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REVIEW ARTICLE

Phytochemistry and medicinal properties of *Psidium guajava* L. leaves: A review

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ABSTRACT

Psidium guajava L. (Myrtaceae), also known as guava, is a medicinal tree native to tropical America that has been introduced and is widely available in many countries. Almost all plant parts of *P. guajava* have a long history of being used to treat a variety of ailments, in addition to applications as foods. Guava leaves are used as both medicine and food purposes, and there are numerous scientific reports on their medicinal uses, chemical composition and pharmacological properties. Cancer, blood pressure, diarrhea, bowel irregularities, diabetes, cough, cold, constipation, dysentery, scurvy, weight loss, improves skins tonicity are some of the diseases treated with guava leaves. Polyphenols, flavonoids, saponins, tannins, terpenoids, glycosides, flavones, cardiac glycosides, cardenolides, phlobatanins, steroids and other classes of bioactive compounds have been identified from the leaves. The primary chemical constituents of guava leaves are phenolic compounds, iso-flavonoids, gallic acid, catechin, quercetin, epicathechin, rutin, naringenin, kaempferol, caryophyllene oxide, p-selinene etc. Several studies have demonstrated its pharmacological activities including antioxidant, antimicrobial, antidiabetic, antitumor, anticancer, antidiarrheal, healing, cytotoxic, hepatoprotective, anti-inflammatory, antimalarial/ anti-plasmodial, dental plaque, antiglycative and many more. This review is aimed on compiling all the literature reported on pharmacological activities and phytochemical compositions of guava leaves as a support to the scientific community for further studies and to provide scientific data to validate its traditional uses.

Abbreviations

ABTS: 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid, ADM: Adriamycin, CH_3Cl: Chloroform, CT: Cholera toxin, CUPRAC: Cupric ions (Cu^{2+}) reducing ability, DPPH: 1,1-diphenyl-2-picrylhydrazyl radical, ELISA: Enzyme-linked immunosorbent assay, ELISPOT: enzyme-linked immune spot, EtOH: Ethanol, FRAP: Ferric ion reducing antioxidant power, FC: Flavonoid content, GAE: Garlic acid equivalents, IL-6: Interleukin-6, LDH: Lactate dehydrogenase, LT: Labile toxin, MeOH: Methanol, MIC: Minimum inhibitory concentration, Min: Minutes, MTT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide, OGTT: Oral glucose tolerance test, ORS: Oral rehydration saline, PGE_2: Prostaglandin E_2, PMA: Phorbol myristate acetate, PSA: Prostate specific antigen, PTP1B: Protein tyrosine phosphatase 1B, QE: Quercetin equivalents, ST: Stable toxin, TBARS: Thiobarbituric acid reactive substances, TEs: Trolox equivalents, TPC: Total phenolic content, Tr: T regulatory.

Background

Psidium guajava L. also known as guava, is a fruit-bearing tree from the Myrtaceae family that is native to tropical America but is now grown throughout the tropics (1). *P. guajava* belongs to the

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Subclass: Rosidae
Order: Myrtales
Family: Myrtaceae
Subfamily: Myrtoideae

The bark is reddish brown, thin, smooth and flaky. The roots are extensive but only superficial. The fruit has a strong, sweet, musky odor and can be round, ovoid, or pear-shaped. The leaves are the most used

part of the plant, followed by the fruits, bark and roots (2).

The leaves are used in traditional system of medicines for febrifuge, antispasmodic, wounds, ulcers and toothache, rheumatism, gargle for sore throats, laryngitis and swelling of the mouth and externally for skin ulcers, vaginal irritation, discharge, vaginal and uterine wash, especially in leucorrhoea (3). They are also used to treat diarrhea, bacterial infections, blood cleansing, astringent, lung problems, dysentery, stomach pain, antibiotics, inflammations, diabetes management, hypertension, sores, boils, cuts and sprains, as well as a boiled preparation for itchy rashes caused by scabies (2-5).

Since most of the conventional medicinal drugs have been claimed for many unwanted effects, people are looking for alternative treatments based on plants. Therefore, strengthening research on pharmacological activities of medicinal herbs is highly important in order to validate its medicinal applications. Therefore, the aim of this review is to compile the most outstanding evidences based data on phytochemistry and pharmacological activity of *P. guajava* leaves that has been published over many years.

Phytochemistry of *P. guajava* leaves

Phytochemicals are classified as either primary or secondary metabolites, depending on their role in plant metabolism. Primary metabolites include common amino acids, sugars, proteins, nucleic acid purines, pyrimidines, etc. Terpenes, alkaloids, lignans, flavonoids, plant steroids, curcumines, phenolics, saponins, flavonoids and glucosides are examples of classes of secondary metabolites (6). Guava leaves contain a wide range of phytochemicals including flavonoids, saponins, alkaloids, tannins, terpenoids, polyphenols and glycosides (7). Guava leaf extracts and essential oil have been discovered to contain a variety of individual chemical constituents, which are listed in Table 1 and Table 2. The Fig. 1 shows some of the important phytochemicals found in guava leaves [Phenolic (gallic acid (8)), Flavonoid (quercetin (9)), Ellagitannins (corilagin (10)), Tannin (pedunculagin (11)) and Terpenoid (β-caryophyllene (12)) respectively.

Pharmacological activities of *P. guajava* leaves

It is important to emphasize that herbal medicines are chemically complex mixtures containing multiple major and minor constituents with multiple potential targets and mechanisms in pharmacological actions. In this review, we provide detailed analysis of pharmacological studies carried out for guava leaves by various researchers and their findings with relevant literature citations, the same is briefly summarized in the Table 3.

Antioxidant activity

Antioxidant refers to a compound that can delay or inhibit the oxidation of lipids or other molecules by inhibiting the initiation or propagation of oxidative chain reactions and which can thus prevent, or repair damage done to the cells of the body by reactive oxygen species or reactive species generated from molecular oxygen. They act by one or more of the following mechanisms: reducing activity, free radical-scavenging, potential complexing of pro-oxidant metals and quenching of singlet oxygen.

It was reported that antioxidant activity and TPC is high on the order of MeOH > butanol > ethyl acetate > hexane fractions of leaf extracts of guava (32). Further, the ABTS scavenging activities (mM TEs/mg extract): MeOH: 3.79 ± 0.003, butanol: 2.90 ± 0.023, ethyl acetate: 2.65 ± 0.065 and FRAP values (EC value, mM/mg extract): MeOH: 3.65 ± 0.038, butanol: 1.15 ± 0.132, ethyl acetate: 1.36 ± 0.032 were reported for corresponding solvent extracts of guava leaves (32). Another research work revealed the presence of guavinoside C, guavinoside F, quercetin, quercetin-3-O-a-L-arabinofuranoside, quercetin-3-O-a-L arabino-pyranoside, quercetin-3-O-b-D galactopyranoside, guavinoside A and guavinoside B in the leaves and they all showed potential antioxidant activity towards the DPPH, ABTS and FRAP assays (33). It was evaluated the TPC and FC of concentrated and spray dried leaf extracts of guava with significant free radical scavenging activity towards DPPH and PMA-stimulation assays (34). According to a study using lipid peroxidation assays of acetaminophen-treated rats (with reduced glutathione, catalase, glutathione peroxidase and superoxide dismutase activities) elevated levels of lipid peroxide were reduced using aqueous extract of leaves and the normalcy of glutathione peroxidase, glutathione, catalase and superoxide dismutase activities were also restored (35). There are published data on DPPH and FRAP of guava leaf extracts in different solvents and the results were summarized as follows (36). Total antioxidant capacity (based on FRAP): MeOH fraction: 4175.1 µmol and EtOH fraction: 1733.4 µmol. Free radical scavenging activity (based on DPPH) - MeOH: 85.8% > acetone: 80.8% > EtOH: 77.9% > ethyl acetate: 73.5% > Petrol ether: 51.9 % > benzene: 60.8% fractions. They also conducted CUPRAC and phosphomolybdenum assays and showed comparable antioxidant activities.

Antimicrobial activities

Antimicrobial activities of water extracts of guava leaves were analyzed using paper disc-diffusion method (37) and found that the extract inhibited the growth of both reference standard strains such as *Staphylococcus aureus* ATCC 25923 and *b-streptococcus* group A 1000s type 28. The extract showed a stronger inhibitory effect on growth of *S. aureus* than *b-streptococcus* for antibiotic susceptibility testing. There are reports on the antibacterial activity assessment of leaf extracts of guava against two gram-negative bacteria (*Escherichia coli* and *Salmonella enteritidis*) and two gram-positive bacteria (*S. aureus* and *Bacillus cereus*) using well-diffusion method (38). Antibacterial activities of MeOH and EtOH extracts against gram-positive bacteria were found to be inhibitory. MeOH extract had antibacterial activity against *B. cereus* and *S. aureus* with mean zones of inhibition of 8.27 mm and 12.3 mm respectively and EtOH extract had a mean zone of inhibition of 6.11 mm and 11.0 mm., while gram-negative bacteria were immune to all solvent extracts (MeOH, EtOH, hexane and water). It was found that antibacterial assays carried out against *E. coli, S.*

Table 1. Chemical constituents identified in *P. guajava* leaves extracts

Extracts Name	Chemical constituents Identified	References
Petroleum ether fraction	psiguadials A, psiguadials B, psidial A, guajadial	(13)
Methanolic water extract	guavinoside A, guavinoside B, guavinoside C, quercetin 3- O-α-L-arabinofuranoside, quercetin 3-O-α-L-arabinopyranoside, quercetin 3-O-β-D-xylopyranoside, quercetin 3-O-β-D-galactopyranoside, quercetin 3- O-β-D-glucopyranoside	(14)
Methanolic water extract	glutamic acid, asparagine, serine, 3-hydroxybutyric acid, acetic acid, citric acid, malonic acid, trans-aconitic acid, ascorbic acid, guanidoacetic acid, cis-aconitic acid, maleic acid, epicatechin, protocatechuic acid, xanthine	(15)
Toluene extract	guajanoic acid, β-sitosterol, uvaol, ursolic acid, oleanolic acid, betulinic acid, lupeol	(16)
n-butanol fraction	avicularin, guaijaverin, leucocyanidin, ursolic acid	(17)
Ethanol water extract	2,6-dihydroxy-3-formaldehyde-5-methyl-4-O-(6"-O-galloyl-β-D-glucopyranosyl)-diphenylmethane, 2,6-dihydroxy-3,5-dimethyl-4-O-(6"-O-galloyl-β-D-glucopyranosyl)-benzophenone, kaempferol, quercitrin, isoquercitrin, guaijaverin, avicularin, hyperoside, reynoutrin	(18)
Methanolic extract	(+)-gallocatechin	(19)
Aqueous extract	HHDP glucose isomer, HHDP glucose isomer, HHDP glucose isomer, gallic acid, prodelphinidin B2 isomer, pedunculagin/casuariin isomer, prodelphinidin dimer isomer, gallocatechin, prodelphinidin dimer isomer, geraniin isomer, pedunculagin/casuariin isomer, geraniin isomer, procyanidin B isomer, procyanidin B isomer, tellimagrandin I isomer, catechin, casuarinin/casuarictin isomer, tellimagrandin I isomer, gallocatechin, myricetin-arabinoside/xylopyranoside isomer, procyanidin B isomer 2, myricetin hexoside isomer, myricetin hexoside isomer, myricetin-arabinoside/xylopyranoside isomer, quercetin-galloylhexoside isomer, quercetin-galloylhexoside isomer, myricetin-arabinoside/xylopyranoside isomer, morin, myricetin-arabinoside/xylopyranoside isomer, ellagic acid, hyperin, quercetin glucuronide, isoquercitrin, reynoutrin, guajaverin, guavinoside A, avicularin, guavinoside C, guavinoside B, guavinoside A isomer, prodelphinidin B2 isomer 2, guavinoside B isomer, guavinoside B isomer, guavinoside B isomer, guavin B, quercetin, naringenin	(20)
Aqueous extract	esculin, quercetin, gallocatechin, 3-sinapoylquinic acid, gallic acid, citric acid, ellagic acid	(21)
Petroleum ether, ethyl acetate, and n-BuOH extracts	2α,3β,6β,23,30-pentahydroxyurs-11,13(18)-dien-28,20β-olide, ehretiolide, ilelatifol D, guavenoic acid, 3β-O-cis-p-coumaroyl actinidic acid, corosolic acid, asiatic acid, brahmic acid, ursaldehyde, 3β-O-cis-pcoumaroyl corosolic acid, 3β-O-trans-p-coumaroyl corosolic acid, 3β-Ocis-p-coumaroyl asiatic acid, 3β-O-trans-p-coumaroyl asiatic acid, alphitolic acid, oleanolic acid, maslinic acid, arjunolic acid, terminolic acid, oleanoaldehyde, 3β-O-cis-p-coumaroyl maslinic acid, 3β-O-trans-p-coumaroyl maslinic acid, 3β-O-cis-p-coumaroyl arjunolic acid, 3β-O-trans-p-coumaroyl arjunolic acid	(22)
Ethanol water extract	caffeic acid, ferulic acid, cinnamic acid, resorcinol, chlorogenic, syringic acid, resormarinic acid, hesperetin, kaempferol, rutin, apigenin, corilagin, kaempfertin, isoquinoline	(23)
Acetone water extract	procyanidin B1, pedunculagin, castalagin, casuarinin, stenophyllanin A, hyperin, isoquercitrin, quercetin-3-O-β-D-glucuronide, ellagic acid	(24)
Ethanolic extract	morin-3-O-α-L-lyxopyranoside and morin-3-O-α-L-arabopyranoside, guaijavarin	(25)

Table 2. Chemical constituents identified in essential oil of *P. guajava* leaves

Extraction method	Chemical constituents identified	References
Hydro-distillation	3-hexenol, 2-hexenol, hexanal, 2-hexenal, benzaldehyde, 3-hexenyl acetate, 6-methyl-5-hepten-2-one, linalool, α-fenchol, trans-pinocarveol, borneol, terpinen-4-ol, α-terpineol, (E)-nerolidol, spathulenol, globulol, ledol, α-cadinol, caryophyllenol, farnesol, α-fenchyl acetate, bornyl acetate, neryl acetate, geranyl acetate, pinocarvone, 1,8-cineole, caryophyllene oxide, α-thujene, α-pinene, camphene, β-pinene, myrcene, α-phellandrene, α-terpinene, ρ-cymene, limonene, (Z)-β-ocimene, γ-terpinene, terpinolene, allo-ocimene, α-muurolene, α-copaene, β-caryophyllene, aromadendrene, α-humulene, allo-aromadendrene, (Z)-α-bisabolene, β-bisabolene, δ-cadinene, (E)- γ-bisabolene	(26)
Hydro-distillation	α-pinene, β-pinene, δ-2-carene, α-phellandrene, α-terpinene, p-cymene, limonene, 1,8-cineole, cis-β-ocimene, trans-β-ocimene, γ-terpinene, terpinolene, *allo*-ocimene, α-terpineol, carvacrol, α-copaene, α-gurjunene, β-caryophyllene, β-copaene, aromadendrene, α-humulene, γ-gurjunene, chamigrene, muuroladiene, germacrene D, β-selinene, α-selinene, valencene, δ-cadinene, α-calamenene, α-calacorene, germacrene B, viridiflorol, spathulenol, β-caryophyllene-oxide, daucol, cedr-8(15)-en-9-ol, cubenol, δ-cadinol, cadalene, selin-7(11)-en-4-α-ol, α-santalol	(27)
Hydro-distillation	1,8-Cineole, (-)-a-copaene, β-Bourbonene, β-Elemene, Trans-caryophyllene, β-cubebene, (+)-aromandrene, α-humulene, β-humulene, 1H-cycloprop[e]azulene, germacrene D, calarene, trans—bisabolene, Δ-cadinene, (+)-spathulenol, caryophyllene oxide, veridiflorol, α-cadinol, valerenol, hexadecanoic acid, isomaturnin	(28)
Hydro-distillation	1-hexanol, α-pinene, camphene, β-pinene, myrcene, α-phellandrene, ρ-cymene, limonene, E-β-ocimene, γ-Terpinene, ρ-cymenene, terpinolene, terpinen-4-ol, α-terpineol, E-piperitol, thymolmethyl ether, bornyl acetate, neryl acetate, α-longipinene, α-copaene, 2,6-dimethoxylcymene, isocaryophyllene, β-caryophyllene, aromadendrene, α-humulene, allo-aromadendrene, 4,5-di-epi-aristolochene, γ-muurolene, β-selinene, α-selinene, β-bisabolene, γ-cadinene, trans-calamenene, δ-cadinene, cadina-1,4-diene, α-calacorene, (E)-nerolidol, caryophyllene oxide, viridiflorol, 1-epi-cubenol, τ-cadinol, α-cadinol	(29)
Steam distillation	α-pinene, β-pinene, β-myrcene, p-cymene, 1 ,8-cineole, borneo, terpinen-4-ol, α-terpineol, verbenone, bornyl acetate, α-copaene, β-caryophyllene, aromadendrene, α-humulene, allo-aromadendrene, myristicin, cedrenol, globulol, ledol	(30)
Supercritical fluid extraction	n-octane, m-xylene, 1,8-cineole, β-phellandrene, α-copaene, β-caryophyllene, aromadendrene, gcrmacrene-D, β-selinene, α-selinene, δ-sclinene, (E)-nerolidol, (E)-nerolidol, caryophyllene epoxide, δ-cadinol, allo-aromadendrene, ethyl hexadecanoate	(31)

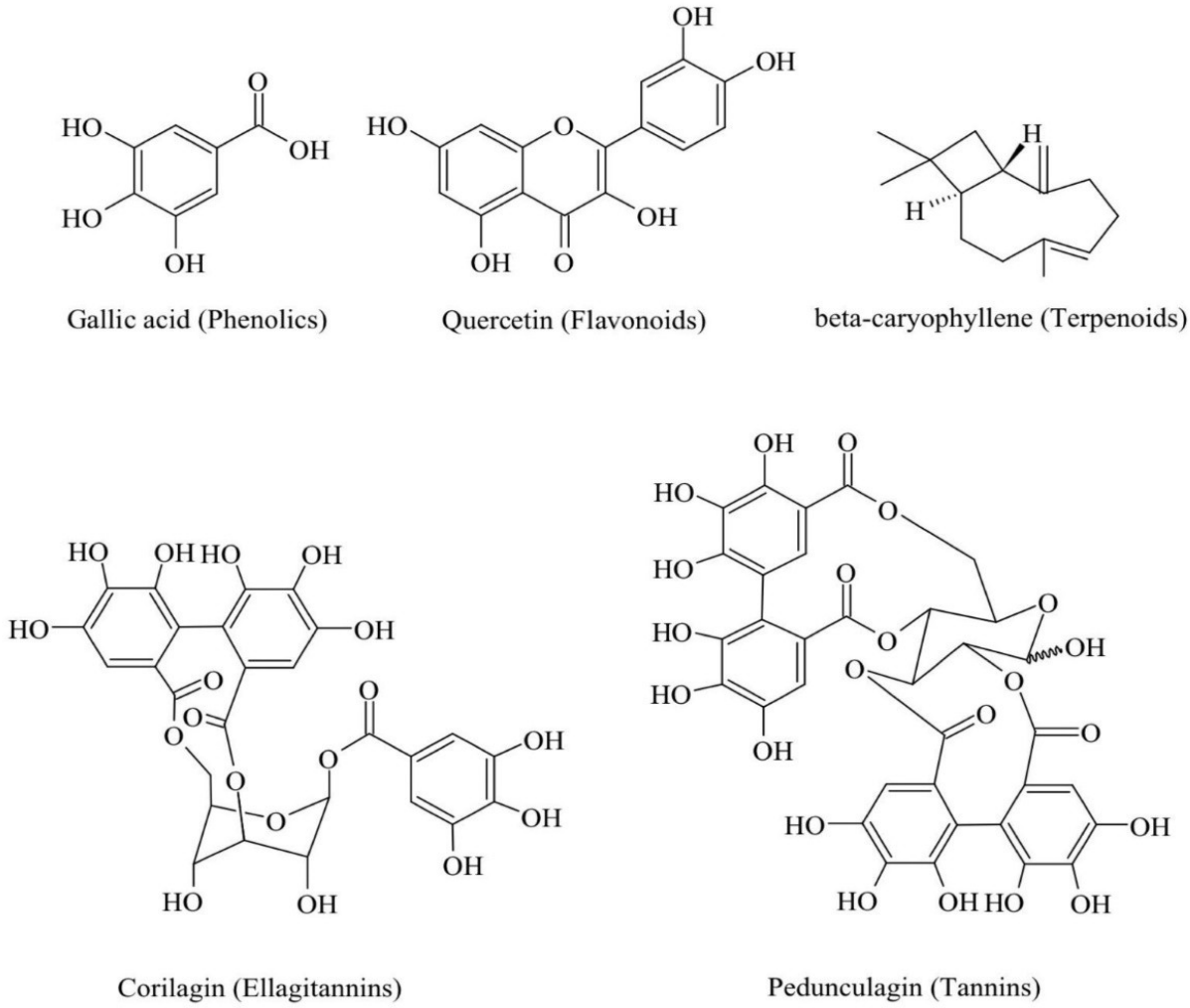

Fig. 1. Some of the important phytochemicals found in guava leaves.

aureus, Vibrio cholerae, Salmonella typhi, Pseudomonas aeruginosa using agar diffusion and broth dilution methods showed that MeOH extract is toxic to all the bacteria tested, but *S. typhi* is most sensitive, with a zone of inhibition: 2 mm at 4 mg/ml (39). In another antibacterial study conducted it was claimed that the aqueous extract of guava leaves is more effective than organic extracts at inhibiting the growth of pathogenic microorganisms (*E. coli, S. pyogenes, S. aureus, P. aeruginosa* and *Proteus mirabilis*) (40). Furthermore, gram-negative bacteria were more resistant to the effects of crude drugs. The crude extracts are more effective under acidic conditions and at low temperatures, according to diameters of growth inhibition zones. Several other works on antibacterial activities based on agar disc diffusion method revealed that MeOH and water extracts of guava leaves inhibited the growth of the all the tested bacteria (*Salmonella typhimurium, Streptococcus suis, E. coli* and *Pasteurella multocida*), but acetone extract exhibited inhibition zones only in colonies of *S. suis* and *P. multocida*. MeOH and water extracts had the same MIC against *P. multocida* (0.156 mg/ml), *E. coli* (5 mg/ml), and *S. typhimurium* (5 mg/ml), while acetone extract only inhibited the growth of *S. suis* and *P. multocida* with a MIC of 0.312 mg/ml (41). Another two groups published their antibacterial assay data as follows. It was reported that, in agar diffusion method both aqueous and MeOH extracts of guava leaves showed strong antibacterial activity against *multidrug-resistant V. cholerae* (42). MIC of both extracts: 1250 mg/ml and 850 mg/ml, respectively against 107 CFU/ml of *V. cholerae*. The antibacterial activity of extract is stable at 100 ^{0}C for around 15-20 min, indicating active components are nonprotein. When 10 mg/ml (wt/v) of crude aqueous mixture was premixed with ORS in the ratio of 1:7 (volume extract/volume ORS), *V. cholerae* growth in rice ORS was fully inhibited. Interestingly, Agar disc diffusion method was used to analyze antifungal property of guava leaf extracts against *Trichophyton tonsurans, Trichophyton rubrum, Candida albicans, Sporotrix schenckii, Candida parapsilosis, Cryptococcus neoformans* and *Microsporum canis* (43). Results revealed that the hexane extract showed the strongest antifungal activity, being active against all the dermatophytes tested. Relative activity was also found in MeOH and acetone extracts.

Antidiabetic activity

It was reported that the *in vitro* studies on antidiabetic properties of guava leaf extracts that they inhibited both α-amylase and α-glucosidase enzymes (44).

Further the extracts inhibitory effect increases in a dose-dependent manner on α-glucosidase enzyme up to 89.4% and α-amylase enzyme up to 96.3 % and later publication from the same group revealed the inhibition of α-amylase and α-glucosidase enzymes by aqueous and EtOH extracts are as follows. α-amylase: 72.1 and 97.5 % and α-glucosidase: 74.8 and 91.8 % respectively (45). With the aid of PTP1B enzyme assay, it was reported that the antidiabetic properties of guava leaf extracts where PTP1B values were significantly inhibited by extract and histological examination of liver of *Leprdb/Leprdb* mice treated with butanol soluble fractions revealed large reductions in the amount of lipid droplets as compared to control mice (46). OGTT model and alloxan induced diabetic test model showed doses of 1.00 g/kg and 0.50 g/kg of extracts significantly ($P<0.05$) decreased blood glucose levels in the oral glucose tolerance test-model as well as 0.75 g/kg dose in alloxan induced diabetic test-model in Wister rats $P<0.001$ (47).

It is noteworthy to report on anti-hyperglycemic activities of guava leaf extracts; Anti-hyperglycemic potential against alloxan induced diabetes in rats are high in fresh leaf extract than in dry leaf extract (48). Reports are on the comparison of the anti-hyperglycemic properties of leaf extract to those of acarbose, a widely used diabetic medication (49). Extract had IC_{50} values of 50.5 µg/ml for α-amylase inhibition and 34.6 µg/ml for α-glucosidase inhibition *in vitro* respectively. However, the IC_{50} values of acarbose, for inhibiting α-amylase and α-glucosidase were 95.3 µg/ml and 1075.2 µg/ml respectively. Finally, the anti-hyperglycemic effect of extract obtained under optimal extraction conditions was higher than that of acarbose. Interestingly, hypoglycemic activity of leaf extracts of guava has also been reported (50) where they have observed statistically significant hypoglycemic activity at 250 mg/kg oral dose on alloxan induced hyperglycemia by MeOH extract of guava leaves in both acute and subacute tests.

Antitumor and anticancer activities

Studies are on the antitumor activities of guava extracts by cell proliferation and ELISPOT assays where, addition of extract to CD4+ splenocytes of C57BL/6 mice with blocked induction of Tr cells by IL-10 *in vitro*, showed the extracts had only a mild/ no effect on production of both Th1 and Th2 cells (51). Tr cells have not been induced in splenocytes of mice when extracts were given orally. Extracts moved the Th1/ Th2 equilibrium to a Th1 dominant state by inhibiting Tr cell activity. Using different analysis techniques such as cell viability and expression of PSA, LDH release assay, cell cycle analysis, TUNEL assay for determination of apoptosis, western blotting analysis, gelatinolytic zymography and treatment in LNCaP prostate cancer xenograft model in nude mice, Another report showed that the aqueous extracts of guava leaves inhibit LNCaP cell growth by inducing cytotoxicity and apoptosis (52). Further it inhibited androgen receptor expression by downregulating phospho-Akt, upregulating phospho-p38 and phospho-ERK1/phospho-ERK2 and arresting the cell cycle at the G1 phase. Extract significantly reduced serum PSA levels and tumor sizes in a xenografted cancer animal model. From a study that analyzed anticancer properties of leaf extracts of guava against HeLa cell-lines, anti-cancer response with 200 µg/ml of both MeOH and CH_3Cl extracts, showing 81 % and 91 % inhibition respectively, while regular drug, doxorubicin, showed about 76 % inhibition. In comparison, CH_3Cl extract obtained better results than MeOH extract (53).

On final account Zhu and co-workers reported following data obtained for three potent components identified from the extract: guavinoside B, guavinoside E and 3,5-dihydroxy-2,4-dimethyl-1-O-(6'-O-galloyl-β-D-glucopyranosyl)-benzophenone on cell viability, colony formation assays, analysis of apoptosis by flow cytometry and immunoblotting. Cell viability assay: two compounds isolated had inhibited the growth of HCT-116 human colon cancer-cell in a dose dependent manner, where one compound was more potent than the other. Cytometry analysis: one compound showed stronger activity in inducing cellular apoptosis in the cancer cells than the other. Specifically former compound increased the levels of p-ERK1/2, p53, p-JNK and cleaved caspases 8 and 9 and later compound increased the levels of p53 and cleaved caspase 8 (54).

Antidiarrheal activity

With the aid of antibacterial assays (microtiter plate-based assay), effect on bacterial colonization: effect on adherence, effect on invasion, effect on bacterial enterotoxins: effect on *E. coli* heat LT and CT, effect on ST, activity against diarrhea causing bacteria was studied (55). They have reported; Decoction of leaves had antibacterial activity against *V. cholerae* and *Shigella flexneri*. It reduced the development of CT and LT, as well as their binding to GM1. It had no effect on development of stable toxin. Decoction also inhibited enteropathogenic *E. coli* adherence and invasion of HEp-2 cells by both enteropathogenic *E. coli* and *S. flexneri* while quercetin not showing any effect. Similar antimicrobial activity of extracts was done by another group using standard cultures of *S. aureus* (ATCC 6538) and *E. coli* (ATCC 15597). Diarrhea inhibition was dose-dependent and comparable to standard medication, as calculated by percentage faucal production relative to positive control. The gastrointestinal motility of extract was also reduced, as determined by the distance traveled by a charcoal plug in the small intestine. The anti-diarrhea effect of extract was thus mediated by a combination of antimicrobial activity and a decrease in gastrointestinal motility (56). Castor oil-induced diarrhea model and gastrointestinal motility test with barium sulphate milk model were carried out and it was reported that EtOH extract of leaves of guava showed antidiarrheal activity at doses of 750 mg/kg and 500 mg/kg based on the castor oil induced diarrhea model ($P<0.001$ and $P<0.01$ respectively) and 750 mg/kg ($P<0.01$), 500 mg/kg and 250 mg/kg ($P<0.05$) doses in the barium sulphate milk model (47).

Healing and cytotoxic effects

It has been reported that guava leaf extracts have potential wound healing activity. Reports are on the *in vivo* clinical and histological evaluation of traumatic lesions in the oral mucosa of rats treated with selected

substances (57). Following data were reported for cytotoxic studies of guava leaf extracts (33). Cytotoxic activities of isolated compounds from guava leaves such as guavinoside A, B, C, D, E and F, quercetin, quercetin-3-O-α-L-arabinofuranoside, quercetin-3-O-α-L-arabinopyranoside and quercetin-3-O-β-D-galactopyranoside were investigated by MTT assay in vitro on SGC-7901, A549 and HeLa cells respectively. Compared with ADM, which gave the IC_{50} values of 1.359 μg/ml 3.118 μg/ml and 2.684 μg/ml against SGC-7901, A549 and HeLa cell lines respectively. The new compound guavinoside C presented obvious inhibition effect on the SGC-7901, A549 and HeLa with the IC_{50} values of 4.277 μg/ml, 7.288 μg/ml and 3.246 μg/ml respectively and compound guavinoside F showed similar significant activity. Quercetin exhibited moderate inhibition against the SGC-7901 and HeLa with the IC_{50} values of 7.878 μg/ml and 8.260 μg/ml respectively. The other remaining compounds were not responsible clearly for cytotoxicity analysis at sample concentration less than 10 μg/ml (33).

Hepatoprotective activity

Serum biochemical assays and histopathological examinations of acetaminophen-treated rats (with elevated aspartate aminotransferase, alkaline phosphatase, alanine aminotransferase, total bilirubin and lowered total protein levels) showed at 500 mg/kg doses of aqueous extract of leaves reduced the elevated levels of all these biochemical parameters and significantly restored total protein normalcy (35). In acetaminophen-treated rats, lipid peroxidation increased significantly in the liver tissue, while reduced glutathione, catalase, glutathione Peroxidase and superoxide dismutase activities decreased. At doses of 500 mg/kg, aqueous extract reduced elevated levels of lipid peroxide and restored glutathione peroxidase, glutathione, catalase and superoxide dismutase to usual (35). It was showed in alcohol-injured clone 9 cell viability and ALT (Hepatoprotective Assay) assays extract had a strong hepatoprotective effect on alcohol-induced liver cell injury at concentrations of 100 μg/ml or less (5 % alcohol for 30 min) (58). The viability of cells has been shown to be reduced when ethanol concentrations are high. However, due to its higher hepatoprotective and lower cytotoxic influence, the protection provided by the hot water plant extract appears to be greater than that provided by the other plant extracts. The cytotoxic activity of extract is invariably induced at higher concentrations; hence, cautious administration is recommended.

Anti-inflammatory activity

In anti-inflammatory studies done using egg albumin (IC_{50}: 15.625 μg/ml) and bovine serum albumin (IC_{50}: 50 μg/ml), the leaf extracts showed the greatest inhibition at concentrations of 125 μg/ml and 500 μg/ml respectively. In the Bovine serum albumin denaturation test, the anti-inflammatory activity was equivalent to the reference drug, Diclofenac sodium and in the egg albumin denaturation test, it was 30-fold higher than the reference drug (59). Using nitrite assay, measurement of PGE_2 and IL-6 levels, ELISA, reverse transcription-polymerase chain reaction, western blot analysis, thermal hyperalgesia assessment and survival study, it was reported that guava leaf extract significantly inhibited lipopolysaccharide-induced nitric oxide and PGE_2 production in a dose-dependent manner (60). Extract inhibited the expression and function of both inducible nitric-oxide synthase and cyclooxygenase-2 in RAW264.7 macrophages by inhibiting ERK1/2 activation. Furthermore, in two separate animal models, the extract showed strong anti-inflammatory activity (60). There are studies on anti-inflammatory activity against acute inflammation, subacute inflammation and chronic inflammation using four groups of mice [control; Group-A (3 % *gum acacia* in 10 ml/kg body weight) there were major inhibitions of paw edema in Group-B (PGE 250 mg/kg body weight), Group-C (PGE 500 mg/kg body weight) and the standard; Group-D (Aspirin 100 mg/kg body weight)] in the acute inflammation ($P<0.05$) (61). In contrast to Group-A, there were major inhibitions of exudate formation in Group-B, Group-C and Group-D during subacute inflammation. In the chronic inflammation study, the Groups-B, Group-C and Group-D showed substantial inhibition of paw edema and weight loss as compared to the Group-A. In contrast to Group-A, downregulation of the arthritis index was also notable in Group-B, Group-C and Group-D. Another research group reported leaves extract decreased inhibitory activity by 40.81 %, 55.45 % and 43.61 % respectively at doses of 125, 250 and 500 mg/kg body weight in carrageenan induced rat paw edema. According to this report, leaf extract has anti-inflammatory properties by reducing edema (62).

Antimalarial property/ Anti-plasmodial activity

Many studies have claimed Antimalarial property/ Anti-plasmodial activity of guava leaf extracts where, EtOH extract has anti-plasmodium activity *in vitro* and *in vivo*. Antimalarial activity of EtOH extract: ED_{50} (mg/kg body weight): 274.69 ± 7.65, IC_{50} (μg/ml): 0.6250 ± 0.2100 (63). In another antimalarial assay *in vitro* IC_{50} (μg/ml) value of dried guava leaf extract was 8 μg/ml for *Plasmodium berghei* while the (IC_{50}, μg/ml) of fresh guava leaf extract for *P. berghei* 8.2 μg/ml. dried guava leaf extract showed higher antimalarial activity than fresh leaf extract (64). Polyherbal formulation with several different plant extracts along with guava leaf extract “Nefang” has shown excellent *in vivo* antimalarial activity against *Plasmodium berghei* and *Plasmodium chabaudi* parasites in acute (single dose) oral toxicity, suppressive activity (Peter’s 4-day test), prophylactic activity and curative activity (Rane’s test) testing (65).

Dental Plaque

Under stressed growth environments, the aqueous extract exhibited bacteriostatic effects on early dental plaque bacteria such as *S. mitis, S. sanguinis* and *Actinomyces* sp. The bacteria appeared to be unable to perform normal biological functions and ultimately ceased to propagate. Exologically, such event will regulate the formation of dental plaque (66). The treatment of early plaque settlers with a 1 mg/ml extract decreased the cell surface hydrophobicity of *S. mitis, Actinomyces sp.* and *S. sanguinis* by 49.9%, 40.6 % and 54.1 % respectively. It was also discovered that the plant extract's anti-adhesive effect on blindness of

the early plaque settlers to the hexadecane is confounding (67).

Antiglycation effect

A group working on kinetic studies on antiglycation effects in physio mimic systems recorded that aqueous extract (0.01–0.625 mg/ml) of guava leaves was having special inhibitory characteristic on LDL glycation effect due to its high polyphenolic content (165.61 10.39 mg GAE/g) by determination of TBARS and TPC (68). To summarize, aqueous extract is an excellent anti-LDL glycate agent with possible therapeutic applications in the prevention of a range of cardiovascular and neurodegenerative diseases linked to glycations. It was also reported that leaf extract has shown potential antiglycative activity in a bio-model of low-density lipoproteins, which can be due to its higher polyphenolic content of leaves (69). The dose-dependent inhibition models were validated using computer simulation. Extract contains a high concentration of polyphenolic compounds Catechin, gallic acid, epicatechin, quercetin, rutin, kaempferol and naringenin are the seven main compounds present in guava leaf extract., whose antiglycative bioactivity is consistent with the inhibition models (kinetic studies) using TBARS studies (69).

Table 3. Summary of pharmacological activities and types of guava leaf extract used for the analysis with the references.

Pharmacological activities	Type of extract used	References
Antioxidant activity	Ethanol, aqueous, petroleum ether, benzene, ethyl acetate, methanol extracts	(32-36)
Antimicrobial activity	Aqueous, ethanol, methanol, hexane, acetone extracts	(37-43)
Antidiabetic activity	Methanol, aqueous, ethanol, hexane, petroleum ether, chloroform, butanol, ethyl acetate extracts	(44-50)
Antitumor and Anticancer Activities	Ethanol, aqueous, methanol, chloroform extracts	(51-54)
Antidiarrheal activity	Ethanol, aqueous extracts	(47, 55-56)
Healing and cytotoxic effects	Ethanol extract	(33, 57)
Hepatoprotective activity	Aqueous, acetone, ethanol extracts	(35, 58)
Anti-inflammatory activity	Aqueous, ethanol extracts	(59-62)
Antimalarial property/ Anti-plasmodial activity	Ethanol, aqueous extracts	(63-65)
Dental Plaque	Aqueous extract	(66-67)
Antiglycation effect	Aqueous extract	(68-69)

Table 3 summarizes individual pharmacological activities, the nature of the extracts and the corresponding references discussed above. This review will be the first and comprehensive scientific repository of guava leaves as this gives a broad analysis of phytochemistry and pharmacological activity of guava leaf including chemical compositions of different guava leaf extracts and essential oil, and pharmacological activities with sufficient proven data.

Conclusion

This review provides literature data on in-depth studies of Guava (*P. guajava*) leaves for biochemical composition and pharmacological activities. In general, it contains a variety of chemical constituents such as alkaloids, polyphenolic compounds, saponins, tannins, flavonoids, terpenoids, carbohydrates, lipids, fats and oils, as well as various types of glycosides, amino acids, etc. Furthermore, structure elucidation of biochemicals present in guava leaves revealed that the plant contains a plethora of chemical compounds such as catechin, quercetin, gallic acids, epicathechin, rutin, naringenin, kaempferol, caryophyllene oxide, p-selinene and others. Because of the presence of such a diverse range of chemicals, this priceless plant has a wide range of pharmacological activities that could be beneficial in treating a variety of health conditions. This review is merely an attempt to compile some of them, and as stated under its pharmacological properties, the leaf extracts have the ability to act as an antioxidant, antimicrobial, antidiabetic, antitumor, anticancer, antidiarrheal, healing, cytotoxic, hepatoprotective, anti-inflammatory, antimalarial/ anti-plasmodial, dental plaque, antiglycative and so on. This would help researchers to quickly select literature on a specific topic of interest. To sum up, guava leaves are multifunctional medicinal green sources with a diverse array of potent secondary metabolites.

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Authors' contributions

All the authors have contributed for collecting research literature and preparation of the manuscript.

Compliance with ethical standards

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