Antimicrobial Activity of *Ardisia serrata* (Cavs.) Pers. Ethanolic and Aqueous Leaf Extract on the Growth and Biofilm Formation of Selected Bacterial Isolates

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ABSTRACT

Background. *Ardisia serrata* (Aunasin) is an endemic Philippine plant of the family Primulaceae, with several studies showing the genus Ardisia as having potential antibacterial, antiangiogenic, cytotoxic, and antipyretic properties.

Objective. This study aims to determine the antibacterial and antibiofilm-forming activity of *Ardisia serrata* ethanolic and aqueous extracts on *Escherichia coli*, Methicillin-Sensitive *Staphylococcus aureus* (MSSA), and Methicillin-Resistant *Staphylococcus aureus* (MRSA).

Methods. This is an experimental study testing the activity against bacterial strains of *E. coli*, MSSA, and MRSA using ethanolic and aqueous extracts of *A. serrata* leaves. Microtiter susceptibility and biofilm inhibition assays were done with two-fold dilutions of the extract against the selected strains using spectrophotometry with optical density (OD) at 600 nm and 595 nm, respectively, to quantify bacterial growth and biofilm inhibition. The bacterial susceptibility and biofilm inhibition activity was reported as percent inhibition (PI). Minimum inhibitory concentration (MIC), and minimum biofilm inhibition concentration (MBIC) values were obtained using logarithmic regression of the PI values.

Results. *A. serrata* ethanolic extracts showed weak growth inhibitory activity against MSSA and MRSA with minimum inhibitory concentration (MIC) values of 2.6192 and 3.2988 mg/mL, respectively, but no biofilm inhibition activity was noted, while the aqueous extracts exhibited negligible biofilm inhibition activity against MSSA and MRSA with minimum biofilm inhibition concentration (MBIC) values of 13.5972 and 8964.82 mg/mL, respectively, and with no growth inhibition activity. Both ethanolic and aqueous extracts showed no growth inhibition and biofilm inhibition activities against *E. coli*.

Conclusion. *Staphylococcus aureus* is susceptible to the bioactivity of the leaf extracts of *A. serrata* and has potential to be used as an antibacterial in the treatment of infectious diseases.

Keywords: Ardisia serrata, *Ardisia pyrmidalis*, *Cavs*, *Methicillin-resistant Staphylococcus aureus*, *Methicillin-sensitive Staphylococcus aureus*, *Escherichia coli*, *ethanolic extract*, *aqueous extract*, *antimicrobial*, *natural product*

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INTRODUCTION

The numerous pathogens causing various infections alongside the progressive increase in antimicrobial resistance of pathogenic strains have both been growing concerns for the healthcare sector. According to the Department of Health Antimicrobial Resistance Surveillance Program (2017), two of the most common isolates prevalent in the healthcare setting are *Escherichia coli* and *Staphylococcus aureus*. Both methicillin-sensitive and methicillin-resistant *S. aureus* are prominent pathogens in cutaneous infections, while *E. coli* can be found mostly in patients with diarrhea or urinary tract infections.

There is growing research interest on plants for their possible antimicrobial properties.[1,2] *Ardisia serrata* (Aunasin), synonymous with *Ardisia pyramidalis* (Cav.) Pers. is an endemic Philippine plant of the family Primulaceae, the genus *Ardisia*. There is limited published literature regarding its bioactivity but other species of the same genus have reported anticancer, antipyretic, antidiarrheic, spermicidal, pesticidal and antimicrobial activities.[1] Methanolic extracts derived from *Ardisia elliptica* and *Ardisia crenata* have been shown to have growth inhibitory properties against both gram-positive and gram-negative bacteria.[2,3] A study by Herrera et al. revealed antiangiogenic activity of ethane extracts from *A. serrata* using Duck *in ovo* chorioallantoic membrane assay and thus has potential chemotherapeutic effects against tumors.[1] Studies have also revealed that spinasterol extracted from *A. serrata* demonstrated a positive vascular damage activity and anti-angiogenic properties characterized by capillary hemorrhaging and ghost vessels using chorioallantoic membrane (CAM) vascularity assay.[4] To date, no published literature has reported regarding the strain-specific potential antibacterial activities of *A. serrata*. The study aims to determine if *Ardisia serrata* has antibacterial properties, which could help in developing therapeutics in the rise of drug-resistant bacteria.

MATERIALS AND METHODS

Plant Sample Collection and Authentication

A. serrata (Cav.) Pers. leaves were collected with permission from multiple sites in Mt. Makiling Forest Reserve, University of the Philippines Los Baños (UPLB), Laguna during the dry season in late February.

Plant extraction

A. serrata leaves were air dried for one month after collection and were coarsely powdered using blenders to sizes not exceeding 1 mm^2. The powdered samples were then soaked in absolute ethanol (≥99.8%), in a ratio of 1:10 gram weight of samples to mL absolute ethanol and distilled water in the same gram-to-mL ratio. Leaf soakings were left to stand for three days. Afterwards, the supernatant was filtered using filter paper (11 μm, standard) to eliminate superfluous particles prior to concentration.

Supernatant concentration and crude extract preparation

The supernatant was subjected to rotary evaporation to remove the solvent. The water bath was maintained at approximately 40°C. The running water in the condenser was kept at a similar temperature with the ice bath. Lyophilization was performed to further remove the ethanol and water traces. The dried crude extracts were then dissolved in dimethylsulfoxide (DMSO) at a ratio of 4 mg extract per mL of DMSO. The dissolved extracts were stored for a day in a refrigerator prior to use for the antimicrobial assays.

Test Microorganisms

The microorganisms tested with *A. serrata* extracts were *E. coli* (ATCC 25922) and Methicillin-sensitive (ATCC 29213) and methicillin-resistant *S. aureus* (ATCC 43300), all obtained from the Department of Microbiology, University of the Philippines Manila. Overnight (24 hrs) subcultures of all strains were prepared prior to use.

Microdilution Susceptibility Assay

The minimum inhibitory concentration (MIC) and inhibitory concentration 50 (IC_{50}) values were obtained using the microdilution susceptibility assays. The MIC and IC_{50} values were computed as the lowest concentration (mg/mL) of the *A. serrata* extract that completely inhibits 100% and 50% growth of the microorganism, respectively, as determined spectrophotometrically (OD_{600}). Two-fold dilutions of the initial extract concentration of 2.5 mg/mL were dispensed in polystyrene 96-well plates. Each well was then inoculated with the selected bacterial species. Amoxicillin, vancomycin, and amikacin were used as positive control for MSSA, MRSA, and *E. coli*, respectively. DMSO was used for negative control. The well optical density was quantitatively measured using a spectrophotometer (OD_{600}) which correlates sample turbidity based on bacterial growth. Blanks containing only serially diluted extracts, bacterial media, and the diluent DMSO were prepared to account for the presence of plant pigments which might interfere with the absorption at 600 nm.

Biofilm Inhibition Assay

The minimum biofilm inhibition concentration (MBIC) and biofilm inhibition concentration 50 (BIC_{50}) values were obtained using serial dilution of the extracts against the selected strains and measuring the biofilm mass formed. The MBIC and BIC_{50} values were computed as the lowest concentration (mg/mL) of the *A. serrata* extract that completely inhibits 100% and 50% of the biofilm formation, respectively, as determined spectrophotometrically (OD_{595}). Aliquots of inocula (100 uL each, 10^6 CFU/mL) were transferred to wells of a 96-well microtiter plate and incubated for 4 hours at 37°C to allow cell attachment and biofilm formation (1 plate per bacterial strain).[5] Starting with concentrations of 2.5 mg/mL, 100 uL of the plant extracts

or of the positive or negative controls were added in serial dilution into the wells for positive and negative control. The plates were incubated for 24 hours after which the wells were rinsed with water, stained using 200 uL Gram's Crystal Violet for 1 minute, rinsed again, and dried. The amount of biofilm biomass was quantified by destaining the wells with 33% acetic acid and measuring the absorbance in a separate microplate using a spectrophotometer (595 nm).[5] Transferred solutions were diluted (33% acetic acid) in cases where the absorbance values exceed the dynamic range of 4.0 optical density units.[5] Azithromycin was used for all three bacteria as positive control and DMSO as negative control.

Analysis

The percentage inhibition (PI) was obtained from the difference between the OD of negative control and experimental, and dividing it by the OD of negative control. The IC_{50} and BIC_{50} were calculated as PI at 50% for the microdilution susceptibility assay and biofilm inhibition assay, respectively. The MIC and MBIC of the extracts were calculated as the concentration at which bacterial growth and biofilm formed was 100% inhibited, calculated by logarithmic curve extrapolation.

The MIC or MBIC of the extract is reported to have strong activity if equal to or lower than 0.50 mg/mL. Moderate microbial inhibitors are described as those plant extracts with MIC or MBIC values ranging between 0.60 mg/ml and 1.50 mg/ml. Lastly, weak microbial inhibitors are classified as those agents with MIC or MBIC values of between 1.60 mg/ml and 8.00 mg/ml.[6] Computations including standard deviations, curve extrapolation, and MIC or MBIC and IC_{50} or BIC_{50} determination were performed using Graphpad Prism 6 program.

RESULTS

Microdilution Susceptibility Assay for Ethanolic and Aqueous Extracts

Increasing ethanolic concentration of *A. serrata* correlated positively with weak inhibitory activity of MRSA (IC_{50} at 0.4773 mg/mL; MIC at 3.2988 mg/mL, Figure 1A) and MSSA (IC_{50} at 0.1439 mg/mL; MIC at 2.6192 mg/mL computed through logarithmic regression; Figure 1B). The ethanolic extract showed no inhibition of *E. coli* (Figure 1C). The aqueous extract showed no inhibition of all bacterial samples (Figures 1D-F).

Biofilm Formation Inhibition Assay

The aqueous *A. serrata* extract had negligible biofilm inhibition on MSSA and MRSA biofilm formation, with small positive linear trends with increasing concentrations (MSSA BIC_{50} at 1.6252 mg/mL and MBIC at 13.5972 mg/mL; MRSA BIC_{50} at 27.1526 mg/mL and MBIC at 8964.82 mg/mL; Figures 2E-F). The ethanolic extract had

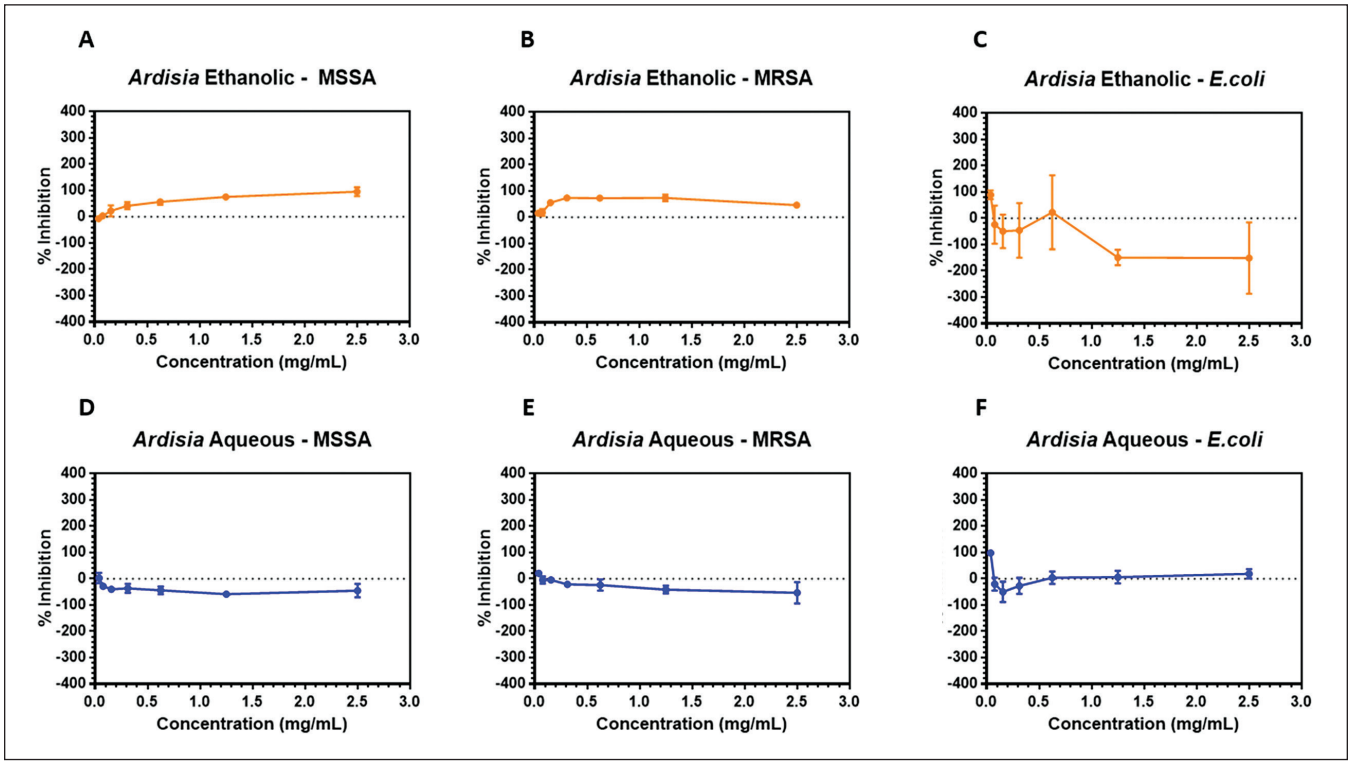

Figure 1. Percent inhibitions of the ethanolic extract against **(A)** MSSA, **(B)** MRSA, and **(C)** *E. coli*, and aqueous extract against **(D)** MSSA, **(E)** MRSA, and **(F)** *E. coli*.

minimal biofilm inhibition on MSSA, with no general trend (Figure 2B), but no effect on MRSA (Figure 2C). *E. coli* biofilm growth was unaffected by both the ethanolic (Figure 2A) and aqueous (Figure 2D) extracts.

DISCUSSION

Microdilution Susceptibility Assay

Ethanolic Extracts

The *A. serrata* ethanolic leaf extracts showed no inhibition of *E. coli*, indicating lack of antibacterial properties of the extract against the organism (Figure 1C). This finding is concordant with previous literature which showed that plant extracts are generally less active against Gram-negative than Gram-positive bacteria.

Gram-negative organisms such as *E. coli* are expected to be more impermeable to exogenous lipophilic solutes due to their structural lipopolysaccharide components.[7,8] The asymmetric lipopolysaccharide-rich phospholipid bilayer of the outer membrane may possibly act as a permeability barrier and retard the entry of lipophilic substances from the ethanolic extract, thereby preventing the inhibition of growth of the organism.

Additionally, it has been postulated that in the presence of ethanol or its derivatives, *Escherichia coli* may undergo reversible alterations in cell membrane lipid-to-protein ratio, which appear to be beneficial for its growth and survival in such an adverse environment.[9,10] Phenotypic modifications such as elevation in levels of acidic phospholipids (e.g., cis-vaccenic acid) appear to be a primary pathway in this adaptive mechanism against the fluidizing property of ethanolic extracts.[11,12]

In a model developed by Cao et al. under ethanol-induced stress states, *Escherichia coli* undergoes adaptive gene mutations with reduced translational misreading, consequently leading to a decrease in non-essential energy consumption, promotion of macromolecule biosynthesis, upregulation of ethanol tolerance genes, and reduced reactive oxygen species production, all culminating in increased survival rates and growth.[13] The expression of the phage shock protein operon (pspABCE) in *E. coli* has also been hypothesized as a potential adaptive response against ethanol-based compounds and other hydrophobic organic solvents.[14] This may explain the lack of inhibition of the extract against the organism.

MSSA and MRSA were both susceptible to the ethanolic extract of *A. serrata* with weak activities for both based on the MIC values of 2.6192 and 3.2988 mg/mL, respectively (Figures 1A and 1B) and with IC_{50} values were 0.4773 mg/mL and 0.1439 mg/mL, respectively. It is possible that further optimization, purification, and isolation of the ethanolic extract will be of value for antimicrobial therapy and further research.

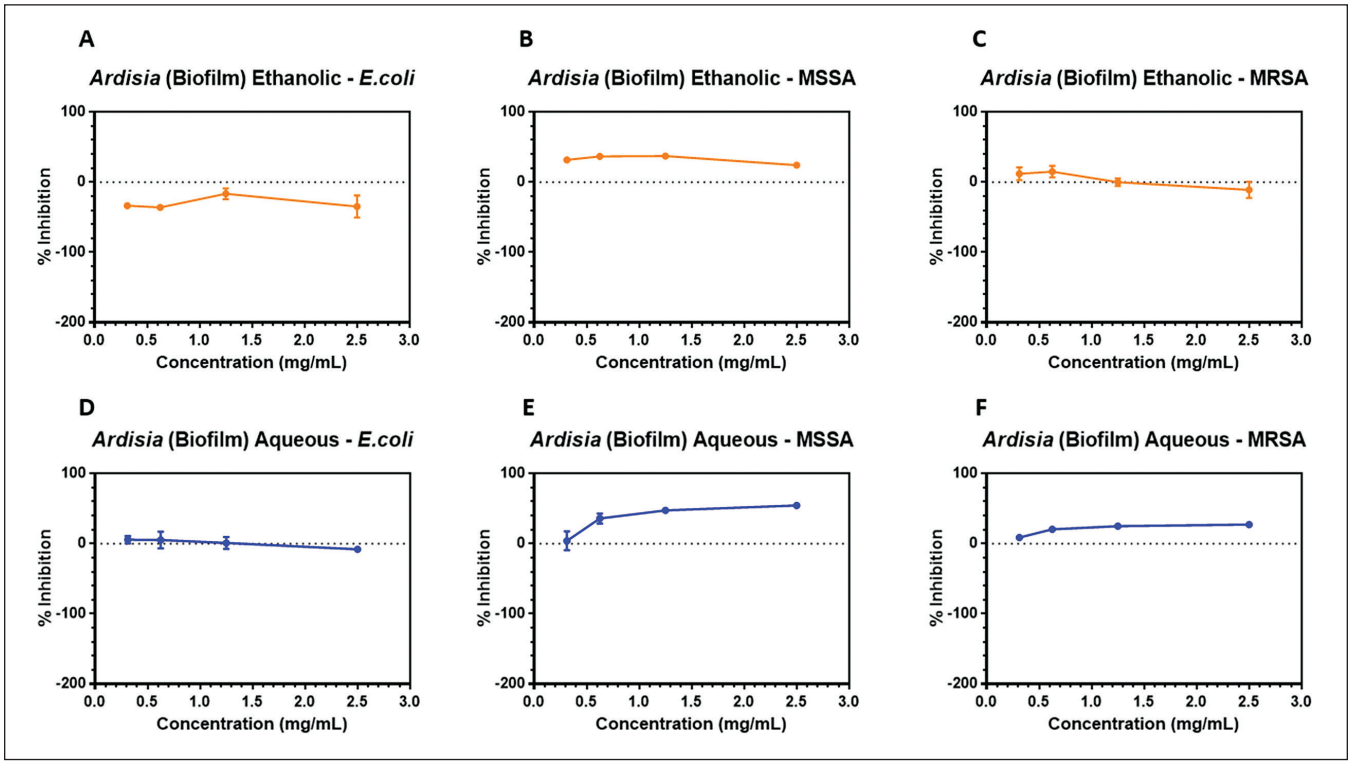

Figure 2. Antibiofilm activities of the ethanolic extract against **(A)** *E. coli*, **(B)** MSSA, and **(C)** MRSA, and aqueous extract against **(D)** *E. coli*, **(E)** MSSA, and **(F)** MRSA.

No phytochemical identification has been done on the ethanolic leaf extract of *A. serrata* and so the metabolites or compounds responsible for the antibacterial activity are still yet to be determined. Different species of *Ardisia* contain triterpenoids α-amyrin, β-amyrin, and bauerenol, which were found to have activities against *S. aureus*.[15] Triterpenoids exhibited the fastest inhibition against cell wall synthesis, thus, predisposing Gram-positive bacteria to lysis and morphological changes often visible through microscopy. These compounds also induce complete inhibition in the incorporation of N-acetyl-d-[1-14C]glucosamine, suggesting that the phenolic compounds compromise the cell wall synthesis and/or cytoplasmic membrane.[16] *A. serrata* may contain any of these triterpenoids supporting its activity against *S. aureus* and is a promising topic for further studies.

Aqueous Extracts

Results showed that the aqueous leaf extracts had no inhibitory activity to *E. coli* (Figure 1F). Although the extract promoted the growth of *E. coli* initially, it showed minimal inhibitory activity as the concentration increased. This can further be explored with increasing concentrations of the extract to see if this trend is consistent.

To date, there are no extensive studies specific to the *Ardisia serrata (Cavs.) Pers* in terms of its phytochemical components and antibacterial activity but closely related *Ardisia* species have been shown to have significant antimicrobial activities against various pathogens.[17]

Quinone and its derivatives have been widely isolated in other *Ardisia* species. Specifically, embelin, a benzoquinone and a phytochemical constituent of *Ardisia japonica*, was found to have antibacterial activity.[18] Four alkylbenzoquinone derivatives extracted from *Ardisia kivuensis* Taton (Myrsinaceae) in a study by Paul et al. exhibited weak activity against gram-negative bacteria.[17] Three distinct alkyldibenzoquinone derivatives from *Ardisia teysmanniana* Scheff. (Myrsinaceae) isolated by Yang in 2001 were tested for inhibitory activity against several pathogens but showed no activity for *E. coli*, as well.[19] Resorcinol, along with its derivatives, is also a compound found in several *Ardisia* species.[19] In 2007, Zheng and Wu looked into the activity of resorcinol derivatives isolated from *Ardisia maculosa* Mez which showed no antimicrobial activity against *E. coli*.[20]

Bergenin, an isocoumarin, and its various derivatives and analogues have also been isolated from the *Ardisia* species.[18] Although no studies have been made to see the activity of bergenin specifically isolated from the *Ardisia* species, bergenin isolated from *Endopleura uchi* (Huber) Cuatrec. exhibited no inhibitory activity against *E. coli* and other gram-negative and gram-positive organisms tested in the study. It was, however, inhibitory to the *Candida* species. No specific mechanisms for the action of bergenin have been found.[21]

All of these studies support the findings in the study that there is no significant inhibitory activity of the *Ardisia* leaf extracts against *E. coli*. This may be due to the additional outer membrane bilayer with its asymmetric structure and lipopolysaccharides (LPS) located exclusively in the outer leaflet found in *E. coli* which confer it selective permeability to block off the entry of noxious and foreign compounds.[22]

The aqueous extracts showed negative percent inhibition of MSSA and MRSA with increasing extract concentrations in the microdilution susceptibility assay (Figures 1D and 1E). This means that instead of inhibiting growth, increasing concentrations of the aqueous leaf extract, promoted the growth of the said bacteria. *S. aureus* has a thick, highly cross-linked peptidoglycan cell wall which may have conferred a stronger resistance against the extract.

The promotion of *S. aureus* growth may also be explained by the alkaline property of the aqueous extract with its pH of 9.75. Results from the study by Anderson et al. found that *S. aureu*s adapts to pH shock by eliciting responses expected of cells coping with pH alteration, including neutralizing cellular pH, DNA repair, amino acid biosynthesis, and virulence factor expression.[23] Cell cultures exposed to prolonged elevated pH maintained their viability and adapted by downregulating their translation machinery, nucleotide biosynthesis, and amino acid metabolism factors. Alkaline-shock conditions increased the expression of amino acid biosynthesis genes, and induced the expression of the Opp gene (believed to mediate the influx of essential amino acids),[23] of genes presumed to maintain intracellular homeostasis and oxidative damage protection,[23] and of reactive species detoxifying proteins and several oxidative DNA damage repair enzymes.[23] In the same study, it was shown that although alkaline conditions resulted in a more pronounced capsule production, this was not likely to directly affect the organism's pH tolerance. In general, alkaline shock conditions resulted in an altered growth phenotype which provides the bacteria with the opportunity to repair and/or eliminate pH-mediated cellular damage. Alkaline conditions also resulted in diminished cellular proliferation in comparison *S. aureus* grown at neutral pH.

Finally, contamination that was unexpected and unaccounted for during the experiment may have inadvertently altered the effect of the aqueous extract on *S. aureus* from one that was expected to be inhibitory to one that was actually promotive. Hence, it is recommended that the experiment be repeated and expanded to include higher concentrations of the extract to confirm the presence or absence of trends.

The ineffectiveness of the *Ardisia serrata* aqueous extract (Figures 1D-F) compared to the ethanolic extract (Figures 1A-C) is consistent with the study by Parekh and Chanda which found that plant extracts in organic solvent (methanol or ethanol) provided more consistent antimicrobial activity as compared to those extracted in water.[24] They explained that this may "be rationalized in terms of the polarity of the compounds being extracted by each solvent…in addition to their intrinsic bioactivity…" Indeed, the study by Mostafa et al. cited that "researchers attributed the inhibitory effect of

these [ethanolic] plant extracts to hydrophobicity characters of these plant extracts which enable them to react with protein of microbial cell membrane and mitochondria disturbing their structures and changing their permeability."[25] The results of the present study are also consistent with that of Parekh and Chanda (2006) in that theirs showed that the extracts were more active against gram-positive bacteria than gram-negative bacteria.[24] While the two different *A. serrata* extract preparations used in this study had quite opposite effects on the gram-positive MSSA and MRSA (with the ethanolic extract inhibiting growth and the aqueous extract promoting growth), neither inhibited gram-negative *E. coli*.

Biofilm Assay

Due to the growing detrimental effects of biofilm in spreading infections through healthcare equipment and instruments, efforts have been made to target either the cell attachment to a substrate or complete destruction of the already formed biofilms.

E. coli is considered to be of high resistance to various antimicrobial agents.[26] It has the ability to form multiple types of biofilm which allows it to not only survive in environments not usually suitable for the bacteria but to sustain its growth amidst the conditions. The lack of inhibition from both the ethanolic and the aqueous extracts of *A. serrata* against *E. coli* may be due to several mechanisms such as restricted penetration of antimicrobial agents into the biofilm, slow growth owing to nutrient limitation, expression of genes involved in the general stress response, and emergence of a biofilm-specific phenotype. Moreover, increased antibiotic resistance was seen in the deeper layers of mature biofilms of *E. coli* possibly due to the emergence of resistant subpopulations aided by the induction of biofilm-specific phenotypes which included both slow growth/no growth and *rpoS* mediated stress response.[26]

In contrast to *E. coli*, the aqueous extract exhibited very weak to negligible biofilm inhibitory activity against both MSSA and MRSA, with MBIC values of 13.5972 mg/mL and 8964.82 mg/mL, respectively (Figures 2E and 2F). The MBIC of the *A. serrata* aqueous leaf extract against MSSA biofilm was significantly different from the MBIC against MRSA biofilm, with MSSA being more susceptible. The ability to form biofilm under standard and biofilm-inducing growth conditions was associated with methicillin-resistance. In a study by Oduwole et al., there was twice biofilm formation in MRSA isolates compared to MSSA when induced with NaCl and glucose.[27] *Staphylococcus aureus* antibiotic resistance and biofilm-forming capacity are highly influenced by the acquisition of the methicillin resistance gene *mecA*. MSSA strains produce an *icaADBC* operon-encoded polysaccharide intercellular adhesin (PIA)-dependent biofilm compared to MRSA biofilm phenotype of major autolysin and release of extracellular DNA (eDNA) and cell surface expression of a number of sortase-anchored proteins.[28] This makes MRSA more resistant to antibiotics compared to MSSA. Acquisition of methicillin resistance gene in MSSA caused repression of PIA-mediated biofilm production, downregulation of the accessory gene regulator (Agr) system, and attenuation of virulence in murine sepsis and device infection models.[28]

CONCLUSION

Both methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* are susceptible to the ethanolic leaf extracts of *Ardisia Serrata, with* weak inhibitory activity, and MIC values of 2.6192 mg/mL and 3.2988 mg/m, respectively, but show no susceptibility to that of aqueous extracts. *A. serrata* shows very weak biofilm inhibitory activity against MSSA *and* negligible activity against MRSA with MBIC values 13.5972 mg/mL and 8964.82 mg/mL, respectively. *Escherichia coli* shows neither susceptibility nor biofilm inhibition to *Ardisia Serrata* extracts, both aqueous and ethanolic. The *Ardisia serrata* ethanolic extract shows promising antimicrobial activity, in terms of bacterial growth inhibition, against both MSSA and MRSA.

Recommendations

The inclusion of biofilm eradication studies in the future may be beneficial as only biofilm inhibition was included in the study. The major inhibitory activities found using the ethanol extract against MSSA and MRSA were classified as 'weak inhibition' but the protocol can be further optimized to enhance the yield of active components. Future directions for the study involve optimizing the extraction protocol, identifying the active phytochemicals, and further purification of the components.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest.

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