ORIGINAL ARTICLE

A Systematic Review of the Philippine Plants' Antibacterial Properties against *Staphylococcus aureus*

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ABSTRACT

Background and Objective. *Staphylococcus aureus* poses a significant public health threat globally, where both community and hospital-acquired infections are prevalent. The escalating antimicrobial resistance highlights the urgent need for alternative therapies. Hence, traditional medicine using plant extracts offers a potential avenue for novel antibacterial agents. This systematic review aimed to evaluate the existing literature on the antibacterial properties of Philippine plants against *S. aureus* to provide focus on drug development of a plant-derived antibacterial for this pathogen.

Methods. Following PRISMA guidelines, a comprehensive search was conducted in PubMed/Medline, SCOPUS, and Herdin databases. Inclusion criteria encompassed in vitro studies evaluating the antibacterial activity of crude plant extracts sourced from Philippine plants against *S. aureus.* Data extraction and quality assessment were performed independently by two reviewers, with discrepancies resolved by the third and fourth reviewers.

Results. Of the 413 initial studies identified, nine met the eligibility criteria. The highest zone of inhibition was demonstrated by *Lippia micromera* leaf essential oil at 26.3±1.5 mm, while moderate antibacterial activity was shown by essential oils from *Alpinia elegans*, *Piper quinqueangulatum*, and *Alpinia cumingii* at MIC values of 512 µg/mL, 512 µg/mL, and 1,024 µg/mL, respectively. Other Philippine plants showed a wide range of activity, with MIC values between 50 µg/mL and 25 mg/mL, MBC values from 78 to 5000 µg/mL, and ZOI ranging from 5 to 38 mm. However, the overall quality of evidence in these other studies are compromised by bias and incomplete reporting.

Conclusion. Leaf essential oils from *Alpinia elegans*, *Piper quinqueangulatum*, and *Alpinia cumingii* demonstrated moderate antibacterial activity against *S. aureus*. Additionally, the essential oils of *Lippia micromera*, *Plectranthus amboinicus* Lour. Spreng, and *Cymbopogon citratus* exhibited antibacterial activity against both *S. aureus* and Methicillin-resistant *S. aureus* (MRSA) in disk diffusion assays, these antibacterial activities may be attributed to their high concentrations of terpenes, terpenoids, and phenolic compounds. Majority of the studies gathered had high risk of bias according to the quality assessment criteria tool used in the study. Thus, this systematic review also emphasizes the need for improved methodological rigor on reporting in vitro antibacterial studies.

Keywords: Philippines, medicinal plants, Staphylococcus aureus, Alpinia, Piper, Lippia, Plectranthus, Cymbopogon, terpenes, terpenoids, phenols, systematic review

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INTRODUCTION

Staphylococcus aureus is a prevalent cause of both community and hospital-acquired infections globally.[1] With its capacity to affect humans, animals, and the environment, it is considered a significant One Health threat.[2] In the Philippines, community-acquired *S. aureus* infections remain high. Nosocomial infections, particularly associated with medical devices and wounds, have been consistently reported.[3–5]

Although most *S. aureus* infections are conventionally treated with antibiotics, the persistent high rates of oxacillin resistance have limited its efficacy as empiric therapy.[3,6] Moreover, the escalation of vancomycin resistance of this pathogen to 1.5% in the past decade necessitates a judicious approach to its use as a reserve antibiotic.[3] The increasing rates of antimicrobial resistance globally constitute a substantial threat to public health, prompting urgent calls for increased funding and innovations in the discovery and development of new antimicrobials and compounds.[7] Furthermore, the World Health Organization listed methicillin-resistant *S. aureus* (MRSA) as high priority for research and development of new antibiotics.[8]

The use of natural products has long been known to humans with as early as 60,000 years ago with fossil records supporting this. Ever since, the practice of traditional medicine largely contributed to the alleviation and treatment of diseases.[9] Philippines has a wide variety of herbal plants with varying pharmacologic activities including antibacterial properties. Despite widespread research efforts on antibacterial activities of these local herbal plant extracts folklorically used for infections, none have consolidated and reviewed the literature to describe their in vitro antibacterial activity particularly against *S. aureus*. Thus, this systematic review aimed to evaluate the existing literature on the antibacterial properties of Philippine plants against *S. aureus* to provide focus on drug development of a plant-derived antibacterial for this pathogen.

METHODS

The systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) to ensure quality of the included studies is intact and reporting of results is complete.[10] The review was registered in the Open Science Framework with the registration code of https://doi.org/10.17605/OSF.IO/SDGW8.

Study Design

The systematic review included in vitro antibacterial assays carried out on crude extracts of Philippine plants against clinical isolates and/or reference strains of *Staphylococcus aureus*. The study incorporated both methicillin-sensitive and resistant strains of *S. aureus*, utilizing various parts of Philippine plants as test materials. Specifically, only crude and semi-purified extracts were considered, with obligatory inclusion of both positive and negative controls in the assays. The review thoroughly documents antibacterial activity assessed through parameters such as the zone of inhibition (ZOI), minimum inhibitory concentration (MIC), and minimum bactericidal concentration (MBC) when available.

Search Strategy and Information Sources

Following the PRISMA guidelines, the researchers independently conducted the documentary search in three English databases namely PubMed/Medline, SCOPUS, and Herdin. The keywords used were categorized as "plant extract," "in vitro antibacterial assays," "*Staphylococcus aureus*," and "Philippines." All other related index terms were added, and the format of the search adjusted depending on the database. Details of the search term can be found in the supplementary materials. Collected journal articles were imported to a systematic review tool (i.e., Covidence) for initial duplicate screening and subsequent review.

Inclusion and Exclusion Criteria

The specific inclusion criteria include that the studies should have authenticated plant material, an appropriate antibacterial assay methodology based on standard protocols, antibacterial activity measured by ZOI and/or its susceptibility in MIC with values ≤8 mg/mL to include plant extracts with low to high antibacterial activity only, and/or MBC, and access to full-text article in English language.[11–13] The study included crude and/or semi-purified plant extract only, excluding plant extracts formulated in a dosage form (e.g., cream, ointment) or studies aimed to establish synergistic effects. All studies were collected from anytime to June 2022.

Selection of Studies

Following the initial database search and elimination of duplicates, journal articles were screened based on their abstracts and titles. Subsequent screening and full-text review were conducted independently by two reviewers adhering to predefined inclusion and exclusion criteria. Covidence was utilized for screening, while full-text journals were uploaded to Zotero version 6.0.36. Any disparities in the inclusion/exclusion process were resolved by the third and fourth reviewers. Furthermore, a quality assessment of the review was carried out by the third reviewer to validate data accuracy.

Data Charting and Synthesis

Primary data extraction included the scientific name of the plant, the plant part, extract/solvent used, and its measured antibacterial activity as ZOI, MIC, and/or MBC, whichever is available. When multiple studies report the same plant but used different scientific names, these were consolidated into a single data row. Secondary data extraction included number of times the plant was studied, time of harvest, source of plant, and phytochemicals. Extracted data underwent standardization of units and conversion of relevant parameters into a unified format for comparative analysis. These data were extracted independently by the two reviewers and verified by the third reviewer to resolve discrepancies.

Quality of Assessment and Bias

Two authors as independent reviewers assessed the risk of bias of each study included in the systematic review. Discrepancies were resolved by the third and fourth review authors. Both internal and external validities of the studies were considered following recommendations from another study with modifications.[14] In this systematic review, the authors developed the in vitro antibacterial studies quality of assessment and bias tool with six criteria to assess the risk of bias namely adherence to established antimicrobial susceptibility assay, clearly stated data analysis and reporting, inclusion of positive and negative control, source identity of the reference bacterial organisms, clear description of culture media and other relevant reagents, and lastly, the inclusion of quality control measures.

For studies with multiple assays conducted, each assay was assessed for risk of bias. The first required criterion is the adherence to established antimicrobial susceptibility assay. Studies must follow the guidelines outlined by the World Health Organization standard antimicrobial assay or adopt other methodologies closely aligned with it. This includes various aspects, including bacterial inoculum concentrations and the duration and temperature during incubation. Utilization of appropriate culture media such as Muller-Hinton Agar (MHA) or Muller-Hinton Broth (MHB) was also deemed essential. Furthermore, other requirements include clearly stated data analysis, where studies must include replicates and transparently interpret the data for both experimental and control groups. The inclusion of negative and positive controls was also required. Additionally, studies must disclose the source identity of the reference bacterial organisms, indicating whether they originate from a laboratory, a clinical facility for clinical isolates, the American Type Culture Collection (ATCC) or other culture collection institution. Failure to meet these first four criteria places the study in the high-risk category.

On the other hand, the last two criteria include the clear description of culture media and other relevant reagents with doses and dilutions. The inclusion of quality control measures, such as growth and sterility controls, was also considered. Failure to satisfy these last two criteria places the study on moderate-risk category.

The careful consideration of these six criteria classified the studies into three risk categories: low risk, moderate risk, and high risk (Table 1). Only those falling into the low and moderate risk categories were included in the final analysis. Studies with high risk of bias were omitted from the analysis.

Data Analysis

The MIC was categorized to weak, moderate, and strong antibacterial activity. Based on Duarte et al., plant extracts with strong antibacterial activity have MIC values up to 500 μg/mL, moderate antibacterial activity for 600 μg/mL to 1,500 μg/mL, and weak for values above 1,600 μg/mL.[12] The MBC/MIC ratio was planned to be computed to identify if the mechanism involves a bactericidal (≤4) or bacteriostatic activity (>4) depending on the availability of data. Other

Table 1. Quality Assessment Criteria for Risk of Bias for In vitro Antibacterial Studies

Criteria	Description	Risk of bias category		
		Low	Mod	High
1. Established antimicrobial susceptibility assay	Must follow standard protocol without significant deviation.	Yes	Yes	No
	Bacterial inoculum size should be 1-2 x 10^8 equivalent to 0.5 McFarland or 0.08-0.1 OD600nm and time of incubation should be 16 to ≤24 h at 35 ± 2°C. Microdilution methods should have an inoculum size of 5 x 10^5 or 2-8 x 10^5 CFU/mL per well.			
	Must use appropriate agar and broth.			
2. Clearly stated data analysis and reporting	Must have used replicates.			
	Must specify statistical method used when available.			
	Data must be correctly interpreted and reported completely for all groups.			
3. Inclusion of negative and positive control	Must specify negative and positive controls used.			
4. Source identity of the reference bacterial organisms	Must have identified clinical isolate or reference strain used and/or source of *S. aureus* mentioned.			
5. Clear description of culture media and other relevant reagents	Reagents and antibiotic standard should be described properly with concentrations and dilutions.	Yes	No	Yes/No
6. Inclusion of quality control measures	Presence of growth and sterility controls.			
	May have presence of positive control and reference strain or clinical isolate quality control checks.			

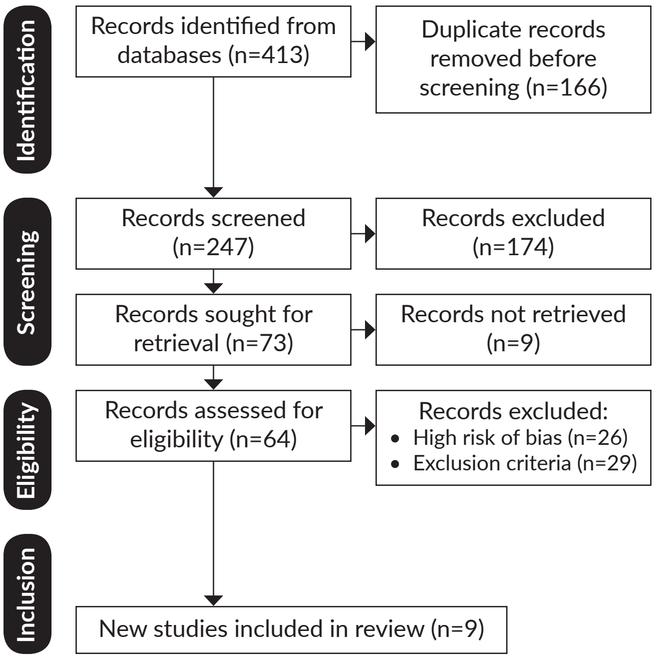

Figure 1. A PRISMA flow diagram of the processes and results involved in the systematic review.[15]

descriptive data relevant to the identification of the plant source and analysis of the antibacterial activity of the extract were provided.

RESULTS

Literature Assessment

In this systematic review, an exhaustive search of databases and registers initially yielded a total of 413 studies, which were subsequently reduced to 247 after eliminating duplicate records. Following abstract screening, 174 studies were excluded based on predefined exclusion criteria, leaving 73 studies for full-text review. Nine of which were removed due to lack of full-text paper. The remaining 64 studies were subjected to eligibility assessment. These studies underwent a rigorous bias assessment, ultimately resulting in the removal of 55 studies based on the exclusion criteria (n=29) and found to be at high risk for bias (n = 26). These studies with high risk for bias are summarized in the supplementary materials. A final selection of nine studies was deemed eligible for inclusion in the systematic review. Note that three included studies performed multiple assays but only one from each study was included in the review. All other assays in these three studies or other excluded studies were deemed high-risk for bias and were discussed and analyzed as such. Figure 1 illustrates this in a PRISMA flow diagram.

Characteristics of Philippine Plants with Antibacterial Activities against *S. aureus*

Included in the review were nine studies with a low to moderate risk of bias. In the nine studies, a total of 26 plants were tested for antibacterial activities against *S. aureus*. Most plant samples were collected from Bago City in Negros Occidental, Mount Makiling in Los Baños, Laguna, and Mount Pangasugan in Leyte. Universities have also been a common source of plant samples. Most of the plant parts used were leaves, followed by stem or stem bark and roots. Majority of the extracts are essential oils followed by ethanolic extract or fractions from ethanolic extract. Methanolic, aqueous, and chloroform extracts were also used in some studies. Table 2 shows the studies for all the plants and their resulting antibacterial activities included in the review. Only one study included assessed antibacterial activity against MRSA.[16]

Table 2. Descriptive Data from the Included Studies Related to the Different Plant Extracts with their Respective Antibacterial Activities

Reference	Plant	ZOI (mm)	MIC (ug/mL)	Plant Part / Type of extract	Location	Harvest Time
Houdkova et al., 2018[17]	*Alpinia cumingii*	–	1,024	Leaf/essential oil	Foothills of Mt. Makiling and Mt. Pangasugan	Apr-May 2017
	Alpinia elegans (Tagbak)[18]	–	512			
	Callicarpa micrantha	–	>1,024			
	Piper quinqueangulatum	–	512			
	Alpinia brevilabris	–	>1,024		University of the Philippines Los Baños	
	Cinnamomum mercadoi (Kaniñgag)[18]	–	>1,024			
Bugayong et al., 2019[16]	*Curcuma longa* L. (Turmeric)	8.7±0.6 at 5µL	–	Leaf/essential oil	Herbanext Farm in Bago City, Negros Occidental, Philippines	–
		10.7±1.2 (MRSA) at 5µL	–			
	Cymbopogon citratus (Lemongrass)	22.3±2.1 at 5µL	–			
		24.0±2.6 (MRSA) at 5µL	–			
	Lippia micromera (False oregano)	26.3±1.5 at 5µL	–			
		29.3±2.5 (MRSA) at 5µL	–			

Table 2. Descriptive Data from the Included Studies Related to the Different Plant Extracts with their Respective Antibacterial Activities *(continued)*

Reference	Plant	ZOI (mm)	MIC (ug/mL)	Plant Part / Type of extract	Location	Harvest Time
Bugayong et al., 2019[16]	*Melissa officinalis* L. (Lemon balm)	17.0±1.0 at 5µL	–	Leaf/essential oil	Herbanext Farm in Bago City, Negros Occidental, Philippines	–
		15.3±1.5 (MRSA) at 5µL	–			
	Ocimum tenuiflorum (Holy basil)	18.0±2.0 at 5µL	–			
		23.0±2.0 (MRSA) at 5µL	–			
	Piper betel L. (Betel pepper)	9.3±1.5 at 5µL	–			
		10.3±1.5 (MRSA) at 5µL	–			
	Plectranthus amboinicus Lour. Spreng (Philippine oregano)	25.7±1.5 at 5µL	–			
		29.0±2.6 (MRSA) at 5µL	–			
	Tagetes erecta L. (Marigold)	12.3±1.2 at 5µL	–			
		11.3±0.6 (MRSA) at 5µL	–			
	Vitex negundo L. (Five-leaved chase tree)	11.7±1.2 at 5µL	–			
		10.0±0.0 (MRSA) at 5µL	–			
Perez et al., 2015[19]	*Merremia peltata* (L.) Merr. (Bulakan)[18]	5.7 at 20 µg/mL	–	Leaf/ethanolic	Rogongon, Iligan City	–
		1-2 at any dose range	–	Leaf/aqueous		
	Rubus spp.	4.8 at 5 ug/mL	–	Leaf/ethanolic		
		1-2 at any dose range	–	Leaf/aqueous		
Tantengco et al., 2016[20]	*Cyanthillium cinereum* (L.) H.Rob. (*Kulantro*)	16.93 ± 1.80 at 25 mg/mL	–	Root/methanolic	Tubo-tubo, Dinalupihan, Bataan	–
	Cyanthillium cinereum (L.) H.Rob. (*Kulantro*)	6.47 ± 0.17 at 50 mg/mL		Leaf/methanolic		
	Vitex parviflora A. Juss (Mulawin)	15.7 ± 1.2 at 100 mg/mL	–			
	Vitex parviflora A. Juss (Mulawin)	13.83 ± 2.58 at 100 mg/mL		Stem/methanolic		
Vital & Rivera, 2009[21]	*Uncaria perrottetii*	8 ± 0 at 25 µL	–	Stem bark/ aqueous layer	Lamau, Bataan	–
		0 at 25 µL	–	Stem bark/ organic layer	Lamau, Bataan	
	Chromolaena odorata (Siam weed)[22]	10 ± 0 at 25 µL	–	Leaf/ethanolic	University of the Philippines Diliman, Quezon City	
Vital & Rivera, 2011[23]	*Voacanga globosa* (Blanco) Merr. (*Bayag-usa*)	13.3 ± 1.2 at 0.1% 25 µL	–	Leaf/ethanolic	Bataan	–
De Las Llagas et al., 2014[24]	*Ficus pseudopalma* (Niyog-niyogan)[18]	13.39 ± 1.12 at 100 mg/mL	–	Leaf/ethanolic	Umali Subdivision, Los Baños, Laguna	–
		13.31 ± 0.75 at 100 mg/mL	–	Leaf/ethanolic – chloroform fraction		
		15.82 ± 0.65 at 100 mg/mL	–	Leaf/ethanolic – ethylacetate fraction		
		6.00 ± 0.00 at 100 mg/mL	–	Leaf/ethanolic – water fraction		
Vital et al., 2010[25]	*Ficus septica* Burm	13.83 ± 4.01 at 25 µL	–	Leaf/ethanolic	University of the Philippines Diliman, Quezon City	–
	Sterculia foetida L.	19.00 ± 2.00 at 25 µL	–			
Dhayalan et al., 2018[26]	*Spathiphyllum cannifolium* (Peace Lily)[27]	16.00 ± 1 at 100 µL	–	Leaf/ethanolic	Manila Central University, Caloocan City	–
		14.67 ± 0.58 at 100 µL	–	Leaf/chloroform		

(–) – not available, not determined and/or not reported, MIC – minimum inhibitory concentration, ZOI – zone of inhibition, MRSA – methicillin-resistant Staphylococcus aureus; Some common names are sourced differently from the original papers

Table 3. Phytochemical Analysis of Different Plant Extracts

Plant extracts	Phytochemicals								
	Sterols	Triterpenes	Flavonoids	Alkaloids	Saponins	Glycosides	Tannins	Anthraquinones	2-deoxysugars
Spathiphyllum cannifolium ethanolic leaf extract	(+)	(+++)	(+++)	(++)	(+++)	(++)	(+++)	NA	NA
Spathiphyllum cannifolium chloroform leaf extract	(+++)	(-)	(++)	(++)	(+)	(++)	(++)	NA	NA
Merremia peltata (L.) Merr. ethanolic leaf extract	(+++)**	(-)	(++)	(+)	NA	(-)*	(-)	(-)	NA
Rubus spp. ethanolic leaf extract	(+++)**	(-)	(+++)	(-)	NA	(-)*	(++)	(-)	NA
Ficus septica ethanolic leaf extract	NA	NA	NA	(+)	NA	NA	(+)	NA	(+)
Sterculia foetida ethanolic leaf extract	NA	NA	NA	NA	NA	NA	(+)	NA	(+)

**Cyanoglycosides, **Steroids, (+) Presence/traces, (++) moderate, (+++) abundant, (-) absence, NA - not available, not determined and/or not reported.*
Note: It is unclear in which procedures the phytochemical testing were different as the methodologies used were not detailed for most studies.

In vitro Antibacterial Activity

Leaf essential oils of *Lippia micromera*, *Plectranthus amboinicus* Lour. Spreng, and *Cymbopogon citratus* had the highest zones of inhibition against *S. aureus* B1350 recorded at 26.3±1.5 mm, 25.7±1.5 mm, and 22.3±2.1 mm, respectively. These essential oils have also shown antibacterial activity against MRSA in the same order.[16]

Only one study had performed MIC determination but without MBC.[17] Among the extracts reported, the leaf essential oils of *Alpinia elegans* and *Piper quinqueangulatum* at 512 µg/mL had the lowest MIC. This is followed by *Alpinia cumingii* leaf essential oil at 1,024 µg/mL.

Phytochemicals

Three (3) of the included studies reported phytochemicals.[19,25,26] Table 3 shows that sterols/steroids, flavonoids, and alkaloids are reported most frequently in four of the six plant extracts. This is followed by glycosides and tannins. No phytochemical studies were reported from the studies with MIC determination.

Further analysis of the essential oils showed different varied chemical compositions as reported in Table 4. Based on gas chromatography/mass spectrometry analysis of the leaf essential oils, terpenes and terpenoids were observed as the main chemical classes.[16,17]

Table 4. Major Chemical Constituent of the Six Philippine Plant's Leaf Essential Oils

Plant source	Major constituent
Alpinia elegans	Caryophyllene epoxide (24.7/30%)
Piper quinqueangulatum	Linalool (12.8/12.7%)
Alpinia cumingii	β-pinene (21.8/20.6%)
Lippia micromera	γ-terpinene (25.6%)
Plectranthus amboinicus	Carvacrol (51.3%)
Cymbopogon citratus	Citral (47.7%)

DISCUSSION

From the nine included studies which met the predefined criteria for eligibility, none demonstrated strong antibacterial activity against *S. aureus*, with, at best, a moderate activity observed in leaf essential oils of A*lpinia elegans*, *Alpinia cumingii*, and *Piper quinqueangulatum*. However, these lacked studies detailing their zones of inhibition, a metric in which the *Lippia micromera* leaf essential oil excelled. Plant samples were primarily collected from Bago City in Negros Occidental, Mount Makiling in Los Baños, Laguna, and Mount Pangasugan in Leyte. The most used plant parts were leaves, followed by stems or stem bark, and roots. Essential oils made up most of the extracts, with ethanolic extracts and their fractions being the next most common.

In the current review, leaf essential oils from *A. elegans*, *P. quinqueangulatum*, and *A. cumingii* exhibited moderate antibacterial activity against *S. aureus* ATCC 29213. As the essential oil is volatile, the researchers used the broth microdilution volatilization method. Through this, both of the antibacterial activities of the liquid and gaseous phases were determined. Only the liquid phase of the volatile oil was included in the review. There was no observed antibacterial activity in the gaseous phase for *S. aureus*. From the leaf essential oils of *A. cumingii*, *A. elegans*, and *P. quinqueangulatum,* a total of 53, 66, and 71 compounds were identified, representing 90.5/90.4%, 91.2/90.0%, and 92.8/90.0% of their total contents, respectively. *A. cumingii* oil had β-pinene as its most abundant component, *A. elegans* oil had caryophyllene epoxide, and *P. quinqueangulatum* oil had predominantly linalool. All these components had previously been studied against *S. aureus*.[17] Only one other study mentioned *A. elegans* essential oil but was from the seed. In this study, an antibacterial activity was observed against *S. aureus*; however, it was conducted using a modified broth microdilution assay for the purpose of validating this new method.[28]

As for the studies on the ZOI, *Lippia micromera* leaf essential oil had the largest inhibition at 26.3 ± 1.5 mm for *S. aureus* and 29.3 ± 2.5 mm for MRSA. These were significantly different and larger from the negative and positive controls. In the same study, the MIC and MBC were determined as 0.12% v/v. Thirty (30) compounds were identified with γ-terpinene (25.6%) as the most abundant component. Majority of these compounds were monoterpenes. β-cymene (23.8%), carvacrol (22.0%), isothymol methyl ether (12.7%), and caryophyllene (3.4%) were also identified.[16] Only one other study has found similar antibacterial activity against *S. aureus* with 16.0 ± 2.0 mm ZOI and 2000 μg/mL MIC. However, the main component identified was thymol (33.7%) followed only by γ-terpinene (14.5%).[29] Interestingly, in a study of terpenes' antibacterial activity, γ-terpinene failed to produce any effect as opposed to thymol which showed strong antibacterial activity.[30] Carvacrol was also found to have strong antibacterial activity and is found abundantly in the local *L. micromera*.[16] Their differences in the composition and amount of the compounds may have resulted to the difference in antibacterial activity against *S. aureus*. The chemical constituents in essential oils may vary depending on the time of harvest, cultivar, and the extraction method.[31]

Of the included studies, many of those with larger ZOI or higher MIC are from leaf essential oils. Essential oils have gained attention as potential antibacterial agents, owing its activity to different multiple bioactive chemicals and mechanisms.[30–33] Primary chemical components are terpenes, terpenoids, and phenols, all of which have shown antibacterial activities. Their mechanism of actions includes but is not limited to membrane disruption, cell protein denaturation, oxidative phosphorylation inhibition, and leakage of cytoplasmic material.[31,33] Terpenes, also known as isoprenoids, have demonstrated a wide range of activities attributed to their lipophilicity.[34] While they exhibit antibacterial effects on gram-negative bacteria, gram-positive bacteria appear to be more susceptible to their effects.[35] When different terpenes, terpenoids, and phenylpropanoids were tested, carvacrol exhibited greatest antibacterial potential. In the same study, it claimed to corroborate previous observations that biological activity of essential oils decreases from phenols, aldehydes, ketones, alcohols, ethers to hydrocarbons.[36] In this review, the same trend may be noticed as essential oils of *Alpinia elegeans* and *Piper quinqueangulatum* with the largest concentration of caryophyllene epoxide (ether) and linalool (alcohol), respectively, have more potent antibacterial activity compared to essential oil of *Alpinia cumingii* with β-pinene (hydrocarbon).

The assessment of risk for bias revealed a concerning prevalence of high-risk studies, with 29 falling into this category. This points to the need for critical evaluation and improvement in the methodology and reporting practices within the field of antibacterial activity studies in the Philippines. Several key issues were identified. A notable percentage of studies failed to clearly state the data analysis and reporting, clearly describe a standard anti-susceptibility assay, and report the use of positive/and or negative controls. Positive control produces a consistent and predictive effect on the in vitro test system, which induces a change in the endpoint that is expected within the quantifiable range of the test. In contrary, the negative control is expected to not produce a response which assures that any response does not come from the solvent. Control items serve as one of the proofs in the validity of the experiments.[37] Omission of any of these is significant in validating an experimental result.

Issues on the quality and reporting of studies of plants with antibacterial activity were observed in this systematic review and were consistent with challenges reported in literature. A considerable number of studies lacked complete details of methodologies, with few having deviations from standard guidelines. Despite having reporting checklist or framework, peer-review process, and journal submission guidelines, the problem in incomplete reporting is far too common in publications.[38,39] This has implications on study transparency and how well the studies can be reproduced and validated. Conducting systematic reviews proved to be a challenge for researchers using studies with incomplete reporting, requiring massive error to fill in the gaps by contacting each author.[39] Systematic errors compound the issue of irreproducibility pointing to potentially inadequate training in the experiments conducted.[40] Lack of replicates within the study groups were also reported, impacting the assessment of the studies' consistency and reliability. Some growth media, environmental conditions, and inoculum size were in deviation from standard protocols. Various in vitro antibacterial assays and reporting guidelines are available to improve rigor and transparency of the studies.

In addition to numerous studies with high risk for bias, the present systematic review acknowledges other certain limitations that may have impacted the comprehensiveness and currency of the findings. One worth mentioning is of publication bias, since some studies, especially those that are in the drug development pipeline are not published due to pending patent applications. In addition, due to the time-intensive nature of the review process, there is a possibility that newer studies reporting on plant extracts with enhanced antibacterial activity may have been published after the completion of this review. Furthermore, while considerable effort was dedicated to designing a robust search strategy, it remains plausible that some relevant papers were inadvertently excluded that can be found from manual search. Some changes were also made from the preregistration plan of the systematic review due to mainly lack of these data. These include removal of the reporting of in vivo data and measuring the MBC/MIC ratio. In addition, phytochemical data of the plant extracts were added to the secondary data extraction. Despite these limitations, this review aims to provide a comprehensive synthesis of the existing evidence on the topic, recognizing the importance of ongoing research and quality reporting to continually refine our understanding of the antibacterial properties of Philippine plants.

CONCLUSION

In conclusion, leaf essential oils from *Alpinia elegans*, *Piper quinqueangulatum*, and *Alpinia cumingii* showed moderate antibacterial activity. Leaf essential oils of *Lippia micromera*, *Plectranthus amboinicus* Lour. Spreng, and *Cymbopogon citratus* also showed antibacterial activities against *S. aureus* and MRSA using disk diffusion assay. These antibacterial activities may be attributed to their high concentrations of terpenes, terpenoids, and phenolic compounds. The issues on adherence to established antimicrobial susceptibility assay, clearly stated data analysis and reporting, inclusion of positive and negative control, source identity of the reference bacterial organisms, clear description of culture media and other relevant reagents, and lastly, the inclusion of quality control measures pose significant challenges to the reproducibility of findings in antibacterial evaluation of plants. This systematic review highlights the need for improved methodological rigor and adherence to reporting guidelines in studies evaluating the antibacterial properties of plant extracts in the Philippines. Thus, a tool for quality assessment for risk of bias for in vitro antibacterial studies of plant extracts is also reported in this study.

Data Availability Statement

Supplementary materials are available from the corresponding author upon reasonable request.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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