Traditional Chinese Medicine is an Alternative Therapeutic Option for Treatment of *Pseudomonas aeruginosa* Infections

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*Pseudomonas aeruginosa* is an opportunistic pathogen causing life-threatening infections in cystic fibrosis patients and immunocompromised individuals, and it is a leading cause of nosocomial infections associated with significant morbidity and mortality. Treatment of *P. aeruginosa* infections is challenging due to the antibiotic resistance to most of the conventional antibiotics. Development of alternative therapeutic options is urgently demanded for the patients who have antibiotic-resistant infections. Traditional Chinese medicine (TCM) has a clinical history of thousands of years for prevention and treatment of infectious diseases in China, taking advantages of improving clinical outcomes, producing less side effects, inhibiting pathogen, and modulating host immunity. Recent research has revealed a variety of natural products derived from TCM showing significant antimicrobial effects on antibiotic-resistant strains of *P. aeruginosa* alone or combined with antibiotics in vitro or in animal models, suggesting that TCM is a promising complementary and alternative therapeutic approach for treatment of chronic *P. aeruginosa* infections. This review summarizes the recent findings attempting to dissect the mechanisms of TCM combating *P. aeruginosa* infections and highlights the molecular targets of TCM on *P. aeruginosa* and host.

**Keywords:** traditional Chinese medicine, *Pseudomonas aeruginosa*, quorum sensing, biofilm, bactericidal effects, immunomodulation

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**Abbreviations:** ABC, ATP-binding cassette; AHL, N-acyl homoserine lactone; C4-HSL, N-butanoyl-L-homoserine lactone; c-di-GMP, bis-(3′-5′)-cyclic dimeric guanosine monophosphate; CF, cystic fibrosis; EPS, extracellular polymeric substances; IQS, integrated quorum sensing system; MATE, multidrug and toxic compound extrusion family; MBC, minimum bactericidal concentration; MDR, multidrug-resistant; MFS, major facilitator superfamily; MIC, minimum inhibitory concentration; 3O-C12-HSL, N-(3-oxododecanoyl)-L-homoserine lactone; NNIS, national nosocomial infections surveillance; PQS, *Pseudomonas* quinolone signal; QS, Quorum sensing; RND, resistance-nodulation-division family; SMR, small multidrug resistance; TCM, traditional chinese medicine; WHO, world health organization.
INTRODUCTION

Pseudomonas aeruginosa is a Gram-negative, rod-shaped, aerobic bacterium that is commonly found in soil and aqueous environments, and is capable of surviving in harsh conditions with minimum nutrition requirement owing to its numerous metabolic pathways and regulatory genes (Moradali et al., 2017). Pseudomonas aeruginosa is also an opportunistic pathogen that can reside on human skin without causing harm in most healthy individuals but causes life-threatening acute infections in immunocompromised individuals and chronic infections in cystic fibrosis (CF) patients (Sadikot et al., 2005). The nosocomial infections caused by P. aeruginosa is a major problem in intensive care units with significant mortality and morbidity, which contributes 10–20% of total nosocomial infection cases (Bodey et al., 1983). According to the data from the National Nosocomial Infections Surveillance (NNIS) System, P. aeruginosa is the second most common cause of nosocomial pneumonia (17%), the third most common cause of urinary tract infection (7%), and the fourth most common cause of surgical site infection (8%) (Richards et al., 1999; National Nosocomial Infections Surveillance, 2004). Importantly, this bacterial pathogen is able to counter many of the currently available antibiotics such as aminoglycosides, quinolones and β-lactams through intrinsic and acquired resistance mechanisms (Pang et al., 2019). The intrinsic mechanisms include low permeability of outer membrane, expression of efflux pumps and production of antibiotic-inactivating enzymes. The acquired resistance mechanisms are achieved by mutational changes or acquisition of resistance genes via horizontal gene transfer, which make the empirical antibiotic treatment become increasingly more difficult and costly (Pang et al., 2019). In particular, the bacterial efflux pumps expelling a broad spectrum of antibiotics from the cell can greatly contribute to multidrug resistance, and they can be classified into five families: resistance-nodulation-division (RND) family, major facilitator superfamily (MFS), ATP-binding cassette (ABC) superfamily, small multidrug resistance (SMR) family, and multidrug and toxic compound extrusion (MATE) family (Sun J. et al., 2014). Furthermore, the RND efflux pumps play a key role in antibiotic resistance in P. aeruginosa, which confer the resistance to a variety of antibiotics including aminoglycosides, quinolones, β-lactams, macrolides, novobiocin, chloramphenicol, tetracyclines, trimethoprim, sulfonamides and lincomycin (Masuda et al., 2000; Terzi et al., 2014). Although the newly developed antibiotics with novel mechanisms of action have shown increased effectiveness in bacterial killing, P. aeruginosa can rapidly evolve resistance and escape from antibiotic targeting through chromosomal mutations, especially in presence of high concentration of antibiotics (Sanz-Garcia et al., 2018; Botelho et al., 2019). Pseudomonas aeruginosa is recognized as one of the six ESKAPE pathogens, including Enterococcus faecium (E), Staphylococcus aureus (S), Klebsiella pneumoniae (K), Acinetobacter baumannii (A), Pseudomonas aeruginosa (P) and Enterobacter Species (E), known for their antimicrobial resistance, and it has been listed by World Health Organization (WHO) as one of the priority bacterial pathogens for research and development of new antibiotics (Taconelli et al., 2018).

The exploration of complementary and alternative therapeutic strategies against P. aeruginosa infections has gained a lot of research attention over the past decade. Many alternative therapeutic approaches including suppression of quorum sensing, inhibition of bacterial lectins, iron chelation, phage therapy, vaccine strategy and nanoparticle application have been assessed and showed antimicrobial activity against multidrug-resistant (MDR) P. aeruginosa in vitro or in animal models (Pang et al., 2019). However, most of them are far from application due to many concerns regarding the cost, side effects and safety. Development of new therapeutic options is still urgently demanded. Traditional Chinese medicine (TCM) has a history over three thousand years, which is a comprehensive health care system comprising of herbal medicine, acupuncture, moxibustion, cupping, massage, and physical exercise (Tang et al., 2008). TCM has a unique therapeutic approach to prevent or treat many diseases such as cancer (Xiang et al., 2019), infectious diseases (Ma et al., 2019), cardiovascular diseases (Hao et al., 2017), Alzheimer’s disease (Howes et al., 2017) and diabetes (Tian et al., 2019) by maintaining or restoring the yin-yang balance. For instance, Liao et al. conducted a retrospective cohort study on 111,564 patients with newly diagnosed lung cancer and found that the patients who received TCM treatment had a 32% lower mortality rate compared to the non-TCM users (Liao et al., 2017). Cardiovascular diseases are the leading cause of death worldwide (Mc Namara et al., 2019). Clinical evidence indicated that the TCM Tiankuijiangya tablet displayed a significant anti-hypertensive effect, which significantly reduced the systolic and diastolic blood pressure in the patients with hypertension by 17.64 and 11.85 mm Hg, respectively, compared to placebo controls (Hao et al., 2017). Alzheimer’s disease is a progressive neurodegenerative disease that is irreversible form of dementia, causing impaired memory and cognitive functions (Cass, 2017). Le Bars et al. demonstrated that 27–37% of the patients with Alzheimer’s disease treated with EGB 761, an extract of Ginkgo biloba L. leaves (Ginkgoaceae), manifested improved cognitive performance and social functioning compared with placebo controls for 6 months to 1 year (Le Bars et al., 1997). More importantly, TCM has a curative effect on infectious diseases with a long history of rich experience, taking advantages of improvement of clinical outcomes, symptom relief, less side effects, pathogen inhibition, and promotion of host immunity during drug-resistant infections (Yu et al., 2017; Ma et al., 2019). Nowadays, a number of important drugs developed from TCM had significant achievements in public health by controlling many serious infectious diseases. For instance, a Chinese scientist Tu Youyou won the 2015 Nobel Prize for the discovery of artemisinin, a drug extracted from Artemisia annua L. (Compositae) leaves for malaria treatment (Tu, 2016). Furthermore, TCM has been clinically applied for treatment of acute or chronic pulmonary infections in China (Yu et al., 2014; Ma et al., 2019; Ren et al., 2020). During COVID-19 pandemic, greater than 85% of SARS-CoV-2-infected patients in China had received TCM treatment, and clinical evidence
indicated that the TCM herbal formulas Qing Fei Pai Du Tang and Lian Hua Qing Wen capsule could significantly alleviate the symptoms, reduce the inflammation, and promote the recovery of COVID-19 patients, and both TCM formulas displayed an effective rate over 90% for COVID-19 treatment (Yang Y. et al., 2020; Du et al., 2020; Li et al., 2020; Ren et al., 2020; Wu et al., 2020).

TCM has been reported to be capable of effectively controlling P. aeruginosa infections through suppression of quorum sensing (QS)(Wei et al., 2020), inhibition of biofilm formation, bactericidal effects, and modulation of host immunity (Hou et al., 2016) (Figure 1). The present review aimed to summarize and discuss the recent findings on the mechanisms of TCM underlying the prevention and treatment of P. aeruginosa infections. The scientific names and corresponding common names of the TCM presented in this review were summarized in Table 1.

**Suppression of Quorum Sensing**

QS is a bacterial cell-cell communication mechanism that regulates bacterial gene expression in a population density-dependent manner (Miller and Bassler, 2001). Pseudomonas aeruginosa utilizes four QS systems, LasI/LasR, RhlI/RhlR, PQS/MvrR and Iqs, to activate expression of many virulence factors, including pyocyanin, pyoverdine, elastases, alkaline protease, lectins, rhamnolipids and exotoxin A, which promote bacterial invasion and impair host immune response (Whiteley et al., 1999; Rutherford and Bassler, 2012; Lee et al., 2013). Specifically, P. aeruginosa pyocyanin is redox-active phenazine that is not only involved in maintaining bacterial fitness and facilitating biofilm formation but also interferes host cellular functions, such as electron transport, cellular respiration, ciliary function and inflammatory response (Rada and Leto, 2013; Jayaseelan et al., 2014). Pyoverdine is the major siderophore of P. aeruginosa that obtains extracellular iron from environment and host proteins, important for bacterial growth and virulence (Meyer, 2000). The elastases produced by P. aeruginosa are capable of damaging host tissues and degrading plasma proteins, including immunoglobulins, coagulation factors and complement proteins (Wretlind and Pavlovskis, 1983). Alkaline protease not only damages host tissues but also facilitates bacterial immune evasion through proteolytic cleavage of monomeric flagellin, thus impairing the Toll-like receptor five signaling (Bardoe et al., 2012). Lectins are adhesion molecules located on bacterial outer membrane, which recognize and bind to host glycoconjugates, allowing the attachment of bacteria to host cell surface (Imberty and Varrot, 2008). Rhamnolipids are a class of glycolipid biosurfactants mainly produced by P. aeruginosa, and they have multiple functions involved in modification of surface properties, modulation of bacterial swimming motility, disruption of biofilm and alteration of epithelial tight junction (Zulianello et al., 2006; Alhede et al., 2014). Exotoxin A is a highly toxic virulence factor of P. aeruginosa that is secreted into the extracellular environment and inhibits host protein synthesis by catalyzing ADP-ribosylation of elongation factor 2 (Michalska and Wolf, 2015).

The LasI/LasR and RhlI/RhlR are two canonical LuxI/LuxR QS circuits in P. aeruginosa, which catalyze the synthesis of N-acetyl homoserine lactone (AHL) autoinducers, N-(3-oxododecanoyl)-
L-homoserine lactone (3O-C12-HSL) and N-butanoyl-L-homoserine lactone (C4-HSL), respectively (Waters and Bassler, 2005; Lee and Zhang, 2015; Moradali et al., 2017). Subsequently, the signal molecules 3O-C12-HSL and C4-HSL bind to their respective cognate transcriptional regulators LasR and RhlR, and activate expression of QS-controlled virulence genes (Lee and Zhang, 2015). The Las system regulates the expression of virulence factors, including exotoxin A, LasA

| TCM scientific names | TCM common names |
|----------------------|------------------|
| Lonicera japonica Thunb. | Japanese honeysuckle, golden-and-silver honeysuckle |
| Scutellaria baicalensis Georgi | Baskal skullcap, Chinese skullcap |
| Forsythia suspensa (Thunb.) Vahl | Weeping forsythia, golden-bell |
| Pulvis Folisi Ursi | Bear bile |
| Cornu Saigae Tataricae | Antelope’s Horn |
| Artemisia argyi H.Lév. & Vaniot | Silvery wormwood or Chinese mugwort |
| Dictamnus dasycarpus Turcz. | Dittany bark |
| Solanum melongena L. | Eggplant |
| Astragalus mongholicus Bunge | Mongolian milkvetch |
| Angelica sinensis (Oliv.) Diels | Chinese angelica, Dang Gui |
| Artemisia annua L. | Sweet wormwood, sweet annie, annual wormwood |
| Reynoutria japonica | Japanese knotweed |
| Houttuynia cordata Thunb. | Fish mint, fish leaf, rainbow plant, chameleon plant, heart leaf, fish worm, Chinese lizard tail |
| Andrographis paniculata (Burm.f.) Nees | Creat, green chiretta, king of bitters |
| Prunus armeniaca L. | Apricot |
| Panax notoginseng (Burrk.) F.H.Chen | Chinese ginseng, notoginseng |
| Areca catechu L. | Betelnut palm |
| Patrinia scabiosifolia Link | Patrina, eastern valerian |
| Patrinia villosa Juiss. | Patrina |
| Fraxinus chinensis subsp. rhynchophylla (Hance) A.E.Murray | Chinese ash |
| Cullen corylifolium (L.) Medik | Babchi, Bakuchi |
| Viola mandshurica W.Becker | Manchurian Violet, sumire |
| Paeonia lactiflora pall. | Chinese peony |
| Soliva miliorhiza Bunge | Red sage, Chinese sage, Tanshen, Danshen |
| Gloeotis sinensis Lam. | Chinese honey locust |
| Glycyrrhiza glabra L. | Liquorice, licorice |
| Pyryos petolosa (Christ et Bar,) Ching | Tongue fern, Japanese felt fern |
| Zingiber striolatum Diels | Yang-he |
| Mentha canadenis L. | American wild mint |
| Paeonia × suffruticosa Andrews | Moutan peony |
| Atractylodes lancea (Thunb.) DC. | Southern tsangshu |
| Phellodendron chinense C.R.Schneid | Chinese corktree |
| Monochasma savatiere Franch. ex Maxim. | Not applicable |
| Chimonanthus praecox (L.) Link | Wintersweet |
| Morus nigra L. | Black mulberry |
| Trichosanthes kirilowii Maxim. | Chinese snake gourd |
| Prunus mume (Siebold) Siebold & Zucc. | Chinese plum |
| Neolitsea cassia (L.) Kosterm | Grey bollywood |
| Sophora tonkinensis Gagnep. | Vietnamese sophora |
| Iphegenia indica (L.) A.Gray ex Kunth | Not applicable |
| Omphalia lapidescens Schroet | Omphalia, Leiwan, Thunder Ball |
| Fritillaria thunbergii Miq. | Zhejiang trillary |
| Echinops latifolius Tausch | Not applicable |
| Panax quinquefolius L. | American ginseng |
| Coix lacryma-jobi var. ma-yuen (Rom.Caill.) Stapf | Not applicable |
| Ephedra sinica Stapf | Chinese ephedra |
| Gypsum Fibrosum | Gypsum |
| Pheretima | Earthworm |
| Arctium lappa L. | Greater burdock |
| Descurainia sophia (L.) Webb ex Prantl | Flixweed |
| Bovis Calculus Artificatus | Artificial ox bezoar |
| Pinellia ternata (Thunb.) Makino | Crow-dipper |
| Ziziphus jujuba Mill. | Chinese jujube |
| Bupleurum chinense DC. | Chinese thoroughwax |
| Panax ginseng C.A.Mey. | Asian ginseng, Chinese ginseng, Korean ginseng |
| Glycyrrhiza glabra L. | Liquorice, licorice |
| Zingiber officinale Roscoe | Garden ginger |
protease, LasB elastase and alkaline protease, whereas the Rhl system regulates the expression of the pyocyanin, LasB elastase, alkaline protease, LecA and LecB lectins, and rhamnolipids (Pearson et al., 1997; Glessner et al., 1999; Winzer et al., 2000; Kariminik et al., 2017). Moreover, Las system has shown to positively regulate Rhl system (Lee and Zhang, 2015). By contrast, the third QS signal, Pseudomonas quinolone signal (PQS), structurally identified as 2-heptyl-3-hydroxy-4-quinolone, is synthesized through multiple operons, including pqsABCDE, phnAB and pqsH, and it binds to the receptor PqsR, also known as MvfR, to activate production of PQS itself and virulence factors, such as LasB elastase, rhamnolipids, lecA lectin and pyocyanin (Lee and Zhang, 2015; Lin et al., 2018). Furthermore, the PQS synthesis was found to be negatively regulated by Rhl system and positively regulated by Las system, whereas PQS positively regulated Rhl system (McKnight et al., 2000; Wade et al., 2005). The fourth QS signal, integrated quorum sensing system (IQS), structurally characterized to be 2-(2-hydroxyphenyl)-thiazole-4-carbaldehyde, is synthesized via a gene cluster ambBCDE, and it is responsible for integrating bacterial stress response with the QS network (Lee and Zhang, 2015). In addition, IQS was identified to be tightly controlled by Las system under rich culture conditions but is activated by phosphate limitation.

**TABLE 2 |** Summaries of the TCM for suppression of *P. aeruginosa* QS.

| TCM                                                     | Suppression of QS | Mechanisms                                                                 | References               |
|---------------------------------------------------------|-------------------|-----------------------------------------------------------------------------|--------------------------|
| Tanreqing                                               | Las, Rhl and PQS  | Repression of QS two-component systems GacS/GacA and PprA/PprB             | Yang et al. (2020a)      |
| Dry distillation oil from the leaf of Artemisia argyi H.Lév. & Vaniot, the root bark of Dictamnus dasycarpus Turcz. and the root of Solanum melongena L. | PQS               | Interruption of the binding of PqsR to pqsA promoter                       | Wei et al. (2020)        |
| Qi Gui Yin                                              | Not specified     | Downregulation of expression of PhzA, PhzB, PhzM and MetQ1                 | Ding et al. (2021a)      |
| Sodium houtuyfonate from Houttuynia cordata Thunb.     | Las               | Inhibition of LasI and LasR expression                                       | Wu et al. (2014)         |
| Baicalin from Scutellaria baicalensis Georgii           | Las, Rhl and PQS  | Downregulation of transcription of lasI, lasR, rhl, rhlR, pqsR and pqsA   | Luo et al. (2017)        |
| Andrographolide compounds from Andrographis paniculata (Burm.f.) Nees | Las and Rhl       | Inhibition of lasI, lasR, rhl and rhlR expression                           | Banerjee et al. (2017); Tan Lim et al. (2021) |
| Seed of Prunus armeniaca L., flower and root of Panax notoginseng (Burkill) F.H.Chen, and seed of Areca catechu L. | Not specified | Impairment of *P. aeruginosa* swarming motility                              | Koh and Tham, (2011)     |
stress, subsequently upregulating Rhl and PQS systems (Lee et al., 2013). The P. aeruginosa QS systems were illustrated in Figure 2.

Many Chinese herbal medicines have been reported to possess anti-QS activities (Table 2) (Koh and Tham, 2011). Tanreqing injection has been widely used as an herbal formula for the treatment of viral pneumonia in China, which consists of the extracts from the flower bud of *Lonicera japonica* Thunb. (Caprifoliaceae; *Lonicerae japonicae Flos*), the root of *Scutellaria baicalensis* Georgi (Lamiaceae; *Scutellariae Radix*), the fruit of *Forsythia suspensa* (Thunb.) Vahl (Oleaceae; *Forsythiae Fructus*), Pulvis Felliis Ursi (Bear bile), and Cornu Saigae Tataricae (Antelope’s Horn) (Liu et al., 2020). Moreover, the side effects of Tanreqing injection include anaphylaxis, drug eruption, nausea, vomiting and arrhythmia (Liu et al., 2020). A recent study by Yang et al. showed that the five components of Tanreqing played the major role in inhibiting the three P. aeruginosa systems, Las, Rhl and PQS, through repression of the upstream two-component systems GacS/GacA and PprA/PprB, leading to decreased expression of QS-regulated virulence genes in P. aeruginosa. Furthermore, the authors demonstrated a Caenorhabditis elegans-P. aeruginosa slow-killing assay and found that the survival rate of the C. elegans fed with Tanreqing-treated P. aeruginosa was significantly increased by 30% compared to those fed with untreated P. aeruginosa, suggesting that Tanreqing reduced the virulence of P. aeruginosa and protected C. elegans from killing (Yang W. et al., 2020). However, the original concentration of Tanreqing injection was not provided in this study. Wei et al. introduced a dry distillation oil prepared from a mixture of the leaf of *Artemisia argyi* H.Lév. & Vaniot (Compositae; *Artemisiae argyi Folium*), the root bark of *Dictamnus dasyacarpus* Turcz. (Rutaceae, *Dictamni radicis cortex*) and the root of *Solanium melongena* L. (Solanaceae) with a mixing ratio of 1 : 1 : 2 (1 part of *Artemisiae argyi Folium*, 1 part of *Dictamni radicis cortex*, and 2 parts of the root of *Solanium melongena* L.) by heating in a flask with condenser tube at 350°C, and they found the oil was able to inhibit P. aeruginosa PQS system by interrupting the binding of the PQS receptor PqsR to its corresponding promoter pqsA (Wei et al., 2020). No side effects of the three TCM herbs have been reported. Qi Gui Yin is a mixture of Chinese herbal medicines, comprising of the root of *Astragalus mongholicus* Bunge (Leguminosae, *Astragali Radix*), the root of *Angelica sinensis* (Oliv.) Diels (Asteraceae, *Angelicae sinensis Radix*), the flower bud of *L. japonica* Thunb. (Caprifoliaceae; *Lonicerae Japonicae Flos*), *Artemisia annua* L. (Compositae), and the root and rhizome of *Reynoutria japonica* Houtt. (Polygonaceae; *Polygonyi Cuspidati Rhizoma et Radix*) at a ratio of 12.3: 3:2:2, and it has been found to effectively eliminate antibiotic-resistant *P. aeruginosa* strains (Kong et al., 2015; Ding et al., 2021a). The safety of Qi Gui Yin decoction has been tested on rats, and no toxic and side effects were observed at a dose of 14.3 g for every kg of body weight for 13 weeks (Ding et al., 2021b). Ding et al. analyzed the protein expression profiles of the *P. aeruginosa* strains treated or not treated with Qi Gui Yin decoction, and found the QS-associated proteins, PhzA, PhzB, PhzM and MetQ1, were downregulated in Qi Gui Yin-treated strains. Further study demonstrated that the serum from Qi Gui Yin-treated rats could effectively reduce the resistance of *P. aeruginosa* to imipenem (Ding et al., 2021a). However, the mechanisms underlying the Qi Gui Yin-mediated QS inhibition were not specified in this study, and the metabolites in the serum of Qi Gui Yin-treated rats need to be further characterized. Sodium houttuynionate is a bioactive compound derived from *Houttuynia cordata* Thunb. (Saururaceae), a well-known TCM botanical drug in East Asia. A study by Wu et al. reported that Sodium houttuynionate was able to inhibit the expression of *P. aeruginosa* LasI and LasR, leading to impaired production of QS-regulated virulence factors, including pyocyanin and LasA (Wu et al., 2014). It is noteworthy that *H. cordata* Thunb. may cause allergic reactions in some people (Shingnaisui et al., 2018). Baicalin is an active compound purified from *S. baicalensis* Georgi, a famous TCM known for its antioxidant, anti-inflammatory and anticoagulant properties (Kong et al., 2014; Lee et al., 2015). Furthermore, baicalin has been found to inhibit the Las, Rhl and PQS systems of *P. aeruginosa* by downregulating the expression of QS regulatory genes, including lasI, lasR, rhlI, rhlR, pqsR and pqsA (Luo et al., 2017). However, *S. baicalensis* Georgi may cause stomach discomfort, diarrhoea and drug eruption in individual patients (Zhao et al., 2019). *Andrographis paniculata* (Burm.f.) Nees (Acanthaceae) is a medicinal plant widely used in many Asian countries, including China, India and Thailand, and it has been extensively applied in treatment of upper respiratory infections (Jiang et al., 2021), and it has no obvious toxic and side effects on human and animals (Jayakumar et al., 2013). Zhang et al. identified that the andrographolide compounds, andrographolide, 14-deoxyandrographolide, 14-deoxy-12-hydroxyandrographolide and neoandrographolide, from *A. paniculata* (Burm.f.) Nees suppressed the gene expression of LasR in the clinical isolates of *P. aeruginosa* PA22 and PA247 (Tan Lim et al., 2021). Additionally, Banerjee et al. indicated that the chloroform extract of *A. paniculata* (Burm.f.) Nees effectively decreased the expression of lasI, lasR, rhlI and rhlR by 61, 75, 41, and 44% in *P. aeruginosa* PAO1, respectively (Banerjee et al., 2017). QS has been found to regulate bacterial swarming motility, which is a flagella-driven movement of bacterial cells on a moist surface (Daniels et al., 2004). Koh et al. used swarming motility as an indicator of QS activity to screen the QS inhibitory effects of TCM plants, and they found that acetone and water (1:1 ratio) extracts from the seed of *Prunus armeniaca* L. (Rosaceae), the flower and root of *Panax notoginseng* (Burkill) F.H.Chen (Araliaceae), and the seed of *Areca catechu* L. (Areaceae) impaired the swarming motility of *P. aeruginosa* PAO1 (Koh and Tham, 2011). However, the inhibitory mechanisms of these TCM botanical drugs were not addressed. Additionally, the side effects of *P. armeniaca* L. remain unknown, whereas *P. notoginseng* (Burkill) F.H.Chen has shown toxic effects on liver and kidney (Wang et al., 2016), and *A. catechu* L. may cause diarrhea, stomach discomfort and nausea (Samappito et al., 2012).

**Inhibition of Biofilm**

A biofilm is an aggregate of microorganisms in which cells adhere to each other on a static surface, and the adherent cells are
embedded within a self-produced matrix of extracellular polymeric substances (EPS), consisting of polysaccharides, proteins, DNA and lipids (Donlan, 2002). Generally, biofilm formation can be divided into five steps: 1) initial attachment of planktonic bacteria to a surface; 2) microcolony formation; 3) formation of matrix by producing EPS; 4) maturation of biofilm into a three-dimensional structure; 5) detachment and dispersion of the biofilm (Figure 3) (Jamal et al., 2018; O’Toole et al., 2000). Bacteria in biofilm are more resistant to antimicrobial agents than planktonic cells because of the poor antibiotic penetration, reduced metabolic and growth rates, induction of adaptive stress responses, and formation of persister cells in biofilm microenvironment (Stewart, 2002; Hoiby et al., 2010). Importantly, approximately 80% of chronic infections are associated with biofilm formation (Jamal et al., 2018). Disruption of biofilm is critical for controlling persistent bacterial infections.

Pseudomonas aeruginosa is a major cause of chronic respiratory infections in CF patients, leading to declined pulmonary function and ultimate mortality (Lyczak et al., 2002). Formation of P. aeruginosa biofilm is regulated by QS systems, two-component regulatory systems, exopolysaccharides and bis-(3′–5′)-cyclic dimeric guanosine monophosphate (c-di-GMP) (Rasamiravaka et al., 2015). Two-component regulatory systems consist of a sensor kinase and a response regulator, which are essential for signaling transduction in bacteria in response to environment stimuli (Mikkelsen et al., 2011). The two-component regulatory systems GacS/GacA and RetS/LadS are responsible for regulation of P. aeruginosa biofilm formation (Rasamiravaka et al., 2015). The exopolysaccharides produced by P. aeruginosa include alginate, Pel and Psl, which contribute to biofilm development and stabilize biofilm architecture (Ghafoor et al., 2011). The c-di-GMP is a nucleotide second messenger that regulates plentiful cellular processes in bacteria, and high levels of c-di-GMP repress bacterial motility and induce production of exopolysaccharides, which promote P. aeruginosa biofilm formation (Ha and O’Toole, 2015).

TCM botanical drugs have manifested inhibitory effects on P. aeruginosa biofilm (Table 3) (Fu et al., 2017; Wang T. et al., 2019; Xu Z. et al., 2019). Herba patriniae, also known as Bai Jiang Cao, is a TCM for heat-clearing and detoxication, consisting of two species of Caprifoliaceae family, Patrinia scabiosifolia Link (Caprifoliaceae) and Patrinia villosa Juss. (Caprifoliaceae) (Gong et al., 2021). Fu et al. reported that the water extract of Herba patriniae was able to disrupt the biofilm formation and alter the biofilm structure of P. aeruginosa PAO1 through inhibition of exopolysaccharide production and biofilm-associated genes including algU, pslM, pslA, algA, and bdlA (Fu et al., 2017). However, the authors did not specify the species of Herba patriniae in this study. Additionally, the mild side effects including temporary leukopenia, dizziness and nausea could be found in the patients treated with inappropriate dose of Herba Patriniae (Gong et al., 2021). As mentioned earlier, sodium houttuyfonate from H. cordata Thunb. could inhibit P. aeruginosa QS systems (Wu et al., 2014). A study by Wang et al. identified that sodium houttuyfonate was able to penetrate P. aeruginosa biofilm and suppress biofilm dispersion by inhibiting the expression of the key biofilm regulator BdlA (Wang T. et al., 2019). Moreover, Wu et al. set up a rat model of P. aeruginosa biofilm infections in airway, and they found that sodium houttuyfonate destructed biofilm formation and the sodium houttuyfonate-treated rat displayed reduced symptoms and pulmonary inflammation (Wu et al., 2016). Zeng et al. examined the effects of several TCM chemical compounds on P. aeruginosa biofilm and found that the Baicalin and Baicalein from S. baicalensis Georgi, the Esculetin and Esculin from F. chinensis subsp. rhynchophylla (Hance) A.E.Murray (Oleaceae), and the Psoralen from C. corylifolium (L.) Medik (Leguminosae) could significantly reduce the mass of P. aeruginosa biofilm (Zeng et al., 2008). The mechanisms involved in the reduction of biofilm biomass by the three active compounds need to be further explored. Furthermore, the side effects of F. chinensis subsp. rhynchophylla (Hance) A.E.Murray and C. corylifolium (L.) Medik have not yet been clinically

PICTURE 3 | Schematic illustration of the steps involved in P. aeruginosa biofilm formation. The formation of P. aeruginosa biofilm has five steps: (A) initial attachment of planktonic bacteria to a surface; (B) microcolony formation; (C) formation of EPS matrix; (D) development and maturation; (E) detachment and dispersion.
reported. *Ligustrum sinense* Lour. (Oleaceae) is an evergreen shrub used in TCM for their anti-oxidative, anti-tumor, and diuretic properties (Ouyang et al., 2003; Yang et al., 2013), and the side effects of this TCM are not clear. A previous study revealed that the water-soluble extract of *L. sinense* Lour. (4 mg/ml) could strongly decrease the biomass of *P. aeruginosa* biofilm, and 1.35 mg/ml of this extract displayed a synergistic inhibitory effect with gentamycin sulphate (2 mg/ml) on the growth of *P. aeruginosa*.

**Table 3** | Summaries of the TCM for inhibition of *P. aeruginosa* biofilm.

| TCM | Effects on biofilm | Mechanisms | References |
|-----|--------------------|------------|------------|
| *Patrina scabiosifolia* Link and *Patrina villosa* Juss. | Disruption of biofilm formation and alteration of biofilm structure | Inhibition of exopolysaccharide production, and the expression of algU, psLM, pepA, algA, and bdiA | Fu et al. (2017) |
| Sodium houttuyniate from *Houttuynia cordata* Thunb. | Suppression of biofilm formation and dispersion | Not specified | Wu et al. (2016); Wang et al. (2019a) |
| Baicalin and Baicalen from *Scutellaria baicalensis* Georgi | Reduction of biofilm biomass | Not specified | Zeng et al. (2008) |
| Esculetin and Esculin from *Fraxinus chinensis* subsp. rhynchophylla (Hance) A.E.Murray | Reduction of biofilm biomass | Not specified | Zeng et al. (2008) |
| Paeoalex from *Paorea corylifolia* L. | Reduction of biofilm biomass | Not specified | Yang et al. (2013) |
| *Ligustrum sinense* Lour. | Reduction of biofilm biomass | Not specified | Xu H. et al. (2019) |
| Lonicerin from *Shuanguanglian* | Inhibition of biofilm formation | Inhibition of alginate secretion by sequestering AlgE | Shen et al. (2019) |
| Qingre Baidu mixture | Inhibition of biofilm development | Downregulation of Al2 | Ding et al. (2021a) |
| Qi Gui Yin | Inhibition of biofilm formation | Downregulate of expression of ArcA and IscU | Banerjee et al. (2017); Tan Lim et al. (2021) |
| Andrographolide compounds from *Andrographis paniculata* (Burm.f) Nees | Suppression of biofilm formation | Not specified | |

**Bactericidal Effects**

A variety of TCMs have shown bactericidal effects against respiratory pathogens by directly killing or inhibiting their growth (Ooi et al., 2006; Liu et al., 2007; Yamada et al., 2016), and some of them could enhance the in vitro antibacterial effects of antibiotics in treatment of MDR *P. aeruginosa* infections (Liu et al., 2007; Xu H. et al., 2019), possibly due to the enhanced stability of antibiotics by the reductive components of TCM (Gim et al., 2009; Chen et al., 2013; Matkowski et al., 2013; Sun W. et al., 2014; Chen et al., 2020), and the inhibitory effects of TCM on bacterial efflux pumps (Huang et al., 2015; Wang et al., 2018; Wang J. et al., 2019), suggesting that TCM could be a good alternative or complement for synthetic antibiotics. The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values of TCM against *P. aeruginosa* were summarized in Table 4.

**Pyrosia petiolosa** (Christ et Bar.) Ching (Polypodiaceae) is a pteridophyte used as a TCM for the treatment of nephritis and bronchitis without causing adverse reactions (Cheng et al., 2020), and the ethanol extract of *P. petiolosa* (Christ et Bar.) Ching has shown significant inhibitory effects on *P. aeruginosa* ATCC27853 with an MIC and an MBC both at 5 mg/ml (Cheng et al., 2014). *Zingiber striolatum* Diels (Zingiberaceae) is a perennial plant widely distributed in southern China, and it has been used for many medicinal purposes for its antioxidant and antimicrobial properties without causing side effects (Shariff-Rad et al., 2017). Tian et al. characterized the chemical components of the essential oil extracted from the rhizomes of *Z. striolatum* Diels by hydrodistillation, including β-phellandrene, sabine, β-pinene, geranyl linalool, terpinen-4-ol, a-pinene and crypton, and determined the MIC of the essential oil against *P. aeruginosa* to be 3.12 mg/ml (Tian et al., 2020).
TABLE 4 | Summaries of the bactericidal effects on TCM on P. aeruginosa.

| TCM | MIC | MBC | References |
|-----|-----|-----|------------|
| Pyrosia petiolaris (Christ et Bar.) Ching | 5 mg/ml | 5 mg/ml | Cheng et al. (2014) |
| Rhizomes of Zingiber striolatum Diels | 3.12 mg/ml | Not specified | Tian et al. (2020) |
| Pentaherb formula composed of the flower bud of Lonicera japonica Thunb., Mentha canadensis L., the root bark of Paeonia × suffruticosa Andrews, Atractylodes lanceae (Thunb.) DC. and the bark of Phellodendron chinense C.K.Schneid | 1 mg/ml | 125 mg/ml | Hon et al. (2018) |
| Phenylethanoid glycosides from Monochasma savatieri Franch. ex Maxim. | 0.5 mg/ml | 2 mg/ml | Liu et al. (2013) |
| Sesquiterpenoids of Chimonanthus praecox (L.) Link | 207.9–249.1 ug/ml | Not specified | Lou et al. (2018) |
| Flavonoids from Morus nigra L. | 2–6 mg/L | Not specified | Chen et al. (2017) |
| Root bark of Paeonia × suffruticosa Andrews | 15–20 mg/L | Not specified | Liu et al. (2007) |
| Ripe pericarp of Trichosanthes kirilowii Maxim. | 1–3 mg/L | Not specified | Liu et al. (2007) |
| Unripe fruit of Prunus mume (Siebold) Siebold & Zucc. | 4–6 mg/L | Not specified | Liu et al. (2007) |
| Neolitsea cassia (L.) Kosterm. | 25–30 mg/L | Not specified | Liu et al. (2007) |
| Root and rhizome of Sophora tonkinensis Gagnep. | >30 mg/L | Not specified | Liu et al. (2007) |
| Bulb of Iphigenia indica (L.) A.Gray ex Kunth | >30 mg/L | Not specified | Liu et al. (2007) |
| Fruit of Forsythia suspensa (Thunb.) Vahl | >30 mg/L | Not specified | Liu et al. (2007) |
| Omphalia lapidescens Schroet | >30 mg/L | Not specified | Liu et al. (2007) |
| Bulb of Fritillaria thunbergii Miq. | 15–20 mg/L | Not specified | Liu et al. (2007) |
| Root of Salvia miltiorrhiza Bunge | 20–25 mg/L | Not specified | Liu et al. (2007) |
| Fuzheng Jiedu Huayu | 200 mg/ml | Not specified | Xu H. et al. (2019) |

Andrews (Paeoniaceae), Atractylodes lancea (Thunb.) DC. (Compositae) and the bark of Phellodendron chinense C.K.Schneid (Rutaceae) with a mixture ratio of 2:1:2:2:2, and it has been shown to effectively treat atopic dermatitis without causing side effects (Hon et al., 2007). Hon et al. determined the MIC and MBC of the water extracts of the Pentaherb formula against P. aeruginosa ATCC 27853 to be 1 mg/ml and 125 mg/ml, respectively (Hon et al., 2018). Monochasma savatieri Franch. ex Maxim. (Orobanchaceae) is a perennial botanical drug widely used in TCM for treatment of many inflammatory diseases, and no toxic effects of this botanical drug have been documented (Gao H. et al., 2017). Liu et al. found that P. aeruginosa ATCC 27853 was sensitive to the phenylethanoid glycosides from M. savatieri Franch. ex Maxim., which had an MIC of 0.5 mg/ml and an MBC of 2 mg/ml (Liu et al., 2013). Furthermore, they demonstrated that the survival rates of the mice pretreated with phenylethanoid glycosides at a dose of 180 mg/kg for every kg of body weight were significantly increased by 75% compared to untreated mice following P. aeruginosa intraperitoneal infections, and the pre-treatment of this drug could reduce the bacterial burden in the lung tissues of the P. aeruginosa lung-infected mice (Liu et al., 2013). Chimonanthus praecox (L.) Link (Calycanthaceae), also known as wintersweet, is a deciduous shrub used for treatment of coughs, rheumatic arthritis, throat wounds, dizziness, nausea and fever, and its side effects are not well-characterized (Kitagawa et al., 2016). The sesquiterpenoids isolated from the ethyl acetate extract of C. praecox (L.) Link stems and roots have been reported to possess antibacterial effects against P. aeruginosa ATCC 10145 with an MIC of 207.9–249.1 ug/ml (Lou et al., 2018). Mulberry is not only a fruit with a lot of nutrients but also a TCM comprising of many antioxidant and anti-inflammatory compounds (Huang et al., 2013), and the MBC of the flavonoids from the fruits of black mulberry Morus nigra L. (Moraceae) against P. aeruginosa was assessed to be 2 mg/ml (Chen et al., 2017). A research group from Taiwan discovered 10 ethanol extracts of Chinese herbal medicines including the root bark of Paeonia × suffruticosa Andrews, the ripe pericarp of Trichosanthes kirilowii Maxim. (Cucurbitaceae; Trichosanthis Pericarpium), the unripe fruit of Prunus mume (Siebold) Siebold & Zucc. (Rosaceae), Neolitsea cassia (L.) Kosterm. (Lauraceae; Ramulus Cinnamomi), the root and rhizome of Sophora tonkinensis Gagnep. (Leguminosae; Sophorae Tonkinensis radix et rhizome), the bulb of Iphigenia indica (L.) A.Gray ex Kunth (Colchicaceae), the fruit of F. suspensa (Thunb.) Vahl, Omphalia lapidescens Schroet (Leiwan), the bulb of Fritillaria thunbergii Miq. (Liliaceae; Fritillariae Bulbus), and the root of S. miltiorrhiza Bunge possessed a broad-spectrum of bactericidal activity against antibiotic-resistant P. aeruginosa strains. Among these herbal medicines, N. cassia (L.) Kosterm. was found to synergize with tetracycline, gentamycin and streptomycin to inhibit P.
TABLE 5 | Summaries of TCM-modulated host immune responses during P. aeruginosa infections.

| TCM                          | Effects on immune responses                  | Mechanisms                                                                                          | References                   |
|------------------------------|----------------------------------------------|------------------------------------------------------------------------------------------------------|------------------------------|
| Qingfei                      | Reduction of lung inflammation                | Suppression of P38/AKT and Ras/MAPK pathways, and impairment of production of TNF-α, IL-6 and RANTES | Hou et al. (2016)            |
| Xiaoan Wan                   |                                              | Not specified                                                                                       | Kawakita et al. (1987a)      |
| Xiao Chai Hu Tang            | Accumulation of polymorphonuclear leukocytes and promotion of the phagocytic activity of macrophages | Inhibition of ERK pathway and NF-κB activation                                                      | Li et al. (2017)             |
| Shufengjiedu capsule          | Aleavition of lung inflammation              | Enhancement of fibroblast proliferation and collagen production, and suppression of skin inflammation | Huang et al. (2004); Yan et al. (2015); Imai et al. (2019) |
| Shiunko                      | Promotion of epithelization in skin wound     | Enhancement of antibody reactivity to β-lactamases and reduction of the levels of IL-1β and Th1/Th2 ratio | Kong et al. (2015)           |
| Qi Gui Yin                   | Increase of B cell response and downregulation of inflammation | Uregulation of the expression of HIF-1α, HIF-2α and VEGF                                            | Shan et al. (2019)           |
| Qingre Baidu mixture         | Promotion of angiogenesis and wound healing   |                                                                                                      |                              |

**Immunomodulation**

A tightly controlled immune response ensures an effective host defense against microbial infection and maintenance of tissue homeostasis (Liu and Cao, 2016). Excessive immune response causes host tissue damage, septic shock and ultimately death (Bortolotti et al., 2018). On the other hand, deficient immune response results in chronic and persistent bacterial infections (Smith et al., 2009). Immunomodulation is an important function of TCM, which activates or suppresses the immune responses of a variety of immune cells, including macrophages (Jian et al., 2019), dendritic cells (Chen et al., 2006), T cells (Guo et al., 2015), B cells (Kawakita et al., 1987a) and NK cells (Hoffman et al., 2020). The immunomodulatory effects of TCM on host immunity in the context of P. aeruginosa infections have been evaluated in past decade (Table 5)(Kong et al., 2015; Hou et al., 2016; Li et al., 2017).

Qingfei Xiaoan Wan, a TCM pill, consists of E. sinica Stapf, Gypsum Fibrosum, Pheretima (earthworm), the ripe fruit of Arctium lappa L. (Compositae; Arctii Fructus), the seed of Descurainia sophia (L.) Webb ex Prantl (Brassicaceae), Bovis Calculus Artificius (Artificial ox bezoar), the seed of P. armeniaca L. and Cornu Saigae Tataricae (Hou et al., 2016), and it has been used in China for treatment of asthma and respiratory tract infections without inducing obvious side effects (Zhao et al., 2013). A study by Hou et al. evaluated the effects of Qingfei Xiaoan Wan suspended in distilled water on a mouse model of P. aeruginosa-induced acute pneumonia, and they demonstrated that the oral administration of Qingfei Xiaoan Wan (18 g for every kg of body weight per day) for 1 week could reduce the P. aeruginosa PAK-induced lung inflammation by decreasing the production of cytokines (TNF-α and IL-6) and chemokine (RANTES) in lung tissues, significantly ameliorating lung injury. Importantly, the authors identified arctigenin, cholic acid, chlorogenic acid and sinapic acid to be the anti-inflammatory ingredients of Qingfei Xiaoan Wan, which suppressed the expression of the regulatory proteins in P38K/ACT and Ras/MAPK pathways (Hou et al., 2016). Xiao Chai Hu Tang is a 7-ingredient TCM consisting of the tuber of Arctium lappa (Compositae), T. kirilowii Maxim., Panax quinquefolius L. (Araliaceae), P. scabiosifolia Link, and Coix lacryma-jobi var. ma-yuen (Rom.Caill.) Stapf (Poaceae) with a mixture ratio of 2.5:2.5:5.2:5.5:1.5:5 (Xu H. et al., 2019). Furthermore, the Fuzheng Jiedu Huayu formula decoction has been applied to treat elderly patients with pneumonia in clinical trials, and no obvious adverse reactions were manifested (Xu et al., 2018). Xu et al. revealed that the Fuzheng Jiedu Huayu decoction with an MIC of 200 mg/ml against P. aeruginosa combined with Imipenem/cilastatin sodium could enhance the in vitro bactericidal and bacteriostatic effects of Imipenem/cilastatin sodium on MDR P. aeruginosa (Xu H. et al., 2019).

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Qingfei Xiaoan Wan, a TCM pill, consists of E. sinica Stapf, Gypsum Fibrosum, Pheretima (earthworm), the ripe fruit of Arctium lappa L. (Compositae; Arctii Fructus), the seed of Descurainia sophia (L.) Webb ex Prantl (Brassicaceae), Bovis Calculus Artificius (Artificial ox bezoar), the seed of P. armeniaca L. and Cornu Saigae Tataricae (Hou et al., 2016), and it has been used in China for treatment of asthma and respiratory tract infections without inducing obvious side effects (Zhao et al., 2013). A study by Hou et al. evaluated the effects of Qingfei Xiaoan Wan suspended in distilled water on a mouse model of P. aeruginosa-induced acute pneumonia, and they demonstrated that the oral administration of Qingfei Xiaoan Wan (18 g for every kg of body weight per day) for 1 week could reduce the P. aeruginosa PAK-induced lung inflammation by decreasing the production of cytokines (TNF-α and IL-6) and chemokine (RANTES) in lung tissues, significantly ameliorating lung injury. Importantly, the authors identified arctigenin, cholic acid, chlorogenic acid and sinapic acid to be the anti-inflammatory ingredients of Qingfei Xiaoan Wan, which suppressed the expression of the regulatory proteins in P38K/ACT and Ras/MAPK pathways (Hou et al., 2016). Xiao Chai Hu Tang is a 7-ingredient TCM consisting of the tuber of Pinellia ternata (Thunb.) Makino (Araceae), the fruit of Ziziphus jujuba Mill. (Rhamnaceae), and the root of S. baicalensis Georgi, Bupleurum chinense DC. (Apiaceae), Panax ginseng C.A.Mey. (Araliaceae), Glycyrrhiza glabra L. (Leguminosae) and Zingiber officinale Roscoe (Zingiberaceae), and it is widely used for treatment of respiratory, hepatic and gastrointestinal diseases (Hsu et al., 2006). However, Xiao Chai Hu Tang has been reported to cause hepatotoxicity due to overdose or long-term use (Gao X. et al., 2017). Kawakita et al. demonstrated that the water extract of Xiao Chai Hu Tang (100 mg for every kg of body weight) was able to protect mice from intraperitoneal infections with P. aeruginosa by promoting the accumulation of polymorphonuclear leukocytes and enhancing the phagocytic activity of macrophages (Kawakita et al., 1987b). The underlying mechanisms need to the further explored.

Shufengjiedu capsule is an oral Chinese patent medicine that has been extensively utilized for treatment of respiratory, hepatic and gastrointestinal diseases (Hsu et al., 2006). However, Xiao Chai Hu Tang has been reported to cause hepatotoxicity due to overdose or long-term use (Gao X. et al., 2017). Kawakita et al. demonstrated that the water extract of Xiao Chai Hu Tang (100 mg for every kg of body weight) was able to protect mice from intraperitoneal infections with P. aeruginosa by promoting the accumulation of polymorphonuclear leukocytes and enhancing the phagocytic activity of macrophages (Kawakita et al., 1987b). The underlying mechanisms need to the further explored.
reported to reduce the *P. aeruginosa* PAK-induced lung inflammation in mice through inhibition of ERK pathway and NF-kB activation, leading to decreased IL-6 production and alleviated lung injury (Li et al., 2017). Furthermore, the active components of Shufengjiedu capsule including verbenalin, phyllirin and emodin were identified to contribute to the regulation of ERK pathway (Li et al., 2017). *Pseudomonas aeruginosa* is one of the common pathogens isolated from chronic wounds, and the infections by *P. aeruginosa* affect wound healing (Serra et al., 2015). Shiunko ointment is a traditional botanic formula used for treatment of wounded skin without causing undesirable side effects in China and Japan (Higaki et al., 1999), and it has been found to accelerate the epithelization of wounded skin infected with *P. aeruginosa* (Huang et al., 2004). The mechanisms underlying the Shiunko-modulated epithelization possibly being through enhancing fibroblast proliferation and collagen production, and suppressing skin inflammation (Yan et al., 2015; Imai et al., 2019). In addition to inhibition of *P. aeruginosa* QS and biofilm formation, Qi Gui Yin decoction (9.9 g for every kg of body weight) was also identified to promote host immune response to *P. aeruginosa* infections by enhancing the antibody reactivity to β-lactamases, including VIM-1, SPM-1, and TEM-1, and manifested anti-inflammatory effects by reducing the levels of IL-1β and Th1/Th2 ratio in a rat model of abdominal infection (Kong et al., 2015). Qingre Baidu mixture was reported to promote angiogenesis and wound healing in a rat model of refractory wounds during *P. aeruginosa* infection by upregulating the expression of HIF-1α, HIF-2α and VEGF (Shan et al., 2019).

**CONCLUSION**

Antibiotic resistance has led to a significant challenge for treatment of *P. aeruginosa* infections in clinical settings. Many alternative therapeutic options have been developed over the past decade and demonstrated promising antimicrobial effects against antibiotic-resistant *P. aeruginosa* infections *in vitro* or in animal models. However, only a few of them has proceeded to clinical trials. By contrast, TCM has been clinically practiced over thousands of years in China with its unique system of theories, diagnostics and therapies for many kinds of diseases. In particular, the Chinese herbal medicines have shown great clinical efficacies in prevention and treatment of chronic infectious diseases. Importantly, TCM was reported to effectively control the infections caused by the clinical isolates of *P. aeruginosa* strains with antibiotic resistance through inhibiting the expression of QS regulatory proteins, disrupting biofilm structure and maturation, directly killing or inhibiting bacterial growth, and modulating host immune responses, including acceleration of the leukocyte accumulation to infection sites, enhancement of macrophage phagocytosis, reduction of host inflammatory response and promotion of wound epithelization. Moreover, some studies indicated that combination of TCM and antibiotics could enhance the effects of antibiotics against *P. aeruginosa* infections, which could be attributed to the antibiotic properties of TCM and the reductive components of TCM stabilizing the antibiotics from degradation (Gim et al., 2009; Chen et al., 2013; Matkowski et al., 2013; Sun W. et al., 2014; Chen et al., 2020). In addition, many TCM active compounds have shown inhibitory effects on the gene expression of bacterial efflux pumps, which could also enhance the antimicrobial effects of antibiotics (Huang et al., 2015; Wang et al., 2018; Wang J. et al., 2019). For instance, baicalin was found to significantly inhibit the mRNA transcription of MsrA efflux pump in *Staphylococcus saprophyticus* (Wang J. et al., 2019). The emodin from *Rheum palmatum* L. (Polygonaceae), the schizandrin from *Schisandra chinensis* (Turcz.) Baill. (Schisandraceae), the berberine from *Berberis vulgaris* L. (Berberidaceae), and baicalin were identified to significantly reduce the expression of the efflux pump gene *hefA* in *Helicobacter pylori* (Huang et al., 2015). However, the role of TCM in regulation of the efflux pumps in *P. aeruginosa* has not yet been elucidated, which could be a direction for future research. Altogether, TCM emerges as a promising complementary and alternative therapeutic approach for treatment of *P. aeruginosa* infections. However, due to the multiple gradients and targets of TCM, the mechanisms involved in the TCM-inhibited *P. aeruginosa* infections are incompletely understood. Future studies need to focus on investigating the effects of a single active component of TCM on *P. aeruginosa* host, which gives a clearer understanding of the drug-host and drug-microbe interactions, allowing development of the TCM with reduced side effects and improved effectiveness in clinical trials.

**AUTHOR CONTRIBUTIONS**

ZP contributed to the study design, data collection and interpretation, and article writing. QZ contributed to article writing and revision. All the authors read and approved the final article.

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