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Review Article

Potential of Indonesian Plants as Polymicrobial Anti-Biofilm

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Abstract

Biofilm infection occurs in 80% of chronic infections caused by 60% of biofilms from plankton cells and polymicrobial biofilms. Due to synergistic interactions between species, infections caused by polymicrobial biofilms are more virulent than monospecies biofilm infections. New anti-biofilm candidates are constantly being developed by tracing the content of active compounds from medicinal plants native to Indonesia. The need to find new plant sources that have the potential as anti-biofilms is increasingly needed along with increasing microbial resistance. Various studies show that active compounds that have anti-biofilm potential are polyphenols, quercetin, curcumin, gallic acid, and ferulic acid. The mechanism of action of anti-biofilms is through the prevention of attachment and formation of biofilms, inhibition of quorum sensing, and inhibition of gene expression in microbes.

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INTRODUCTION

Antimicrobial resistance represents a significant global health challenge. According to statistics from the World Health Organization (WHO), the utilization of antibiotics is expected to surge by 200% by 2030[1]. The ineffectiveness of antibiotic treatments, a phenomenon observed in 65% of chronic human infections, can be attributed to microbial infections linked to biofilms[2,3]. Bacteria forming biofilm layers can communicate through a quorum sensing (QS) system, forming polymicrobial microcolonies that may include bacteria, fungi, or viruses. This collective interaction makes these microorganisms approximately 10,000 times more resistant to antibiotic treatments[4]. Infections originating from polymicrobial biofilms exhibit greater virulence than those from monospecies biofilms. This heightened virulence is attributed to the synergistic interactions among different species, leading to an elevated fatality risk in acute and chronic infectious diseases[5,6]. Polymicrobial-induced infections can be observed in various health conditions, including lower lung infections characterized by chronic inflammation in individuals with cystic fibrosis. These infections are also evident in inner ear infections (otitis media), where polymicrobial biofilm complexes pose a risk of both partial and complete hearing loss[7].
Furthermore, urinary tract infections can also be attributed to polymicrobial biofilms. Notably, a significant percentage, ranging from 60% to 90%, of infections occurring in the oral cavity, such as dental caries, originate from polymicrobial infections. Another condition associated with polymicrobial biofilms is diabetic foot wounds, which lead to tissue damage,

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chronic inflammation, and the formation of a biofilm layer. This biofilm formation contributes to delayed wound healing, potentially necessitating amputations and elevating the risk of mortality[8,9]. The need to find anti-biofilm candidates, especially from active compounds native to Indonesia, is increasingly needed along with increasing microbial resistance[10].

The growing necessity for discovering potential anti-biofilm agents, particularly among active compounds of plant origin, is escalating in response to the rising levels of microbial resistance[11]. Plants have a long history of use in traditional medicine, contain diverse natural compounds, and offer a promising source for discovering new antibiofilm agents. Their potential therapeutic benefits, lower resistance development, and relative safety make them an attractive avenue for research in the fight against biofilm-related infections[12].

Indonesia, an equatorial archipelago comprising more than 17,000 Southeast Asian islands, is recognized for its remarkable biodiversity. It ranks as the world's second-most biodiverse country, trailing only Brazil, and boasts a diverse array of 47 unique natural ecosystems teeming with plant and animal resources[13]. Additionally, Indonesia is home to a substantial number of island-specific species. The country is renowned for its invaluable biological heritage, deeply rooted cultural traditions, and sizable population, which underscore its significant role in the herbal medicine industry[14].

Indonesia boasts an impressive flora, with over 38,000 plant species, of which approximately 9,600 are classified as medicinal plants[15]. Despite this wealth of botanical resources, the Indonesian National Agency of Drug and Food Control (NADFC or *Badan Pengawas Obat dan Makanan Republik Indonesia*, BPOM RI) has scientifically examined only around 300 plant species to assess their medicinal properties, officially registering them for commercial use in traditional medicine. A substantial portion of the plant species remains unexplored, necessitating further research and screening to uncover their potential medicinal attributes[16]. Many studies have been conducted to explore the biological properties of commonly used plants in Indonesian traditional medicine. However, it's worth noting that there has been limited exploration of Indonesian medicinal plants concerning their potential for anti-biofilm activity[17,18].

POLYMICROBIAL BIOFILM

A biofilm represents an assembly of microbial cells firmly adhered to a surface and enclosed within a matrix of extracellular polymeric substances (EPS) that cannot be easily dislodged[19]. Microorganisms proficient in forming biofilm structures often demonstrate heightened resistance to antibiotics, disinfectants, and phagocytosis and are the primary culprits behind human infections, presenting considerable treatment challenges[20,21]. Biofilm-related infections are responsible for 80% of chronic infections, including persistent wounds. Biofilms also possess an inherent adaptability that can give rise to both acute infections and long-lasting inflammation. Traditional antimicrobial agents like antibiotics are typically designed to eliminate or hinder the growth and division of planktonic cells, but they lose their effectiveness when dealing with infections linked to biofilms[22]. While a combination of antibiotic treatments may effectively address up to 60% of biofilms originating from planktonic cells, the success rate drops significantly to just 22% when dealing with infections associated with polymicrobial biofilms[23].

The EPS layer in biofilms leads to persistent infections, rendering treatment considerably more challenging. The biofilm matrix layer accounts for half of the biofilm's composition and possesses a thickness ranging from 0.2 to 1.0 mm. The production of EPS plays a pivotal role in facilitating microbial adhesion to cell surfaces and cell-to-cell adhesion. This polymer matrix is responsible for imparting mechanical stability to the biofilm. Additionally, The EPS layer serves as a shield, protecting microorganisms from hostile environments that are inhospitable to microbial growth, as well as from chemical toxins and antimicrobial agents. This layer can bind cations along with antimicrobial agents, such as chlorhexidine and antimicrobial peptides, preventing their penetration into the deeper layers of the biofilm, consequently diminishing the efficacy of antimicrobial treatments[24]. The formation of the biofilm structure is determined by various factors, including the microorganisms' capacity to adhere to surfaces, the production of EPS, inter-microbial signaling, and the dispersion of microbes as planktonic cells. Bacteria, fungi, and viruses can coexist in clinical scenarios, forming intricate communities within polymicrobial biofilms. This complexity poses challenges when selecting suitable antibiotic treatments, particularly in cases involving antibiotic-resistant microorganisms[25,26].

ACTIVE COMPOUNDS OF INDONESIAN PLANTS AS POLYMICROBIAL ANTI-BIOFILM POTENTIALS

Indonesia boasts a rich diversity of medicinal plants, representing a significant wellspring for drug discovery. The outcomes of a literature review focused on Indonesian plant species with the potential for combating polymicrobial biofilms are outlined in **Table I**.

Table I. Indonesian medicinal plants with anti-biofilm activity.

No	Local name (Scientific name)	Polymicrobial bacteria	Chemical compounds
1	*Masoyi (Mossaia aromatica)*[27]	Degradation of *Candida albicans, Pseudomonas aeruginosa,* and *Staphylococcus aureus* biofilm formation	Essential oil, massoia lactone
2	White turmeric/*temu rapet/kunci pepet (Kaempferia rotunda)* [27]	Degradation of *P. aeruginosa* AO1 and *S. aureus* Cowan I biofilm formation	Flavonoids, quercetin, flavonols
3	*Secang/sapang (Caesalpinia sappan)* [27]	Degradation of *P. aeruginosa* AO1 and *S. aureus* Cowan I biofilm formation	Triterpenoids, flavonoids, and phenolic compounds
4	Cinnamomum/*kiamis/ holim manis/ kanigar (Cinnamomum burmannii)* [27]	Degradation of *P. aeruginosa* AO1 and *S. aureus* Cowan I biofilm formation	Essential oils cinnamaldehyde and cinnamyl acetate, ethyl cinnamate, beta-caryophyllene, linalool, and methyl chavicol
5	*Sintok/huru sintok/madang lawang (Cinnamomum sintoc)* [27]	Degradation of *P. aeruginosa* AO1 and *S. aureus* Cowan I biofilm formation	Essential oil eugenol
6	Lotus/*tunjung (Nymphaea nouchali)* [27]	Degradation of *P. aeruginosa* AO1 and *S. aureus* Cowan I biofilm formation	The flowers contain quercetin, luteolin, isoquercetin, kaempferol, galuteolin, and alkaloids. The seeds contain quercetin and isoquercitrin
7	Cinnamomum verum/*manis jangan/huru mentek (Cinnamomum zeylanicum)*[28]	Inhibits communication between bacteria to inhibit the formation of *Escherichia coli* and *Pseudomonas* sp. biofilms	Essential oils, cinnamaldehyde, eugenol
8	Curcuma/*koneng/temu tombak (Curcuma xanthorrhiza)* [28]	The ethyl acetate fraction can inhibit plankton and biofilm in dental caries, destroy cell walls, inhibit enzymatic activity, and prevent bacterial attachment	Phenolic, Xanthorrhizol
9	*Melinjo/maninjo/tangkil (Gnetum gnemon)*[29]	Leaves water extract can inhibit cell attachment through the penetration of compounds into the EPS layer biofilm	Saponins, alkaloids, tannins and steroids
10	Clove/*cangke/lawang/ singke (Syzygium aromaticum)* [28]	Degradation of biofilm formation	Essential oils, eugenol
11	Ginger/*jahe/halia/tipakan (Zingiber officinale)*[21]	Degradation of biofilm formation	Essential oils, terpenoids
12	Mangosteen/*manggu/manggus/manggista* (*Garcinia mangostana*)[30]	Prevents communication between biofilm-forming bacteria and reduces the ability to form antibiotic resistance genes	Flavonoids
13	Clove leaves/*cangke/lawang/singke* (*Syzygium aromaticum*)[28,30]	Inhibit the growth of *E. coli*, *Salmonella enteritidis*, and *S. aureus* by inhibiting communication between bacteria in the formation of biofilms	Essential oils, eugenol
14	Henna/*pacar kuku/pacar petok/inai parasi (Lawsonia inermis)* [28]	Inhibit biofilm formation. Leaves ethyl acetate extract inhibits *Streptococcus pneumoniae* ATCC 49619 >90% and inhibits >98% MDRSP 2506	Phenolics, benzene derivatives, naphthoquinones, saponins, flavonoids, steroids
15	Lemongrass/*sere/bubu* (*Cymbopogon citratus*) [28]	Degradation of biofilm formation	Essential oils
16	*Senggani/senduduk* (*Melastoma candidum*)[17]	Ethanol and ethyl acetate extract from leaves can inhibit quorum sensing of *Aeromonas hydrophila* infection in fish	Tannins, flavonoids

17	*Kersen/seri/ceri/talok* (*Muntingia calabura*) [17]	Ethanol and ethyl acetate extract from leaves can inhibit quorum sensing of *Aeromonas hydrophila* infection in fish	Flavonoids, polyphenols, flavonols, steroids, triterpenoids, alkaloids and tannins
18	Turmeric/*kunyit/kunir/koneng/hunik* (*Curcuma longa*)[31]	0.5% pure curcumin isolates can destroy polymicrobial EPS biofilm layers of *S. aureus, P. aeruginosa, E. coli*, and *C. albicans* on catheters. 1% curcumin can inhibit biofilm formation in the middle and maturation phases by 62.23%	Curcumin
19	Creeping woodsorrel/small sour/*calincing/lela* (*Oxalis corniculata*)[32]	1% ethanol extract of *O. corniculata* leaves can inhibit *C. albicans* biofilm formation in the intermediate phase by 68.23%	Flavonoids, tannins, essential oils, saponins
20	Areca nuts/*pineng/ jambe/pining* (*Areca catechu*)[33]	Ethanol extract and water fraction can inhibit the biofilm-forming bacterium of *S. aureus*	Flavonoids, tannins, alkaloids, quinones, terpenoids and saponins
21	Papaya leaves/*kates/gedang/betik* (*Carica papaya*)[29]	This extract can inhibit cell attachment and degrade biofilms by 41.176% and 49.02%, respectively	Alkaloids, tannins, flavonoids, steroids/terpenoids
22	*Kepayang/kluwek/keluak* (*Pangium edule*)[34]	Ethanol extract can destroy *Streptococcus sanguinis* ATCC 10556 biofilm	Phenols, tannins, flavonoids, alkaloids, saponins, and fatty acids
23	*Bawang tiwai/bawang dayak/bawang sabrang/berlian/bawang lubak* (*Eleutherine bulbosa*)[35]	Ethanol extract and methanol soluble fraction can degrade biofilm	Phenolics and naphthoquinones
24	Coriander seeds/*ketumbar/hatumbar* (*Coriandrum sativum*)[36]	Ethanol extract inhibits the formation of *Streptococcus mutans* ATCC 25175	Linalool, phenolics, and flavonoids
25	Jackfruit/*nongko/langge/anane* (*Artocarpus heterophyllus*)[37]	*Artocarpus heterophyllus* leaves extract can destroy *S. sanguinis* ATCC 10556 biofilm	Saponins, flavonoids, and tannins
26	A combination of *S. aromaticum* leaves and *C. verum* bark[38]	Combination of 27 : 73 can inhibit *S. mutans* biofilm formation	Polyphenols, essential oils
27	*Melinjo leaves/maninjo/tangkil* (*Gnetum gnemon*)[39]	A concentration of 25% could inhibit the growth of 43.09% and degrade 43.04% of *P. aeruginosa*	Phenolics, alkaloids, tannins, saponins, and steroids
28	Mangosteen/*manggis/manggu/manggus/manggista* (*Garcinia mangostana*)[30]	Minimum biofilm inhibitory concentration (MBIC) of 0.78% against *S. mutans*	Flavonoids

Mossaia aromatica

Indonesian people use *M. aromatica* to treat several diseases, such as diarrhea, fever, vaginal discharge, stomach cramps, and postpartum. Existing research states that *M. aromatica* contains essential oils that can be obtained from the bark, stems, and fruit of *M. aromatica*[40]. Massoia lactone (**Figure 1**; 92.05%) was the main constituent of *M. aromatica* essential oil[41]. *Mossaia aromatica* has been proven to be able to inhibit the formation of biofilm by *S. aureus* by 50% with a concentration of 0.03%, while the use of essential oil from the bark of *M. aromatica* with a concentration of 0.12% can disrupt the biofilm that has already been formed by 50%[42]. The mechanism of action of massoia lactone is to damage the EPS so that the cell and nutrient communication pathways between microbes are cut off so that microbes that previously wanted to form biofilm ultimately cannot form biofilm, causing these microbes to lyse or die because of loss of nutrients as a component of biofilm formation[41].

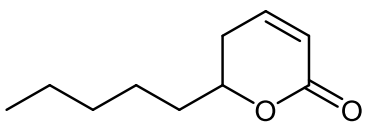

Figure 1. Massoia lactone (PubChem CID 39914)[41].

Kaempferia rotunda

Kaempferia rotunda is commonly known as white ginger by Javanese and Malay people in Indonesia. *Kaempferia rotunda* ethanol extract has been proven to have antibacterial and antibiofilm effects, with the mechanism of action inhibiting eDNA

production in *S. aureus* biofilm biomass. *Kaempferia rotunda* extract can reduce biofilm formation at concentrations ranging from 0.019 to 0.625 mg/mL. Curcumin is the active compound that plays a vital role in this effect (**Figure 2**)[44].

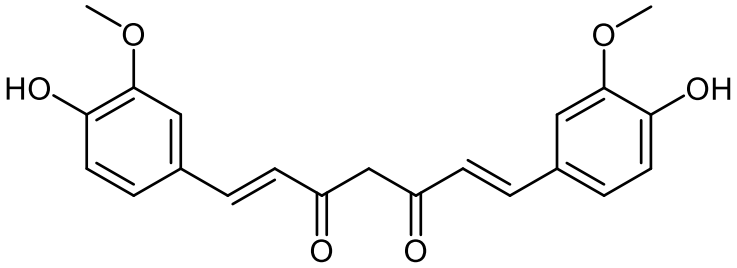

Figure 2. Curcumin (PubChem CID 969516)[44].

Caesalpinia sappan

Caesalpinia sappan is a plant from the Caesalpiniaceae family that has many benefits and is often consumed by Indonesian people as a medicine for wounds, stopping bleeding, anti-diarrhea, pain relief, and increasing body stamina. *Caesalpinia sappan* wood contains compounds like brazilin, sappanin, brazilein, and essential oils[45]. Brazilin (**Figure 3**) showed antibacterial activity, including minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of 0.5 mg/mL[46]. Based on research conducted by Utami *et al*.[47], the leaves and stems of *C. sappan* were proven to have antibacterial and antibiofilm activity against *S. mutans*. The inhibitory ability of bacterial biofilms is thought to be the role of the flavonoid compounds in *C. sappan*. The mechanism of action of this substance is to inhibit bacterial infections, which is related to its ability to form bonds with proteins, thereby inhibiting bacterial adhesion. The brazilin content of *C. sappan* stem can be well absorbed into the bacterial walls, resulting in leakage of the cytoplasmic membrane and inhibiting bacterial growth and is responsible for inhibiting the formation of bacterial biofilm mass.

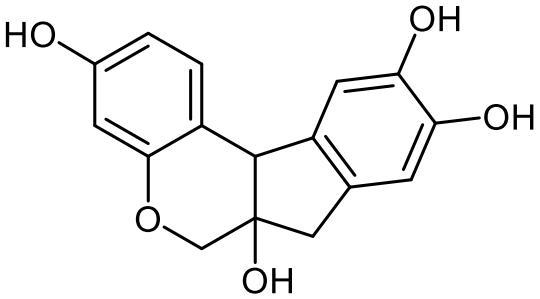

Figure 3. Brazilin (PubChem CID 73384)[48].

Cinnamomum burmannii

Cinnamomum burmannii, known as *kiamis*, *holim manis*, and *kanigar* by Indonesian people. *Cinnamomum burmannii* bark has a distinctive smell and is widely used for various purposes, such as flavoring food or cakes. Al-Dhubiab[49] states that the most significant chemical components in *C. burmannii* are cinnamic alcohol, coumarin, cinnamic acid, cinnamaldehyde, anthocyanin, and essential oils containing sugar, protein, simple fat, pectin, and others. The main contents of *C. burmannii* essential oil are cinnamaldehyde (**Figure 4**) and eugenol[50]. Cinnamon oil has several benefits such as antimicrobial, antioxidant, antidiabetic, and antiallergenic effects. The active compounds contained in cinnamon have been proven to have antibacterial and antibiofilm effects through a mechanism of action in the form of inhibiting the formation of bacterial biofilm mass. As an anti-biofilm agent, *C. burmannii* has an MBIC value of 0.01%[51]. The active compound cinnamaldehyde can dissolve well in the polar groups of bacterial walls so that phospholipid molecules will break down into glycerol, carboxylic acid, and phosphoric acid. This change will cause leakage of the cytoplasmic membrane and inhibit bacterial growth. The eugenol content can also be dissolved well in the polar group of bacterial glucosyltransferase enzymes to interfere with the formation of bacterial biofilm mass[47].

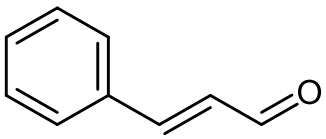

Figure 4. Cinnamaldehyde (PubChem CID 637511) [50].

Cinnamomum sintoc

Cinnamomum sintoc, known as *sintok* by Indonesian people, is used for traditional medicine such as diarrhea and wound healing. Based on research conducted by Muhamad[52], methanol extract of *C. sintoc* leaves (50 mg/mL) has activity against *S. aureus* and *P. aeruginosa*. As an anti-biofilm agent, *C. sintoc* has an MBIC value of 0.06%[51]. The active compounds detected in *C. sintoc* leaves extract include terpenoids, phenols, and tannins. One of the active compounds that plays a major role as an antibacterial is terpenoids, which react by forming strong polymer bonds, destroying porins in bacteria. This damage will reduce the permeability of the bacterial walls and result in bacterial cells lacking nutrition so that bacterial growth is hampered and they die[53].

Nymphaea nouchali

Nymphaea nouchali or lotus is known as *tunjung* by Indonesian people. Based on research by Dash *et al*.[54], the methanol extract of *N. nouchali* flowers has antibacterial activity against *Bacillus subtilis*, *Sarcina lutea*, *E. coli*, and *Klebsiella pneumoniae*. The antibacterial activity is believed to be due to secondary metabolite compounds such as alkaloids, tannins, steroids, phenols, saponins, and flavonoid compounds, which were previously reported to have antimicrobial properties.

Cinnamomum zeylanicum

Cinnamomum zeylanicum, or cinnamon, is a plant that has a distinctive aroma. This species has been used in traditional medicine for its properties, including its activity as an astringent, aphrodisiac, antiseptic, aperitif, aromatic, carminative, digestive, stimulant, hypertensive, sedative, tonic, vasodilator, antidiabetic, antinociceptive, astringent, and diuretic. Essential oil components include cinnamaldehyde (65-78%) and eugenol (4-10%)[55]. The research results prove that cinnamon has antibacterial activity against *P. aeruginosa*, *E. coli*, and *S. aureus* strains. This research also shows anti-biofilm activity through a mechanism that prevents the formation of biofilms and planktonic cells, making bacterial biofilms unstable[56].

Curcuma xanthorrhiza

Koneng or *temu tombak* is another name for *C. xanthorrhiza* for Indonesian people. This plant has antibacterial and antifungal effects. Phytochemically, *C. xanthorrhiza* was detected to have active components in the form of alkaloids, flavonoids, phenolics, saponins, triterpenoids, and glycosides. According to research, *C. xanthorrhiza* has an antimicrobial effect against several microorganisms, especially against *B. subtilis*, *E. coli*, and *S. aureus*. The active substances in *C. xanthorrhiza* that can be antibacterial are curcumin (curcuminoids) and essential oils. Essential oils can lyse bacterial cell membranes, and curcumin can inhibit the proliferation of bacterial cells[57]. When present at a concentration of 1%, polyphenolic compounds like curcumin have demonstrated the ability to impede approximately 62.23% of the intermediate phase and 59.43% of the maturation phase in biofilm development. Furthermore, curcumin exhibits a remarkable eradication rate of 55.79% against polymicrobial biofilms involving *S. aureus*, *P. aeruginosa*, *E. coli*, and *C. albicans*. It also achieves a 50% inhibition of polymicrobial biofilm formation on catheters through the disruption of the polymer-based EPS[31].

Gnetum gnemon

Gnetum gnemon or melinjo/maninjo/tangkil contains active compounds such as alkaloids, flavonoids, steroids, and tannins. Based on Kinning *et al*.[58], *G. gnemon* leaves extract inhibited biofilm cell attachment by 49.8%. This inhibitory process is attributed to direct antibacterial activity, in others to QS disruption or unknown causes, perhaps inhibition of sortases or adhesins. Tannins and flavonoids are compounds contained in *G. gnemon* leaves extract that are thought to inhibit biofilm

formation by binding to one of the bacterial adhesin proteins, which is used as a bacterial surface receptor, resulting in a decrease in bacterial adhesion and inhibition of protein synthesis for cell wall formation.

Syzygium aromaticum

Syzygium aromaticum is known for its use as a spice in cooking. *Syzygium aromaticum* essential oil exhibits anti-inflammatory, cytotoxic, and anesthetic activities in addition to antimicrobial, antifungal, antiviral, antioxidant, and insecticidal properties. The research results prove that *S. aromaticum* can influence the homeostasis of the formed bacterial biofilm. The eugenol compound (**Figure 5**) contained in *S. aromaticum* oil provides a bactericidal effect that decreases the number of planktonic cells and changes the ability of bacterial cell attachment[59].

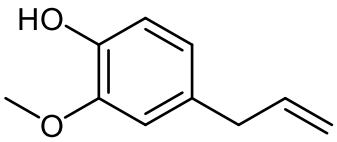

Figure 5. Eugenol (PubChem CID 3314)[59].

Zingiber officinale

Phytochemical studies of *Z. officinale* show that *Z. officinale* has anti-inflammatory and antioxidant properties and can potentially prevent cancer. Their active compound components are polyphenols, such as 6-gingerol (**Figure 6**), and their derivative compounds. Other compounds directly related to antibiofilm and antibacterial activity are curcumin, 6-shogaol, and zingerone[60].

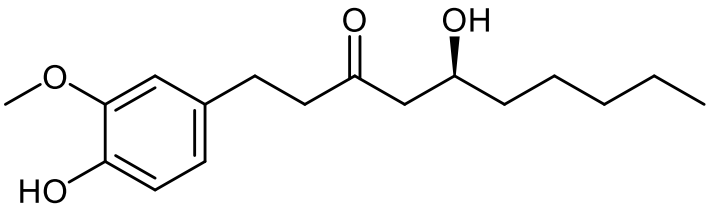

Figure 6. Eugenol (PubChem CID 442793)[60].

Garcinia mangostana

The main chemical content in the roots, bark, and rind of the *G. mangostana* fruit is saponin. The stems contain flavonoids and polyphenols, and the pericarp contains flavonoids, steroids/terpenoids, and quinones. Research results prove that *G. mangostana* fruit can inhibit biofilm with a percentage of 48.8% to 84%. Flavonoids in fruit skin can damage bacterial cell membranes by destroying the lipid layer on the bacterial membrane and causing obstruction of cell membrane function[61]. Flavonoid compounds in the phenol group inactivate a bacterial enzyme that stimulates the activity of the glucosyltransferase enzyme used by bacteria to synthesize sucrose in the medium into glucan. As a result, biofilm formation is hampered because of the amount of glucan as a medium for attaching small or limited bacteria[62].

Lawsonia inermis

Lawsonia inermis is known as *pacar petok* or *inai* by the Indonesian people. This plant was proven to have antibiophilic activity, with inhibition reaching 84.9%. Research results prove that the active compounds that play a role in this effect are the presence of glycosides, phytosterols, steroids, saponins, tannins, and flavonoids[63].

Cymbopogon citratus

Cymbopogon citratus or lemongrass essential oils have been widely used as traditional medicine and are famous for their antimicrobial properties. *Cymbopogon citratus* oil has been proven to reduce biofilm formation by 45-76% in *Candida tropicalis* strains by inhibiting the formation of planktonic cells in bacterial biofilms[64,65].

Melastoma candidum

Acetone extract of *M. candidum* showed a good bactericidal effect. The MIC and MBC for the acetone extract were 0.02 to 0.64 mg/mL and 0.08 to 2.56 mg/mL, respectively, while 95 mL/100 mL for the ethanol extract[66]. Antibacterial substances, especially flavonoids, can destroy bacterial cell walls and cytoplasmic membranes, causing leakage from the cytoplasm[67].

Muntingia calabura

Compounds that have been isolated from *M. calabura* include three flavones and one chalcone: 5,7-dihydroxy-3,8-dimethoxyflavone, 2',4'-dihydroxychalcone, 5-hydroxy-3,7-dimethoxyflavone, and 3,5,7-trihydroxy-8-methoxyflavone. *Muntingia calabura* leaves have been proven to respond as an antibiofilm against *P. aeruginosa*. The antibacterial activity of *M. calabura* leaves is thought to come from the active compound 2',4'-dihydroxychalcone (**Figure 7**)[68]. The mechanism of action of the methanol extract of *M. calabura* leaves anti-quorum sensing in bacteria so that biofilm formation can be inhibited[69].

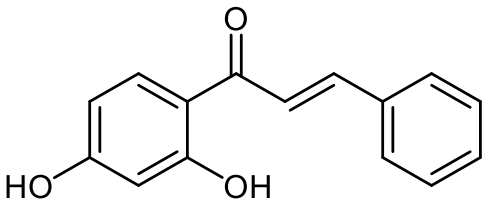

Figure 7. 2',4'-dihydroxychalcone (PubChem CID 6433293) [68].

Curcuma longa

Curcuma longa, known as turmeric, has been proven in the methanol fraction at a concentration of 0.5-5% to inhibit biofilm formation, so it can be concluded that this extract has anti-biofilm activity. One of the main components detected from the methanol fraction of *C. longa* is curcumin, an active substance that plays a vital role in inhibiting bacterial biofilm. Curcumin can inhibit biofilm formation by reducing the expression of genes involved in quorum-sensing mechanisms that cause biofilm maturation in bacteria[70].

Oxalis corniculata

Oxalis corniculata, known as calincing/lela by Indonesian people, has empirical properties as a medicine for stomach aches and coughs. Scientifically, data has been obtained that the leaves of this plant have an antimicrobial effect. Hamzah *et al*.[71] research results prove that 1% ethanol extract of *O. corniculata* provides anti-biofilm activity on *S. aureus* of 69.333%.

Areca catechu

Areca catechu, or *pinang* by the Indonesian people, has various activities, including methanol extract, which is proven to have anti-bacterial activity. The active compounds detected in the methanol extract of *A. catechu* palm were flavonoids, tannins, alkaloids, quinones, terpenoids, and saponins. *Areca catechu* nuts contain catechins, tannins (15%), gum, and alkaloids[72]. Methanol extract from *A. catechu* nuts has been proven to have anti-biofilm activity by forming complex compounds with proteins through hydrogen bonds, causing changes in the structure of proteins and nucleic acids. These structural changes can cause the proteins that makeup EPS and biofilms to be degraded. The high phenolic content of *A. catechu* nuts, gallic acid (**Figure 8**), is important in anti-biofilm activity[33,73]. When isolated at a 100 µg/mL concentration, gallic acid exhibited the highest level of inhibition in biofilm formation. The findings from the anti-biofilm assessment indicated a dose-dependent effect, meaning that the anti-biofilm activity increased as the concentration of gallic acid increased[74]. Gallic acid derivatives like methyl gallate belong to the phenolic compounds category and can act through various mechanisms, including enzyme inhibition via oxidized compounds, reactions involving sulfhydryl groups, or non-specific interactions with microbial proteins[75,76].

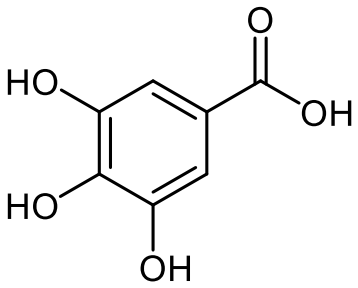

Figure 8. Gallic acid (PubChem CID 370) [74].

Carica papaya

Carica papaya or *kates* leaves contain the active compounds carpainin alkaloids, carpaine, ferulic acid, vitamins C and E, choline, papain proteolytic enzymes, saponins, flavonoids, and tannins. With a concentration of 25%, the extract of *C. papaya* leaves can inhibit the growth of biofilms by 39.837%[77]. *Carica papaya* leaves extract has been proven to have anti-biofilm activity with a mechanism in the form of binding to one of the bacterial adhesin proteins, which is used as a bacterial surface receptor, resulting in a decrease in bacterial adhesion and inhibition of protein synthesis for cell wall formation[78]. The stems, leaves, and young fruit of *C. papaya* contain white sap, which contains a protein-breaking enzyme or proteolytic enzyme called papain. Papain is thought to play an important role in degrading the EPS layer in the bacterial biofilm that forms[29]. Another compound that plays a vital role in anti-biofilm activity is ferulic acid (**Figure 9**). Research has reported that gallic acid and ferulic acid display potent preventive effects on biofilms formed by *P. aeruginosa*, *Listeria monocytogenes*, and *S. aureus*, with significant activity observed at concentrations exceeding 1 mg/mL[79]. Ferulic acid, in particular, disrupts the exopolymeric matrix of biofilms, impacting various cellular targets, including adhesion proteins, cell surface proteins, exopolymers, and communication pathways among biofilm cells during the maturation phase[80].

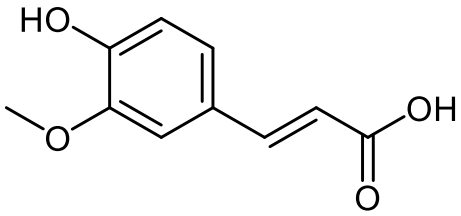

Figure 9. Ferulic acid (PubChem CID 445858) [79].

Pangium edule

Pangium edule, or *kluwek* by Indonesian people, especially on the island of Java, contains tannins, natural polyphenolic compounds that inhibit microbial growth by changing the permeability of their cell walls. An extract concentration of 4-8% effectively inhibits the growth of *S. aureus*, *E. coli*, and *P. aeruginosa*[81]. *Pangium edule* seeds has antibiofilm properties toward *S. sanguinis* biofilm ability of extract concentration 1.25% and 2.5%[34].

Eleutherine bulbosa

Eleutherine bulbosa has active compounds in the form of phenolic and flavonoid derivatives, naphthalene, anthraquinones, and naphthoquinones. Scientific investigations reveal that various pharmacological activities of *E. bulbosa* include anticancer, antidiabetic, antibacterial, antifungal, antiviral, anti-inflammatory, dermatological problems, antioxidant, and antifertility. *Eleutherine bulbosa* tuber extract shows good microbial inhibition against pathogenic bacteria such as *S. aureus*. *Eleutherine bulbosa* ethanolic extract has been proven to inhibit forming and degrade biofilms in *S. aureus*. Methanol soluble fraction at concentration 0.01 - 0.5 mg/mL can degrade biofilms from tested bacteria, while the ethanolic extract can only degrade the biofilms on *S. aureus*[35]. Microbial inhibition is caused by interference from alkaloid compounds and the formation of peptidoglycan components, thereby disrupting microbial cell walls[82,83].

Coriandrum sativum

Coriandrum sativum or coriander is often used as a kitchen spice and traditional medicine. *Coriandrum sativum* extracts and essential oils have been shown to exhibit antibacterial, antioxidant, free radical, antidiabetic, and anticancer activities. The strongest anti-biofilm activity of *C. sativum* essential oil was found against *Stenotrophomonas maltophilia* and *S. aureus* with a mechanism of action in the form of preventing the formation of biofilms and planktonic cells so that the bacterial biofilm becomes unstable[84]. The $MBIC_{50}$ and $MBIC_{90}$ of *S. maltophilia* of *C. sativum* essential oils were 7.49 and 7.96 µL/mL, respectively, while for *B. subtilis* were 7.42 and 6.95 µL/mL, respectively[59].

Artocarpus heterophyllus

Artocarpus heterophyllus or jackfruit is believed to help treat fever, boils, skin diseases, anti-diarrhea, analgesics, and immunomodulators[85]. The results of the phytochemical screening of *A. heterophyllus* leaves extract contained several compounds: phenolics, flavonoids, alkaloids, saponins, steroids, and tannins. Based on research by Khan *et al*.[86], *A. heterophyllus* leaves have antibacterial activity against *S. aureus*, *P. aeruginosa*, and *E. coli*. Extract from *A. heterophyllus* completely inhibited the growth of primary cariogenic bacteria at 3.13–12.5 µg/mL[87]. The MIC of *A. heterophyllus* leaves extract against *S. aureus* was found at 320 µg/mL[88].

Combination of Syzygium aromaticum leaves and Cinnamomum verum bark

The combination of *S. aromaticum* and *C. verum* essential oils was proven to be an effective antibacterial agent by showing high antibacterial activity against extended-spectrum beta-lactamases (ESBL)-producing *E. coli* and *K. pneumoniae* isolates, as evidenced by the diameter of the inhibition zone and MIC values. The MBC values of *S. aromaticum* and *C. verum* essential oils ranged from 0.078% to 0.156% for all bacteria tested. Morphological changes in each test bacterial cell were observed via scanning electron microscopy. Every test bacterium treated with *S. aromaticum* and *C. verum* essential oils showed cell shrinkage and lysis. *Syzygium aromaticum* leaves and *C. verum* bark contain various essential oils with different antibacterial activities. *Syzygium aromaticum* contains 15-20% essential oils, dominated by eugenol (70-85%), eugenyl acetate (15%), and β-caryophyllene (5-12%). Eugenol is a bioactive compound with bactericidal activity that causes damage, such as holes in the envelope and deformation of bacterial cells. *Cinnamomum verum* contains 0.5-1% essential oils consisting of cinnamaldehyde (63.69%), cinnamyl acetate (9.93%), and 1,8-cineole (8.75%). Cinnamaldehyde also has bactericidal activity which can affect membrane permeability and integrity as well as bacterial cell morphology[89].

CONCLUSION

Bacteria capable of forming biofilm layers are driving an escalation in antibiotic resistance. Numerous studies have indicated the presence of various active compounds with potential as anti-biofilm agents, including flavonoids, tannins, and polyphenols like gallic acid, ferulic acid, and curcumin. These compounds' modes of action against microorganisms encompass hindering attachment and biofilm formation, impeding quorum sensing, and suppressing gene expression in microbes.

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Project administration: -
Resources: Sylvia Utami Tunjung Pratiwi, Yosi Bayu Murti, Ema Damayanti
Software: -
Supervision: Sylvia Utami Tunjung Pratiwi, Yosi Bayu Murti
Validation: Sylvia Utami Tunjung Pratiwi, Yosi Bayu Murti
Visualization: -
Writing - original draft: Rafika Sari
Writing - review & editing: Sylvia Utami Tunjung Pratiwi, Yosi Bayu Murti

DATA AVAILABILITY

None.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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