Chapter 4

Quorum Sensing Inhibition and Anti-Biofilm Activity of Traditional Chinese Medicines

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Abstract

Bacterial biofilm, a special stage which a large amount of bacteria are adhere to surface, increase resistance to antimicrobial agents. However, all the bacteria are possibly developed into biofilm, and bacterial biofilm is more difficult to remove from environment comparing to planktonic bacteria, which can be a strike to food industry. Many researchers have showed that traditional Chinese medicines contribute to the reduction of bacterial formation, since the important factor (quorum sensing) in biofilm formation is inhibited by traditional Chinese medicines. In this review, the effect of traditional Chinese medicines and its inhibition mechanism of biofilm formation on common bacterium biofilm are summarized, which provide a new direction for the removal of bacterial biofilm.

Keywords: Chinese medicine composition, biofilm, quorum sensing

1. Introduction

Bacterial biofilms, a bacterium growth state, which can attach to living and non-living surfaces, consist of a small part of bacteria and self-produced hydrated matrix of extracellular polymeric substances. Biofilm bacteria are more resistant to antimicrobials compared with planktonic bacteria, which cause their elimination from food processing facing great challenges [1]. The emergence of bacterial resistance to conventional antimicrobials clearly shows that new biofilm control and removal strategies need to be proposed. Quorum sensing (QS), is an important mechanism of bacteria protection that enable bacteria to deliver special signal in response to changes of cell density in a certain environment, causing biofilm formation and other virulence factors [2]. When the bacterial population densities reach a certain threshold,

bacteria will regulate virulence, biofilm formation, luminescence and etc. Virulence expression and biofilm formation, protecting bacteria from adverse environment, are considered to be harmful for pathogen therapy and human healthy life [3]. The normal operation of QS system requires the participation of signal molecules, such as acylhomoserine lactone [4]. In a word, the reagents that can inhibit QS regulation will interfere with biofilm formation, which means that the reagent possess ability of QS inhibition (QSI) [5]. As we know, traditional Chinese medicine has been applied for antibacterial and anti-inflammatory for many years. However, studies on traditional Chinese medicine for drug discoveries have focused mainly on its antibacterial property. A few attention has been given to its quorum sensing inhibition and anti-biofilm activity [6]. Thus, the ability to disrupt this signaling process and QS signals may be advantageous in the removal or prevention of bacterial biofilm. Different Chinese medicine composition shows different effects on QS [7]. In order to provide references for QSI to control biofilm formation, the effects of traditional Chinese medicines and its inhibition mechanism of biofilm formation—QS on common bacterium biofilm are reviewed in this article.

2. Different QS on gram positive and gram negative bacterium

Quorum sensing, a cell-to-cell communication system, plays a key role in biofilm formation. When cell-to-cell signals arrive at a certain threshold, bacteria will secrete adhesion molecule and develop into biofilm with three dimensional structures [8]. Biofilm formation is a dynamic state which consists of (i) attachment, (ii) microcolony formation, (iii) maturation and (iv) dispersion [9, 10]. Quorum sensing affects the whole process of biofilm development. It is recognized that biofilms are mainly regulated by quorum sensing [11]. With quorum sensing response to the environment, bacterium occurs to the secretion of signaling molecules, the expression of the corresponding gene, and the secretion of extracellular polysaccharide (EPS) [12]. The study showed that the content of proteins, carbohydrates, and nucleic acids matrix increased significantly in the mature biofilm, since the biofilm matrix could protect the embedded cells from harmful conditions [13]. It has been reported that signal molecules play an initial role in QS system, and different signaling molecules are secreted by different bacterium: (i) N-Acyl homoserine lactones (AHLs), which are synthesized by LuxI-type enzyme, are mainly functioned in gram-negative bacterium, such as *Aeromonas hydrophila* [14] and *Pseudomonas aeruginosa* [15]. Most of gram-negative bacteria generate and detect several autoinducers, including C4-HSL, 3OH C4 HSL, lsovalery-HSL and etc. The chain length of AHLs can vary from 4 to 18 carbons, where oxidation status of the third carbon can change from fully reduced to fully oxidized [16]. The regulation of AHLs controls a series of target functions, such as biofilm formation, motility, fluorescence synthesis, expression of virulence genes and production of virulence factors [17]. When the concentration of signals arrives at a certain threshold, AHLs automatically enter the bacterium, binding to the cognate receptor to form an autoinducer-receptor complex, which causes the expression of functional gene (**Figure 1**). AHLs defective *P. aeruginosa* produced less virulence factors and less biofilm, and are diffusible signal molecules that may cause infections in human [16]. (ii) Gram-positive

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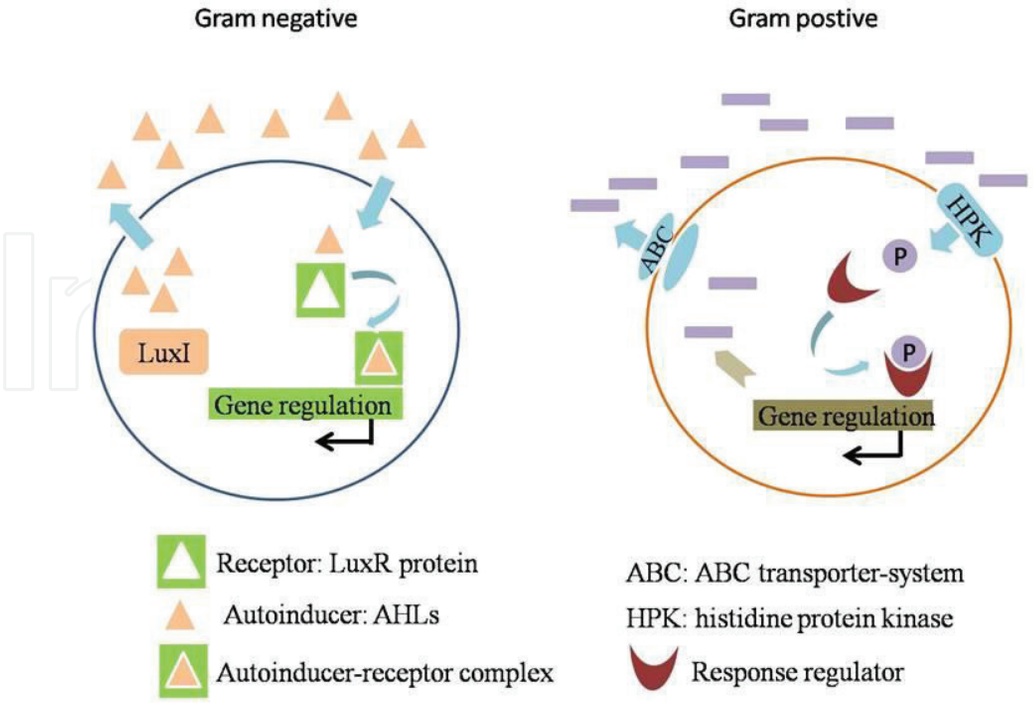

Figure 1. A graphic diagram of QS molecular signaling network.

bacterium is mainly regulated by autoinducing peptides (AIPs) [18]. Since AIPs cannot pass through the cytoderm by itself, bacterium response to the environment through two-component protein, transmit the signal to the cell. The activation of the receptor kinase takes place when reaching the threshold level. The sensor kinase protein can be activated and then phosphorylate the response regulator protein, which bind to the target promoter, and subsequently transcriptional activates the genes for the two-component regulatory system, resulting in autoinduction in a dynamic range [19]. The production of AIP is expressed by relevant genes, then releasing out of extracellular membrane (**Figure 1**). (iii) Autoinducer-2 (AI-2), a signal molecule produced by LuxS, widely existed in both gram-positive and gram-negative bacterium. AI-2, which involved in regulating the many bacterium biofilms, was thought to be a universal signal molecule [20]. It has been demonstrated that regulation of AI-2 plays a significant role in biofilm formation in many kinds of bacteria. DPD is known to undergo intra-molecular cyclization to form distinct biologically active signal molecules, which collectively called AI-2. Thus, the AI-2 signal should not be recognized as a single structure, but a family of isomers, each bacterium representing a different mode of perception [21]. (2S, 4S)-2-methyl-2, 3, 3, 4 tetrahydroxytetrahydrofuryl borate (S-THMF-borate) is the AI-2 signal of *Vibrionaceae*, while *S. Typhimurium* produces (2R, 4S)-2-methyl-2, 3, 3, 4- tetrahydroxytetrahydrofuran (R-THMF) as AI-2 signal. Quorum sensing pathways of AI-2 differs due to different bacterial species [22]. Most of the gram-positive bacteria are sensitive to penicillin, while gram-negative bacteria are not usually influenced by penicillin. Thus, the application of QS inhibitor is of great significance in biofilm inhibition and bacteria removal [23]. The process of QS can be disrupted by different mechanisms: (i) inhibiting the production of QS signal molecules (AHL, AI-2 and AIP), (ii) reducing the activity of QS signal molecules, (iii) degradation

of QS signal molecules, (iv) designing the analogues of signal molecules as QSI [24]. The regulation of QS may play a dual role on bacteria. Interferon with QS process can prevent bacteria from biofilm protection and virulence expression, but it is limited that antibiotic---antimicrobial cannot disrupt QS regulation. Traditional Chinese medicine is popular as QS inhibitors to disrupt QS signals, and thereby destroy bacterial biofilm and virulence expression without killing bacterium itself [25].

3. QSI on gram positive bacteria

Staphylococcus is one of the kinds as common and representative gram positive bacterial pathogens in the research of QS and biofilm development. Quorum-sensing regulation plays a vital role in the biofilm formation of many bacterial pathogens [26]. As previous mentioned, *LuxS* emzyme participated in the synthesis of AI-2, which had an indispensable impact on biofilm development of staphylococci quorum-sensing system. Δ*luxS* mutant strain shows more biofilm formation in vitro and enhanced virulence in *Staphylococcus epidermidis* of biofilm-associated infection. The inhibitors of *luxS* expression in vitro can be a promising QS inhibitor for the prevention of biofilm and virulence [27]. Burdock leaf ethanol fraction suppressed biofilm formation of *S. aureus* and *Listeria monocytogenes*. It was found that burdock leaf ethanol fraction (1.25 mg/ml) entirely inhibited (100%) the *S. aureus* biofilm formation, which was lower than MIC of the fraction. GC–MS/MS analysis shows that eight active compounds from burdock leaf fraction interfered with quorum sensing regulation and disrupted the composition of signaling molecules, thereby affecting the function of the quorum sensing system and disturbing biofilm formation. Eight active compounds should be exactly identified for real applications [28]. Later study analyzed 34% ethanol elution fraction of burdock leaf, found that 10 active compounds exhibited anti-biofilm activity, including chlorogenic acid, caffeic acid, p-coumaric acid, quercetin, ursolic acid, rutin, luteolin, crocin, benzoic acid and tenacissoside I. According to the metabolic fingerprints of burdock leaf fractions, chlorogenic acid and quercetin were demonstrated to be a potential antibiofilm of *Salmonellaty phimurium* compounds in burdock leaf [29]. *S. aureus* strains were tested for a relation between the ability of *S. aureus* attachment in polystyrene and the agr quorum-sensing system phenotype. Less of agr-positive strains cause biofilm formation, showing a vital impact of agr on biofilm development. Inhibitor of agr is as quorum-sensing blockers for *S. aureus* prevention [30]. The emergence of methicillin resistant *S. aureus* (MRSA) caused antibiotic invalidity and required new drugs for treating infectious diseases. *Chamaecyparis obtusa* essential oil had antibacterial effect against MRSA, finding *agr*A expression was inhibited with *C. obtusa* essential oil. Thus, *C. obtusa* essential oil regulates quorum-sensing to inhibit MRSA biofilm formation [31]. Study shows a certain concentration of *baicalein* (32 μg/mL and 64 μg/mL) clearly inhibited biofilm formation in vitro, and the combined use of vancomycin and baicalein generally enhance disruption of biofilms. 32 μg/mL and 64 μg/mL *baicalein* downregulate the quorum-sensing system regulators agrA and affecting biofilm development. Therefore, *baicalein* can inhibit the quorum sensing system while enhancing the permeability of *vancomycin* and reducing the production of staphylococcal enterotoxin A and α-hemolysin as well

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as inhibiting *S. aureus* biofilm formation. It is predicted that *baicalein* will be a novel drug candidate for *S. aureus* infections [32]. There are differences on the combination of ethanolic extracts of eight traditional Chinese medicines and four antibiotics. The ethanolic extracts of *Isatis tinctoria*, *Scutellaria baicalensis* and *Rheum palmatum* enhance the antimicrobial activity of four antibiotics on resistance of methicillin resistant *S. aureus* [33]. In summary, traditional Chinese medicine extracts inhibit QS and biofilm formation by controlling QS molecular signals, and usually regulating the cell to cell QS---AI-2. Recently, scientists deeded crude extract of anti-QS activity and Chinese herbal medicinal ingredient should be taken in-depth study in the future.

4. QSI on gram negative bacteria

Previous studies have demonstrated that a large majority of traditional Chinese medicine show great sensitivity to gram negative bacteria QS and biofilm. It is well-known on the research of QS that *Chromobacterium violaceum CV026* and *P. aeruginosa* PA01 is regard as two biomonitor strains to detect QSI on traditional Chinese medicine [34]. Twenty kinds of traditional Chinese medicine plants generally used in South-East Asia were screened for QS inhibition using two biomonitor strains, *P. aeruginosa* and *C. violaceum* CV026 PA01—gram negative bacteria. *C. violaceum* CV026, which can produce AHL signal molecule, produce purple pigment. *P. aeruginosa* PA01 control swarming through QS regulation. Thus, the change of purple pigment and swarming can be used to reflect the regulation of QS. This study found that 8 kinds of traditional Chinese medicine extracts possess QSI ability in *C.violaceum* CV026, and 4 kinds of traditional Chinese medicine extracts possess QSI ability in PA01. *Lilium brownie* and *Panax pseudoginseng* extracts possess QSI ability both in PA01 and CV026, which are meaningful for various biofilm inhibitions. The findings revealed that there are rich sources of plants on traditional Chinese medicine that contain components are able to break QS and QS-related virulence factors. However, the specific compounds and mechanism should be applied into deeper study [35]. Four organic solvents (n-hexane, DCM, methanol and 50% v/v acetone) were used to extract *Ficus carica* and *Perilla frutescens* in another study. The tests of *C. violaceum* CV026 and *P. aeruginosa* PA01 finds the extract of *F. carica* with dichloromethane and *of P. frutescens* with MeOH show the obvious inhibition of QS activity. Both of them display anti-QS ability. It is not sure the ingredient and inhibition concentration of crude extracts [36]. Study found that methanolic extract of *Phyllanthus amarus* interrupted the ability of *C. violaceum* CV026 to response towards exogenously supplied N-hexanoylhomoserine lactone, exhibiting the anti-quorum sensing activity. In addition, as the concentrations of the methanolic extracts of *P. amarus* increased, swarming motility, pyocyanin production and *lecA: lux* expressions in *P. aeruginosa* PA01 were reduced. Methanolic extracts of *P. amarus* may serve as promising anti-pathogenic drugs due to its anti-quorum sensing properties [37]. Ginseng aqueous extract at concentrations of 0.5–2.0% significantly inhibited *P. aeruginosa* biofilm formation. Oral administration of ginseng extracts in mice did not affect phagocytosis of a PAO1-filM mutant. According to previous study, Ginseng aqueous extract may prevent biofilm development by the regulation of QS [38]. Quorum sensing inhibitors could inhibit biofilm formation,

but the exact role of quorum sensing in various stages of biofilm attachment, maturation, and dispersal is not clear. In vitro the combination of antibiotic and QS inhibitor generally lead to increase bacterial lethality, compared with treatment by an antibiotic alone. The combination of tobramycin and baicalin hydrate reduced the *burkholderia cenocepacia* infection. Among this study, baicalin hydrate targets the acylhomoserine lactone-based QS system present in *B. cepacia* complex organisms [39]. Curcumin from *Curcuma longa* (turmeric), an anti-QS agent, was demonstrated to inhibit the biofilm formation of *E. coli*, *P. aeruginosa* PAO1, *Proteus mirabilis* and *Serratia marcescens*, interfering with their QS systems. The treatment with curcumin may attenuate the QS-dependent factors, including exopolysaccharide production, alginate production, swimming and swarming motility of uropathogens. Curcumin is as a QSI for urinary tract treatment [40]. Three anthocyanidins (pelargonidin, cyanidin and delphinidin) decreased the formation of *P. aeruginosa* PAO1 biofilm at low sub-MIC (0.125 MIC). Comparing with ampicillin and streptomycin, delphinidin show the most active of anti-biofilm activity. Water-soluble delphinidin structure could be used for the design of the novel and more effective anti-biofilm agents [41]. N-acylhomoserine lactone (AHL)-based QS plays vital role in biofilm formation and virulence expression. Three Chinese herbal ingredients namely are salicylic acid, tannic acid and trans-cinnamaldehyde, are as AHL synthase inhibitors to inhibit quorum sensing. Natural products targeting AHL synthase may provide anti-QS signal synthesis for prevention of pathogenic bacteria [42]. Traditional Chinese herbs could inhibit key biofilm-associated genes in *P. aeruginosa*. *Herba patriniae* extract showed significantly reduction on the biofilm formation and change the structure of the *P. aeruginosa* biofilms. Further studies showed *H. patriniae* extract promoted its swarming motility. The possible inhibition mechanism is that *H. patriniae* may regulate QS to control bacterial biofilm and swarming [43]. Study found that 30 mg/ml of *Melia dubia* seed ethanolic extract inhibited biofilm, hemolysis and swarming motility by 92.1, 20.9, and 48.52%, suggesting that the ethanolic extract possessed potency to restrain quorum sensing of uropathogenic *E. coli* [5]. It has been demonstrated that quorum sensing quenching effect exists in traditional Chinese medicine plants, foreseeing the tremendous prospect of QSI application on traditional Chinese medicine [44]. The concrete mechanism of traditional Chinese herbs is unsure, but some chemical components have been found in traditional Chinese herbs. It is believed that most of traditional Chinese medicines are as promising QS inhibitors for bacterial infection and biofilm disruption. Traditional Chinese medicines may be a novel material for infectious diseases and food safety with antibiotic.

5. Active constituent of traditional Chinese medicines

To sum up the above arguments, most researches of QSI on gram negative bacteria have been taken into deep consideration. It has been demonstrated that *P. aeruginosa* PA01 and *C. violaceum* CV026 can detect QSI of gram negative bacteria. Furthermore, the active constituent of traditional Chinese medicines also has been shown in the research. Most of active constituents are extracts of water-alcohol, since aqueous extracts are more effective on biofilm inhibition than organic solvent. *Panax pseudoginseng* extracts on mouse test and experiment in vitro

Type	Components of TCM	Bacterium	References
Flavonoids	Baicalein	*S. aureus*	[32]
	Baicalin	*B. cenocepacia*	[39]
	Anthocyanidin	*P. aeruginosa*	[41]
	Curcumin	*E. coli* & *P. aeruginosa*	[40]
Organic acid	Salicylic acid	*P. aeruginosa*	[42]
	Chlorogenic acid	*Salmonella*	[29]
Essential oil	*Chamaecyparis obtusa*	MRSA	[31]

Table 1. Effective components of TCM on bacterial biofilm.

found that aqueous extracts control biofilm formation by the regulation of QS [45]. In addition, methyl alcohol and ethyl alcohol, especially ethanol extract, are regarded as the common solvent to extract traditional Chinese medicines. Anthocyanidins, salicylic acid, baicalin and curcumin show inhibition of QS and QS-dependent biofilm, which can be assumed traditional Chinese medicines plants containing these components control QS regulation (**Table 1**). Now the combination of these components and antibiotic to kill bacteria are more effective that single antibiotic, so it is hopeful that the components can treat bacterial infection efficiently. Except for Staphylococcus, QSI on other gram negative bacteria is less mentioned. Ethanol extract of traditional Chinese medicines also possess strongly anti-biofilm property, but the mechanism of QS to biofilm inhibition is still unsure. Similarly, the active constituents on gram positive bacteria are flavonoid and organic acid, such as chlorogenic acid, chrysophanic acid and baicalein (**Table 1**). In summary, it is found that flavonoids extracted on TCM can be used as a hopeful QS inhibitor. Some of organic acid and essential oil not only reveal antibacterial property, but also show biofilm inhibition. Thus, it is believed that traditional Chinese medicines containing these components can hinder QS regulation and biofilm formation, and the plants with anti-QS and anti-biofilm property should be taken into consideration.

6. Conclusion

Different components of traditional Chinese medicine also exert anti-QS activities on the gram-positive bacteria and gram-negative bacteria. Gram-negative bacteria seems sensitive to QS inhibitor, since *C. violaceum* CV026 and *P. aeruginosa* PA01 are usually as biomonitor strains for detection of QSI [46]. Common pathogenic bacteria, such as *S. epidermidis* [47], *S. aureus* [48], *E. coli* [49] and *P. aeruginosa* [50], are mainly interfered with biofilm development and toxicant release by QS regulation. It has been found that the combination of traditional Chinese medicine and antibiotics could improve the antibacterial activity and remove bacterial biofilm effectively. Nowadays most of traditional Chinese medicines are screened for a pathogenic bacterium QSI. However, less reports show a broad spectrum QS activity on traditional Chinese medicines [51]. Therefore,

screening traditional Chinese medicine ingredients with anti-QS function, can treat the common pathogens biofilm and remove drug-resistant bacteria, being promising drugs for antibiotics auxiliary treatment. Antibiosis activity has been shown in many Chinese medicine ingredients, but now antibiotics are still the priority drugs for clinic treatment of infectious diseases. The following problems are for the better development of traditional Chinese medicine in the future. The first step is to explore QS mechanism of traditional Chinese medicine, enable traditional Chinese medicine ingredients inhibit the specific pathogens biofilm this phenomenon reach a theoretical stage thus people can have a more profound understanding. Secondly, the researches of traditional Chinese medicine still experience in a basically experimental stage. Experimental in vivo and clinical trials on traditional Chinese medicine should be strengthened, only which can lead to a further application. The last but not least, the specific efficacy of traditional Chinese medicine should be confirmed, and try to use new methods on extracting them. Since traditional Chinese medicine work usually by complex inducers, novel methods like metabolic engineering can be applied to increase the active ingredient dramatically in the meanwhile decrease the cost. It is hoped that traditional Chinese medicine could be used for food safety in the food industry.

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Conflict of interest

All authors declare that they have no conflict of interest.

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