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REVIEW

Botany, traditional usages, phytochemistry, pharmacology, and toxicology of *Guilandina bonduc* L.: a systematic review

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Abstract

Guilandina bonduc L. is popularly known as a fever nut that grows widely in evergreen forests and moist deciduous forests with a pantropical distribution. The plant is highly therapeutic in various systems of medicine, including Ayurveda, Siddha, and homeopathy. The purpose of this review is to analyze the published data on *G. bonduc*, including traditional uses, taxonomic position, botanical description, phytochemistry, pharmacological properties, and toxicological assessment of its various parts. Phytochemical and pharmacological studies were the main focus of this review. The previously published research on *G. bonduc* was tracked from scientific databases such as Online Library, Google, Taylor and Francis, PubMed, Research Gate, Scopus, Springer, Wiley, Web of Sciences. Numerous phytochemical, pharmaceutical, and pharmacological studies have been carried out on the various parts of *G. bonduc*. To date, more than 97 phytochemicals have been isolated from the leaves, roots, stems, stem bark, flowers, twigs, and seeds of this plant. The phytochemicals isolated from the plants are flavonoids, homoisoflavonoids, terpenoids, diterpenoids, steroids, fatty acids, alkanes, acids, phenols, ketones, esters, amides, azides, silanes, and ether groups. This plant has been extensively studied in *in vitro* and *in vivo* pharmacological experiments, where it showed analgesic, anti-inflammatory, antioxidant, antiviral, antidiabetic, abortive, anticataleptic, immunomodulatory, and antiestrogenic effects. This comprehensive review revealed that phytochemicals isolated from various parts of *G. bonduc* have significant therapeutic efficacy, with promising anticancer, antidiabetic, hepatoprotective, antioxidant, and antimicrobial activities. This review provides a good source of information for the development of a drug using modern scientific tools, in view of its underexplored traditional uses. Further studies on preclinical and clinical trials and toxicological studies on the bioactive molecules of *G. bonduc* to validate its traditional uses are warranted.

Keywords *Guilandina bonduc* L. · Botany · Traditional usages · Phytochemistry · Pharmacology · Toxicology

Abbreviations

Bcl-2	B-cell lymphoma 2
BUN	Blood urea nitrogen
COVID-19	Coronavirus disease
DPPH	2,2-diphenylpicrylhydrazyl
EAT	Ehrlich ascites tumor
HDL	High-density lipoprotein
HPLC	High-performance liquid chromatography

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IC50	The half-maximal inhibitory concentration
INR	Indian rupee
LDL	Low-density lipoprotein
NF-κB	Nuclear factor kappa B
PCOS	Polycystic ovary syndrome
PPBG	Postprandial blood glucose
SARS CoV-2	Severe acute respiratory syndrome coronavirus 2
TNF-α	Tumor necrosis factor alpha
WHO	World Health Organization

Introduction

Guilandina bonduc L. is popularly referred to as fever nut, nicker bean, bonduc nut, and knicker nut, which belongs to the family Fabaceae. The plant is distributed in different countries in Asia, Africa, South America, and some parts of southern North America. It is found at an altitude of 1000-m above sea level in the Himalayas and in wastelands across India, as well as in the delta regions of western, eastern, and southern India. Moreover, it grows mainly in the tropical part of India, especially in evergreen and moist deciduous forests. This species is also grown as a fence plant in agricultural lands (Watson and Fowden, 1973). All parts of this plant, including the root, stem, leaves, seeds, and seed pods, have been widely used in various Indian nature-based medical systems, such as Ayurveda, Siddha, homeopathy, and folk medicine. Ayurveda recommends healing tumors, cysts, and cystic fibrosis. In Unani, the leaves and seeds of the plant are recommended for inflammation, blood-purifying, antispasmodic, septic, seasonal fever, bronchial asthma, bronchitis, ascites, hydrocele, and pleurisy (Khare 2007).

The ripened seeds of *G. bonduc* are used by ethnic people for various therapeutic purposes, including chronic wounds with severe suffering, muscle thrones, gastric complaints, constipation, intestinal warmth, bowel problems, immune boosters, hemorrhoids, leprosy, lymphatic filariasis, and polycystic ovary syndrome (Kandasamy and Balasundaram 2021). Owing to their potential therapeutic properties, seeds are sold in folk medicine shops under various traditional names across India. The seeds of this plant are known as *kalatchikkai* (கழற்சிக்காய்) in Tamil and fever nut in English (Khare 2007). This species is found in tropical regions worldwide and is referred to as the paleotropics.

From 1930 to the present, a large number of studies have proven that *G. bonduc* has an extensive spectrum of pharmacological effects on COVID-19, diabetes, abortion, antithyroid, hypolipidemic, immunomodulatory activity, and estrogen, and the list continues (Billah et al. 2013; Lilaram and Ahmed, 2014; Gaur et al. 2008). Researchers have isolated a vast number of phytoconstituents from *G. bonduc* over the last few decades, but not all phytochemicals have been subjected to pharmacological research. With the existence of various phytochemicals and pharmacological properties, the clinical use of *G. bonduc* in this scenario is increasing significantly.

In recent years, several researchers have devoted themselves to exploring this valuable taxon to investigate its traditional uses, phytochemistry, and pharmacology. However, to date, no extensive review has been published on *G. bonduc*. Existing information reveals that there is only a brief overview of *G. bonduc* in terms of phytochemistry and pharmacology, which may not be sufficient for scientists to realize the value of *G. bonduc*. In this context, the present review provides comprehensive information on the aspects of traditional uses, botany, phytochemistry, and pharmacological properties of *G. bonduc*, which will also help scientists gain a stronger and deeper knowledge of this plant and its products.

Methods

For this review, the data were collected from various databases, including Online Library, Google, Taylor and Francis, PubMed, Research Gate, Springer, and Wiley and other peer-reviewed publishers and journals from 1932 to the present. The key terms, traditional uses, phytochemicals, and pharmacological potential along with the following keywords: *Guilandina bonduc*, *C. bonduc*, *C. bonducens*, *C. crista*, fever nut, Latakaranja, Kasharchikai, and Kalarchikai were used to retrieve the data in the plant to compile this review. Data were also collected from published reviews, Tamil Maruthuvam, and published articles on wet laboratory experiments. A well-known taxonomic database, http://www.worldfloraonline.org/, was used to obtain the synonyms and distribution of *G. bonduc*.

Botanical description

G. bonduc grows as a climbing shrub or a liana. It grows up to 8 m in height and has thorns on its stems and leaf stalks. The leaves are bipinnate, 50 cm long, pinnate, and consist of four to five pairs. The petiole consists of five to eight leaflets. The leaves were ovate or elliptical oblong in shape. Leaf bases were rounded. The apices of the leaves were obtuse and mucronate. The petiole length was 15 cm. The petiole was 15 cm in length. It possesses stipules. The flowers are simple or branched racemes that are yellow in color. The flowering period lasted from August to December. The fruits are oblong-ovate with inflated pods, beaked tips, and densely spined; seeds 1 or 2 are hemispherical and shiny (Fig. 1). Fruiting begins in October (Khare 2007).

Fig. 1 Morphology of *Guilandina bonduc* L.

Taxonomic treatment
Kingdom: Plantae
Clade: Magnoliophyta
Clade: Magnoliopsida
Clade: Angiospermae
Order: Fabales
Family: Fabaceae/Caesalpiniaceae
Genus: *Guilandina*
Species: *bonduc*
Binomial name: *Guilandina bonduc* (L.) Roxb.
Synonyms of the plant
Caesalpinia bonducella (L.) Fleming
Bonduc minus Medik.
Caesalpinia crista Thunb.
Caesalpinia bonduc L.
Caesalpinia cristata Prowazek
Caesalpinia grisebachiana Kuntze
Caesalpinia sogerensis Baker f.
Guilandina bonduc Griseb.
Guilandina bonducella L.
Guilandina gemina Lour (https://wfoplantlist.org/plant-list)

Local/Traditional names of *Guilandina bonduc*

As the plant resembles the eyes of the Kubera (Hindu god of wealth), the local people in India in several states refer to this plant seed as Kuberakshi. This plant is commonly referred as *fever nut*, *bonduc nut*, *knicker nut* and *nicker seed* (Khare 2007).

Ethnobotanical and ethno-pharmacological applications

The plant has a long history of traditional use since 1932. According to previous reports, it has a wide range of therapeutic potential, as shown in Table 1. In folk medicine, various parts of this plant are taken alone and/or formulated as polyherbs, along with other medicinal plants, which are subsequently used to treat various diseases. Chopra et al. (1956) and Nadkarni et al. (1954) reported that young leaves of the plant are prescribed to treat infections, elephantiasis, smallpox, and liver disease, and to exorcize intestinal worms, while young leaf extracts can be used to treat sore throats by gargle.

Table 1 Ethnomedicinal and ethnopharmacological uses of *Guilandina bonduc* L.

Parts used	Ailments treated	Ingredients used	Reference
Root	Anti-periodic, antispasmodic, emmenagogue, and purgative	-	Ali et al. (1997); Suttee et a. (2011)
	Asthma, fish poison and malaria	-	Jalali et al. (2019); Ekka (2016); Yetein et al. (2013)
Root bark	Epilepsy	-	Jain et al. (2016)
	Fever, intestinal worms, tumors, amenorrhea, cough, and the removal of the placenta after childbirth	-	Chopra et al. (2006); Chopra et al. (2009); Nadkarni, 1954)
Stem bark	Anti-malarial, reducing sugar levels, antipyretic, and anti-rheumatic		Ali et al. (1997); Udenigwe et al., 2007)
	Antiperiodic and rubefacient	-	D'souza, 1998; Cheenprach et al., (2006)
Leaf	Liver disease, burns, emmenagogic, laxative, tonic, digestive, emetic, antipyretic, and cathartic	-	Ali et al. (1997); Udenigwe et al. (2007); Suttee et a. (2011), Sagar and Vidyasagar (2010); Muruganantham et al. (2011)
	Hydrocele	-	Ramakrishna et al. (2014)
	Elephantiasis and smallpox	-	Kokate (1997)
	Collyrium	-	D'souza (1998); Cheenprach et al. (2006)
	Liver, nerve problems, sore throats, elephantiasis, smallpox, liver diseases, and expel intestinal worms	-	Chopra et al. (1956); Nadkarni (1954)
	Tumor and liver disorder	-	Sagar et al. (2009)
	Eliminate vata and relieve constipation	Ghee	Vikhe and Nirmal (2018)
	Asthma	-	Bellomaria and Kacou (1995)
	Emmenagogue and facilitate delivery in pregnant women	-	Datté et al. (1996); Saleh et al. (1996)
Leaf and twig	Tumors, liver disorders, and toothache	-	Khandelwal (2006)
Leaf, bark, root, seed	Piles	-	Qureshi and Reddy (2017)
Leaf, seed, root, bark	Colic fever, intermittent fever, malaria, menstrual complaints, pneumonia, skin diseases, swelling, tonic, pulmonary tuberculosis and as a uterine stimulant, to cleanse the uterus, fever, edema, and abdominal pain	-	D'souza (1998); Cheenprach et al. (2006)
Leaf, seed	Skin ailments, hydrocele, leprosy, spasms, orchitis, paralysis, and analogical nervous complaints	-	Ali et al. (2009); Kirtikar and Basu (1975)
Fruit	Pneumonia and gastric troubles	-	Hazarika et al. (2016)

Table 1 (continued)

Parts used	Ailments treated	Ingredients used	Reference
Seed	Skin diseases, intestinal worms, dyspepsia, cough, leprosy, colic, hemorrhoids, dysentery, fever, anthelmintic, digestive, stomach-strengthening, liver-strengthening, and malarial fever	-	Ali et al. (1997); Muruganantham et al. (2011); Kannur et al. (2012); Ravikanth et al., 2014; Quisumbing (1978)
	Vomiting, hydrocele pain indigestion, dysentery, piles, worms, cough, diabetes, skin diseases, fever, arthritis, resettlement of disturbed joints, and bones specially after trauma	-	Nandagopalan et al. (2016); Rajurkar et al. (2018); Ramakrishna et al. (2014); Qasim et al. (2014); Deletta and Parthipan (2018); Ramakrishna and Saidulu (2014)
	Diabetes and fever	Black pepper	Khandelwal (2006)
	Malaria and antiperiodic properties	Pepper	Kokate (1997)
	Hydrocele, orchitis (external application) and vesicant	Castor oil	Kokate (1997)
	Helminthiasis, colic pain, malaria, hydrocele	-	Kokate (1997)
	Snake bite	water	Khandelwal (2006)
	Expectorant	Pepper, honey	Khandelwal (2006)
	Styptic, purgative, anthelmintic and cures inflammations; useful in colic, malaria, hydrocele, skin diseases and leprosytonic, febrifuge, anthelmintic, and anti-blennorrhagic	Water	Singh and Raghav (2012); Nazeerullah et al. (2012)
	Hydrocele, skin diseases, and leprosy, tumors,	-	Chopra et al. (1956)
	Common cold, fever, and dysentery	-	Jiangsu (1977)
	Nourish the uterus, regularize the menstrual discharge in oligomenorrhea, and reduce pain in the lower abdominal region	Pepper and honey	Moon et al. (2010)
	Leucorrhea, cough, and asthma	-	Pandey et al. (2018)
	Malaria	-	Quisumbing (1978)
	Microfilaricidal, macrofilaricidal, and female-sterilizing efficacy	-	Gaur et al. (2008)
	Hypoglycemic, pathogenesis, and progression of diabetes	-	Peter et al. (1997); Rao et al. (1994); Biswas et al. (1997); Baynes (1991); Hideaki et al. (1999)
	Headache and fever	-	Datté et al. (1996); Saleh et al. (1996)
	Curing hydrocele and orchitis	-	Handa and Kaul (1996)
Seed, seed oil	Colic, convulsions, leprosy, palsy, soften the skin, and remove pimples	-	D'souza, 1998); Cheenprach et al. (2006)
Seed oil	Convulsions and paralysis	-	Moon et al., 2010
Seed, root bark	Hemorrhages, fevers, asthma, and colic; antiperiodic and febrifuge; swelling, restraining hemorrhage, and infectious diseases	Honey or castor oil	Wu et al. (2014a,b); Mandal et al. (2013); Dang et al. (2015); Yadav et al. (2009); Ata et al. (2009a); Ata et al. (2009b)
Seed, leaf, and root	Pneumonia, piles, asthma, skin ailments, cough, and arthritis	-	Kashif Husain et al. (2020)

Table 1 (continued)

Parts used	Ailments treated	Ingredients used	Reference
Whole plant	Asthma, seizures, skin diseases, cough, headache, stomach upset, intermittent fever, diarrhea, antipyretic, anti-periodic, antispasmodic, laxative, nematocidal, abortive, and anthelmintic	-	Handa and Kaul (1996); Kirtikar and Basu, 1975Kumar et al. (2005); Komal et al. (2010); Tummin and Katti (1930)
	Eye sores, hemorrhages, leprosy, tuberculosis, asthma, toothache, fever, emmenagogue, and emollient	-	Gopalan (1976); Said, 1970)
	Cough, fever, headache, and stomach problems	-	Yadav et al. (2007)
	Effective stomachic, digestive and is used as liver tonic in the treatment of jaundice, liver disorders and rejuvenation of body	-	Shrikantha Murthy (2000)
	Treating eye sores, hemorrhages, leprosy, inflammations, tuberculosis, asthma, toothache, and fever	-	Baquar (1989); Sastri (1950)
	Diarrhea, cerebral hemorrhage, infantile convulsion and facilitates delivery	-	Kerharo and Bouquet (1950); Vangah (1986)
	Counteract toothache	-	D'souza, 1998; Cheenprach et al. (2006)

Handa and Kaul (1996) reported that *G. bonduc* seed powder should be used together with castor oil to prepare ointments and applied topically to treat hydrocele and orchitis. Kokate (1997) reported that oil extracted from seeds can be topically applied to manage convulsions and paralysis. They also reported that when malaria patients consumed an equal proportion of *G. bonduc* seed powder and pepper, they had antimalarial properties. D'souza (1998) reported that the whole plant was used as an anthelminthic by tribes in the Satpuda region of India. They also noted that their seeds were worn by them as necklaces. Oil from the seed is applied to the skin to soften it and remove the pimples. Leaf decoction is also used as a collyrium by traditional people. According to the ethnobotanical research of Acharyya and Sharma (2004), the seeds of *G. bonduc* have been mixed with other plant products as polyherbs and used to cure pneumonia (5 g mixed seeds) and diphtheria (7 g mixed seeds).

The bark of *G. bonduc* is employed as an antiperiodic, rubefacient, and pain reliever for toothache problems (Cheenprach et al. 2006). The root bark of *G. bonduc* has been employed to treat fever, intestinal worms, tumors, menstrual problem, cough, and the elimination of the placenta subsequent to childbirth (Chopra et al. 2006; Chopra et al. 2009). According to the review by Suryawanshi and Patel (2011), the leaves, seeds, roots, and bark of *G. bonduc* are used to treat a variety of health conditions, including colic, intermittent fever, malaria, menstrual cramps, pneumonia, skin diseases, swelling, tonics, and pulmonary tuberculosis, and are also used as a uterine stimulant to clean the uterus. Singh and Raghav (2012) reported that the seeds are used for various therapeutic purposes, such as hemostatic, laxative, anthelmintic, inflammatory, colic, malaria, skin diseases, and leprosy. The extract made from the seeds is also consumed as a tonic and is used as an anthelmintic and anti-blennorrhagic agent (Nazeerullah et al. 2012). This anthelmintic drug is traditionally called karanjawa and is made by mixing honey or castor oil with the seed extract (Chopra and Nayar 1956). The juice of *G. bonduc* is prescribed by traditional people for 2 weeks to cure intermittent fever. The leaves of this plant are also used by the fishing tribe of Assam, India, as a decoction, infusion, or vegetable for worm infections. Traditionally, in India, this herbal formulation is sold as kusere, which is used to treat anthelmintics (Gogoi and Yadav, 2016). In some parts of southern India, especially in Chennai, seed powder has also been used to make an ointment with castor oil for topical treatment of hydrocele and orchitis (Subramani et al. 2014).

A recent review by Sasidharan et al. (2021a) revealed that oral consumption of roasted and ground seeds is the most effective way to treat health problems. Similarly, in a review of the polycystic ovary syndrome (PCOS) potential of *G. bonduc*, Kandasamy and Balasundaram (2021) pointed

out the traditional uses of this versatile species. According to a report by Sagar et al. (2009), the leaves of this plant are used in folk medicine to treat inflammation, tumors, and liver diseases. Billah et al. (2013) reported that the seeds of *G. bonduc* have antifilarial, antiasthmatic, antispasmodic, analgesic, immunomodulatory, anxiolytic, antifeedant, antidiarrheal, hypoglycemic, antioxidant, adaptogenic, antispasmodic, insecticidal, and antiamoebic effects. Oral administration of leaves after frying in ghee reduces Vata and constipation; therefore, it is also effective for hemorrhoids. Additionally, finely ground seeds are taken with honey to thin phlegm and to relieve coughs (Pandey et al. 2018).

Burnt seed ash with alum and areca nuts is used to heal tooth decay, gum blisters, and spongy gums. This plant has strong anti-inflammatory properties and effectively balances Vata and Kapha (Vikhe and Nirmal, 2018). To strengthen the uterus, control the blood circulation in case of menstrual irregularities, and relieve pain in the lower abdomen, 15–18 seeds of the plant are ground as a fine powder with equal amounts of pepper and can be orally administered with honey. The seed kernel of the plant has the capacity to treat leucorrhea, and the seeds have contraceptive activity. It is also used to treat cough and asthma because it balances the Kapha dosha. Young leaves are mixed with honey and taken orally to fight off mucous discharge (Pandey et al. 2018; Kandasamy and Balasundaran 2021). The oil extracted from the leaves is considered to be an excellent nervine tonic (Pandey et al. 2018).

Since ancient times, *G. bonduc* has been considered a good remedy for stomach pain caused by flatulence because of its effectiveness in relieving Vata dosha. The seeds were roasted and powdered to refresh their body and relieve pain. They have also been used to relieve stomach pain caused by post-delivery and are prepared as lehyam with a combination of asafoetida, ghee, and sufficient salt. Seed coat has been used to treat dysentery, diarrhea, and colitis. To relieve itching in the anal area caused by worm infestation, roasted seed powder or leaf juice can be taken along with Amra, Haridra, and Palasa. The roasted seeds were combined with pippali in a 1:1 ratio and sold in India under the name Latakaranja. It is a recommended herbal remedy for malaria that can be administered at time intervals (3/day) of 0.5 g for 3–4 days (Singh et al. 2016). The enlarged spleen caused by malaria was effectively alleviated by extracts of this plant (Nadkarni and Nadkarni, 1954). They also documented that the seeds of this plant are used to stimulate uterine function, increase menstrual flow during oligomenorrhea, and relieve abdominal pain during menstruation. The seed coat is extremely useful in fluoride treatment and is therefore used to absorb the fluoride content in drinking water. Oil extracted from the leaves of *Guilandina bonduc* is used as a powerful nerve tonic (Nadkarni and Nadkarni 1954), and seed paste is very effective in treating snake bites (Khandelwal 2006).

The seed powder of this plant is sold in the market under the name "Sagargota" for the treatment of diabetic complications and is manufactured by Biotic Nature Products. The seed powder of this plant is sold by Mooligai Organics. The preparation methods and combinations of this seed powder with other herbs have been described for treating ulcers, ascites, abscesses, goiter, liver problems, asthma, leprosy, paralysis, hemostasis, skin problems, laxatives, diarrhea, constipation, inflammation, joint pain, fever, orchitis, malaria, hydrocele, expectorants, gum disease, and prostate enlargement (https://www.moolihai.com/benefits-of-bonduc-nut/). It is sold under the trade name "bonduc nut."

The seeds of this plant are used to treat vomiting, leprosy, blood disorders, stomach disorders, and spleen problems in the Ayurvedic system. Furthermore, various parts of this plant, such as the root, leaf, and fruit, are used in Siddha to treat hydrocele, orchitis, intercostals, neuralgia, enuresis, urinary calculi, and gastrointestinal problems. Similarly, leaves, seeds, and seed pods are used in homeopathy to treat fevers, headaches, mental distress, splenomegaly, and malaria (Vaidya Ratnam Varier 1996; Srikantha Murthy 2004). In addition, the seeds are utilized in traditional medicine for sexual debility, fever, and hydrosol production (Singh and Raghav 2012). Recently, the authors researched the traditional usage of *G. bonduc* among traditional people and discovered that it is consumed to cure polycystic ovarian syndrome. Various parts of this plant are used to cure different diseases in Indian natural medicine, such as Ayurveda, Siddha, and homeopathy. This plant is known as Latakaranja in Ayurveda, Kazharchikai in Siddha, and Kalarchikai in homeopathy (Khare 2007).

Phytochemicals of *Guilandina bonduc*

Quantitative phytochemical

The leaves of *G. bonduc* contain 4.490% terpenoids and phenols, 0.885% alkaloids, 25.745% alkaloids, 25.745% N-oxides, 8.850% lipids and waxes, and 60% fiber (Kakade et al. 2017). Pandey et al. (2018) performed a similar quantitative phytochemical study using 0.67% phenol, 0.941% alkaloids, and 0.36% flavonoids. The high proportion of the dietary flavonoquercetin (in 0.2854 g/mL) was also measured by HPLC.

Isolated and identified chemical constituents

According to the present statement, almost 97 secondary metabolites have been isolated from the young twigs, leaves, seeds, seed kernel, bark, and roots of *G. bonduc* using ethanol, methanol, *n*-hexane, alkaline, and petroleum ether solvents (Fig. 2). *G. bonduc* contains flavonoids, terpenoids,

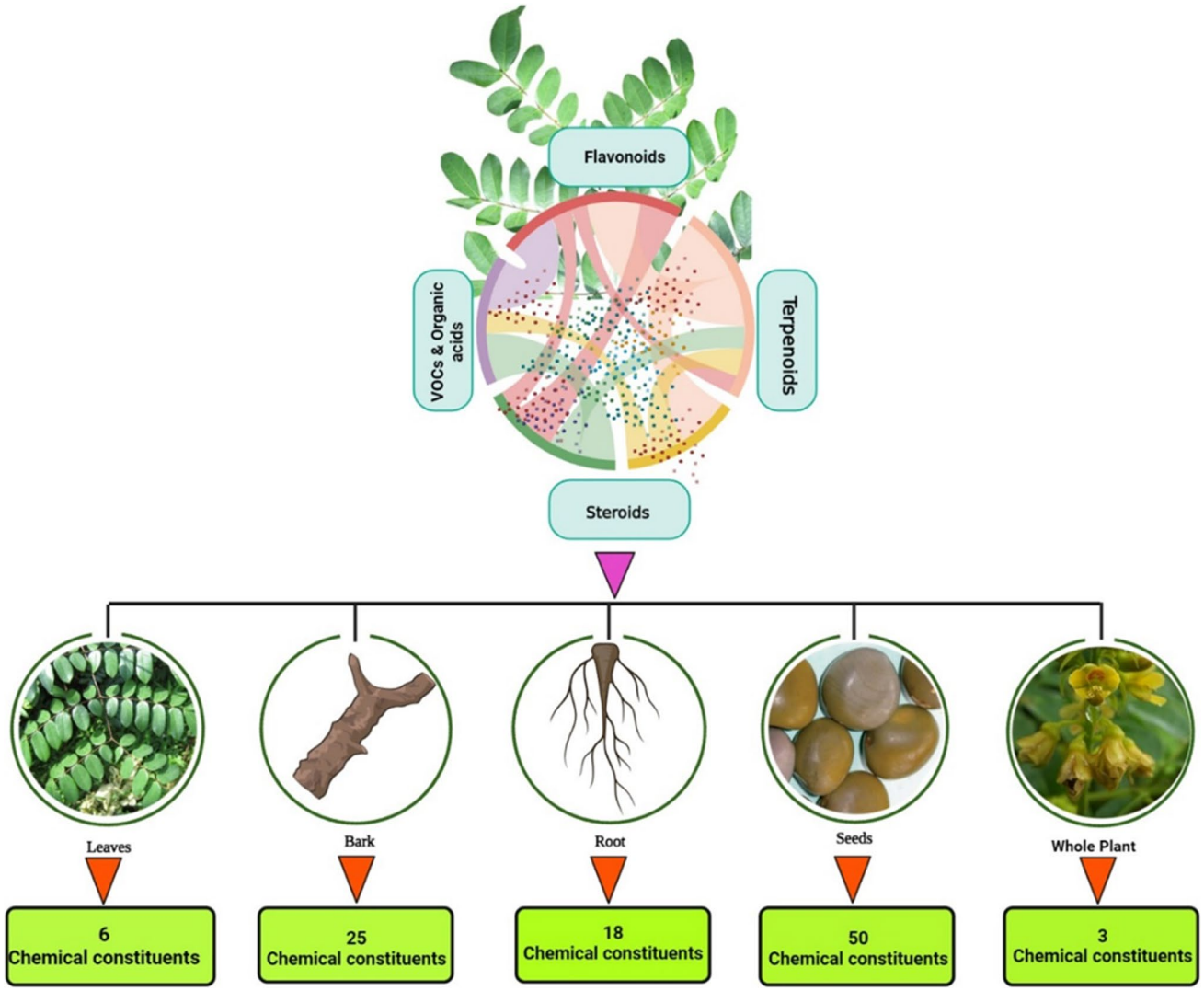

Fig. 2 Number of phytocomponents isolated and identified from different parts of *Guilandina bonduc* L.

steroids, volatile compounds, organic acids, and amino acids. The names of phytoconstituents along with their classes, obtained plant parts, and solvents used for extraction are provided in Tables 2, 3, 4, and 5, and the structures of these molecules are summarized in Figs. 4, 5, and 6. The bitter taste of the seeds is attributed to the chemical components of bonducin, bonducellin, caesalpin, phytosterol, and citrulline.

Flavonoids

Depending on their chemical composition, degree of unsaturation, and degree of oxidation of the carbon ring, flavonoids are sub-grouped into anthocyanins, isoflavonoids, flavanoneols, flavans, chalcones, and flavanones. They have been reported to exhibit antibacterial, antiangiogenic, antioxidant, antimalarial, anticancer, antiviral, antitumor, antiproliferative, and neuroprotective effects (Ullah et al. 2020). Eleven flavonoid chemical components were identified and isolated from different parts of *G. bonduc*. The names of the chemical constituents, their presence, the solvent used for extraction, and the structure of the constituents are presented in Table 2 (1-11) and Fig. 3.

Terpenoids

Terpenoids are terpenes containing oxygen molecules created by the removal or addition of methyl groups (Masyita et al. 2022). They have been classified into alcohols, aldehydes, esters, ethers, epoxides, ketones, and phenols, which have complex structures, a broad spectrum of activity, and multiple biological modes of action (Hyldgaard et al. 2012). A total of 47 terpenoid chemical components were identified and isolated from different parts of *G. bonduc*, which

Table 2 Isolated and identified phytoconstituents from different parts of *Guilandina bonduc* L.

S.No.	Name of the phytoconstituents	Plant parts (source)	Solvents used in extraction	Reference
	Flavonoids			
1.	7-hydroxy-4′-methoxy-3,11-dehydrohomoisoflavanone	Leaf, young twigs	Ethanol	Iheagwam et al. (2019)
2.	4,4′-dihydroxy-2′-methoxy-chalcone	Leaf, young twig	Ethanol	Iheagwam et al. (2019)
3.	7,4′-dihydroxy3,11-dehydroho-moisoflavanone	Leaf, young twig	Ethanol	Iheagwam et al. (2019)
4.	Luteolin	Leaf, young twig	Ethanol	Iheagwam et al. (2019)
5.	Quercetin-3-methyl	Leaf, young twig	Ethanol	Iheagwam et al. (2019)
6.	Kaempferol-3-O-β-D-xylopyranoside.	Leaf, young twig	Ethanol	Iheagwam et al. (2019)
7.	Kaempferol-3-O-α-L-rhamnopyranosyl-(1→2)-βD-xylopyranoside	Legumes	Methanol	Pournaghi et al. (2021)
8.	Kaempferol	Legumes	Methanol	Pournaghi et al. (2021)
9.	Caesalpinianone	Bark	Ethanol	Ata et al. (2009a); Purushothaman et al. (1982)
10.	6-O-methylcaesalpinianone	Bark	Ethanol	Ata et al., 2009a); Purushothaman et al. (1982)
11.	Quercetin-3-methyl ether	Legumes	Methanol	Pournaghi et al. (2021)
12.	17-methylvouacapane 8 (14),-9(11)-diene	Bark	Ethanol	Ata et al. (2009b)
13.	Neocaesalpin H	Bark	Ethanol	Ata et al. (2009b)
14.	Cordylane A	Bark	Ethanol	Ata et al. (2009b)
15.	Caesalpinin B	Bark	Ethanol	Ata et al. (2009b)
16.	Bonducellpin E	Bark	Ethanol	Ata et al. (2009b)
17.	Caesalls H	Seed kernels	Ethanol	Wu et al. (2014a); Wu et al. (2014b)
18.	Caesalls I	Seed kernels	Ethanol	Wu et al. (2014a); Wu et al. (2014b)
19.	Caesalls K	Seed kernels	Ethanol	Wu et al. (2014a); Wu et al. (2014b)
20.	Caesalls L	Seed kernels	Ethanol	Wu et al. (2014a); Wu et al. (2014b)
21.	Neocaesalpin P	Bark	Ethanol	Ata et al. (2009b)
22.	Neocaesalpins B, C, and D	Seed and bark	Petroleum ether and chloroform	Pascoe and Caesalpin (1986); Kinoshita (2000); Ata et al. (2009b)
23.	Neocaesalpins C	Seed and bark	Petroleum ether and chloroform	Pascoe and Caesalpin (1986); Kinoshita (2000); Ata et al. (2009b)
24.	Neocaesalpins D	Seed and bark	Petroleum ether and chloroform	Pascoe and Caesalpin (1986); Kinoshita (2000); Ata et al. (2009b)
25.	Caesaldekarin A	Root	Aqueous	Lyder et al. (1998)
26.	Caesaldekarin C	Root	Aqueous	Lyder et al. (1998)
27.	Caesaldekarin H	Root	Aqueous	Lyder et al. (1998)
28.	Caesaldekarin I	Root	Aqueous	Lyder et al. (1998)
29.	Caesaldekarin J	Root	Aqueous	Lyder et al. (1998)
30.	Caesaldekarin K	Root	Aqueous	Lyder et al. (1998)
31.	Caesaldekarin L	Root	Aqueous	Lyder et al. (1998)
32.	Demethylcaesaldekarin C,	Root	Aqueous	Lyder et al. (1998)
	Terpenoids			

Table 2 (continued)

S.No.	Name of the phytoconstituents	Plant parts (source)	Solvents used in extraction	Reference
33.	Cordylane A,	Bark	Ethanol	Ata et al. (2009b); Yadav et al. (2007)
34.	Caesalpinolide-C	Plant material	Ethanol	Yadav et al. (2009)
35.	Caesalpinolide-D	Plant material	Ethanol	Yadav et al. (2009)
36.	Caesalpinolide-E	Plant material	Ethanol	Yadav et al. (2009)
37.	Caesalpinin	Seed, seed kernels, bark and root	Ethanol/methanol	Wu et al. (2014a); Dang et al. (2015); Ata et al. (2009b); Peter et al. (1997)
38.	Caesalpinin D	Seed, seed kernels, bark and root	Ethanol/methanol	Wu et al. (2014a); Dang et al. (2015); Ata et al. (2009b); Peter et al. (1997)
39.	Caesalpinin H	Seed, seed kernels, bark and root	Ethanol/methanol	Wu et al. (2014a); Dang et al. (2015); Ata et al. (2009b); Peter et al. (1997)
40.	Caesalpinin J	Seed, Seed Kernels, Bark and Root	Ethanol/methanol	Wu et al. (2014a); Dang et al. (2015); Ata et al. (2009b); Peter et al. (1997)
41.	Caesalpinin K	Seed, seed kernels, bark and root	Ethanol/methanol	Wu et al. (2014a); Dang et al. (2015); Ata et al. (2009b); Peter et al. (1997)
42.	Bonducellpin D	Seed, seed kernels, bark and root	Ethanol/methanol	Wu et al. (2014a); Dang et al. (2015); Ata et al. (2009b); Peter et al. (1997)
43.	Bonducellpin F	Seed, seed kernels, bark and root	Ethanol/methanol	Wu et al. (2014a); Dang et al. (2015); Ata et al. (2009b); Peter et al. (1997)
44.	Bonducellpin G	Seed, seed kernels, bark and root	Ethanol/methanol	Wu et al. (2014a); Dang et al. (2015); Ata et al. (2009b); Peter et al. (1997)
45.	α-Caesalpin	Seed kernels	Petroleum ether	Pascoe and Caesalpin (1986); Peter et al. (1997)
46.	β-Caesalpin	Seed kernels	Petroleum ether	Pascoe and Caesalpin (1986); Peter et al. (1997)
47.	γ-Caesalpin	Seed kernels	Petroleum ether	Pascoe and Caesalpin (1986); Peter et al. (1997)
48.	δ-Caesalpin	Seed kernels	Petroleum ether	Pascoe and Caesalpin (1986); Peter et al. (1997)
49.	ε-Caesalpin	Seed kernels	Petroleum ether	Pascoe and Caesalpin (1986); Peter et al. (1997)
50.	Caesalpin F	Seed kernels	Petroleum ether	Pascoe and Caesalpin (1986); Peter et al. (1997)
51.	Caesalpin G	Roots	Aqueous	Peter et al. (1997)
52.	Caesalpin H	Roots	Aqueous	Peter et al. (1997)
53.	α-amyrin	Seeds	Methanol	Saeed and Sabir (2003)
54.	β-amyrin	Seeds	Methanol	Saeed and Sabir (2003)
55.	Lupeol	Seeds	Methanol	Saeed and Sabir (2003)
56.	Lupeol acetate	Seeds	Methanol	Saeed and Sabir (2003)
57.	Norcaesalpinin MC	Seed kernels	Ethanol	Wu et al., 2014a
58.	Caesalpinolide A	Bark	Ethanol	Yadav et al. (2007); Ata et al. (2009b)
59.	caesalpinolide B	Bark	Ethanol	Yadav et al. (2007)
	Steroids			
60.	Cholesterol	Seed kernel	n-hexane	Sultana et al., 2012)
61.	Campesterol	Seed kernel	n-hexane	Sultana et al. (2012)

Table 2 (continued)

S.No.	Name of the phytoconstituents	Plant parts (source)	Solvents used in extraction	Reference
62.	β-sitosterol	Seed kernel	n-hexane	Sultana et al. (2012)
63.	Stigmasterol	Seed kernel	n-hexane	Sultana et al. (2012)
64.	D5-avenasterol	Seed kernel	n-hexane	Sultana et al. (2012)
65.	D7-avenasterol	Seed kernel	n-hexane	Sultana et al. (2012)
66.	D7-stigmastenol	Seed kernel	n-hexane	Sultana et al. (2012)
67.	Carpesterol	Seed kernel	n-hexane	Sultana et al. (2012)
68.	Fucosterol	Seed	Ethanol	Priya et al. (2019)
69.	Stigmast-5-En-3-Ol	Seed	Ethanol	Priya et al. (2019)
70.	Tetrapentacontane	Seed	Ethanol	Priya et al. (2019)

Table 3 Identified volatile compounds from *Guilandina bonduc* L.

S. No.	Name of the chemical constituents	Solvents used in extraction	Reference
1.	1-Undecanol	Ethanol	Priya et al. (2019)
2.	1-tetradecanol	Ethanol	Priya et al. (2019)
3.	N-nonadecanol-1	Ethanol	Priya et al. (2019)
4.	9,12-octadecadien-1-Ol	Ethanol	Priya et al. (2019)
5.	2-(1-phenylethyl)-phenol	Ethanol	Priya et al. (2019)
6.	2,4-bis(1-phenylethyl)-phenol	Ethanol	Priya et al. (2019)
7.	Hematoxylol	Ethanol	Ata et al. 2009a
8.	Stereochenol A	Ethanol	Ata et al. 2009b
9.	D (+)-pinitol	Methanol	Mondal et al. 1993
10.	1-hentetracontanol	Ethanol	Sandhia et al. 2021
11.	2-hydroxy-4-methoxy-7-methyl-7,8,9,10,11,12,13,14-Octahydro-6- Oxabenzocyclododecen-5-One	Ethanol	Priya et al. 2019
12.	Pregn-4-En-17(alpha),20(alpha)-diol-3-one	Ethanol	Priya et al. 2019
13.	1,2,4-trimethoxy-5-(1-propenyl)-benzene	Ethanol	Priya et al. 2019
14.	Ethylphenoxy-benzene	Ethanol	Priya et al. 2019

Table 4 Organic acids isolated from the *Guilandina bonduc* L.

S. No.	Name of the acids	Source	Solvents used	References
1.	Palmitic acid	Seed kernel, seed and bark	n-hexane and Ethanol	Priya et al. (2019)
2.	Tetradecanoic acid	Seed	Ethanol	Priya et al. (2019)
3.	Pentadecanoic acid	Seed	Ethanol	Priya et al. (2019)
4.	Benzenecarbothioic acid	Seed	Ethanol	Priya et al. (2019)
5.	4′-O-acetylloganic acid	Bark	Ethanol	Ata et al. (2009a)
6.	6 ′-O-acetylloganic acid	Bark	Ethanol	Ata et al. (2009a)
7.	2-O-β-D-glucosyloxy-4-methoxybenzenepropanoic acid	Bark	Ethanol	Ata et al. (2009b)
8.	1,2-benzenedicarboxylic Acid	Seed	Ethanol	Priya et al. (2019)
9.	Hexadecanoic acid	Seed	Ethanol	Priya et al. (2019)
10.	N-hexadecanoic acid	Seed	Ethanol	Priya et al. (2019)
11.	9,12-octadecadienoic acid	Seed	Ethanol	Priya et al. (2019)
12.	9-octadecanoic acid	Seed	Ethanol	Priya et al. (2019)
13.	Silicic acid (H4sio4)	Seed	Ethanol	Priya et al. (2019)

Table 5 Amino acids identified from the seeds of *Guilandina bonduc* L.

S. No.	Name of the amino acids	Form	Reported literature
1.	Arginine	Seed	Raj and Singh (2000)
2.	Cysteine	Seed	Raj and Singh (2000)
3.	Histidine	Seed	Raj and Singh (2000)
4.	Leucine	Seed	Raj and Singh (2000)
5.	Isoleucine	Seed	Raj and Singh (2000)
6.	Lysine	Seed	Raj and Singh (2000)
7.	Methionine	Seed	Raj and Singh (2000)
8.	Hreonine	Seed	Raj and Singh (2000)
9.	Tryptophan	Seed	Raj and Singh (2000)
10.	Valine	Seed	Raj and Singh (2000)
11.	Palmitic	Seed	Sultana et al. (2012)
12.	Stearic	Seed	Sultana et al. (2012)
13.	Oleic	Seed	Sultana et al. (2012)
14.	Linoleic	Seed	Sultana et al. (2012)
15.	Lignoceric	Seed	Sultana et al. (2012)

are summarized in Table 2 (12-59) and Fig. 3. They belong to the furanocassan, cassan, monoterpene, diterpene, and triterpene subgroups. Based on previous phytochemical studies, the present review proposes that the taxon consists of a larger amount of terpenoids than other phytochemical groups such as flavonoids and steroids.

Steroids

In phytosterols are plant fat compounds that constitute the largest portion of unsaponifiable components of plant lipids. They contain an additional methyl group, ethyl group, or double bond compared to other groups of phytoconstituents. They consist of a steroid backbone with a saturated linkage between the C-5 and C-6 of the sterol moiety. They contain a hydroxyl group at the C-3 atom and an aliphatic side chain at the C17 atom (Piironen et al. 2003, Fassbender, et al. 2008; Salehi et al. 2021). Eleven steroid chemical components have been identified and isolated from different parts of *G. bonduc*. The names of the chemical constituents, their presence, the solvent used for extraction, and the structure of the constituents are shown in Table 2 (60-70) and Fig. 3.

Volatile compounds

Volatile organic molecules, which play an important role in plant growth, are released from plants because of their interactions with biotic and abiotic stimuli. In flowers, these compounds serve as pest repellent and pollinator-attracting substances. To date, nearly 1700 volatile compounds have been isolated and identified from both flowering and non-flowering plants (Knudsen and Gershenzon 2006). They are mainly secreted by flowers, but are also found in other parts of plants, such as fruits, leaves, stems, and roots (Farré-Armengol et al. 2016; PicazoAragonés et al., 2020). According to the phytochemical statements made thus far, almost 14 compounds have been isolated and identified from different parts of this plant. Among these, most molecules were extracted using ethanol solvent. The names of the chemical constituents, their presence, the solvent used for extraction, and the structure of the constituents are shown in Table 3 and Fig. 4.

Organic acids

Organic acids form a major part of the root exudates and are intermediate products of the tricarboxylic acid cycle of cellular metabolism. The biosynthesis of organic acids is often stimulated by many environmental factors, and organic acids are released from the roots of plants (Poonam et al., 2021). This could also be the case for *G. bonduc* as previous findings identified and isolated 14 organic acids in the various parts of *G. bonduc*. The names of the chemical constituents, their presence, the solvent used for extraction, and the structure of the constituents are shown in Table 4 and Fig. 5.

Amino acids

Nutritional studies have shown that supplementation with multiple amino acids, such as arginine, glutamine, glutamate, leucine, and proline, modulates gene expression, promotes the growth of the small intestine and reduces excess body fat and skeletal muscle. In addition, functional amino acids play a key role in the prevention and treatment of metabolic diseases and disorders, including obesity, diabetes, and cardiovascular disorders. They also act effectively against intrauterine growth, infertility, intestinal and nervous disorders, and microbial infectious diseases (Wu et al., 2014a, b). It is estimated that the seed powder of *G. bonduc* could be sold in the market for the treatment of diabetes owing to the presence of functional amino acids. As shown in Table 5, 14 amino acids were previously identified in the crude extract of this plant seed.

Pharmacological profile of *G. 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 phytocomponents 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,

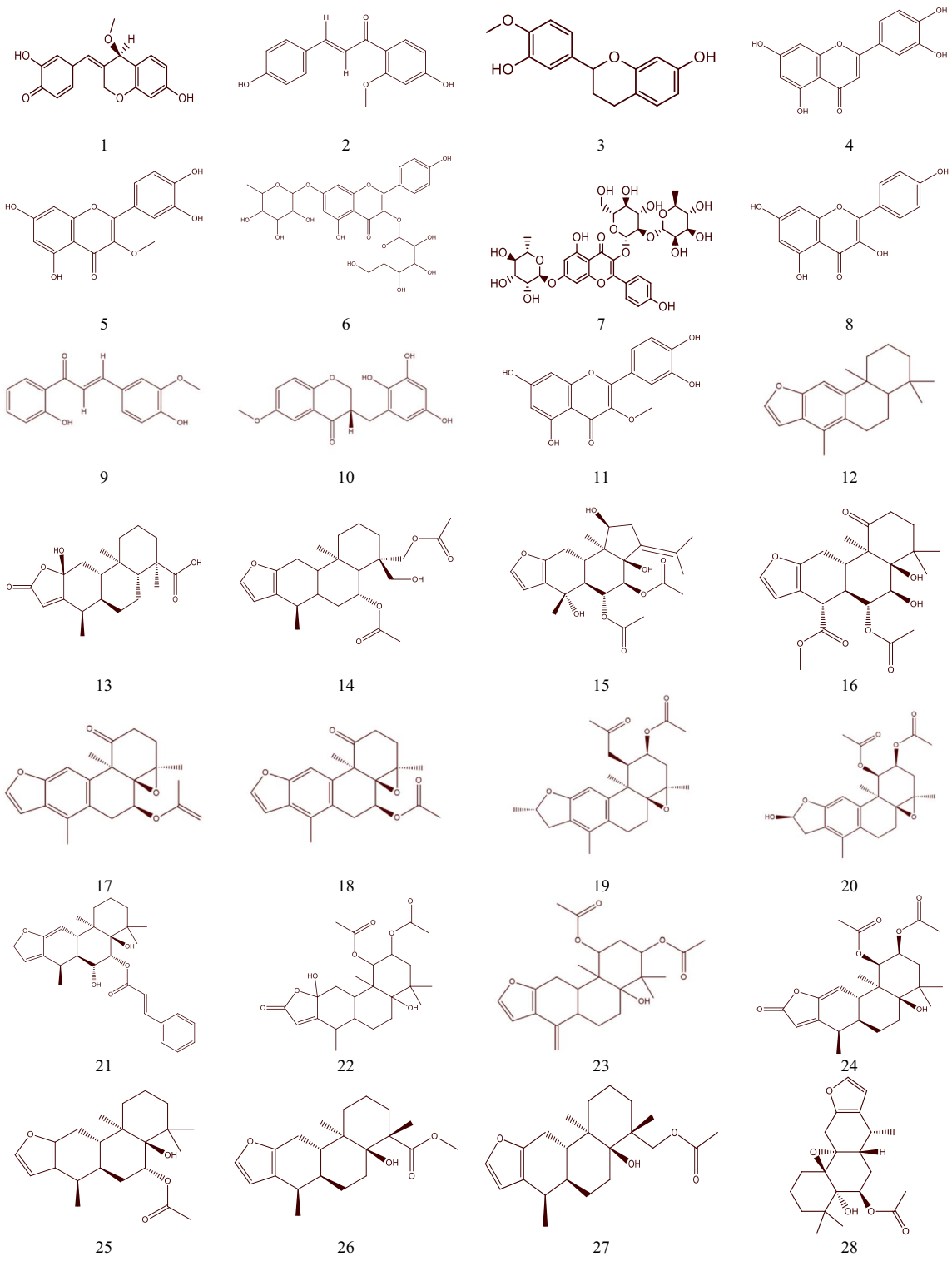

Fig. 3 Isolated and identified phytochemicals from *Guilandina bonduc* L.

and the list goes on (Fig. 6; Table 6). Apart from in vitro and in vivo experiments, it was found that different parts of *G. bonduc* are widely used to treat different diseases, as shown in Table 1. 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.

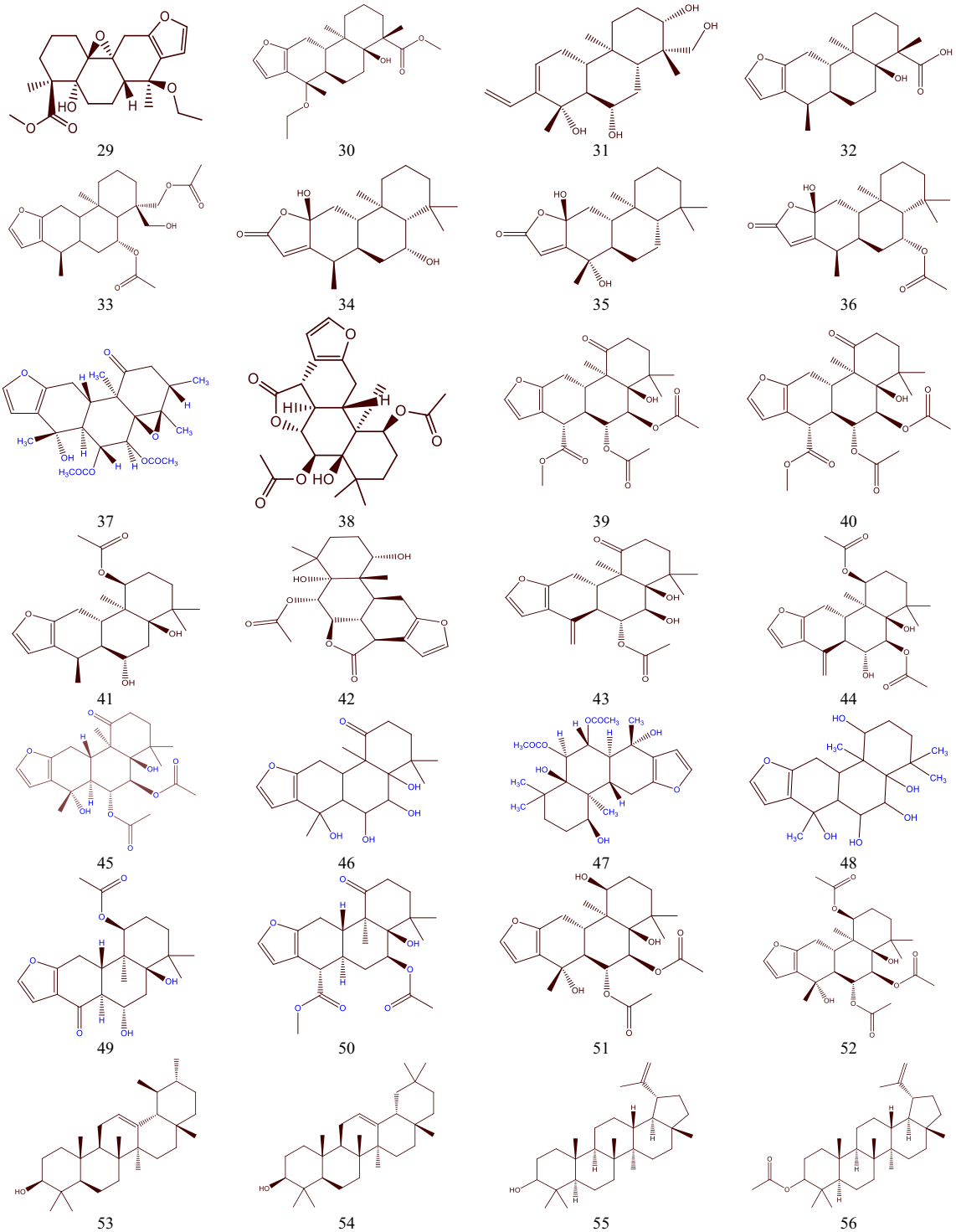

Fig. 3 (continued)

Analgesic effects

The anti-inflammatory effects of radiation therapy cause delayed effects characterized by persistent pain relief that occurs many weeks after treatment. To relieve such pain, analgesics are used to temporarily relieve pain and, in some cases, eliminate sensations in certain organs. Since some synthetic analgesics (non-opioid analgesics) cause serious side effects with long-term or over-dose treatment, scientists around the world are looking for alternative drug molecules

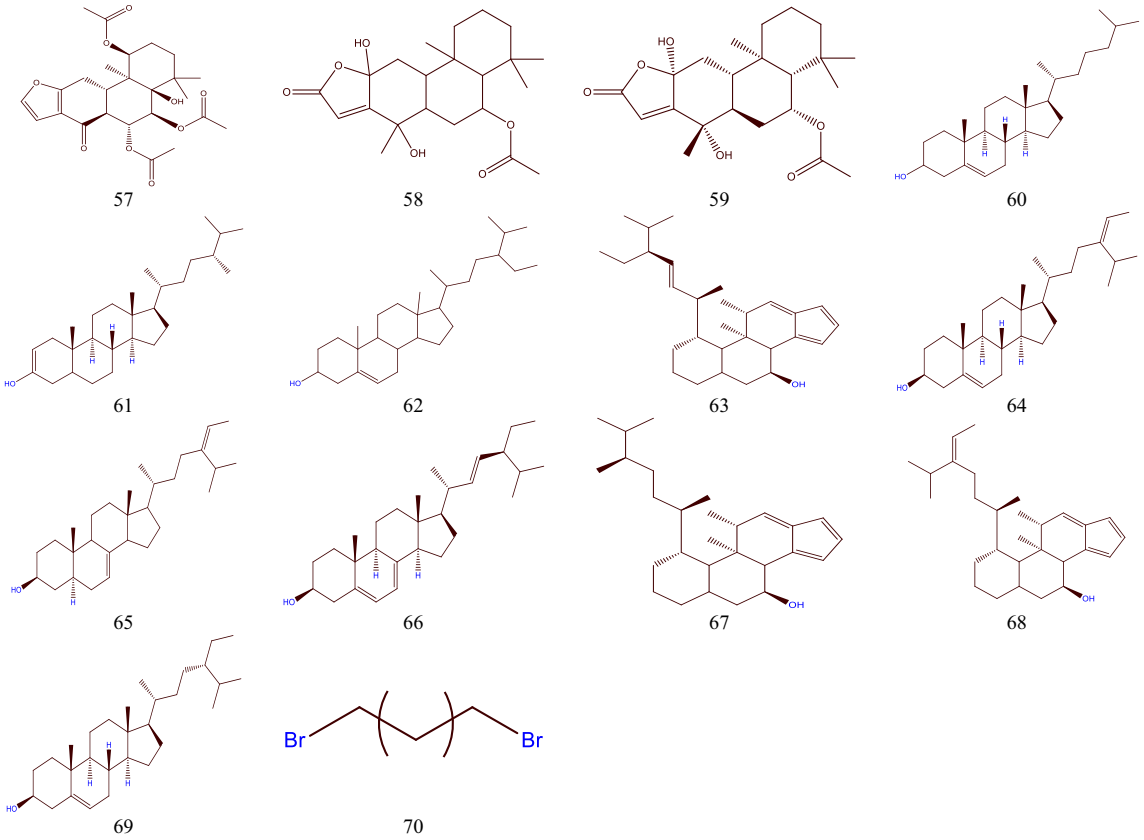

Fig. 3 (continued)

from natural sources. For instance, Kannur et al. (2012) investigated the analgesic potential of the seeds of *G. bonduc* since it has been reported to have an analgesic effect in folk medicine. Seed extracts were used after extracting with 95% ethanol. To confirm the properties of the extracts, they applied two methods to induce paw edema, carrageenan-induced paw edema, and egg albumin-induced paw edema, revealing that it has powerful analgesic properties (Table 6). A similar study was performed by Mahfoozurrahman et al. (2012), where seed extracts suppressed edema-inducing effects in rats, inhibited the fumbling reactions of rats, and increased their reaction times in the hot plate test. Aruna Devi et al. (2008) revealed the dose-dependent analgesic effect of *G. bonduc* flower extract with the doses of 30, 100, and 300 mg/kg which were administered orally to rats with pain elicited by capsaicin, formalin, and acetic acid-induced writhing test, hot plate test, and tail flick test. Their experiment showed a significant dose-dependent analgesic effect in all animals (Table 6).

Anticancer effects

Cancer is the leading cause of death worldwide compared to other human diseases and disorders. According to reports from the World Health Organization (WHO) (2002), the prevalence of cancer is expected to increase by 75% by 2030 owing to population growth and lifestyle changes. Although various chemotherapeutic agents with different biochemical/molecular targets are widely used worldwide to treat this disease and its complications, they cause deleterious effects and sometimes fail to cure it (Nurgali et al. 2018). However, treatments for certain types of cancer are expensive. Therefore, researchers are currently searching for novel anticancer drugs from natural sources that have fewer side effects.

Deepika et al. (2014) investigated the anticancer potential of *G. bonduc* seeds after extraction with petroleum ether. This extraction has been found to be responsible for cell death in Ehrlich ascites carcinomas. They concluded that the seed extract could be a new drug candidate for breast cancer. Sandhia and Bindu (2021) studied the anticancer properties of *G. bonduc* bark extracts with tryptophan dye exclusion strategy by in vitro cytotoxicity at the doses of 10, 20, 50, 100, and 200 µg/mL in Dalton ascite lymphoma cells (Table 6). Their results showed that at concentrations of 100 µg/mL, 100% cytotoxicity prevails in *in vitro* research, and they concluded that the anticancer properties of stem bark may be due to the presence of high levels of flavonoids and phenols in its extracts.

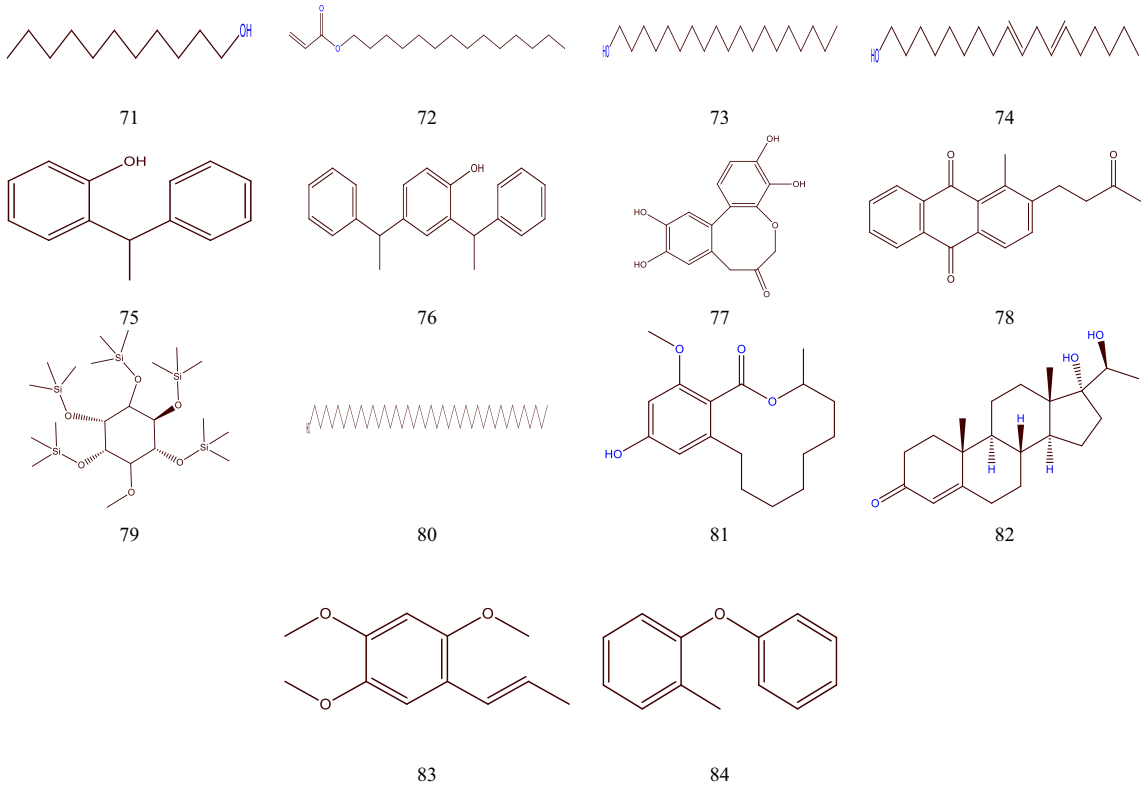

Fig. 4 Isolated and identified volatile compounds from *Guilandina bonduc* L.

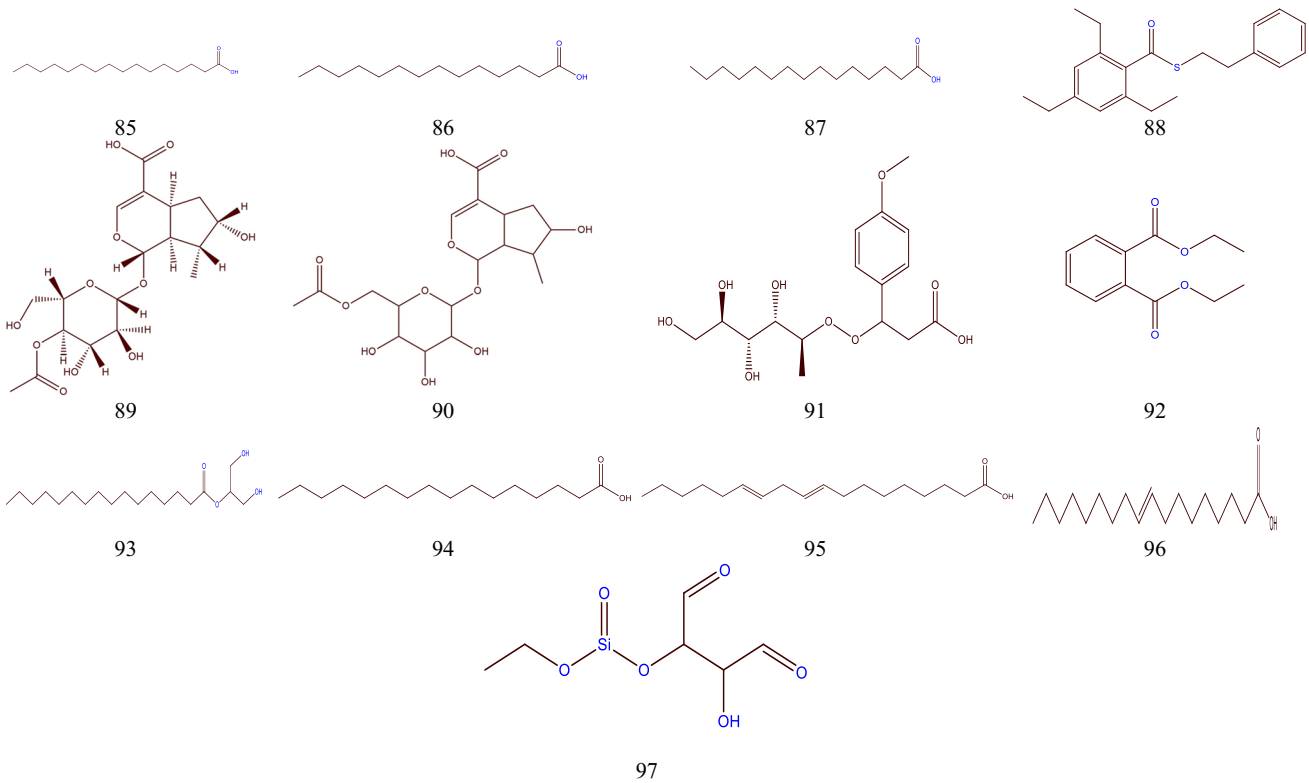

Fig. 5 Isolated and identified organic acids from *Guilandina bonduc* L.

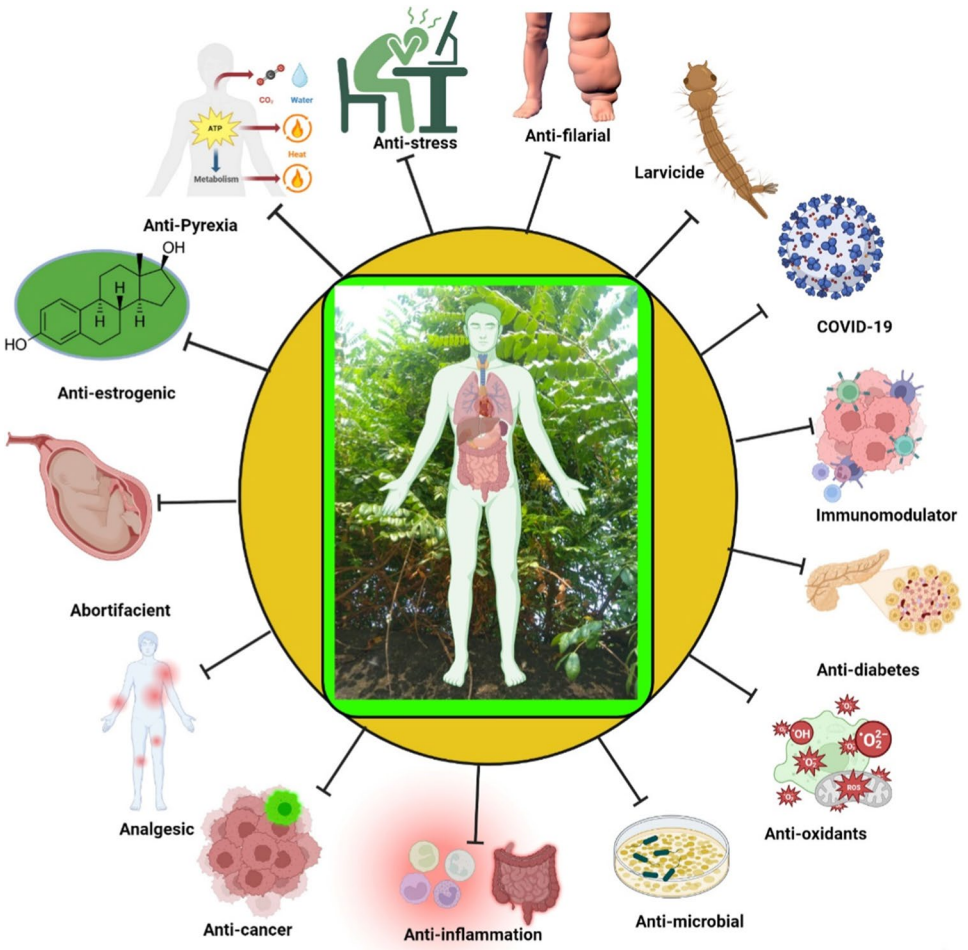

Fig. 6 Pharmacological potentials of *Guilandina bonduc* L.

Various doses of the methanolic extract of the plant *G. bonduc* were tested on Ehrlich ascites tumor (EAT) cell lines to screen their antiproliferative and proapoptotic effects (Shivaprakash et al. 2016). At a dose of 200 mg/kg, the extracts exhibited a reduction of 51.6% in viable cells and 65% in ascites volume in EAT cells. The methanolic extract-treated EAT cells died more frequently from apoptosis than from necrosis, and this extract treatment significantly reduced anti-apoptotic Bcl-2 expression and increased pro-apoptotic Bax expression, according to the molecular mechanism analysis (Table 6). Their research suggested that the methanolic extract of the plant had antiproliferative and proapoptotic activities, suggesting that it could be developed as an anticancer therapeutic drug.

Anti-inflammatory effects

Inflammation is a complicated shielding response of the host to external stimuli and can be fought by controlling signaling pathways such as TNF-α, NF-κB, inducible nitric oxide synthase, interleukin-6, and cyclooxygenase-2 (Fan et al. 2020). The bark of *G. bonduc* was used to test its anti-inflammatory potential in a dose-dependent manner in male albino Wistar rats after inducing carrageenan paw edema and showed effective anti-inflammatory properties at all doses (Mahfoozurrahman et al., 2012). This study showed remarkable anti-inflammatory effects in carrageenan-induced rats; in particular, it significantly reduced carrageenan-induced paw edema in rats, decreased writhing in rats, and prolonged response time in the hot plate test (Table 6). According to their findings, the seeds of *G. bonduc* contain potent anti-inflammatory properties after being extracted with water. A similar study was performed by Kale et al. (2010) with the seed kernel of *G. bonduc* which was examined to assess its anti-inflammatory properties after extraction with petroleum ether. Prior to the experiments, paw edema was induced in male Wistar rats by injecting 0.1 mL of carrageenan. Subsequently, inflammation-induced rats were treated with formulated *G. bonduc* seed extracts in a dose-dependent manner. Their study suggested that the treatment of this extraction showed outstanding anti-inflammatory activity at a dose of 100 mg/kg (Table 6). However, they concluded that this could be because of the presence of phytosterols in the seed kernels of the plant.

Table 6 Pharmacological effects and mechanism of action of *G. bonduc*

S. No.	Parts Used	Mode of study	Extract/dose concentration	Mechanism of action	Reference
Analgesic effects					
1	Seed	*In vivo*	95% ethanol	Reduces the pain factor and decreases inflammation	Kannur et al. (2012)
2	Seed	*In vivo*	Aqueous extract; 400 mg/kg	Inhibits writhing response in rats and inhibits cyclo-oxygenase	MahfoozurRahman et al. (2012)
3	Flower	*In vivo*	Ethanolic extract; 300 mg/kg	Antinociceptive effect and no toxic effect	Aruna Devi et al. (2008)
Anti-cancer effects					
4	Seed	*In vitro*	Ethanolic extract; 7.8125 to 1000 µg/mL	Inhibits the EAC cells	Deepika et al. (2014)
5	Stem bark	*in vitro*	Ethanolic extract; 100 µg/mL	Reveals 100% cytotoxicity effects	Sandhia and Bindu (2021)
6	Seed	*In silico*	BCL-2 protein	The least binding energy 6.42 kcal/mol	Deepika et al. (2014)
7	Leaf	*in vivo*	Methanolic extract; 200 mg/kg	Decreases the level of anti-apoptotic, BCL-2 expression and increasing pro-apoptotic BAX level	Shivaprakash et al. 2016
Anti-inflammatory effects					
8	Seed	*in vivo*	Aqueous extract; 14 mg/kg	Reduces carrageenan-induced paw edema in rats and decreases writhing in rats	Mahfoozurrahman et al., 2012
9	Seed kernel	*in vivo*	Petroleum ether; extract 100 mg/kg	Reduces inflammation	Kale et al. (2010)
Anti-microbial effects					
10	Seed	*In vitro*	Methanol extract; 500 ppm	Inhibits the growth of *E. coli*, *B. subtilis*, *S. aureus*	Simin et al. (2001)
11	Seed	*In vitro*	Ethanol extract; 100 mg/kg	Inhibits the growth of *S. aureus*, *S. agalactiae*, and *P. aeruginosa*	Ata et al., 2009a
12	Seed kernel and coat	*In vitro*	Ethanol extract; 100 mg/mL	Inhibits the growth of *S. aureus* and *P. aeruginosa*	Arif et al. (2009)
13	Leaf	*In vitro*	Aqueous extract; 100 mg/mL	Inhibits the growth of *E. coli*, *B. subtilis*, *S. aureus*, *A. flavus* and *C. glaberata*	Khan et al. (2011)
14	Seed	*In vitro*	Aqueous extract; 100 µl	Inhibits the growth of *C. albicans*, *A. niger*, *A. flavus*, *A. solani* and *F. oxysporum*	Shukla et al. (2011)
15	Leaf	*In vitro*	Methanol extract; 100 µg/mL	Inhibits the growth of *B. subtilis*, *S. aureus*, *E. coli*, *K. aerogenes*, *A. niger* and *P. chrysogenum*	Kakade et al. (2017)
16	Leaf, stem bark	*in vitro*	Chloroform extract; 100 µg/mL	Inhibits the growth of *B. subtilis*, *P. aeruginosa* and *E. coli*	Santosh Kumar et al. (2019)
Anti-oxidant properties					
17	Leaf	*In vivo*	Petroleum ether extract; 200 mg/kg	Increases vitamin E, vitamin C, SOD Catalas, and GSH activities	Gupta et al. 2008
18	Seed	*In vitro*	Ethanolic extract; 200 µg/mL	Inhibits DPPH, hydroxyl radical, nitric oxide, and superoxide free radicals	Shukla et al. (2009a, b)
19	Seed	*In vitro*	Ethanolic extract; 8.25 mg/mL	Inhibits DPPH free radical	Jayakrishnan et al. (2014)
20	Leaf	*In vitro*	Ethanol, aqueous, ethyl acetate; 10 to 100 mg/mL	Inhibits DPPH and nitric oxide free radicals	Pandey and Lokesh (2019)

Table 6 (continued)

S. No.	Parts Used	Mode of study	Extract/dose concentration	Mechanism of action	Reference
Against COVID-19					
21	Leaf		With other plant extracts	Boosting immune system	Kashif Husain et al. 2020
Anti-diabetic effects					
22	Seed kernel	*In vivo*	Ethyl acetate extract; 400 mg/mL	Reduces blood glucose level	Parameshwar et al. (2002).
23	Seed	*In vivo*	Petroleum ether; 300 mg/kg	Increases antihyperglycemic action, reduces cholesterol, LDL and BUN levels	Kannur et al. (2006)
24	Seed shell	*In vivo*	Aqueous extract; 250 mg/kg	Reduces blood sugar level	Biswas et al. (1997)
25	Seed	*In vivo*	Aqueous extract; 250 mg/kg	Increases the glucose uptake and reduces blood glucose	Patil et al. (2011)
26	Seed	*In vivo*	Methanolic extract; 250 mg/kg	Increases antihyperglycemic and antioxidant enzymes activity like catalase and SOD	Jana et al. (2012)
27	Seed	*In vivo*	Ethanolic extract; 500 mg/kg	Decreases postprandial blood glucose and increase insulin levels	Widhiantara et al. (2018)
28	Seed kernel	*In vivo*	Ethyl acetate extract; 100 mg/kg	Reduces glucose level and oxidative stress	Parameshwar et al. (2002)
Anti-catalepsy effects					
29	Seed	*In vivo*	Ethanol extract; 100 mg/kg	Decreases the milk allergen-induced eosinophil and leukocyte counts and reduce clonidine-induced mast cell degranulation	Vikhe and Nirmal (2018)
Immunomodulatory effects					
30	Seed	*In vivo*	Ethanol extract; 500 mg/kg	Increases neutrophil adhesion and reduces hypersensitivity reaction	Shukla et al. (2009a, b)
Anti-estrogenic effects					
31	Seed	*In vivo*	Ethanol extract; 10 mg/kg	Reduced uterinelumen, mild disorganization of endometrium and vacuolation; drease ovarian weight; decrease size of follicular antrum and detachment of primary oocyte	Salunke et al. (2011)
Anti-pyrexia and anti-nociceptive effects					
32	Seed oil	*In vivo*	Seed oil; 400 mg/kg	Reduces paw volumes, pyrexia, and writhes and reduces the yeast-elevated rectal temperature	Shukla et al. (2011)
33	Flower	*In vivo*	Ethanolic extract; 300 mg/kg	Antinociceptive effect and reveals no toxicity effect	Aruna Devi et al. (2008)
34	Seed kernel	*In vivo*	Ethanolic extract; 300 mg/kg	Reduces formalin-induced hind paw licking in mice and increases pain threshold	Archana et al. (2005)
Anti-stress effect					
35	Seed kernel	*In vivo*	Petroleum ether; 300 mg/kg	Decreases cholesterol and LDL level and reduces stress	Kannur et al. (2006)
Anti-filarial activities					
36	Seed	*In vitro*	Aqueous fraction; 2000 mg/kg	Decreases the growth of *L. sigmodontis*	Gaur et al. (2008)

Table 6 (continued)

S. No.	Parts Used	Mode of study	Extract/dose concentration	Mechanism of action	Reference
Larvicidal effects					
37	Seed oil	*In vitro*	Petroleum ether, ethanol and aqueous extract; 1% solution	100% of mortality	Saravanan et al. (2007)
Toxicity assessments					
38	Leaf and stem bark	*In vivo*	Methanol extract; 400 mg/kg	Reveals no cytotoxic effects; altered serum enzymes and the hematological parameters	Kumar et al. (2005)
39	Seed kernel	*In vivo*	Ethanolic extract; 300 mg/kg	Increases erythrocytes, leukocytes, platelet counts, hemoglobin levels, and packed cell volume	Lilaram and Ahmed (2014)
40	Leaf	*In vivo*	Ethanolic extract; 300 mg/kg	No mortality, alter in the biomarkers and induces cellular damage to the liver	Ogunlana et al. (2013)

Ref: Shukla, S., Mehta, A., Mehta, P., Vyas, S.P., Shukla, S. and Bajpai, V.K., 2010. Studies on anti-inflammatory, antipyretic and analgesic properties of Caesalpinia bonducella F. seed oil in experimental animal models. Food and Chemical Toxicology, 48(1), pp.61-64. Saravanan KS, Periyanayagam K, Ismail M. Mosquito larvicidal properties of various extract of leaves and fixed oil from the seeds of Caesalpinia bonduc (L) Roxb. J Commun Dis. 2007 Sep;39(3):153-7

Antimicrobial effects

Recently, invasive microbial infections have proven fatal, particularly in patients with compromised immune systems (Loeffler and Stevens 2003; Groll and Lumb 2012; Prabhu et al. 2021). Currently, infections with harmful pathogens, such as bacteria, fungi, and viruses, are increasing and causing deadly diseases. Therefore, to cure diseases caused by these microorganisms or to control these microbial populations, there is an urgent need to discover new active molecules from natural sources. To find a novel antibiotic against such deadly pathogens, *G. bonduc* was previously tested on harmful pathogens by Simin et al. (2001), and they studied the antimicrobial and phytotoxic profiles of newly isolated diterpenoid bondenoids from *G. bonduc* using methanol extract, ethyl acetate fractions, and a water-soluble portion of the methanol extract. The methanol leaf extracts were tested against *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, *Epidermophyton floccosum* var. *nigricans*, and *Candida glabrata*. Among the microbial strains tested, the extract showed inhibitory potential against the growth of *E. coli* and *E. floccosum* var. *nigricans*, whereas moderate zones of inhibition were observed in all tested microbes. The extracts were found to show inhibitory potential against *E. coli* and *E. floccosum* compared to the antibiotics used, and their research suggested that the plant extract could be used as an antibiotic (Table 6).

Some diterpenoid chemicals were isolated from the bark of *G. bonduc* using ethanolic solvent. The isolated phytochemicals such as neocaesalpin H, cordylane A, caesalpinine B, bondellpin E, caesalpinolide A, and 17-methylvouacapane-8(14), -9(11)-diene were reported to have antibacterial potential against *Staphylococcus aureus*, *Streptococcus agalactiae*, and *Pseudomonas aeruginosa*, and the results revealed negligible inhibitory effect on the bacterial strains studied, whereas none of these compounds strongly inhibited glutathione-S-transferase (Ata et al., 2009a).

Arif et al. (2009) investigated the antimicrobial potential of *G. bonduc* seed kernels against antibiotic-resistant strains, namely, *S. aureus* and *P. aeruginosa*, and the results showed inhibitory effects against the tested strains. The hydroalcoholic extracts of the seed kernel and seed coat of *G. bonduc* were further studied in rats with chronic pneumonia caused by *P. aeruginosa*. Rats were injected subcutaneously with the extracts, and significant clearance of bacteria in the lungs and a lower incidence of lung abscesses were observed after 2 weeks of extract administration in rats with chronic pneumonia. The results revealed that the seeds of the plant may be considered as a promising natural remedy for cysts and cystic fibrosis in patients with chronic *P. aeruginosa* lung infections (Table 6).

Khan et al. (2011) studied the antimicrobial, antispasmodic, and Ca++ antagonistic effects of *G. bonduc* extracts after extraction by n-butanol, ethyl acetate, and ethanol. The ethyl acetate extraction exhibited a broader spectrum of inhibition against the tested bacteria, including *E. coli* and *B. subtilis.* The extracts also showed potent antifungal activity against *Candida glabrata* (80%), whereas 65–70% growth of *Aspergillus flavus* was significantly reduced by the extracts of n-butanol, chloroform, and crude extract (Table 6). Based on the antibacterial, antifungal, spasmolytic, and C++

channel-blocking effects of the plant, they concluded that it might have active therapeutic agents to cure the diseases caused by these microorganisms.

The antifungal potential of *G. bonduc* seeds was assessed by Shukla et al. (2011) after extracting with different solvents, including ethyl acetate, aqueous, and petroleum ether with the fungal strains *Aspergillus niger*, *Candida albicans*, *Fusarium oxysporum*, and *Alternaria solani*. The seed extract prepared with ethyl acetate and aqueous solution showed strapping inhibition of the growth of all fungal strains tested, and the observations led the researchers to conclude that the extracts could be useful in combating fungal pathogens (Table 6). Likewise, the leaves of *G. bonduc* analyzed by Kakade et al. (2017) for antimicrobial properties against *B. subtilis*, *S. aureus*, *E. coli*, *K. aerogenes*, *A. niger*, and *P. chrysogenum* (Table 6). Their results suggest that leaf extracts can be used as an alternative therapy for those suffering from the complications of these microorganisms.

Santosh Kumar et al. (2019) studied phytochemicals from *G. bonduc* in vitro and in silico to discover their antimicrobial potential. Bacteria such as *B. subtilis*, *P. aeruginosa*, and *E. coli* were used in the in vitro assays. The growth of *P. aeruginosa* was strongly suppressed by the extract of chloroform with a zone of inhibition range of 16.10 ± 1.10 mm. To identify the active chemical components, phytochemicals, such as β-sitosterol and methyl-(4E)-5-[2-[1E)-buta-1,3-dien-1-yl]-4,6-dihydroxyphenyl] pent-4-Enoate were subjected to in silico research on these bacterial strains after isolation from the leaf with chloroform and bark with ethanol extract. In this *in silico* validation, β-sitosterol and methyl (4E)-5-[2-[1E)-buta-1,3-dien-1-yl]-4,6-dihydroxyphenyl] pent-4-enoate had better docking scores and hydrogen-bonding contacts with the residues of the bacterial DNA gyrase (Table 6). Based on the docking studies, methyl (4E)-5-[2-[1E)-buta-1,3-dien-1-yl]-4,6-dihydroxyphenyl] pent-4-enoate was tested on *P. aeruginosa*, which showed a notable zone of inhibition with a range of 16.50 ± 0.58 mm.

Antioxidant properties

The formation of reactive oxygen species in the body leads to an oxidative stress response under certain pathophysiological conditions, which can impair the function of cells or organs. Parameshwar et al. (2002) reported that the aqueous extract of the seed kernel failed to scavenge free radicals in *in vitro* studies, but the ethyl acetate extract showed a maximum activity of 49% after 1 h. Ethyl acetate extract has antioxidant properties that may help fight oxidative stress associated with diabetes.

The flavonoids and triterpenoids present in the *G. bonduc* leaves were studied in antioxidant metabolic processes related to the lipid peroxidation end product malondialdehyde, enzymatic antioxidants such as catalase and superoxide dismutase, and nonenzymatic antioxidant glutathione and the levels of vitamin C and vitamin E (Gupta et al. 2008). In addition to transaminase enzyme activity, serum studies measuring bilirubin, total protein, and uric acid levels were also performed by Gupta et al. (2008). Their study reported that plant extracts increased protein and uric acid levels in the body and decreased bilirubin activity, with high antioxidant properties.

The antioxidant effects of *G. bonduc* seeds at doses of 20, 40, 50, 100, and 200 g/mL were studied by Shukla et al. (2009a, b), and the results were found to have DPPH activity in the range of 38.93–74.77% (Table 6), which was close to that of ascorbic acid (64.26–82.58%). Likewise, the IC50 values of the extract and ascorbic acid were determined to be 74.73 and 26.68 μ/mL in DPPH radical scavenging tests. This extract also inhibited hydroxyl radicals, nitric oxide, and superoxide anions with IC50 values of 109.85, 102.65, and 89.84 μg/mL, respectively, and the results suggested that seeds of *G. bonduc* have tremendous potential for use as a natural antioxidant. *G. bonduc* seed extracts showed promising antioxidant effects on the enzymes, catalase, and superoxide dismutase and reduced the lipid peroxidation levels ($P < 0.05$) in diabetic animals with promising antioxidant potential (Jana et al. 2012).

Jayakrishnan et al. (2014) investigated the antioxidant potential of *G. bonduc* seeds after extraction with ethanol in DPPH assay; the results showed an EC_{50} value of 7.5 mg with powerful antioxidant properties. Pandey et al., 2018 revealed strong DPPH free radical and nitric oxide scavenging actions of the crude extracts of *G. bonduc*, and they concluded that it could be useful for future applications in food and pharmaceutical industries in the development of antioxidant-based products.

Shukla and Mehta (2017) studied the antioxidant potential of *G. bonduc* aqueous seed extract in DPPH assay, and the inhibition percentage ranges from 36.93 to 70.57% at doses of 20, 40, 50, 100, and 200 g/mL, which was close to that of ascorbic acid (64.26 to 82.58%) with the IC50 value of 86.31 g/mL. The aqueous extract also significantly inhibited the hydroxyl radicals, nitric oxide, and superoxide anions with IC50 values of 139.95, 114.70, and 83.62 g/mL, respectively, and the results of the study suggest that *G. bonduc* has tremendous potential for use as a natural antioxidant.

Shukla et al. (2009b) also investigated the antioxidant potential of *G. bonduc* in the ethanol extracts in DPPH assay, and the plant extract showed dose-dependent inhibition at the doses of 20, 40, 50, 100, and 200 g/mL with the inhibition percentage of 38.93% to 74.77%, while the standard ascorbic acid recorded with 64.26 to 82.58% of inhibition. The IC50 concentration of the extracts was registered as 74.73 g/mL. They reported that this extract suppressed hydroxyl radicals, nitric oxide, and superoxide anions with IC50 values of 109.85, 102.65, and 89.84

g/mL, respectively. Based on their findings, the researchers concluded that *G. bonduc* has tremendous potential for use as a natural antioxidant agent.

Against COVID-19

In general, coronaviruses cause mild-to-moderate respiratory diseases in humans. However, some patients become seriously ill and require medical attention. In particular, older people and those with chronic respiratory diseases, cardiovascular diseases, diabetes, and cancer are at a higher risk of mortality due to viral respiratory infections. Anyone of any age can contract COVID-19 and become seriously ill or die (WHO, 2023). However, according to the latest polyherbal treatment, it can be controlled at any stage by drinking the herbal extracts three times a day (Husain et al. 2020). Interestingly, extracts of *G. bonduc* are used in the complications of SARS CoV-2 to boost the immune system and alleviate upper respiratory tract infections caused by the coronavirus (Table 6). It was also stated that it has been prescribed by the Ministry of Ayush, India, to treat coronaviruses.

Antidiabetic effects

Diabetes mellitus is characterized by various metabolic processes in the body, including higher glucose levels (hyperglycemia), lower glucose levels (hypoglycemia), high lipid levels (hyperlipidemia), low lipid levels (hypolipidemia), and disorders of lipid and protein metabolism. Approximately 3.5 million deaths occur annually due to diabetic complications such as diabetic coma, diabetic ketoacidosis, nephropathy, neuropathy, and retinopathy. Despite advances in disease diagnosis and prevention, disease-related mortality and morbidity have increased. Therefore, researchers are currently looking for novel antidiabetic drugs that do not incur costs and have no side effects.

G. bonduc is used as an antidiabetic agent by the people of the Andaman and Nicobar Islands and the Caribbean Islands (Sasidharan et al. 2021b). It has also been previously reported to have noticeable hyperglycemic properties (2002). Parameshwar et al. (2002) carried out the antidiabetic effect of the various extracts made from the *G. bonduc* seed kernel extracts on rats with alloxan diabetes using ethyl acetate, ether, petroleum ether, and aqueous. The diabetes-related changes, such as liver lipid and glycogen levels, were reversed by aqueous ethyl acetate, and petroleum ether extracts had no effect on diabetic rats (Table 6). Because of the antidiabetic potential of the aqueous and ethyl acetate extracts, these extracts were subjected to phytochemical analysis and were revealed to be rich in triterpenoid glycosides. Based on their research, the extracts exhibited antidiabetic potential owing to the presence of triterpenoid glycosides in the extracts of aqueous extracts and ethyl acetate.

The seed extracts of *G. bonduc* were used to evaluate their antidiabetic effects in rats with alloxan-induced hyperglycemia by Kannur et al. (2006), and the results exhibited that oral administration of the extracts (300 mg/kg) had a significant antihyperglycemic effect and significantly reduced BUN levels. It has also been found to have significant effects on hyperlipidemia caused by diabetes, where it also lowers elevated cholesterol and LDL levels. Their results hypothesized that it might exert its antihyperglycemic effects by blocking glucose absorption and seemed to confirm the alleged antidiabetic effects of this traditional medicinal plant.

The hypoglycemic effect of the *G. bonduc* seed coat in stereoptozotocin and alloxan-induced diabetic rats was studied by Biswas et al. (1997), and the treatment resulted a very impressive drop in blood sugar ($P < 0.005$) within 5 h. Patil et al. (2011) investigated the antidiabetic effect of *G. bonduc* root extracts of aqueous, ethanol, and chloroform on glucose tolerance in alloxan-induced diabetic rats. These three combinations showed excellent protection and normalized glucose levels in a glucose tolerance test, and a significant drop in blood sugar levels was observed after 3 h at a dose of 250 mg/kg body weight in diabetic rats. On the other hand, the chloroform and ethanol extracts showed protection rate of 22.28 and 23%, respectively. On days 0, 3, 5, 7, and 10, the blood glucose, triglyceride, cholesterol, and urea levels were examined in rats receiving long-term treatment for alloxan diabetes to assess the extent of protection (Table 6). Chloroform and ethanol extracts have been shown to have an excellent glucose-reducing effect in rats with glucose- and alloxan-induced diabetes. They concluded that the extracts might have an antidiabetic effect by increasing pancreatic secretion or glucose uptake.

Jana et al. (2012) reported that the seed extracts of *G. bonduc* restored carbohydrate-metabolizing enzymes along with fasting blood glucose and glycogen levels better than untreated diabetic rats, and the enzyme toxicity parameters were significantly reduced by the seed extract ($P < 0.05$). The healing properties of the seed extract were far superior to those of the commonly used antidiabetic drug, glibenclamide. Widhiantara et al. (2018) investigated the hypoglycemic potential of *G. bonduc* seeds on streptozotocin and nicotinamide-induced type II diabetes in albino Wister rats. The animals were treated twice daily for 14 days, and at the end of the day, blood sugar and plasma insulin levels were measured. They found that animals treated with seed extract significantly lowered the postprandial blood glucose (PPBG) levels, whereas animals treated with distilled blood had significantly higher PPBG levels, and the results revealed that *G. bonduc* seeds are more effective in lowering postprandial blood glucose levels than glibenclamide.

The seed kernel of *G. bonduc* has significant hypoglycemic effects after extraction with petroleum ether, ether, ethyl acetate, and water (Parameshwar et al. 2002). The

ethyl acetate and aqueous extracts had minimal hypoglycemic effects in normal animals compared to the corresponding drug, glibenclamide. In contrast, the polar solvent extracts (ethyl acetate and aqueous extracts) exhibited significant hypoglycemic effects in diabetic animals, reversing the changes in lipid and liver glycogen levels. Among the nonpolar extracts, ether extract had a moderate antidiabetic effect. Parameshwar et al. (2002) pointed out that the richness of chemicals, especially triterpenoid glycosides in the extracts of polar solvents, could possibly contribute to the antidiabetic effect in diabetic animals (Table 6). Based on these results, they concluded that the folk claims of *G. bonduc* in terms of its antidiabetic activity could be effective at higher doses.

Abortiflora

After implantation loss, the number of dead fetuses and the percentage of abortions in semen extract–treated rats decreased markedly, while the number of pups, implantation index, number and size of live fetuses, placenta weight, progesterone levels, and the number of deaths also diminished considerably. In rats treated with the *G. bonduc* seed extract, the rate of reduction increased. Lilaram and Ahmed (2014) found that the female rats treated with the seed extract of *G. bonduc* had a significant reduction in maternal final weight, number of implantation sites, live fetuses, implantation index, mean pup weight, placenta weight, percent survival rates, progesterone, and post progesterone levels as well as substantial growth in resorption index, post implantation loss, number of fetal deaths, and abortion rates (Table 6). Treatment with the seed extract resulted in degeneration of the junctional zone and labyrinth of the placenta in rats.

Anti-catalepsy effects

Catalepsy is a nervous disorder characterized by muscle stiffness, rigid posture, and decreased sensitivity to pain independent of external stimuli. It manifests symptoms such as a rigid body, rigid limbs, lack of muscle control, and slowdown of physical functioning (Sanberg et al., 1988, b) and also leads to epilepsy and Parkinson's disease. Vikhe and Nirmal (2018) studied the catalepsy effects of *G. bonduc* extracts of ethanol solvent. In their study, the extract inhibited clonidine-induced catalepsy at doses of 50 and 100 mg/kg, significantly decreased milk allergen-induced eosinophil and leukocyte counts, and prevented clonidine-induced mast cell degranulation (Table 6).

Immunomodulatory effects

In general, a substance stimulates the immune system, which can also help fight diseases. For instance, monoclonal antibodies, cytokines, and vaccines are immunomodulatory agents that enhance the immune response (Kajaria et al. 2013). Shukla et al. (2009a) studied the immunomodulatory effects of *G. bonduc* seeds extract of ethanol solvent, and the percentage of adhesion of neutrophils to nylon fibers was obviously improved; antibody titers were dose-dependently improved and delayed the process that triggers hypersensitivity reactions (Table 6). They also reported that a carbon clearance phagocytosis experiment in rats showed exceptional resistance to cyclophosphamide-induced myelosuppression by altering immune function, which may provide therapy to prevent autoimmune diseases.

Anti-estrogenic effects

Existing estrogen blockers and antiestrogenic drugs pose mild-to-serious risks in women. In particular, estrogen blockers can lead to blood clots and uterine cancer. Existing anti-estrogen drugs cause night sweats, mild nausea, bone pain, hot flashes, and vaginal dryness. To avoid such risks in anti-estrogen treatment, researchers are looking for natural drugs to regulate estrogen levels. For instance, Salunke et al. (2011) studied the anti-estrogenic effects of *G. bonduc* seeds and revealed with significant changes in histological appearance, including ovarian follicular degeneration and vacuolar dilatation and the uterus disorganized by the extract. In contrast, the weight of the ovaries and the length of the estrus cycle decreased significantly ($P < 0.05$), and there were no regular fluctuations in uterine weight or estrogen or progesterone levels in the blood (Table 6). Based on their histological findings in ovaries, Salunke et al. (2011) hypothesized that the alcoholic seed extract of *G. bonduc* would decrease estrogen secretion by inhibiting its antiestrogenic abilities.

Anti-pyrexia and anti-nociceptive effects

Shukla et al. (2011) examined the anti-pyrexia and acute and chronic inflammatory effects by administering the *G. bonduc* seed oil at doses of 100, 200, and 400 mg/kg to carrageenan-induced rat paw edema, brewer's yeast-induced fever, and acetic acid–induced writhing in experimental rats. The hot plate test showed a significant licking effect in rats. In addition, paw volume, fever, and frizz were significantly lower in experimental rats than in control rats ($P < 0.05$). Based on their research, they documented that *G. bonduc* seed oil could be a promising source of anti-inflammatory, antipyretic, and analgesic drugs. Moreover, Devi et al. (2008) reported potent antipyretic effects of the flower extracts of *G. bonduc* in brewer's yeast-inducing pyrexia rats.

A study by Archana et al. (2005) showed that the seed kernel of *G. bonduc* has remarkable antipyretic and antinociceptive effects in albino Wister rats when treated with different doses. The extract was orally administered to rats with

brewer's yeast–induced pyrexia, and in experiments with hot plates and tail-flicks, it was found to have an analgesic effect (Table 6). Based on their findings, they concluded that the seed kernel of *G. bonduc* has active therapeutic agents to cure the complications associated with pyrexia and nociception and further confirmed its use in the treatment of pain and febrile illnesses.

Anti-stress

The seed extracts of *G. bonduc*, especially the seed coat and seed kernel, have been reported to have potent anti-stress effects in cold stress and swim endurance models. Kannur et al. (2006) reported that that it helps stressed animals overcome imbalances such as lower glucose levels, falling serum cortisol levels, and an increased total white blood cell count. To assess its anti-stress effects, seed extracts were formulated with ethanol, petroleum ether, and seed coat extract, in which ethanol was found to have a greater effect on stressed animals (Table 6).

Anti-filarial activities

Lymphatic filariasis is a debilitating disease affecting people in tropical countries. Since existing drugs are not effective in fighting these diseases, effective anti-filarial drugs are urgently needed for proper treatment of the disease. Therefore, Gaur et al. (2008) attempted to find an alternative drug from *G. bonduc*. In their study, microfilaremic cotton rats and *Mastomys coucha* carrying *Litomosoides sigmodontis* and *Brugia malayi* were administered with the crude extract of *Guilandina bonduc* seed kernel for 5 days to test the anti-filarial efficacy. The results showed that in the *L. sigmodontis* cotton rat model, the extract showed a gradual decrease from the eighth day after treatment, reaching a drop of more than 95% at the end of the observation period. It also showed 96% macrofilaricidal efficacy and 100% sterilizing efficacy in female rats (Table 6). Based on these results, they concluded that both the crude extract and the fractions showed filaricidal effects, such as microfilaricidal, macrofilaricidal, and female-sterilizing activity against *L. sigmodontis* and microfilaricidal and female-sterilizing activity against *B. malayi* in animal models, indicating the potential of this plant to develop new anti-filarial drugs.

Larvicidal effects

Culex quinquefasciatus (also known as the house mosquito) is a major vector responsible for West Nile fever at St. Louis encephalitis, Japanese encephalitis, and viral infection in birds and horses. To control this vector population, the dried leaf extract of petroleum ether, ethanol, and aqueous and seed oil of *G. bonduc* was investigated in preliminary laboratory experiments on *C. quinquefasciatus* larvae. It was observed that a mortality of 100% was observed at 1% concentration of petroleum ether and ethanolic leaf extract, while at a concentration of 2.5% of the aqueous extract, it was 55%, and the fixed oil at a concentration of 2.5% was 92.6% (Saravanan et al. 2007). Therefore, they proposed isolating the active ingredient responsible for mortality to develop a promising larvicidal drug that is economical, non-toxic, and environmentally friendly.

Toxicity assessments

Since ancient times, plants have been used by people for a variety of purposes, most notably for medicine (Yuet Ping et al. 2013), and the people all over the world feel that herbal products are safer or have minimal side effects. However, a recent study has revealed that several herbal medicines have side effects (Ugwah-Oguejiofor et al. 2019). As the safety of medicinal plants remains a major concern, it is important to conduct toxicity studies to determine their safety profile (Rasool et al. 2022). Furthermore, the assessment of the toxicological effects of medicinal plant extracts intended for use in animals or humans is an important aspect in assessing possible toxic effects (Ugwah-Oguejiofor et al. 2019; Rasool et al. 2022). Although *G. bonduc* has a wide range of pharmacological profiles for a variety of diseases, its toxicity parameters, such as hematological, biochemical, and histopathological parameters, have been studied by a few research groups.

A toxicity study of this plant extract of methanol solvents was performed by Kumar et al. (2005), who investigated toxicity parameters such as hematological, biochemical, and histopathological parameters in Swiss albino mice after oral administration twice a week for 13 weeks. There were no changes in the studied parameters at doses of 100 and 200 mg/kg; however, at a dose of 400 mg/kg, increased serum levels and altered hematological parameters were observed. Based on these results, they reported that the methanol extract of *G. bonduc* had no adverse effects at 100 and 200 mg/kg doses.

Lilaram and Ahmed (2014) reported that the seed kernel of *G. bonduc* is protective of tissues by increasing the number of erythrocytes, leukocytes, platelet counts, hemoglobin levels, and packed cell volume. It also showed notable modifications in serum biochemistry levels, especially reduced cholesterol, triglyceride, and creatinine levels, while HDL levels were significantly increased in all the treated groups. Therefore, the ethanolic seed extract of *G. bonduc* likely possesses bioactive metabolites with cytoprotective potential and should be further explored as a source of natural remedies.

Likewise, the toxicity level of leaves and young twigs of *G. bonduc* was explored by Ogunlana et al. (2013) by studying the acute and subacute toxicological effects on albino rats after extraction with ethanol solvent. For the subacute trial, daily doses ranging from 200 to 1600 mg/kg body weight were orally administered for 28 days, and recovery was assessed for 14 days after extract administration. In contrast, doses ranging from 2000 to 5000 mg/kg were orally administered and observed for 14 days to assess acute toxicity. No deaths were observed in the test animals at any of the acute treatment doses, and significant changes in biomarkers and cellular damage to the liver were observed at all acute treatment doses. At a dose of 200 mg/kg of this plant extract of ethanol compared with the control, the biomarkers assessed were unaffected by acute toxicity. At a dose of 400 mg/kg, significant changes in biochemical parameters were observed in rats. Ogunlana et al. (2013) conclude that consuming an overdose of *G. bonduc* could be toxic to certain organs.

Conclusions

This overview reveals systematic research information on *G. bonduc* with regard to its ethnomedicinal, phytochemical, and pharmacological activities. Since ancient times, this plant has been traditionally used by tribes and indigenous people in different parts of the world to treat various health complications, evident in ethnomedical and ethnopharmacological applications. Especially, Indian medical systems such as Ayurveda, Unani, and Siddha have similar or different applications based on the processing of the drug formulation, and *G. bonduc* is commonly called Karanjwa in all three systems. Furthermore, since *G. bonduc* has antipyretic, antimicrobial, anti-inflammatory, and immunomodulatory effects, it has been recommended by the Indian Ayush Ministry to strengthen and relieve immunity against upper respiratory infections caused by the coronavirus. The different solvent extractions of *G. bonduc* have been extensively studied for their analgesic, anti-inflammatory, antioxidant, COVID-19, antidiabetic, abortifacient, anticataleptic, immunomodulatory, and anti-estrogenic effects. According to the *in vitro* and *in vivo* pharmacological findings, the *G. bonduc* extracts of ethanol, methanol, petroleum, and aqueous were found to have significant therapeutic effects.

To date, more than 120 phytochemicals have been isolated from the leaves, roots, stems, stem bark, flowers, young twigs, seed kernels, and seed cotyledons of this plant, using various solvents. Phytochemicals belong to the group of flavonoids, homoisoflavonoids, terpenoids, diterpenoids, steroids, fatty acids, alkanes, acids, phenols, ketones, esters, amides, azides, silanes, and ethers and were isolated. The phytochemicals listed in the supplementary data are already isolated and reported in many plants (Supplementary Data 1). However, some unique phytochemicals of *G. bonduc* such as Neocaesalpin H, Cordylane A, Bonducellpin E, Caesalls H, I, K and L, Neocaesalpin P, Neocaesalpins B, C, & D, Neocaesalpins C, Neocaesalpins D, Caesaldekarin A, C, H, I, J, K and L, Demethylcaesaldekarin C, Cordylane A, caesalpinolide-C, caesalpinolide-D, caesalpinolide-E, Caesalpinin B, D, H, J, K, Bonducellpin D, F and G, α-caesalpin, β-caesalpin, γ-caesalpin, δ-caesalpin, ε-caesalpin, caesalpin F, G and H, α-amyrin, Norcaesalpinin MC, caesalpinolide A, and caesalpinolide B have not been studied or reported against diseases demonstrated in ethnobotanical and ethnopharmacological applications and pharmacological properties. Therefore, such compounds need to be studied to know their pharmacological effects in terms of their ethnomedicinal and ethnopharmacological and pharmacological activities. To know the specific mechanisms of action of phytochemicals against the diseases studied in *in vitro* and *in vivo* using different solvent extracts of *G. bonduc*, the phytochemicals need to be studied using *in silico* strategy. Toxicity studies in pharmacology and traditional medicine must be performed to identify the specific enzymatic pathways that lead to side effects. This systemic review would be a good source of information about *G. bonduc* for those researchers willing to study *G. bonduc*. This review also indicates the need for further studies on the pharmacological effects of this plant to prove its therapeutic potential against certain deadly diseases.

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Declarations

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