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Novel Advances in Bioactive Components and Pharmacological Effects of Guava (*Psidium guajava* L.) Fruits and Leaves: A Review of Progress over the Past Five Years

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ABSTRACT: The fruit of guava (*Psidium guajava* L.) comes from a tropical plant with both edible and health-beneficial values. Guava leaves are often processed into guava leaf tea for consumption. Its fruit and leaves contain polysaccharides, phenolic acids, flavonoids, terpenoids, vitamins, and minerals, but the strength of evidence varies markedly across preparations and outcomes. This review critically evaluates studies published mainly during the past five years and links organ-specific composition, extraction conditions, mechanisms, preclinical outcomes, clinical evidence, and product development. Reported guava leaf total phenolic contents range from 53.24 to 438.80 mg gallic acid equivalents/g, while guava leaf polysaccharides showed a DPPH-scavenging rate of $65.43 \pm 2.56\%$ and α -glucosidase IC₅₀ values of 790–904.67 $\mu\text{g/mL}$ in preclinical assays. Mechanistically, phenolic compounds and polysaccharides may directly scavenge radicals and modulate Keap1–Nrf2–ARE, PI3K–Akt–GLUT4, NF- κ B, and carbohydrate-hydrolyzing enzymes; guajadial and guaijaverin provide compound-level examples, although most causal evidence remains biochemical, cellular, or animal-based. Four randomized studies ($n = 31$ –120) reported changes in postprandial glucose, blood lipids, blood pressure, inflammatory indices, or viral-clearance time, but heterogeneity, short follow-up, incomplete blinding, and predominantly healthy or mildly affected populations preclude firm clinical conclusions. Compared with earlier descriptive reviews, this review integrates fruit–leaf similarities and differences, explicitly appraises evidence strength and study limitations, and connects composition and processing to biological function and translation. Standardized extracts, exposure–response studies, and adequately powered multicenter trials are priorities for determining efficacy, safety, and practical value.

Keywords: guava; guava leaves; guaijaverin; guajadial; bioactive components; biological activities; antioxidant; antidiabetic.

1. Introduction

Diet-related chronic diseases, including obesity and type 2 diabetes, have increased interest in foods that may complement established preventive strategies^[1]. In the process of social development, the incidence of chronic diseases such as obesity and type 2 diabetes has been on the rise, and there has emerged a demand for

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promoting healthier lifestyles through dietary interventions ^[2]. Guava is relevant to this discussion because its fruit is widely consumed and its leaves are used in traditional preparations.

Guava (scientific name: *Psidium guajava* L.) is an evergreen shrub belonging to the genus *Psidium* in the family Myrtaceae. Native to the Caribbean region, Central America, and South America, it is now widely cultivated in tropical and subtropical areas worldwide ^[3]. Since ancient times, guava has been a common fruit integrated into daily life. In traditional Chinese medicine, both the leaves and fruits of guava are frequently utilized as traditional Chinese medicinal materials ^[4]. In China, guava is a widely consumed fruit, and China is a major guava cultivating and producing country. It is mainly distributed in regions such as Hainan, Guangdong, and Guangxi, with an annual output exceeding 10 million tons. Additionally, guava serves as an important cash crop in many countries. Possessing strong adaptability, it is well-suited for cultivation in tropical regions and is also extensively grown in Taiwan of China, Southeast Asia, as well as countries including India, Brazil, and Mexico ^[5]. In folk traditions, guava possesses numerous traditional uses and health-beneficial values. Guava leaf tea is widely recognized for its potential hypoglycemic and hypolipidemic effects. Guava leaves are traditionally used to repel mosquitoes, prevent and treat mosquito bites, and relieve toothache. Both guava leaves and fruits have been used to alleviate gastrointestinal discomfort, while guava leaves also possess antibacterial, analgesic, and hemostatic properties ^[6-8]. Guava leaves and fruits have diverse applications, serving as animal feed and being utilized in traditional ritual activities ^[9]. In traditional Chinese medical theory, both the leaves and fruits of guava are often used for detoxification, anti-inflammation, regulating spleen-stomach function, and hemostasis ^[6]. From a nutritional perspective, guava fruit is a low-calorie and high-nutrient-density fruit, rich in various nutrients and antioxidant components ^[8]. In pharmacology, both guava leaves and fruits exhibit antibacterial, anti-inflammatory, antioxidant, hypoglycemic, and other related effects, thereby endowing them with significant development potential in modern medicine, particularly in the prevention, treatment, and adjuvant therapy of chronic diseases ^[10, 11]. Beyond traditional Chinese medicine, guava also holds an important position in global traditional medicine due to its whole-plant medicinal properties, and it is widely used in the treatment of digestive system diseases, inflammation, infections, chronic diseases, and other related conditions ^[12]. Over the past five years, a multitude of studies have been conducted on the therapeutic potential of phytochemical components in guava leaves and fruits for treating diseases. Research on guava has progressed from general descriptions of nutritional composition and traditional uses toward advanced extraction technologies, detailed phytochemical characterization, pathway-oriented mechanistic studies, and preliminary clinical evaluation. However, the available evidence remains heterogeneous because studies differ substantially in plant organ, cultivar, maturity, extraction method, preparation, dose, and experimental model. Moreover, chemical identification, biological activity in crude extracts, compound-specific target validation, and clinical efficacy are not always clearly distinguished. For example, research by Huynh et al. demonstrated that guava extract exhibits significant inhibitory effects on bacteria, coupled with potent antibacterial and anti-inflammatory activity ^[13]. Concurrently, mounting evidence indicates that guava

extracts possess potent antioxidant and hypoglycemic properties, with guava also demonstrating therapeutic effects in tumor treatment ^[14]. As a botanical resource, guava offers comprehensive edible and medicinal value, serving not only as a health food but also holding immense potential for pharmaceutical development and economic value. Guava can be exploited for the development of functional foods and new drugs, and it can also be applied in the fields of industrial cosmetics production and ecological agriculture. The comprehensive values of guava await further exploration ^[8, 15]. Advancements in science and technology, coupled with the impetus of market demand, will accelerate the application and innovative development of guava in multiple fields.

Accordingly, this review aims to: (1) summarize recent advances in the composition, extraction, and identification of bioactive compounds in guava fruits and leaves; (2) compare their shared and organ-specific biological activities and mechanisms; (3) evaluate evidence from preclinical studies, clinical trials, and product applications; and (4) identify priorities for standardization, mechanistic validation, safety assessment, and clinical research. Its main contribution is an integrated composition–mechanism–evidence framework linking guava constituents with biological mechanisms, evidence strength, and translational applications.

2. Literature search methods

This narrative review was updated through structured searches of PubMed and Google Scholar for records published from January 2021 to September 2026. Search terms combined "*Psidium guajava*" or "guava" with "fruit", "leaf", "extract", "polysaccharide", "polyphenol", "guaijaverin", "guajadial", "bioactivity", "mechanism", "clinical trial", "safety", and "functional food". Earlier studies were retained when they provided foundational extraction methods, reference composition data, or the limited human evidence. Eligible reports examined guava fruits, leaves, extracts, or isolated constituents and reported composition, extraction, mechanism, safety, clinical outcomes, or product application. Duplicate records were removed by DOI and title. Studies without identifiable methods, records unrelated to guava, and reports lacking sufficient methodological information were excluded. Primary studies were preferred; reviews were used to locate primary reports and provide context, rather than being treated as independent evidence. Because preparations, models, and endpoints were heterogeneous, findings were synthesized narratively by organ, preparation, study model, and evidence level.

3. Botanical characteristics and chemical composition of guava fruits and leaves

Guava fruits are usually oval, pyriform, or round, with cultivar-dependent diameters of approximately 4–10 cm and masses of 50–500 g ^[16]. Peel color changes from pale green during immaturity to yellow or reddish-yellow at maturity, whereas flesh color ranges from white to deep red ^[17, 18]. These visible traits are relevant to composition: flesh color and ripening status can accompany differences in carotenoids, vitamin C, and phenolic abundance, and red-fleshed cultivars often show higher measured antioxidant capacity than white-fleshed cultivars. Guava leaves are simple, opposite, elliptical to oblong, approximately 10 × 5 cm, with prominent pinnate venation and a pubescent lower surface ^[5, 19]. Leaf veins and epidermal tissues are also sites

of localized phenolic accumulation, including quercetin and chlorogenic acid [20, 21]. Guava flowers are generally white and axillary, and mature trees reach approximately 3–10 m [22–24].

3.1. Primary metabolites and micronutrients in guava fruits and leaves

3.1.1. Comparative composition and functional implications

Guava fruits are rich in macronutrients and micronutrients, including 52.18% moisture, 2.42% ash, 6.54% fat, 10.64% protein, 8.57% carbohydrates, 116.17 mg/100g vitamin C (ascorbic acid), and 383 mg GAE/g total phenolic compounds [7, 25]; Guava leaves are also rich in various macronutrients and micronutrients, including 82.47% moisture, 3.64% ash, 0.62% fat, 18.53% protein, 12.74% carbohydrates, 103 mg/100g vitamin C (ascorbic acid), and 1717 mg GAE/g total phenolic compounds [7, 26]. The general approximate contents of bioactive components in guava fruits and leaves are presented in **Table 1**. As indicated in the table, guava leaves exhibit higher moisture content, ash content, protein content, and fiber content, while guava fruits have higher fat content and vitamin C content. These values should not be compared directly because the cited reports do not consistently specify or harmonize wet-weight, dry-weight, and extract-equivalent bases. Apparent differences may therefore reflect tissue water content, cultivar, maturity, extraction, and analytical method rather than organ-specific composition alone.

Table 1. Proximate composition and key bioactive components of guava fruit and leaves.

	Guava Fruit	Guava Leaf
Moisture ^[7, 26]	52.18%	82.47%
Ash ^[7, 26]	2.42%	3.64%
Fat ^[7, 26]	6.54%	0.62%
Protein ^[7, 26]	10.64%	18.53%
Carbohydrate ^[7, 26]	8.57%	12.74%
Vitamin C(Ascorbic Acid) ^[25, 26]	0.116%	0.103%
Total Phenolic Compounds(TPC) ^[25, 26]	383 mg GAE/g	1717 mg GAE/g

3.1.2. Extraction workflow and reported activities of guava leaf polysaccharides

Among macronutrients, polysaccharides are ubiquitous in animals and plants in nature. Composed of monosaccharides linked through long polymer chains, plant-derived polysaccharides exhibit diverse biological activities and pharmacological properties, such as antioxidant, anti-inflammatory, antibacterial, antitumor, hypoglycemic, and immunomodulatory effects [27–29]. Reported preparation of guava leaf polysaccharides (GLPs) can be organized into five steps: leaf drying and milling, aqueous dispersion of the powder, ultrasonic-assisted extraction (reported at 100 W), separation and concentration of the aqueous phase, and ethanol precipitation followed by recovery and purification of the polysaccharide fraction [13, 30, 31]. The cited studies do not consistently report extraction time, temperature, solid-to-liquid ratio, final ethanol concentration, molecular-weight distribution, or purification yield; this limits reproducibility and cross-study comparison. One preparation contained 64.42% total sugar and 9.13% uronic acid [31]. In chemical assays, GLPs scavenged DPPH, hydroxyl, and superoxide-anion radicals; reported values included $65.43 \pm 2.56\%$ DPPH scavenging, $23.30 \pm 1.29\%$ hydroxyl-radical scavenging, and a DPPH IC₅₀ as low as 45.18 µg/mL after ultrasonic-assisted extraction [32, 33]. GLPs also inhibited α -glucosidase in vitro, with reported IC₅₀

values of 790–904.67 $\mu\text{g/mL}$, whereas α -amylase inhibition was weaker or incompletely quantified [13, 34–37]. Acarbose primarily inhibits intestinal brush-border α -glucosidases and also inhibits pancreatic α -amylase; its gastrointestinal adverse effects result from fermentation of incompletely digested carbohydrate, not from elevated blood glucose [38, 39]. Claims that GLPs are superior to acarbose are therefore not justified unless both are tested under the same assay conditions and comparison basis. Current GLP data support preclinical antioxidant and enzyme-inhibitory activity, but not clinical antidiabetic efficacy [31, 40].

3.1.3. Proteins, vitamins, and minerals

Proteins are fundamental components of life activities, participating in energy supply, tissue construction and repair, enzyme formation, intracellular transport and storage of substances, as well as immunomodulation and hormonal functions. They also play a crucial role in intercellular signal transduction [41, 42]. Proteins, carbohydrates, and dietary fiber contribute to the nutritional value and processing behavior of guava tissues [39, 40]. Reported protein measurements in guava leaves vary with the analytical basis, including values of 65.87–133.51 g BSAE/100 g in extract-based assays and approximately 9.73% on a dry-weight basis [43]. Owing to its rich content of proteins, carbohydrates, and dietary fiber, guava leaves can be developed as a novel food source for further research in the future [15].

Vitamins and minerals, as micronutrients, are indispensable components for human nutrient supplementation. Guava is rich in various vitamins and minerals, with vitamin C content being particularly prominent—reaching 200–400 mg per 100 g of pulp. This renders guava a potent natural antioxidant, contributing to immune enhancement and collagen synthesis promotion [44, 45]. In addition, guava is also rich in vitamin A (present as β -carotene, with a content of approximately 30–50 $\mu\text{g}/100\text{ g}$), which is crucial for maintaining visual acuity and skin health [46, 47]. In terms of minerals, guava is a good source of potassium (containing approximately 400–500 mg per 100 g of pulp), and also contains magnesium (about 20–30 mg/100 g), calcium (around 15–20 mg/100 g), and iron (roughly 0.2–0.5 mg/100 g) [5, 48–50]. In addition, guava also contains trace amounts of zinc and selenium. Trace zinc and selenium may support antioxidant enzymes, but their low concentrations do not justify attributing extract-level pharmacological effects to these minerals alone [8, 9, 51]. These reporting limitations make preparation-specific characterization essential before composition is linked to biological activity.

3.2. Secondary metabolites in guava leaves

Although plant leaves are often considered useless, they can provide a rich source of nutritionally valuable and medicinal compounds. Guava leaves are abundant in bioactive compounds. Among all plant organs, leaves accumulate the highest concentration of bioactive compounds, such as plant secondary metabolites. Specifically, guava leaves are rich in secondary metabolites including essential oils, flavonoids, and polyphenols [6, 52–54].

Guava leaves are rich in chemical essential oil components. According to a study by Kamalpreet Jassal and Sonia Kaushal, the main components of guava leaf essential oil include monoterpenes, sesquiterpenes, and their oxygenated derivatives, among which limonene and β -caryophyllene are the core components.

Specifically, the major monoterpenes in guava leaf essential oil include limonene and α -pinene. The main sesquiterpenes and oxygenated sesquiterpenes include β -caryophyllene, 8-cineole (eucalyptol), caryophyllene oxide, and δ -cadinol. Other components include α -selinene, β -selinene, veridiflorol, and trans-caryophyllene [54–56]. Limonene, as the major monoterpene, imparts a distinctive lemon aroma to the essential oil, while β -caryophyllene, a significant sesquiterpene, exhibits notable anti-inflammatory and antibacterial activities [57, 58]. In addition, guava leaf essential oil contains a relatively high proportion of oxygenated compounds, such as 8-cineole, which plays important roles in antioxidation and antibacterial activity. The diverse types and substantial content of essential oils further enhance the application value of guava leaves [26, 59, 60].

Foods rich in bioactive compounds with therapeutic effects on chronic diseases are gaining increasing attention. Compounds found in guava fruit and leaves exhibit outstanding antioxidant and hypoglycemic activities, attributable not only to the fruit's high content of proteins, polysaccharides, vitamins, and minerals, but also closely linked to its abundant phenolic compounds. Guava leaves contain diverse secondary metabolites including phenolic acids, flavonoids, triterpenes, sesquiterpenes, glycosides, alkaloids, and saponins [61]. Phenolic compounds form the foundation of guava's significant biological activity: Epidemiological studies confirm that polyphenolic compounds exert positive regulatory effects in the prevention and treatment of chronic diseases such as tumors, diabetes, neurodegenerative disorders, and cardiovascular diseases [62–64]. They intervene in various physiological processes—including cellular proliferation, regulation of cellular redox potential, and neurotransmitter signaling pathways—thereby influencing multiple chronic conditions [65]. Phenolic compounds in guava fruits and leaves primarily include gallic acid, quercetin, catechin, ellagic acid, chlorogenic acid, and ferulic acid [26, 66]. Within guava plants, leaf tissue exhibits significantly higher polyphenolic content than fruit. Gallic acid and quercetin are widely recognized as the core bioactive components in leaves [67, 68]. Total phenolic content (TPC) measured using the Folin–Ciocalteu method ranged from 53.24 to 438.80 milligrams gallic acid equivalent per gram (mg GAE/g). Significant variations existed between different origins and extraction methods: for instance, guava leaves from Pakistan yielded a total phenolic content of 83.34 mg GAE/g after methanol extraction. , with significant variations observed across different origins and extraction methods. For instance, Pakistani guava leaves yielded 83.34 mg GAE/g after methanol extraction; Indian guava leaves extracted with methanol reached 125.77 mg GAE/g; Thai guava leaves extracted with 70% ethanol yielded a high total phenolic content of 310.98 mg GAE/g; Chinese guava leaves processed using an enzyme-assisted extraction method (employing cellulase, xylanase, and β -glucosidase) yielded a total phenolic content of 438.80 mg GAE/g, significantly higher than most other extraction methods. The total flavonoid content (TFC) is determined as quercetin equivalent (QE), ranging from 29.66 to 92.38 mg QE/g. Additionally, cultivar variation has a significant impact on TFC: for instance, the flavonoid content of guava leaves from the Indian Karela cultivar is the highest, while the flavonoid content of the ethyl acetate extract from the Indian Allahabad Safeda cultivar is the lowest [13]. A 2024 study verified that the total phenolic content (TPC) and total flavonoid content (TFC) in guava leaves extracted by microwave - assisted extraction and ultrasonic - assisted extraction technologies are

significantly higher than those obtained by traditional solvent extraction methods, which further optimizes the extraction efficiency of phenolic compounds [30]. As shown in **Table 2 (Supplementary Figure S1–S4)**, guava leaves were analyzed using high-performance liquid chromatography coupled to electrospray ionization quadrupole–time-of-flight mass spectrometry (HPLC–ESI–QTOF–MS). The phenolic compounds identified in guava leaves include guajaverin, quercetin, avicularin, myricetin, hyperin, kaempferol, apigenin, gallic acid, rutin, chlorogenic acid, pyrogallol, isoquercitrin, caffeic acid, luteolin, morin, prodelphinidin dimer isomer, pedunculagin, casuariin, vanillic acid, ellagic acid, myrciaphenone B, vescalagin, delphinidin-3-O-glucoside, gallocatechin, catechin, protocatechuic acid, resveratrol, and cyanidin-3-O-glucoside [7, 56].

Table 2. Chemical classification and evidence-specific bioactivity of compounds reported in guava leaves.

Components	Classification	Source and extraction/identification	Evidence-specific key bioactivity	Refs.
Limonene	Cyclic monoterpene	Guava leaf essential oil; hydrodistillation or steam distillation; GC-MS.	Present in antioxidant/antimicrobial essential-oil fractions	[58, 59]
α - Pinene	Bicyclic monoterpene	Guava leaf essential oil; hydrodistillation or steam distillation; GC-MS.	Present in bioactive essential-oil fractions	[58, 59]
β - Caryophyllene	Bicyclic sesquiterpene	Guava leaf essential oil; hydrodistillation or steam distillation; GC-MS.	Anti-inflammatory and antibacterial activity reported; contribution within guava oil not quantified	[58, 59, 61]
1,8 - Cineole (Eucalyptol)	Oxygenated monoterpene	Guava leaf essential oil; hydrodistillation or steam distillation; GC-MS.	Associated with antioxidant and antimicrobial essential-oil activity	[58, 59, 61]
Guajaverin	Flavonol O-glycoside	Guava leaves; solvent, UAE, MAE, or enzyme-assisted extraction; HPLC–ESI–QTOF–MS/NMR.	Isolated-compound α -glucosidase inhibition; antioxidant and signaling effects mainly preclinical	[59, 61, 62]
Quercetin	Flavonol	Guava leaves; solvent, UAE, MAE, or enzyme-assisted extraction; HPLC–ESI–QTOF–MS/NMR.	Radical scavenging and proposed Nrf2, insulin-signaling, antimicrobial, and immunomodulatory effects	[59, 61, 62]
Avicularin	Flavonol O-glycoside	Guava leaves; solvent, UAE, MAE, or enzyme-assisted extraction; HPLC–ESI–QTOF–MS/NMR.	Identified in guava leaves; compound-specific activity not established in the cited guava studies	[59, 61, 62]
Myricetin	Flavonol	Guava leaves; solvent, UAE, MAE, or enzyme-assisted extraction; HPLC–ESI–QTOF–MS/NMR.	Identified in guava leaves; compound-specific activity not established in the cited guava studies	[59, 61, 62]
Hyperin	Flavonol O-glycoside	Guava leaves; solvent, UAE, MAE, or enzyme-assisted extraction; HPLC–ESI–QTOF–MS/NMR.	Identified in guava leaves; compound-specific activity not established in the cited guava studies	[59, 61, 62]
Kaempferol	Flavonol	Guava leaves; solvent, UAE, MAE, or enzyme-assisted extraction; HPLC–ESI–QTOF–MS/NMR.	Proposed antimicrobial and immunomodulatory effects; most target evidence is not guava-specific	[59, 61, 62]
Apigenin	Flavone	Guava leaves; solvent, UAE, MAE, or enzyme-assisted extraction; HPLC–ESI–QTOF–MS/NMR.	Immunomodulatory activity reported for the isolated flavone; contribution in guava extracts not quantified	[59, 61, 62]

Gallic acid	Hydroxybenzoic acid	Guava leaves; solvent, UAE, MAE, or enzyme-assisted extraction; HPLC–ESI–QTOF-MS/NMR.	Antioxidant and glucose-metabolism-related activity proposed; guava-extract attribution remains indirect	[59, 61, 62]
Rutin	Flavonol O-glycoside	Guava leaves; solvent, UAE, MAE, or enzyme-assisted extraction; HPLC–ESI–QTOF-MS/NMR.	Present in antioxidant/metabolic leaf extracts; isolated contribution not quantified	[59, 61, 62]
Chlorogenic acid	Hydroxycinnamic-acid ester	Guava leaves; solvent, UAE, MAE, or enzyme-assisted extraction; HPLC–ESI–QTOF-MS/NMR.	Present in antioxidant and glucose-regulatory leaf extracts; isolated contribution not quantified	[59, 61, 62]
Pyrogallol	Benzenetriol/simple phenol	Guava leaves; solvent, UAE, MAE, or enzyme-assisted extraction; HPLC–ESI–QTOF-MS/NMR.	Identified in guava leaves; compound-specific activity not established in the cited guava studies	[59, 61, 62]
Isoquercitrin	Flavonol O-glycoside	Guava leaves; solvent, UAE, MAE, or enzyme-assisted extraction; HPLC–ESI–QTOF-MS/NMR.	Identified in guava leaves; compound-specific activity not established in the cited guava studies	[59, 61, 62]
Caffeic acid	Hydroxycinnamic acid	Guava leaves; solvent, UAE, MAE, or enzyme-assisted extraction; HPLC–ESI–QTOF-MS/NMR.	Identified in guava leaves; compound-specific activity not established in the cited guava studies	[59, 61, 62]
Luteolin	Flavone	Guava leaves; solvent, UAE, MAE, or enzyme-assisted extraction; HPLC–ESI–QTOF-MS/NMR.	Identified in guava leaves; compound-specific activity not established in the cited guava studies	[59, 61, 62]
Morin	Flavonol	Guava leaves; solvent, UAE, MAE, or enzyme-assisted extraction; HPLC–ESI–QTOF-MS/NMR.	Identified in guava leaves; compound-specific activity not established in the cited guava studies	[59, 61, 62]
Pedunculagin	Ellagitannin	Guava leaves; solvent, UAE, MAE, or enzyme-assisted extraction; HPLC–ESI–QTOF-MS/NMR.	Reported as a leaf ellagitannin; activity is mainly inferred from polyphenol-rich fractions	[59, 61, 62]
Casuarinin	Ellagitannin	Guava leaves; solvent, UAE, MAE, or enzyme-assisted extraction; HPLC–ESI–QTOF-MS/NMR.	Reported as a leaf ellagitannin; activity is mainly inferred from polyphenol-rich fractions	[59, 61, 62]
Vanillic acid	Hydroxybenzoic acid	Guava leaves; solvent, UAE, MAE, or enzyme-assisted extraction; HPLC–ESI–QTOF-MS/NMR.	Identified in guava leaves; compound-specific activity not established in the cited guava studies	[59, 61, 62]
Ellagic acid	Polyphenolic dilactone	Guava leaves; solvent, UAE, MAE, or enzyme-assisted extraction; HPLC–ESI–QTOF-MS/NMR.	Antioxidant and antifungal activity reported; contribution in guava extracts not quantified	[59, 61, 62]
Myrciaphenone B	Acylphloroglucinol derivative	Guava leaves; solvent, UAE, MAE, or enzyme-assisted extraction; HPLC–ESI–QTOF-MS/NMR.	Identified in guava leaves; compound-specific activity not established in the cited guava studies	[59, 61, 62]
Vescalagin	Ellagitannin	Guava leaves; solvent, UAE, MAE, or enzyme-assisted extraction; HPLC–ESI–QTOF-MS/NMR.	Identified in guava leaves; compound-specific activity not established in the cited guava studies	[59, 61, 62]
Delphinidin - 3 - O - glucoside	Anthocyanin glycoside	Guava leaves; solvent, UAE, MAE, or enzyme-assisted extraction; HPLC–ESI–QTOF-MS/NMR.	Identified in guava leaves; compound-specific activity not established in the cited guava studies	[59, 61, 62]

Galocatechin	Flavan-3-ol	Guava leaves; solvent, UAE, MAE, or enzyme-assisted extraction; HPLC–ESI–QTOF-MS/NMR.	Identified in guava leaves; compound-specific activity not established in the cited guava studies	[59, 61, 62]
Catechin	Flavan-3-ol	Guava leaves; solvent, UAE, MAE, or enzyme-assisted extraction; HPLC–ESI–QTOF-MS/NMR.	Present in bioactive leaf extracts; isolated contribution not quantified	[59, 61, 62]
Protocatechuic acid	Hydroxybenzoic acid	Guava leaves; solvent, UAE, MAE, or enzyme-assisted extraction; HPLC–ESI–QTOF-MS/NMR.	Identified in guava leaves; compound-specific activity not established in the cited guava studies	[59, 61, 62]
Resveratrol	Stilbene	Guava leaves; solvent, UAE, MAE, or enzyme-assisted extraction; HPLC–ESI–QTOF-MS/NMR.	Identified in guava leaves; compound-specific activity not established in the cited guava studies	[59, 61, 62]
Cyanidin - 3 - O - glucoside	Anthocyanin glycoside	Guava leaves; solvent, UAE, MAE, or enzyme-assisted extraction; HPLC–ESI–QTOF-MS/NMR.	Identified in guava leaves; compound-specific activity not established in the cited guava studies	[59, 61, 62]

Quercetin is the primary phenolic compound responsible for the bioactive properties of guava leaves. Silva et al. increased the total phenolic content (TPC) of guava leaves by 30% via microwave-assisted extraction (MAE), while the TPC extraction efficiency of ultrasonic-assisted extraction (UAE) was significantly superior to that of the traditional maceration method. Specifically, the TPC extraction efficiency of UAE was enhanced by approximately 184% to 210.5% [69–71]. Traditional chromatographic techniques (e.g., Sephadex LH-20 column chromatography and reversed-phase thin-layer chromatography) are used for the separation and purification of phenolic compounds. Combined with nuclear magnetic resonance (NMR) and mass spectrometry (MS) for structural identification, these methods have revealed the molecular basis underlying the antioxidant and antibacterial activities of these compounds [72, 73]. Emerging technologies such as MALDI-TOF mass spectrometry imaging have been further applied for the in situ analysis of phenolic compounds. It has been found that quercetin and chlorogenic acid are mainly accumulated in leaf veins and epidermal cells, which may be associated with photoprotective functions [20, 21]. These advances connect tissue structure to chemistry, although direct links between spatial localization and pharmacological outcomes remain to be tested. Together, the compositional data identify plausible active fractions, while the following section evaluates whether their proposed pathways are supported by organ- and preparation-specific evidence.

4. Comparative bioactivities of guava fruits and leaves

Guava fruits and leaves converge on three recurring process-level mechanisms: direct radical scavenging and metal chelation; inhibition of carbohydrate-hydrolyzing enzymes or intestinal glucose transport; and modulation of redox, inflammatory, and insulin-signaling networks, including Keap1-Nrf2-ARE, NF-κB, and PI3K-Akt pathways. These common pathways do not imply equivalent efficacy. Fruit studies usually examine edible matrices rich in vitamin C, fiber, and pulp phenolics, whereas leaf studies more often use concentrated phenolic or polysaccharide extracts and extend to antitumor and immunomodulatory outcomes. Mechanisms inferred from crude extracts are treated as proposed unless isolated-compound experiments, target-engagement assays, or intervention studies identify the responsible constituent and node.

Mechanisms proposed on the basis of crude extracts are described as proposed unless direct evidence is available from isolated compounds, target-engagement assays, or intervention studies.

4.1. Antioxidant activity of guava fruit

Oxidation is one of the most common chemical reactions in daily life, where substances react with oxygen, resulting in the loss of electrons or changes in their chemical structure [74]. In organisms, oxidation reactions are often associated with the generation of free radicals. Free radicals are particles that lack one or more electrons in their molecular structure, typically highly reactive, which attack cells and molecules, causing cellular damage or aging, and may even trigger diseases [75]. The production of free radicals in the human body can contribute to inflammatory diseases, neurological disorders, hemochromatosis, acquired immunodeficiency syndrome (AIDS), and other conditions [76]. The antioxidant activity of phenolic compounds primarily relies on the phenolic hydroxyl groups (–OH) in their molecular structure. They can prevent free radical-induced cellular damage by scavenging free radicals and neutralizing oxidizing substances [77]. In addition, phenolic compounds further reduce the risk of oxidative damage by donating electrons to reduce oxidized metal ions, chelating metal ions, and inhibiting lipid peroxidation [78]. As a tropical fruit with prominent antioxidant activity, the guava fruit's effects stem from its rich bioactive components, including polyphenols (such as gallic acid and ellagic acid; the total phenolic content in red-fleshed varieties reaches 32 mg/g dry weight), flavonoids (such as quercetin; content: 1.8 mg/g dry weight), vitamin C (200–400 mg/100g fresh weight), and pectic polysaccharides (5–10%). As shown in **Figure 1**, Guava-associated antioxidant effects can be separated into direct chemical reactions and inducible cellular defenses. Fruit polyphenols and flavonoids donate hydrogen or electrons in DPPH and ABTS assays, vitamin C scavenges aqueous radicals, and polysaccharides may chelate Fe²⁺ and Cu²⁺, thereby limiting Fenton chemistry [9, 79]. **Figure 1** connects these constituents to the Keap1–Nrf2–ARE axis: Keap1 normally promotes Nrf2 degradation [77, 80]. At the pathway regulation level, quercetin-containing guava preparations may modulate the Keap1–Nrf2–ARE pathway, promoting the nuclear translocation of Nrf2 to bind to ARE, which initiates the transcription of antioxidant enzymes such as SOD, CAT, and GSH-Px, thereby significantly reducing the production of the lipid peroxidation product MDA [81, 82]. Related evidence from another food–medicine homologous plant showed that a flavonoid-rich mulberry leaf extract enhanced hepatic and plasma antioxidant capacity, increased CAT and GSH-Px activities, and reduced oxidative stress in a high-fat-diet mouse model [83]. Although this evidence is not guava-specific, it supports the broader biological plausibility that flavonoid-rich preparations can modulate endogenous antioxidant defenses in addition to exerting direct radical-scavenging effects. In addition, extraction processes and cultivars have a significant impact on its antioxidant activity, red-fleshed fruit has been reported to contain approximately 32 mg/g dry weight total phenolics, 1.8 mg/g dry weight quercetin, and 200–400 mg/100 g fresh weight vitamin C, while methanolic fruit extracts showed up to 78.4% DPPH scavenging under one assay condition. These findings provide molecular-level theoretical support and process optimization directions for the application of guava fruit in functional food and pharmaceutical fields [84].

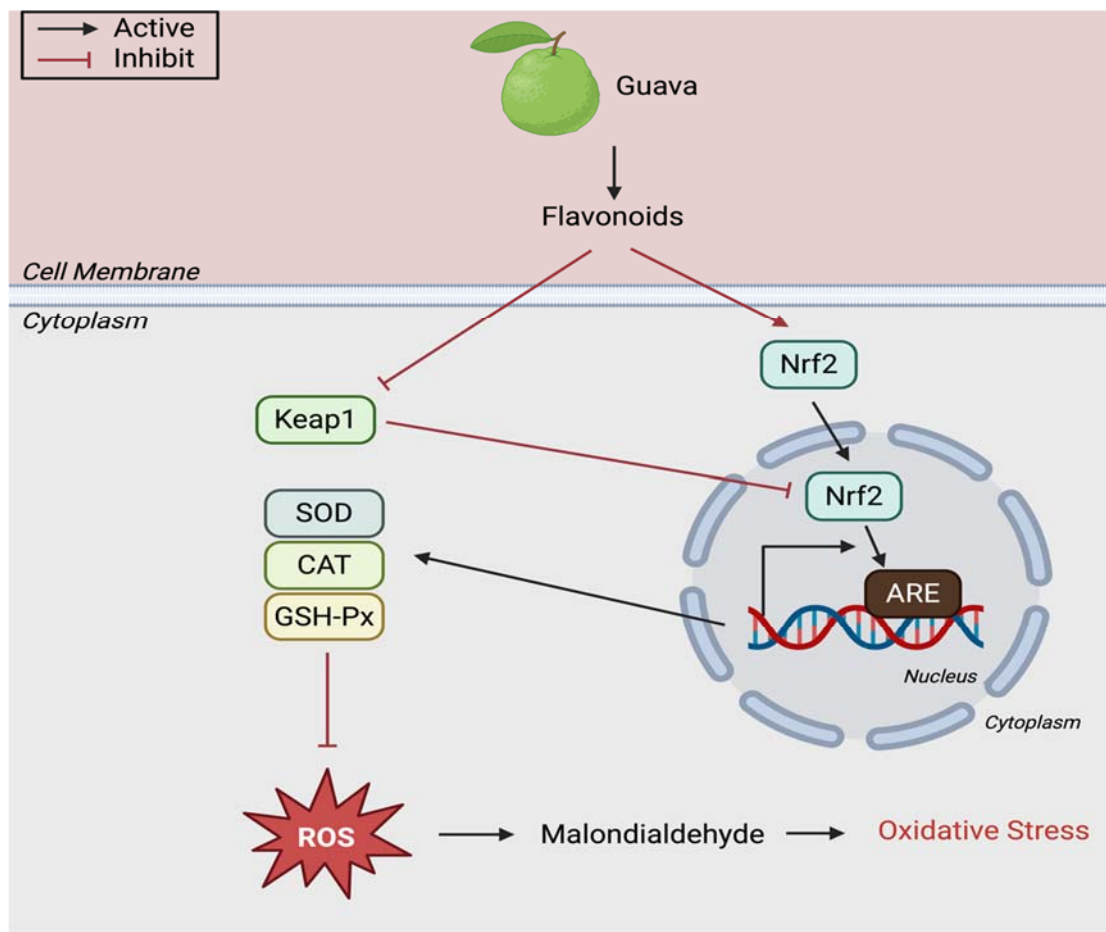


Figure 1. Proposed antioxidant pathway of guava fruit. Quercetin-containing flavonoids are mapped to Kelch-like ECH-associated protein 1 (Keap1) inhibition and nuclear factor erythroid 2-related factor 2 (Nrf2) translocation; antioxidant response element (ARE) activation increases superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px), thereby reducing reactive oxygen species (ROS).

4.2. Antidiabetic activity of guava fruit

Diabetes mellitus is a metabolic disease characterized by hyperglycemia, primarily caused by insufficient insulin secretion or impaired insulin action. It can be classified into Type 1 diabetes, Type 2 diabetes, and gestational diabetes, among other types. Type 2 diabetes is the most prevalent, typically closely associated with factors such as genetics, obesity, unhealthy diet, and lack of physical activity. Chronic hyperglycemia can damage vital organs including the heart, kidneys, nerves, and eyes, thereby triggering complications such as cardiovascular diseases, diabetic nephropathy, nerve damage, and retinopathy. In the human digestive system, α -amylase hydrolyzes the 1,4-glycosidic linkages of polysaccharides (e.g., starch and glycogen) and disaccharides, while α -glucosidase hydrolyzes disaccharides into monosaccharides, leading to postprandial hyperglycemia [85-88].

Guava preparations have therefore been studied against four relevant processes: carbohydrate digestion, intestinal glucose transport, insulin signaling, and hepatic glucose production. Additionally, the polyphenol content in red-fleshed cultivars is significantly higher than that in white-fleshed ones, resulting in stronger antidiabetic activity [89, 90]. Candidate fruit constituents include quercetin and gallic acid, which may affect insulin-signaling and redox pathways; ursolic acid, which has been associated with insulin sensitivity; pectic

polysaccharides, which can inhibit carbohydrate-hydrolyzing enzymes; and chromium, which may influence insulin-receptor function [88-92]. Red-fleshed and white-fleshed cultivars differ in phenolic content, but cultivar comparisons are confounded when maturity, extraction, and dose are not matched. [91-93].

Figures 2 and 3 separate intestinal, peripheral, and hepatic glucose-regulatory mechanisms. In **Figure 2**, inhibition of α -amylase and α -glucosidase reduces the formation of absorbable monosaccharides, while modulation of sodium-glucose cotransporter 1 (SGLT1) and glucose transporter 2 (GLUT2) may reduce intestinal glucose transport [94]. In skeletal muscle and adipose tissue, insulin-receptor substrate 1 (IRS-1), phosphoinositide 3-kinase (PI3K), and protein kinase B (Akt) promote glucose transporter 4 (GLUT4) translocation and glucose uptake [95-97]. Hepatocytes predominantly express GLUT2 rather than GLUT4; hepatic PI3K-Akt signaling instead suppresses glucose-6-phosphatase catalytic subunit (G6pc) and phosphoenolpyruvate carboxykinase (PEPCK) and supports glycogen synthesis [96]. Nrf2 activation and reductions in tumor necrosis factor α (TNF- α) and interleukin 6 (IL-6) may protect pancreatic β -cells in diabetic animal models [97-101]. These links remain a proposed multi-target model because the cited studies use different preparations and experimental systems. This distinction between peripheral GLUT4-mediated uptake and hepatic GLUT2-mediated transport is also applied to the leaf and guaijaverin pathways below.

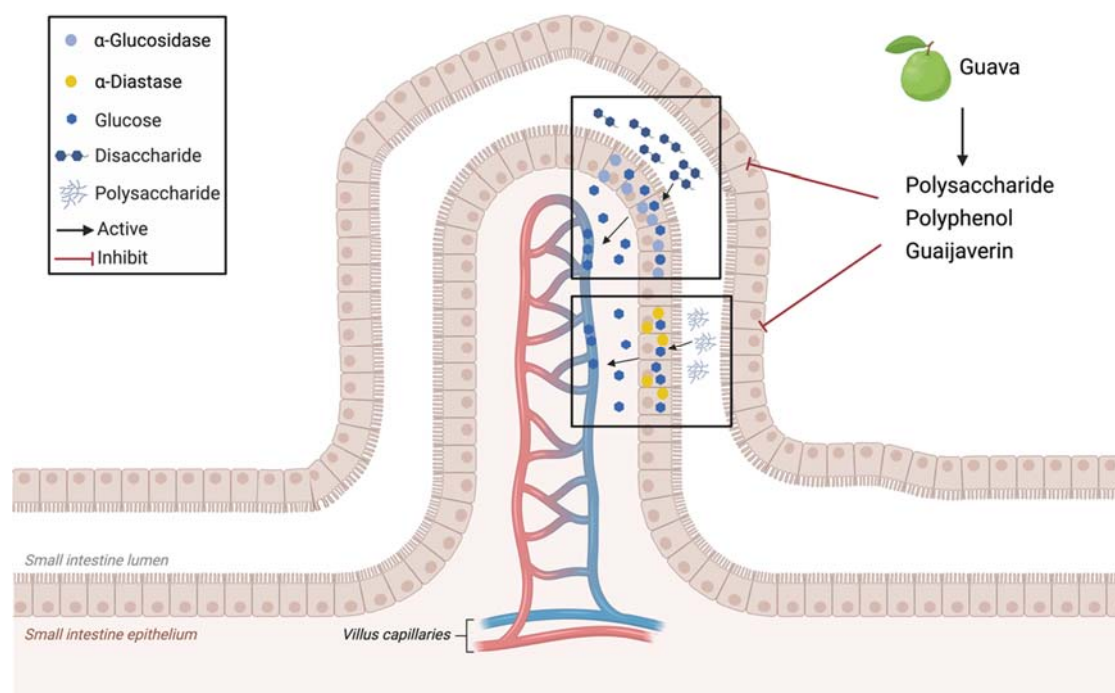


Figure 2. Proposed intestinal glucose-regulatory actions of guava. Guava leaf polysaccharides, polyphenols, and guaijaverin are mapped to inhibition of α -glucosidase and α -diastase (α -amylase), reducing conversion of dietary carbohydrate to absorbable glucose. The figure does not quantify inhibition or establish equivalent potency among preparations.

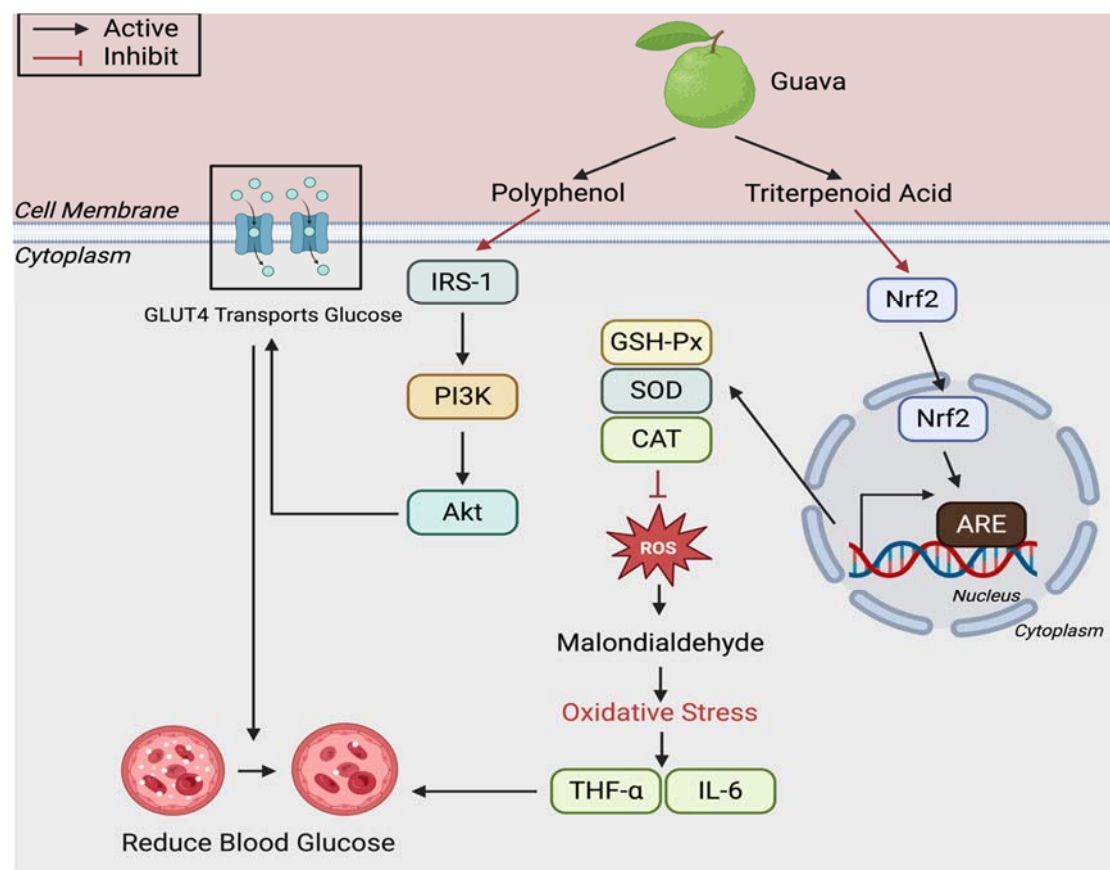


Figure 3. Proposed glucose-regulatory and antioxidant pathways of guava fruit. Polyphenols are mapped to insulin receptor substrate 1 (IRS-1), phosphoinositide 3-kinase (PI3K), protein kinase B (Akt), and glucose transporter 4 (GLUT4) in skeletal muscle and adipose tissue; triterpenoid acids are mapped to Nrf2-ARE signaling. SOD, CAT, GSH-Px, ROS, tumor necrosis factor α (TNF- α), and interleukin 6 (IL-6) denote downstream redox and inflammatory markers.

4.3. Anti-inflammatory and antibacterial activities of guava fruit

In the human body, the inflammatory response is a complex defensive reaction of the organism to harmful stimuli such as infection, injury, or toxins. Its core function lies in eliminating pathogens, repairing damaged tissues, and restoring homeostasis ^[102]. The inflammatory response can be divided into acute and chronic phases. The former is characterized by redness, swelling, heat, pain, and dysfunction, while the latter is associated with persistent immune activation and tissue remodeling ^[103]. The pathogenesis of inflammation involves a cascade process of immune recognition, vascular response, and mediator release: Pathogen-Associated Molecular Patterns (PAMPs) or Damage-Associated Molecular Patterns (DAMPs) activate signaling pathways such as NF- κ B through pattern recognition receptors (e.g., TLRs), triggering the release of pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6) and lipid mediators. Among these, 5-LOX, as a key metabolic enzyme, catalyzes arachidonic acid to produce leukotrienes (LTB₄, CysLTs), which in turn mediate effects including neutrophil chemotaxis, increased vascular permeability, and smooth muscle contraction. It is significantly upregulated in chronic inflammatory diseases such as asthma and atherosclerosis ^[104, 105]. Notably, the 5-LOX and cyclooxygenase (COX) pathways synergistically regulate the inflammatory process. Their products, leukotrienes and prostaglandins, collectively amplify inflammatory signals. However, under specific conditions, this enzyme can also participate in the synthesis of pro-resolving mediators (e.g., lipoxins), indicating the bidirectionality of its effects ^[106].

In terms of anti-inflammatory activity, as shown in **Figure 4**, guava fruit exerts its effects primarily by regulating inflammatory signaling pathways and the balance of oxidative stress, with core mechanisms focusing on NF- κ B pathway inhibition and pro-inflammatory cytokine downregulation [107]. Quercetin-containing preparations are proposed to limit NF- κ B p65 nuclear translocation, thereby reducing transcription of TNF- α , IL-1 β , and IL-6, while vitamin C and phenolics may activate Nrf2-dependent antioxidant defenses. In cell and mouse models, guava fruit extracts reduced selected cytokines, myeloperoxidase activity, neutrophil infiltration, joint effusion, and synovial hyperplasia [108]. In an osteoarthritic inflammatory cell model, treatment with a high dose of guava fruit extract significantly reduced the intracellular levels of TNF- α and IL-6 compared with the model group. Meanwhile, it markedly inhibited the activity of inflammation-related enzymes (e.g., myeloperoxidase, MPO) and decreased neutrophil infiltration [109, 110]. In addition, vitamin C and polyphenols in guava can activate the Nrf2-ARE pathway to upregulate the activity of antioxidant enzymes such as SOD and CAT, reduce the content of the lipid peroxidation product MDA, and alleviate oxidative stress-induced tissue damage. The attenuation of oxidative stress further inhibits the amplification of the inflammatory cascade, forming an "anti-inflammatory-antioxidant" synergistic effect [110, 111]. An *in vivo* experiment, intervention with guava fruit extract significantly improved the pathological manifestations of joint inflammation in mice, reducing joint effusion and synovial hyperplasia. These findings support anti-inflammatory activity under the tested animal conditions. No liver- or kidney-function abnormalities were reported, but this limited observation does not establish general safety or biocompatibility [112].

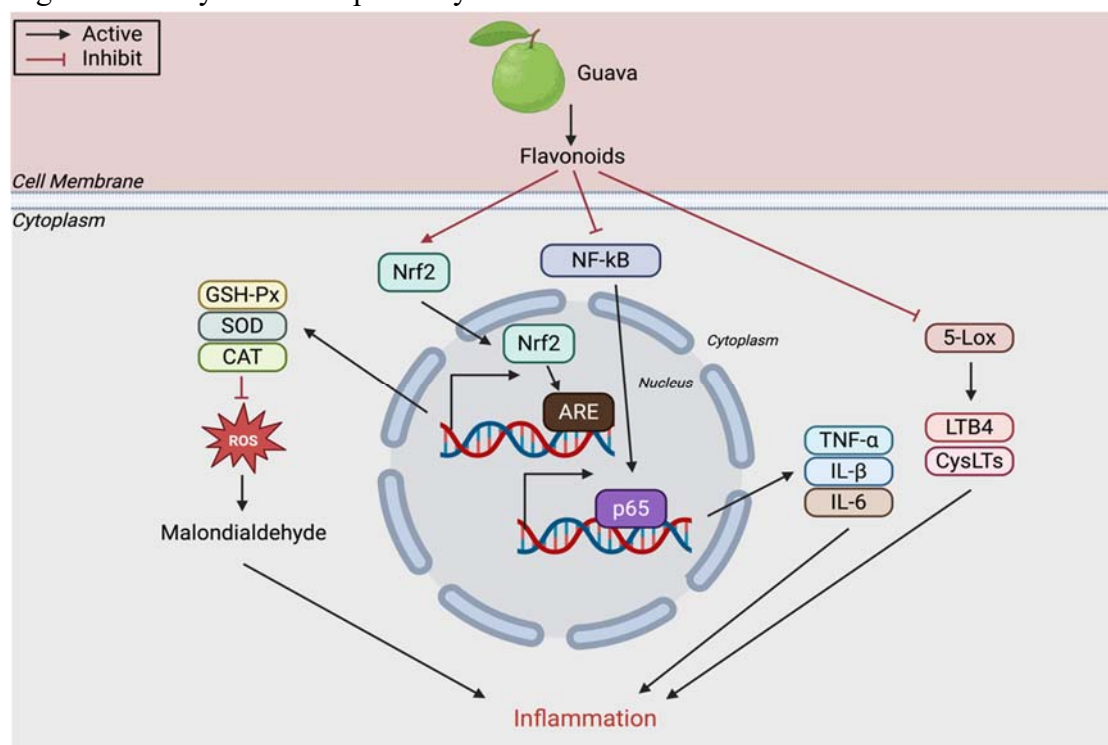


Figure 4. Proposed anti-inflammatory pathways of guava fruit flavonoids. The mapped nodes include Nrf2-ARE antioxidant signaling, nuclear factor kappa B (NF- κ B) and its p65 subunit, 5-lipoxygenase (5-LOX), leukotriene B4 (LTB4), cysteinyl leukotrienes (CysLTs), TNF- α , interleukin 1 β (IL-1 β), and IL-6. These links summarize preclinical evidence and do not represent clinical effect sizes.

As shown in **Figure 5**, in terms of antibacterial activity, guava fruit extract exhibits broad-spectrum inhibitory effects against both Gram-positive bacteria (e.g., *Staphylococcus aureus*) and Gram-negative bacteria (e.g., *Escherichia coli*, *Salmonella*, *Shigella*), with the core mechanism being the disruption of bacterial cell membrane structure and function [15]. Tannins in guava can bind to the lipid bilayer on the surface of bacterial cell membranes, increasing membrane permeability and leading to the leakage of intracellular biomacromolecules such as proteins and nucleic acids, which ultimately induces bacterial lysis [13]; Quercetin, on the other hand, can inhibit the activity of key enzymes involved in bacterial cell wall synthesis, impeding the establishment of cell wall integrity and leading to bacterial death due to osmotic imbalance [113]. *In vitro* antibacterial tests have shown that the minimum inhibitory concentration (MIC) of the methanol extract from guava fruit against *Bacillus* is 0.195 mg/mL [114]. In addition, guava extract can inhibit the expression of bacterial virulence factors—for instance, reducing the secretion of staphylolysin from *Staphylococcus aureus* and decreasing its invasive capacity against host cells. For fungi, its inhibitory effect is achieved by binding to ergosterol in the fungal cell membrane, disrupting membrane fluidity, and inhibiting fungal hypha formation and biofilm construction, which further expands its antibacterial spectrum [115, 116]. Because membrane disruption, enzyme inhibition, and biofilm effects were measured in different organisms and preparations, they should not be interpreted as a single validated mechanism for every guava fruit extract.

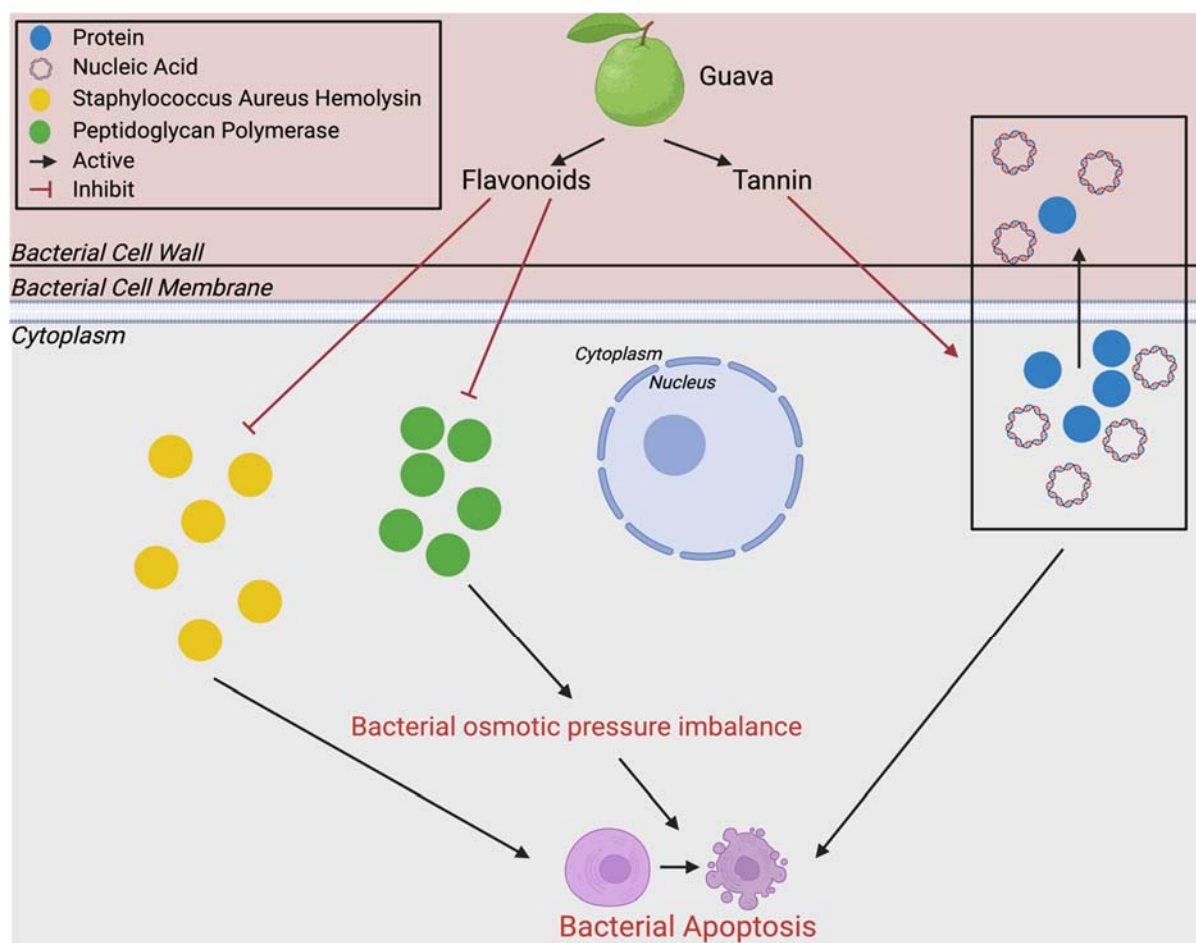


Figure 5. Proposed antimicrobial actions of guava fruit flavonoids and tannins. The diagram maps flavonoids to reduced staphylococcal hemolysin production and interference with peptidoglycan synthesis, and tannins to membrane disruption with leakage of proteins and nucleic acids. These events lead to osmotic imbalance and bacterial cell death rather than apoptosis.

4.4. Biological activities of guava leaves

Guava leaves have been widely used in traditional Chinese medicine. Guava leaves and fruits share core signaling pathways responsible for antioxidant, hypoglycemic, anti-inflammatory and antibacterial effects. The preceding subsections identify pathways shared by fruits and leaves. A separate leaf-focused discussion is retained because leaves generally provide more concentrated phenolic extracts, are processed differently from edible fruit, and have been studied for antitumor and immunomodulatory outcomes in addition to metabolic and antimicrobial activity.

4.4.1. Antidiabetic activity of guava leaves

Guava leaf extracts contain epicatechin, rutin, chlorogenic acid, catechin, gallic acid, and other constituents ^[13]. The bioactive components of guava leaves primarily target the PI3K-Akt signaling pathway to regulate various type 2 diabetes-related genes, modulate the levels of insulin, vitamin D, and DPP4, and address the restricted expression of retinoic acid X receptor (RXR) during type 2 diabetes onset ^[117, 118]. As shown in **Figure 6**, the bioactive components of guava leaves exert antidiabetic effects by regulating the PI3K-AKT signaling pathway, type 2 diabetes regulatory processes, and insulin resistance pathways. In the human body, insulin binds to insulin receptors, triggering signal transduction to activate PI3K, thereby promoting the synthesis and translocation of GLUT4 ^[117, 119-121]. In skeletal muscle and adipose tissue, GLUT4 mediates insulin-stimulated glucose uptake, whereas hepatocytes predominantly express GLUT2; hepatic PI3K-Akt signaling mainly regulates gluconeogenesis and glycogen synthesis ^[122]. Meanwhile, PIP3 produced by PI3K can activate the Akt family, and activated Akt regulates cell growth cycle, metabolism, and glycolysis through phosphorylation ^[123]. In the insulin resistance pathway, TNF can increase free fatty acids to enhance glycogen production in hepatocytes. TNF can activate NF- κ B, and then the activated NF- κ B can in turn further activate TNF, forming a positive feedback mechanism to interfere with the signal transduction of insulin receptors, thereby leading to insulin resistance ^[124, 125]. Heteroterpenoids such as Psiguadial A in the aqueous extract of guava leaves can also enhance the insulin signaling pathway by inhibiting PTP1B, thereby improving insulin resistance. Additionally, flavonoid components in the ethanol extract of guava leaves, such as quercetin-3-O-arabinoside, can promote glucose uptake in adipocytes, and their efficacy in antidiabetic activity is superior to that of insulin ^[126, 127]. Validated by both *in vivo* and *in vitro* experiments, guava leaf extract significantly enhances cellular insulin sensitivity and glucose uptake, while increasing the tyrosine phosphorylation level of Akt in cells ^[119, 128]. GSK-3 is a protein kinase that serves as a crucial downstream component in the PI3K-Akt signaling pathway. Its activity can be inhibited through Akt-mediated phosphorylation of Ser9 on GSK-3 β ^[129]. In experiments combining guava leaf extract with insulin for diabetes treatment, compared with insulin alone, the combination therapy significantly increased the phosphorylation level of GSK-3 β . Furthermore, guava leaf extract reduced the expression of G6pc, a key gene promoting glycolysis and glycogenolysis, enhanced insulin signal activation, promoted glycogen synthesis, and inhibited gluconeogenesis in hepatocytes ^[119, 130, 131]. Guava leaf extract significantly reduces the fasting plasma glucose levels in mice, improves glucose tolerance and insulin sensitivity, increases hepatic glycogen

accumulation and glucose uptake in mice, and decreases the mRNA expression levels of gluconeogenic genes. Thus, it exerts an effective inhibitory effect on diabetes ^[132].

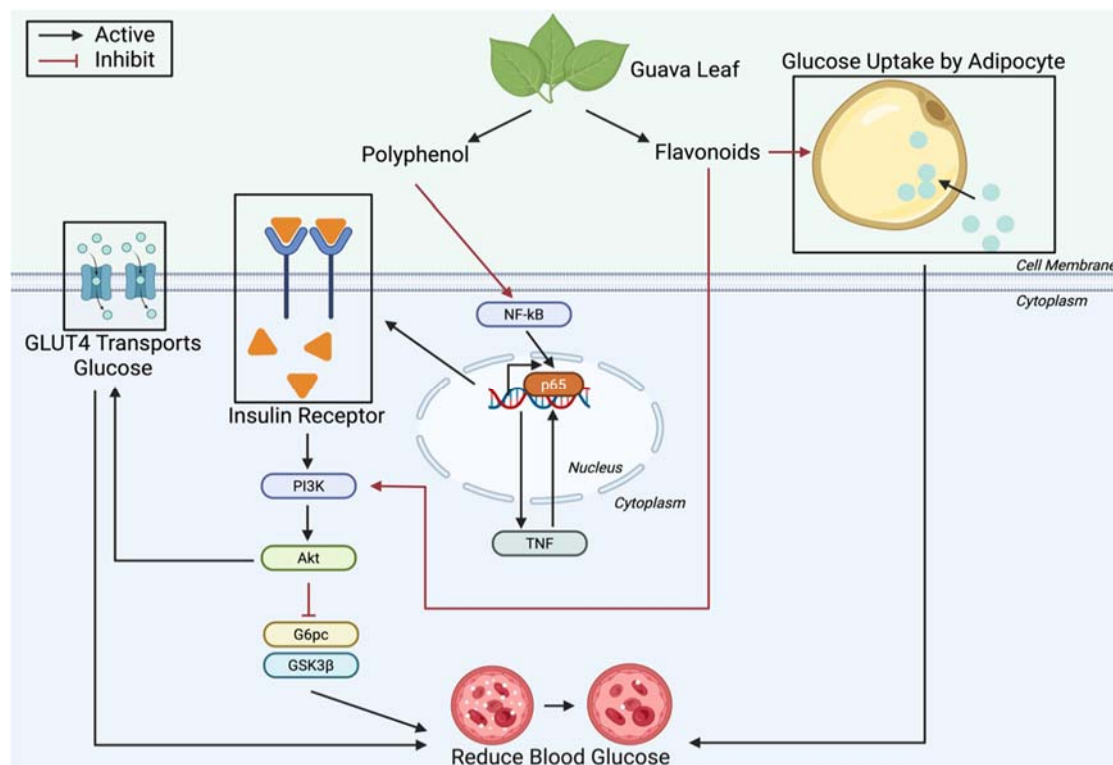


Figure 6. Proposed antidiabetic pathways of guava leaves. Leaf flavonoids are mapped to adipocyte and skeletal-muscle glucose uptake through IRS-1-PI3K-Akt-GLUT4 signaling, while hepatic effects involve glucose transporter 2 rather than GLUT4, suppression of glucose-6-phosphatase catalytic subunit (G6pc), and regulation of glycogen synthase kinase 3 β (GSK-3 β). NF- κ B and TNF denote nuclear factor kappa B and tumor necrosis factor, respectively.

4.4.2. Antitumor activity of guava leaves

A tumor refers to a phenomenon where, under the influence of various tumor-inducing factors, the normal genetic regulation of cells in local tissues is disrupted, leading to abnormal cell growth in the human body ^[133]. Malignant tumors, also known as cancer, are characterized by invasiveness and metastasis. Tumor cells can disrupt normal tissue structures and spread throughout the body via the blood or lymphatic systems, posing a threat to the patient's life ^[134]. Tumorigenesis is a complex, multi-step process involving multiple factors and mechanisms, including gene mutations, dysregulation of cell cycle control, abnormal DNA damage repair, suppression of apoptosis, and immune evasion ^[135]. Activation of oncogenes such as RAS and MYC, along with inactivation of tumor suppressor genes like p53 and RB, can also induce tumors. Furthermore, numerous environmental factors like smoking and radiation interact with genetic mutations to promote tumor formation ^[136]. Tumor cells exhibit characteristics including unlimited proliferation, strong anti-apoptotic capacity, promotion of angiogenesis, and evasion of immune surveillance. Within the tumor microenvironment, abnormal expression of signaling pathways (e.g., PI3K-Akt pathway, MAPK pathway) and overexpression of pro-inflammatory factors (e.g., tumor necrosis factor- α /TNF- α , interleukin-6/IL-6) drive tumor cell progression and metastasis ^[137, 138].

Guava leaf extracts contain candidate antitumor constituents, including oleanolic acid, vitexin, proanthocyanidins, and other phenolics. Proposed mechanisms involve cell-cycle arrest, mitochondrial

apoptosis, reduced extracellular-matrix remodeling, and altered PI3K–Akt–mTOR or Wnt/ β -catenin signaling (Figure 7) [139–142].

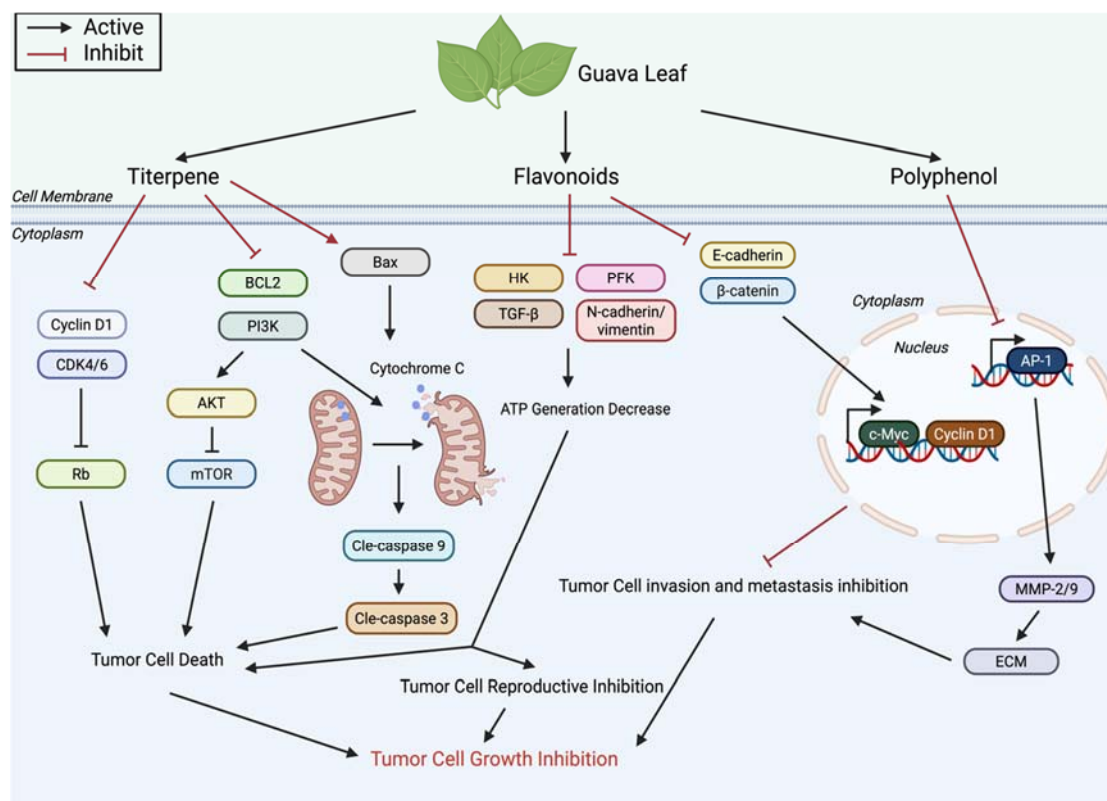


Figure 7. Proposed antitumor mechanisms of guava-leaf constituents. Oleanolic acid is mapped to cyclin D1/cyclin-dependent kinase 4/6 (CDK4/6), phosphoinositide 3-kinase (PI3K)-Akt-mechanistic target of rapamycin (mTOR), B-cell lymphoma 2 (Bcl-2), Bcl-2-associated X protein (Bax), and caspases; vitexin is mapped to hexokinase (HK), phosphofructokinase (PFK), and β -catenin; proanthocyanidins are mapped to activator protein 1 (AP-1) and matrix metalloproteinases 2 and 9 (MMP-2/9). Transforming growth factor β (TGF- β), retinoblastoma protein (Rb), extracellular matrix (ECM), and epithelial-mesenchymal transition markers are also shown.

In terms of inhibiting tumor cell proliferation and inducing apoptosis, different bioactive components exhibit precise targets of action. As a core triterpenoid antitumor component, oleanolic acid can arrest tumor cells at the G0/G1 phase by regulating key cell cycle proteins: it significantly downregulates the expression of cyclin D1 and CDK4/6, inhibits the phosphorylation of retinoblastoma protein (Rb), and prevents cells from transitioning from the G1 phase to the S phase, thereby suppressing the proliferation of hepatocellular carcinoma HepG2 cells and breast cancer MCF-7 cells [143–145]. Oleanolic acid can activate the mitochondrial apoptotic pathway, promote the expression of the pro-apoptotic protein Bax, inhibit the activity of the anti-apoptotic protein Bcl-2, induce a decrease in mitochondrial membrane potential, and thereby activate the caspase-9/caspase-3 cascade reaction to induce tumor cell apoptosis [146, 147]. Vitexin inhibits proliferation by interfering with the energy metabolism of tumor cells: it can inhibit the activity of hexokinase (HK) and phosphofructokinase (PFK), key enzymes in glycolysis, reduce ATP production from anaerobic glycolysis in tumor cells, and simultaneously inhibit the function of mitochondrial respiratory chain complex I to cut off energy supply. The proliferation inhibition rate of vitexin on colorectal adenocarcinoma Caco-2 cells can reach 71.6% [139, 148].

In terms of inhibiting tumor invasion and metastasis, the bioactive components in guava leaves exert their effects by regulating extracellular matrix remodeling and metastasis-related signaling pathways [149]. Proanthocyanidins can significantly reduce the expression and activity of matrix metalloproteinases (MMPs), especially MMP-2 and MMP-9. They inhibit the activation of the transcription factor AP-1, reduce the transcription of MMPs genes, and directly bind to the active sites of MMPs to block their degradation of the extracellular matrix (ECM), thereby inhibiting the invasive ability of gastric cancer SGC-7901 cells [150, 151]. *In vitro* Transwell assays showed that the number of transmembrane cells in the proanthocyanidin-treated group decreased by 67.9% compared with the control group [152]. Isorhamnetin focuses on regulating the epithelial-mesenchymal transition (EMT) process. It can upregulate the expression of the epithelial marker E-cadherin, downregulate the levels of the mesenchymal markers N-cadherin and vimentin, inhibit transforming growth factor- β (TGF- β)-mediated Smad2/3 phosphorylation, block the EMT signaling pathway, and reduce the migratory ability of breast cancer MDA-MB-231 cells [149, 153, 154].

In regulating tumor-related signaling pathways, the bioactive components in guava leaves primarily function by inhibiting the activation of oncogenic pathways and activating tumor suppressor pathways. In the PI3K-Akt-mTOR pathway, oleanolic acid can directly inhibit the activity of PI3K, reduce the production of PIP3, thereby inhibiting the phosphorylation of Akt and mTOR, blocking the transmission of downstream pro-proliferative and anti-apoptotic signals, and significantly suppressing this pathway in pancreatic cancer PANC-1 cells [155, 156]. In the Wnt/ β -catenin pathway, vitexin can promote the binding of β -catenin to adenomatous polyposis coli (APC) protein, accelerate the ubiquitin-dependent degradation of β -catenin, reduce its accumulation in the nucleus, thereby inhibiting the expression of downstream target genes such as c-Myc and Cyclin D1, and exerting a significant inhibitory effect on the activity of this pathway in colorectal cancer SW480 cells [157]. *In vivo* experiments further confirmed that after intragastric administration of guava leaf ethanol extract rich in the aforementioned bioactive components to tumor-bearing mice, the tumor volume of the mice was reduced, the tumor weight was decreased, and the levels of serum tumor markers (such as CEA and CA19-9) were significantly lowered. No obvious liver or kidney damage was reported under the tested conditions, but this finding does not establish systemic safety, long-term tolerability, or human biocompatibility [158]. The antitumor evidence is therefore limited to cell and animal models and requires standardized extracts, exposure data, and independent replication.

4.4.3. Antibacterial and immunomodulatory activities of guava leaves

The antibacterial and immunomodulatory activities of guava leaves rely not only on common components such as epicatechin and rutin but also on diverse bioactive substances contained therein, including quercetin, kaempferol, ursolic acid, and ellagic acid. These multiple bioactive compounds collectively form an inhibitory network against pathogenic bacteria and a regulatory system for the body's immune function through multi-pathway and multi-target mechanisms of action [13].

In terms of antibacterial activity, the abundant flavonoids in guava leaves exhibit an inhibitory effect on drug-resistant strains such as *Candida albicans*, which is comparable to that of the antifungal drug fluconazole.

The underlying antibacterial and immunomodulatory mechanisms involve disrupting the integrity of cell membranes and inhibiting biofilm formation [159, 160]. The bioactive components in guava leaves achieve efficient inhibition by targeting key physiological processes of pathogenic bacteria. As a core triterpenoid component, ursolic acid can directly act on the bacterial cell wall synthesis pathway, inhibit the activity of peptidoglycan polymerase, leading to incomplete cell wall structure and lysis of Gram-positive bacteria (such as *Streptococcus pneumoniae* and *Staphylococcus epidermidis*) due to osmotic imbalance [161]; Ursolic acid can block the expression of outer membrane proteins in Gram-negative bacteria (such as *Pseudomonas aeruginosa* and *Shigella*), thereby reducing the adhesion and invasion of bacteria to host cells [162]. Quercetin and kaempferol exert their effects by interfering with bacterial energy metabolism and signal transduction: quercetin can inhibit cytochrome c oxidase in the bacterial respiratory chain, blocking the ATP synthesis pathway and leading to the interruption of bacterial energy supply; kaempferol can downregulate the expression of luxI/luxR genes in the bacterial quorum sensing system, inhibit the synthesis of virulence factors (such as hemolysin and protease), and reduce bacterial pathogenicity [163, 164]. In addition, ellagic acid exhibits a significant inhibitory effect on fungi (such as *Candida albicans* and *Trichophyton rubrum*). This compound binds to ergosterol in fungal cell membranes, disrupting membrane fluidity while simultaneously inhibiting chitinase activity within fungal cell walls, thereby preventing cell wall repair. In vitro antifungal studies indicate that the minimum inhibitory concentration (MIC) of guava leaf ethanol extract against *Candida albicans* ranges from 0.31 mg/mL to 2.50 mg/mL, demonstrating superior efficacy compared to traditional plant-derived antifungal agents [165, 166]. The antibacterial mechanism of guava leaves is illustrated in **Figure 8**.

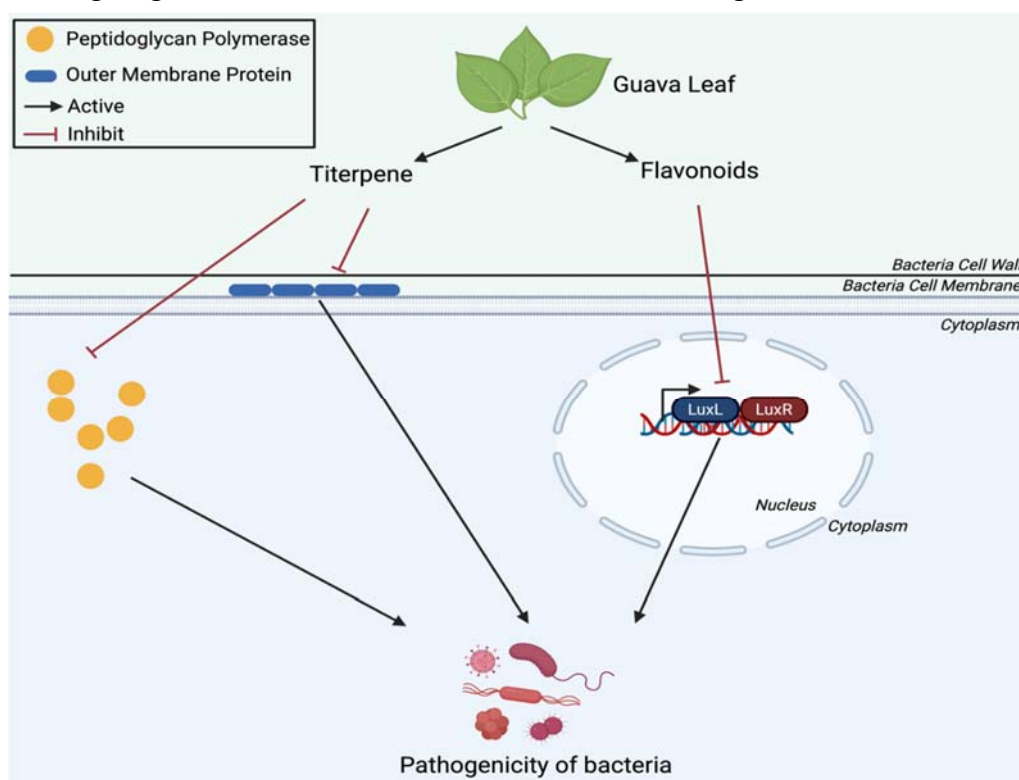


Figure 8. Proposed antibacterial actions of guava-leaf constituents. Ursolic acid and related triterpenes are mapped to peptidoglycan synthesis and outer-membrane proteins, while quercetin and kaempferol are mapped to quorum-sensing nodes, including autoinducer synthase LuxI and its receptor LuxR. The diagram represents mechanistic hypotheses across different bacterial species and preparations.

In terms of immunomodulatory activity, the chemical constituents in guava leaves can optimize the body's immune status by precisely regulating immune cell function and cytokine balance [6]. Quercetin significantly enhances the cytotoxicity of natural killer (NK) cells, promoting their recognition and elimination of tumor cells and infected cells. Simultaneously, it stimulates the maturation of dendritic cells (DCs), enhancing their antigen-presenting capacity and laying the foundation for specific immune responses [167]. Kaempferol, meanwhile, focuses on regulating immune inflammation: It inhibits NLRP3 inflammasome activation, reduces the cleavage and activation of caspase-1, thereby decreasing the release of pro-inflammatory factors interleukin-1 β (IL-1 β) and interleukin-18 (IL-18), and alleviates excessive inflammatory responses within the body. In addition, kaempferol can promote the differentiation of regulatory T cells and inhibit the excessive proliferation of effector T cells by secreting IL-10, maintaining immune tolerance [168, 169]. Ursolic acid exerts a unique regulatory effect on mucosal immunity. It can promote the secretion of mucin 2 (MUC2) by intestinal mucosal epithelial cells, enhance the intestinal mucosal barrier function, and simultaneously stimulate B cells in gut-associated lymphoid tissue (GALT) to secrete secretory immunoglobulin A (sIgA), thereby improving the anti-infection capacity of the mucosal surface [170, 171]. In the PI3K-Akt-mTOR pathway, ursolic acid can activate the phosphorylation of Akt to promote the metabolism and proliferation of immune cells. Meanwhile, by inhibiting the activity of mTOR, it prevents immune exhaustion caused by the excessive activation of immune cells [172]. As shown in **Figure 9**, in the JAK-STAT pathway, quercetin can inhibit the phosphorylation of JAK2 and STAT3, block the transmission of inflammatory signals into the nucleus, and reduce the transcription of inflammatory factors (such as IL-6 and IFN- γ) [172]; *In vivo* experiments confirmed that after intragastric administration of guava leaf extract (rich in newly identified bioactive components) to immunosuppressed mice, the ratio of CD4⁺T cells to CD8⁺T cells in the mouse spleen was significantly increased, and the serum levels of immunoglobulins IgG1 and IgA were significantly higher than those in the model group. These results indicate that guava leaf extract exerts a favorable restorative effect on impaired immune function [173]. Future studies should include chemically matched controls, standardized positive comparators, blinded outcome assessment, pharmacokinetics, and replication across independent models. This leaf-focused evidence extends beyond the shared antioxidant and metabolic pathways, but most compound-to-target assignments remain preclinical.

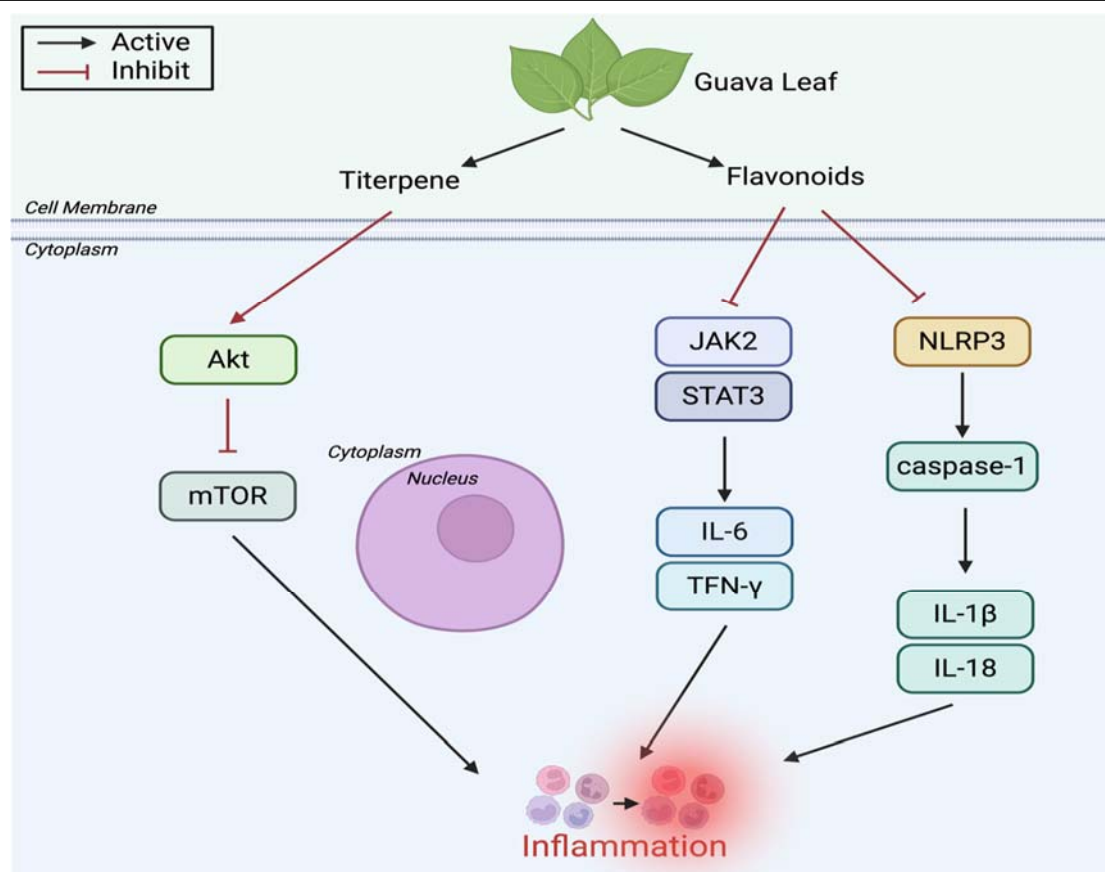


Figure 9. Proposed immunomodulatory pathways of guava-leaf constituents. Ursolic acid is mapped to Akt and mechanistic target of rapamycin (mTOR); quercetin to Janus kinase 2 (JAK2), signal transducer and activator of transcription 3 (STAT3), interleukin 6 (IL-6), and interferon γ (IFN- γ); and kaempferol to NOD-like receptor protein 3 (NLRP3), caspase-1, interleukin 1 β (IL-1 β), and interleukin 18 (IL-18).

5. The biological activities of the specific compounds guajadial and guaijaverin

These two compounds are newly discovered bioactive components with unique structures in guava in recent years, and a growing number of studies have revealed their multi-target mechanisms of action. Specific compounds can also promote synergistic effects; the combined use of guajadial and quercetin can synergistically inhibit tumor angiogenesis^[14]; Moreover, the structural modification of guaijaverin (such as glycosylation) can enhance its bioavailability, providing a direction for the development of novel antidiabetic drugs^[174].

5.1. Antitumor mechanisms proposed for guajadial

Guajadial is a meroterpenoid isolated from guava leaves. Its α,β -unsaturated carbonyl system and lipophilic side chains have motivated studies of oxidative stress, apoptosis, and tumor-cell migration. These proposed mechanisms are supported mainly by *in vitro* and animal experiments; target specificity and achievable human exposure have not been established^[175, 176].

In terms of inducing tumor cell apoptosis, enriched guajadial was obtained from the crude dichloromethane extract of guava leaves extracted by Rizzo et al. In *in vitro* experiments, guajadial exhibited significant selective antiproliferative activity against MCF-7 and MCF-7 BUS breast cancer cells, with TGI values of 5.59 and 2.27 $\mu\text{g/mL}$, respectively^[176]. Guajadial promotes the excessive production of reactive oxygen species (ROS). When ROS levels exceed the oxidative stress tolerance threshold of tumor cells, it

triggers lipid peroxidation, disrupting cell membrane integrity. Concurrently, excessive ROS can directly attack mitochondria, leading to mitochondrial membrane potential collapse, mitochondrial permeability transition pore (mPTP) opening, and the release of apoptosis-related factors such as cytochrome c and Smac/DIABLO into the cytoplasm [26, 177, 178]. The released cytochrome c binds to Apaf-1 to form an apoptosome, activating caspase-9 and subsequently initiating the caspase-3/7 cascade, ultimately inducing tumor cell apoptosis [179]. *In vitro* experiments have shown that guajadial E exhibits particularly strong inhibitory effects on cancer cells, with half-maximal inhibitory concentration (IC₅₀) values of 6.30, 7.78, 7.77, and 5.59 $\mu\text{g/mL}$ against A549, MCF7, HL60, and SMMC-7721 cells, respectively [180].

As shown in **Figure 10**, in terms of inhibiting tumor invasion and metastasis, guajadial exerts its effects by regulating key factors in the tumor microenvironment. On one hand, it can significantly inhibit the transcription and activity of matrix metalloproteinase-9 (MMP-9): guajadial binds to the p65 subunit of the transcription factor NF- κ B, preventing its translocation into the nucleus, thereby inhibiting the promoter activity of the MMP-9 gene, reducing MMP-9 synthesis, and suppressing the invasive ability of tumor cells [14, 176, 181].

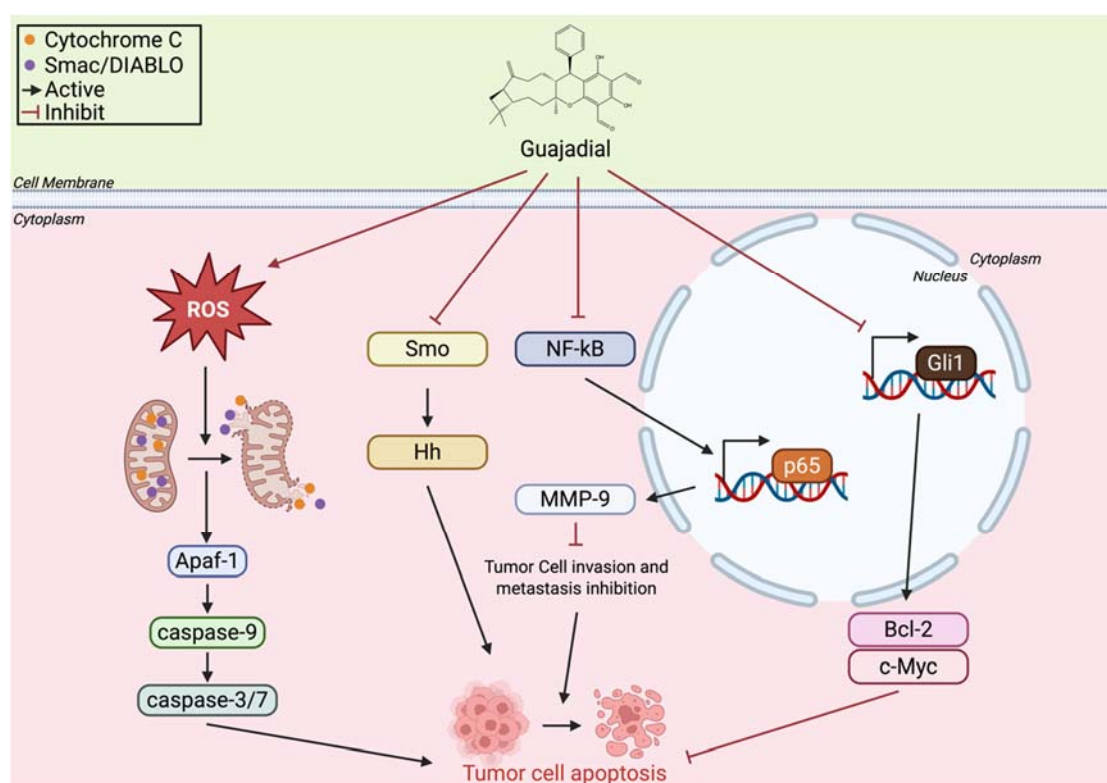


Figure 10. Proposed antitumor mechanisms of guajadial. Guajadial is mapped to reactive oxygen species (ROS)-associated mitochondrial apoptosis involving apoptotic protease-activating factor 1 (Apaf-1), caspase-9, caspase-3/7, and second mitochondria-derived activator of caspases/direct inhibitor-of-apoptosis-binding protein with low pI (Smac/DIABLO); to Smoothed (Smo)-Hedgehog (Hh)-Gli1 signaling; and to nuclear factor kappa B (NF- κ B)/p65 regulation of matrix metalloproteinase 9 (MMP-9). Bcl-2 and c-Myc are downstream survival-related proteins.

In regulating tumor-related signaling pathways, guajadial exhibits a particularly prominent targeted inhibitory effect on the Hedgehog (Hh) signaling pathway, which plays a crucial role in the occurrence and development of various malignant tumors (such as basal cell carcinoma and pancreatic cancer). Guajadial can bind to Smoothed (Smo), a key membrane protein in the Hh pathway, blocking its translocation from the

endoplasmic reticulum to the cell membrane and inhibiting Smo activation. Concurrently, it downregulates the expression of the downstream transcription factor Gli1, reducing Gli1-mediated transcription of pro-oncogenes (such as Bcl-2 and c-Myc) [135, 182, 183]. In addition, Psiguajavadiol A, a derivative of guajadial, inhibits the migration of human colorectal adenocarcinoma cells by blocking the PI3K-Akt pathway [14].

5.2. The hypoglycemic and antioxidant activities of guaijaverin

Guaijaverin (quercetin-3-O-arabinoside) has shown enzyme-inhibitory and antioxidant activity in biochemical and preclinical models. Its glycoside structure may influence solubility and metabolism, but descriptions of high efficiency or clinical efficacy are premature without pharmacokinetic and comparative human data [26, 184].

Figures 2 and 11 summarize three proposed glucose-regulatory levels. First, guaijaverin inhibited α -glucosidase with a reported IC₅₀ of $17.23 \pm 0.75 \mu\text{M}$ and also inhibited α -amylase in the cited in vitro assay [185, 186]. Second, preclinical studies associate guaijaverin-containing interventions with lower G6pc and PEPCK expression and greater glycogen synthase activity [13, 187]. Third, IRS-1/PI3K/Akt activation could promote GLUT4 translocation and cellular glucose uptake [188]. These findings differ in evidential directness: enzyme inhibition uses the isolated compound, whereas several gene and signaling claims arise from extract, cellular, animal, or computational contexts and require compound-specific target validation [189].

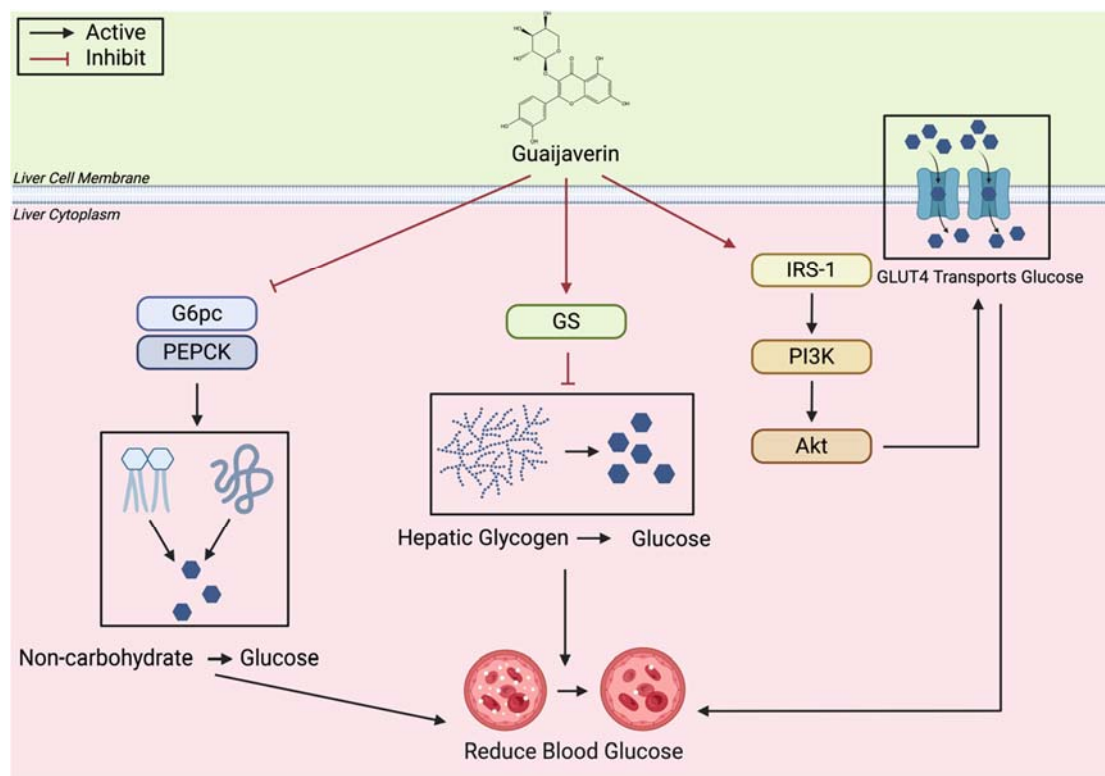


Figure 11. Proposed glucose-regulatory actions of guaijaverin. Hepatic nodes include glucose-6-phosphatase catalytic subunit (G6pc), phosphoenolpyruvate carboxykinase (PEPCK), and glycogen synthase (GS); peripheral glucose uptake is mapped separately to insulin receptor substrate 1 (IRS-1), phosphoinositide 3-kinase (PI3K), protein kinase B (Akt), and glucose transporter 4 (GLUT4) in skeletal muscle and adipose tissue. The tissue distinction is essential because hepatocytes predominantly express glucose transporter 2, not GLUT4.

In terms of antioxidant activity, as shown in **Figure 12**, guaijaverin adopts a core mechanism of "directly scavenging free radicals - activating antioxidant systems - inhibiting oxidative damage" to effectively

alleviate oxidative stress in the organism. On one hand, the phenolic hydroxyl groups in the molecular structure of guaijaverin (especially the ortho-diphenolic hydroxyl groups in the B ring) can directly bind to free radicals, thereby scavenging them from the body [7, 68]. *In vitro* antioxidant assays have confirmed that all extracts from guava leaves possess a high capacity for scavenging DPPH and FRAP free radicals [190]. On the other hand, guaijaverin can activate the body's own antioxidant defense system: it upregulates the expression of nuclear factor E2-related factor 2 (Nrf2), promotes the translocation of Nrf2 from the cytoplasm to the nucleus, binds to antioxidant response elements (ARE), and initiates the gene transcription and protein synthesis of downstream antioxidant enzymes (superoxide dismutase, SOD; glutathione peroxidase, GSH-Px; catalase, CAT), thereby enhancing the body's ability to scavenge reactive oxygen species [188, 191]. *In vitro* experiments have demonstrated that guaijaverin can increase the activity of superoxide dismutase (SOD) in HepG2 cells with oxidative damage induced by hydrogen peroxide (H_2O_2) [192]. Thus, isolated-compound enzyme data are more direct than extract-level antioxidant observations, and the two evidence types should not be conflated.

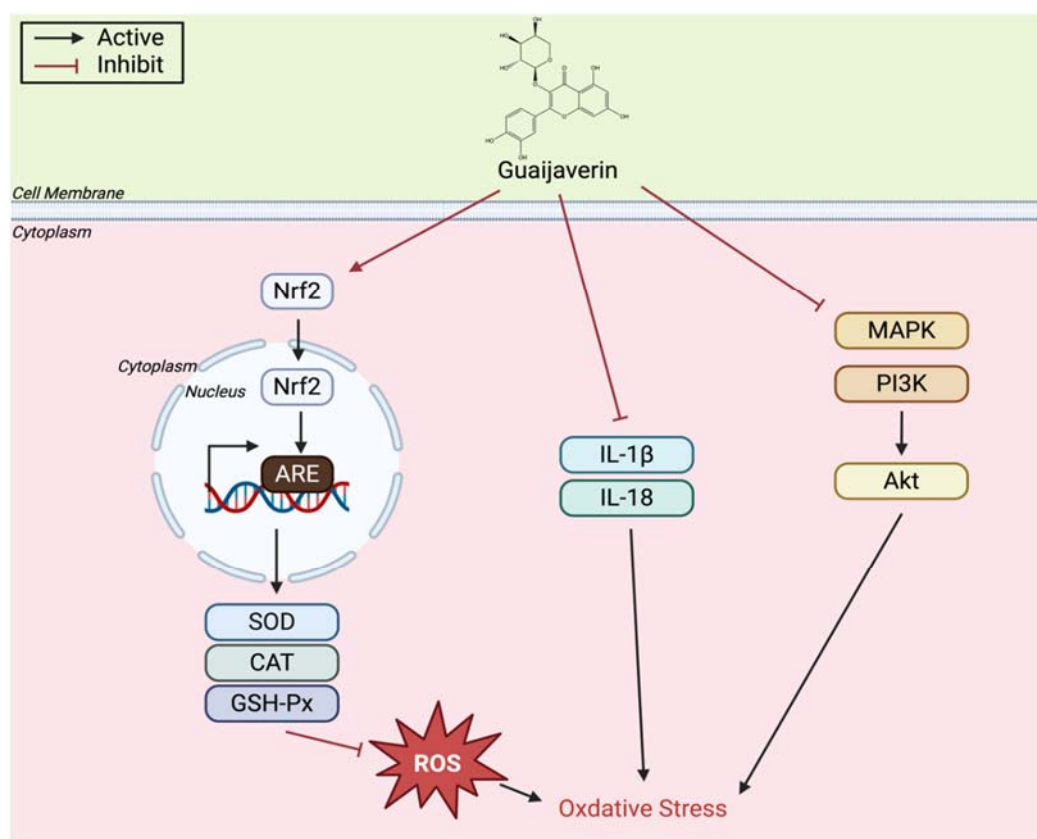


Figure 12. Proposed antioxidant and anti-inflammatory pathways of guaijaverin. Guaijaverin is mapped to nuclear factor erythroid 2-related factor 2-antioxidant response element (Nrf2-ARE), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), interleukin 1 β (IL-1 β), interleukin 18 (IL-18), mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K), protein kinase B (Akt), and reactive oxygen species (ROS). Most pathway links remain preclinical.

6. Applications of guava fruits and leaves in functional foods and health products

Commercial application currently centers on conventional foods and beverages rather than standardized therapeutic products. Fruit is processed into juice, puree, jam, jelly, powder, dried fruit, and fermented

beverages, whereas leaves are mainly marketed as loose tea, tea bags, or beverage ingredients [9, 31, 193]. Product format determines exposure: fruit products retain varying amounts of vitamin C, fiber, and phenolics, while leaf products may deliver more concentrated and less standardized phytochemical mixtures.

Specific products illustrate this distinction. In China, Jianlibao lists a Fifth Season guava fruit beverage (www.jianlibao.com.cn/diwuji.html), and a Yunfu municipal product catalogue includes sun-dried guava leaf tea (250 g per bag) and guava tea (300 g per tin) (http://www.yunfu.gov.cn/nyncj/zdht/sy/nyxw/content/post_1861507.html). In Japan, POKKA SAPPORO markets a 500 mL caffeine-free beverage made from roasted guava leaves with added vitamin C (<https://www.pokkasapporo-fb.jp/products/cha/guava-tea/WR39.html>), while ORIHIRO markets roasted guava-leaf tea in 2 g tea bags (<https://health.orihiro.com/product/detail/?id=493>). These examples document commercial formats and labelled composition; they do not demonstrate prevention or treatment of disease. The main translation bottleneck is the gap between product identity and biological evidence. Commercial foods rarely report cultivar, maturity, extraction yield, marker-compound content, batch variability, or exposure to the proposed active constituents. Future product studies should therefore link a defined preparation and dose to stability, bioaccessibility, safety, and prespecified outcomes before mechanistic findings are used in health claims. The next section therefore evaluates whether current human studies support these proposed applications.

In the future, research on guava can be further expanded in multiple directions. In terms of active ingredient research, it is necessary to further explore the potential active ingredients in guava, conduct in-depth analysis of their mechanisms of action, especially for specific compounds such as guajadial and guaijaverin, to investigate the mechanisms of their synergistic effects with other ingredients, thereby providing a more solid theoretical foundation for the research and development of new drugs. In processing technology innovation, develop green and efficient processing technologies, such as supercritical fluid extraction and membrane separation technology, to maximize the retention of the bioactive components of guava, while reducing production costs, improving product quality, and enhancing market competitiveness [193].

Combining domestic and international research progress, this article systematically summarizes their application directions and mechanisms of action. Both guava fruits and leaves can exert excellent effects in blood glucose-lowering and diabetes management products, and they show significant potential in regulating blood glucose [119]. Studies have shown that the flavonoid components in its leaf extracts can delay the digestion and absorption of carbohydrates by inhibiting the activities of α -amylase and α -glucosidase [43]. In addition, the chromium element in guava can improve blood glucose levels by regulating insulin secretion, making it suitable for the adjuvant treatment of diabetic patients [194]. Technologies now exist to extract hypoglycemic functional factors from guava for use in health food production (e.g., capsules, tea infusions). Additionally, combined with fruit juice and wine processing technologies, low-sugar and high-fiber health products have been developed to meet the daily needs of diabetic patients [9].

The antioxidant capacities of guava fruits and leaves are closely associated with their high contents of vitamin C and polyphenolic substances [67]. Studies have shown that the total phenolic content and DPPH free radical scavenging rate of the peel of red-fleshed guava are significantly higher than those of other varieties, and its antioxidant activity can be retained during processing by optimizing extraction techniques such as ultrasonic-assisted extraction [18]. After solid-state fermentation, the polysaccharides from guava leaves (GLPs) exhibit enhanced antioxidant activity and significantly increased scavenging rates, making them suitable for developing anti-aging oral liquids or skincare products such as facial masks [49]. Meanwhile, flavonoids and terpenoid components such as β -caryophyllene in guava leaves can synergistically enhance antioxidant effects by chelating metal ions, providing a theoretical basis for developing more potent composite antioxidant supplements in the future [13].

The dietary fiber content in guava fruit can reach 5-10%, and guava leaves are also rich in dietary fiber. Intake of dietary fiber from guava and its leaves can promote intestinal peristalsis, accelerate toxin excretion, and improve constipation and intestinal flora imbalance [8, 18]. Due to their astringent and antidiarrheal properties, guava leaf extracts can be used as an adjuvant therapy for acute and chronic enteritis and dysentery. Relevant products include granules and microencapsulated dietary fiber powder [195, 196].

In the development of health foods for cardiovascular health and metabolic syndrome, the antioxidant components in guava can reduce low-density lipoprotein (LDL) levels in the blood and lower the risk of atherosclerosis. Extracts from guava leaves can assist in regulating hypertension by inhibiting the activity of angiotensin-converting enzyme (ACE) [197, 198], demonstrating significant development potential.

7. Clinical trials on guava fruits and guava leaves

As above, multiple evidence has supported the developmental potential of guava fruit and leaves in fields including antioxidant, anti-inflammation, and blood glucose and lipid metabolic disorders in both in vitro and in vivo studies. However, translation from experiments to clinical practice needs more validation via well-designed clinical trials. As following, a few clinical trials with clear results have tried to answer if guava fruit and leaves has beneficial effects for us against infection and metabolic disorders by providing primarily data and evidence [199].

7.1. Clinical trials on blood glucose regulation

A clinical trial reported that guava fruit consumption balanced postprandial blood glucose. By double-blinded, randomized crossover trial, a total of 31 healthy adults were included in this study [200]. Results indicated that participants who consumed guava extract (supercritical CO₂) were found with less fluctuation of blood glucose content at timepoint of 30- and 90-minute after consumption according to a standard procedure of oral glucose tolerance test (OGTT), comparing with participants consuming placebo. Meanwhile, the related basic study from same research team bioactive compounds originated from guava was found with capability in inhibition against intestinal glucose absorption via SGLT1 and GLUT2 [201], which inspired the research about this clinical trial and perhaps this clinical trial just primarily proved clinical development potential of Guava.

Also, consumption difference in specific part of fruit was also regarded as an important variable and studied in a randomized and controlled trial ^[202]. This study pointed that either consumption with or without peels of guava fruit pulp would cause significant difference in glucose concentration in plasma of healthy adults. Specifically, consumption of guava after removal of peels would benefit in less plasma glucose amount, as well as total cholesterol (TC), triglycerides (TG) and low-density lipoprotein cholesterol (LDLc) while enhancement of high-density lipoprotein cholesterol (HDLc). These results together indicates that preparation and consumption method matters in guava for health benefit achievement.

7.2. Clinical trials on blood lipids and cardiovascular health

Guava consumption was believed to achieve health benefit against cardiovascular risks. Specifically, a 12-week, single-blinded and randomized clinical trial offered strong evidence via guiding totally 61 participants with hypertension on consumption of guava fruits around 0.5-1.0 kg per day, comparing to 51 participants without consumption ^[203]. According to the final results, the experimental group which consumed guava daily achieved health benefits significantly compared to the control group of restrictions including decreased serum TC, TG, both systolic and diastolic blood pressure alongside increase in HDLc. This study implied health benefits of guava consumption could be attributed to the synergistic effects for its dietary fiber, potassium, vitamin C and polyphenols, with modulation effect on lipid metabolism and improvement effect on vascular function.

Also, the above mentioned clinical about guava consumption with/without peels also confirmed the lipid metabolism modulation effect including descend in TC, TG and LDLc while ascend in HDLc ^[203]. Accordingly, these results strengthens the developmental potential on guava as functional food with health benefit on cardiovascular function normality.

7.3. Clinical trials on antiviral and anti-inflammatory effects

Besides metabolic disease, guava leaf extracts have also found with developmental potential against viral infection and inflammation. Specifically, a single-blinded, randomized clinical trial focused on the treatment effect of guava leaf extracts for patients with COVID-19 with mild symptom or the asymptomatic ones ^[204]. After 7-days' consumption, ones with guava leaf extract treatment (n=41) was found with less inflammation markers including lower neutrophil percentage, lower neutrophil-to-lymphocyte ratio (NLR) and higher lymphocyte percentage, comparing to the control group (n=40). Also, the guava leaf extracts consumption group was found with a shorter PCR-based viral clearance period (14 days vs. 16 days) and higher recovery rate at timepoint of 2-and 4-week. Together, these results suggested that guava leaf with abundant flavonoid showed health benefit in immunity modulation and developmental potential against viral infection in next-stage study.

7.4. Summary and prospects

Related clinical trial regarding guava has already summarized and presented with major information in **Table 3 (Supplementary Table S1)**. These studies together offered primarily evidence in supporting further

development of guava and its leaf on blood glucose control, blood lipid and pressure modulation, inflammation and viral infection prevention. However, it is also noticed that most available studies are with limitation about small sample size and relatively short study period. In the next stage, perhaps, studies should be designed with a large-scale, long-term, multi-center, double-blinded and randomized clinical trials, perhaps recruiting participants with diabetes, metabolic syndrome, chronic inflammation or serious viral infection, to further discuss the efficacy and safety. Meanwhile, consideration about extraction method, consumption of edible parts, concentration-gradient and bioavailability including short-and long-term should be also included for systematic investigation on clinical and nutraceutical application development of guava and its related products based on evidence.

Table 3. Clinical studies on guava fruits and guava leaves.

Guava Part/Extract Type	Study Design	Target Population	N (Sample Size)	Main Clinical Endpoints/Findings	Approval/Trial ID
Guava Fruit Extract (CO ₂ Extraction) ^[200]	Double-Blind, Randomized Crossover	Healthy Volunteers	31	↓ Postprandial glucose response at 30 & 90 min; trend for ↓ insulin secretion	415-E/2319/15-2018
Guava Fruit (with/without peel) ^[202]	Randomized Controlled Trial	Healthy Human Subjects	45	Without peel: ↓ FPG, TC, TG, LDL-C; with peel: ↑ FPG, TC, TG, LDL-C	Not stated
Guava Fruit ^[203]	Randomized, Single-Blind Trial	Patients with Essential Hypertension	120 (61 vs 59)	↓ Serum TC (9.9%), TG (7.7%), BP (9.0/8.0 mmHg); ↑ HDL-C (8.0%)	Not stated
Guava Leaf Extract (Psidii®) ^[204]	Single-Blind, Randomized Clinical Trial	Mild/Asymptomatic COVID-19 Patients	81 (40 vs 41)	↓ Neutrophil %, NLR; ↑ Lymphocyte %; shorter PCR conversion time; higher recovery rate at 2 & 4 weeks	NCT04810728

8. Limitations and future research priorities

At present, guava and guava leaves still face multiple restrictions in research, development and industrial application, which restricts their transformation from basic research to clinical practice and marketization. In terms of research evidence, the existing achievements are obviously insufficient in human clinical trials. There are some problems such as small sample size and short intervention period. Multi-center, large-scale randomized controlled trials for patients with chronic diseases such as diabetes and metabolic syndrome are still relatively few. Therefore, the verification of its core efficacy (such as blood sugar regulation and blood lipid improvement) and its safety is still insufficient. With regard to the study of bioactive compounds, although it has been confirmed that guava fruits and leaves contain bioactive substances, such as polyphenols, flavonoids, polysaccharides and terpenoids, and specific compounds, such as guajadial and guajaverin, have been identified, the understanding of their mechanism of action is still limited. The synergistic interaction between these bioactive components has not been fully clarified, and the exploration of potential undiscovered bioactive components is not sufficient.

The processing and industrialization of guava are also facing bottlenecks. Its key bioactive components, such as polysaccharides, are sensitive to temperature, and traditional high-temperature processing is likely to lead to activity loss. Although this problem can be alleviated by low-temperature freeze-drying and microencapsulation, these methods have the problems of high production cost and difficulty in expanding production. At present, the commonly used extraction technology shows low standardization, and the extraction parameters change greatly under different conditions. Comparable studies of other food–medicine homologous polysaccharides have demonstrated that drying, grinding, extraction, and purification conditions can substantially alter extraction yield, molecular weight, monosaccharide composition, physicochemical properties, and biological activity ^[205, 206]. This leads to instability in the level and purity of bioactive components in the extract. In addition, the current application scenarios and industrial layout are still relatively limited, mainly focusing on traditional functional foods and health care products. The research on new applications, such as food preservation and agricultural pest control, is still concentrated in the laboratory stage, lacking a large number of industrial solutions. Therefore, the whole industrial value of guava is still largely undeveloped. Experience with other medicinal and edible resources also indicates that translating antioxidant polysaccharides and terpenoids into cosmetic products requires preparation-specific efficacy evaluation, safety assessment, formulation optimization, and analysis of the gap between laboratory evidence and commercially available products ^[207].

In order to solve the limitations encountered in the application of guava, the research and utilization of guava and guava leaves should be promoted from multiple dimensions in the future, and the existing research foundation should be combined with the industrial demand, thus accelerating its transition to industrialization and clinical application. In clinical research, priority should be given to multi-center, large sample and long-term follow-up randomized controlled trials for people with diabetes, metabolic syndrome and chronic inflammation. These experiments should focus on verifying the long-term efficacy and safety of guava in blood sugar control, blood lipid regulation and reducing the risk of cardiovascular disease, and should also solve the applicability of special people. This will accumulate enough clinical data to establish a complete clinical evidence system. When exploring the action mechanism of bioactive components, molecular biology and metabonomics should be used to deeply analyze the action targets and signal transduction paths of known specific bioactive components, with the focus on exploring the synergistic mechanism between different components. At the same time, high- throughput screening and separation/purification technology should be adopted to explore potential new bioactive components.

In the field of processing technology of guava and related products, we should not only develop green and efficient processing technology, but also promote processing standardization through unified technical specifications. We can develop diversified product forms on the basis of existing products, such as anti-aging skin care products and intestinal health formulas, and actively explore new applications of food preservatives to establish a comprehensive industrial application system. In addition, it is necessary to strengthen interdisciplinary cooperation in food science, medicine, agriculture and other fields, and accelerate the

transformation of laboratory research results into large-scale production and listing. These priorities are consistent with the recent development framework proposed for food and medicine homology research, which emphasizes high-level clinical evidence, whole-chain standardization and safety control, precise identification of active components, artificial intelligence, multi-omics, green processing, and interdisciplinary industrial translation ^[208].

9. Conclusion

Guava is a plant with both edible and medicinal value. Owing to its unique chemical composition and biological activities, it has shown considerable potential for development in the food, pharmaceutical, and related industries. In recent years, guava research has progressed beyond descriptive studies of chemical composition to encompass extraction optimization, compositional profiling, pathway-oriented mechanistic investigations, and early randomized clinical trials. The most widely supported mechanistic model suggests that vitamin C, dietary fiber, phenolic compounds, and polysaccharides in guava fruits, together with phenolic compounds enriched in guava leaves, exert biological activities through direct radical scavenging, inhibition of carbohydrate-hydrolyzing enzymes, and modulation of signaling pathways such as Keap1–Nrf2–ARE, PI3K–Akt–GLUT4, and NF- κ B. Although substantial evidence supports their chemical and preclinical activities, causal evidence for individual bioactive compounds remains insufficient, and clinical evidence is still limited, warranting further investigation. Guava fruit can be regarded as a nutrient-dense food, while guava leaf extracts and their isolated bioactive compounds also show promising application prospects. Therefore, the establishment of standardized preparation protocols, well-designed mechanistic intervention studies, and adequately powered multicenter clinical trials will be essential for determining the true clinical value and industrial potential of guava-derived products.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

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