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Potential Bioactivity of Guava Leaf Extract (*Psidium guajava* L.) as a Natural Therapeutic Agent: A Review

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Abstract: Guava leaves (*Psidium guajava* L.) from the family Myrtaceae are known to have many health benefits. This review identifies the main active compounds in guava leaves, such as flavonoids, tannins, saponins, and terpenoids, which contribute to its pharmacological activities. The purpose of this article is to evaluate the effectiveness and safety of guava leaves in providing therapeutic effects, such as antimicrobial, anti-inflammatory, and anticancer activities. A literature review with a qualitative approach of 10 articles was used in this research. Research shows that guava leaf extract is effective as an antidiabetic by inhibiting α the α-amylase enzyme and regulating glucose uptake. In addition, this extract functions as an antioxidant to fight free radicals, as well as an immunomodulator that increases phagocyte activity. The antibacterial and anti-inflammatory activities of this extract can inhibit the growth of pathogenic microbes and suppress inflammatory responses, making it potentially useful for the treatment of infection and inflammation. Anticancer activity has also been demonstrated, mainly through inhibition of cancer signalling pathways and induction of apoptosis. Thus, guava leaves have prospects as a potential natural ingredient for the development of herbal medicines to treat various health conditions, especially enzyme inhibition, increased phagocyte activity, and inhibition of inflammation and pathogenic microbial growth.

Keywords: Antioxidant and Antimicrobial; Guava Leaves (*Psidium guajava* L.); Pharmacological Activities.

Introdution

Indonesia is known for its extraordinary biological richness, with around 30,000 species of higher plants. To date, 7,000 plant species have known benefits, and less than 300 species are used in the pharmaceutical industry [1]. People have traditionally used plants for health, and for many years, Indonesian people have used plants to address health and traditional medicines. The use of plants is based on customs, beliefs, or habits practised by the local community [2]. The utilization of natural products for the community is very important, especially for people in remote areas who find it difficult to get medical services or modern medicine [3].

A phytopharmaceutical drug is defined as a purified and standardized portion of an extract of a medicinal plant or its part containing at least four bioactive or phytochemical compounds for internal or external use by humans or animals for the diagnosis, treatment, mitigation, or prevention of any disease or disorder, but does not include parenteral administration [4]. Phytopharmaceutical preparations or herbal medicines derived from natural ingredients must go through several stages of testing, one of which is bioactivity testing[36]. This test aims to assess the effectiveness and safety of herbal preparations in producing therapeutic effects, such as antimicrobial, anti-inflammatory, and anticancer. This bioactivity test involves the use of a specialized testing system to identify the biological activity of the tested sample [5].

Guava is one of the medicinal plants often used for health purposes. Guava *(Psidium guajava* L.), which belongs to the family Myrtaceae [6], is known to have various health benefits. Commonly utilized plant parts include leaves, fruit, bark, and roots. Guava leaves have a single shape and emit a distinctive aroma when squeezed. The leaves grow crosswise, with an opposite arrangement and pinnate leaf bone pattern [7].

Guava leaves contain a variety of beneficial bioactive compounds, including flavonoids, triterpenoids, tannins, sesquiterpenes, heteroterpenes, benzophenone glycosides, and meroterpenoids [8]. Flavonoid compounds contained in guava leaves are known to be effective in treating diarrhea [9]. In addition to containing flavonoids, guava leaves also contain tannins that are efficacious for the digestive system and improve blood circulation [9]. Guava also acts as an antioxidant thanks to its polyphenol and carotenoid content. Guava leaves are reported to have many pharmacological effects, including hypotensive, hypoglycemic, antidiarrheal, antioxidant, antitumor, and antibacterial [10]. However, to maximize its potential use as a phytopharmaceutical, further research is needed that focuses on three important aspects, namely molecular mechanisms, clinical trials in humans, and interactions with other drugs.

Based on the above, the purpose of this research is to assess the effectiveness and safety of guava leaf extracts that have antimicrobial, anti-inflammatory, and anticancer activities. In addition, this article also aims to evaluate the therapeutic potential of guava leaves as a natural treatment alternative for medical conditions, such as microbial infections, chronic inflammation, and cancer cell growth, based on existing scientific evidence.

Research Methods

The research method was conducted as a literature review study using database sources such as PubMed and

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Google Scholar. The search used the following keywords to identify relevant articles and journals for inclusion: "guava leaf bioactivity, guava leaf activity screening, and guava leaf bioactivity" were searched thoroughly. In this article review, the source articles used were from the last 10 years (2014). The selection of articles was determined by inclusion criteria such as: (1) Potential Bioactivity of Guava Leaf Extract (*Psidium guajava* L.*)* as a Natural Therapeutic Agent, (2) documents used that are original/conducted research. Article screening was filtered through reading the 'title' and the 'abstract'. In addition to inclusion, the exclusion criteria in this study also include (1) articles published more than 10 years ago and (2) article review documents.

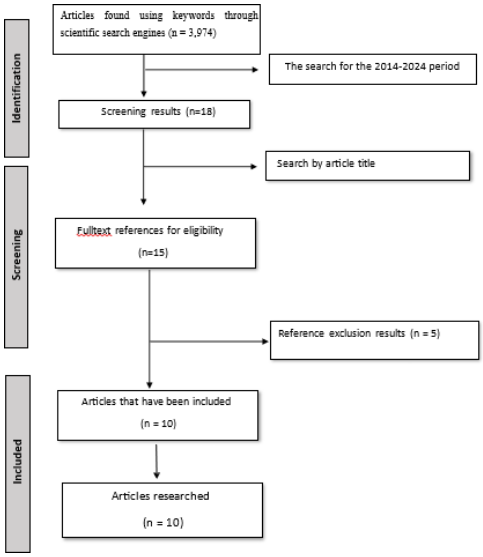

Figure 1. Schematic of the article search strategy

Results and Discussion

Guava leaves (*Psidium guajava* L.) contain a variety of bioactive compounds that support their various therapeutic effects. Based on research conducted by [1], it is known that guava leaves contain a number of bioactive compounds, such as alkaloids, phenols, flavonoids, saponins, steroids/terpenoids, and tannins, which are detected specifically in the leaves.

Additional research shows that flavonoid compounds have broad biochemical and pharmacological activities, including as antioxidants, anti-allergic, anti-inflammatory, hepatoprotective, anticarcinogenic, antiviral, and antithrombotic. In addition, tannins in guava leaves exert important pharmacological effects, used in medicine as anti-hemorrhoidal, homeostatic, and antidiarrheal agents [34].

The saponins contained in these leaves also act as anti-inflammatory agents and antioxidants that are beneficial in lowering cholesterol levels. Terpenoid compounds in guava leaves have also been reported to have significant benefits in accelerating the wound healing process [19]. With this complete bioactive compound profile, guava leaves show great potential in natural medicine for various health conditions [33].

Antidiabetic Bioactivity

Guava leaves have promising antidiabetic activity, according to many studies. According to research by Nafis and Septiarini [1], the enzyme α-amylase can be inhibited by guava leaf extract, with an IC_{50} value of 25.89 ppm. The inhibitory effect was achieved by extracting semi-polar chemical substances, namely flavonoids, from guava leaves using the semi-polar solvent ethyl acetate [23]. These flavonoids are essential to help lower blood sugar levels through regenerating pancreatic beta cells and increasing insulin production. Flavonoids not only increase insulin production but also protect beta cells from oxidative damage and make the cells more sensitive to insulin through their antioxidant properties [24]. Guava leaf has the ability to preserve beta cells and improve the body's reaction to insulin, making it a promising natural remedy for diabetics to use in managing their blood sugar levels. Another mechanism involved is the inhibition of GLUT2 (Glucose Transporter type 2), which is the main transporter in the gut that helps lower blood sugar levels [25]. Flavonoids also inhibit phosphodiesterase, which results in an increase in cAMP in pancreatic beta cells, stimulating the release of protein kinases that produce insulin, thereby reducing blood glucose levels [9]. Flavonoids are also known to have a hypoglycemic effect by inhibiting the reabsorption of glucose in the kidneys and increasing the solubility of glucose in the blood, thus facilitating its excretion through the urine [26]. Research with treatment in rats induced by alloxan. From the results obtained, blood glucose levels showed that the results obtained were a decrease of 18.11%, 28.49% at 325 mg/kg BW, and 31.66% at 1300 mg/kg BW, which shows the higher the dose, the better the effect in reducing blood sugar levels, these results are comparable to the effect of the positive control drug glibenclamide [20]. In the oral glucose tolerance test, the high-dose group showed the best glucose inhibition, with glucose levels that were not significantly different from the normal control from the 30th to the 180th minute, a result close to the effect of acarbose, or the control drug for the glucose tolerance test [27].

Guava polysaccharide (GLP) showed potential antidiabetic benefits in rats that had been on a high-fat diet and added streptozotocin (STZ) [8]. Fasting blood sugar levels in the diabetic control group were much higher than those in the polysaccharide group. In addition, the extract also showed positive effects on the body weight of the rats, helping to stabilize the previously decreased body weight due to diabetes [28]. Guava leaf extract also regulated the lipid profile with reduced levels of total cholesterol and triglycerides, which are important indicators in the management of diabetic complications [29]. A decrease in creatinine levels after administration may prove that guava leaf extract can prevent chronic kidney damage.

Antioxidant Bioactivity

The antioxidant activity of guava leaves has been proven through several studies. [11] found that guava leaves contain phenolic substances, flavonoids, and tannins, according to phytochemical tests. When $FeCl_3$ is added, the color changes to dark blue or blackish green, indicating the presence of phenol groups [40]. The antioxidant activity of guava leaves was tested in this study using two different extraction techniques. The antioxidant test findings showed that ultrasonically extracted guava leaves had an IC_{50} value of 111.3 ppm. Meanwhile, an IC_{50} value of 115.97 ppm was obtained from the extract tested using the maceration extraction process. Both extraction techniques showed IC_{50} values that belong to the moderate antioxidant activity

category [30].

Free radical scavenging assays against DPPH, OH, and ABTS were used to demonstrate the antioxidant activity of guava leaf (GLP) in a study [8]. The results showed that GLP was effective against free radicals, as seen from the IC_{50} values obtained, 102.82 µg/mL, 175.52 µg/mL, and 46.49 µg/mL. Based on these figures, GLP is a better antioxidant than positive controls such as ascorbic acid or trolox. Furthermore, research [16] showed the antioxidant effectiveness by using as many as three different solvents, namely methanol, chloroform, and hexane. The test results showed that the methanol extract had the highest antioxidant activity, followed by the chloroform extract and then the hexane extract. The methanol extract showed a lower IC_{50} value in the DPPH test, indicating a stronger antioxidant ability, which was attributed to the high content of phenolic and flavonoid compounds in it.

Table 1. Article search results

Source	Extraction Method	Testing Method	Activity Type	Result
[1]	70% ethanol maceration method	α-Amylase Enzyme Inhibition Method	Antidiabetes	Various secondary metabolites can be found in red guava leaves. Such as tannins, steroids or terpenoids, alkaloids, phenols, flavonoids, and saponins. Using a combination of ethanol, n-hexane, ethyl acetate, and water. 50IC values of 25.89 ppm, 33.80 ppm, 65.16 ppm, and 42.41 ppm were obtained from the α-amylase enzyme inhibition activity test, respectively.
[11]	Maceration extraction method with 96% ethanol and ultrasonic extraction	DPPH method	Antioxidants	The antioxidant activity test showed IC50 values of 111.3 ppm for the ultrasonic extract and 115.97 ppm for the macerated extract. Both were classified as having moderate antioxidant activity, with no significant difference in antioxidant activity between the two extraction methods ($P > 0.05$).
[12]	Maceration method with 70% ethanol	Writhing Test and Dosage Treatment of Guava Leaf Ethanol Extract	Analgesics	With a dose of 350 mg/kgBB, ethanol extract of guava leaves relieves pain in acetic acid-induced rats. This dose resulted in a writhing reduction of 54.15% and an effectiveness rate of 96.77%, almost the same as the results of the positive control group with diclofenac sodium, which resulted in a writhing reduction of 55.95% and an effectiveness rate of 100%.
[13]	Soxhlet extraction method with petroleum ether, chloroform, ethyl acetate, methanol and ethanol	Human Red Blood Cell (HRBC) Membrane Stabilization Method	Anti-inflammatory	The methanol extract showed the highest anti-inflammatory activity with a hemolysis inhibition percentage of 93.28% in comparison to the ethanol extract, which showed reduced activity, at a concentration of 100 pg/mL and 187% at 200 ug/mL, respectively. This effect comes from the content of flavonoids, tannins, and other phenolic compounds that stabilize cell membranes and reduce the inflammatory response.
[14]	Maceration method with 70% ethanol	Phagocytosis mice	Immunomodulators	The ethanol extract of guava leaves showed significant immunomodulatory effects. In mice with doses of 100 mg/kg BW and 500 mg/kg BW, the activity and phagocytic capacity of macrophages increased, although the results were not as good as Stimuno. This effect is due to active ingredients such as flavonoids and saponins in guava leaves, which support the body's immune function.

[15]	Maceration extraction method with 96% ethanol	Disc diffusion	Antibacterial	Guava leaf extract at 10% concentration Inhibited the development of Vibrio cholerae (6.96 mm inhibition zone) and Escherichia coli (8.16 mm), both from young and old leaves. Old leaves, which contained more tannins (7.092% GAE), showed a wider zone of inhibition than young leaves.
[16]	Meceration extraction method with 70% ethanol	Sample administration and measurement of rat blood glucose levels	Anti-hyperglycemic	In alloxan diabetic rats, ethanol extract of guava leaves improved glucose tolerance and showed antihyperglycemic properties. At a dose of 1300 mg/kg BW, this extract was 31.66% more effective than glibenclamide in reducing blood sugar, and inhibited glucose absorption with similar effects to acarbose.
[17]	Polysaccharides with 95% ethanol	Two Different Radical Deterrence Assays: DPPH and OH (Antioxidant), diabetic rats induced with STZ	Antidiabetic and antioxidant	In addition to reducing the levels of serum Glycogen protein, malonaldehyde, total cholesterol triglycerides, and fasting blood sugar, GLP can protect against free radicals including DPPH, OH, and ABTS GLP has a good ability to fight free radicals, which plays an important role in suppressing oxidative stress in the body.
[9]	Maceration method with methanol, hhexane, and chloform	DPPH, FRAP, and GC-MS	Antioxidant and anticancer	The antioxidant activity of the tested extracts were ranked based on their effectiveness methanol, chloroform hexane. The highest activity was in methanol. The MTT assay showed that the guava leaf hexane extract was most effective in reducing cancer cell viability, with a low IC50 (20-22 µg/mL) in all three cancer cell types tested.
[8]	Maceration method with ethanol	In vivo methods with (antidiarrheal testing in mice, measurement of water content in faeces and calculation of EPEC bacterial colony co unts)	Antidiarrheal	PGE at doses of 200 mg/kg and 400 mg/kg, as well as its main compound, quercetin at 50 mg/kg, showed strong antidiarrheal effects. These effects were seen in a decrease in the amount of watery stool, a reduction in stool weight, and a decrease in the frequency of defecation.

Immunomodulatory Bioactivity

The immunomodulatory activity of the ethanol extract of guava leaves showed that these leaves can increase the response of the immune system through increased phagocytic activity of macrophage cells [14]. Giving guava leaf extract to mice in two doses, namely 100 mg/kg BW and 500 mg/kg BW. At a dose of 100 mg/kg BW, the percentage of phagocytosis activity reached 75%, while the dose of 500 mg/kg BW increased to 82.8%. Phagocytosis capacity also increased significantly in both doses, reaching 111% and 134.6%, respectively. This immunomodulating activity is due to the content of active compounds, especially flavonoids. Flavonoids play a role in increasing the activity of immune cells such as neutrophils and macrophages that are important for fighting infection [39]. However, when compared to the stimuno suspension used as a comparison and containing meniran extract, the effectiveness of guava leaf extract as an immunomodulator is below it. The percentage of macrophage cell phagocytosis activity and ability in the stimuno-treated group reached 86.5% and 176.6%, higher than the guava leaf extract group in both test doses. This proves that guava leaf extract has the potential to be a natural immunomodulator that is effective in strengthening the immune response, making it a candidate for complementary therapy in treating infections and enhancing the body's immunity, but its effectiveness is not yet comparable to stimuno.

Antibacterial Bioactivity

According to many studies, guava leaves contain antimicrobial properties. According to a study conducted by [21], guava leaves have strong antibacterial properties that can effectively fight bacteria such as Vibrio cholerae and Escherichia coli, the two most common bacteria that cause diarrhea. The researchers in this study extracted

guava leaves by adjusting the proportion of young and old leaves, then the testing method used was disc diffusion to measure the zone of inhibition, which indicates the level of effectiveness of the antibacterial extract. The results showed that old guava leaves had a wider zone of inhibition against the growth of both bacteria, especially at 10% extract concentration. The zone of inhibition in old guava leaves in E. coli was 8.16 mm, and V. cholerae was 6.96 mm. The greater concentration of tannin molecules in older guava leaves is responsible for its antibacterial effect [38]. One way tannins protect cells is by preventing germs from attaching to their surfaces, interfering with the action of bacterial enzymes, and preventing bacteria from transporting important proteins through their cell membranes. In addition, tannins can also damage bacterial cell membranes and form bonds with metal ions, which increases their toxic effect on bacteria [9].

Anti-Inflammatory Bioactivity

Guava leaves also have anti-inflammatory activity. The study of [18] conducted an anti-inflammatory activity test using a technique that stabilises the human red blood cell (HRBC) membrane. The solvents used were methanol and ethanol, both of which were tested for their ability to prevent hemolysis or rupture of erythrocyte membranes induced by hypotonicity, and are considered indicative of anti-inflammatory activity. The study found that the methanol extract of guava leaves had the highest anti-inflammatory activity compared to the ethanol extract. The percentage of hemolysis inhibition by the methanol extract reached 93.28% at a concentration of 100 µg/mL and 187% at a concentration of 200 µg/mL. This anti-inflammatory effect is due to the flavonoids, tannins, terpenoids, and glycosides in guava leaf extract that help stabilise cell membranes and reduce inflammatory responses.

Anticancer Bioactivity

The ability of guava leaves has anticancer activity. On anticancer activity research showed that guava leaf extract has significant anticancer effects against several types of human cancer cells, including leukaemia (KBM5), tongue carcinoma (SCC4), and multiple myeloma (U266) [16]. Anticancer activity tests using the MTT method showed that guava leaf hexane extract was the most effective in reducing cancer cell viability, with low IC_{50} values (around 20-22 µg/mL) in all three types of cancer cells tested. The effectiveness of the hexane extract as an anticancer is thought to be due to bioactive compounds such as terpenoids (vitamin E) and triterpenoids (squalene and β- β-sitosterol) that work through various mechanisms, including suppressing the NF-κB signalling pathway associated with inflammation and cancer development. These mechanisms allow the extract to inhibit the growth of cancer cells and increase the apoptotic potential of such cells.

Antidiarrheal Bioactivity

Guava leaf extract has effective antidiarrheal activity against enteric pathogenic Escherichia coli (EPEC) infection, which is the main cause of diarrhea [12]. The extract decreased the amount of EPEC in the phases, reduced the water content in the phases to overcome watery diarrhea and restored the ion balance in the intestine through increasing the activity of Na+/K+-ATPase enzymes. In addition, guava leaf extract reduces inflammation in the gut by lowering the concentration of inflammation-promoting cytokines, including IL-1β and TNF-which helps accelerate the recovery of damaged gut tissue. In this activity, the main active compounds are flavonoids, especially quercetin, which plays a major role in antibacterial, anti-inflammatory, and regenerative effects. This indicates that guava leaves are useful as a potential natural agent for treating infectious diarrhea.

Extraction Method

Various studies have been conducted by researchers to determine the type of bioactivity in guava leaves (*Psidium guajava* L.). Extraction is necessary to identify the bioactive compounds contained in the leaves. The researchers used maceration, polysaccharide and Soxhlet extraction. In addition, there are also ultrasonic extraction researchers conducted by [11]. The maceration extraction method is widely chosen by researchers because it is easy to implement. In line with research [22] which states maceration has many advantages, such as low cost and does not damage the active substances contained in it, because this process is carried out without involving heating.

The effect of solvents on extraction yields is seen in different activities, depending on the chemical properties of the solvent and the target compounds in guava leaves [31]. The concentration of solvent used can affect the solvent's ability to extract different bioactive compounds, depending on its polarity. Some of the solvents used include ethyl acetate, ethanol, methanol, and hexane, each of which attracts specific compounds according to their polarity. Such as ethyl acetate and ethanol, as semi-polar and polar solvents, can extract flavonoid and tannin compounds that have antioxidant and antibacterial potential [32]. Ethyl acetate showed significant antidiabetic activity by inhibiting the α-amylase enzyme, while methanol produced higher anti-inflammatory activity than ethanol.

Conclusions

Guava (*Psidium guajava* L.) leaf extract shows several potential bioactive properties in the health field, especially as antidiabetic, antioxidant, analgesic, immunomodulatory, antibacterial, anti-inflammatory, anticancer, and antidiarrheal agents. Flavonoid and tannin bioactive compounds found in guava leaves contribute significantly to their pharmacological effects through various mechanisms, including enzyme inhibition, increased phagocyte activity, and inhibition of inflammation and pathogenic microbial growth. As a result, guava leaves have prospects as a potential natural ingredient for the development of herbal medicines to treat various health conditions.

Author's Contribution

Risa Dwi Apriani: contributed to the literature search and preparation of the initial draft of the manuscript. Dia Septiani: contributed to the conceptual framework. Nabilla Faoziyah: contributed to literature analysis. Meisya Dwi Ananda: helped review and refine the final version of the manuscript.

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