

"UNVEILING THE THERAPEUTIC POTENTIAL OF GUILANDINA BONDUC: A REVIEW OF CURRENT RESEARCH AND FUTURE DIRECTIONS"

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Article Received on
29 April 2025,

Revised on 20 May 2025,
Accepted on 09 June 2025

DOI: 10.20959/wjpr202512-36834



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ABSTRACT

Guilandina bonduc, a plant with a rich history in traditional medicine, is gaining attention for its diverse therapeutic potential. This review synthesizes current research on *G. bonduc*, exploring its traditional uses, phytochemical composition, and pharmacological activities. The study highlights the plant's applications in treating various ailments, including inflammation, cancer, microbial infection, diabetes mellitus, catalepsy, tumors, pyrexia and digestive issues, immunomodulatory effect, antioxidant agent, anti-estrogenic, larvicide effect, anti-filarial effect as documented in traditional Indian medical systems like Ayurveda and Unani. We examine the bioactive compounds identified in *G. bonduc*, such as flavonoids, alkaloids, and terpenoids, and their contribution to its medicinal properties. Furthermore, this review discusses the existing scientific evidence supporting the plant's efficacy, including in vitro and in vivo studies. Finally, it identifies gaps in current research and suggests future directions, such as the need for more clinical trials, exploration of specific mechanisms of

action, and investigation of novel therapeutic applications. This comprehensive overview aims to provide insights into the therapeutic potential of *G. bonduc* and encourage further research to unlock its full medicinal value.

KEYWORDS: *Guilandina bonduc* L., Botany, Traditional usages, Phytochemistry, Pharmacology, Drug discovery, and development.

INTRODUCTION

Guilandina bonduc L., commonly referred to as fever nut, nicker bean, bonduc nut, and knicker nut, is a member of the Fabaceae family. This plant can be found in various parts of Asia, Africa, South America, and regions of southern North America. It thrives at altitudes of up to 1000 meters in the Himalayas and is often seen in desolate areas throughout India, where it particularly flourishes in tropical and delta landscapes, especially within evergreen and moist deciduous forests. *G. bonduc* is also commonly utilized as a fencing species in agricultural zones.^[64] All parts of this plant—roots, stems, leaves, seeds, and seed pods—have been extensively used in different traditional Indian medical practices, including Ayurveda, Siddha, homeopathy, and folk medicine. In Ayurveda, it is recognized for its use in treating tumors, cysts, and cystic fibrosis. The Unani system utilizes the leaves and seeds of *G. bonduc* for addressing various ailments such as inflammation, blood purification, antispasmodic problems, septic conditions, seasonal fevers, bronchial asthma, bronchitis, ascites, hydrocele, and pleurisy.^[29] Local populations utilize the mature seeds of *G. bonduc* for an array of therapeutic applications, including the management of chronic wounds, muscle pain, digestive issues, constipation, intestinal warmth, bowel complications, immune enhancement, hemorrhoids, leprosy, lymphatic filariasis, and polycystic ovary syndrome in folk medicine outlets across India, such as kalatchikkai in Tamil and fever nut in English. The species is largely distributed in tropical areas worldwide and is classified within the paleotropics. Since 1930, extensive studies have shown the broad pharmacological effects of *G. bonduc*, which encompass influences on COVID-19, diabetes, abortion, antithyroid activities, lipid metabolism, immune modulation, and estrogenic effects, among other results.^[9,15] Though many phytochemicals have been isolated from *G. bonduc* over the years, not all have undergone pharmacological assessment. The rich variety of bioactive compounds and their related pharmacological characteristics have garnered increased clinical interest in this plant. Recently, numerous researchers have focused on this valuable plant, investigating its traditional uses, phytochemical content, and pharmacology. Nonetheless, a comprehensive review addressing all facets of *G. bonduc* is still missing. The current literature provides only a cursory overview of its phytochemical and pharmacological properties, which may not adequately represent the plant's significance to scientists. This review seeks to offer an in-depth analysis of *G. bonduc*'s traditional applications, botanical attributes, phytochemical composition, and pharmacological effects, thus improving scientists' comprehension of this plant and its potential uses. *Guilandina bonduc*, known for its long-standing history of traditional applications, has gained significant attention recently due to its therapeutic

prospects. With its wide variety of bioactive compounds and notable pharmacological activities, *Guilandina bonduc* presents a promising opportunity for developing new treatments for various health issues. This review aims to provide a thorough evaluation of the current research landscape regarding *Guilandina bonduc*, highlighting its therapeutic potentials and proposing future research directions. By synthesizing existing knowledge and identifying areas in need of further investigation, this review aspires to facilitate the advancement of *Guilandina bonduc* as an essential resource for improving human health and wellness.^[25]

Biological description

G. bonduc is a climbing shrub or liana that can reach heights of up to 8 meters and features thorns on its stems and leaf stalks. Its leaves are bipinnate, measuring 50 cm in length, and typically have four to five pairs of leaflets, which are ovate or elliptical oblong in shape. The bases of the leaves are rounded, while the tips are obtuse and mucronate. The petiole is 15 cm long and bears stipules. The flowers appear in simple or branched racemes, displaying a yellow color, and bloom from August to December. The resulting fruits are oblong-ovate, characterized by inflated pods with beaked tips and dense spines; they contain one or two shiny, hemispherical seeds (Fig. 1). Fruiting starts in October.^[29]

Guilandina bonduc (L.) Roxb.

- **Synonym:** *Caesalpinia bonduc* (L.) Roxb.
- **Basionym (original name):** *Dolichos bonduc* L.
- **Family:** Fabaceae (Leguminosae)
- **Subfamily:** Caesalpinioideae

Classification (Taxonomy)

- **Kingdom:** Plantae
- **Clade:** Angiosperms
- **Clade:** Eudicots
- **Clade:** Rosids
- **Order:** Fabales
- **Family:** Fabaceae
- **Genus:** *Guilandina*
- **Species:** *Guilandina bonduc*

Common Names

- **English:** Gray Nicker, Fever Nut
- **Hindi:** Katkaranj, Karanjwa
- **Tamil:** Kazharchikai
- **Ayurveda:** Latakaranja



Fig. 1: Morphology of Guilandina bonduc L.

➤ Key Phytochemicals

- **Flavonoids:** Guilandina bonduc is rich in flavonoids, recognized for their antioxidant and anti-inflammatory effects.
- **Phenolic Compounds:** The seeds and leaves of the plant include phenolic compounds, which play a role in its pharmacological properties.
- **Terpenoids:** Guilandina bonduc contains terpenoids that have demonstrated antimicrobial and antifungal effects.
- **Saponins:** The seeds of the plant feature saponins, which have been noted for their hypoglycemic and hypocholesterolemic benefits.
- **Alkaloids:** This plant comprises alkaloids, which can contribute to its health benefits, such as antimalarial and antibacterial properties.

➤ **Seed-Specific Compounds**

- **Linoleic Acid:** The oil derived from *Guilandina bonduc* seeds is high in linoleic acid (68%), known for its vesicant properties and used in rheumatism treatment.
- **Bitter Extract:** Extracted from the seeds, this bitter substance is referred to as "poor man's quinine" and is employed in malaria treatment.^[1]

➤ **Pharmacological Activities**

- **Antibacterial and Antifungal Properties:** The seeds of *Guilandina bonduc* are known to possess antibacterial and antifungal capabilities, making them effective against various infections.
- **Anti-Inflammatory and Antioxidant Effects:** Extracts from the plant have shown anti-inflammatory and antioxidant capabilities, which could enhance its therapeutic potential.
- **Hypoglycemic and Hypcholesterolemic Effects:** Research has indicated that the seeds of *Guilandina bonduc* may help manage blood sugar and cholesterol levels due to their hypoglycemic and hypcholesterolemic properties.^[5]

The phytochemicals located in various parts of *Guilandina bonduc*

➤ **Seeds**

- **Linoleic Acid:** A primary element of the oil from the seeds, linoleic acid possesses vesicant qualities and is utilized for rheumatism treatment.
- **Bitter Extract:** A bitter extract derived from the seeds is employed against malaria and is called "poor man's quinine."
- **Flavonoids:** Present in the seeds, these contribute to antioxidant and anti-inflammatory effects.
- **Saponins:** They have been reported to help lower blood sugar and cholesterol levels.

➤ **Leaves**

- **Phenolic Compounds:** Found in the leaves, these contribute to pharmacological effects.
- **Flavonoids:** Also occurring in the leaves, these enhance the plant's antioxidant and anti-inflammatory properties.
- **Terpenoids:** Some research indicates the presence of terpenoids in the roots, likely contributing to antimicrobial effects.
- **Alkaloids:** These may be found in the roots, potentially adding to the plant's medicinal benefits.

➤ Other Parts

- **Stem:** It may contain some phytochemicals similar to those in the leaves and seeds, though it's less studied.
- **Pods:** The seed pods may have a similar phytochemical profile to the seeds, but research on this is limited.

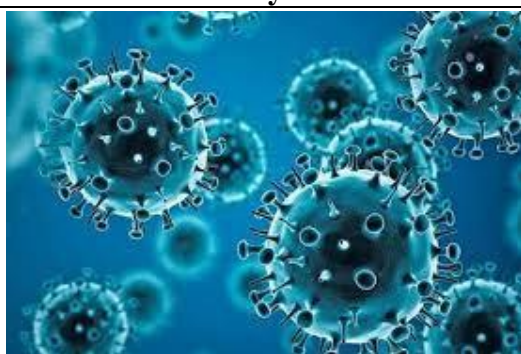
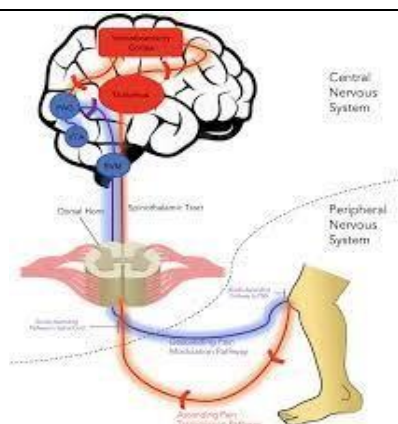
The specific makeup and levels of phytochemicals can vary based on factors like the plant's maturity, environmental conditions, and extraction techniques.

Major Chemical constituents of *G. bonduc* (Karanjwa)

S.NO.	G.BONDU PLANT PART(S)	Name of chem.constituents	Refernces
1.	Seed Seed Kernel	Bonducin- A bitter substance Phytosterinin Fatty acids, Caesalpins (α , β , γ , δ and ψ), Bonducellin (Homois of lavone) Citrulline Cassanediterpenes, Neocaesalpins C, D Bondenolide Neocaesalpin P, Neocaesalpin H Cordylane A, CaesalpininB Bonducellpin E, Caesalpinolide A Caesalpinolide C, D and E Cassane Diterpinoids Cassane Furanoditerpene	[11] [30] [41] [68]
2.	Bark	Caesaldekarin J Pipatalin	[60]
3.	Young Twigs Leaves	Cytotoxic Flavonoids	[36]
4.	Roots	Caesaldekarin A	[33]

PHARMACOLOGICAL ACTIVITY OF GUILDIANA BONDUC

The pharmacological activity of the various parts of *G. bonduc* crude extracts and their metabolites have been researched in recent years as a rich source of vital phytochemicals that make it a potent antibiotic agent. Meanwhile, based on in vivo and in vitro experiments, the extracts of *G. bonduc* are regarded as the promising source of pharmacological effects as analgesic, anti-inflammatory, antioxidant, COVID-19, antidiabetic, abortifacient, anticataleptic, immunomodulatory, and antiestrogenic agents, and the list goes on (Fig.2). Apart from in vitro and in vivo experiments, it was found that different parts of *G. bonduc* are widely used to treat different diseases. However, the pharmacological effects of this plant have not been extensively studied. However, phytochemicals have not been extensively investigated in wet laboratory experiments. The pharmacological effects of *G. bonduc* are precisely revealed in the following sections.

**Anti- Stress****Anti Filarial****Anti-Pyrexia****Anti-Diabetics****Covid-19****Anti-Cancer****Analgesic****Inflammation****Anti-Inflammation**

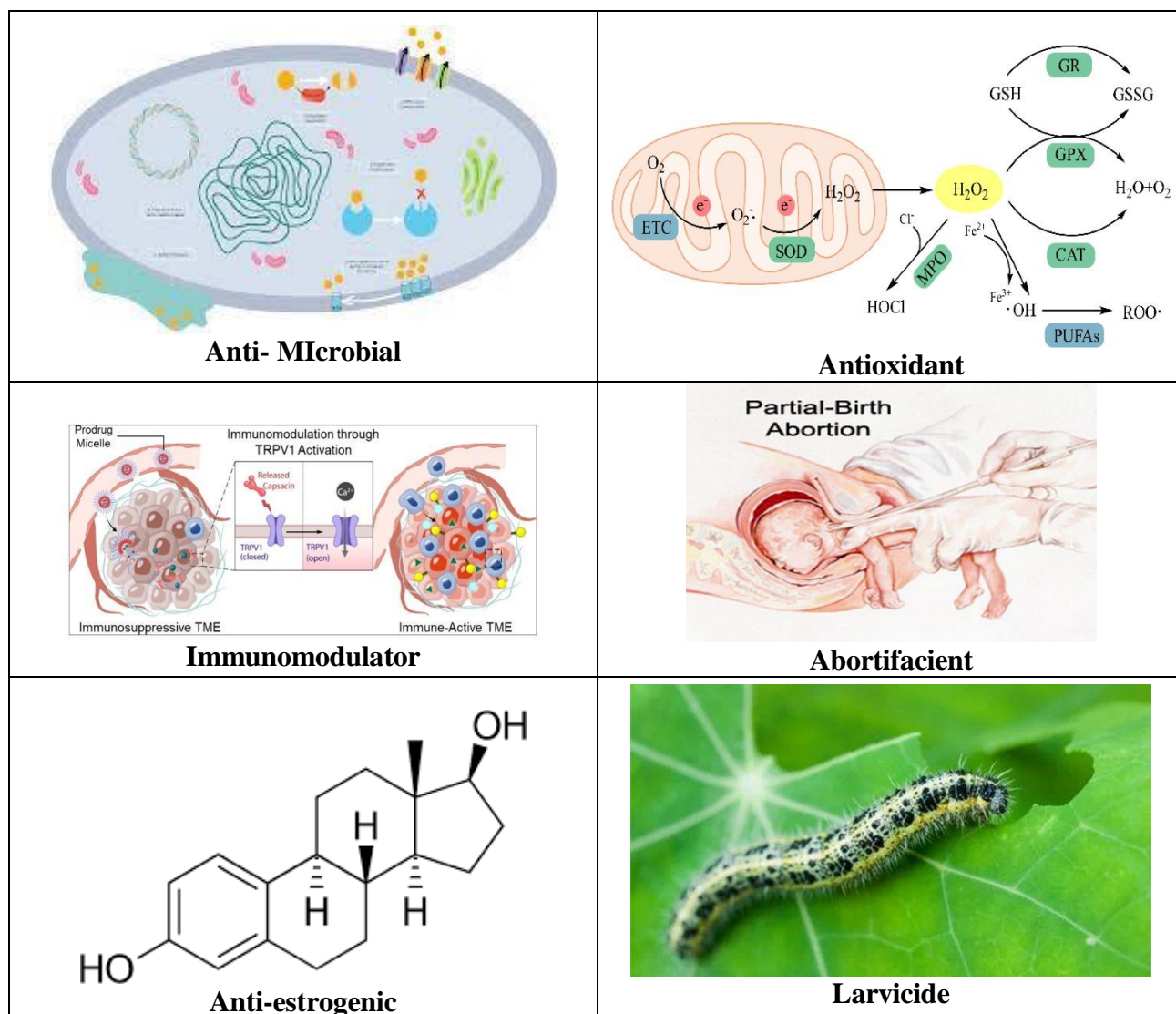


Fig. 2: Pharmacological Potentials Of Guilandina Bonduc L.

ANALGESIC EFFECT

The anti-inflammatory properties of radiation therapy can lead to delayed analgesic effects, characterized by prolonged pain relief that may manifest several weeks post-treatment. To alleviate this pain, analgesics are employed for short-term relief and may sometimes fully block sensations in specific organs. However, certain synthetic non-opioid analgesics can result in severe side effects when used long-term or in excessive doses, prompting researchers globally to seek alternative compounds from natural sources. For example, Kannur et al. (2012)^[27] explored the analgesic potential of *G. bonduc* seeds, known for their analgesic use in traditional medicine. They prepared seed extracts using 95% ethanol and conducted two different edema-inducing tests—carrageenan-induced and egg albumin-induced paw edema—to validate the extracts' analgesic properties, which yielded positive results. Similarly, Mahfoozurrahman et al. (2012)^[34] found that seed extracts significantly reduced edema in rats, lessened their

fumble responses, and enhanced their reaction times in hot plate tests. Additionally, Aruna Devi et al. (2008)^[5] demonstrated a dose-dependent analgesic effect from *G. bonduc* flower extract. They administered doses of 30, 100, and 300 mg/kg orally to rats experiencing pain induced by capsaicin, formalin, and acetic acid in writhing tests, hot plate tests, and tail flick tests. Their findings indicated a significant analgesic response that depended on the dosage in all test subjects.

Anticancer Effects

Cancer remains the leading cause of mortality globally, surpassing other diseases and disorders. The World Health Organization (WHO) (2002)^[67] has projected that cancer prevalence could rise by 75% by 2030, largely due to increasing population numbers and changes in lifestyle. While various chemotherapeutic agents targeting different biochemical and molecular pathways are widely applied in cancer treatment, they can have harmful side effects and may not always effectively cure the disease (Nurgali et al. 2018).^[69] Moreover, costs associated with certain cancer treatments can be prohibitively high. Consequently, researchers are actively seeking new anticancer agents derived from natural sources that are associated with fewer adverse effects. Deepika et al. (2014)^[13] explored the anticancer potential of *G. bonduc* seeds extracted using petroleum ether, which was found to induce cell death in Ehrlich ascites carcinomas. They suggested that this seed extract could serve as a new candidate for breast cancer therapy. Similarly, Sandhia and Bindu (2021)^[47] examined the anticancer effects of *G. bonduc* bark extracts utilizing a tryptophan dye exclusion method to evaluate in vitro cytotoxicity at concentrations of 10, 20, 50, 100, and 200 µg/mL in Dalton ascite lymphoma cells. Their findings indicated that, at 100 µg/mL, the extracts achieved 100% cytotoxicity, which they attributed to the high levels of flavonoids and phenols present in the bark extract. Furthermore, Shivaprakash et al. (2016)^[50] tested various doses of methanolic extracts from *G. bonduc* on Ehrlich ascites tumor (EAT) cell lines to assess antiproliferative and pro-apoptotic effects. At a dosage of 200 mg/kg, the extracts led to a 51.6% reduction in viable cells and a 65% decrease in ascitic volume in EAT cells. The analysis revealed that the cells treated with the methanolic extract were more likely to undergo apoptosis instead of necrosis, accompanied by a significant decrease in anti-apoptotic Bcl-2 expression and an increase in pro-apoptotic Bax expression. The study concluded that the methanolic extract demonstrated antiproliferative and pro-apoptotic properties, indicating its potential as a therapeutic agent for cancer treatment.

Anti-Inflammatory Effects

Inflammation is a complex protective response of the body to external stimuli, which can be managed by regulating specific signaling pathways, including TNF- α , NF- κ B, inducible nitric oxide synthase, interleukin-6, and cyclooxygenase-2 (Fan et al., 2020).^[14] The bark of *G. bonduc* was tested for its anti-inflammatory capabilities in male albino Wistar rats through a dose-dependent approach after inducing paw edema with carrageenan. The results indicated significant anti-inflammatory properties across all doses (Mahfoozurrahman et al., 2012).^[34] Notably, this research showed substantial reductions in carrageenan-induced paw swelling, decreased writhing behavior in the rats, and extended response times in the hot plate test. The findings suggested that the seeds of *G. bonduc* possess strong anti-inflammatory effects, especially when water-extracted. A related study by Kale et al. (2010)^[24] investigated the anti-inflammatory properties of *G. bonduc* seed kernels extracted with petroleum ether. In this study, male Wistar rats had paw edema induced by injecting 0.1 mL of carrageenan, and they were then treated with the *G. bonduc* seed extracts in a dose dependent manner. The results indicated remarkable anti-inflammatory activity at a dose of 100 mg/kg, leading the researchers to conclude that the effects could be attributed to the presence of phytosterols in the seed kernels.

Antimicrobial Effects

Recently, invasive microbial infections have posed significant risks, especially for individuals with weakened immune systems (Loeffler and Stevens, 2003; Groll and Lumb, 2012; Prabhu et al., 2021)^[16,32,40] The rise in infections caused by harmful pathogens, including bacteria, fungi, and viruses, is alarming and necessitates the urgent discovery of new active compounds from natural sources to combat these diseases. In the quest for a novel antibiotic, *G. bonduc* was evaluated against harmful pathogens by Simin et al. (2001)^[58] who examined the antimicrobial and phytotoxic properties of newly isolated diterpenoid bondenoids derived from *G. bonduc* using methanol extracts, ethyl acetate fractions, and a water-soluble component of the methanol extract. The methanol extracts from the leaves were tested against various microbial strains, including *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, *Epidermophyton floccosum* var. *nigricans*, and *Candida glabrata*. The extracts demonstrated inhibitory effects on *E. coli* and *E. floccosum* var. *nigricans*, with moderate inhibition seen across all tested microbes. These findings indicate that the plant extract might serve as an antibiotic option.

Additionally, some diterpenoid compounds were isolated from the bark of *G. bonduc* using ethanol as a solvent. Phytochemicals such as neocaesalpin H, cordylane A, caesalpinine B, bondellpin E, caesalpinolide A, and 17-methylvouacapane-8(14), 9(11)-diene displayed antibacterial potential against *Staphylococcus aureus*, *Streptococcus agalactiae*, and *Pseudomonas aeruginosa*. However, these compounds exhibited limited inhibitory effects on the tested bacterial strains, and none significantly inhibited glutathione-S-transferase (Ata et al., 2009).^[7] Arif et al. (2009)^[4] investigated the antimicrobial effects of *G. bonduc* seed kernels against antibiotic-resistant strains, specifically *S. aureus* and *P. aeruginosa*, finding that these extracts did have inhibitory effects on the tested strains. Hydroalcoholic extracts from the seed kernel and seed coat of *G. bonduc* were also administered to rats suffering from chronic pneumonia induced by *P. aeruginosa*. The treatment resulted in significant bacterial clearance in the lungs and reduced occurrences of lung abscesses after two weeks, suggesting the seeds may serve as a promising natural remedy for lung infections linked to *P. aeruginosa*, including cysts and cystic fibrosis.

Khan et al. (2011) evaluated the antimicrobial, antispasmodic, and calcium channel-blocking properties of *G. bonduc* extracts obtained through n-butanol, ethyl acetate, and ethanol. Their findings revealed that the ethyl acetate extracts exhibited a broader range of inhibition against bacteria such as *E. coli* and *B. subtilis*. Additionally, potent antifungal activity was observed against *Candida glabrata* (80%), while n-butanol, chloroform, and crude extracts led to a significant reduction in the growth of *Aspergillus flavus* by 65%–70%. Based on the antibacterial, antifungal, spasmolytic, and calcium channel-blocking properties, the researchers concluded that these plant extracts might harbor effective therapeutic agents against diseases caused by these microorganisms.^[28]

The antifungal potential of *G. bonduc* seeds was assessed by Shukla et al. (2011) using various solvents, including ethyl acetate, water, and petroleum ether, against fungal strains such as *Aspergillus niger*, *Candida albicans*, *Fusarium oxysporum*, and *Alternaria solani*. The ethyl acetate and aqueous extracts exhibited strong inhibitory effects on all tested fungal strains, indicating their potential utility in combating fungal infections.^[51]

Antioxidant Properties

The production of reactive oxygen species in the body can trigger an oxidative stress response under various pathological conditions, potentially damaging cellular and organ function. Parameshwar et al. (2002)^[38] found that while the aqueous extract from *G. bonduc* seed

kernels was ineffective at scavenging free radicals in vitro, the ethyl acetate extract demonstrated a maximum activity of 49% after one hour. This ethyl acetate extract has antioxidant properties that could aid in alleviating oxidative stress linked to diabetes. Research by Gupta et al. (2008)^[17] investigated the flavonoids and triterpenoids found in *G. bonduc* leaves and their involvement in antioxidant metabolic processes, such as in relation to malondialdehyde (a lipid peroxidation byproduct), as well as enzymatic antioxidants like catalase and superoxide dismutase, along with non-enzymatic antioxidants such as glutathione and vitamins C and E. The study also measured transaminase enzyme activity, bilirubin, total protein, and uric acid levels in serum. Their findings indicated that the plant extracts elevated protein and uric acid levels while reducing bilirubin activity, showcasing strong antioxidant effects.

Shukla et al. (2009a, b)^[53,54] assessed the antioxidant activity of *G. bonduc* seeds at doses of 20, 40, 50, 100, and 200 g/mL, noting a DPPH scavenging activity ranging from 38.93% to 74.77%, which was comparable to ascorbic acid (64.26% to 82.58%). The IC₅₀ values for the extracts and ascorbic acid were found to be 74.73 and 26.68 µg/mL, respectively, in DPPH radical scavenging tests. Additionally, the extracts inhibited hydroxyl radicals, nitric oxide, and superoxide anions, exhibiting IC₅₀ values of 109.85, 102.65, and 89.84 µg/mL, respectively, suggesting that *G. bonduc* seeds have significant potential as natural antioxidants. These extracts also demonstrated promising antioxidant effects on catalase and superoxide dismutase enzymes and reduced lipid peroxidation levels in diabetic animals (Jana et al., 2012).^[21] Jayakrishnan et al. (2014)^[22] examined the antioxidant capabilities of *G. bonduc* seeds extracted with ethanol using the DPPH assay, obtaining an EC₅₀ value of 7.5 mg, which indicated strong antioxidant properties. Pandey et al. (2018) reported robust DPPH free radical and nitric oxide scavenging activity from crude extracts of *G. bonduc*, concluding that these extracts could be valuable for future applications in food and pharmaceuticals focused on developing antioxidant-based products.^[37]

Shukla and Mehta (2017)^[52] evaluated the antioxidant potential of aqueous seed extracts of *G. bonduc* using the DPPH assay, showing an inhibition percentage between 36.93% and 70.57% at doses of 20, 40, 50, 100, and 200 g/mL, which closely matched the results for ascorbic acid (64.26% to 82.58%) with an IC₅₀ value of 86.31 g/mL. The aqueous extract significantly inhibited hydroxyl radicals, nitric oxide, and superoxide anions, with IC₅₀ values of 139.95, 114.70, and 83.62 g/mL, respectively, reinforcing the plant's potential as a natural

antioxidant. Shukla et al. (2009b)^[55] also explored the antioxidant properties of ethanol extracts in the DPPH assay, observing a dose-dependent inhibition ranging from 38.93% to 74.77%, while ascorbic acid recorded 64.26% to 82.58% inhibition. They noted an IC₅₀ concentration of 74.73 g/mL for the extracts, which effectively suppressed hydroxyl radicals, nitric oxide, and superoxide anions with IC₅₀ values of 109.85, 102.65, and 89.84 g/mL, respectively. Based on these results, the authors concluded that *G. bonduc* has strong potential to be utilized as a natural antioxidant agent.

Antidiabetic effects

Diabetes mellitus is marked by various metabolic changes in the body, such as elevated blood glucose levels (hyperglycemia), reduced blood glucose levels (hypoglycemia), increased lipid levels (hyperlipidemia), decreased lipid levels (hypolipidemia), and disturbances in lipid and protein metabolism. Every year, around 3.5 million deaths result from complications related to diabetes, including diabetic coma, diabetic ketoacidosis, nephropathy, neuropathy, and retinopathy. Despite improvements in diagnosing and preventing the disease, mortality and morbidity associated with it have risen. As a result, researchers are actively seeking new antidiabetic medications that are inexpensive and free from side effects.

G. bonduc is utilized as an antidiabetic remedy by the inhabitants of the Andaman and Nicobar Islands and the Caribbean Islands (Sasidharan et al. 2021b)^[49] Prior studies have indicated its notable hyperglycemic properties. Parameshwar et al. (2002)^[38] investigated the antidiabetic effects of various extracts from the seeds of *G. bonduc* on rats suffering from alloxan-induced diabetes, utilizing ethyl acetate, ether, petroleum ether, and aqueous extracts. The alterations associated with diabetes, such as changes in liver lipid and glycogen levels, were reversed by the aqueous and ethyl acetate extracts, while extracts using petroleum ether had no impact on diabetic rats. Owing to the antidiabetic properties exhibited by the aqueous and ethyl acetate extracts, these were analyzed for their phytochemical content and found to be rich in triterpenoid glycosides. Their research indicates that the extracts demonstrated antidiabetic activity due to the presence of triterpenoid glycosides in both the aqueous and ethyl acetate extracts.

The antidiabetic effects of *G. bonduc* seed extracts were assessed in rats with alloxan-induced hyperglycemia by Kannur et al. (2006)^[26] demonstrating that oral administration of the extracts (300 mg/kg) produced a significant antihyperglycemic effect and considerably decreased BUN levels. It was also noted to significantly affect hyperlipidemia linked to

diabetes, effectively lowering elevated cholesterol and LDL levels. Their findings suggested that it may exert its antihyperglycemic effects by inhibiting glucose absorption, supporting the claimed antidiabetic properties of this traditional medicinal plant.

The hypoglycemic effect of the *G. bonduc* seed coat on diabetic rats induced by streptozotocin and alloxan was researched by Biswas *et al.* (1997)^[10] with the treatment resulting in a remarkable decrease in blood sugar ($P < 0.005$) within five hours. Patil *et al.* (2011)^[39] examined the antidiabetic effects of *G. bonduc* root extracts—aqueous, ethanol, and chloroform—on glucose tolerance in alloxan-induced diabetic rats. All three extracts provided excellent protection and normalized glucose levels during a glucose tolerance test, with a significant reduction in blood sugar levels observed after three hours at a dosage of 250 mg/kg body weight in diabetic rats. Conversely, the chloroform and ethanol extracts displayed protection rates of 22.28% and 23%, respectively. On days 0, 3, 5, 7, and 10, blood glucose, triglyceride, cholesterol, and urea levels were measured in rats undergoing long-term treatment for alloxan diabetes to evaluate the degree of protection. Chloroform and ethanol extracts demonstrated a strong glucose-reducing effect in rats with glucose- and alloxan-induced diabetes. They concluded that the extracts might exhibit antidiabetic effects by enhancing pancreatic secretion or increasing glucose uptake. Jana *et al.* (2012)^[21] found that seed extracts of *G. bonduc* improved carbohydrate-metabolizing enzymes, along with fasting blood glucose and glycogen levels more effectively than untreated diabetic rats, and significantly reduced enzyme toxicity parameters ($P < 0.05$). The healing effects of the seed extract were notably more effective than those of the widely used antidiabetic medication, glibenclamide. Widhiantara *et al.* (2018)^[66] examined the hypoglycemic effects of *G. bonduc* seeds on type II diabetes induced by streptozotocin and nicotinamide in albino Wistar rats. The subjects received treatment twice daily for 14 days, after which blood sugar and plasma insulin levels were evaluated. They observed that the animals given the seed extract exhibited a significant reduction in postprandial blood glucose (PPBG) levels, while those administered distilled blood showed significantly elevated PPBG levels, indicating that *G. bonduc* seeds are more effective in reducing postprandial blood glucose levels than glibenclamide. The seed kernel of *G. bonduc* demonstrated considerable hypoglycemic effects following extraction with petroleum ether, ether, ethyl acetate, and water (Parameshwar *et al.* 2002).^[38] The extracts of ethyl acetate and water had limited hypoglycemic effects in normal animals compared to the commonly prescribed drug, glibenclamide. Conversely, the polar solvent extracts (ethyl acetate and aqueous) showed pronounced hypoglycemic effects in diabetic animals, reversing

alterations in lipid and liver glycogen levels. Among the nonpolar extracts, the ether extract exhibited a moderate antidiabetic effect. Parameshwar et al. (2002)^[38] noted that the abundance of compounds, particularly triterpenoid glycosides in the polar solvent extracts, may play a role in the observed antidiabetic effects in diabetic animals. They concluded that folk beliefs regarding the antidiabetic properties of *G. bonduc* could indeed be valid at higher dosages.

ABORTIFOLIA

After experiencing implantation loss, the number of deceased fetuses and the percentage of abortions in rats treated with semen extract significantly decreased. Alongside this, the number of pups, the implantation index, the count and size of live fetuses, placenta weight, progesterone levels, and the rate of deaths also showed a considerable reduction. In rats given the *G. bonduc* seed extract, the reduction rates were even more pronounced. Lilaram and Ahmed (2014) observed that female rats receiving the seed extract of *G. bonduc* exhibited a significant decline in maternal final weight, the number of implantation sites, live fetuses, implantation index, mean pup weight, placenta weight, survival rates, progesterone levels, and post-progesterone levels. In contrast, there was a notable increase in the resorption index, post-implantation loss, the number of fetal deaths, and abortion rates. The treatment with the seed extract led to degeneration in both the junctional zone and the labyrinth of the placenta in the rats.^[70]

ANTI-CATALEPSY

Catalepsy is a neurological condition marked by muscle stiffness, a rigid posture, and reduced responsiveness to pain, regardless of external stimuli. It is characterized by symptoms such as a rigid body and limbs, diminished muscle control, and slowed physical activity (Sanberg et al., 1988, b)^[46] and can be associated with conditions like epilepsy and Parkinson's disease. Vikhe and Nirmal (2018)^[62] investigated the effects of *G. bonduc* extracts derived from ethanol on catalepsy. Their findings showed that the extract effectively inhibited clonidine-induced catalepsy at doses of 50 and 100 mg/kg, significantly reduced eosinophil and leukocyte counts induced by a milk allergen, and prevented the degranulation of mast cells triggered by clonidine.

IMMUNOMODULATORY EFFECT

In general, substances that stimulate the immune system can aid in combating diseases. For example, immunomodulatory agents such as monoclonal antibodies, cytokines, and vaccines

enhance the immune response (Kajaria et al. 2013). Shukla et al. (2009a) researched the immunomodulatory effects of *G. bonduc* seed extract obtained from ethanol. They found a significant improvement in the adhesion percentage of neutrophils to nylon fibers, with antibody titers increasing in a dose-dependent manner and delaying the onset of hypersensitivity reactions. Their study also included a carbon clearance phagocytosis experiment involving rats, which demonstrated notable resistance to cyclophosphamide-induced myelosuppression by modifying immune function, potentially offering a therapeutic approach to prevent autoimmune diseases.^[23,53]

Table: Pharmacological studies on *Guilandina bonduc*.

Sr.No.	Activity	Part\Extract	Experimental studies/Cell Lines/Animal Model/Microorganism
1.	Antidiabetic	Alcoholic Extract- Seed Polyphenol Extract	Alloxan Induced Diabetic Male Albino Rats ^[34] Different doses of extract to hyperglycemic rats restored blood and serum glucose, insulin, reduced oxidative stress in pancreatic β cells by restoring free radical scavenging potential ^[19]
		Seed and shell Extract	in-vitro ^[59]
		Seed Extract	Showed a significant Antidiabetic activity in alloxan induced hyperglycemia in rats ^[27]
		Aqueous and Ethanolic Extracts -Seeds	Significant blood sugar lowering effecting both type 1 and 2 diabetes mellitus in Long Evans rats ^[12]
2.	Anti inflammatory Antipyretic and Analgesic	Seed Oil	The oil exhibited anti-inflammatory activity in experimental rats in a paw edema test induced by carrageenan ^[51]
		Ethanolic extract of whole seeds	In experimental albino rats ^[51]
		Ethanolic extract (70%) of seed kernel	Exhibited marked antipyretic activity against Brewer's yeast- induced pyrexia in rats, significant central analgesic activity and peripheral analgesic effect in both mice and rats In adult albino rats or mice ^[3]
		Ethanolic extract (70%) of seed kernel	Reduced pyrexia in adult mice in carrageenan-induced inflammation, cotton pellet induced chronic granulomatous inflammation and autacoids-induced inflammation ^[6]
3.	Antibacterial and Cytotoxic activities	Methanolic Seed extract	Inhibited growth of Gram-positive and Gram-negative bacteria by the diffusion method and exhibited a similar activity of the standard antibacterial kanamycin ^[45]
		Methanol extract and	The extracts showed different zones of inhibition against four gram-positive and five

		fractions of leaves	gram-negative bacteria ^[8]
		Methanolic leaf and Bark extracts	Gram positive and Gram negative bacteria ^[1]
4.	Anti-cancer	Phytochemicals from young twigs and leaves	In silico interaction between phytochemicals and cancer target proteins (TK, VEGF, and MMP) compared with their respective drug inhibitors ^[20]
5.	Anticonvulsive	Petroleum Ether	Exhibited activities in convulsions models ^[2]
6.	Antioxidant	Ethanollic extract	in vitro-showed a high free radical-scavenging activity ^[56]
		Chloroform Extract	Exhibited in vitro radical scavenging effect ^[44]
7.	Anti-filarial	crude extract or fractions of the seed kernel	Exhibited gradual fall in microfilariae count in <i>L. sigmodontis</i> -cotton rat model ^[15]
8.	Antimalarial	Aqueous, cold alcoholic and hot alcoholic extracts	Exhibited inhibition in growth of <i>Plasmodium falciparum</i> ^[43]
		Root Extract	Exhibited dose-dependent suppression of parasite growth in vivo in mice ^[35]
9.	Anti-Tumour	Methanol extract	Exhibited significant antitumor activity in Ehrlich ascites carcinoma (EAC)-bearing Swiss albino mice ^[17]
10.	Immunomodulatory	Ethanollic Seed Extract	in vivo experiments- sheep red blood cell and rats ^[54]
		Aqueous Seed Extract	in vivo, cell mediated and humoral components of the immune system in rats ^[52]

➤ Drug Discovery and Development

- **Phytochemical Analysis:** More than 97 phytochemicals have been extracted from different parts of *G. bonduc*, including flavonoids, terpenoids, and steroids. These compounds showcase notable therapeutic properties, justifying further investigation for drug development.
- **Anti-Cancer Investigations:** Molecular docking analyses have revealed potential anti-cancer flavonoids sourced from the young twigs and leaves of *G. bonduc*. These compounds exhibited strong binding interactions with proteins related to cancer, indicating their promise as lead compounds for developing anti-cancer drugs.
- **Diabetes Treatment:** Polyphenol extracts derived from *G. bonduc* have proven effective in reducing hyperglycemia in diabetic rats by enhancing insulin secretion and inhibiting the JNK signaling pathway, underscoring its potential as a therapeutic agent for diabetes.

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➤ **Agronomic and Ecological Research**

- **Sustainable Farming:** Due to its resilience in tropical and subtropical climates, *G. bonduc* has the potential to be grown in arid and saline-affected regions, aiding in sustainable agriculture and soil preservation.
- **Invasive Species Control:** Studies examining the competitive dynamics between *G. bonduc* and native plants, such as *Cyperus atlanticus*, can guide conservation efforts and the management of invasive species within island environments.

➤ **Clinical and Preclinical Trials**

- **Clinical Trials on Humans:** To confirm the therapeutic effectiveness of *G. bonduc*, well-structured clinical trials are necessary. These studies should emphasize dosage optimization, safety assessments, and long-term effects.
- **Preclinical Research:** Additional *in vivo* investigations are required to evaluate the pharmacokinetics, bioavailability, and potential adverse effects of *G. bonduc* extracts, ensuring their appropriateness for human consumption.

➤ **Ethnopharmacological and Socioeconomic Research**

- **Recording Traditional Uses:** Systematic documentation of traditional practices surrounding *G. bonduc* across different cultures can offer valuable perspectives for contemporary pharmacological studies.

➤ **Modern applications**

- **Integrated Medicine:** In the late 20th and early 21st centuries, *Guilandina Bonduc* attracted attention in the context of integrated and alternative medicine. Its potential treatment applications have continued to be studied, especially in areas such as plant-based drugs, where it can be used with common treatment plans.
- **Current research:** Current research to confirm the traditional use, to explore new applications and to understand the action mechanisms of its biological active compounds. Studies to discover its potential in the treatment of different conditions, including cancer, diabetes and an anti-inflammatory agent.

➤ **Regulatory Status and Future Prospects**

- **Regulatory Challenges:** It is like many traditional measures, *Guilandina Bonduc* faces

challenges related to normalization, quality control and clinical testing needs more stringent to establish its efficiency and safety in modern medicine.

- **Sustainability and conservation:** When the interest in phyel therapy develops, the same thing happens with the long -term harvest needs of *Guilandina Bonduc*, as well as conservation of its natural living environment.

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