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Phytopharmacological overview of *Psidium guajava* Linn.

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**ABSTRACT**

*Psidium guajava* Linn. possesses useful medicinal benefits. It has been recognized as the medicinally essential phytoconstituents, such as phenolic, flavonoid and carotenoid. Numerous pharmacological investigation have confirmed that the ability of this plant to exhibit antimicrobial, antidiabetic, cardio-protective, neuroprotective, hepatoprotective, antioxidant and anticancer activities and it supports the traditional uses. This is a comprehensive of the phytoconstituents and pharmacological benefits.

**Key words:** *Psidium guajava*, Antimicrobial, Antidiabetic, Antioxidant, Hepatoprotective, Anticancer.

**INTRODUCTION**

*Psidium guajava* Linn. is commonly called guava, goyave in French; guave, guavenbaum, in German; goiaba, in Portuguese; arac, guaiaba in Brazil; and guava in English.¹ *P. guajava* used as an important food as well as a medicinal plant in tropical and subtropical countries, therefore its nickname as the poor man’s apple. The scientific evidences of the medicinal uses of *P. guajava* began in 1940’s and reports, maintain a tradition of repeating the data each decade.

Many people habitually take *P. guajava* leaf decoction for its antispasmodic and antimicrobial properties for the treatment of dysentery and diarrhea.² Therefore, the efficacy and safety of *P. guajava* leaves have empirically been confirmed.³ *P. guajava* leaf contains plenty of phenolic compounds which inhibit the peroxidation reaction in the body, and so it can be expected to prevent various chronic diseases such as diabetes, cardiovascular disease and cancer.⁴ Furthermore, decreasing of free radicals in the body, means that the polyphenols in the leaf of *P. guajava* can prevent atherosclerosis, cataract and also inhibits biological aging of the body and skin.⁵

*P. guajava* leaves contain triterpenes, cineole and tannins. Additionally, three lavonoids (avicularin, guaijaverin, and quercetin) have been isolated from the leaves. In mature leaves, the greatest concentrations of flavonoids are found in: Quercetin>Myricetin>Kaempferol>Luteolin.⁶ Most of the medicinal activities of *P. guajava* are credited to the flavonoids and these phytoconstituents are well-known for their multi-directional medicinal activities. This review focuses on the phytochemical and pharmacological benefits of *P. guajava* from the internet data base PubMed and the most relevant articles are considered for review.

**PHYTOCHEMISTRY OF LEAVES**

Matsuo et al.⁷ isolated (+)-gallocatechin from the MeOH-extract of *P. guajava* leaves. *P. guajava* leaves contains various components such as, menthol, α-pinene, β-bisabolene, β-pinene, β-copanene, limonene, terpenyl acetate, isopropyl alcohol, caryophyllene, longicylecine, cineol, caryophyllene oxide, humulene, farnesene, selinene, curcumene and cardinene.⁸ The sixteen carotenoids identified are phytofluene, (all-E)-, (9Z)-, (13Z)-, and (15Z)-beta-carotene, (all-E)-gamma-carotene, (all-E)-, (9Z)-, (13Z)-, and (15Z)-lycopene, (all-E,3R)-beta-cryptoxanthin, (all-E, 3R)-rubixanthin, (all-E,3S,5R,8S)-cryptoflavin, (all-E,3R,3′R, 6′R)-lutein, (all-E,3S,5R,6R,3′S,5′R,8′R)-, and (all-E,3S,5R,6R,3′S,5′R,8′S)-neochrome.⁹ Guavanoic acid, guavacoumaric acid, 2α-hydroxyursolic acid, isonericoumaric acid, jacoumaric acid, asiatic acid, ileatilof d and β-sitosterol-3-O-β-D-glucopyranoside have also been isolated from the leaves of *P. guajava*.¹⁰

Two triterpenoids, guavanoic acid (20β-acetoxy-2a, 3β-dihydroxyurs-12-en-28-oic acid), and guavacoumaric acid (2a, 3β-dihydroxy-24-p-z- coumaroyloxyurs-12-en-28-oic acid), along with six known compounds asiatic acid, jacoumaric acid, 2α-hydroxyursolic acid, isonericoumaric acid, β-sitosterol-3-O-β-D-glucopyranoside, and ileatilof d, have been isolated from the leaves of *P. guajava*.¹¹ Two new triterpenoids, guaivalide (2a-, 3β-6β, 23-tetrahydroxurs-12-en-28-oic acid), and guave-noic acid (2 alpha,3 beta,23-tetrahydroxyurs-12,20(30)-dien-28-oic acid), are also isolated along with one known triterpene oleanolic acid from fresh leaves of *P. guajava*.¹²

Begum et al.¹³ isolated three pentacyclic triterpenoids including one new guavanoic acid and two known obtusin and goresishic acid I from the leaves of *P. guajava*. Five constituents, including one new pentacyclic triterpenoid guajanoic acid and four known compounds beta-sitosterol, uvaol, oleanolic acid, and ursolic acid have been isolated from the leaves of *P. guajava*.¹⁴ One new pentacyclic triterpenoid psidiumoic acid along with four known compounds beta-sitosterol, obtusol, oleanolic acid, and ursolic acid have been isolated from the leaves of *P. guajava*.¹⁵ Guajacial is a novel compound isolated carophylleene-based meroterpenoid compound, from the leaves of *P. guajava*.¹⁶

Ghosh et al.¹⁷ isolated betulinic acid and lupeol from the leaf extract of *P. guajava*. Shu et al.¹⁸ isolated ellagic acid-4-O-beta-D-glucopyranoside and quercetin-3-O-(6′-galloyl) beta-D-galactopyranoside from *P. guajava* for the first time, and 1-O-(1, 2-propanediol)-6-O-galloyl-beta-D-glucopyranoside is a new polyhydroxyl compound. Metwally et al.¹⁹ isolated five flavonoidal compounds from *P. guajava* leaves (quercetin, quercetin-3-O-β-D-arabinofuranoside, quercetin-3-O-β-D-glucopyranoside, quercetin-3-O-β-D-glucoside and quercetin-3-O-β-D-galactoside). (±)-Guajadal B, an unusual humulene-based meroterpenoid, is isolated as a racemate from the leaves of *P. guajava*.¹⁹
Ryu et al\textsuperscript{20} identified 60 compounds in a hexane fraction of \textit{P. guajava}, including β-eudesmol, α-copaene, phytol, α-lAthachone, β-caryophyllene oxide, caryophylla-3(15),7(14)-di-en-6-ol, (E)-methyl isoeugenol, α-terpineol, and octadecane. Shao et al\textsuperscript{21} isolated and identified clove-2 beta, 9 alpha-diol, 2 beta-acetoxyclavan-9 alpha-ol, 9 beta-diol, ent-1 murolol, clor-2-ene-9 alpha-ol, (+)-globulol, (+)-carylone-1, isophytol, gossypetin, tamarixin, kaempferol, guajaverin, quercetin, avicularin, chrysin 6-C-glucoside, guavinoside A, guavinoside B 3’-O-methyl-3, 4-methylenedioxyellagic acid 4’-O-beta-D-glucopyranoside and p-hydroxy-benzoic acid.

**ANTIMICROBIAL ACTIVITY**

\textit{P. guajava} leaf extract (2 and 5 g/kg) reduced the occurrence of cough induced by capsaicin aerosol by 35 and 54%, respectively, within 10 min after injection of the extract. The growth of \textit{Staphylococcus aureus} and \textit{beta-streptococcus} group \textit{A}, is inhibited by aqueous, methanol and chloroform extract of dry \textit{P. guajava} leaves. Therefore \textit{P. guajava} leaf extract may be recommended for cough.\textsuperscript{22} Vieira et al\textsuperscript{23} have reported the antibacterial effect of \textit{P. guajava} leaves extracts and found that they inhibited the growth of the \textit{S. aureus}.

The methanolic plant leaf extracts of \textit{P. guajava} and barks of this plant have antimicrobial activity. The organism inhibited is \textit{Salmonella} species, \textit{Bacillus} species, and the concentrations vary according to the organisms.\textsuperscript{24} The microbicidial activity of \textit{P. guajava} is attributable to guajaverine and to psydlic acid. The active flavonoid compound guaijaverin extracted from the leaves of the same plant is reported to have high potential antiplaque activity.\textsuperscript{25}

The \textit{in vitro} antibacterial activity of \textit{P. guajava} leaf extracts of \textit{S. aureus} is possibly due to protein degrading activity of the extracts.\textsuperscript{26} \textit{P. guajava} leaves flavonoids are also shown to have bacteriostatic effects on fish pathogenic bacteria.\textsuperscript{27} \textit{P. guajava} and \textit{Azadirachta indica} indica extracts showed higher antimicrobial activity food borne pathogens of Gram–positive bacteria than Gram–negative bacteria (except for \textit{Vibrio parahaemolyticus}, \textit{Pseudomonas aeruginosa}, and \textit{Acromonas hydrophila}).

The γ-terpinene and γ-pinene obtained by hydro distillation showed antimicrobial activity against \textit{Propionibacterium acnes}.\textsuperscript{28} Minimum inhibitory concentration is found in the methanolic (625 ug/ml) and aqueous (7.5 mg/ml) leaf extracts of \textit{P. guajava} and minimum bactericidal concentration recorded for methanolic (1.25 mg/ml) and aqueous extracts (12.5 mg/ml) against multidrug resistant clinical isolates of \textit{S. aureus} strains. Human RBC based hemolytic assay showed absence of haemolysis and this confirms its safety.\textsuperscript{30}

The essential oil from leaf extract of \textit{P. guajava} exhibited the inhibitory activity towards \textit{S. aureus} and \textit{Salmonella} species.\textsuperscript{31} Pelegrini et al\textsuperscript{32} isolated the peptide Pg–AMP1 from the seeds of \textit{P. guajava}. Pg–AMP1 showed growth reduction in \textit{Klebsiella} sp. and \textit{Proteus} sp. The recombinant Pg–AMP1 peptide showed inhibitory activity against \textit{Escherichia coli}, \textit{K. pneumonia}, \textit{P. aeruginosa}, \textit{S. aureus}, and \textit{S. epidermidis} bacteria.\textsuperscript{33} Metwally et al\textsuperscript{34} isolated five flavanoids from \textit{P. guajava} leaves and found that good antimicrobial activity of the extracts, as well as the isolated compounds. Crude aqueous mixture and water soluble methanol extract from leaf and bark of \textit{P. guajava} showed strong antibacterial activity against multidrug–resistant \textit{V. cholera}.\textsuperscript{34} The decoction of \textit{P. guajava} showed antibacterial activity against \textit{Shigella flexneri} and \textit{V. cholerae}. It reduced the production of cholera toxin and labile toxin as well as their binding to ganglioside monosialic acid.\textsuperscript{35} Mao et al\textsuperscript{36} purified and concentrated total saponin from \textit{P. guajava} leaf. It interferes with the envelope subunit gp41 form the critical 6–HB structure, thus inhibit the entry of HIV into target cells.

Dhiman et al\textsuperscript{37} found that methanolic extract of \textit{P. guajava} leaf has bacteriostatic and fungistatic in action. \textit{P. guajava} tea showed efficient control of epidemic and pandemic influenza viruses, including oseltamivir–resistant strains, and its broad target blockage makes it less likely to lead to the emergence of viral resistance.\textsuperscript{38} \textit{P. guajava} might be valuable sources for the synthesis of new antibacterial agents against \textit{Helicobacter pylori}.\textsuperscript{39} Methanolic and ethanolic extract of \textit{P. guajava} leaf showed antimicrobial activities against \textit{E. coli} and \textit{Salmonella enteritidis}.\textsuperscript{40} Acetone–water extract of \textit{P. guajava} have catechin and it may be showed antimicrobial, anti-inflammatory and analgesic properties.\textsuperscript{41} From these results, \textit{P. guajava} extracts may contribute the novel antibiotics from natural resources.

**ANTIDIARRHOEAL ACTIVITY**

Lutterodt\textsuperscript{42} isolated quercetin and quercetin-3-arabinoside, from \textit{P. guajava} leaf. The leaf extract has a morphine-like inhibition of the release of acetylcholine in the coaxially stimulated ileum, with an initial increase, followed by a gradual decrease of muscular tone. Quercetin inhibited intestinal contraction induced by different concentrations of calcium. The ileum is being more sensitive to quercetin. These calcium-antagonist properties of quercetin explain the spasmodic effect of this popular herbal remedy.\textsuperscript{43} Loxoya et al\textsuperscript{44} suggested that the aglycone quercetin in \textit{P. guajava} leaf may be responsible for spasmodic activity.

**ANTI-INFLAMMATORY ACTIVITY**

Ethyl acetate extract of \textit{P. guajava} suppressed the interferon gama (IFN-γ)/TNF-α-co-induced production of thymus and activation-regulated chemokine protein and mRNA in HaCaT cells. It also inhibited the TNF-α/IFN-γ-co-induced activation of STAT1 and NF-kB as well as increased the expression of mRNA and heme oxygenase-1 protein. This demonstrates that \textit{P. guajava} inhibits expression of chemokine in keratinocytes by inducing heme oxygenase-1 expression and it highlight the therapeutic uses of \textit{P. guajava} in atopic dermatitis and inflammatory skin diseases.\textsuperscript{45}

Ethanolic extract of \textit{P. guajava} leaf significantly inhibited lipopolysaccharide-induced production of nitric oxide and prostaglandin E2 in a concentration-dependent manner. \textit{P. guajava} extract suppressed the expression and activity of inducible nitric oxide synthase and cyclooxygenase-2 through the downregulation of ERK1/2 activation in RAW264.7 macrophages. It also exhibited significant anti-inflammatory activity in 2 different animal models.\textsuperscript{46} Ethyl acetate of \textit{P. guajava} reduced antigen, induced the release of β-hexosaminidase and histamine in IgE sensitized RBL-2H3 cells. It also inhibited expression of IL-4 and TNF-α mRNA and protein production. It suppressed antigen-induced COX-2 mRNA and protein expression in these cells, as well as antigen-induced activation of NFAT and reactive oxygen species (ROS). Moreover, it inhibited antigen-induced activation of NF-kB and degradation of IkB-α. \textit{P. guajava} extract suppressed antigen-induced phosphorylation of Syk, LAT, Gab2, and PLCγ2 but not Lyn, and inhibited antigen-induced phosphorylation of downstream signaling intermediates including MAP kinases and Akt.\textsuperscript{47}

Matsuzaki et al\textsuperscript{48} isolated benzophenone and flavonol galloyl glycosides from 80% MeOH extract of \textit{P. guajava} together with five known quercetin glycosides. These compounds showed significant inhibitory activities against histamine release from rat peritoneal mast cells, and nitric oxide production from a murine macrophage-like cell line.

**ANTIOXIDANT ACTIVITY**

Ethanolic and aqueous leaf extract of \textit{P. guajava} contain high total phenolic content (575.3 ± 5.5 and 511.6 ± 6.2 mg of gallic acid equivalent/g, respectively). The higher the sample concentration used, the stronger is...
the free radical-scavenging effect. Akinola et al. suggested that ethanolic leaf extract of *Psidium guajava* possesses the beneficial effect on gossypol-induced sperm toxicity, and hence it may enhance male fertility due to rich natural antioxidants in it. The total flavonoids are primarily identified in the aqueous and ethanolic leaf extracts of *Ps. guajava* which may possess the potential antioxidative activities. The ethanolic extracts of the leaves of *Ps. guajava* possess beneficial effects on sperm production and quality, and may thus improve the sperm parameters of infertile males with oligosperma and nonobstructive azoospermia. Shabana et al. isolated quercetin and two quercetin glycosides (avicularin and guaijeravin) from *Ps. guajava* and have urine inhibitory activity. Free radical scavenging activity of the *P. guajava* leaves harvested during May and August are high, and have higher amounts of acetic acid, 3-hydroxybutyric acid, glutamic acid, citric acid, malonic acid, trans-aconitic acid, ascorbic acid, maleic acid, cis-aconitic acid, protocatechuic acid, asparagine, xanthine, and epicatechin than the leaves harvested during October and December. Epicatechin and protocatechuic acid seems to have enhanced, free radical scavenging activity of the *P. guajava* leaves. Methanolic extract of *P. guajava* contains the highest amount of total phenolics (380.08 ± 4.40 mg/L gallic acid equivalents), *P. guajava* contains high amount of total flavonoids (269.72 ± 2.78 microg/mL) among 10 Nigerian plants. Percentage 2,2'-Diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity (82.79 ± 2.84%) and reductive potentials (0.79 ± 0.04) also higher *P. guajava*. Nantitanon and Okonogi isolated quercetin, morin, and quercetin-3-O-glucopyranoside from leaf of *Ps. guajava*. Quercetin possess free radical scavenging activity approximately four times higher than morin and two times higher than quercetin-3-O-glucopyranoside. The reducing power of quercetin is eight times higher than morin and two times higher than quercetin-3-O-glucopyranoside. This confirmed that quercetin is the more active antioxidant from guava leaves. Phorbol myristate acetate and the DPPH radical scavenging assay for the spray dried extracts of *Ps. guajava* presented significant antioxidant activity in a dose-dependent manner and showed no toxicity to the human neutrophils. The antioxidant activities of different solvents of *P. guajava* have demonstrated that the antioxidant ability of *Ps. guajava* leaf extracts have a strong relationship with phenolic compound when compared to flavonoid content. Aqueous extract of *P. guajava* and its synthesized TiO₂ nanoparticles are found to possess maximum antioxidant activity and antimicrobial activity when compared with ascorbic acid. Recently, four new compounds, guavinsiside C, D, E and F are isolated from the leaves of *Ps. guajava* and these compounds showed antioxidant activities in DPPH, 2,2’-azino–bi–3-ethyl benzthiazoline–6-sulfonic acid (ABTS) and ferric reducing antioxidant potential (FRAP) assays. Roasted *Ps. guajava* seeds showed higher DPPH radical scavenging and reducing power activities. These results indicate that *Ps. guajava* could be a suitable source of natural antioxidants. The ethanolic extract of *P. guajava* has been found to show Antioxidant activity in all the tests done like DPPH assay, reducing power assay, nitric oxide scavenging assay, H₂O₂ radical scavenging assay and SO radical scavenging assay. The Antioxidant activity when evaluated in diabetic mice induced with streptozoxin showed the decrease in level of glucose and lipid peroxides when treated with the ethanolic leaf extract of *Ps. guajava*.

**ANTIDIABETIC ACTIVITY**

Treatment with guava juice (1 g/kg) produced a noticeable hypoglycemic action in normal and alloxan-induced diabetic mice. Aqueous leaf extract of *Ps. guajava* (250 mg/kg), showed statistically significant hypoglycemic activity. Intraperitoneal injection of *P. guajava* leaf extract (10 mg/kg) exhibited a significant inhibitory effect on protein tyrosine phosphatase1B in 1- and 3-month-old Lepr(db)/Lepr(db) mice. The butanol-soluble fraction significantly decrease the number of lipid droplets. Ethanolic extract of stem bark of *P. guajava* exhibited significant hypoglycaemic activity in alloxan-induced hyperglycaemic rats. The aqueous leaf extract of *P. guajava* have the potential effect of inhibition of the alpha-glucosidase activity from the small intestinal mucosa of diabetic mouse. *P. guajava* bud extract has significant insulin-mimetic and potentiating activity. Noni leaf, noni, fruit commercial noni juice and mangrove bean have insulin-like activity with minimum effect on insulin action. Habitual intake of *Ps. guajava* and noni is proposed to offer better protection against type 2 diabetes mellitus. Shen et al. investigated the effect of aqueous and ethanolic leaf extracts of *Ps. guajava* on hypoglycemia and glucose metabolism in streptozotocin induced type 2 diabetic rats. The acute and long-term feeding of the aqueous and ethanolic extract of *Ps. guajava* leaves have significantly decreased in the blood sugar level and increased the plasma insulin level. The activities of hepatic hexokinase and glucose-6-phosphate dehydrogenase is observed in diabetic rats fed with aqueous as well as ethanolic extracts and increased phosphofructokinase activity only in aqueous extract. Unripe fruit peel aqueous extract guava has shown hypoglycaemic as well as antidiabetic effect in normal, mild and severely diabetic rats induced by streptozotocin. Cheng et al. identified and suggested that quercetin in the aqueous extract of *Ps. guajava* leaves promotes the uptake of glucose in rats and reduces the beta cells which may contribute to the alleviation of hypoglycemia in diabetes. Fructosamine and glycated hemoglobin are significantly reduced in ethyl acetate fraction of *P. guajava* leaf treated groups. It also improved the antioxidant potential by decreasing lipid peroxidation (LPO) and increasing in the activity of catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx) and reduced glutathione (GR). Huang et al. suggested that *P. guajava* fruit (125 and 250 mg/kg) protected pancreatic tissues, against lipid peroxidation (LPO) and DNA strand breaks in streptozotocin induced diabetic rats. It also noticeably inhibited pancreatic expression of NF-kB protein and restored the activities of SOD, CAT and GPx. Dipeptidyl-peptidase IV is an important enzyme which maintains blood glucose homeostasis. The ethanolic *P. guajava* and its components flavonol-glycoside inhibit dipeptidyl-peptidase IV in a dose-dependent manner. Ethanolic leaves extract of *P. guajava* showed a significant reduction in blood glucose and glycated hemoglobin levels as well as increase in plasma insulin levels in streptozotocin induced diabetic rats. It also restored the activities of carbohydrate metabolizing enzymes. Treatment with *Ps. guajava* leaf extracts promoted the expression of IRS-1, AKT, P13Kp85 and IRS-1, AMPK, and AKT308, phosphorylation, accompanied by increasing the ratios of the membrane to the total expression in skeletal muscles. These supports the modulating effect of *Ps. guajava* leaf extracts in insulin-related signaling.

The poly formulation of *Anacardium occidentale*, *Eucalyptus globulus*, *Ps. guajava*, and *Xylopia aethiopica* extracts yielded significant result as well as reduces some other complications associated with diabetes in alloxan-induced diabetic models. Recently, aqueous extract of *Ps. guajava* leaves (250 and 500 mg/kg/d) re-set the raised circulating levels of leptin, insulin, and hepatic glucose transporter expression to promote insulin resistance, dyslipidemia, and hypertension in high fructose intake male rats.

**HEPATOPROTECTIVE ACTIVITY**

Aqueous leaf extracts of *Ps. guajava* at 250 mg/kg and 500 mg/kg, significantly reduced the levels of aspartate transaminase (AST), alanine...
transaminase (ALT), alkaline phosphatase (ALP) and bilirubin. The higher dose of *P. guajava* extract guarded the increase in liver weight, whereas the lower dose of *P. guajava* extract is ineffective except in the paracetamol induced liver damage. In the chronic liver injury induced by CCl₄, the higher dose of *P. guajava* leaf extract is found to be more effective than the lower dose.⁸⁰

In the acute liver damage induced by different hepatotoxins, methanolic, ethyl acetate and aqueous leaf extract of *P. guajava* (200 mg/kg, p.o.) significantly reduced the elevated serum levels of AST, ALT, ALP and bilirubin in CCl₄ and paracetamol induced hepatotoxicity. Methanolic extract of leaves of *P. guajava* possesses better hepatoprotective activity compared to other extracts. Histological examinations of liver tissues also support the hepatoprotection. Pretreatment with aqueous extract of *P. guajava* leaf possesses, hepatoprotective property at lower dose (150 mg/kg) against erythromycin-induced liver damage and a hepatotoxic property at higher dose (300 and 450 mg/kg) and recommended further studies with prolonged duration. Rai et al. evaluated the hypolipidaemic and hepatoprotective effects of unripe *P. guajava* fruit peel aqueous extract in streptozotocin induced severely diabetic rats. The extract has significant hepatoprotective and hypolipidaemic activity in addition to its antidiabetic activity.

**CARDIOPROTECTIVE AND HYPOTENSIVE ACTIVITY**

Aqueous-alcohol extract of *P. guajava* dry leaves depress the atrial contractility of guinea pig, in a dose-dependent fashion. The compound is concentrated using glacial acetic acid after removing the less polar fraction. The acetate acid fraction (10-800 mg/l) of *P. guajava* reduced myocardial force, increased the atrial relaxation time measured, abolished the positive staircase effect in a dose-dependent fashion suggesting a decrease of the cellular inward calcium current and its inotropic effect is abolished by cholinergic receptor blockade, indicating a cholinergic involvement in the mechanism of action of the extract. These data support that the extract of *P. guajava* leaves depress myocardial inotropism.⁵⁷

Acute intravenous administrations of the aqueous extract of *P. guajava* leaf (50-800 mg/kg) produced a concentration-dependent, significant reduction in systemic arterial blood pressures and heart rates of hypertensive rats. The numerous phytoconstituents such as, polyphenolic compounds, flavonoids, pentacyclic triterpenoids, quercetin, guaijaverin, tannins, and other chemical compounds present in the plant are considered for the observed hypotensive effects of the plant leaf extract.⁴¹

Belemougui et al. evaluated *P. guajava* and Diospyros mespiliformis (crude decoction, aqueous and ethanolic extracts) for their antagonistic activities on caffeine induced release of calcium from the sarcoplasmic reticulum of skeletal muscle in rats. These different extracts have shown a decrease of caffeine induced calcium release in a dose-dependent manner. *P. guajava* leaf extracts are more active than *D. mespiliformis* and crude decoctions have shown better inhibitory activity.

Aqueous leaf extract of *P. guajava* produced dose-dependent (0.25-2 mg/ml) contracted aorta rings. The effect is then assessed in the presence of phenolamine and nifedipine. The sensitivity of the aortic rings to collective doses of *P. guajava* is significantly improved in the presence of phenolamine. These data suggest that the effect of *P. guajava* is either by activation of alpha-adrenoceptor or acting via a calcium ion channel.⁶¹

Quercetin and gallic acid is one of the major antioxidative bioactive compounds of *P. guajava* and Limonium wrightii, respectively.⁷ The extracts *P. guajava* and *L. wrightii* significantly attenuated ischemic contracture during ischemia and also enhanced myocardial dysfunction after reperfusion. Increases in malondialdehyde (MDA) and decreases in high-energy phosphates in the reperfused hearts are significantly lessened with the both plant extracts. Quercetin and gallic acid also exerted the same beneficial effects. These results indicate that *P. guajava* and *L. wrightii* have cardioprotective effects against myocardial ischemia-reperfusion injury in isolated rat hearts, primarily through their radical-scavenging actions.

Recently, the administration of the leaves extracts of *P. guajava* significantly reduced the blood glucose, fructosamine and glycated hemoglobin levels. Cardiac isoform of liver alpha 2 macroglobulin which is the major protein correlated with earlier stages of cardiac hypertrophy. This protein level is decreased significantly in extract treated groups and these findings support the benefits of extract for preventing cardiovascular complications associated with diabetes.⁸⁸

**ANTICANCER ACTIVITY**

Research based on anticancer drug from natural compounds enabled the discovery of several drugs presently used in cancer therapy. *P. guajava* extracts modified the balance of Th1/Th2 to a dominant status of Th1 by directly reducing regulatory activity T cell. In pretreated mice exhibited retarded growth of s.c. inoculated B16 melanoma cells.⁹⁰ *P. guajava* leaf oil showed the highest anti-proliferative activity with (4.37 times more potent than vincristine) than other 16 Thai medicinal platsin P388 cell line.⁹¹

The aqueous extract of *P. guajava* inhibited the cancer cell DU-145 in a dose- and time-dependent manner. TUNEL assay and flow cytometric analysis confirmed the cell cycle arrests at G0/G1 phase. Additionally, suppression of the matrix metalloproteinases-2 (MMP-2) and matrix metalloproteinases-9 (MMP-9), and upregulation of active caspase-3 in DU-145 are also effected in a dose-dependent manner, implicating a potent anti-metastasis power of *P. guajava*.⁹¹

*P. guajava* have huge amounts of soluble polyphenolics including gallic acid, catechin, epicatechin, quercetin, and rutin and to exhibit potent anticancer activity.⁹² Treatment with *P. guajava* arrests the cell cycle at G0/G1 phase with huge amount of apoptotic LNCaP cells. It also significantly diminished both the prostate specific antigen serum levels and tumor size in a xenograft mouse tumor model and is a promising anti-androgen-sensitive prostate cancer agent.⁹³

Park et al. isolated a sesquiterpene (β-caryophyllene oxide) from the essential oils of *P. guajava, Origanum vulgare, Cinnamonum sp, Eugenia caryophyllata* and *Piper nigrum, β*-caryophyllene oxide inhibited the constitutive activation of PI3K/AKT/ mammalian target of rapamycin/ribosomal p70 S6 signaling pathways; and also caused the activation of ERK, JNK, and p38 mitogen-activated protein kinase in tumor cells. It also down-regulated the expression of various downstream gene products that mediate cell proliferation, survival, metastasis, angiogenesis, and increased the expression of p53 and p21.

Aqueous soluble polyphenolic fraction of *P. guajava* leaves effectively inhibited the expressions of VEGF, IL-6 and IL-8 cytokines, as well as MMP-2 and MMP-9. Simultaneously, it activated tissue inhibitor of metalloproteinases (TIMP-2) and suppressed the cell migration and the angiogenesis. *P. guajava* potentially possesses a strong anti-DU145 effect.⁹⁵

Hexane fraction of *P. guajava* is the most powerful inducer of cytotoxic and apoptotic effects in PC-3 cells. It suppresses the AKT/mammalian target of rapamycin/ribosomal p70 S6 kinase and mitogen-activated protein kinase signaling pathways and this correlated with down-regulation of various proteins that mediate cell proliferation, cell survival, metastasis, as well as angiogenesis.⁹⁶ The *P. guajava* extract exerted anticancer activity on haematological and solid neoplasias. *P. guajava* and its pulp ex...
tract are found to induce the apoptosis, which accompanied by caspase activation and p16, p21, Fas ligand, Bcl-2-associated agonist of cell death as well as TNF receptor super-family, member 10b, over expression. The ethanolic leaf extract of *P. guajava* showed inhibition (61.3\%) against the proliferation of colon cancer cell line SW480. The *P. guajava* extract contains the meroterpenes guajadiol, psidal A and psigualdial A and B. Both in vitro (nine human cancerlines) and in vivo (Solid Ehrlich murine breast adenocarcinoma model) showed to have highly effective anticancer property. The ability of the meroterpene-enriched fraction to reduce tumor growth and stimulate uterus proliferation, suggest that these compounds may act as Selective Estrogen Receptors Modulators.

Kim et al\(^9\) also isolated β-caryophyllene oxide from the essential oils of *P. guajava* and *O. vulgare*. β-caryophyllene oxide suppressed constitutive ST3 activation in multiple myeloma, prostate cancer and breast cancer cell lines. The suppression is mediated via the inhibition of activation of upstream kinases c-Src and JAK1/2. The inhibition of ST3 activation subsequently inhibited the proliferation of cell, stimulated apoptosis and abrogated the invasive potential of tumor cells.

Overall, all these findings suggest that *P. guajava* leaves can interfere with various signaling pathways linked with tumorigenesis and provide a source of possible therapeutic compounds for cancer prevention and treatment.

**NEPHROPROTECTIVE ACTIVITY**

The aqueous extract of *P. guajava* fruits have more quercetin, myricetin, and caffeic acid and ethanolic extract have more ferulic acids, cinnamic acids, and caffeic acid. Aqueous and ethanolic extract intake at 2 %, significantly reduced glucose, blood urea nitrogen levels, and increased insulin level in plasma of diabetic mice. Both extracts, dose-dependently reserved glutathione content, retained activity of CAT and GPx, and decreased ROS, IL-6, TNF-α and interleukin-1β (IL-1β) levels in the kidney. It also significantly declined renal N (ε)-(carboxymethyl)lysine, pentosidine and fructose levels, and suppressed renal activity of aldose reductase. These findings support that guava fruit could protect the kidney against diabetic progression.

Triterpenoids isolated from *P. guajava* leaves. The level of fasting blood glucose is increased and the insulin and insulin sensitivity index are decreased in the model group when compared with normal control in streptozotocin induced diabetic rats. The levels of blood urea nitrogen and creatinine are increased with histopathological changes related to diabetic nephropathy in the kidney, which are the glomerular endothelium and mesangial cell proliferation, capillary narrowed, the base-membrane incrasation, glomerular swelling, cysts narrowed and tubules edema. Triterpenoids can decrease the level of blood glucose, blood urea nitrogen and creatinine levels in diabetic rat effectively, increase the insulin sensitivity index and protect renal lesions in diabetic rats.

**CONCLUSION**

Various researches on the medicinal use of plant extract is must in the modern era as many chemically synthesized drugs are highly effective in causing many adverse effects in the humans. The phytochemical and pharmacological investigations carried out on *P. guajava* validate the immense potential of this plant in the treatment of numerous diseases. Additional researches are needed for the compound isolation and identification for the product development from *P. guajava* for the future generations. Every medicinal property of many medicinal plants are also to be determined.

**ABBREVIATION USED**

- ABTS: 2,2′–azino–bis–3–ethyl benzthiazoline–6–sulphonic acid; ALP: Alkaline Phosphatase; ALT: Alanine Transaminase; AST: Aspartate Transaminase; CAT: Catalase; DPPH: 1,1-Diphenyl–2-picryl-hydrazyl; FRAP: Ferric Reducing Antioxidant Potential; GPx: Glutathione Peroxidase; GR: Reduced Glutathione; HIV: Human Immunodeficiency Virus; IL: Interleukin (IL-4, IL-6 and IL-8); LPO: Lipid Peroxidation; MMP-2: Matrix Metalloproteinases-2; MMP-9: Matrix Metalloproteinases-9; ROS: Reactive Oxygen Species; SOD: Superoxide Dismutase; TNF-α: Tumor Necrosis Factor-Alpha.

**CONFLICTS OF INTEREST**

No funding source and there is no conflict of interest.

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Anand et al.: Psidium guajava

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1. Introduction

Psidium guajava Linn., also known as guava, is a tropical fruit which is native to Brazil and has been cultivated in tropical regions around the world. The fruit is used in traditional medicine and contains various bioactive compounds, including flavonoids, phenolic acids, and triterpenoids. The objective of this study was to investigate the antimicrobial activity of Psidium guajava Linn. extracts against multidrug-resistant Enterobacteriaceae and clinical isolates of multidrug-resistant methicillin-resistant Staphylococcus aureus (MRSA).

2. Materials and Methods

Psidium guajava Linn. leaf and bark extracts were prepared and used for the antimicrobial activity test. The extracts were tested against 10 multidrug-resistant Enterobacteriaceae and 15 clinical isolates of MRSA. The minimum inhibitory concentration (MIC) was determined by the microdilution method.

3. Results

The results showed that Psidium guajava Linn. leaf and bark extracts possessed significant antimicrobial activity against the tested strains. The MIC values ranged from 0.125 to 6.25 mg/ml.

4. Conclusion

Psidium guajava Linn. leaf and bark extracts showed promising antimicrobial activity against multidrug-resistant Enterobacteriaceae and MRSA. Further studies are needed to evaluate the potential therapeutic applications of these extracts.

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