance oral bioavailability, with promising results in antioxidant and hepatoprotective assays ⁵.

Standardized extracts: HPLC/HPTLC-based standardized dry extracts normalized to bonducellin or total cassane diterpenoid content

are under development for use in clinical trials, enabling dose precision and reproducibility across batches ^{2,16}.

12. REGULATORY STATUS AND QUALITY CONTROL

Caesalpinia bonduc seed (Latakaranja) is listed in the Ayurvedic Pharmacopoeia of India (API), Volume I, which provides official monograph standards for identity, purity, and strength ¹. The drug is also listed in the Indian Herbal Pharmacopoeia (IHP) and several state-level formularies. Internationally, the plant is referenced in the WHO Monographs on Selected Medicinal Plants Series; however, full regulatory approval as a new botanical drug (under CDSCO/AYUSH guidelines for Ayurvedic drugs) remains in the classical use category rather than as a modern phytopharmaceutical ^{1,13}.

For publication and export purposes, the plant drug must comply with: (1) API physicochemical limits; (2) WHO good agricultural and collection practices (GACP) ¹³; (3) WHO/ICH guidelines on heavy metals (Pb $\leq$ 10 ppm, As $\leq$ 3 ppm, Cd $\leq$ 0.3 ppm, Hg $\leq$ 0.2 ppm); (4) Aflatoxin limits (B1+B2+G1+G2 $\leq$ 4 ppb); and (5) pesticide residue limits as per European Pharmacopoeia ¹³.

13. RESEARCH GAPS AND FUTURE PERSPECTIVES

Despite decades of pre-clinical research, several critical gaps limit the translation of *C. bonduc* from traditional use to modern therapeutic application ^{1,2,5}:

1. Clinical trials: No randomized controlled clinical trials (RCTs) have been conducted for any pharmacological indication ². Well-designed Phase I/II trials for antidiabetic and antimalarial



activity, using standardized, characterized extracts, are urgently needed ^{2,5}.

2. Mechanism elucidation: Detailed molecular mechanisms—target identification, receptor binding studies, signal transduction pathways—remain incomplete for most pharmacological activities ². Network pharmacology and molecular docking approaches should be systematically applied ².

3. Comprehensive toxicology: Sub-chronic, chronic, teratogenicity, and genotoxicity studies conforming to OECD guidelines using characterized extracts are lacking ². Herb–drug interaction studies are essentially absent ².

4. Bioavailability and pharmacokinetics: ADME profiles of key compounds (bonducin, caesalpinin, major diterpenoids) in relevant animal models and ultimately humans are unavailable, hindering rational dose selection ^{2,5}.

5. Isolation of novel compounds: Advanced analytical techniques (LC-MS/MS, NMR, X-ray crystallography) should be applied to less-studied plant parts (flowers, roots, fresh latex) to identify additional bioactive compounds ^{3,4}.

6. Conservation and sustainability: Given increasing interest in the plant, wild-harvesting pressures are rising ⁵. Tissue culture-based propagation, sustainable cultivation practices, and quality standardization across growing regions warrant attention ^{2,5}.

7. Nanotechnology-based delivery: Nano-encapsulation of poorly soluble diterpenoids to improve bioavailability, along with targeted delivery systems for anticancer applications, represents a high-priority research direction ^{2,5}.

14. CONCLUSION

Caesalpinia bonduc (L.) Roxb. is a pharmacologically exceptional medicinal plant deeply embedded in the traditional medicine systems of tropical Asia ^{1,2}. Its chemical complexity—anchored by a unique suite of cassane and norcassane diterpenoids alongside diverse flavonoids, phenolic acids, and sterols—underpins a remarkably broad spectrum of biological activities: antidiabetic, antimalarial, anti-inflammatory, antimicrobial, antifungal, antioxidant, anticancer, hepatoprotective, anticonvulsant, immunomodulatory, antifilarial, and antiestrogenic, among others ^{3,5,6,7,8,9,10,11,12,14}.

The convergence of traditional ethnopharmacological evidence and modern pre-clinical validation strongly supports the potential of *C. bonduc* as a source of novel therapeutic agents, particularly for antidiabetic, anticancer, and antimalarial drug development ^{2,5}. Cassane furanoditerpenes, in particular, represent an underexplored scaffold for medicinal chemistry optimization ³.

However, the journey from bench to bedside remains incomplete ². The critical next steps—systematic clinical trials, comprehensive toxicological studies, pharmacokinetic characterization, and mechanistic molecular pharmacology—are necessary before *C. bonduc*-derived preparations can be endorsed for mainstream therapeutic use ². With appropriate scientific rigour and investment, this remarkable fevernut has the potential to yield valuable contributions to modern medicine in the coming decade ^{2,5}.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest associated with this review.

ABBREVIATIONS

- ABTS — 2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)
- ADME — Absorption, Distribution, Metabolism, Excretion
- API — Ayurvedic Pharmacopoeia of India
- COX — Cyclooxygenase
- DPPH — 2,2-Diphenyl-1-picrylhydrazyl
- DTH — Delayed-Type Hypersensitivity
- EECS — Ethanolic Extract of *Caesalpinia bonduc* Seeds
- FRAP — Ferric Reducing Antioxidant Power
- GACP — Good Agricultural and Collection Practices
- GHS — Globally Harmonized System (of Classification and Labelling of Chemicals)
- HPTLC — High-Performance Thin-Layer Chromatography
- IC₅₀ — Inhibitory Concentration (50%)
- LD₅₀ — Lethal Dose (50%)
- MES — Maximal Electroshock Seizure
- MIC — Minimum Inhibitory Concentration
- PCOS — Polycystic Ovary Syndrome
- PTZ — Pentylentetrazole
- RCT — Randomized Controlled Trial
- ROS — Reactive Oxygen Species
- SAR — Structure–Activity Relationship
- SERM — Selective Estrogen Receptor Modulator
- SOD — Superoxide Dismutase
- SRBC — Sheep Red Blood Cells
- STZ — Streptozotocin
- TLC — Thin-Layer Chromatography

- WHO — World Health Organization.

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