Review Article

A Review of Bioactive Compounds of Guava: Biosynthesis and Mechanism Against Multidrug-Resistant (MDR) Bacteria

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Submission Date: 14-05-2022; Revision Date: 22-06-2022; Accepted Date: 19-07-2022.

ABSTRACT

Aim/Background: Antimicrobial resistance remains to be a "silent" pandemic that immensely affects global populations and imminently challenges medical professionals on infection control and patient management. In combating such a global health crisis, overarching actions on antibiotic innovation potentially fill the gap against multidrug resistance. In that light, *Psidium guajava* Linnaeus, locally known as guava, is used in folk and traditional medicine for a variety of ailments. Focusing on antimicrobial activity, several guava-derived bioactive compounds (GBC) have provided guava with its antimicrobial properties against bacterial invasion. As such, the evaluation of guava's antimicrobial activity against multidrug-resistant (MDR) bacteria interrelated with an understanding of the biosynthesis and mechanism of GBCs would be the highlight of this paper. **Materials and Methods:** While employing a systematic narrative approach, a total of 570 publications were gathered using Zotero from various library databases. Towards the conduct of the stratified screening, only 15 journals have satisfied the eligibility criteria. These publications expound on the biosynthesis and mechanisms of GBCs, and their activity against MDR bacteria. **Results and Conclusion:** Extensive analysis of collected literature has revealed that GBC production has been associated with the guava's photosynthetic ability that passes through various pathways. Whereas, most GBCs specify an inhibition mechanism as the predominant antimicrobial action. As such, guava extracts, depending on the extraction solvent and guava part used, provide remarkable *in vitro* antimicrobial activity against MDR bacteria. With the emerging antimicrobial applications of guava, further studies shall be explored specifically on antibiotic innovation such as synergistic studies, *in vivo* studies, and clinical trials.

Keywords: Biosynthesis, Guava, Mechanism, Multidrug-Resistant Bacteria, Phytochemicals.

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INTRODUCTION

A "ticking time bomb"-antimicrobial resistance (AMR) remains a century-old public health crisis that alarms the medical workers and the public of the possible "silent" pandemic with the incessant decline in effective antimicrobials. Knowing that the misuse and overuse of antimicrobials induce such resistance, infection control and management imminently became a challenge to medical professionals with limited antibiotic development.[1] In fact, a report on antimicrobial resistance highlights various multidrug-resistant (MDR) bacteria that have caused varying severity of infections and fatalities reflected in the annual 2.8 million cases and 35,000 deaths just in the United States alone.[2] In a larger sense, MDRs are a series of bacteria found to be *in vitro* resistant to two or more antibiotics designed to kill or inhibit them.

In particular, MDR bacteria are stratified into three categories based on priority—critical, high, and medium. Included in the list of critically resistant bacteria are carbapenem-resistant *Acinetobacter baumannii*,

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DOI: 10.5530/ajbls.2022.11.39

Pseudomonas aeruginosa, and *Enterobacteriaceae* (including Extended Spectrum β-Lactamase [ESβL]-producing species). Meanwhile, some high-priority bacteria are vancomycin-resistant *Enterococcus faecium*, methicillin-resistant *Staphylococcus aureus*, clarithromycin-resistant *Helicobacter pylori*, and cephalosporin-resistant *Neisseria gonorrhoeae*. Whereas, some medium-priority bacteria are characterized as penicillin-resistant *Streptococcus pneumoniae*, ampicillin-resistant *Haemophilus influenzae*, and fluoroquinolone-resistant *Shigella* spp.[3] Not only limited to the aforementioned bacteria, but this public health crisis demands further antibiotic development and innovation suppress the seemingly worsening world condition. Thus, interventions in antibiotic innovation remain an overarching action towards suppressing drug resistance and further addressing the so-called "silent" pandemic.

In that light, *Psidium guajava* Linnaeus, also known as guava, draws the limelight not only for its therapeutic and herbal applications but also for its indicative antimicrobial properties. Widely used in folk and traditional medicine, distinct parts of the guava plant are being considered therapeutic options in cases of diarrhoea, stomach aches, and even chronic diseases such as diabetes, cardiovascular diseases, and cancer.[4-5] Focusing on its antimicrobial activity, the phytochemical analysis revealed that the presence of different bioactive compounds such as saponins, terpenoids, tannins, and alkaloids provide guava with its antimicrobial properties against bacterial pathogens.[6]

Hence, the general objective of this narrative review focuses on the evaluation of guava's antimicrobial activity against MDR bacteria. Specifically, understanding the biosynthesis of guava-derived bioactive compounds (GBC) and their mechanisms toward MDRs will be the highlight of this review paper. In addition, while this review paper mainly accentuates the reality of antimicrobial resistance, the progress in antibiotic innovation, specifically from organic products such as guava, is regarded as a giant leap toward filling in the gaps against the antibiotic crisis and suppressing the said public health threat.

MATERIALS AND METHODS

Literature Search

Library databases such as Google Scholar, PubMed, ScienceDirect, BASE, and EBSCO were used to retrieve related literature while Zotero, an open-source reference manager, was utilized for efficient journal management and screening. Keyword combinations not limited to ("Guava" OR "*Psidium guajava* L.") AND "Multidrug-Resistant Bacteria" OR "Phytochemical" OR "Antibacterial Mechanism" OR "Susceptibility" OR "Biosynthesis" were interchangeably used in the search for articles related to guava-derived bioactive compounds and MDR bacteria.

Eligibility Criteria

***Inclusion criteria*:** Articles published from credible databases that are related to the (1) biosynthesis of guava-derived bioactive compounds, (2) their antimicrobial mechanisms, and (3) susceptibility tests specific to guava and MDRs were mainly included in the study.

***Exclusion criteria*:** Journals retrieved from (1) predatory sites and (2) published before 2017 were immediately excluded from the study while (3) review papers, (4) duplicate articles, (5) non-relevant articles, (6) non-English texts, and (7) non-availability of full-text manuscripts were further omitted.

Selection Strategy

A stratified screening of each article was performed by the six authors which is centred on eligibility and discrepancies. Preliminary screening of title and abstract was performed followed by the full-text manuscript screening of candidate journals for eligibility. Meanwhile, any discrepancies encountered were settled through group members-adviser coordination.

Data Extraction

Information was extracted from eligible journals that contain the publication information such as the article author's name, publication year, type of sample, MDR bacteria, susceptibility test, bioactive compounds, and key findings which are essential to the study. Meanwhile, some of the journal's abstract and discussion parts may also provide additional information for the researcher's intensified analysis. Particularly, the six authors initially extracted the journal data which was then verified and validated by their research mentor. Table 1 presents the list of articles considered eligible and thus, are included in the study.

RESULTS

From a wide range of data sources, varying keyword combinations and filters were inputted to different databases that gathered and recorded a total of 570 journals which were organized using Zotero as the reference manager. Omission of duplicate articles (n=168) was conducted that reduced the records to 402. Upon title and abstract screening, the list was systematically narrowed down to only 57 journals which will require a guided full-text manuscript reading.

Table 1: General Characteristics of Included Studies.

	References	Type of Sample	MDR Bacteria	Susceptibility Test	Bioactive Compounds	Key Findings
1	Bisi-Johnson, *et al.*, 2017	Acetone Leaf Extract	ESβL-producing *Salmonella enterica* serovar Typhimurium	Serial Dilution Microplate Method	Quercetin-3-O-arabinopyranoside	Extract is active against enteropathogens. MIC: 0.078mg/mL
2	Dzotam and Kuete, 2017	Methanolic Fruit, Leaf, and Bark Extract	Multidrug-Resistant Clinical Enteric Bacteria (*E. coli, Enterobacter aerogenes, K. pneumoniae, Providencia stuartii, P. aeruginosa*)	Rapid INT colorimetric assay	Alkaloids, Polyphenols, Flavonoids, Coumarins, Tannins, Triterpenes, Sterols, Saponins	*P. guajava* is inhibitory against both Gram positive and negative bacteria. Methanolic extract exhibits significant inhibitory activity against MDR bacteria.
3	Chakraborty, *et al.*, 2018	Ethanolic Leaf Extract	20 samples of Methicillin-Resistant *Staphylococcus aureus*	Disk Diffusion Method	Alkaloids, Saponin, Flavonoids, Tannins, Cardiac Glycosides, Phenols, Terpenes, Resins, Steroids	Largest ZOI: 24.73±0.55mm
4	Edwin, *et al.*, 2018	Dimethyl Sulfoxide (DMSO) Leaf Extract	Multidrug clinical isolates (*S. aureus, Streptococcus pyogenes, E. coli, P. aeruginosa*)	Disk Diffusion Method	Lipophilic flavonoids, Tannins	*P. guajava* complexes with extracellular proteins and bacterial cell walls. Presence of lipophilic flavonoids that disrupt cell membrane
5	Emmanuel, *et al.*, 2019	Ethanolic Leaf Extract	Methicillin-Resistant *S. aureus*	Disk Diffusion Method	Saponins, Glycosides, Tannins, Flavonoids, Alkaloids, Triterpene	ZOI: 11mm
6	Gilford, *et al.*, 2019	Methanolic Leaf Extract	50 Methicillin-Resistant *S. aureus* and 17 drug-resistant *P. aeruginosa*	Agar Well-Diffusion Method	Flavonoids	90% of MRSA were susceptible 47.06% of drug-resistant *P. aeruginosa* were susceptible
7	Khadka, *et al.*, 2019	Ethanolic Leaf Extract	Clinical Isolates: 32 MDR *P. aeruginosa*; 3 ESβL-producing *P. aeruginosa*	Agar Well Diffusion Method	Alkaloids, Flavonoids, Tannins, Saponins, Glycosides, and Terpenoids	ZOI: 11mm
8	Moses, *et al.*, 2019	Methanolic Leaf Extracts	Multidrug-resistant Bacteria (*S. aureus, S. typhi, Bacillus cereus,* and *E. coli*)	Well-Diffusion Method	Polyphenols, Carotenoids, Flavonoids, and Tannins	ZOI: 18.22 mm (*S. aureus*);6.77 mm (*S. typhi*); 18.77 mm (*B. cereus*);4.11 mm (*E. coli*)
9	Daswani, *et al.*, 2020	Decocted (Aqueous) Leaf Extract	43 Clinical Isolates of *Shigella* spp.	Agar Dilution Method	Flavonoid (Quercetin)	23 isolates were susceptible to the extract
10	Festus, *et al.*, 2020	Methanol and Ethyl Acetate Leaf Extract	Multidrug-Resistant Bacteria (*S. epidermidis, B. cereus, P. aeruginosa, Proteus mirabilis, E. coli,* and *S. saprophyticus* saphrophyti)	Agar Well Diffusion Method	Terpenoids, Steroids, Saponins, Flavonoids, Tannins, Cardiac Glycosides, Alkaloids, Anthraquinones	Methanolic extracts possess greatest antimicrobial activity against MDRs
11	S, *et al.*, 2020	Ethanolic Leaf Extract	Methicillin-resistant *S. aureus*	Broth Microdilution Method	Alkaloids, Tannins, Hydroxyanthraquinones, Triterpenoids, Steroids, Saponins	MIC: 125µg/mL; MBC: 500µg/mL

continued...

Table 1: Cont'd.

	References	Type of Sample	MDR Bacteria	Susceptibility Test	Bioactive Compounds	Key Findings
12	Serunjogi, 2020	Ethanolic Leaf Extract	ESβL-producing *K. pneumoniae*	Broth Microdilution Method	Saponins, Phenolic Compounds, Reducing Sugars, Polyuronoids, Flavonoids, morin-3-O-alpha-L-lyxopyranoside, morin-3-O-alpha-L-arabinopyranoside	MIC and MBC: 6.25mg/mL
13	Chidebelu, *et al.*, 2021	Methanolic Leaf Extracts	*Escherichia coli, Klebsiella pneumoniae, Enterococcus faecalis*, and *Pseudomonas aeruginosa*	Broth Microdilution Method	Alkaloids, Flavonoids, Terpenoids, Tannins	MIC: 50mg/mL (*E. coli* and *K. pneumoniae*); 25 mg/mL (*E. faecalis* and *P. aeruginosa*)
14	Owosu, *et al.*, 2021	Ethanolic and Aqueous Leaf Extracts	MDR wound isolates- *E. coli* (24), *P. aeruginosa* (12), *S. aureus* (11), and Coagulase-negative *Staphylococci* (2)	Agar Well Diffusion Method	Saponins, Phenolics, Reducing Sugar, Flavonoids, Anthracenosides, Phytosterol	*P. guajava* exhibits antimicrobial activity against MDRs from post-operative wounds. Extract inhibits growth of MDR *S. aureus*.
15	Thapa, *et al.*, 2021	Methanolic and Hydro Ethanolic Leaf Extract	30 MDR *P. aeruginosa* isolates and 6 Metallo β-Lactamase (MβL)-producing *P. aeruginosa*	Well-Diffusion Method	Flavonoids, Saponins, Tannins, Eugenol, and Triterpenes	*P. guajava* exhibits antimicrobial activity against MDR *P. aeruginosa*.

Whereas, after the comprehensive manuscript screening of such 57 articles, only 15 journals have specified and satisfied both the cited inclusion and exclusion criteria. That being said, these 15 journals were then considered by the authors as the articles to be included in the review paper. Figure 1 presents the schematic flow of literature gathering using the PRISMA model.

Biosynthesis of Guava-derived Bioactive Compounds

Bioactive compounds derived from guava—alkaloids, saponins, terpenoids, tannins, phenols, and flavonoids—are phytochemicals which have potential applications to human health. Such compounds may be produced in plants as by-products of metabolic and biochemical processes, thereby being considered primary and secondary metabolites. The synthesis of phytochemicals in guava plants provides protection against invading pathogens such as viruses, fungi, and bacteria. By mechanism, upon pathogen invasion, a pool of nutrients and amino acids will be consumed in the production of phytochemicals necessary for defence against external pathogens.[7]

Depending on the bioactive compound, phytochemical production follows varying biosynthetic pathways. For instance, alkaloids are produced from the aliphatic amino acids formed following the citric acid cycle; terpenoids and saponins are formed by mevalonic acid metabolism through the mevalonate pathway but only the latter undergoes the methyl erythritol pathway.[8-9] Meanwhile, in a two-fold shared metabolic process, the shikimic acid and phenylpropanoid pathways synthesize the flavonoids and polyphenols.[9-10] Figure 2

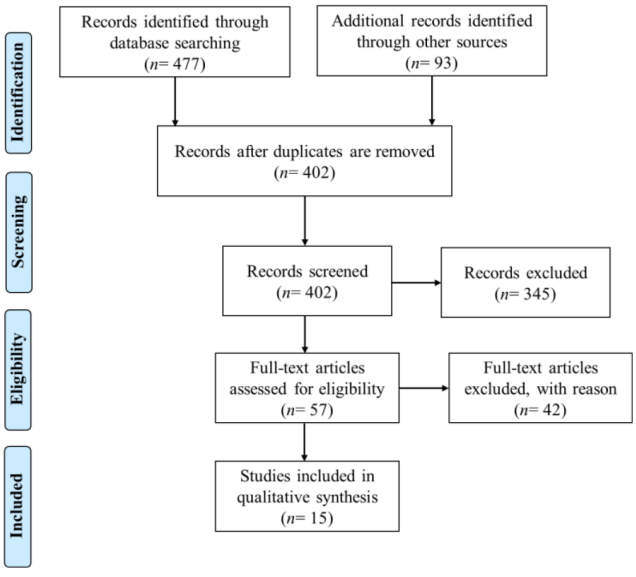

Figure 1: Schematic Flow of the Literature Methodology.

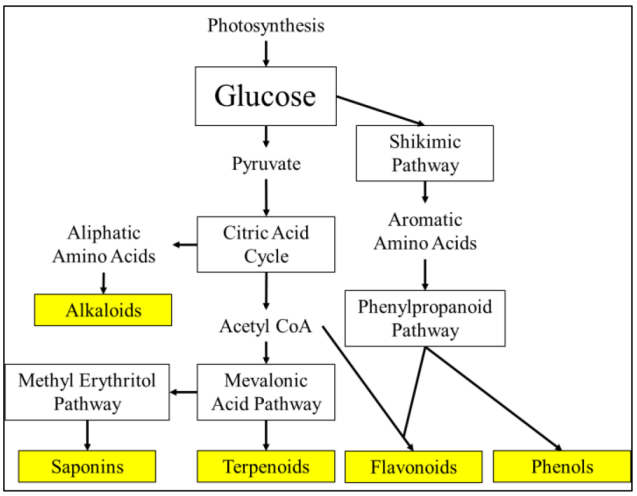

Figure 2: Biosynthetic Pathway of GBCs.

Table 2: Distribution of GBCs to different Guava Parts.

Bioactive Compound	Guava Leaves	Guava Stems	Guava Fruits
Alkaloids	+	+	-
Saponins	+	+	-
Tannins	+	+	-
Phenols	+	+	+
Terpenes	+	+	+
Flavonoids	+	+	+

(+) presence of phytochemical; (-) absence of phytochemical

provides the biosynthetic pathway of guava-derived bioactive compounds such as alkaloids, saponins, terpenoids, flavonoids, and phenols. In addition, tannins are biosynthesized through condensation and polymerization of catechins and anthocyanidins.[11]

Distribution and Concentration of GBCs among Different Guava Parts

With vast therapeutic claims, different parts of guava—the leaves, barks/stems, fruits, and roots—render different compositions which are responsible for their respective bioactive properties. Dzotam and Kuete (2017) have outlined the approximate phytochemical percent (%) yield of guava leaves, stems, and fruits which are 5.47%, 4.17%, and 6.12%, respectively.[12] Table 2 presents the qualitative distribution of guava-derived bioactive compounds among the leaves, stems, and fruits. Focusing on antimicrobial activity, alkaloids, saponins, tannins, phenols, and terpenes provide guava with its bactericidal and bacteriostatic properties.[6] In that sense, guava leaves and stems contain the mentioned phytochemicals, while guava fruits lack alkaloids, saponins, and tannins. However, other phytochemicals have also been recorded to provide guava with additional antimicrobial activity such as flavonoids and steroids.[12] By concentration, Oncho, *et al.* (2021) have highlighted that alkaloid, saponin, total phenol, and tannin contents are 98.67 mg/g, 29.00 mg/g, 0.20 mg/g, and 0.15 mg/g in guava leaves, respectively. Meanwhile, 72.33 mg/g, 19.00 mg/g, 0.13 mg/g, and 0.09 mg/g are their respective concentrations in guava stems.[6] At length, guava leaves have consistently greater antimicrobial bioactive compounds when compared with guava stems.

Mechanism of Action of Guava-derived Bioactive Compounds

With significant phytochemical contents identified from various parts, guava potentially provides antibacterial activity against MDRs. Mechanisms suggest bacteria-specific actions towards a particular bacteria. Such antibacterial mechanisms may cause destruction, inhibition, or inactivation of bacterial membranes, substances, organelles, or even the genetic makeup. Table 3 provides the summary of guava-derived bioactive compounds and their corresponding antibacterial mechanisms of action.

Susceptibility of MDRs against Guava Extracts

Several extraction solvents—mostly alcoholic and aqueous—have been utilized to evaluate the susceptibility of different classes of MDR bacteria using different susceptibility tests. By understanding the antimicrobial and resistance mechanisms, guava extracts

Table 3: Antimicrobial Mechanisms of Action of Guava-derived Bioactive Compounds.

Guava-derived Bioactive Compound	Mechanism of Action
Quercetin-3-O-arabinopyranoside	• High antiplaque property which inhibits growth of *S. mutans*[13]
Tannins	• Iron and nutrient deprivation[14] • Phosphorylation, enzyme, and protein synthesis inhibition[15]
Flavonoids	• Bacterial cell wall disruption[16] • Inactivation of microbial adhesion and protein transport[15]
Terpenoids	• Disruption of lipophilic compounds in bacterial membrane[16]
Saponins	• Surface tension reduction leading to increase cell wall permeability and leakage[17]
Phenolic Compounds	• Bacterial membrane disruption and biofilm and virulence inhibition[18]
Alkaloids	• Efflux pump inhibition[19]

are deemed to exhibit antibacterial activity against MDRs. For instance, Bisi-Johnson, *et al.* (2017) used acetone leaf extract against ESβL-producing *S. enterica* resulting in a minimum inhibitory concentration (MIC) value of 0.078 mg/mL. The same study also suggested the extracts' effectiveness against enteropathogens.[13] Meanwhile, the aqueous leaf extract of guava has proven effective and susceptibility against 23 clinical isolates (n=43) of *Shigella* species.[20]

Furthermore, Moses, *et al.* (2019) revealed in their experiment that the methanolic leaf extract of guava produced a ZOI value of 18.22mm for *S. aureus*, 6.77mm for *S. typhi*, 18.77mm for *B. cereus*, and 4.11mm for *E. coli*.[21] In addition, the same type of extract inhibits growth at 50mg/mL for *E. coli* and *K. pneumoniae* and 25mg/mL for *E. faecalis* and *P. aeruginosa*.[22] Parallel to that, Gilford, *et al.* (2019) have concluded in their experiment that 90% of MRSA samples (n=50) and 47.06% of drug-resistant *P. aeruginosa* isolates (n=17) have been found to be significantly susceptible to the said extract.[23]

Moreover, in an investigation made by Emmanuel, *et al.* (2019), the ethanolic leaf extract of guava provided an approximate ZOI value of 11mm against MRSA.[24] To a much greater extent, Chakraborty, *et al.* (2018) have revealed a larger ZOI value of 24.73±0.55mm using 20 MRSA isolates and the same type of extract.[25] In consideration of minimum inhibitory and bactericidal concentration values, S, *et al.* (2020) utilized the ethanolic leaf extract against MRSA which eventually resulted in a MIC of 125 μg/mL and MBC of 500 μg/mL.[16] Apart from MRSA, Khadka, *et al.* (2019) have highlighted 32 MDR *P. aeruginosa* isolates having an average ZOI value of 11mm against the said extract.[26] In the same manner, Thapa, *et al.* (2021) have emphasized that *P. guajava* exhibits activity against the said MDR *P. aeruginosa*.[27] Similarly, Serunjogi, *et al.* (2020) tested the susceptibility of ESβL-producing *K. pneumoniae* against the same type of leaf extract which resulted in a MIC and MBC of 6.25 mg/mL.[28] Table 1 presents the type of extract used, the MDR bacteria involved, the susceptibility test used, their corresponding bioactive compounds, and other key findings.

DISCUSSION

In traditional and folk medicine, various guava parts have been used as a therapeutic treatment for a variety of ailments, but guava leaves are the most commonly used. Essentially, guava leaves contain the highest concentration of phytochemicals among the guava parts. Such compounds are alkaloids, saponins, phenols, flavonoids, tannins, and terpenes.[6] Their production has been associated with the plant's photosynthetic ability that passes through a series of pathways such as, but not limited to, the citric acid cycle, mevalonic acid pathway, methyl erythritol pathway, and shikimic acid pathway.[8-10]

Generally, while understanding that the stimulant for phytochemical synthesis is pathogen invasion among plants, these phytochemicals were viewed as valuable to the pharmaceutical industry as organic supplements that render similar protection to humans once phytochemical-containing plants were consumed.[29] Apparently, this is the primary reason for guava's array of therapeutic applications in folk and traditional medicine—serving its purpose as an antioxidant, anti-inflammatory, anti-diarrheal, and antimicrobial agent.[30] Known that guava extract exhibits bacteriostatic and bactericidal effects, their mechanisms of action against bacteria specify cell membrane destruction and inhibition mechanism where the latter remains the predominant action exhibited by most GBCs.

Having established that guava extracts have antimicrobial activity against bacteria, fortunately, the same type of extract also provides antibacterial activity against Multidrug-Resistant (MDR) Bacteria. For instance, Bisi-Johnson, *et al.* (2017) have emphasized the antiplaque property of guava demonstrated by Quercetin-3-O-arabinopyranoside that established a MIC of 0.078 mg/mL against ESβL-producing *S. enterica*.[13] Similarly, S, *et al.*(2020) have revealed that MRSA is susceptible to guava extract with an MIC value of 125 μg/mL and MBC of 500 μg/mL.[16] This is due to the bacterial membrane disruption caused by flavonoids and terpenoids. Aside from the quantitative results, varying *P. guajava* extracts have been implicated as bacteriostatic to both Gram-positive and negative bacteria whereas methanolic extracts provide greater antimicrobial activity against MDRs.[12,31] In that light, *P. guajava* form complexes with microbial cell walls and extracellular proteins.[32] In addition, the same guava-derived extracts are effective antimicrobials against multidrug-resistant enteropathogens and post-operative wound bacteria.[13,33]

CONCLUSION AND RECOMMENDATIONS

Guava extracts, depending on the extraction method and the guava part used, provide remarkable *in vitro* antimicrobial activity against MDR bacteria. Whereas, the highest concentration of phytochemicals is apparent among guava leaf-derived extracts. Various mechanisms have been implicated to explain how guava-derived

phytochemicals exhibit bacteriostatic or bactericidal actions such as cell membrane destruction, inhibition of biofilm formation, DNA and protein synthesis, and efflux pump inhibition. Furthermore, extensive studies on guava's antimicrobial activity may be explored to further expand its applications in antibiotic innovation such as synergistic studies and the open possibility for clinical trials and *in vivo* studies. As such, knowledge of pharmacodynamics and pharmacokinetics may also be necessary.

ACKNOWLEDGEMENT

The authors would like to extend their sincerest recognition to the Almighty God for the opportunity for progress and development. Deepest gratitude is also extended to their research adviser, Ms Kristina Maria R. Petalcorin, RMT, MSMT(c), for her outstanding support, expertise, and dedication towards the conduct of this study; to their research professors, Mr Bernardino M. Hagosojos, RMT, and Ms Laarni Hannah Lacorte, RMT, MSMT for their guidance towards the writing of this review paper. Finally, the authors would also like to extend their warmest appreciation to their families and colleagues, for their unwavering support and words of encouragement throughout the conduct of this research endeavour.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AMR: Antimicrobial resistance; **DNA:** Deoxyribonucleic acid; **DMSO:** Dimethyl sulfoxide; **ESBL:** Extended-spectrum β-Lactamase **GBC:** Guava-derived bioactive compounds; **MBC:** Minimum bactericidal concentration; **MDR:** Multidrug resistance; **MRSA:** Methicillin-resistant *Staphylococcus aureus*; **MIC:** Minimum inhibitory concentration; **ZOI:** Zone of inhibition.

SUMMARY

Antibiotic misuse and overuse accompanied by the continuous decline in antimicrobial production have led to more severe cases of antimicrobial resistance and worse, multidrug resistance. As such, interventions leading to antibiotic development and innovation remain an overarching action towards potentially addressing such a health crisis. In that light, *Psidium guajava* Linnaeus, locally known as guava, has a wide history of traditional and therapeutic use centred on alleviating discomfort. In addition, the antimicrobial property has also been evident with the presence of guava-derived bioactive compounds (GBC). Given that, understanding GBC biosynthesis along with their respective antimicrobial mechanisms provides the evaluation of the guava's antimicrobial activity against MDR bacteria.

Pertaining to that, results suggest that most GBCs are produced in different guava parts at varying concentrations through a series of pathways preceded by photosynthesis. Whereas, antimicrobial mechanisms specify destruction and inhibition, the latter remains the predominant action exhibited by most GBCs. Given that, several susceptibility tests have proven the effectiveness of guava leaf extracts as an antimicrobial agent against MDR bacteria.

Hence, guava extracts, depending on the extraction solvent and guava part used, provide remarkable *in vitro* antimicrobial activity against MDR bacteria. With guava's emerging antimicrobial applications, extensive studies shall be conducted specifically on antibiotic development and innovation such as synergistic studies, *in vivo* studies, and clinical trials.

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Cite this article: Ilagan CPM, Austria AES, Bunao KDS, Reyes ILL, Tumbale JAP, Loyzaga AMM, Petalcorin KMR. A Review of Bioactive Compounds of Guava: Biosynthesis and Mechanism Against Multidrug-Resistant (MDR) Bacteria. Asian J Biol Life Sci. 2022;11(2):294-301.