





# *In vitro* antibacterial activity of *Psidium guajava* (guava) extracts against MRSA and MSSA

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**Dates:**

Received: 22 Jan. 2025  
 Accepted: 14 Mar. 2025  
 Published: 09 May 2025

**How to cite this article:**

Nsele, N.W., Mathobela, K.P., Radebe, S.P. & Thembane, N., 2025, 'In vitro antibacterial activity of *Psidium guajava* (guava) extracts against MRSA and MSSA', *Journal of Medicinal Plants for Economic Development* 9(1), a280. <https://doi.org/10.4102/jomped.v9i1.280>

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**Background:** Methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *Staphylococcus aureus* (MSSA) are significant pathogens responsible for a range of infections, including those in diabetic patients. The increasing resistance to antibiotics necessitates the exploration of alternative antibacterial agents. The *Psidium guajava* (guava) plant has demonstrated antimicrobial properties, but its efficacy against *S. aureus* strains remains underexplored.

**Aim:** To evaluate the *in vitro* antibacterial activity of ethanol and water extracts of guava leaf extracts against MRSA and MSSA.

**Setting:** *In vitro* study conducted under controlled laboratory settings at Mangosuthu University of Technology, Department of Biomedical Sciences, Kwa-Zulu Natal, South Africa.

**Methods:** Guava leaf extracts were prepared using ethanol and water. Antibacterial activity was assessed using the Kirby-Bauer disc diffusion method and minimum inhibitory concentration (MIC) assays. The zone of inhibition size and MIC values were measured for both MRSA and MSSA.

**Results:** The water-based extract produced larger zones of inhibition and lower MIC values compared to the ethanol extract, indicating higher potency. However, both extracts showed reduced activity against MRSA, which may be attributed to the presence of the *mecA* gene, conferring resistance to  $\beta$ -lactam antibiotics.

**Conclusion:** While the water-based guava extract demonstrated significant antibacterial potential against both MRSA and MSSA, further research is needed to isolate specific bioactive compounds and assess clinical applicability.

**Contribution:** These findings suggest that guava leaves may offer a natural alternative or adjunctive treatment for *S. aureus* infections, including those caused by antibiotic-resistant strains.

**Keywords:** guava; type 2 diabetes; methicillin-resistant *Staphylococcus aureus*; methicillin-sensitive *Staphylococcus aureus*; antimicrobial resistance.

## Introduction

### Background

Type 2 diabetes (T2D) is a chronic metabolic disorder that affects millions of adults worldwide and ranks as the ninth leading cause of mortality (Abdul Basith Khan et al. 2020). It is characterised by insulin resistance, impaired glucose metabolism and persistent hyperglycaemia, which together contribute to a compromised immune response. Type 2 diabetes is increasingly recognised as an inflammatory condition driven by mechanisms such as Toll-like receptor activation and endoplasmic reticulum stress. This ultimately leads to systemic inflammation and immune dysfunction (Berbudi et al. 2020; Hameed et al. 2015). This immune dysfunction, coupled with hyperglycaemia, significantly increases the risk of infections, particularly bacterial infections caused by *Staphylococcus aureus* (hereafter, *S. aureus*), including both methicillin-resistant *S. aureus* (MRSA) and methicillin-sensitive *S. aureus* (MSSA).

*Staphylococcus aureus* is a highly adaptable pathogen responsible for a variety of infections, including bacteraemia and device-related complications, with diabetic individuals exhibiting heightened susceptibility as a result of immune dysfunction (Tong et al. 2015). Notably, diabetes is associated with a 2.8-fold increased risk of *S. aureus* bacteraemia compared to non-diabetic individuals, with this risk further exacerbated by poor glycaemic control, prolonged disease duration and diabetes-related complications (Smit et al. 2016). Diabetic foot ulcers, a common

complication in T2D, are particularly susceptible to MRSA infections, with colonisation rates as high as 34% (Cervantes-García et al. 2015). In addition to foot ulcers, *S. aureus* is a leading cause of skin and musculoskeletal infections in diabetic patients, particularly in those with hyperglycaemia, although the underlying mechanisms remain unclear (Butrico et al. 2023). Moreover, it can lead to severe infections in the endocardium, meninges and bones, thereby exacerbating health risks (Obeng-Nkrumah et al. 2015). Bacterial growth and impaired immune responses, which are promoted by hyperglycaemia, along with the growing challenge of antibiotic resistance, contribute to the heightened infection risk in T2D (Darwitz, Genito & Thurlow 2024). Patients with T2D also often exhibit a blunted humoral immune response, characterised by reduced levels of total IgG (Immunoglobulin G) and *S. aureus*-specific IgG, further compromising their ability to fight infections (Farnsworth et al. 2015). As a result, individuals with T2D face delayed wound healing, more severe infections and higher rates of hospitalisation, complications and amputations.

The rise of antibiotic resistance, particularly in MRSA strains, presents a major obstacle in treating infections in diabetic patients. Methicillin-resistant *S. aureus*'s resistance to  $\beta$ -lactam antibiotics because of the *mecA* gene makes infections difficult to treat, leading to poor clinical outcomes (Lade & Kim 2023). Antibiotic resistance contributes to an estimated 4.95 million deaths globally each year, with the greatest burden in low- and middle-income countries (Murray et al. 2022). This worsening resistance crisis highlights the urgent need for novel, alternative therapeutic strategies that can target antibiotic-resistant pathogens without contributing to further resistance.

*Psidium guajava* (guava), native to Central and South America but now widely cultivated in Africa, is known for its antimicrobial properties. Laboratory studies have shown that bioactive compounds, such as tannins and flavonoids, in guava possess antibacterial activity against pathogens, including *S. aureus* (Yahaya et al. 2019). Recent research has explored the potential of guava leaves, specifically, in treating diabetic wounds (Bilal et al. 2024). Guava leaf decoction has been identified as a promising wound-washing solution for diabetic foot ulcers, improving patient care practices and promoting healing (Bilal et al. 2024; Harahap et al. 2022; Novitasari & Nooratri 2024). In addition, a gel formulation containing tannin-enriched fractions from guava leaves demonstrated significant wound contraction in diabetic rats, attributed to the presence of gallic acid, a known antimicrobial agent (Jayakumari, Sangeetha & Ali 2018). Furthermore, the antimicrobial properties of guava leaves have been shown to help reduce malodour in diabetic ulcers, further supporting their therapeutic potential (Novitasari & Nooratri 2024).

A combination of guava and *Melastoma malabathricum* Linn leaves in gel form has also exhibited antimicrobial activity and promoted wound healing in diabetic rats, suggesting that guava's wound-healing effects could be enhanced when used

in combination with other plant materials (Maigoda & Refdanita 2022). These findings highlight guava leaves, both as a standalone treatment and in combination with other plants, as a promising natural option for managing diabetic wounds.

However, despite the growing body of research on guava's antimicrobial properties, most studies have focussed on non-diabetic populations. Limited research has explored its potential effectiveness in individuals with T2D, particularly in regions like Africa, where the disease burden is rising rapidly (Niohuru 2023). The immune dysfunction and chronic inflammation typical of T2D may affect the plant's antibacterial activity, especially against *S. aureus* strains. This study aims to address this gap by investigating the *in vitro* antibacterial activity of guava extracts specifically against MRSA and MSSA, the two strains of *S. aureus* most involved in diabetic infections. By evaluating guava's efficacy against these bacterial strains, we aim to better understand its potential as an adjunctive therapy for managing infections in individuals with T2D, particularly in settings where access to expensive antibiotics may be limited.

## Research methods and design

### Bacterial strains

In this study, two *S. aureus* strains, one MRSA and one MSSA, were used to evaluate the antibacterial activity of guava extracts. The MRSA strain (ATCC 33591) and the MSSA strain (ATCC 25923), were both sourced from Davies Diagnostics, South Africa. These specific American Type Culture Collection (ATCC) strains were chosen for their widespread use as reference strains in antibacterial studies, ensuring the reliability and reproducibility of the results, and were cultured on nutrient agar slopes at 4°C for long-term storage. Prior to testing, the strains were sub-cultured onto blood agar plates and incubated at 37°C for 24 h to ensure fresh and viable bacterial cultures for the experiments.

### Culture media preparation

For antibacterial testing, Mueller–Hinton Agar (MH agar) was prepared according to the manufacturer's instructions (Oxoid). A total of 38 grams of Mueller–Hinton powder was dissolved in 1 litre of distilled water, and the solution was sterilised by autoclaving at 121°C for 15 min. After sterilisation, the agar was poured into Petri dishes and allowed to solidify at room temperature. In addition, nutrient broth was prepared by dissolving 40 grams of nutrient broth powder in 1 litre of distilled water, followed by sterilisation via autoclaving at 121°C for 15 min. The broth was stored in bijou bottles for use during bacterial inoculum preparation.

### Plant material and extract preparation

Fresh leaves of *Psidium guajava* (hereinafter *P. guajava*) (guava) were collected from the Silverglen Nature Reserve in Chatsworth, Kwa-Zulu Natal, South Africa, early in the morning (around 8 a.m.) to minimise the degradation of bioactive compounds. The leaves were collected between the

Spring and Summer seasons. After collection, they were immediately processed to prevent loss of active ingredients and were used to prepare both ethanol- and water-based extracts using 96% v/v ethanol and distilled water, respectively.

The extract preparation followed a modified HAB 3a method from the German Homeopathic Pharmacopoeia (Benyunes 2005). To prepare the ethanol-based extract, 50 grams of minced guava leaves were mixed with 150 mL of 96% ethanol, resulting in a 1:3 ratio (w/v). The mixture was shaken for 5 min and left to macerate at room temperature (20°C or less) for 10 days, with daily agitation to ensure thorough extraction of active compounds. After the maceration period, the extract was filtered through 100% cotton and a membrane filter to remove any residual plant material. It was then stored in 100 mL glass containers at 2°C to 8°C until use.

For the water-based extract, the same amount of fresh guava leaves (50 grams) were combined with 150 mL of distilled water in a 1:3 ratio. This mixture was shaken for 5 min and allowed to macerate for 14 days with daily mixing. During mixing, the mixture was assessed visually for any visible contamination. After the maceration period, the water extract was also filtered and stored in 100-mL glass containers at temperatures between 2°C and 8°C for future use. The extracts were used up within 5 days after preparation.

### Antibacterial testing

The antibacterial activity of both ethanol- and water-based *P. guajava* extracts was evaluated using the Kirby–Bauer disc diffusion method. This method was employed to assess the broad-spectrum antimicrobial efficacy of the extracts against both MRSA and MSSA.

To prepare the bacterial inoculum, each bacterial strain was cultured overnight in nutrient broth at 37°C. The bacterial cultures were then adjusted to 0.5 McFarland turbidity by visually matching the inoculum with a known standard. This standardised inoculum was swabbed evenly across the surface of Mueller–Hinton agar plates to ensure uniform bacterial growth.

Sterile 6 mm paper discs were impregnated with 100 µL of either the ethanol or water extract (at a concentration of 100 mg/mL). Control discs with only water or only ethanol were included. The vancomycin antibiotic disc was used as a positive control for both MSSA and MRSA. The discs were then placed on the inoculated agar plates. Plates were incubated at 37°C for 24 h, after which the zone of inhibition (the area around the disc where bacterial growth was inhibited) was measured in millimetres using a Vernier calliper. The size of the zone of inhibition is directly proportional to the antibacterial potency of the extract.

To quantify the minimum amount of extract required to inhibit bacterial growth, the minimum inhibitory

concentration (MIC) of each extract was determined using a serial dilution method. Twofold serial dilutions of the ethanol and water extracts were prepared in nutrient broth, starting from an initial concentration of 100 mg/mL. The dilution series ranged from 100 mg/mL to 0.78 mg/mL. Each dilution was then inoculated with 100 µL of the standardised bacterial suspension (10<sup>6</sup> CFU/mL). The inoculated microplates were incubated at 37°C for 24 h. The MIC was defined as the lowest concentration of extract that prevented visible bacterial growth, as indicated by the absence of turbidity in the broth.

### Statistical analysis

All experiments were conducted in triplicate to ensure reliability, and each bacterial strain was tested six times against both the ethanol and water extracts, resulting in a total of 12 tests per microbial strain. The zone of inhibition data were recorded for each extract, and MIC values were obtained from the dilution method.

The data were analysed using two-sample *t*-tests to compare the antibacterial activities between ethanol and water extracts. A one-way analysis of variance (ANOVA) was employed when comparing multiple concentrations within the same extract group. Statistical significance was set at  $p < 0.05$ . All results are presented as the mean  $\pm$  standard deviation (SD).

### Ethical considerations

Ethical clearance to conduct this study was obtained from the Mangosuthu University of Technology Department of Biomedical Sciences on 22 January 2025.

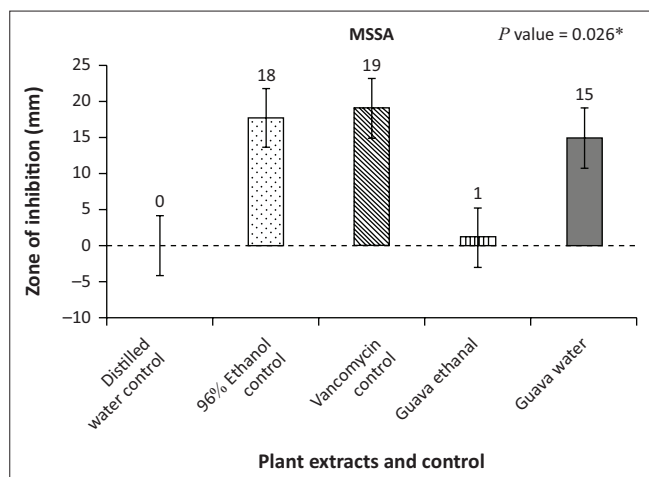
## Results

### Kirby–Bauer antimicrobial sensitivity test

Figure 1 and Figure 2 illustrate the antibacterial activity of ethanol and water extracts of *P. guajava* against MRSA and MSSA. The figures display the zone of inhibition, in millimetres, for each extract and bacterial strain. The error bar graph shows that *P. guajava* water extract exhibits stronger antibacterial activity against MSSA (15 mm  $\pm$  1.5) than MRSA (11 mm  $\pm$  1.2), indicating reduced susceptibility in MRSA as compared to MSSA. Statistical significance was determined using a two-sample *t*-test ( $p < 0.05$ ), and the *p*-values are indicated. Only the results of the water-based extracts were significant, and, therefore, the MIC was detected for those extracts. The statistical values indicate the significant *p*-values for both MRSA (0.042) and MSSA (0.026).

### Minimum inhibitory concentration

The MIC represents the concentration of the antimicrobial agent at which there is complete inhibition of growth. In reading the endpoints, a barely visible haze of growth or a single colony was disregarded. Figure 3 summarises *P. guajava* water-based MIC results against the MRSA and MSSA strains. No growth was observed for the 1 in 2 dilution,



MSSA, methicillin-sensitive *Staphylococcus aureus*.

\*Significant *p*-values.

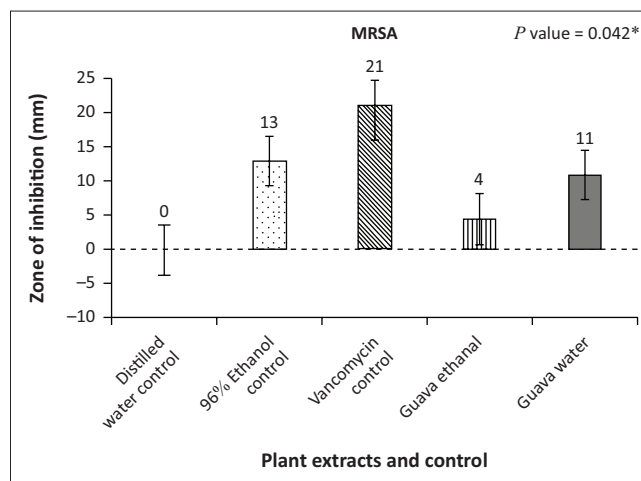
**FIGURE 1:** Antibacterial activity of *Psidium guajava* extracts against methicillin-sensitive *Staphylococcus aureus* strain.

whilst for the 1 in 4, 1 in 8 and 1 in 16 dilutions against MRSA, 100% growth was observed. The MIC for the 1 in 2 and 1 in 4 dilutions against MSSA was 0% growth, and for the 1 in 8 and 1 in 16 dilutions against MSSA, it was 100% growth. The results of the MICs for the extracts were always compared with the water control, which always showed 100% growth.

## Discussion

This study evaluated the antibacterial properties of guava (*P. guajava*) leaf extracts against MSSA and MRSA. Both water- and ethanol-based extracts exhibited antibacterial activity, with the water-based extract showing stronger effectiveness. The water extract produced inhibition zones of 15 mm against MSSA (Figure 1) and 11 mm against MRSA (Figure 2), comparable with the 15.4 mm observed at a 5% concentration in a study done by Phong and Lum (2021), indicating comparable antibacterial activity at similar concentrations. In contrast, the ethanol extract showed smaller inhibition zones. This suggests that the water-based extract, likely containing higher concentrations of hydrophilic compounds such as tannins, saponins and flavonoids, is more effective because of the enhanced solubility and bioavailability of these compounds in water. The significant *p*-values (0.042 for MRSA and 0.026 for MSSA) confirmed the superior antibacterial activity of the water extract. This finding aligns with the work of Kumari et al. (2024), who indicated that hydrophilic compounds in certain plant extracts are often more potent against specific bacterial strains.

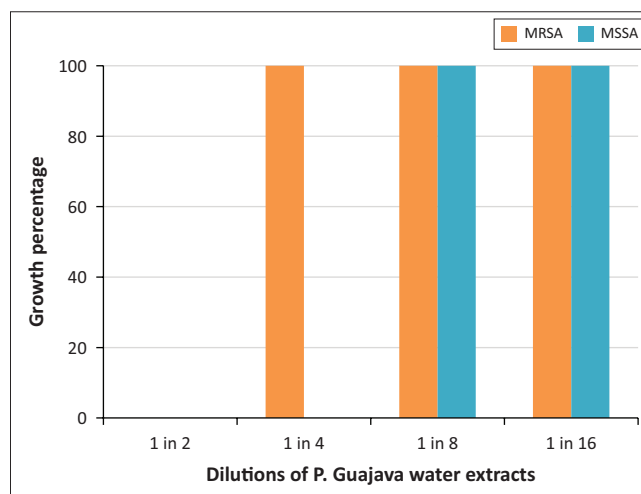
The ethanol extract, whilst containing both hydrophilic and lipophilic compounds, was less effective, possibly because of the need for higher concentrations or the presence of compounds with lower antibacterial activity. Both extracts showed reduced activity against MRSA as compared to MSSA. Methicillin resistance in *S. aureus* arises from the acquisition of the *mecA* gene within the staphylococcal cassette chromosome *mec* (SCC*mec*), which has eight defined types based on SCC*mec* and chromosomal background (Li et al. 2011), and the *mecA* gene encodes penicillin-binding protein 2a (PBP2a), enabling MRSA to resist  $\beta$ -lactam



MRSA, methicillin-resistant *Staphylococcus aureus*.

\*Significant *p*-values.

**FIGURE 2:** Antibacterial activity of *Psidium guajava* extracts against methicillin-resistant *Staphylococcus aureus* strain.



MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

**FIGURE 3:** *Psidium guajava* water extract minimum inhibitory concentration results.

antibiotics (Lee et al. 2018). This resistance mechanism may also reduce the effectiveness of some of the antibacterial compounds found in guava leaf extracts. However, the fact that both extracts still demonstrated some activity against MRSA suggests that guava leaf compounds may help overcome bacterial resistance, indicating potential for further research into their role in treating resistant strains.

## Comparison with previous studies

Previous research has also highlighted the antibacterial properties of guava leaf extracts, particularly against *S. aureus*. For instance, Pereira et al. (2023) found that guava leaf extracts inhibited the growth of both MSSA and MRSA, which supports the findings of this study. However, this study further expands on those findings by comparing the antibacterial effects of water- and ethanol-based extracts, providing a deeper understanding of how different extraction solvents influence the efficacy of guava leaves. Anas et al. (2008) suggested that the strong antibacterial activity of

*P. guajava* leaf extracts could be because of their protein-degrading properties. The results are consistent with those of Elekwa, Okereke and Ekpo (2008), Emmanuel (2010) and Biswas et al. (2013), who reported that the aqueous extract of *P. guajava* showed stronger antimicrobial activity than the ethanolic extract. The present study's findings regarding the water extract align with the work of Altemimi et al. (2017), who demonstrated that compounds such as flavonoids and tannins in guava leaves contribute significantly to antibacterial effects. These results support the hypothesis that hydrophilic compounds are more effective in aqueous solutions, particularly against *S. aureus*.

### Mechanisms of action

The antibacterial activity of guava leaf extracts is driven by bioactive compounds, primarily tannins, flavonoids and saponins. Tannins have been shown to inhibit bacterial adhesion and disrupt bacterial cell membranes, leading to leakage of cellular contents (Biswas et al. 2013). Flavonoids, found abundantly in guava leaves, are known for their ability to destabilise bacterial cell membranes and interfere with microbial enzymes involved in bacterial metabolism (Zhang et al. 2016). In addition, a study done by Ugbogu et al. (2022) reported that benzyl isocyanate obtained from the methanol extract of *P. guajava* leaves inhibited *S. aureus*. These compounds likely contribute to the observed antibacterial activity, with water-based extracts being more effective because of the increased solubility and availability of these hydrophilic compounds.

In addition, saponins may play a role by interacting with membrane sterols, increasing membrane permeability and leading to bacterial cell death (Hassan et al. 2010). However, more research is needed to fully understand how these compounds interact with bacterial cells and to identify the precise mechanisms behind the antibacterial effects of guava leaf extracts.

### Diabetic wound healing

The potential of guava leaf extracts is particularly relevant in the context of diabetic wounds, where *S. aureus* infections are prevalent. Given that individuals with T2D often experience impaired immune responses and chronic inflammation, which can complicate wound healing, guava leaf extracts could provide valuable treatment alternatives for managing such infections. Diabetic foot ulcers, which are commonly infected with *S. aureus*, are often difficult to treat because of these immune system impairments. The antibacterial properties of guava leaf extracts could aid in the management of such infections, potentially reducing the need for more conventional, costly and sometimes less effective treatments.

Further studies should investigate the effectiveness of guava leaf extracts in healing diabetic wounds and clearing *S. aureus* infections in diabetic models. In addition, evaluating the impact of guava extracts on biofilm formation in chronic wounds could be beneficial, as biofilms complicate wound healing and treatment outcomes.

### Public health implications

As the global burden of antibiotic resistance continues to grow, especially with hospital-acquired infections like MRSA, alternative antimicrobial agents are urgently needed. Guava, a widely available and affordable plant, offers promise as a natural remedy. In areas with limited access to conventional antibiotics, guava leaf extracts could be a cost-effective, sustainable option for managing *S. aureus* infections. Its low toxicity profile makes it an attractive candidate for widespread use in resource-limited settings. This has the potential to substantially decrease healthcare expenditures and provide an alternative when traditional therapies prove ineffective or are not readily available.

### Limitations and future research directions

Whilst the present study provides valuable insight into the antibacterial potential of guava leaf extracts, it is limited to *in vitro* testing. Further studies involving *in vivo* models are essential to evaluate the therapeutic potential and safety of guava extracts in actual infection scenarios. Testing these extracts on animal models of infection, such as wound healing models, would be particularly useful for assessing their applicability in clinical settings.

Moreover, the optimal dosage and administration of guava extracts in living organisms still need to be determined. Research aimed at identifying the most effective dosage for treating infections and understanding the potential for any adverse effects would be beneficial. It is also important to consider the bioavailability of the active compounds in guava leaves and how they may interact with other treatments or antibiotics. Future research should combine genetic or proteomic analyses to better understand the molecular mechanisms behind bacterial strain responses to guava leaf extracts. In addition, focussing on phenolic compounds, such as gallic acid, catechin, ellagic acid, naringenin and rutin, could provide further insights into the antibacterial mechanisms of guava leaf extracts. Expanding the range of bacterial pathogens studied will offer a more comprehensive understanding of the therapeutic potential of these extracts.

### Recommendations

The recommendations of this study include conducting comparative analyses of guava leaf extracts from various regions to evaluate potential variations in their bioactive compound profiles and antibacterial activity. In addition, it is essential to investigate the synergistic effects between guava leaf extracts and conventional antibiotics to enhance the treatment of resistant bacterial strains. Advanced extraction techniques should be explored to optimise the yield of bioactive compounds, and molecular analyses should be performed to isolate and characterise the specific compounds responsible for antibacterial properties. Finally, developing standardised formulations of guava extracts is crucial to ensure consistent potency and safety for potential therapeutic applications.

## Conclusion

This study underscores the potential of guava leaf extracts as a natural antibacterial agent against *S. aureus*, with the water-based extract showing greater effectiveness, likely because of the enhanced solubility of hydrophilic compounds such as flavonoids, tannins and saponins. Whilst activity against methicillin-resistant *S. aureus* was limited, the observed inhibition suggests that guava may contain bioactive compounds capable of influencing bacterial resistance mechanisms.

To fully explore the therapeutic value of guava extracts, further research is needed to isolate and characterise these active compounds using advanced techniques such as high-performance liquid chromatography, gas chromatography-mass spectrometry and nuclear magnetic resonance spectroscopy. Understanding how these compounds interact with bacterial cells – whether by disrupting cell walls, inhibiting enzymes or interfering with resistance pathways – will be essential in determining their potential as antimicrobial agents. In addition, refining extraction methods to enhance potency, assessing possible synergies with conventional antibiotics and conducting *in vivo* studies, particularly in diabetic wound models, will provide critical insights into their real-world applications. Toxicity and biocompatibility assessments will also be necessary to ensure their safety for therapeutic use.

Although this study highlights the promise of guava leaf extracts as a complementary approach to combating bacterial infections, particularly in the context of antibiotic resistance, further rigorous biochemical, pharmacological and clinical investigations are required before they can be considered for medical application.

## Acknowledgements

### Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

### Authors' contributions

N.W.N conceptualised the study and contributed towards the methodology, formal analysis, investigation, project administration and funding acquisition. K.P.M. and S.P.R. contributed towards the formal analysis, visualisation, resources, reviewing and editing. N.T. contributed towards the formal analysis, original draft, visualisation, software, validation, resources, reviewing and editing.

### Funding information

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

### Data availability

The authors confirm that the data supporting the findings of this study are available within the article.

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