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Original Article

A SYSTEMATIC REVIEW OF POTENTIAL PHYTOCHEMICAL COMPOUND BARK OF *PARAMERIA LAEVIGATA* ON BIOFILM FORMATION

WIRDA ANGGRAINI[1,2], DJOKO AGUS PURWANTO[1*], ISNAENI[1], IDHA KUSUMAWATI[1], SURYANTO[2]

[1]Faculty of Pharmacy, Airlangga University, Surabaya, 60286, Indonesia, [2]Departement of Pharmacy, Faculty of Medicine and Health Science, Maulana Malik Ibrahim State Islamic University, Malang, 65151, Indonesia
[*]Email: djokoagus@ff.unair.ac.id

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ABSTRACT

Objective: Infectious disease is one of the problems in the health sector that continues to grow from time to time. Microorganisms can differentiate and develop in complex ways to form new morphologies that grow on the surface, known as biofilms. *Parameria laevigata* contains a variety of secondary metabolites, so that it has potential as an anti-biofilms. The purpose of this research was to examine the effect of the compounds contained in the bark of *Parameria laevigata* in forming biofilms.

Methods: This systematic review research method was Systematic-Meta Analysis, which identifies research articles from journal databases including Microsoft Academic Search, Google Scholar, PubMed, and Science Direct. Meta-Analysis was used to analyze, determine, and interpr*et al.* l the data in the systematically served articles.

Results: Using a specific search prism guideline, the search result for research article found 28 research journals as primary data for systematic review research. The results of this systematic review showed that the bark of *Parameria laevigata* contains alkaloids, flavonoids, tannins, and saponins. Alkaloids can interfere with the components of peptidoglycan in bacteria. Flavonoids have able to inhibit the growth of microorganisms. Tannins have a role in influencing cell wall polypeptides so that the formation of cell walls becomes less than perfect. Saponins hydrolyze bacterial cell walls.

Conclusion: The bark of *Parameria laevigata* has the potent activity to develop as antimicrobial by inhibiting biofilms formation mechanism.

Keywords: Biofilm formation, Natural product, *Parameria laevigata*, Phytochemical

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INTRODUCTION

Infectious disease is one of the problems in the health sector that continues to grow from time to time. Microorganisms can differentiate and develop in complex ways to form new morphologies that grow on surfaces known as biofilms [1, 2]. As self-defense, bacteria create a layer of mucus called a biofilm. Biofilms formed from interactions between bacteria in an environment allow a group of bacteria to attach and live on both biological (biotic) and non-biological (abiotic) surfaces [2]. Biofilms can protect bacteria from the host's defences and neutralize adverse environmental influences such as extreme pH, low oxygen content, and extreme pressure and temperature. Biofilm cells can separate from each other and join other matrix systems. It causes the cells that make up the biofilm more difficult to suppress than non-biofilm bacteria [3, 4].

Microbes in forming biofilms secrete various protective substances called Extracellular Polymeric Substances (EPS), increasing their survival efficiency. EPS serves as a structural framework that strengthens the structure of bacterial biofilms. The formation of biofilms depends on the concentration of available nutrients and is regulated by a complex chemical substance released by cells as communication between cells. Both gram-positive and gram-negative bacteria can produce biofilms. Gram-Positive bacteria can produce biofilms such as *Staphylococcus aureus* and *Staphylococcus epidermis*. Gram-negative bacteria such as *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Pseudomonas aeruginosa* [5, 6]. The mechanism or stages of biofilm formation consists of five steps, namely, adhesion or adhesion (reversible), permanent attachment (irreversible), formation of complex layers to form microcolonies, maturation of biofilms and release of biofilm bacteria [7].

Biofilms are currently considered the primary mediator of infection, with an estimated 80% of diseases associated with biofilm formation. Biofilm-related infections include otitis media, periodontitis, cystic fibrosis, chronic bacterial prostatitis and native valve endocarditis [1, 8]. The formation of biofilms on microorganisms can increase tolerance to antimicrobials and disinfectants, so biofilms play a significant role in resistance and chronic disease. EPS can also contribute to the antimicrobial resistance properties of biofilms by inhibiting the bulk transport of antibiotics through the biofilm [9]. The bacteria that produce EPS can be protected from the human immune system. Antibiotic therapy, in general, will only kill planktonic cells, while the tightly packed form of bacteria in the biofilm will survive. It is because antibiotics cannot penetrate the biofilm layer. This condition causes persistent and chronic infections because bacteria that produce biofilms are more difficult to treat and are resistant to antibiotic treatment [10]. Bacteria that form biofilms cause failure of antibiotic therapy. After forming a biofilm, bacteria can escape from the human immune system [11].

The search for alternatives in the control of biofilm bacteria are still being pursued. Another alternative in biofilm control with herbal medicine. Herbal medicines are used because they contain herbal substances that have no side effects and are safe. The natural compounds that contained and have the potential antibacterial are steroids, tannins, polyphenols, flavonoids, alkaloids, saponins [12]. One of the plants that contain these compounds is *Parameria laevigata*.

Parameria laevigata is a traditional plant often used by the community to treat wounds, sores, dysentery and uterine pain after childbirth [13, 14]. The organic extract is traditionally obtained from the bark of Pameria laevigata. Based on the study results, it was found that Pameria laevigata contained flavonoids, saponins, steroids, the plant parts used are mainly the skin. *Parameria laevigata* contains flavonoid compounds, polyphenols and tannins, while the leaves contain saponins, tannins and prothocatetic acids [15-17]. Previous studies have shown that the extract of N-hexane from the bark of *Parameria laevigata* has antimicrobial activity against the growth of *Escherichia coli* [18]. And then the study showed that Parameria laevigata can be an antibacterial and anti-inflammatory ointment [19].

Based on the description of the background above and considering the difficulty of therapy due to the formed biofilm, this systematic review aims to examine the effect of the phytochemical content of the bark of *Parameria laevigata* on growth inhibition and biofilm formation so that it can be used as a reference or basis for scientific thinking related to the development of herbal medicine for *Parameria laevigata* as an anti-biofilm.

MATERIALS AND METHODS

This systematic review research is was conducted using the Systematic-Meta Analysis (PRISMA) method [20-22].

Article selection criteria

The selection criteria for articles used inclusion and exclusion criteria. Inclusion criteria include the year of publication of the article in the last ten years, articles in English and Indonesian, original articles, articles on biofilm formation and phytochemical content of *Parameria laevigata*. In comparison, the exclusion criteria include article reviews, books and articles that can't be accessed in Full text.

Article search and selection steps

The initial step taken was to identify the focus of the review guided by the question "Does the bark of *Parameria laevigata* have activity as an inhibitor of biofilm formation and what is the mechanism of the secondary metabolite content of the *Parameria laevigata* plant as an anti-biofilm agent". The second step is to create a specific search strategy with PRISMA flowcharts to help write and report the results of the journal data found. The article selection process uses the PRISMA Guideline flow chart, namely the identification stage, by entering the keywords "Biofilm formation, Natural product, *Parameria laevigata*, Phytochemical" in the journal database (Microsoft Academic Search, Google Scholar, Science Direct and PubMed). At this stage, the removal of duplicate journals was found, carefully reading the titles and abstracts of the relevant journals, the screening stage, reading the entire journals found by paying attention to the inclusion and exclusion criteria of the research that have been set. Then the primary journal data that was used as the target of linguistic analysis and articles deemed relevant were included as supporting analysis in this systematic review.

Data analysis

Data collection from each research article was analyzed using the Systematic-Meta Analysis method. This method is a quantitative analysis study of various scientific research results that have been published to obtain conclusions according to the objectives of this systematic review.

RESULTS

Article selection

After doing a specific article search strategy from the problem formulation stage, identification stage, screening stage. Then the results of the article selection carried out with the PRISMA guideline chart obtained 28 research articles (22 articles from Google Scholar, two articles from Microsoft Academic Search, two articles from PubMed, and two articles from Science Direct) relevant to this systematic review study fig. 1.

Research criteria

Four research articles that discuss the secondary metabolite content bark of *Parameria laevigata* and 24 research articles related to the mechanism of secondary metabolites associated with the *Parameria laevigata* plant, which has a mechanism in biofilm inhibition. The graph shows that the most articles found were in 2019 in fig. 2, and the least in 2014. In the graph, there are differences in the number of studies related to the compound content of the plant *Parameria laevigata* and the journal mechanisms of secondary metabolites as anti-biofilms found, where the research journal *Parameria laevigata* was the most little find in the journal database. It proves that the research journal is still little researched.

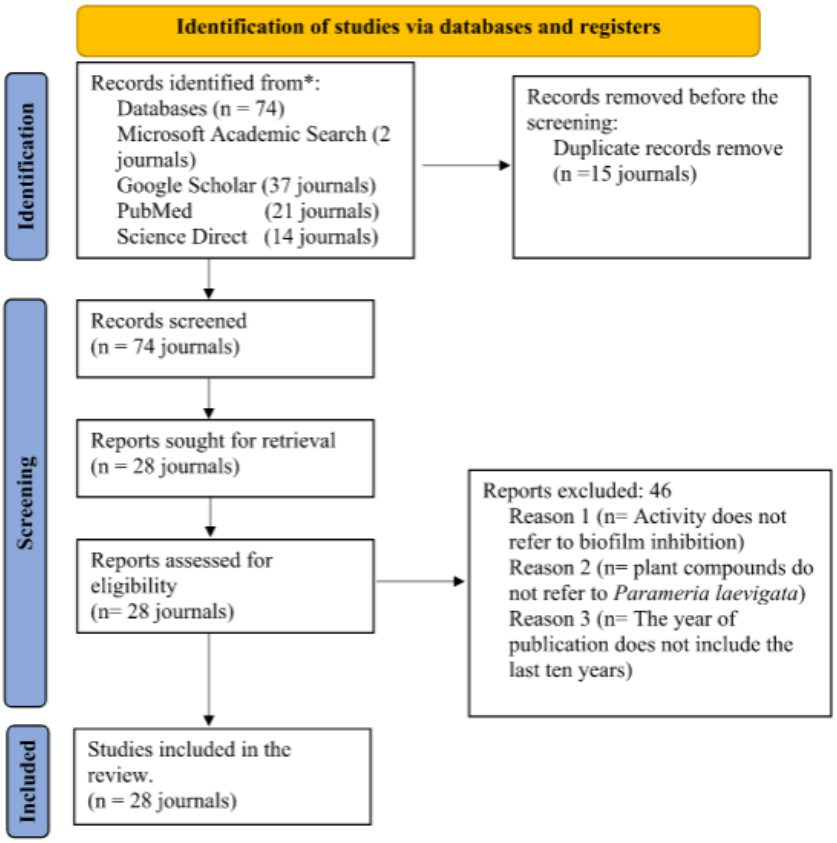

Fig. 1: Flow diagram of the study selection process following the preferred reporting for systematic reviews (PRISMA) guideline

Table 1: Research results related to secondary metabolite content of *Parameria laevigata*

No.	Author	Plant part	Content	Observation
1.	Muharrami *et al.*, 2020	Bark of *Parameria laevigata*	Flavonoids, Saponins, Steroids	Colour test
2.	Barus *et al.*,2019	Bark of *Parameria laevigata*	Alkaloids, Flavonoids, Saponins, Steroids, Tanin, Quinon	Colour test
3.	Saludarez *et al.*, 2019	Bark of *Parameria laevigata*	Alkaloids, Flavonoids, Saponins, Steroids, Tanin	Colour test
4.	Muharrami *et al.*, 2017	Bark of *Parameria laevigata*	Flavonoids, Polifenol, Saponins, Steroids	Colour test

Table 2: Research results related to the mechanism of secondary metabolites as antibiofilms

No.	Author	Content	Mechanism of action of anti-biofilms
1.	Hartady *et al.*, 2020; Sari *et al.*, 2020; Yuanita *et al.*, 2020; Dewatisari, 2019; Kumara *et al.*, 2019; Nugroho *et al.*, 2019; Radita *et al.*, 2019; Suhartono *et al.*, 2019; Primasari *et al.*, 2018; Rizky and Sogandi, 2018; Widyarman *et al.*, 2018; Andriani *et al.*, 2017; Bhunu *et al.*, 2017; Hayat and Sabri, 2016; Kining *et al.*,2016	Flavonoids	• Flavonoids function to inhibit the growth of microorganisms (gram-positive and gram-negative bacteria). • Inhibition is permeable of cell walls and bacterial cell membranes. • Binds to protein, there by interfering with the metabolic activity of bacteria. • Inhibits the activity of glucosyltransferase enzymes in bacterial cells. • Able to block N-Acyl homoserine lactones (AHLs) and Quorum sensing (QS) signals • Inhibition is the production of pyocyanin in bacterial cells. • Inhibition is bacterial energy metabolism in the synthesis of macromolecules (DNA, RNA, and protein).
2.	Marco *et al.*, 2020; Dewatisari, 2019; Nugroho dkk, 2019; Primasari *et al.*, 2018; Sun *et al.*, 2018; Lestari *et al.*,2017; Hayat and Sabri, 2016; Chakotiya *et al.*, 2016; Kining *et al.*,2016; Silvia *et al.*, 2016	Alkaloids	• Inhibits transport and secretion of N-Acyl homoserine lactone (AHL). • Has the function of interfering with the constituent components of poly-peptidoglycan in bacteria and as a DNA interchelate. • It Inhibit the bacterial cell topoisomerase enzyme. • It Inhibit bacterial growth by acting on bacterial cell amino acids. • Provides a significant reduction in the biofilm formation of *E. Coli* bacteria with a non-microbicidal mechanism. • Can interfere with the constituent components of peptidoglycan in bacterial cells and communication signals (Quorum sensing). • It is reported to have an inhibitory effect on the growth of *Pseudomonas aeruginosa*.
3.	Sari *et al.*, 2020; Andrade *et al.*, 2019; Dewatisari, 2019; Kumara *et al.*,2019; Nugroho *et al.*,2019; Primasari *et al.*, 2018; Rizky and Sogandi, 2018; Bhunu *et al.*, 2017; Hayat and Sabri, 2016; Sadowska, 2014	Saponins	• Has the function of increasing membrane permeability, resulting in cell hemolysis • Capable of damaging cell membranes, damage to cell membranes causes important substances to leave the bacterial cell. • It has an inhibitory effect on the growth of *Pseudomonas aeruginosa* by interfering with bacterial cell components. • Reported to inhibit microbial adhesion, enzymes, cell envelope and transport proteins. • Causes cell lysis by interacting with proteins and enzymes in bacterial cells. Has antibiofilm activity on *Candida albicans*, *Candida utilis*, *Bacillus mesenteries*, and *Pseudomonas lachryman*.
4.	Sari *et al.*, 2020; Andrade *et al.*, 2019; Borowski *et al.*, 2019; Dewatisari, 2019; Kumara *et al.*,2019; Nugroho *et al.*,2019; Suhartono *et al.*, 2019; Primasari *et al.*, 2018; Rizky and Sogandi, 2018; Andriani *et al.*, 2017; Bhunu *et al.*, 2017; Hayat and Sabri, 2016; Kining *et al.*, 2016	Tannin	• It can damage the cell wall permeability and inhibit the activity of bacterial cells by damaging the cell membrane. • It has a function in maintaining the extracellular matrix to reduce the mass of the biofilm and the hydrophobicity of the bacterial cell surface. • Inhibits reverse enzyme Transcriptase and DNA topoisomerase so that bacterial cell proteins cannot be formed. • Forming hydrogen bonds with bacterial cell proteins causing changes in bacterial cell protein molecules • Inhibits intercellular adhesion genes icaA and icaD • Anti-bacterial activity against *staphylococcus aureus* and *staphylococcus epidermidis*. • It has an inhibitory effect on the growth of *Pseudomonas aeruginosa* by interfering with bacterial cell components.

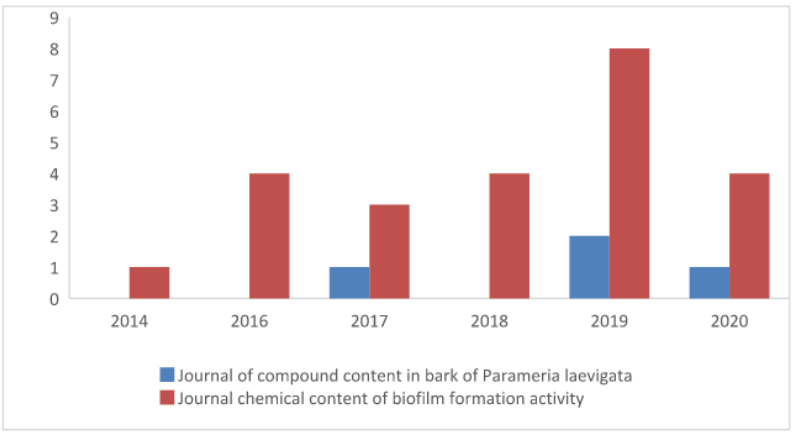

Fig. 2: Years of publication of research articles in the last ten years

DISCUSSION

A Biofilm is a structural form of a group of microorganisms protected by an extracellular matrix called Extracellular Polymeric Substance (EPS). EPS is a product that is produced by these microorganisms and can protect against adverse environmental influences. EPS makes up 50-90% of biofilm organic carbon, including exopolysaccharides (1-2%), proteins (1-2%), nucleic acids (DNA and RNA<1%), and water (up to 97%) [23]. Biofilms are currently considered the primary mediators of infection, with an estimated 80% of infections associated with biofilm formation [8]. Biofilms can cause resistance and chronic disease because the bacteria that produce EPS can be protected from the human immune system and antibiotics. Some bacteria that can cause infection and form biofilms are positive bacteria such as *Staphylococcus aureus* and *Staphylococcus epidermis*. Gram-negative bacteria such as *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Pseudomonas aeruginosa* [5, 24, 25].

The mechanism of biofilm formation, in general, has four stages, including attachment of bacteria to a surface, (2) formation of microcolony, (3) maturation of biofilm, and (4) release of biofilm or dispersal in fig. 3 [26]. At the attachment stage, it is divided into two processes, namely reversible and irreversible attachment. Bacteria use various extracellular organelles and proteins for sensing and attaching to surfaces, including phili, flagella, fimbriae, curly fimbriae, and outer membrane proteins. After the initial attachment, an irreversible attachment will be formed. Then microcolony are formed, characterized by EPS as the matrix and the formation of a complex layer of biomolecules [7, 27]. EPS serves as a structural framework that strengthens the structure of bacterial biofilms. In addition, EPS protects bacterial cells against various stresses such as antimicrobial, host immune system, oxidation and metal cations. As the cells grow, a thicker layer will form so that the microbes attached to the surface in the deepest layer will lack nutrients, resulting in the accumulation of toxic waste products [28-30]. In its development, bacterial cells in the matrix will issue chemical signals or quorum sensing. This signalling molecule plays a role in shaping the characteristics of a more mature biofilm and in coordinating biofilm activity. After the biofilm matures, some bacterial cells move to planktonic growth. These scattered cells explore other surfaces and attach themselves to new surfaces. So dispersal is not only the final stage of the biofilm life cycle [31].

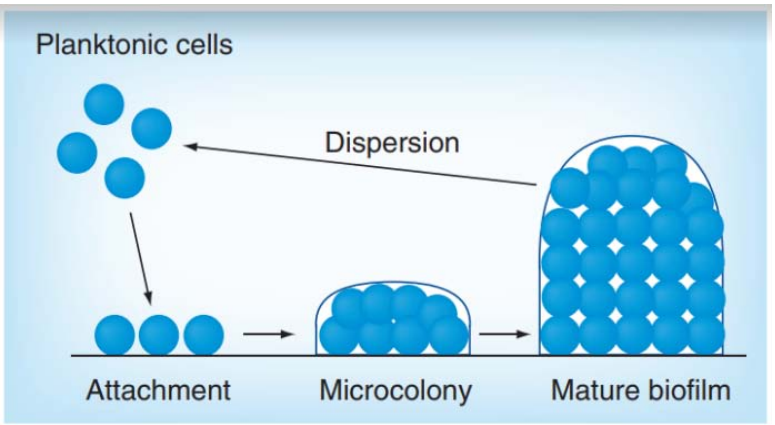

Fig. 3: Mechanism of biofilm formation [27]

Parameria laevigata is a type of medicinal plant commonly known as Kayu Rapet in the Java Region, while in South Kalimantan, it is commonly known as Manggarsih [14, 32]. Traditionally, the roots and stems of this plant are usually used by the community as pain relievers and women's ingredients by boiling with water [13]. In previous studies, it was stated that the stems of *Parameria laevigata* contain compounds of Alkaloids, Flavonoids, Saponins, Steroids, Tannins, Quinones table 1 [13, 16, 19, 33]. These compounds are known to have function ED as antibacterial and biofilm formation with different mechanisms [1, 34, 35].

Alkaloids are secondary metabolites abundant in plants and are one of the broadest classes of compounds with diverse pharmacological properties. Alkaloid compounds have several functions and mechanisms in influencing the formation of biofilms, including inhibiting the transport and secretion of N-Acyl Homoserine Lactone (AHL) or to interfering with enzymatic signaling molecules in bacterial cells [28]. It is known that AHL is a significant component of quorum sensing (QS) in gram-negative bacteria and plays an essential role in biofilm formation [30]. The mechanism of action of alkaloids as an antibacterial is by interfering with the constituent components of poly-peptidoglycan in bacterial cells. The cell wall layer is not fully formed and causes cell death. Another mechanism for antibacterial alkaloids is that the alkaloid component is known as a DNA interchelate and inhibits the bacterial cell topoisomerase enzyme [36, 37]. In the study of Primasari *et al.* (2018), it was stated that alkaloid compounds have primary groups containing one or more nitrogen atoms to react with bacterial amino acids so that they affect the bacterial wall. This reaction causes changes in the structure of amino acids and bacterial DNA to undergo lysis. Then the alkaloid compounds can inhibit bacterial growth by penetrating bacterial cell walls so that they can interfere with communication signals (Quorum Sensing) between bacteria that play a role in biofilm formation or inactivate genes in bacteria that trigger EPS synthesis [1, 4, 6]. Alkaloids are reported to be able to inhibit gram-negative bacteria, including having an inhibitory effect on the growth of *Pseudomonas aeruginosa* by disrupting bacterial cell components and providing a significant reduction in the formation of biofilms of *E. coli* bacteria with non-microbicidal mechanisms [34, 38, 39].

Saponins are triterpene and sterol glycosides detected in more than 90 plant genera. Glycosides are complexes between reducing sugars (glycones) and non-sugars (aglycones) [40]. Saponin compounds have several mechanisms in influencing the formation of biofilms, including saponins compounds that can interact with bacterial membrane lipids, thereby increasing cellular permeability, which results in cell hemolysis. Saponins also can disrupt the surface tension of bacterial cell walls. When the surface tension of the bacterial cell wall is disturbed, other antibacterial compounds can quickly enter the bacterial cell and interfere with cell metabolism, resulting in bacterial death [6, 12, 37, 41–44]. Saponins are antibacterial by damaging cell membranes; damage to cell membranes causes important substances to leave the cell and prevents the entry of essential materials into cells. So it can't select the entry and exit of substances such as water and enzymes. It results in disrupted cell metabolism, thereby inhibiting the process of ATP formation for cell growth. If this process continues, it will cause cell death [36, 37, 45]. Saponin compounds were also reported to have anti-biofilm activity on *Candida albicans*, *Candida utilis*, *Bacillus mesenteries*, *Pseudomonas lachryman*, and *Pseudomonas aeruginosa* by interfering with bacterial cell components [34, 46].

Tannins are a group of polyphenols that can be distinguished from other phenols because of their ability to precipitate proteins [40]. Tannin compound's mechanisms in influencing biofilms formation include tannins can form hydrogen bonds with bacterial cell proteins. If the tannins form hydrogen bonds with bacterial cell proteins, it will cause changes in bacterial cell protein molecules. Changes in these protein molecules can disrupt of bacterial cell metabolism, damage cell wall permeability, and result in inhibition of bacterial cell activity [12, 37, 42, 47, 48]. Tannin compounds can interact with bacterial polysaccharides, thereby inactivating enzymes responsible for maintaining the extracellular matrix, reducting biofilm mass and cell surface hydrophobicity [41]. Tannin compounds work on the DNA synthesis system by inhibiting the reverse transcriptase and DNA topoisomerase enzymes so that bacterial cell proteins cannot be formed [36, 43]. Tannin compounds can inhibit biofilm growth because they can inhibit intercellular adhesion genes icaA and icaD. This gene can synthesise Polysaccharide Intercellular Adhesion (PIA), which has an essential role in cell aggregation and EPS formation in the formation of biofilms in *Staphylococcus aureus* bacteria [4]. Tannins are reported to have antibacterial activity against *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Staphylococcus epidermidis* bacteria by interfering with bacterial cell components, inhibiting bacterial cell walls [34, 49–51].

CONCLUSION

The bark of *Parameria laevigata* has the potent activity to develop as antimicrobial by inhibiting biofilms formation mechanism.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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