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Potential Secondary Metabolites in Guava (Psidium guajava) Assisted by Radar Chart Analysis (RCA) and Area Under Curve (AUC)

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Abstract

Background: Diarrhea is a common health problem worldwide, with causes ranging from microbial infections to gastrointestinal disorders. Conventional diarrhea treatments usually involve synthetic drugs, but medicinal plant-based therapies, such as those containing secondary metabolite compounds in guava leaves, show promising potential. In this systematic review, we aimed to identify potential metabolite compounds.

Objective: In this systematic review, we aim to identify potential secondary metabolite compounds in medicinal plants with antidiarrheal effects and explore the biological mechanisms of action involved.

Methods: Using a literature review, relevant articles were analyzed from reputable scientific databases.

Results: The results of the review indicate that compounds such as flavonoids, polyphenols, tannins, and saponins in guava leaves possess antidiarrheal potential, contributing to the regulation of intestinal motility, inhibition of inflammation, and alteration of the gut microbiota composition.

Conclusion: The results of this study indicate that medicinal plants and their secondary metabolites can be a promising alternative for safer and more efficient antidiarrheal therapy.

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INTRODUCTION

Indonesia is an archipelago rich in biodiversity and is home to the world's second-largest tropical forest. It is recognized as one of the top two mega-biodiversity countries, along with Brazil. Indonesian forests are rich in medicinal plants, with approximately 20,000 species, of which 1,000 have been documented and 300 have been used in traditional medicine [1]. Conventional medicine is not limited to developing countries; it has also begun to be adopted in developed nations.

The World Health Organization (WHO) reports that approximately 60% of cases are affected. Traditional medicine is utilized in developed countries, whereas in developing countries, it is used by approximately 80% of the population. This interest is driven by the rise in degenerative diseases and more reports on the side effects of modern drugs, making the "Back to Nature" trend in treatment [2] a practical choice.

Ethnomedicine is a belief and treatment practice related to indigenous cultures and is not derived from the conceptual framework of modern medicine. Ethnomedicine research is essential for discovering new chemical compounds with fewer side effects, addressing the emergence of resistant effects from existing drugs, and anticipating the emergence of new diseases.

Disease is the result of the development of disorders in the body. This study will focus on diarrhea, a common gastrointestinal disorder that various factors, including microbial infections, inflammatory bowel diseases, and reactions to certain medications, can cause. While conventional pharmacological therapies, such as loperamide or antibiotics, can be practical, side effects and microbial resistance often hinder their use. Therefore, research into natural alternatives, particularly those derived from medicinal plants, has garnered attention in recent decades.

One example of a medicinal plant that can be utilized is the guava plant (Psidium guajava L.). Guava or guava klutuk contains high pectin, which can reduce the potential for diarrhea, and tannins that help facilitate digestion [3]. Guava leaves are classified as incomplete because they only consist of stalks (petiolus) and strands (lamina), which are called stemmed leaves. Judging from the location of the widest part of the leaf, the widest part of the guava leaf (P. Guajava L.) is in the middle and has a jorong section because the ratio of length: width is 1.5 – 2.1 (13 - 15: 5.6 - 6 cm). Guava leaves (P. Guajava L.) have pinnate leaf bones, which have A single prominent bone running from the base to the tip, continuing from the petiole to the side of the branch bones, creating an arrangement that resembles fish fins. Guava has a blunt leaf tip. In general, the color of the upper leaves appears greener when compared to the lower side of the leaf. The petiole is cylindrical and does not thicken at its base, where it attaches to the stem.

Secondary metabolite compounds in medicinal plants possess various biological activities that support their therapeutic potential, including their use as antidiarrheal agents. These compounds, including flavonoids, alkaloids, tannins, and saponins, may interact with various molecular mechanisms involved in the development of diarrhea. However, although several studies have explored this potential, the

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specific mechanisms behind the antidiarrheal effects of these compounds remain poorly understood.

This systematic literature review aimed to identify secondary metabolite compounds found in medicinal plants that exhibit anti-diarrheal and antioxidant inhibitory effects and explore the percentage of polyphenols, flavonoids, and catechins involved in the treatment process.

METHODS

Search Strategy

A thorough literature review was conducted using prominent scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search keywords included "plant metabolites," "secondary metabolites," "anti-diarrheal," "mechanisms of action," and "medicinal plants," with a focus on the antidiarrheal properties of guava (*Psidium guajava*). Only articles published from 2000 to 2024 were considered.

Inclusion and Exclusion Criteria

The articles chosen for this review needed to fulfil the following inclusion criteria:

- Studies that identified polyphenol, flavonoid, and catechin secondary metabolite compounds in guava with antidiarrheal effects.
- Studies that reveal the mechanism of anti-diarrheal action and antioxidant inhibition of these compounds.
- Experimental studies (in vitro, in vivo) or relevant clinical trials.

Regarding the exclusion criteria, studies that evaluate the antidiarrheal effect using synthetic drugs or that do not involve secondary metabolite compounds in medicinal plants are excluded.

Selection Procedure

Articles identified from the initial search were screened based on keywords, titles, and abstracts. Articles that met the inclusion criteria were then examined in detail by reading the full text. Data from eligible articles were qualitatively analyzed to identify secondary metabolite compounds and their mechanisms of action.

RESULTS

Percent Level of Polyphenols Present in Guava Leaves.

Most studies use extracts to measure actual levels in the literature review on guava leaf polyphenols. Results vary: Thi Ngoc-Dung and Nguyen (2024) reported 152.954 mg GAE/g DW in wild leaves, which are antioxidants and enzyme inhibitors [6]. Kainat Bilal et al. (2024) found 57.5 A + 0.37 µg gallic acid equivalents per mg, indicating antioxidant and antibacterial potential [7], as shown in Table 1.

In the literature review on the flavonoid content in guava leaves, most research measures flavonoids using guava leaf extract. Some studies report variations in the levels of flavonoids. For example, 46.2 mg of total flavonoids GAE per gram of dry weight in ethyl acetate extract of wild guava leaves, indicating antioxidant properties [13], as shown in Table 2.

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Table 1. Guava Leaf Research with Parameters of % polyphenol content.

Sample Name	Parameter
	% polyphenol content
Guava Leaf	The journal showed that under optimal extraction conditions, the total phenolic content (TPC) in wild guava leaves was 152.954 mg GAE/g DW. https://doi.org/10.1177/1934578X241308480. The journal showed that nanofiltration (NF) significantly increased the phenolic content in guava leaf extract (GE), achieving a retention coefficient of 99%. https://doi.org/10.1016/j.fbio.2022.101997. The journal indicates that the total phenolic content (TPC) is 37.72 mg GAE/g in the aqueous extract (AFPG) and 84.91 mg GAE/g in the methanol extract (MEPG) of Psidium guajava L. leaves. https://doi.org/10.52711/0974-360X.2023.00172 The journal reports that this study aimed to determine the total phenolic content (TPC) of Psidium guajava L. leaf extract (PGLE), which was found to be 57.5 ± 0.37 µg gallic acid equivalents per milligram of extract. https://doi.org/10.1016/j.sajb.2023.12.026 The journal reported that the highest TPC content, at 190 g/100 g per cup, was obtained from guava leaf extract. https://doi.org/10.33263/BRIAC112.93469357.

Percent Flavonoid Content in Guava Leaves

Table 2. Guava Leaf Research with Parameters of % flavonoid content

Sample Name	Parameter
	% flavonoid content
Guava Leaf	The journal "Analysis Of Total Flavonoid Content And Antioxidant Activity Assay Of Guava Variety Crystal (Psidium Guajava L.) Leaves Extract" reports that the ethyl acetate extract of crystal guava leaves contains the highest flavonoid level at 171.91 mg/L. The journal reported that the total flavonoid content in the ethyl acetate fraction of Psidium guajava leaves was 46.2 mg per gram of extract. https://doi.org/10.34117/bjdv8n11-229 The journal reported that the average total flavonoid content in natural guava leaves (GL) from five batches was 9.89 mg/g dry weight (DW). https://doi.org/10.1002/jssc.201600552 The journal "Quantification of flavonoids of Psidium guajava L. preparations by Planar Chromatography (HPTLC)" reported that the quercetin content in Psidium guajava L., a flavonoid compound, ranged from 0.181% to 0.393%, as determined by High Performance Thin Layer Chromatography (HPTLC). The study published in the journal reported that the total flavonoid content in freeze-dried wild guava leaves was 24.46 ± 0.78 mg quercetin equivalents per gram of dry weight (mg QE g-1 dw). https://doi.org/10.1080/07373937.2022.2145305

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Percent Catechin Content in Guava Leaves

Table 3. Guava Leaf Research with Parameters of % Catechin Content

Sample Name	Parameter
	% catechin content
Guava Leaf	The journal reported that catechins are the most abundant bioactive compounds in guava leaf extract, with a concentration of 2.215 ± 0.031 mg per gram. https://doi.org/10.3390/plants11243514
	The journal does not specify the exact percentage of catechin content in guava. However, it notes that guava leaves contain catechins, contributing 40.2% to their effect, as shown in the instrumentation analysis. https://doi.org/10.52461/ijnms.v1i2.834
	The journal reports that the catechin content in guava (Psidium guajava L.) is exactly 22%. Additionally, the leaves contain various phytochemicals, including catechins, which contribute to their bioactivity. https://doi.org/10.3390/foods10040752.
	The journal titled "Antimicrobial Activities Of Tannins Extract From Guava Leaves (Psidium Guajava L) On Microbial Pathogens." The exact percentage of catechin in guava leaves is not specified. This study primarily examined the antimicrobial properties of tannin extracts derived from guava leaves containing 9% tannin.
	The journal demonstrated that this extraction method produced approximately 20.05 units and exhibited a BSLT LD50 of 41.21 ppm, indicating high toxicity and efficiency in isolating the target compounds. https://doi.org/10.3390/MOL2NET-1-a002

Most studies use guava leaf extract to determine the catechin content in the literature review on the percentage of catechin content in guava leaves. Some research results show variations in catechin levels in guava leaf extract. For example, a 2022 survey reported a content of 2,215 ± 0.031 mg per gram of extract in wild guava leaf extract, which exhibits antioxidant benefits. This finding is supported by prior research, which has also identified the presence of tannins and catechins in the phytochemical screening of guava leaves, as demonstrated in a 2022 study, as shown in Table 3.

Research on the antioxidant inhibition potential of guava leaf extract reveals variations. Murniati et al. (2021) found that at 50 ppm, the inhibition was 15.71%; at 75 ppm, 23.34%; at 100 ppm, 27.25%; at 125 ppm, 29.78%; and at 150 ppm, 47.65%, indicating that increased concentration boosts inhibition. The following measurements for the tested n-hexane extracts: 70.80 ± 1.46 mg TE/g in the CUPRAC assay, 26.01 ± 0.97 mg TE/g in the FRAP assay, 24.83 ± 0.35 mg EDTAE/g in the MCA assay, and 2.58 ± 0.14 mmol TE/g in the PM assay [17], as shown in Table 4.

The literature review on antidiarrheal activity in guava leaf samples indicates that most research utilizes guava leaf extract to evaluate its potential. Variations in activity were observed; Murniati et al. (2021) reported an antioxidant activity of 70%, with a usable extract weight of 150mg/kg, as noted in Sumi Wijaya's 2017 research, as shown in Table 5.

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Percent Inhibition of Antioxidants in Guava Leaves

Table 4. Guava Leaf Research with Parameters of % Antioxidant Inhibition

Sample Name	Parameter
	% antioxidant inhibition
Guava Leaf	The journal states that wild guava leaves exhibit antioxidant activities of 124,990 mg TE/g DW (DPPH) and 194,730 mg TE/g DW (ABTS). https://10.1177/1934578X241308480 The journal reports that Psidium guajava (Guava) leaf extract exhibits notable antioxidant activity, reaching 93.44% at a concentration of 250 mg/mL. This high level of inhibition highlights the potent antioxidant properties of guava leaves. https://10.22271/tpi.2023.v12.i12a.24374 The journal states that the 96% ethanol extract of guava leaves (Syzygium aqueum) exhibits increasing % inhibition of DPPH radicals as concentration rises: 15.71% at 50 ppm, 23.34% at 75 ppm, 27.25% at 100 ppm, 29.78% at 125 ppm, and 47.65% at 150 ppm, demonstrating strong antioxidant activity. https://doi.org/10.37874/ms.v9i2.1148 The study titled " The antioxidant inhibition percentage for guava leaves was not provided. The antioxidant potential of the n-hexane extract was reported as 70.80 ± 1.46 mg TE/g (CUPRAC), 26.01 ± 0.97 mg TE/g (FRAP), and 24.83 ± 0.35 mg EDTAE/g (MCA). Additionally, the essential oil showed a value of 2.58 ± 0.14 mmol TE/g in the phosphor-molybdenum assay. https://doi.org/10.3390/molecules27248979 The study found that guava leaf methanol extract exhibited significant antifungal activity, inhibiting Fusarium solani by 21.66 ± 2.05%. The percentage of antioxidant inhibition for guava leaves was not specified. Enzyme activities for catalase (CAT) and peroxidase (POD) were higher in fresh leaves compared to fruit extracts, suggesting a more substantial antioxidant potential in the leaves. https://doi.org/10.22271/phyto.2024.v13.i1a.14804)

Percent Antidiarrheal Potential in Guava Leaves

Table 5. Guava Leaf Research with Parameters of % antidiarrheal potency

Sample Name	Parameter
	% antidiarrheal potency
Guava Leaf	The journal shows that the study evaluated guava leaves (Psidium guajava L) as an antidiarrheal medicine and found 70.0% effectiveness. https://www.semanticscholar.org/paper/The-Evaluation-of-the-Utilization-of-Guava-Leaf-as-Murniati-Roos-velt/9d37ca4e4ed3e1c9820e48b49bc5344657716dbd). The journal reported that guava leaves (Psidium guajava) at 150 mg/kg body weight significantly reduced diarrhea in animals. However, it did not specify the exact antidiarrheal contribution of guava leaves. https://doi.org/10.29244/jji.v2i3.38).

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The journal documents preclinical and clinical studies demonstrating an 83% antidiarrheal effect of Psidium guajava L. leaves. It emphasizes the importance of further research on guava leaf extracts for their potential as antidiarrheal agents. https://doi.org/10.3390/foods10040752

The study investigated the antibacterial properties of guava leaf extracts. Four extracts were examined: ethanol, methanol, ethyl acetate, and hot water. The methanol extract demonstrated strong antibacterial activity (100%), with an MIC above 250 µg/mL. Ethanol extracts demonstrated 38%-65% effectiveness, inhibiting clinical E. coli isolates at concentrations greater than 500 µg/mL and V. cholerae strains at concentrations exceeding 750 µg/mL. The responses of ethyl acetate and hot water extracts were less potent, with MIC values exceeding 750 µg/ml. Resistance to these treatments ranged from 6.3% to 88%. https://10.7897/2277-4343.06124

In the journal, Psidium guajava leaf extract (PGE) demonstrated 78% antidiarrhoeal activity by reducing castor oil-induced diarrhea dose-dependently. It decreased the defecation score and stool weight, highlighting its potential in managing diarrhea. https://doi.org/10.1540/jsmr.44.195

Determination of Area Under Curve and Radar Chart Analysis values

Table 6. Calculation of the Average Value of each Parameter

Sample Name	Parameters				
	% polyphenol content	% flavonoid content	% catechin content	% anti-oxidant inhibition	% antidiarrheal potency
Guava Leaf	52,954	71,91	31	12,499	70
	84,91	46,2	40,2	19,473	65
	37,72	9,89	22	47,65	83
	57,5	39	9	70,80	88
	190	24.46	41,21	21,66	78
Mean	**53,144**	**63.46**	**62**	**31,972**	**76.8**

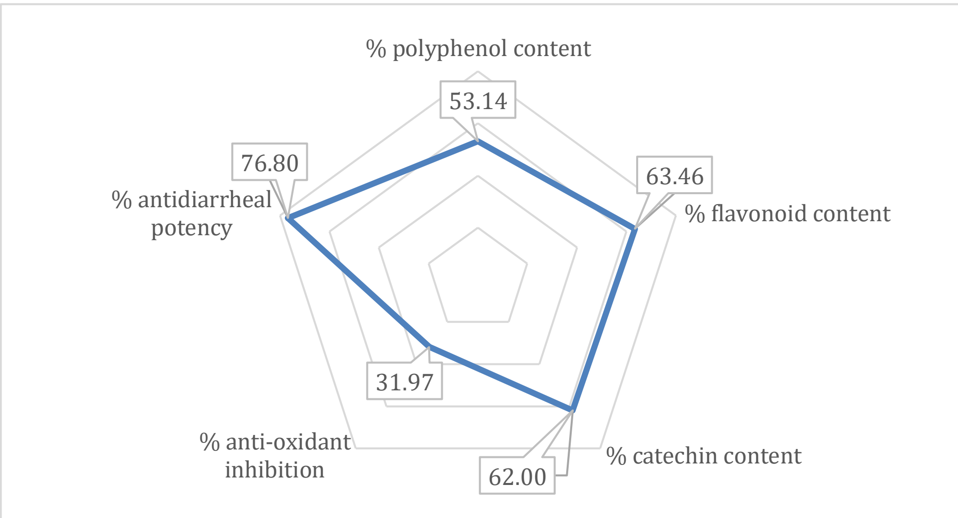

Figure 1. Radar Chart Analysis of Guava Leaf

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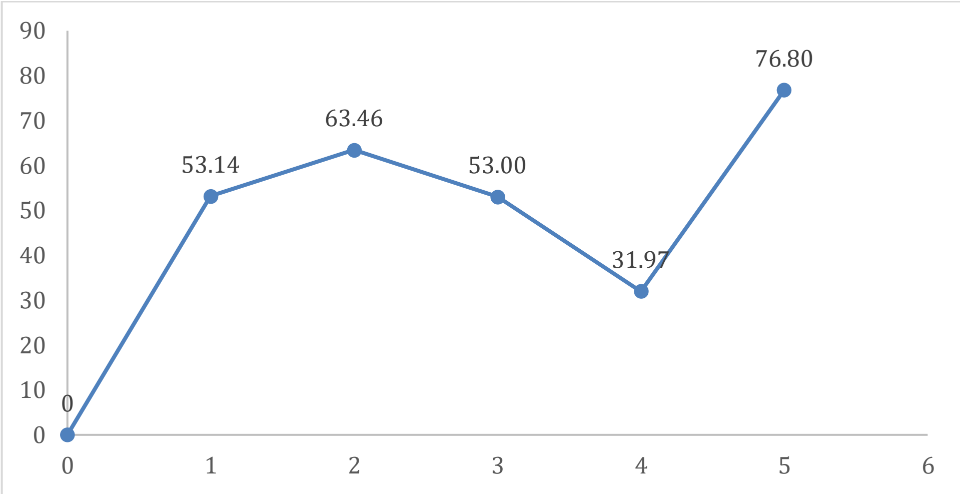

Figure 2. Guava Leaf Parameter Graph

Table 7. AUC calculation

X	Y	Calculation	AUC
0	0	0	0
1	53.14	((0+53.14)/2)*(1-0)	26.57
2	63.46	((53.14+63.46)/2)*(2-1)	58.3
3	53.00	((63.46+53)/2)*(3-2)	58.23
4	31.97	((53+31.97)/2)*(4-3)	42.485
5	76.80	((31.97+76.80)/2)*(5-4)	54.385
	TOTAL		239.97

AUC stands for Area Under the Curve, which represents the curve's part showing the drug concentration needed for a person to achieve optimal therapeutic effects, as shown in Table 6. Based on the data from Table 6, calculations for Radar Chart Analysis (RCA) and AUC can be performed. The AUC calculation uses the trapezoidal formula based on the average value of each parameter. From the calculation results, we will get a graph of each parameter. Furthermore, based on the data from Figure 2, the AUC is calculated using the trapezoidal formula on the graph. Each AUC is then summed to find the total AUC value.

DISCUSSION

Several secondary metabolite compounds identified in this study showed significant antidiarrheal potential, including flavonoid compounds, which are recognized for their anti-inflammatory, antioxidant, and antimicrobial activities[18]. Studies indicate that flavonoids, such as quercetin, can inhibit the activity of enzymes responsible for intestinal fluid secretion and alleviate inflammation associated with diarrhea. Then, Alkaloids such as morphine and pilocarpine have an inhibitory effect on intestinal motility, which helps reduce the frequency of bowel movements in diarrhea[19]. Tannins can reduce fluid secretion and increase electrolyte absorption in the intestines, thus speeding up the recovery process from diarrhea. Saponins have antimicrobial effects that can reduce bacterial infections that cause diarrhea and boost immunity[20].

The mechanisms involved in the antidiarrheal effects of secondary metabolite compounds include several aspects, such as the Modulation of intestinal motility. Compounds such as flavonoids and alkaloids can regulate the movement of intestinal smooth muscle through influences on ion channels or the enteric nervous system[21]. Inhibition of inflammation in Tannins and flavonoids has anti-inflammatory activity that can reduce intestinal inflammation, which often occurs in inflammatory diarrhea[18]. Specific secondary metabolites, such as saponins, can influence the gut microbiota, restoring the healthy balance of beneficial bacteria in patients suffering from diarrhea. Regulation of fluid secretion with some compounds can affect fluid secretion in the gut by regulating ion channels, reducing fluid loss in diarrhea[20].

Polyphenols constitute a class of chemical compounds found in plants. These compounds have a distinctive property characterized by many phenol groups in their molecules. Polyphenols often exist as polar glycosides and are readily soluble in polar solvents [4]. Some essential polymeric materials in plants, such as lignin, melanin, and tannin, are polyphenolic compounds, and phenolic units are sometimes present in proteins, alkaloids, and terpenoids [5].

Phenol compounds are susceptible to enzyme oxidation and can be lost during isolation due to the activity of phenolase enzymes found in plants. Extracting plant phenol compounds with boiling ethanol generally prevents enzyme oxidation. All phenol compounds are aromatic, exhibiting strong absorption in the UV spectrum. Additionally, when bases are added, phenol compounds typically show a bathochromic shift in their spectra. Therefore, spectrometry is essential for identifying and quantitatively analyzing phenol compounds [5].

Among these compounds, flavonoids are secondary metabolites whose presence in plant tissues is thought to be influenced by photosynthesis, meaning young plants or leaves usually have fewer flavonoids [8]. They are pigments responsible for various plant colours: anthocyanins produce blue, violet, and red shades; flavones and flavanols appear as faint yellow; chalcones and aurones give bright yellow hues; and isoflavones and flavanols are generally colourless [9].

Functionally, flavonoids provide multiple protective and regulatory roles in plants. Using flavonoids in plants protects against environmental stress conditions, regulates plant growth, shields against ultraviolet radiation, and attracts insect pollinators, fungi, viruses, and bacteria [10]. In addition to regulating hormones and acting as enzyme inhibitors, flavonoids also contribute to UV filtration, symbiotic fixation, and flower pigmentation [11]. In humans, flavonoids act as stimulants to the heart, diuretics, and stabilize blood sugar levels, while also possessing antifungal, anti-inflammatory, antitumor, antiallergic, and antibacterial properties, which can help prevent osteoporosis [12].

Within this group, catechins are secondary metabolite compounds naturally produced by plants and are part of the flavonoid group. This compound has antioxidant properties thanks to its phenol group. It can help repair cognitive

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damage, inhibit fat accumulation, and provide many other benefits. Catechins also exhibit essential biological activities, including anti-tumor and antioxidant effects[14]. Additionally, medically, catechin compounds in tea offer numerous advantages, including reducing the risk of cancer and tumors, lowering cholesterol levels, preventing hypertension, killing bacteria and fungi, and eliminating influenza viruses [15]. Polyphenols also enhance the immune system and have anti-microbial, anti-cancer, and antioxidant properties [16].

Antioxidants are substances that can capture free radicals and highly reactive molecules to prevent oxidation reactions that cause damage to the human body[22]. While inhibiting these reactions can potentially lead to increased damage, it is vital to research the potential of antioxidants[22].

Diarrhea is a common condition experienced by many people. Although often perceived as a minor annoyance, diarrhea can signify a more serious health issue requiring medical attention[23]. It is defined as having increased bowel movements with liquid or watery stools. It may also include other symptoms, such as nausea, vomiting, abdominal cramps, and occasionally weight loss[23]. The community can harness the potential of guava leaves as an antidiarrheal and valuable medicinal plant[24].

In the context of pharmacology, accurate dosing is essential. AUC, or Area Under the Curve, represents the crucial drug concentration measure required for optimal therapeutic effects. Incorporating AUC into pharmacokinetic calculations ensures that patients receive the correct medication dose that maximizes efficacy while minimizing toxicity, especially kidney-related side effects[25]. If the AUC is too high, the risk of toxicity escalates alarmingly; if it is too low, the drug's effectiveness diminishes drastically. RCA (Radar Chart Analysis) is a powerful visual technique for displaying multivariate data in two dimensions to support complex data interpretation. Using radii to represent quantitative variables, RCA provides a straightforward star-shaped plot reflecting magnitudes and interrelationships[26]. Although secondary metabolite compounds show significant potential in antidiarrheal treatment, many challenges remain. One major issue is the limited number of clinical studies confirming the effectiveness and safety of using medicinal plants. More research is needed to determine optimal doses, potential side effects, and detailed mechanisms of action[27].

CONCLUSION

This study revealed that secondary metabolite compounds in medicinal plants, such as flavonoids, polyphenols, and catechins, have potential as antidiarrheal agents through biological mechanisms and antioxidant inhibition. Although the existing research results are auspicious, Further research is required to comprehensively elucidate medicinal plants' molecular mechanisms and therapeutic potential in managing diarrhea.

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