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Review Article

A review on pharmaceutical and environmental applications of guava (*Psidium guajava*) leaves

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Abstract

Psidium guajava (Guava) is a commonly cultivated fruit in tropical regions that has been long recognized for its therapeutic applications. The leaves host diverse bioactive compounds, including phenols, flavonoids, terpenoids like gallic acid, and water-soluble tannins. This intricate chemical profile, particularly gallic acid, imparts the leaves with remarkable inhibitory effects against various pathogens, including bacteria and fungi. Compounds such as pyrocatechol, taxifolin, psiguadials, guaijaverin, and avicularin, among others, contribute to their hypoglycemic, antioxidant, anticancer, and antidiarrheal effects, showcasing the leaves' multifaceted therapeutic potential. Apart from having therapeutic potential, guava leaves have also been implicated in adsorbing heavy metals such as zinc, cadmium, arsenic, lead, iron, and chromium, as well as dyes such as methylene blue, congo red, brilliant green, amaranth, auramine, nile blue and photocatalytic dyes from contaminated water sources owing to their porous structure and presence of functional groups. The leaves contain compounds acting as natural coagulants and adsorbents, aiding in flocculation, sedimentation, and removal of impurities. This review aims to provide an overview of the phytochemical profile of guava leaves and further discusses its potential as a therapeutic drug and bioremediation targeting heavy metals and dyes. This eco-friendly approach offers numerous advantages, including affordability, accessibility, and biodegradability, thereby reducing reliance on synthetic adsorbents and promoting sustainability. This amalgamation of traditional medicinal significance with innovative environmental applications underscores the inherent potential of guava leaves as a sustainable and versatile botanical resource. Moreover, the various ongoing studies and the diverse properties of guava discussed herein may serve as a guide for the discovery of new pharmaceutics by the scientific fraternity.

Keywords: Anticancer, Antidiabetic, Antidiarrheal, Dye removal, Heavy metal, Guava leaves

INTRODUCTION

Psidium guajava, commonly known as guava, is a ubiquitous fruit cultivated across various tropical regions, with India being among its prominent cultivators. Beyond its culinary significance, guava has long been recognized for its therapeutic properties, particularly in traditional folk medicine, primarily observed in central parts of America (Dange *et al.,* 2020).

Guava leaves have been studied in pharmaceuticals for their antimicrobial, anti-inflammatory, anti-diarrhoeal, anti-diabetic, and antioxidant properties. Guava leaves are also useful for promoting wound healing. Crushed guava leaves or their extracts may be applied topically to cuts and abrasions for fast healing (Naseer *et al.*, 2019). Infusions made from guava leaves have been used to alleviate diarrhea as they contain compounds with anti-diarrheal effects which help to reduce the symptoms (Ojewole, 2006). Chewing guava leaves is a traditional remedy for maintaining oral hygiene. The leaves possess antibacterial properties that can help combat oral infections and reduce the formation of dental plaque (Ravi and Divyashree, 2014). Guava leaf extracts (GLEs) have been employed to alleviate respiratory conditions such as coughs and bronchitis. The leaves contain compounds with expectorant properties that may help in clearing respiratory passages (Gutiérrez *et al.,* 2008). They also contribute to regulating blood sugar levels. Infusions made from guava leaves are also being consumed for potential benefits in managing diabetes (Díaz-de-Cerio *et al*., 2016). Leaf extracts contain antioxidants that may help neutralize free radicals in the body, contributing to overall health and potentially reducing the risk of chronic diseases (Bilal *et al.,* 2024).

It has also been observed that guava leaves have demonstrated potential in environmental applications, particularly in water treatment. Guava leaves contain compounds that act as natural coagulants (Balamurugan and Shunmugapriya *et al.,* 2019 and El-Sesy and Mahran, 2020) and are an essential step in water treatment, where particles and impurities clump together for easier removal (Jiang, 2015). GLEs can aid in flocculation and sedimentation, leading to clearer water and hence have applications in drinking and wastewater treatment (Shukla *et al.,* 2017 and Abouelenien *et al.,* 2022). When used as an adsorbent, they can remove heavy metal ions that get leached in water due to various natural and anthropogenic factors (Priti and Paul, 2016).

Heavy metals such as cadmium, chromium, lead, arsenic etc. dissolved in water can be easily adsorbed from water using guava leaves through mechanisms such as electrostatic attraction, ion exchange, and surface complexation (Abdelwahab *et al.,* 2015). As an adsorbent, guava leaves also can remove industrial dyes from water (Salleh *et al.,* 2011). Methylene blue, congo red, auramine etc. are some dyes used in a variety of industries such as paper, textile and leather industry (Mulushewa *et al.,* 2021). These dyes are then discharged into water bodies without proper treatment leading to water pollution (Al-Tohamy *et al.,* 2021). The presence of sulphur and nitrates in these dyes impart negative effects on aquatic life as well as on humans (Manzoor and Sharma, 2020), hence removing them is necessary, in which guava leaves can play an important role.

This eco-friendly approach offers numerous advantages. Guava leaves are readily available at low cost, promoting affordability and accessibility. Their utilization reduces reliance on synthetic adsorbents, thus contributing to sustainability efforts. Furthermore, guava leaves are biodegradable, allowing for easy disposal or composting after use. This review aims to integrate these diverse facets, exploring the therapeutic potential of guava and innovative approaches for heavy metal and dye removal. By examining the latest research findings, we seek to provide a comprehensive understanding of the multifaceted applications of guava in medicine and the evolving strategies to mitigate the impact of heavy metals on the environment.

POLYSACCHARIDE AND ELEMENTAL COMPOSITION OF GUAVA LEAVES

Guava leaves exhibit a diverse composition of polysaccharides, as reflected in the following percentages: Fucose (1.44%), Rhamnose (3.88%), Arabinose (22.6%), Galactose (29.41%), Glucose (33.79%), Mannose (0.59%), and Xylose (7.71%) (Kim *et al.,* 2016). Additionally, guava leaves contain significant amounts of Phenol (15.28%), Sulfate (18.58%), Carbohydrate (48.13%), and Sulfate Polysaccharide (66.71%) (Kim *et al.,* 2016 and Luo *et al.,* 2018). Guava leaves also contain some essential elements such as Potassium (1.11%), Phosphorus (0.23%), Nitrogen (1.02%), and Ascorbic acid (142.55%) (Dutta *et al.,* 2014).

ESSENTIAL OILS IN GUAVA LEAVES

Guava leaves include a diverse array of essential oils. Among these compounds, limonene (54.7%) dominates with a significant presence, imparting a citrusy scent. Other notable constituents include 1,8-cineole (32.14%), known for its aromatic and respiratory benefits, and β-caryophyllene (2.91%), recognized for its anti-inflammatory properties (Soliman *et al.,* 2016). Additionally, α-terpineol (1.79%) and α-pinene (1.53%) contribute to the overall terpenoid profile, each possessing unique characteristics. The presence of benzaldehyde, p-cymene, β-cis-ocimene, γ-terpinene, and α-humulene in smaller percentages adds complexity to the volatile composition of guava leaves (Jassal and Kaushal, 2019).

PHENOLIC COMPOUNDS IN GUAVA LEAVES

Guava leaves boast a rich phytochemical profile, with various extracts revealing distinct compounds. The organic extracts of guava leaves exhibit the presence of quercetin, apigenin, guaijaverin, kaempferol, hyperin, and myricetin (Wang *et al.,* 2010). Gallic acid, chlorogenic acid, epicatechin, mono-3-hydroxyethyl-quercetin-glucuronide, rutin, isoquercitrin, quercetin-3-O-α-L-arabinofuranoside, quercetin-3-O-β-D-xylopyranoside, quercitrin, kaempferol-3-arabofuranoside, and kaempferol are some other compounds extracted in organic solvent (Wang *et al.,* 2017). Avicularin is found both in organic and aqueous extracts (Díaz-de-Cerio *et al.,* 2016). These compounds are known for their antioxidant and anti-inflammatory properties, contributing to the potential health benefits. The aqueous extract, on the other hand, contains gallic acid, catechin, epicatechin, quercetin, chlorogenic acid, epigallocatechin gallate, and caffeic acid, further diversifying the array of bioactive constituents (Liu *et al.,* 2014).

METHODS OF EXTRACTION OF BIOACTIVE COMPOUNDS FROM THE LEAVES

Various extraction methods are employed to isolate bioactive compounds from guava leaves (Fig. 1). Common techniques include water extraction through infusion or decoction which are suitable for heat-sensitive and polar compounds (Díaz-de-Cerio *et al.,* 2015 and Birdi *et al.,* 2020). Steam distillation is utilized to extract essential oils from guava leaves, particularly when dealing with volatile and temperature-sensitive compounds (da Silva *et al.,* 2019). Solvent extraction methods, such as ethanol, methanol, and acetone, dissolve a broad spectrum of phytochemicals (Azizan *et al.,* 2020). Cold pressing is utilized for mechanically extracting essential oils without heat application (Bonaccorsi *et al.,* 2011). Supercritical fluid extraction (SFE) utilizes carbon dioxide as a supercritical fluid, offering efficiency and avoiding the use of harmful solvents (Moura *et al.,* 2012). Microwave-assisted extraction (MAE) (Rezzadori *et al.,* 2022) and ultrasound-assisted extraction (UAE) (Wani and Uppaluri, 2022) leverage modern technologies for rapid and efficient extraction. Enzyme-assisted extraction is used to break down cell walls using enzymes, facilitating the release of bioactive compounds in the medium (Wang *et al.,* 2017). The choice of extraction method depends on the specific compounds of interest, the intended use of the extract, and the characteristics of the target bioactive components, with each method having distinct advantages and limitations. Researchers typically select the most suitable method based on their experimental goals, contributing to the comprehensive understanding of guava leaf biochemistry.

THERAPEUTIC USES OF GUAVA EXTRACT

In recent years, there has been a burgeoning interest in exploring the vast potential of plant products for thera-

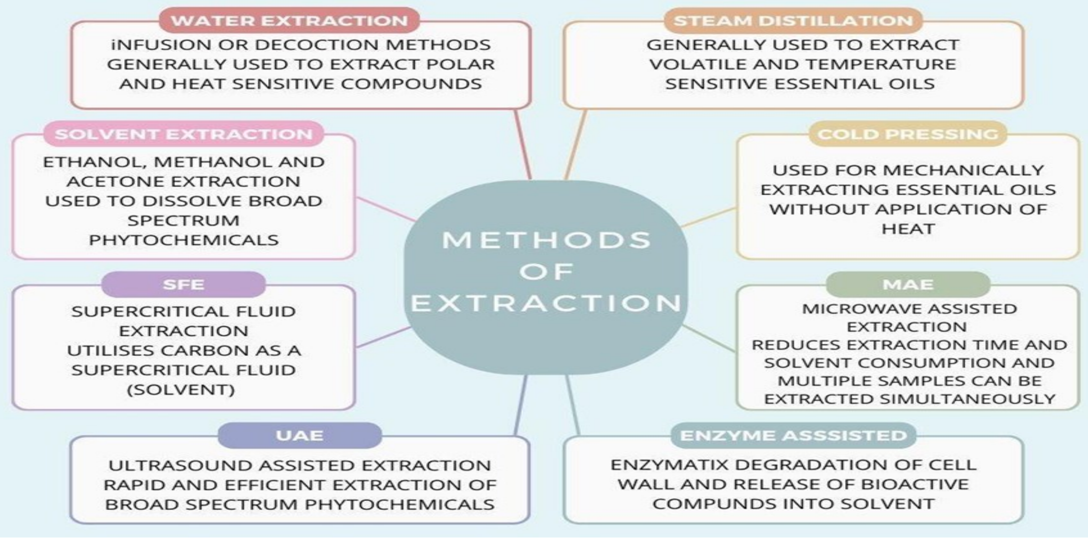

Fig.1. *Methods of extraction of bioactive compounds from leaves*

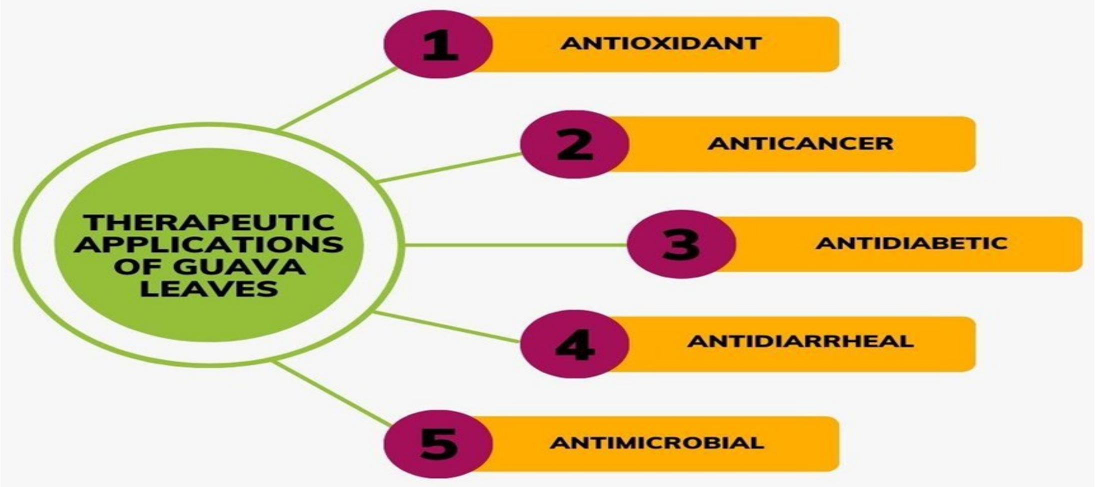

Fig. 2. *Therapeutic application of guava leaves*

peutic applications. The complex biochemical composition of plants offers a rich source of compounds with profound medicinal properties (Wangchuk, 2018). Transitioning from the broader exploration of plant products for therapeutic applications, emphasising the specific therapeutic potential of guava leaves. Rich in phytochemicals, antioxidants, and other bioactive constituents, guava leaves stand as a promising source for various therapeutic uses (Fig. 2).

Guava's rich repertoire of phenolic acids, flavonoids, tannins, and terpenoids contributes to its therapeutic potential (Raj *et al.,* 2020). The various compounds in guava leaves have garnered attention for their reported antimicrobial properties against a spectrum of commonly found bacterial and fungal species. GLEs are effective against pathogens such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Staphylococcus aureus*, *Bacillus subtilis*, and *Aspergillus niger* (Melo *et al.,* 2020 and Ratnakaran *et al.,* 2020). Notably, gallic acid, identified in GLE, has demonstrated inhibitory effects on ergosterol and glucosamine which are crucial for fungal growth (Kumar *et al.,* 2021). Similarly, the presence of water-soluble tannins in GLE has been linked to preventing bacterial growth by destroying the cell membrane (Mailoa *et al.,* 2014). The components obtained from extracts of guava leaves also demonstrate a range of biological activity across numerous directions, encompassing anticancer, antioxidant, antidiabetic, anti-lipid, and antidiarrheal effects.

Antioxidant and anticancer activity

The antioxidant properties of guava leaves can be attributed to phenolic compounds, including but not limited to gallic acid, pyrocatechol, taxifolin, ellagic acid, ferulic acid, and various others (Farag *et al.,* 2020). Jiang *et al.* (2020) also documented the antioxidant properties of flavonoids, volatile oils, psiguadials, triterpenoids, sesquiterpenes, tannins, benzophenone glycosides, and other quinones found in guava leaves.

The anticancer activity of guava leaves was first documented twenty years ago by Manosroi *et al.* (2006), who reported the antiproliferative activity of GLE to be 4.37 times more potent than the anticancer drug vincristine against the KB (human mouth epidermal) cancer cell line, and the P388 (murine leukaemia) cancer cell line. They also proposed myrcetin and apigenin as the prominent antioxidants.

GLE inhibited brain-derived prostate cancer cells (PCa DU-145), matrix metalloproteinases MMP-2 and MMP-9, and the upregulation of active caspase-3 in *vitro* culture (Chen *et al.,* 2007). In 2009, they attributed this activity to the rhamnoallosan polyphenol in the budding guava leaves. GLEs are also found to be effective against L929sA (murine fibrosarcoma) and Michigan Cancer Foundation-7 (MCF7) benign human breast cancer (Kaileh *et al.,* 2007). Fermented GLE is being reported to suppress Nuclear factor-kappa B (NF-kB) transcriptional activation in mice macrophages, which has been implicated in cancers (Choi *et al.,* 2008).

Table 1. A compilation of various studies showing the anti-cancer properties of guava leaves, highlighting identified compounds, biological effects, and key findings across different experiments

Compounds Identified	Cell Lines/Systems Studied	IC_{50} Values	Study
Various extracts: Methanol, Chloroform, Hexane, Ethanol	KBM5, SCC4, U266	IC_{50} varied	Ashraf *et al.* (2015)
Ethanolic extract	HepG2, U-118 MG, Caco-2, MCA-MB-231, MCF7	>200 µg/mL (HepG2, Caco-2, MDA-MB-231, MCF7), 133.55 µg/mL (U-118 MG)	Wang *et al.* (2019)
Benzophenones: Guavinoside E, Guavinoside B, 3,5-dihydroxy-2,4-dimethyl-1-O-(6′-O-galloyl-β-D-glucopyranosyl)-benzophenone	HCT116	Not specified	Zhu *et al.* (2019)
Aqueous extract	Antioxidant activity	IC_{50}: 46.49 µg/mL (DPPH), 175.52 µg/mL (OH), 102.82 µg/mL (ABTS)	Luo *et al.* (2019)
Ethanolic extract, Essential oils	HepG2, CCD-45-SK	Aqueous and ethanol extracts >0.1 mg/mL, Essential oils 0.1 mg/mL	Kemegne *et al.* (2020)
Vitamin E, β-caryophyllene, Flavonoids (Apigenin)	HT-29, Caco-2, SW480	Not specified	Lok *et al.* (2020)
Aqueous, Methanol, Ethanol extracts	Antioxidant activity	IC_{50} varied across different solvents	Beidokhti *et al.* (2020)
Oil extracted from guava leaves	HepG2, MCF-7	Concentration-dependent inhibitory effects	Mandal *et al.* (2022)
Crude extract	Saliva of breast cancer patients	Not specified	Mukherjee *et al.* (2022)
Crude extract	HepG2, MCF-7, HCT, A549	IC_{50}: 52 µg/ml (HepG2), 97 µg/ml (MCF-7), 193 µg/ml (HCT), 500 µg/ml (A549)	Abdel-Aal *et al.* (2022)
Fractions: n-hexane, Ethyl acetate, Ethanol	T47D, MCF-7, HeLa	IC_{50}: 8.92 (T47D), 4.28 (MCF-7), 85.98 (HeLa)	Prakoso and Nita (2023)

Guava leaf hexane fraction also induces apoptotic effects in prostate cancer-3 (PC-3) cells (Ryu *et al.,* 2012). Recent studies on the potential of GLEs against various cancer cell lines and free radicals have been discussed further (Table 1).

Compounds like psiguadials A and B which are present in guava leaves reduce tumor growth and stimulate uterus proliferation. This compound also acts as a selective estrogen receptor modulator and has anticancer activity. Psiguadial C and D also inhibit protein tyrosine phosphatase 1B (PTP1B) in hepatocellular carcinoma cells (HepG2) (Rizzo *et al.,* 2014). These compounds make the GLE potent for the treatment of hepatocellular carcinoma and uterine tumours.

Phenolic content, including flavonoids, of the methanol, chloroform, and hexane GLEs were also evaluated for their impact on human carcinoma cell lines (KBM5, SCC4, and U266). Notably, the hexane extract demonstrated potent cytotoxic and antitumor properties. Additionally, these extracts exhibited inhibition of TNF-α (Tumour Necrosis Factor α) and induced NF-κB incitement in KBM5 cells (Ashraf *et al.,* 2015). In a similar analysis, the activity of ethanolic GLE was studied on HepG2, glioblastoma cells (U-118 MG), Caco-2, and breast cancer cells (MCA-MB-231 and MCF7) and the half maximal inhibitory concentration IC_{50} values indicate their potential anticancer properties (Wang *et al.,* 2019).

Flavonoids and terpenoids found in guava leaves show anticancer effects by controlling the immune system, inhibiting signal transmission and tumour cell adherence, and obstructing tumour angiogenesis and cell proliferation (Biswas *et al.,* 2019). Vitamin E, β-caryophyllene, and apigenin (flavonoid) in GLEs have shown potent antiproliferative effects on human colon cancer cell lines. HT-29, Caco-2, and SW480 (Lok *et al.,*2020). A similar study by Zhu *et al.* (2019) pointed out three benzophenones, guavinoside E, guavinoside B, and 3,5-dihydroxy-2,4-dimethyl-1-O-(6′-O-galloyl-β-D-glucopyranosyl)-benzophenone, isolated from guava leaves inhibited the growth of HCT116 human colon cancer cells.

Essential oils, including Nerolidol, α-humulene, β-sesquiphellandrene, Benzaldehyde, isodaucene, 8-cineole β-bisabolol, and β-caryophyllene showed an impact on HepG2 and healthy human skin fibroblasts (CCD-45-SK). (Kemegne *et al.,*2020). Oil extracted from guava leaves was evaluated against HepG2 and MCF-7, which revealed a notable inhibitory potential in the oils. The extracted oils demonstrated comparable efficacy against lower concentrations of breast and hepatic cancer cells. As the concentration of the oils increased, a slight downregulation in the percentage of cell viability was observed. At higher concentrations, the oils displayed a consistent incremental change in inhibitory activity against both HepG2 and MCF-7 cells (Mandal *et al.,* 2022).

Aqueous GLE, characterized by low molecular weight polysaccharides (3.64 kDa), were used for *in vitro* antioxidant assays using for DPPH (2,2-diphenyl-1-picrylhydrazyl), OH (hydroxyl), and ABTS (2,2′-azino-bis-(3-ethylbenzothiazoline-6-sulfonic) acid) possesses potent ability to neutralize free radicals (Luo *et al.,* 2019). In a similar study done by Beidokhti *et al.* (2020), aqueous, methanol, and ethanol extracts, emphasizing phenolics, were used to determine their antioxidant potential through *in vitro* DPPH assay. They reported that the IC_{50} value was highest for the ethanolic extract and lowest for the methanolic extract, indicating varying degrees of antioxidant activity across different solvents. This variability highlights the influence of extraction methods on the composition and efficacy of GLEs as antioxidants.

Inhibition of salivary MMP-2 was studied by adding crude GLE to the saliva of breast cancer patients significantly reduced MMP-2 activity compared to controls (Mukherjee *et al.,* 2022).

In vitro, anticancer activity of GLE (n-hexane, ethyl acetate, and ethanol fraction) on T47D, MCF-7, and Henrietta Lacks (HeLa) cells for cervical cancer and found that the n-hexane fraction has high activity and selectivity to cancer cells (Prakoso and Nita, 2023).The number of viable cells (surviving fraction) of cell line types HepG2, MCF-7, HCT, and A549 were inhibited after treatment with crude GLE (Abdel-Aal *et al.,* 2022). The studies suggest that GLEs have potent antioxidant activity against free radicals and anticancer activities against the cancer cell lines KBM5, SCC4, U266, HepG2, U-118 MG, Caco-2, MCA-MB-231, MCF7, HCT116, CCD-45-SK, HT-29, SW480, HCT, A549, T47D, and HeLa.

Antidiabetic and antilipid activity

The antidiabetic activity of GLE was first reported in 2005 (Oh *et al.,* 2005). They reported that the extract at a dose of 10 mg/kg lowered blood glucose and lipid droplets in the liver of mice. A decrease iin blood glucose in Kunmig mice was observed by administering edible alcohol-soluble extracts of wild guava leaves (Wang *et al.,* 2005). Similar findings were reported in diabetic albino rats and STZ-induced (Streptozotocin-induced) rats (Shukla and Dubey, 2009; Roh *et al.,* 2009). Ethanolic extract from guava leaves decreased blood glucose and total cholesterol, triglycerides, LDL (low-density lipoprotein) cholesterol and HDL (high-density lipoprotein) cholesterol levels in alloxan-induced diabetic rats (Divya and Ilavenil, 2012). Several recent studies on various rat and mouse models have been done to check the potency of GLEs for lowering blood sugar and lipid levels (Table 2).

GLE flavonoids guaijaverin and avicularin are associated with significant improvement in the role of pancreatic

Table 2. Hypoglycemic and antidiabetic effects of guava leaves, presenting identified compounds, biological effects, and outcomes in different experimental settings

Compounds Identified	Animal/Cell Models	Key Findings	Reference
Guaijaverin, Avicularin	In vitro: 3T3-L1 adipose cells	Inhibition of dipeptidyl-peptidase IV; Avicularin prevents lipid aggregation	Eidenberger *et al.* (2013)
Crude extract	Alloxan-induced diabetes in Wistar rats	Significant reduction in blood glucose levels with GLE administration	Mazumdar *et al.* (2015)
Polysaccharides	In vitro: α-glucosidase activity assay	Reduction in α-glucosidase activity, preventing glucose catabolism	Luo *et al.* (2018)
Crude extract	STZ-induced diabetic male Sprague Dawley rats	Decreased HSL activity, increased glycogen levels, improved lipid profiles	Tella *et al.* (2019)
Flavonoids: Guaijaverin, Avicularin	Diabetic mice	Significant improvement in pancreatic islets' β-cells and hepatocytes morphology	Zhu *et al.* (2020)
Flavonoids: Guaijaverin, Avicularin	Kunming mice with STZ-induced diabetes and high-fat diet	Hypoglycemic effects, improved glucose tolerance, and positive metabolic changes	Zhu *et al.* (2020)
Crude extract	Rat cells C2C12, 3T3-L1, H4IIE	Inhibition of α-glucosidase,	Beidokhti *et al.* (2020)

islets' β-cells and the morphology of hepatocytes (Zhu *et al.,* 2020). Blood glucose homeostasis enzyme dipeptidyl-peptidase IV was shown to be inhibited by guaijaverin (Eidenberger *et al.,* 2013). Avicularin is shown to prevent intracellular lipid aggregation *in vitro* by blocking glucose uptake through GLUT-4 (Glucose transporter type 4) and did not exhibit any apparent toxicity towards 3T3-L1 adipose cells (Fujimori and Shibano, 2013). The ethanolic GLE significantly reduced blood glucose levels (Mazumdar *et al.,* 2015). An ultrasound-assisted ethanolic GLE containing polysaccharides studied *in vitro* demonstrated the repressing of α-glucosidase activity, reducing the catabolism of glucose and preventing flatulence without attenuating α-amylase activity (Luo *et al.,* 2018). Ethanol and ethyl acetate extract containing flavonoids (guajaverin and avicularin) administration while not preventing the reduction in body weight induced by STZ, exhibited hypoglycemic effects, and improved glucose tolerance. It lowered total cholesterol (TC), triglycerides (TG), and LDL-C. It also improved beta cell islet function and insulin resistance, and reduced kidney and liver indices (Zhu *et al.,* 2020). Lyophilized aqueous GLE significantly decreased hormone-sensitive lipase (HSL) activity in the diabetic rat liver and adipose tissue. This reduction in HSL activity was associated with increased glycogen levels, decreased levels of TC, TG, and LDL-C, and an increase in HDL-C (Tella *et al.,* 2019). Crude GLE was administered to rat skeletal muscle cells (C2C12), 3T3-L1, and hepatoma (H4IIE cells). The leaf extract inhibited α-glucosidase action and significantly increased the TG buildup in 3T3-L1 cells. These results suggest the potential application of GLE in the treatment of type 2 diabetes (Beidokhti *et al.,* 2020).

Antidiarrheal properties

Leaf extract of *P. guajava* contains tannins, saponins, carbohydrates and cardiac glycosides, which might have conferred antidiarrheal effect (Shekins and Dorathy, 2014 and Naseer *et al.,* 2018). GLEs demonstrated potential antidiarrheal effects in in vivo studies (Table 3). Aqueous GLE, administered orally to rats and mice produced a substantial and dose-dependent defence towards castor oil-induced diarrhoea (Ojewole *et al.,* 2008). Additionally, the extract slowed gastric emptying and impeded intestinal transit, showcasing its potential as an antidiarrheal agent. Similar in vivo experiments conducted with Wistar rats, the ethanolic GLE exhibited significant antidiarrheal effects in a castor oil-induced diarrheal model (Mazumdar *et al.,* 2015). These findings suggest that both water, and ethanolic extracts from guava leaves possess promising antidiarrheal properties, indicating their potential therapeutic applications. A clinical trial of oral guava leaf decoction (GLD) was conducted on 109 adults (18–60 years) suffering from acute diarrhea, (57% females, 43% males). Three doses of GLD (6-leaf, 10-leaf and 14-leaf) were compared with controls receiving oral rehydration solution. The 14-leaf (7.4 g) decoction was reported to be the most effective (Birdi *et al.,* 2020). Addition of GLE in the diet of piglets reduce levels of D-lactate, endothelin-1 and diamine oxidase in the serum, and increased expression of zonula occludens-1, Claudin-1, Occludin and Na^+/H^+ exchanger 3 in the intestines (Wang *et al.,* 2021).

Antimicrobial properties

The misuse of antibiotics has created a surge in antibiotic-resistant bacteria, rendering existing treatments ineffective for many infections (Subramaniam and Girish, 2020). Due to this, there has been a shift towards developing natural antimicrobials (Cheesman *et al.,* 2017). These plant-derived products offer a potential alternative. Unlike conventional antibiotics, they might be effective against antibiotic-resistant strains and come with fewer side effects (Chandra *et al.,* 2017). Additionally, some herbs exhibit a broader spectrum of antimicrobial activity, targeting a wider range of microbes (Vaou *et al.,* 2021). Furthermore, the complex mix of compounds within these plants could create a synergistic effect, where their combined power is greater than the sum of their individual effects (Zhou *et al.,* 2016). Guava leaves have been studied in this regard for their potential antimicrobial properties. GLEs have various modes of action against microbes, which leads to their antimicrobial properties. The extract penetrates the lipid bilayer of the cell membrane, which results in increased permeability, leading to the loss of cytoplasmic content (Kwamin *et al.,* 2019). The flavonoids in guava leaves form complexes with extracellular proteins and are capable of solubilizing bacterial cell walls. The tannins found in guava leaf bind with proline-rich proteins that interfere with protein synthesis, thus exerting antibacterial activity (Jebashree *et al.,* 2011). These polyphenolic compounds also damage the cell membrane by reacting with its phospholipids. Hence, damage to the cell membrane leads to leakage of essential metabolites and shutting down the bacterial enzyme system. This also prevents the entry of nutrients in the microbes which is necessary for generating energy (Mailoa *et al.,* 2014). These factors collectively may lead to inhibition of bacterial cell population. Inhibition of fungi could be linked to damaged hyphal structures caused due to the plant extracts (da Cruz Cabral *et al.,* 2013). This could be because these extracts inhibit the production of chitin, a main component in the cell wall of fungi.

Various types of GLEs have been evaluated for their antimicrobial activity against different microbial species, aqueous and ethanolic extracts are the prominent ones. bacterial inhibition has been documented against some common pathogenic bacteria and fungi, periodontal bacteria, and food pathogens (Table 4).

Researchers have documented microbial growth inhibition using GLEs on the various pathogenic species of microbes. *S. aureus* which is responsible for food poisoning, skin infections and toxic shock syndrome, *E. coli* responsible for urinary tract and gastrointestinal infections, *C. albicans*, overgrowth of which leads to candidiasis and vaginal yeast infections, *A. niger*, *L. monocytogenes* which causes listeriosis, *V. parahaemolyticus* responsible for gastroenteritis, *A. faecalis* which cause sepsis, wound infections and urinary tract infections, *A. hydrophila* which can cause ulcers and tail rot in freshwater fishes and amphibians. Many others are listed in Table 4.

Table 3. Antidiarrheal effects of guava leaves, detailing identified compounds, biological effects, experimental models, and key findings contributing to potential therapeutic applications

Extract type	Model/Subjects	Key Findings	Reference
Ethanolic extract	Wistar rats	Ethanolic extract exhibited significant effects at doses of 750 and 500 mg/kg in a castor oil-induced diarrheal model	Mazumdar *et al.* (2015)
Guava Leaf Decoction	109 adults (18–60 years) with acute infectious diarrhoea	14-leaf (7.4 g) guava leaf decoction reported as most effective; Three doses (6-leaf, 10-leaf, 14-leaf) compared with controls receiving oral rehydration solution; Normalcy achieved within 72 hours with TDS (thrice daily) dose	Birdi *et al.* (2020)
Crude extract	Piglet intestines	Reduced levels of D-lactate, endothelin-1, and diamine oxidase in serum; Increased expression of zonula occludens-1, Claudin-1, Occludin, and Na+/H+ exchanger 3	Wang *et al.* (2021)

Table 4: Antimicrobial activity of GLEs against various microbial species

Extract Type	**Microbial Species Tested**	**Minimum Inhibitory Concentrations (MICs)**	**Reference**
Ethanolic	L. monocytogenes, S. aureus, V. parahaemolyticus, A. faecalis, A. hydrophila	0.1 mg/mL, 0.1 mg/mL, 0.1 mg/mL, 0.4 mg/mL, 0.4 mg/mL	Mahfuzul Hoque et al. (2007)
Aqueous	S. aureus, E. coli, C. albicans	5.25 µg/ml, 10.5 µg/ml, 5.25 µg/ml	Metwally et al.(2010)
Methanolic	E. coli, S. aureus, C. albicans, A. niger	0.78 µg/ml, 25 µg/ml, 12.5 µg/ml, Not specified	Dhiman et al. (2011)
Aqueous, Methanolic, Acetone	P. multocida, E. coli, S. typhimurium, S. suis,	0.156 mg/mL, 5 mg/mL, 5 mg/mL, 0.312 mg/mL	Puntawong et al. (2012)
Aqueous and Ethanolic	P. gingivalis, A. actinomycetemcomitans	75 µL/mL (both), 50 µL/mL (aqueous), 3.12 µL/mL (ethanolic)	Shetty et al. (2018)
Ethanolic	S. aureus, E. coli, Streptococcus sp., Bacillus sp., Salmonella sp., Shigella sp.	20 mg/mL, 40 mg/mL, 10 mg/mL, 20 mg/mL, 40 mg/mL, 10 mg/mL	Ngene et al. (2019)
Ethanolic	Carbapenem-resistant K. pneumoniae	6.25 mg/mL	Hackman et al. (2020)
Ethanolic	S. pyogenes , P. aeruginosa	721.21 ppm, 3085.91 ppm	Halim et al. (2022)
Aqueous	S. aureus, S. pseudintermedius	6.8 mg/mL	Pereira et al. (2023)

Application of guava leaves in environmental restoration

Water is a fundamental resource for life, essential for the survival and well-being of all living organisms. Clean water is crucial for maintaining human health, as it is a cornerstone of proper hydration and sanitation. The sustainable management of water resources is essential for maintaining ecological equilibrium. Heavy metals and dyes are two significant pollutants in water bodies (Elgarahy *et al.,* 2021). Heavy metals, defined as metallic elements with an atomic density greater than 4 g cm^{-3}, present a unique environmental challenge (Tchounwou *et al.,* 2012). These elements, characterized by their high density and potential toxicity, can permeate ecosystems through various pathways, necessitating our attention to their impact on living organisms and the environment. Their widespread use in industrial, domestic, agricultural, medical, and technological applications has led to their extensive distribution in the environment (Mishra *et al.,* 2019). Commonly encountered heavy metals include lead, mercury, arsenic, chromium, and cadmium (Joseph *et al.,* 2019). While these metals play essential roles in various biological and physiological processes, excessive levels can lead to toxic effects (Jaishankar *et al.,* 2014). Heavy metal toxicity can cause damage or reduction in mental and central nervous function, lower energy levels, and damage to blood composition, lungs, kidneys, liver, and other vital organs (Ungureanu *et al.,* 2022; Nguyen, 2023). Therefore, understanding and managing heavy metals is crucial for public health and environmental sustainability. Guava leaves serve as an adsorbent to remove heavy metal ions from contaminated water.

In a similar vein to heavy metals, dyes also contaminate water bodies. Dyes are widely used in various industries for colouring products, including textiles, paper, and cosmetics. When dyes are not properly treated before disposal, they can enter water streams through various pathways, posing carcinogenic and mutagenic effects on both aquatic life and humans (Oladoye *et al.,* 2022). Therefore, their removal from water bodies is necessary. Guava leaves have been used as an adsorbent for dyes such as methylene blue, congo red, and brilliant green, involving various physical and chemical processes (Bulgariu *et al.,* 2019). The porous structure of guava leaves allows them to adsorb dye molecules physically on their surface. The porous nature of the leaves provides a large surface area for the interaction between the adsorbent (guava leaves) and the dye molecules. Functional groups in guava leaves, such as hydroxyl (-OH) groups, may interact with dye molecules.

Heavy metal adsorption

Pollution and contamination of water sources with heavy metals pose significant threats to human health, ecosystems, and biodiversity (Balali-Mood *et al.,* 2021). Heavy metals such as cadmium upon ingestion can cause stomach irritation, nausea and vomiting. Chronic effects include kidney failure, osteoporosis, respiratory failure and increased risk of cancer (Genchi *et al.,* 2020). Excess levels of chromium may cause respiratory, carcinogenic and mutagenic effects (Hossini *et al.,* 2022). Short-term effects of arsenic include severe vomiting, diarrhoea, dehydration, and weakness. Chronic effects include skin problems, heart disease, neurological disorders, diabetes, and cancer (Prakash and Verma, 2021 and Abdul *et al.,* 2015). Exposure to lead can cause brain damage, seizures, developmental problems, high blood pressure, kidney, and reproductive problems (Ara and Usmani, 2015). Contact with nickel can cause skin irritation, nausea, vomiting and diarrhoea (Begum *et al.,* 2022). While generally safe, other heavy metals can have toxic effects in high quantities (Jaishankar *et al.,* 2014).

These heavy metal contaminations can come either from natural sources, such as volcanic eruptions, sea-salt sprays, and forest fires, or from anthropogenic sources, such as mineral extraction, mining, industries, agricultural practices, power plants, and biomedical waste (Kapoor and Singh, 2021; Sonone *et al.,* 2020). Heavy metals are input into water bodies by leaching contaminated urban soil and road-deposited sediment from intrinsic and extrinsic sources, such as vehicular traffic and industrial and domestic emissions (Hanfi et al., 2020). However, industrial effluent is the prime culprit (Vardhan *et al.,* 2019).

There are various methods for the treatment of water contaminated with heavy metals. Chemical treatment methods, such as ion exchange, precipitation, electrochemical processes, or adsorption onto activated carbon, are the conventional wastewater treatment processes for eradicating heavy metals in large-scale applications (Deliyanni and Bandosz, 2011; Li *et al.,* 2013). However, these methods are expensive and, additionally, can lead to a further pollution load. Adsorption has been proven to be one of the most promising candidates since it can present a high level of effectiveness, with a lower cost and simpler operational design of the procedure compared to the other mentioned chemical methods (Przepiórski, 2006; Slatni *et al.,* 2020). At present, guava leaves in particular leaf adsorbents are being extensively studied as an alternative to chemical adsorbents. Heavy metals such as zinc, cadmium, lead, iron, nickel, arsenic, aluminium, and chromium are adsorbed by guava leaves and the optimum conditions for adsorption have been discussed in Table 5

Dye removal

Dyes are substances that impart color to materials.

Dyes are widely used in industries such as textile, pharmaceutical, food, cosmetics, plastics, photographic, and paper. It is estimated that over 10,000 different dyes and pigments are used industrially and over 700,000 tons of synthetic dyes are produced worldwide annually. During the dyeing and finishing operations, up to 200,000 tons of these dyes are lost to effluents every year due to the inefficiency of the dyeing process (Singha *et al.,* 2021). This waste often ends up in water bodies. Due to direct contact, the presence of dye in water can have severe implications for aquatic life. For humans, there have been observations from skin irritations to cancer-like diseases (Maheshwari *et al.,* 2021). Most of these dyes escape conventional wastewater treatment processes and persist in the environment due to their high stability to light, temperature, water, detergents, chemicals, and soap (Chequer et al., 2013). Due to the inefficacy and non-biodegradability of conventional treatments, new methods of dye adsorption using various plant-based products are being explored (Mathuram *et al.,* 2018). These plant-based adsorbents are cost-effective, less toxic, and biodegradable. Along with others, guava leaves have also been used to adsorb dyes such as methylene blue, congo red, auramine, etc. from water. The optimum conditions for the maximum dye adsorption are listed in Table 6.

Conclusion

The multifaceted potential of *Psidium guajava* (guava)

Table 5. Adsorption characteristics of guava leaves for various metals, including the optimum pH, adsorbent dosage, and equilibrium period

Adsorbent Type	Metal(s) Adsorbed	Optimum pH	Adsorbent Dosage	Contact time	Reference
Crushed and dried guava leaves	Chromium	2	2 g/L	90 min	Kartohardjono et al. (2009)
Raw guava leaves (fine powder 1.25 mm to 420 µm)	Arsenic	4	4 g/L	8 hours	Kamsonlian et al. (2012)
Magnetic nanopores from GLE	Nickel		15 mg/L	120 min	Capangpangan et al(2019)
Fe_2O_3-Ag nanocomposite of GLE	Chromium	4	0.06 g	90 min	Biswal et al. (2020)
Raw guava leaves (fine powder - 150 µm)	Lead, Cadmium	7	1000 mg/L	60 min	Pindiga et al. (2022)
Raw guava leaves (fine powder - 0.3 to 0.4 mm)	Cadmium	6	0.5 g	120 min	Ali et al. (2022)
KOH-treated guava leaves (fine powder - 0.39 mm)	Arsenic	6	100 mg/50 mL	10 hours	Behera et al. (2022)
Crude extract	Rust Iron	Not specified	5 g	Not specified	Dey et al. (2022)
KOH-treated guava leaves	Zinc	3	100 mg/L	20 min	Sireesha et al. (2023)
Raw guava leaves (fine powder - 0.3 to 0.4 mm)	Aluminium	6	0.5 mg	120 min	Mustafa et al. (2023)

Table 6. Removal of different dyes using guava leaves, including the type of adsorbent, dye removed, dosage, contact time, and other relevant conditions

Adsorbent Type	Dye Removed	Dye Dosage	Adsorbent Dosage	Contact Time	Conditions	Reference
Guava leaf powder	Methylene blue	100 mg/dm^3	2 g/dm^3	Not specified	pH 8	Ponnusami *et al.* (2008)
Withered guava tree leaves and activated carbon	Auramine	150 mg/L	2 g	120 min	pH 8–9	Gaikwad and Kinldy (2009)
Guava leaf powder	Brilliant Green Dye	Not specified	0.2 g	Not specified	Temperature: 50 °C, pH 4	Rehman *et al.* (2015)
Acetone-treated guava leaf powder	Amaranth dye	Not specified	0.4 g	20 min	Temperature: 40 °C, pH 3	Rehman *et al.* (2015)
Guava leaf-based activated carbon	Congo red	10-50 mg/L	10 mg/250 mL	Not specified	Temperature: 30 °C	Ojedukun and Bello (2017)
Tin oxide nanoparticles synthesized using GLEf	Reactive yellow 186 dye	Not specified	Not specified	180 min	Photocatalytic activity under sunlight, nanoparticles sized 8-10 nm	Kumar *et al.* (2018)
Guava leaf-based magnetic nanocomposite	Methylene blue	10 mg/L	1.0 g/L	90 min	pH 7	Abdulla *et al.* (2019)
Activated carbon and guava leaf powder	Nile blue dye	Not specified	0.5 g	30 min	Conditions: 100 RPM, positive correlation with dye concentration	Aly *et al.* (2019)

leaves has been extensively explored, emphasizing their traditional medicinal significance and innovative environmental applications. The intricate chemical profile of guava leaves, including phenols, flavonoids, and terpenoids, contributes to their hypoglycemic, antioxidant, anticancer, antidiabetic , antimicrobial, anitlipid and antidiarrheal effects. Noteworthy compounds like pyrocatechol, taxifolin, psiguadials, guaijaverin, and avicularin showcase the leaves' diverse therapeutic potential. The leaves also demonstrate antimicrobial properties and have inhibitory effects against a spectrum of pathogens, including bacteria and fungi. The compounds in guava leaves, such as gallic acid and water-soluble tannins, prevent bacterial and fungal growth. These properties, attributed to the diverse bioactive constituents, make guava leaves a promising source for various therapeutic applications. The rich presence of phytochemicals and antioxidants in guava leaves extends their utility beyond traditional medicine to environmental remediation. Guava leaves exhibit remarkable heavy metal adsorption capabilities, effectively adsorbing zinc, cadmium, arsenic, lead, iron, chromium, and various dyes from contaminated water sources. The studies highlighted guava leaves as an effective and eco-friendly adsorbent for heavy metals in water, showcasing their potential to address environmental challenges associated with metal pollution. Guava leaves, with their porous structure and functional groups, have shown promise in adsorbing dyes like methylene blue, congo red, brilliant green and others. This aspect further expands the environmental applications of guava leaves, positioning them as a potential solution for mitigating water pollution caused by textile dyes. This dual functionality underscores the inherent potential of guava leaves as a sustainable and versatile botanical resource. Integrating traditional medicinal knowledge with modern scientific exploration highlights guava leaves as a valuable resource with diverse applications in medicine and environmental sustainability. Further research and exploration are warranted to unlock the full potential of guava leaves in addressing global health and environmental challenges.

Conflict of Interest

The authors declare that they have no conflict of interest.

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