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Anti-quorum Sensing, Anti-bacterial, and Immunomodulatory Properties of *Panax ginseng*

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ABSTRACT

The increased emergence of multi-drug and pandrug resistant bacteria necessitates the identification of new therapies. Although antibiotics are used to treat infections, the novel antibiotic discovery rate lags behind development of resistance. Antibiotics in clinical use combat infection through bactericidal or bacteriostatic action, which allows for selection of resistant strains. To impede or avoid resistance, treatments targeting microbial cell pathways critical for virulence and pathogenicity, but not essential for viability are being explored. One such signaling pathway is quorum sensing (QS) which regulates virulence factor expression in many pathogenic bacteria. Interference with this signaling pathway results in attenuation of pathogenicity and allows the host immune response system to eradicate the infection. Natural products have long been a rich source of antibiotic scaffolds as well as inhibitors of QS. *Panax ginseng* has been used as an herbal panacea for thousands of years, yet its ability to inhibit bacterial growth and QS is only beginning to be characterized. This review provides a brief outline of the microbial infection process, an overview of quorum sensing, an introduction to the use of natural products as alternative therapies, and a synopsis of the current literature describing the anti-bacterial and anti-QS activities of *Panax ginseng*.

Keywords: anti-quorum sensing, alternative therapy, *Panax ginseng*, *Pseudomonas aeruginosa*, virulence factor

Abbreviations: **3OHC$_4$HSL**, *N*-(3-hydroxybutanoyl) homoserine lactone; **3OC$_{12}$-HSL**, *N*-3-oxo-dodecanoyl homoserine lactone; **3OC$_6$HSL**, *N*-3-(oxo-hexanoyl)-homoserine lactone; **AI**, autoinducer; **AIP**, autoinducing peptide; **C$_4$-HSL**, butyryl homoserine lactone; **CF**, cystic fibrosis; **DPD**, 4,5-dihydroxy-2,3-pentadione; **HHQ**, 2-heptyl-4(1H)-quinolone; **HSL**, N-acylhomoserine lactone; **IL**, interleukin; **MDR**, multi-drug resistant; **MIC**, minimum inhibitory concentration; **PQS**, *Pseudomonas* quinolone signal; **QS**, quorum sensing

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INTRODUCTION

The continuous use and abuse of antibiotics selects for resistant strains of bacteria. Consequently, the problem of antibiotic resistance has been growing at an alarming rate in recent years. Of the 2 million patients that acquire nosocomial infections, it was estimated 90,000 will die as a result and more than 70% will be infected by multi-drug resistant bacteria requiring more than one antibiotic for treatment (National Institutes of Health, NIAID 2006). Thus, there is an urgent need for novel antibiotics.

The rate of finding new antibiotics has slowed by 56% in the past 20 years as evidenced by the number of drugs approved by the FDA (Fischbach and Walsh 2009). Inefficient screening and the great cost and time required to bring a new antibiotic to market are part of the reason for this decreasing trend in the development of novel antibiotics. To effectively eradicate infections, either novel antimicrobials or alternative therapies are needed. These can be synthesized in the laboratory, derived from natural products, or a combination of both. The study of ethnobotany has led to the identification of many botanical sources with antimicrobial activity at a rate greater than random screening (Khafagi and Dewedar 2000). The focus of this review is the potential therapeutic use of extracts and compounds from *Panax ginseng*, which has been used since ancient times as a "cure-all." *P. ginseng* has been shown to affect Gram positive and Gram negative bacteria growth and pathogenicity both directly and indirectly as detailed in this review. Brief summaries of the infection process and quo-

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Invited Review

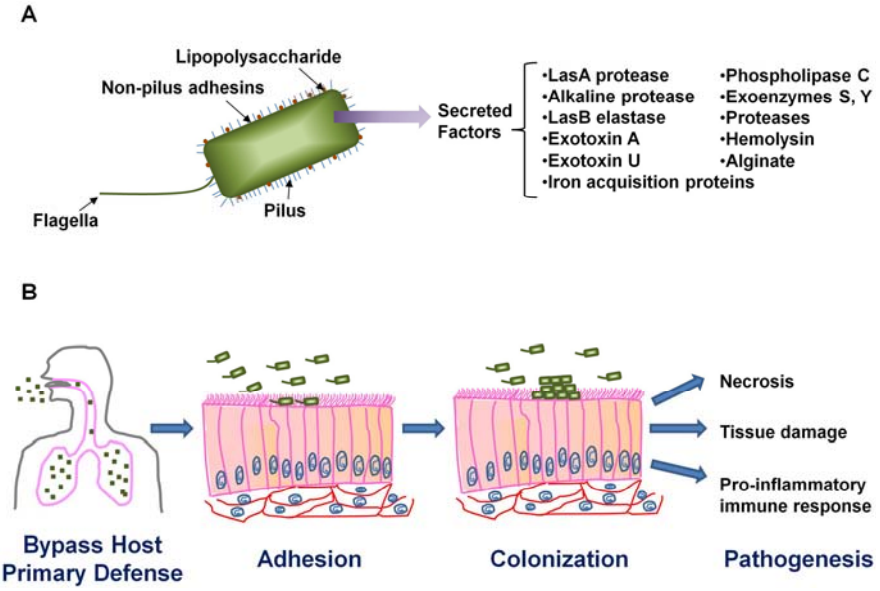

Fig. 1 ***Pseudomonas aeruginosa*** **infection.** (**A**) *Pseudomonas aeruginosa* structures and factors important for virulence (**B**) *Pseudomonas aeruginosa* infection process: bypass of host primary defense, adhesion, colonization and host effects.

rum sensing (QS) are provided as background to fully appreciate the effects of ginseng on microbial pathogenesis.

AN OVERVIEW OF THE INFECTION PROCESS

Bacteria, are relatively simple in structure, yet have evolved complex metabolisms which allow them to inhabit diverse environments, one of which is the human body. Although many are commensal or avirulent, invasion of primarily sterile sites in the body by opportunistic and pathogenic bacteria may cause disease. For this to occur, bacteria must enter the host, adhere and colonize the site, acquire nourishment, and evade host defenses. Different bacteria use methods unique to their species to invade tissues and disseminate through the body while dealing with local and systemic inflammatory responses. For the purpose of this review, which focuses on the ability of *P. ginseng* to inhibit bacterial growth and virulence, only the infection process for *Pseudomonas aeruginosa*, a common ubiquitous, opportunistic pathogen, will be detailed.

Individuals most often infected by *P. aeruginosa* are burn victims (Tredget *et al.* 2004), those receiving mechanical ventilation (Garau and Gomez 2003; Cao *et al.* 2004), immunocompromised individuals, including those with AIDS or neutropenia (Obritsch *et al.* 2005), and those afflicted with compromised lung function, such as individuals with diffuse panbronchiolitis (Homma *et al.* 1983) or cystic fibrosis (CF) (Phair *et al.* 1970; Mearns *et al.* 1972; Hoiby 1974; Frederiksen *et al.* 1999). *P. aeruginosa* has become quite successful in establishing infection due to its intrinsic antibiotic resistance, low outer membrane permeability, presence of multidrug efflux pumps, hypermutability and ability to form biofilms. Fifty percent of hospitalized patients are colonized by *P. aeruginosa* (Pollack 2000). Initial infection is acute, however, in chronic infections, as in the case of individuals with CF, *P. aeruginosa* infection results in host lung damage and eventual mortality (Hoiby *et al.* 1977).

P. aeruginosa that initially infect the host are planktonic, motile cells that produce and secrete numerous toxins and virulence factors necessary for establishing and maintaining an infection (**Fig. 1**). After successfully passing the host's primary line of defense, the next step in the infection process is adhesion via binding to any of several different glycoproteins (**Fig. 1**). *P. aeruginosa* accomplishes this by producing virulence factors that help compromise the host defenses, including the AprA alkaline protease (Duong *et al.* 1992), protease IV/PrpL (Wilderman *et al.* 2001), LasB elastase (Bever and Iglewski 1988), LasA staphylolytic protease (Goldberg and Ohman 1987; Toder *et al.* 1991), phospholipase C (Liu 1966), pyocyanin (Stewart-Tull and Armstrong 1972), pyoverdin (Ankenbauer *et al.* 1985), rhamnolipids (Burger *et al.* 1962; Edwards and Hayashi 1965), exotoxin A (Liu 1973; Liu and Hsieh 1973; Liu *et al.* 1973), lipopolysaccharide (LPS) (Homma and Suzuki 1961; Homma *et al.* 1963) and exoenzymes S and U (Iglewski *et al.* 1978; Finck-Barbancon *et al.* 1997). These enable multiple stages of the infection process including host tissue damage, cellular necrosis, and pro-inflammatory immune response. Many of these virulence factors must be secreted by *Pseudomonas aeruginosa* to exert their action on the host. To secrete the extracellular products, *P. aeruginosa* makes use of six different secretion systems (Ma *et al.* 2003; Saier 2006). All of these affect virulence by facilitating transport of the aforementioned virulence factors (Wretlind and Pavlovskis 1984; Lindgren and Wretlind 1987; Yahr *et al.* 1996; Yahr *et al.* 1997; Duong *et al.* 2001; Ochsner *et al.* 2002; Mougous *et al.* 2006; Hood *et al.* 2010).

Biofilm formation also plays a pivotal role in colonization (Costerton *et al.* 1999; Drenkard 2003). This occurs when dense aggregates of cells adhere to surfaces and become embedded in a matrix consisting of extracellular DNA, proteins and polysaccharides such as alginate, Pel (pellicle formation) and Psl (polysaccharide synthesis locus) (Evans and Linker 1973; Friedman and Kolter 2004a, 2004b). Biofilm formation is associated with increased antibiotic resistance as well as chronic *P. aeruginosa* infections (Nickel *et al.* 1985a, 1985b; Nichols *et al.* 1989; Drenkard 2003).

Thus the *P. aeruginosa* infection process, like that of all pathogenic bacteria, is multilayered and complex. Underlying virtually every step of this process, adherence, colonization, virulence factor production, secretion and biofilm formation, is the ability of the bacteria to communicate with members of its own species and others to coordinate the infection process and improve the chance of success. This is accomplished through a signaling pathway called quorum sensing (QS).

OVERVIEW OF QUORUM SENSING

QS is a type of communication process bacteria use to coordinate and synchronize their behavior (Nealson and Hastings 1979; Fuqua *et al.* 1996). In QS, bacteria synthesize and secrete chemical signals that alter the transcriptional program in a cell density dependent manner (Nealson *et al.*

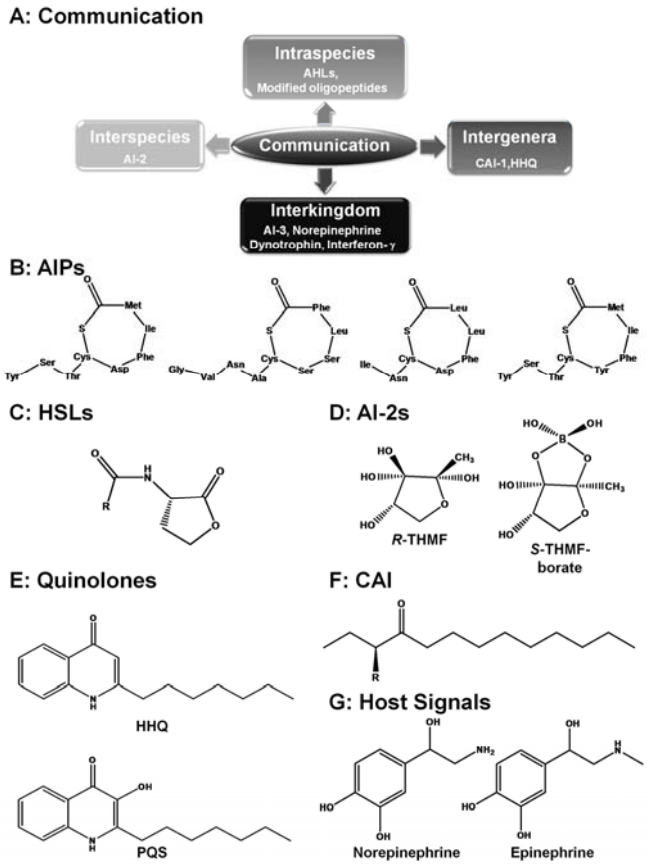

Fig. 2 Communication pathways affecting microbial virulence and structures of the most well characterized quoromones. (**A**) Summary of communication types; (**B**) Structures of AIP-I – IV (from left to right); (**C**) HSL structure. The R group can vary as indicated in **Table 1**. (**D**) Structures AI-2 from *Salmonella* (left) and *Vibrio* (right). (**E**) Structure of the quinolonoes HHQ and PQS. (**F**) Generic structure of CAI-I. R may be a hydroxyl group (CAI-1) or an amino group (Amino-CAI-1). (**G**) Structures of norepinephrine (left) and epinephrine (right). (**B-F**) adapted from (Ng and Bassler 2009).

1970). Although first discovered in the bioluminescent bacteria *Vibrio fischeri* (Kempner and Hanson 1968; Nealson *et al.* 1970; Eberhard 1972), QS systems have been identified in many bacteria and, in addition to bioluminescence, affect various cellular processes including conjugation, sporulation, biofilm formation, virulence factor production and secretion (**Table 1**).

The QS signals are also called autoinducers or quoromones. Specifically, quoromones identified in Gram positive bacteria include linear, modified, and cyclic peptides and γ-butyrolactones, and 4,5-dihydroxy-2,3-pentandione (DPD) derivatives (autoinducer 2 (AI-2)) (Havarstein *et al.* 1995; Ji *et al.* 1995; Solomon *et al.* 1996; Surette and Bassler 1998; Surette *et al.* 1999; Miller *et al.* 2004). Gram negative bacteria have been shown to use *N*-acylhomoserine lactones (HSLs), 2-alkyl-4-quinolones, fatty acid methyl esters, long-chain fatty acid derivatives, peptides, γ-butyrolactones, furanones, AI-2 and autoinducer 3 (AI-3) as indicators of population density. These signals may serve to communicate with members of the same species, (intraspecies), different species (interspecies), different genera (intergenera) or between the bacteria and the host (interkingdom) (**Fig. 2A**). A comprehensive review of QS is beyond the scope of this review, thus only one or two examples of each will be discussed.

Gram negative bacteria intraspecies communication

The major paradigm of intraspecies QS system in Gram negative bacteria, including *P. aeruginosa*, is the LuxI/LuxR system. The LuxI/R QS system was first identified in *V. fischeri* as a regulator of bioluminescence through activation of the luciferase *luxICDABEG* operon (Eberhard *et al.* 1981; Engebrecht *et al.* 1983; Engebrecht and Silverman 1984, 1987; Swartzman *et al.* 1990). The "I" and "R" proteins are at the heart of this type of QS, encoding the quoromone synthase and cytoplasmic receptor/transcriptional activator, respectively. The quoromone involved in the LuxI/R QS system is an HSL (**Fig. 2C**). HSLs contain a homoserine lactone (HSL) ring and an acyl side chain (Eberhard *et al.* 1981; Engebrecht and Silverman 1984, 1987). The side chain varies between four and 18 carbons in length and may contain a modification, primarily at the C_3 position depending upon the species (**Table 1**). The LuxI protein synthesizes the HSL by transfer of a fatty acid chain from an acylated carrier protein to S-adenosyl methionine creating HSL and 5'-methylthioadenosine (Schaefer *et al.* 1996). The HSL is transported into and out of the cell by diffusion (Kaplan and Greenberg 1985).

As the population density increases, the intracellular concentration of HSL increases due to diffusion into the cell. Inside the cell, HSL binds the LuxR protein (Urbanowski *et al.* 2004). The stable ligand-bound LuxR binds and activates gene expression (Urbanowski *et al.* 2004).

QS signaling is so vital to the bacteria that often they have more than one LuxI/R system or utilize the LuxI/R system with other QS systems (Waters and Bassler 2005). For example, *P. aeruginosa*, utilizes two LuxI/R based systems, the Las and the Rhl systems, and also synthesizes 2-heptyl-3-hydroxy-4(1*H*)-quinolone (*Pseudomonas* quinolone signal or PQS), which is part of an additional regulatory circuit of the Las and Rhl pathways (reviewed in Williams and Camara (2009)).

Gram positive bacteria intraspecies communication

In Gram positive bacteria, the chemical signal is often a modified oligopeptide (Solomon *et al.* 1996) or autoinducing peptide (AIP) as is the case for *Staphylococcus aureus* (Ji *et al.* 1995) (**Fig. 2B**). Transport of these across the membrane usually requires special transporters and peptide modifications such as processing and/or cyclization. Extracellular accumulation of these signaling oligopeptides results in activation of a two-component signaling system which results in altered gene expression (reviewed in Novick and Geisinger (2008)).

Interspecies communication – the LuxS-based system

The LuxS system is a form of interspecies communication; it is widespread and both Gram negative and Gram positive bacteria synthesize and respond to this class of quoromone; termed AI-2 (reviewed in Ng and Bassler (2009)). This phenomenon was first observed in the marine bacteria *Vibrio harveyi* (Greenberg *et al.* 1979).

V. harveyi synthesizes and recognizes three types of quoromones (Henke and Bassler 2004). One is an intraspecies communication molecule; the *N*-(3-hydroxybutanoyl) HSL (3OHC_4-HSL) (Cao and Meighen 1989; Bassler *et al.* 1993). A second has been proposed to be an intergenera signal, CAI-1, which has not yet been purified from *V. harveyi*, but was identified as (*S*)-3-hydroxytridecan-4-one in *Vibrio cholerae* (Higgins *et al.* 2007) (**Fig. 2F**). The third is the interspecies signal AI-2 (Surette *et al.* 1999; Schauder *et al.* 2001; Chen *et al.* 2002) (**Fig. 2D**).

AI-2 is used by both Gram negative and positive bacteria, and is often referred to as a universal signal. Even bacteria, such as *P. aeruginosa*, that do not synthesize AI-2, can detect AI-2 in the environment and alter gene expression accordingly, further emphasizing its role as a universal signal (Duan *et al.* 2003; Duan and Surette 2007; Rezzonico and Duffy 2008). Synthesis of AI-2 begins with LuxS con-

Table 1 Gram negative bacteria with QS regulated virulence.

Bacteria	Gene	Autoinducer molecule (AI)*	Virulence Factor	Reference
Aeromonas hydrophila	*ahyI/ahyR*	C_4-HSL	Type VI secretion system, biofilm and metalloprotease production	Khajanchi *et al.* 2009
Aeromonas salmonicida	*asaI/asaR*	C_4-HSL and C_6-HSL	Virulence factors	Rasch *et al.* 2007
Agrobacterium tumefaciens	*traI/traR*	$3OC_8$-HSL and C_6-HSL	Ti plasmid conjugation	Zhang *et al.* 1993 Hwang *et al.* 1994
Brucella melitensis	*vbjR*	C_{12}-HSL	Virulence factor production	Weeks *et al.* 2010
Burkholderia cenocepacia	*cepI/R*	C_6-HSL and C_8-HSL	Virulence factor, protease, chitinase, siderophore, biofilm and AidA production and swarming motility	Lewenza *et al.* 1999; Sokol *et al.* 2000; Huber *et al.* 2001; Lewenza and Sokol 2001; Aguilar *et al.* 2003
		HHQ	Colony morphology and elastase production	Diggle *et al.* 2006a
	bcam 0581	BDSF	Virulence factor, motility, biofilm formation, metalloprotease, lipase, lipase chaperone and siderophore expression, and *Candida albicans* morphology	Boon *et al.* 2008; Deng *et al.* 2009; Ryan *et al.* 2009
Burkholderia mallei	*bmaI1/R1*	C_8-HSL and $3OC_8$-HSL	Virulence factor	Ulrich *et al.* 2004b
	bmaI3/R3	C_8-HSL, OC_8-HSL and C_{10}-HSL	Virulence factor	Ulrich *et al.* 2004b
	bmaR4		Virulence factor	Ulrich *et al.* 2004b
	bmaR5		Virulence factor	Ulrich *et al.* 2004b
Burkholderia pseudomallei	*pmlI1/R1*	C_8-HSL, C_{10}-HSL, and $3OHC_8$-HSL	Virulence factor, MprA protease production and colonization	Ulrich *et al.* 2004a; Valade *et al.* 2004
	bpmI2/R2	C_8-HSL, C_{10}-HSL, and $3OHC_8$-HSL	Virulence factor and colonization	Ulrich *et al.* 2004a
	bpmI3/R3	C_8-HSL, C_{10}-HSL, and $3OHC_8$-HSL		
	bpmR4			
	bpmR5			
	hhqA/E	HHQ	Colony morphology, elastase production	Diggle *et al.* 2006b
Burkholderia vietnamiensis G4	*cepI/R*	C_6-HSL and C_8-HSL		Lutter *et al.* 2001; Conway and Greenberg 2002; Malott and Sokol 2007
	bviI/R	C_6-HSL, C_8-HSL, C_{10}-HSL, C_{12}-HSL and $3OC_{10}$-HSL		Lutter *et al.* 2001; Malott and Sokol 2007
Chromo-bacterium violaceum	*cviI/cviR*	C_6-HSL	Biofilm formation and virulence factors	McClean *et al.* 1997
Erwinia carotovora subsp. *betavasculorum*	*ecbI/ecbR*	$3OC_6$-HSL	Antibiotic and exoenzymes	Costa and Loper 1997
Erwinia carotovora subsp. *carotovora* 71	*hslI/hslR*	$3OC_6$-HSL	Exoenzymes	Chatterjee *et al.* 1995
Erwinia carotovora subsp. *carotovora* GS101	*carI/carR*	$3OC_6$-HSL	Carbapenems and exoenzymes	Pirhonen *et al.* 1993; Swift *et al.* 1993
Erwinia carotovora subsp. *carotovora* SCC3193	*expI/expR1,expR2*	$3OC_8$-HSL and $3OC_6$-HSL	Virulence factors and exoenzyme	Pirhonen *et al.* 1993; Chatterjee *et al.* 2005; Sjoblom *et al.* 2006
Klebsiella pneumoniae		AI-2	Biofilm formation	Balestrino *et al.* 2005
Pantoea agglomerans pv. 'gypsophilae'	*pagI/pagR*	C_6-HSL	Gall development	Chalupowicz *et al.* 2008
Pantoea stewartii subsp. *Stewartii* (formerly *Erwinia stewartii*)	*easI/esaR*	$3OC_6$-HSL	EPS and virulence factors	Beck von Bodman and Farrand 1995
Pseudomonas aeruginosa	*lasI/lasR*	$3OC_{12}$-HSL	Alkaline protease, pyocyanin, hydrogen cyanide, lectins, and elastase	Gambello and Iglewski 1991; Pearson *et al.* 1994; Brint and Ohman 1995; Latifi *et al.* 1995; Ochsner and Reiser 1995; Winson *et al.* 1995
	rhlI/rhlR	C_4-HSL	Induces LasB and RhlI expression	Brint and Ohman 1995; Latifi *et al.* 1995; Ochsner and Reiser 1995; Pearson *et al.* 1997; Winzer *et al.* 2000
	qscR	$3OC_{12}$-HSL	Represses virulence factor expression	Lequette *et al.* 2006
	pqs	HHQ	Virulence factors	Pesci *et al.* 1999
Pseudomonas aureofaciens 30-84	*phzI/phzR*	C_6-HSL	Virulence factors and biofilm production	Pierson *et al.* 1994; Wood and Pierson 1996
	csaI/R	Unknown	Colonization, exoprotease production, and suppression of mucoid phenotype	Zhang and Pierson 2001

Table 1 (Cont.)

Bacteria	Gene	Autoinducer molecule (AI)*	Virulence Factor	Reference
Pseudomonas fluorescens 2P24	*pcoI/R*	$3OC_8$-HSL	Biofilm formation and wheat rhizosphere colonization	Wei and Zhang 2006
Pseudomonas fuscovaginae	*pfsI/R*	C_{10}-HSL and C_{12}-HSL	Virulence factors	Mattiuzzo *et al.* 2011
	pfvI/R	$3OC_{10}$-HSL and $3OC_{12}$-HSL	Virulence factors	Mattiuzzo *et al.* 2011
Pseudomonas putida PCL1445	*ppuI/R*	$3OC_6$-HSL, $3OC_8$-HSL, $3OC_{10}$-HSL and $3OC_{12}$-HSL	Biofilm architecture	Dubern *et al.* 2006
Pseudomonas syringae pv. 'syringae'	*ahlI/ahlR*	C_8-HSL	Antibiotic production	Quinones *et al.* 2004; Quinones *et al.* 2005
Pseudomonas syringae pv. 'tabaci'	*psyI/psyR*	$3OC_6$-HSL	Biofilm formation and virulence factors	Shaw *et al.* 1997
Ralstonia solanacearum	*solI/solR*	C_6-HSL and C_8-HSL	Unknown	Flavier *et al.* 1997
	phc	3-OH PAME	Production of EPS and exoenzyme synthesis	Brumbley *et al.* 1993; Flavier *et al.* 1997
Rhodobacter sphaeroides	*cerI/cerR*	C_{14}-HSL	Phenazine antibiotic production	Puskas *et al.* 1997; Kirwan *et al.* 2006
Serratia liquefaciens	*swrI/swrR*	C_4-HSL and C_6-HSL	Swarming motility	Eberl *et al.* 1996
Vibrio anguillarum	*vanI/vanR*	$3OC_{12}$-HSL	Unknown	Milton *et al.* 1997; Croxatto *et al.* 2002
	vanM/vanN	C_6-HSL and $3OHC_6$-HSL	Extracellular protease, pigment and biofilm formation	Milton *et al.* 2001
	vanS/vanQ	AI-2	Extracellular protease, pigment and biofilm formation	Croxatto *et al.* 2004
Vibrio cholerae	*luxP/luxQ*	AI-2	Biofilm and virulence factor production repression	Miller *et al.* 2002
	cqsS/cqsA	CAI-1, amino-CAI-1		Miller *et al.* 2002; Higgins *et al.* 2007; Kelly *et al.* 2009
Vibrio fischeri	*luxI/luxR*	$3OC_6$-HSL	Bioluminescence	Eberhard *et al.* 1981
	ainS/R	C_8-HSL		Gilson *et al.* 1995
	luxS/luxP, *luxQ*	AI-2		Chen *et al.* 2002
Vibrio harveyi	*luxM/luxN*	$3OHC_4$-HSL	Bioluminescence. metalloprotease, siderophore, and exopolysaccharide production	Lilley and Bassler 2000; Mok *et al.* 2003
	luxS/luxP, *luxQ*	AI-2		Surette *et al.* 1999; Schauder *et al.* 2001; Chen *et al.* 2002
	cqsA/cqsS	CAI-1		Henke and Bassler 2004
Vibrio parahaemo-lyticus	*opaI/ opaR*	Unknown	Haemolysin and protease production, opacity, regulation of TTSS	McCarter 1998; Henke and Bassler 2004
Vibrio salmonicida	*luxI/luxR1, luxR2*	$3OC_6$HSL	Virulence factors	Nelson *et al.* 2007
Vibrio vulnificus	*luxS/luxP, luxQ*	AI-2	Virulence factors	Kim *et al.* 2003
Xanthomonas campestris	*rpfC/rpfG*	$11CH_3C_{12}$-HSL	Virulence factors	Torres *et al.* 2007; He and Zhang 2008
Yersinia pestis	*yepI/yepR*	C_8-HSL, $3OC_6$-HSL and C_6-HSL	Virulence factors	Atkinson *et al.* 1999; Gelhaus *et al.* 2009
Yersinia pseudo-tuberculosis	*ypsI/ypsR*	C_6-HSL, $3OC_6$HSL,	Aggregation and motility	Atkinson *et al.* 1999; Ortori *et al.* 2007
	ytbI/ytbR	$3OC_7$-HSL, C_8-HSL, $3OHC_8$-HSL, $3OC_{12}$-HSL		

*Abbreviations used, AI-2, furanosyl borate diester; BDSF, *cis*-2-dodecenoic acid; CAI-1, Cholera autoinducer: HSL, homoserine lactone; C_4-HSL, *N*-butanoyl-L-HSL; $3OHC_4$-HSL, *N*-3-hydroxybutanoyl-L-HSL; C_6-HSL, *N*-hexanoyl-L-HSL; $3OC_6$-HSL, *N*-3-oxo-hexanoyl-HSL; $3OHC_6$-HSL, *N*-3-hydroxyhexanoyl-L-HSL; $3OC_7$-HSL, *N*-3-oxo-septanoyl-L-HSL; C_8-HSL, *N*-octanoyl-L-HSL; $3OHC_8$-HSL, *N*-3-hydroxy-octanonoyl-L-HSL; $3OC_8$-HSL, N-3-oxo-octanoyl-L-HSL; $3OC_{10}$-HSL, *N*-3-oxodecanoyl-L-HSL; $3OC_{12}$-HSL, *N*-3-oxododecanoyl-L-HSL; $11CH_3C_{12}$-HSL, cis-11-methyl-2-dodecenoic acid; C_{14}-HSL, 7,8-cis-*N*-tetradecenoyl-L-HSL; HHQ, 2-heptyl-3-hydroxy-4-quinolone; 3-OH PAME, 3-OH-palmitic acid methyl ester

verting ribose-homocysteine into homocysteine and DPD (Schauder *et al.* 2001). Spontaneous rearrangement of DPD results in the formation of different AI-2 compounds, depending upon the environmental chemistry (Miller *et al.* 2004). One of the most well characterized pathways is that of *V. harveyi*, which utilizes a furanosyl borate diester, (*2S,4S*)-2-methyl-2,3,3,4-tetrahydroxytetrahydrofuran borate (**Fig. 2D**, right panel) (Chen *et al.* 2002). *Salmonella enteric* serovar Typhimurium and *Escherichia coli* use (*2R,4S*)-2-methyl-2,3,3,4-tetrahydroxytetrahydrofuran (**Fig. 2D**, left panel) (Chen *et al.* 2002; Miller *et al.* 2004).

Interkingdom signaling

The infection process is complex and bacteria have evolved to coordinate this process not only with members of their own species and kingdom, but also with other kingdoms capable of co-infecting the host and the host itself. This is accomplished by signaling that feeds into the QS systems.

The microbial intestinal flora present in the healthy human gut, produce another autoinducer termed autoinducer 3 (AI-3), which regulates the operons within the locus for enterocyte effacement (LEE operons) and flagella genes in enterohemorrhagic *E. coli* (Sperandio *et al.* 2003). The LEE operons encode the proteins involved in Type 3 secretion systems and adhesion (Elliott *et al.* 1998). AI-3 is detected by a two component system, QseBC, which also recognizes norepinephrine and epinephrine (**Fig. 2G**) (Sperandio *et al.* 2003; Clarke *et al.* 2006; Kendall *et al.* 2007; Reading *et al.* 2007). It has been proposed that this may be a mechanism the bacteria use to sense that it is in the gut (reviewed in Moreira and Sperandio (2010)). The synthesis and chemical structure of AI-3 remains to be elucidated. The detection pathway has been shown to be present in numerous Gram negative bacteria; however, its role in commensal organisms needs further characterization.

Pseudomonas aeruginosa QS

The QS systems in *P. aeruginosa* are well characterized, most likely because of their importance in virulence. *P. aeruginosa* exhibits intraspecies, interspecies and interkingdom signaling. As described above, *P. aeruginosa* can respond to, but not synthesize AI-2 (Duan *et al.* 2003; Duan and Surette 2007).

P. aeruginosa synthesizes and detects two HSLs, N-3-oxo-dodecanoyl homoserine lactone ($3OC_{12}$-HSL) and butyryl homoserine lactone (C_4-HSL) which bind LasR and RhlR, respectively (reviewed in Fuqua *et al.* (1996)). These complexes directly or indirectly regulate transcription of more than 10% percent of the *P. aeruginosa* genome (Schuster and Greenberg 2006). These two pathways in part appear hierarchical, with the Las system upstream from the Rhl system, although the Rhl pathway can be activated during stationary phase in the absence of Las signaling (Latifi *et al.* 1996; Pesci *et al.* 1997; Dekimpe and Déziel 2009).

A third receptor, QscR (quorum-sensing-control repressor), has also been identified in *P. aeruginosa* (Chugani *et al.* 2001). QscR was initially shown to antagonize Las and Rhl signaling and *qscR* mutants were hypervirulent (Chugani *et al.* 2001). Microarray studies show that the QscR regulon is distinct, but partially overlaps that of LasR and RhlR (Lequette *et al.* 2006). QscR has a relatively relaxed specificity, leading to the suggestion that QscR may respond to HSLs produced by other bacteria present in a mixed infection (Lequette *et al.* 2006; Oinuma and Greenberg 2011).

Recently, LasR-, RhlR-, and QscR-independent *N*-decanoyl-homoserine lactone (C_{10}-HSL) signaling was observed in *P. aeruginosa* (Chugani and Greenberg 2010). Receptor-independent, C_{10}-HSL-dependent gene regulation requires anthranilate produced by the kynurenine pathway (Chugani and Greenberg 2010). Under the experimental conditions used, the kynurenine pathway is the main source of anthranilate used for PQS synthesis (Farrow and Pesci 2007), the signaling molecule used in the third QS pathway (Pesci *et al.* 1999; McKnight *et al.* 2000), suggesting another layer of control. Synthesis of PQS (**Fig. 2E**) is accomplished through condensation reactions of anthranilate and β-keto-(do)decanoate (Bredenbruch *et al.* 2005). The genes responsible, *pqsA*, *pqsB*, *pqsC*, and *pqsD*, part of the *pqsABCDE* operon, also synthesize over 50 2-alkyl-4-quinolones (Lepine *et al.* 2004; Bredenbruch *et al.* 2005). Many of these are in low quantities and their physiological function is unknown (Déziel *et al.* 2004). One of these, however, is the immediate precursor of PQS, 2-heptyl-4(1*H*)-quinolone (HHQ) (**Fig. 2E**) (Déziel *et al.* 2004). The *pqsABCDE* operon is conserved in *Burkholderia pseudomallei*, *Burkholderia thailandensis*, and *Burkholderia cenocepacia* (Diggle *et al.* 2006b). These organisms synthesize HHQ, not PQS, and thus, HHQ has been proposed to be an intergenera signaling molecule. Expression of the *pqsABCDE* operon is also regulated by interkingdom signaling, as it has been shown to be activated by mammalian interferon-gamma (IFN-γ) and dynorphin (Wu *et al.* 2005; Zaborina *et al.* 2007). PqsE is important for host-pathogen adaptation (Rampioni *et al.* 2010).

The presence of many different QS systems serves as a testament to the idea that QS serves an important role in bacteria. By coordinating their behavior and only turning on specific genes, such as those for virulence, at high cell density, the bacteria are able to achieve their goal successfully and establish infection.

ANTIBIOTIC RESISTENCE

The discovery of penicillin by Alexander Fleming in the 1920's heralded the golden age of antibiotics (Fleming 1929; Kong *et al.* 2010). At the time, many believed that the discovery of these antibiotics would eradicate infectious disease. Of course, concomitant with the use of antibiotics was the appearance of resistant strains. Interestingly, penicillin resistance was central in Fleming's seminal paper (Fleming 1929).

Today, emerging antibiotic resistance in three groups of pathogens is of particular public health concern: methicillin-resistant *S. aureus* (MRSA), multidrug resistant (MDR) and extensively drug-resistant (XDR) *Mycobacterium tuberculosis*, and pandrug-resistant (PDR) and MDR Gram negative bacteria (Weigel *et al.* 2003; Falagas *et al.* 2005; Klevens *et al.* 2007). MRSA was first isolated in the United States in 1968 (Barrett *et al.* 1968). It is estimated that invasive MRSA led to 18,650 in-hospital deaths in the US in 2005 (Klevens *et al.* 2007). MRSA is treated with vancomycin. Fortunately, only a handful of vancomycin resistant *S. aureus* strains have been reported, nine in the US (Finks *et al.* 2009). In 2008, there were an estimated 11.1 million people with *M. tuberculosis* and 1.8 million *M. tuberculosis*-related deaths (World Health Organization 2010). It is also estimated that 3.6% of all *M. tuberculosis* infections are MDR and in some sections of the former Soviet Union, as many as 28.3% of all new tuberculosis cases were with MDR with 10% of these being XDR bacteria (World Health Organization 2010). Recent reviews have addressed the increased occurrence of MDR and PDR Gram negative pathogens: *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *E. coli*, and *P. aeruginosa* (Giske *et al.* 2008; Fischbach and Walsh 2009; Pfeifer *et al.* 2010). This increase not only results in greater mortality rates, but also a heavier economic burden (Giske *et al.* 2008). Unfortunately, the development of novel antibiotics is not keeping pace with the emergence of MDR and PDR Gram negative pathogens. This is adding to the inherent resistance of these organisms. For example, the rate of ceftazidime resistance for *P. aeruginosa* increased by 22% from 1997 to 2001 (Solomon *et al.* 2003). For especially pernicious infections caused by *P. aeruginosa*, more than one antibiotic is needed for eradication.

ALTERNATIVE THERAPIES

Alternative therapies are another avenue for treatment. Since ancient times, people have used natural products to treat infection. Antimicrobial activities have been identified in plants from every continent including Antarctica (for example: Romero *et al.* 2005; Ivanova *et al.* 2007; Oliveira *et al.* 2007; McGaw *et al.* 2008; Goncalves *et al.* 2009; Ahameethunisa and Hopper 2010). The antimicrobial properties of essential oils are also well established (Edris 2007; Alviano and Alviano 2009). Several classes of plant compounds, including phenols, polyphenols, phenolic acid, quinones, flavonoids, flavones, flavonols, tannins, coumarins, and polyacetylenes were found to be antimicrobial (Toda *et al.* 1992; King and Tempesta 1994; Perrett *et al.* 1995; Fernandez *et al.* 1996; Avato *et al.* 1997; Peres *et al.* 1997).

Besides possessing antibacterial properties, herbal remedies can also target QS. By targeting QS, an infective property of the bacteria, one can potentially impede the rate of resistance and infection. Halogenated furanones, synthesized by *Delisea pulchra*, were the first natural products to exhibit anti-QS effect by competitively binding to LuxR (Manefield *et al.* 1999, 2002). Evidence suggests that these compounds may also inhibit AI-2 signaling (Ren *et al.* 2001). Six south Florida medicinal plants, *Conocarpus erectus*, *Bucida buceras*, *Callistemon viminalis*, *Quercus virginiana*, *Tetrazygia bicolor* and *Chamaesyce hypericifolia*, were shown to inhibit QS in *Chromobacterium violaceum*, *Agrobacterium tumefaciens* and *P. aeruginosa* (Adonizio *et al.* 2006, 2008a). Aqueous extracts from three of these, *C. erectus*, *B. buceras*, and *C. viminalis*, significantly reduced the levels of pyoverdin, LasA protease, LasB elastase and biofilm formation (Adonizio *et al.* 2008a). Use of reporter constructs and HSL quantification suggested that *C. erectus* and *B. buceras* extracts inhibited both $3OC_{12}$-HSL and C_4-HSL expression while *C. viminalis* extracts specific-

ally inhibited $3OC_{12}$-HSL expression (Adonizio *et al.* 2008a). Further testing of these three extracts in a *Caenorhabditis elegans* model system demonstrated that they inhibited *P. aeruginosa* gut infection death and toxin-dependent mortality in 60% and 50-90% of the worms, respectively, without host cytotoxic effects (Adonizio *et al.* 2008b).

Garlic extracts have also been shown to inhibit QS. In DNA microarray experiments, addition of garlic extracts down-regulated 92 QS-regulated *P. aeruginosa* genes (Rasmussen *et al.* 2005). The exact mechanism of anti-QS action is unknown but believed to act upon either the I or R protein since the mRNA levels of the key QS players were unaffected (Rasmussen *et al.* 2005). Further experiments demonstrated a synergistic effect of garlic and tobramycin on *P. aeruginosa* biofilms in mice lungs (Bjarnsholt *et al.* 2005). Garlic altered the biofilm structure, increasing the bacteria's sensitivity to tobramycin, thus enhancing bacterial clearance from the lung (Bjarnsholt *et al.* 2005; Rasmussen *et al.* 2005). Garlic also has antibacterial effects (Tessema *et al.* 2006). Moving from a mouse model to human, a recent study was conducted analyzing the effect of garlic in patients with cystic fibrosis (Smyth *et al.* 2010). This is the first study conducted using an anti-QS agent in humans. Levels of HSLs were used as a marker for anti-QS; however, only $3OC_{12}$-HSL was detected. Overall, it was reported there was no significant difference between garlic-treated patients and their placebo counterparts. This may be attributed to small sample sizes (Smyth *et al.* 2010).

Other plants have been researched for their anti-infective properties based on their traditional use. One, *P. ginseng*, is the main focus of this review.

Panax ginseng

Ginseng has a long history of medicinal use, especially in China, Japan and Korea, and is highly valued. Used for rejuvenation of the body, it is considered an adaptogen, able to bolster the body's immune system during times of stress (Brekhman and Dardymov 1969). It is also believed to improve stamina and concentration (Petkov *et al.* 1994). In addition, it is believed to maintain homeostatic balance of the body. This is probably due to a wide range of chemicals found in the plant.

The Latin name for Asian ginseng is *P. ginseng.* The term "ginseng" is derived from the Chinese phonetic pronunciation of *ginseng*, which is rén shēn, or "the image of man," because of the roots' anthropomorphic resemblance to the human body. Ginseng belongs to the genus *Panax,* derived from the Greek word for cure all, "panacea," because it was believed to be a universal remedy. There are about 11 species of the genus *Panax*. All are characterized by the presence of ginsenosides. Besides *P. ginseng*, American ginseng (*Panax quinquefolius*) is also used in herbal medicine and extensively researched. In addition, Tienchi or Sanchi (*Panax notoginseng*), Japanese ginseng (*Panax japonicus*), and Vietnamese ginseng (*Panax vietnamensis*) are also widely grown and used as folk remedies (Yun 2001). While some compounds are shared by many of the *Panax* species, some are only found in one. These distinctions are useful in determining purity of ginseng preparations. For example, the ginsenoside Rf, is found in *P. ginseng* but not in *P. quinquefolius* (Li *et al.* 2000).

P. ginseng is typically found in the cooler regions of the Northern Hemisphere. Often reaching a height of six to 18 inches, the slow growing perennial plant has one to three umbels of 15 to 30 flowers and bears a round, small-sized, red berry (Fleming 1998). Roots are often harvested at four to six years of age. Roots are yellowish white and contain a primary root divided into rootlets and root hairs. Depending on the time of harvest and processing of the root, it can be called either white or red ginseng (Yun 2001). White ginseng is when the peeled root has been dried in the sun and retains a white color. Red ginseng refers to the steaming and boiling of the root resulting in the titular color. Both types of ginseng yield different kinds of compounds because of the processing method employed, causing partial hydrolysis of esters and glycosides (Blumenthal 2003).

Several bioactive compounds have been identified in *P. ginseng*, including polysaccharides, polyenes, flavonoids, volatile oils and ginsenosides (Hou 1977). Of these, the ginsenosides are perhaps the best characterized. Ginsenosides or saponins contain four ring hydrophobic steroid-like structures with attached sugars which may be a glucose, maltose, fructose, galactose, pentose, or methylpentose (Liu and Xiao 1992; Coates 2005). It is in the variation, number, and position of the sugar group that account for each ginsenosides' unique physiological effect on the body. To date, 38 ginsenosides have been isolated from *P. ginseng*, far exceeding the number of ginsenosides found in any other species (Choi 2008). Ginsenosides have been divided into groups based on their structure. Most ginsenosides belong to one of two main groups, protopanaxadiols (PPD) and protopanaxatriols (PPT), which differ at the C_6 position (Leung and Wong 2010). There are also rare ginsenosides, such as oleanane (Leung and Wong 2010). Ginsenoside content varies depending upon the age of the plant and season at the time of harvest, the part of the plant used, and how the plant material is processed (preserved and extracted) (Liberti and Der Marderosian 1978). Interestingly, the ratio of ginsenosides can determine physiological effect (Jin *et al.* 1999).

Due to the complex chemical composition of ginseng, many different physiological effects have been noted to be consistent with its use as a panacea. The literature is vast, thus the reader is referred to several recent reviews summarizing ginseng's immune system modulatory, anti-cancer and cytotoxic, neuroprotective, memory and learning stimulatory, antihyperglycemic, aphrodisiac and cardiovascular effects (Radad *et al.* 2006; Choi 2008; Christensen 2009; Jia *et al.* 2009; Lee *et al.* 2009b). This chapter focuses on the antimicrobial effects of *P. ginseng* extracts and components. Three mechanisms of microbial inhibition have been attributed to *P. ginseng:* inhibition of infection via immune system modulation, direct antibacterial activity, or inhibition of virulence factor production.

To better understand how *P. ginseng* affects the immune system response to microbial infection, a brief summary of the immune system focusing on aspects affected by ginseng is warranted. The initial response is detection of the pathogen by the innate immune system. This occurs by recognition of pathogen-associated molecular patterns (PAMPs) by its cognate Toll-like receptor (TLR) (Janeway 1989; Medzhitov *et al.* 1997; Uematsu and Akira 2008). PAMP binding to TLRs activates a signaling pathway that requires the adapter protein, myeloid differentiation primary response gene 88 (MyD88) (Lord *et al.* 1990; Medzhitov *et al.* 1998). Depending upon which TLR is conducting the signal, different cytokines are secreted which in turn activate the adaptive immune response (Medzhitov and Janeway 1999). This includes differentiation of CD4 cells into various T helper (Th) cell lineages including Th1, Th2, and Th17 (reviewed in Zhu *et al.* 2010). The Th1 response is required to clear intracellular pathogens, the Th2 response is important for extracellular pathogens, and the Th17 response targets Gram negative bacteria, fungi and select protozoa (reviewed in Fietta and Delsante 2009)). In a Th1 response, secretion of IFN-γ, interleukin-2 (IL-2), and tumor necrosis factor alpha (TNF-α) (Mosmann *et al.* 1986; Killar *et al.* 1987) leads to macrophage activation and cellular immunity (Meltzer *et al.* 1982). Interleukin 12 (IL-12) is important for the Th1 response because it induces IFN-γ and TNF production, natural killer cell and T-cell proliferation and CD-4 to Th1 cell differentiation (Trinchieri *et al.* 1992). A Th2 response results in humoral immunity through secretion of interleukin 4 (IL-4), interleukin 5 (IL-5), and interleukin 13 (IL-13) (Mosmann *et al.* 1986; Killar *et al.* 1987) which in turn suppress macrophage activation and stimulate IgE production, as well as eosinophil and mast cell activation (reviewed in Deo *et al.* 2010). If the pathogen enters macro-

phages, a Th2 response would cause extensive tissue damage without affecting the pathogen, while the inflammation caused by the Th1 response would not be as damaging and would likely slow disease progression due to increased pathogen clearance. *P. aeruginosa* infection promotes a Th2 response, in part by production of $3OC_{12}$-HSL (Telford *et al.* 1998).

P. ginseng has long been known to have immunomodulatory activities (reviewed in Spelman *et al.* 2006). Modulation of the immune system by *P. ginseng* also enhances bacterial clearance (Song *et al.* 1997a). Crude aqueous extracts administered subcutaneously to a *P. aeruginosa* infected chronic pneumonia rat model system resulted in less severe lung pathology and a reduction in numbers of mast cells in lung foci, total immunoglobulin (IgG) levels and bacterial load with respect to infected animals treated with cortisone or saline instead of ginseng (Song *et al.* 1997a). The polymorphonuclear cell oxidative burst response and serum IgG2 levels were increased compared to the untreated or uninfected controls (Song *et al.* 1998). Interestingly, similar results were also observed in athymic rats (Song *et al.* 1997b). Together, these data suggest that ginseng activates innate immunity, enhances the Th1 response and down-regulates the Th2 response (Song *et al.* 1997a, 1997b, 1998). These studies did not measure cytokines.

Cytokines were measured in studies using a commercial preparation of ginseng, Gerimax ginseng, on the same *P. aeruginosa* rat model infection system (Song *et al.* 2002). Daily ginseng treatment resulted in decreased serum IgM and lung IL-4 levels seven days post infection. By day 21, lung IgA, IFN-γ, IL-4 and TNF-α and serum IgG2a responses were increased and lung pathology and *P. aeruginosa* colony forming units were reduced (Song *et al.* 2002). This is suggestive that ginseng promotes a shift from a Th2 to Th1 response. An *in vitro* assay showed that addition of Gerimax ginseng aqueous extracts in the presence of LPS and IFN-γ to peripheral blood mononuclear cells increased IL-12 production by at least 5% compared to control, further suggesting that ginseng can stimulate the Th1 response (Larsen *et al.* 2004). Experiments with *P. ginseng* using a mouse chronic *P. aeruginosa* infection model also corroborate this effect, IFN-γ and TNF-α levels as well as IFN-γ/IL-4 ratio were higher and IL-4 levels were lower in the ginseng-treated animals relative to the control group (Song *et al.* 2003). As before, there was a milder lung pathology and increased bacterial clearance (Song *et al.* 2003).

Although it is possible that the aqueous *P. ginseng* extract affected *P. aeruginosa* clearance only by modulating the immune system, recent studies have shown that it directly inhibits *P. aeruginosa* QS (Song *et al.* 2010). Addition of ginseng extract to PAO1 cultures resulted in decreased $3OC_{12}$-HSL and C_4-HSL production, LasA and LasB activity, without affecting growth. Since $3OC_{12}$-HSL stimulates the Th2 response, and ginseng promotes the Th1 response over that of Th2, it is possible that this is accomplished at least in part through QS inhibition. In agreement with this, aqueous *P. ginseng* extracts reduced biofilm formation and disrupted pre-formed biofilms in *P. aeruginosa* (Wu *et al.* 2011). Twitching and swimming motility were enhanced while swarming was also reduced (Wu *et al.* 2011). Biofilm formation and swarming are both QS-dependent (Davies *et al.* 1998, Kohler *et al.* 2000). Recently, an acetone:water extract of *P. notoginseng* flowers were shown to have antibacterial and anti-QS activity against *C. violaceum* and inhibit swarming in *P. aeruginosa* (Koh and Tham 2011).

Thus, ginseng seems to offer promise as an anti-*Pseudomonas* therapeutic agent, however, more investigation is needed. As previously stated, overproduction of alginate and conversion to a mucoid phenotype by *P. aeruginosa* leads to poor patient prognosis. Addition of aqueous ginseng extract to a well-characterized mucoid variant of PAO1 stimulated alginate production, yet reduced biofilm formation *in vitro* (Song *et al.* 2010; Wu *et al.* 2011). This may be explained by the observation that alginate production promotes formation of three-dimensional biofilms, while reducing biofilm formation in a solid-surface assay (Hay *et al.* 2009). Thus, additional studies must be performed to determine the suitability and conditions of ginseng use in treatment of acute and chronic *P. aeruginosa* infections. Also, since these observations were made using a crude extract, it is possible that different compounds are responsible for the different activities. Purification, characterization and identification of the active compounds may facilitate the development of therapeutics with different modes of action.

Purified components of *P. ginseng* also modulate the immune system to facilitate bacterial clearance (Lim *et al.* 2002; Ahn *et al.* 2006a). Ginsan is an acidic polysaccharide present in the ethanol insoluble aqueous fraction that consists of α(1→6) glucopyranoside and β(2→6) fructofuranoside (Lee *et al.* 1997; Ahn *et al.* 2006a, 2006b). Ginsan does not have a direct antibacterial effect on *S. aureus in vitro* (Lim *et al.* 2002; Ahn *et al.* 2006b), but has an anti-septicaemic effect in mice infected with *S. aureus* (Lim *et al.* 2002). Pretreatment of mice with ginsan protected the animals from death due to *S. aureus* infection (Lim *et al.* 2002; Ahn *et al.* 2006a). Increased bacterial clearance was observed that may be due to a reduced early acute inflammatory response and enhanced macrophage activation (Lim *et al.* 2002; Ahn *et al.* 2006a). Ginsan did increase the *in vitro* phagocytic activity of macrophages (Ahn *et al.* 2006b). To further analyze if ginsan was acting through macrophages *in vivo*, mice were treated with the anti-cancer drug etoposide, which depletes macrophages (Ahn *et al.* 2006b). Etoposide treatment and ginsan lowered bacterial levels and increased survival rates compared to mice treated with just etoposide, suggesting that the anti-bacterial activity was not through ginsan acting on macrophages (Ahn *et al.* 2006b), however, it is possible that the etoposide did not completely deplete the macrophages.

Ginsan may act by down-regulating inflammatory cytokines. In sepsis, Toll-like receptor and MyD88 are also key players in the inflammatory response as they detect PAMPs and transduce the signal to induce expression of relevant genes and certain cytokines (Peck-Palmer *et al.* 2008). *In vivo*, pretreatment of mice with ginsan prior to infection with *S. aureus*, resulted in decreased levels of IL-1β, IL-6, TNF-α, IFN-γ, IL-12 and IL-18 (Ahn *et al.* 2006b), which are usually elevated in sepsis. Ginsan treatment decreased levels of Toll-like receptor and MyD88 in mouse peritoneal macrophages treated with heat-killed *S. aureus in vitro* (Ahn *et al.* 2006b). By activating macrophages and down-regulating inflammatory cytokines, ginsan is able to impart a protective effect on mice. Ginsan treatment combined with vancomycin administration enhances survival in this mouse septic model system (Lim *et al.* 2002).

Besides being a biological response modifier, acidic polysaccharides purified from *P. ginseng* display anti-adhesive activities (Belogortseva *et al.* 2000; Lee *et al.* 2004a, 2004b, 2006, 2009a). The structures of these are not as well characterized as ginsan, however, these polysaccharides are pectin-like and are rich in uronic acid, with the majority being galacturonic acid (Lee *et al.* 2009a). These effectively inhibit adhesion of the gut pathogen, *Helicobacter pylori*, the oral pathogens *Porphytomonas gingivalis* and *Actinobacillus actinomycetemcomitans*, and the skin pathogens *Propionibacterium acnes* and *S. aureus* (Lee *et al.* 2004b, 2006, 2009a). Interestingly, these polysaccharides did not affect adhesion of the commensal bacteria *Staphylococcus epidermidis*, *E. coli*, *Lactobacillus acidophilus* and *Bifidobacterium bifidum* (Lee *et al.* 2006, 2009a). The polysaccharides did not affect growth of either the mammalian cells or the bacteria (Lee *et al.* 2006, 2009a). These properties of only targeting pathogenic bacteria without harming the natural flora or the host cells make these compounds potential therapeutics.

Polyacetylenes have also been isolated from *P. ginseng* (Fujimoto and Satoh 1988; Matsunaga *et al.* 1989; Fujimoto *et al.* 1990). One of these, panaxytriol, inhibits growth of *H.*

Table 2 Summary of anti-microbial effects of *Panax ginseng*.

Panax ginseng component	Target organism	Effect	Reference
Aqueous extract	*P. aeruginosa*	Immunoclearance	Song *et al*. 1997a
		Shift to Th1 response	Song *et al.* 1997a, 1997b, 1998
		QS inhibition	Song *et al.* 2010
		Reduced biofilm formation	Wu *et al*. 2011
		Reduced swarming, enhanced motility	Wu *et al*. 2011
Ginsan	*S. aureus*	Reduced acute inflammatory response, enhanced macrophage activation, anti-septicaemic effect	Lin *et al*. 2002, Ahn *et al.* 2006a
		Enhanced macrophage phagocytic in vitro activity	Ahn *et al.* 2006b
Uronic acid-rich polysaccharides	*H. pylori*, *P. gingivalis*, *S. aureus*, *P. acnes*, *A. acitinomycetemcomitans*	Adhesion inhibition	Lee *et al.* 2004b, 2006, 2009a
Panaxytriol	*H. pylori*	Growth inhibition	Bae *et al.* 2001
Ginsenosides	*S. aureus*, *S. epidermis*, *S. typhimuriaum*, *V. vulnificus*	Growth inhibition	Sung and Lee 2008

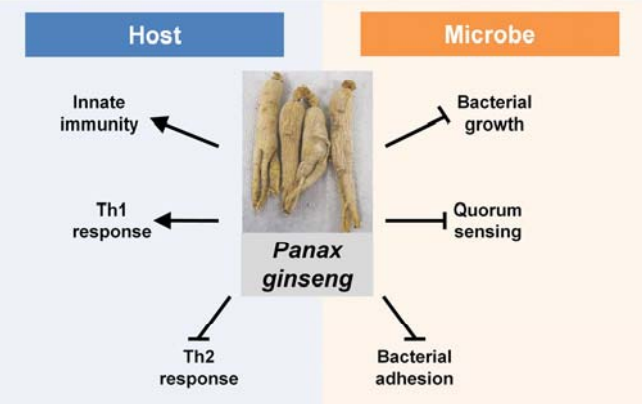

Fig. 3 Summary of *Panax ginseng* activities affecting microbial growth and pathogenesis.

pylori (Bae *et al.* 2001). Panaxytriol is also a cell cycle inhibitor, arresting a mouse lymphoma cell line, P388D1 at G2/M (Kim *et al.* 2002). To date, there is limited literature on the anti-bacterial activity of *P. ginseng* derived polyacetylenes, although polyacetylenes isolated from other sources have been demonstrated to affect microbial growth (Lechner *et al.* 2004; Schinkovitz *et al.* 2008).

Ginsenosides have also been identified as having antibacterial and immunomodulatory activities. A ginsenoside fraction purified from *P. ginseng* containing Rb_1, Rb_2, Rc, Rd, Re, Rf, Rg_1, Rg_2, Rg_3, Rh_2 inhibited growth at a minimum inhibitory concentration (MIC) of 100 µg/ml of *S. aureus*, *S. epidermidis*, *Salmonella typhimurium*, and *Vibrio vulnificus* (Sung and Lee 2008). The ginsenosides were not as effective as the positive controls, nisin (MIC against the Gram positive bacteria, 40 µg/ml) and propionic acid (MIC against Gram negative bacteria, 50 µg/ml). The ginsenosides exhibited a synergistic effect with kanamycin and cefotaxime against MRSA (Sung and Lee 2008). The exact mechanism for this effect is unknown but since ginsenosides are amphipathic they may interact with the cell membrane and allow entry of the antibiotic into the cell. In agreement with perturbation of the cell membrane by the ginsenosides, addition of the ginsenosides to calcein-encapsulated large unilamellar vesicles resulted in a dose-dependent leakage of dye (Sung and Lee 2008). Mitogen-induced lymphocyte proliferation was reduced by treatment with Rb_2, Re and Rg_1, but not Rb_1 (Cho *et al.* 2002). A caveat to these results is that the ginsenosides used were purified from *P. ginseng* and the fraction may contain other compounds, although the fractions shown to have immunomodulatory effects were >95% pure.

CONCLUSION

In summary, ginseng contains immunomodulatory, antimicrobial and anti-QS compounds that may be useful in treatment of bacterial infections (**Fig. 3, Table 2**). While some active compounds have been isolated and characterized, limited studies have been performed and the main compounds responsible for the anti-*Pseudomonas* immune system modulation and anti-QS effect remain to be purified. Once the bioactive compound(s) have been isolated they can be characterized for their effects alone and in combination with other effective compounds and antibiotics *in vitro* and in animal models. These studies will pave the way for ginseng use as an anti-infective therapeutic.

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REFERENCES

Adonizio A, Kong KF, Mathee K (2008a) Inhibition of quorum sensing-controlled virulence factor production in *Pseudomonas aeruginosa* by South Florida plant extracts. *Antimicrobial Agents and Chemotherapy* **52**, 198-203

Adonizio A, Leal SM Jr., Ausubel FM, Mathee K (2008b) Attenuation of *Pseudomonas aeruginosa* virulence by medicinal plants in a *Caenorhabditis elegans* model system. *Journal of Medical Microbiology* **57**, 809-813

Adonizio AL, Downum K, Bennett BC, Mathee K (2006) Anti-quorum sensing activity of medicinal plants in southern Florida. *Journal of Ethnopharmacology* **105**, 427-435

Aguilar C, Friscina A, Devescovi G, Kojic M, Venturi V (2003) Identification of quorum-sensing-regulated genes of *Burkholderia cepacia*. *Journal of Bacteriology* **185**, 6456-6462

Ahameethunisa AR, Hopper W (2010) Antibacterial activity of *Artemisia nilagirica* leaf extracts against clinical and phytopathogenic bacteria. *BMC Complementary and Alternative Medicine* **10**, 6

Ahn JY, Choi IS, Shim JY, Yun EK, Yun YS, Jeong G, Song JY (2006a) The immunomodulator ginsan induces resistance to experimental sepsis by inhibiting Toll-like receptor-mediated inflammatory signals. *European Journal of Immunology* **36**, 37-45

Ahn JY, Song JY, Yun YS, Jeong G, Choi IS (2006b) Protection of *Staphylococcus aureus*-infected septic mice by suppression of early acute inflammation and enhanced antimicrobial activity by ginsan. *FEMS Immunology and Medical Microbiology* **46**, 187-197

Alviano DS, Alviano CS (2009) Plant extracts: search for new alternatives to treat microbial diseases. *Current Pharmaceutical Biotechnology* **10**, 106-121

Ankenbauer R, Sriyosachati S, Cox CD (1985) Effects of siderophores on the growth of *Pseudomonas aeruginosa* in human serum and transferrin. *Infection and Immunity* **49**, 132-140

Avato P, Vitali C, Mongelli P, Tava A (1997) Antimicrobial activity of polyacetylenes from *Bellis perennis* and their synthetic derivatives. *Planta Medica* **63**, 503-507

Bae EA, Han MJ, Baek NI, Kim DH (2001) *In vitro* anti-*Helicobacter pylori*

activity of panaxytriol isolated from ginseng. *Archives of Pharmacal Research* **24**, 297-299

Barrett FF, McGehee RF Jr., Finland M (1968) Methicillin-resistant *Staphylococcus aureus* at Boston City Hospital. Bacteriologic and epidemiologic observations. *New England Journal of Medicine* **279**, 441-448

Bassler BL, Wright M, Showalter RE, Silverman MR (1993) Intercellular signalling in *Vibrio harveyi*: Sequence and function of genes regulating expression of luminescence. *Molecular Microbiology* **9**, 773-786

Belogortseva NI, Yoon JY, Kim KH (2000) Inhibition of *Helicobacter pylori* hemagglutination by polysaccharide fractions from roots of *Panax ginseng*. *Planta Medica* **66**, 217-220

Bever RA, Iglewski BH (1988) Molecular characterization and nucleotide sequence of the *Pseudomonas aeruginosa* elastase structural gene. *Journal of Bacteriology* **170**, 4309-4314

Bjarnsholt T, Jensen PO, Rasmussen TB, Christophersen L, Calum H, Hentzer M, Hougen HP, Rygaard J, Moser C, Eberl L, Hoiby N, Givskov M (2005) Garlic blocks quorum sensing and promotes rapid clearing of pulmonary *Pseudomonas aeruginosa* infections. *Microbiology* **151**, 3873-3880

Blumenthal M (2003) *The ABC Clinical Guide to Herbs*, Theime, New York, 510 pp

Boon C, Deng Y, Wang LH, He Y, Xu JL, Fan Y, Pan SQ, Zhang LH (2008) A novel DSF-like signal from *Burkholderia cenocepacia* interferes with *Candida albicans* morphological transition. *ISME Journal* **2**, 27-36

Bredenbruch F, Nimtz M, Wray V, Morr M, Muller R, Haussler S (2005) Biosynthetic pathway of *Pseudomonas aeruginosa* 4-hydroxy-2-alkylquinolines. *Journal of Bacteriology* **187**, 3630-3635

Brekhman, II, Dardymov IV (1969) New substances of plant origin which increase nonspecific resistance. *Annual Review of Pharmacology* **9**, 419-430

Burger M, Glaser L, Burton RM (1962) The synthesis of a rhamnolipid by enzyme preparations from *Pseudomonas aeruginosa*. *Biochimica et Biophysica Acta* **56**, 172-174

Cao B, Wang H, Sun H, Zhu Y, Chen M (2004) Risk factors and clinical outcomes of nosocomial multi-drug resistant *Pseudomonas aeruginosa* infections. *Journal of Hospital Infection* **57**, 112-118

Cao JG, Meighen EA (1989) Purification and structural identification of an autoinducer for the luminescence system of *Vibrio harveyi*. *Journal of Biological Chemistry* **264**, 21670-21676

Chen X, Schauder S, Potier N, Van Dorsselaer A, Pelczer I, Bassler BL, Hughson FM (2002) Structural identification of a bacterial quorum-sensing signal containing boron. *Nature* **415**, 545-549

Cho JY, Kim AR, Yoo ES, Baik KU, Park MH (2002) Ginsenosides from *Panax ginseng* differentially regulate lymphocyte proliferation. *Planta Medica* **68**, 497-500

Choi KT (2008) Botanical characteristics, pharmacological effects and medicinal components of Korean *Panax ginseng* C A Meyer. *Acta Pharmacologica Sinica* **29**, 1109-1118

Christensen LP (2009) Ginsenosides chemistry, biosynthesis, analysis, and potential health effects. *Advances in Food and Nutrition Research* **55**, 1-99

Chugani S, Greenberg EP (2010) LuxR homolog-independent gene regulation by acyl-homoserine lactones in *Pseudomonas aeruginosa*. *Proceedings of the National Academy of Sciences USA* **107**, 10673-10678

Chugani SA, Whiteley M, Lee KM, D'Argenio D, Manoil C, Greenberg EP (2001) QscR, a modulator of quorum-sensing signal synthesis and virulence in *Pseudomonas aeruginosa*. *Proceedings of the National Academy of Sciences USA* **98**, 2752-2757

Clarke MB, Hughes DT, Zhu C, Boedeker EC, Sperandio V (2006) The QseC sensor kinase: A bacterial adrenergic receptor. *Proceedings of the National Academy of Sciences USA* **103**, 10420-10425

Coates PM, Blackman MR, Cragg GM, Levine M, Moss J, White JD (2005) *Encyclopedia of Dietary Supplements* (1st Edn), Marcel Dekker, New York, 819 pp

Conway BA, Greenberg EP (2002) Quorum-sensing signals and quorum-sensing genes in *Burkholderia vietnamiensis*. *Journal of Bacteriology* **184**, 1187-1191

Costerton JW, Stewart PS, Greenberg EP (1999) Bacterial biofilms: A common cause of persistent infections. *Science* **284**, 1318-1322

Davies DG, Parsek MR, Pearson JP, Iglewski BH, Costerton JW, Greenberg EP (1998) The involvement of cell-to-cell signals in the development of a bacterial biofilm. *Science* **280**, 295-298

Dekimpe V, Déziel E (2009) Revisiting the quorum-sensing hierarchy in *Pseudomonas aeruginosa*: The transcriptional regulator RhlR regulates LasR-specific factors. *Microbiology* **155**, 712-723

Deng Y, Boon C, Eberl L, Zhang LH (2009) Differential modulation of *Burkholderia cenocepacia* virulence and energy metabolism by the quorum-sensing signal BDSF and its synthase. *Journal of Bacteriology* **191**, 7270-7278

Deo SS, Mistry KJ, Kakade AM, Niphadkar PV (2010) Role played by Th2 type cytokines in IgE mediated allergy and asthma. *Lung India* **27**, 66-71

Déziel E, Lépine F, Milot S, He J, Mindrinos MN, Tompkins RG, Rahme LG (2004) Analysis of *Pseudomonas aeruginosa* 4-hydroxy-2-alkylquinolines (HAQs) reveals a role for 4-hydroxy-2-heptylquinoline in cell-to-cell communication. *Proceedings of the National Academy of Sciences USA* **101**, 1339-1344

Diggle SP, Cornelis P, Williams P, Camara M (2006a) 4-quinolone signalling in *Pseudomonas aeruginosa*: Old molecules, new perspectives. *International Journal of Medical Microbiology* **296**, 83-91

Diggle SP, Lumjiaktase P, Dipilato F, Winzer K, Kunakorn M, Barrett DA, Chhabra SR, Camara M, Williams P (2006b) Functional genetic analysis reveals a 2-alkyl-4-quinolone signaling system in the human pathogen *Burkholderia pseudomallei* and related bacteria. *Chemistry and Biology* **13**, 701-710

Drenkard E (2003) Antimicrobial resistance of *Pseudomonas aeruginosa* biofilms. *Microbes and Infection* **5**, 1213-1219

Duan K, Dammel C, Stein J, Rabin H, Surette MG (2003) Modulation of *Pseudomonas aeruginosa* gene expression by host microflora through interspecies communication. *Molecular Microbiology* **50**, 1477-1491

Duan K, Surette MG (2007) Environmental regulation of *Pseudomonas aeruginosa* PAO1 Las and Rhl quorum-sensing systems. *Journal of Bacteriology* **189**, 4827-4836

Dubern JF, Lugtenberg BJ, Bloemberg GV (2006) The *ppuI-rsaL-ppuR* quorum-sensing system regulates biofilm formation of *Pseudomonas putida* PCL1445 by controlling biosynthesis of the cyclic lipopeptides putisolvins I and II. *Journal of Bacteriology* **188**, 2898-2906

Duong F, Bonnet E, Geli V, Lazdunski A, Murgier M, Filloux A (2001) The AprX protein of *Pseudomonas aeruginosa*: A new substrate for the Apr type I secretion system. *Gene* **262**, 147-153

Duong F, Lazdunski A, Cami B, Murgier M (1992) Sequence of a cluster of genes controlling synthesis and secretion of alkaline protease in *Pseudomonas aeruginosa*: Relationships to other secretory pathways. *Gene* **121**, 47-54

Eberhard A (1972) Inhibition and activation of bacterial luciferase synthesis. *Journal of Bacteriology* **109**, 1101-1105

Eberhard A, Burlingame AL, Eberhard C, Kenyon GL, Nealson KH, Oppenheimer NJ (1981) Structural identification of autoinducer of *Photobacterium fischeri* luciferase. *Biochemistry* **20**, 2444-2449

Edris AE (2007) Pharmaceutical and therapeutic potentials of essential oils and their individual volatile constituents: A review. *Phytotherapy Research* **21**, 308-323

Edwards JR, Hayashi JA (1965) Structure of a rhamnolipid from *Pseudomonas aeruginosa*. *Archives of Biochemistry and Biophysics* **111**, 415-421

Elliott SJ, Wainwright LA, McDaniel TK, Jarvis KG, Deng YK, Lai LC, McNamara BP, Donnenberg MS, Kaper JB (1998) The complete sequence of the locus of enterocyte effacement (LEE) from enteropathogenic *Escherichia coli* E2348/69. *Molecular Microbiology* **28**, 1-4

Engebrecht J, Nealson K, Silverman M (1983) Bacterial bioluminescence: Isolation and genetic analysis of functions from *Vibrio fischeri*. *Cell* **32**, 773-781

Engebrecht J, Silverman M (1984) Identification of genes and gene products necessary for bacterial bioluminescence. *Proceedings of the National Academy of Sciences USA* **81**, 4154-4158

Engebrecht J, Silverman M (1987) Nucleotide sequence of the regulatory locus controlling expression of bacterial genes for bioluminescence. *Nucleic Acids Research* **15**, 10455-10467

Evans LR, Linker A (1973) Production and characterization of the slime polysaccharide of *Pseudomonas aeruginosa*. *Journal of Bacteriology* **116**, 915-924

Falagas ME, Bliziotis IA, Kasiakou SK, Samonis G, Athanassopoulou P, Michalopoulos A (2005) Outcome of infections due to pandrug-resistant (PDR) Gram-negative bacteria. *BMC Infectious Diseases* **5**, 24

Farrow JM III, Pesci EC (2007) Two distinct pathways supply anthranilate as a precursor of the *Pseudomonas* quinolone signal. *Journal of Bacteriology* **189**, 3425-3433

Fernandez MA, Garcia MD, Saenz MT (1996) Antibacterial activity of the phenolic acids fractions of *Scrophularia frutescens* and *Scrophularia sambucifolia*. *Journal of Ethnopharmacology* **53**, 11-14

Fietta P, Delsante G (2009) The effector T helper cell triade. *Rivista di Biologia* **102**, 61-74

Finck-Barbancon V, Goranson J, Zhu L, Sawa T, Wiener-Kronish JP, Fleiszig SM, Wu C, Mende-Mueller L, Frank DW (1997) ExoU expression by *Pseudomonas aeruginosa* correlates with acute cytotoxicity and epithelial injury. *Molecular Microbiology* **25**, 547-557

Finks J, Wells E, Dyke TL, Husain N, Plizga L, Heddurshetti R, Wilkins M, Rudrik J, Hageman J, Patel J, Miller C (2009) Vancomycin-resistant *Staphylococcus aureus*, Michigan, USA, 2007. *Emerging Infectious Diseases* **15**, 943-945

Fischbach MA, Walsh CT (2009) Antibiotics for emerging pathogens. *Science* **325**, 1089-1093

Fleming A (1929) On the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of *B. influenzae*. *British Journal of Experimental Pathology* **10**, 226-236

Fleming T (1998) *Physician Desk References for Herbal Medicine*, Medical Economics Company, New Jersey, 1101 pp

Frederiksen B, Koch C, Hoiby N (1999) Changing epidemiology of *Pseudomonas aeruginosa* infection in Danish cystic fibrosis patients (1974-1995). *Pediatric Pulmonology* **28**, 159-166

Friedman L, Kolter R (2004a) Genes involved in matrix formation in *Pseudomonas aeruginosa* PA14 biofilms. *Molecular Microbiology* **51**, 675-690

Friedman L, Kolter R (2004b) Two genetic loci produce distinct carbohydrate-

rich structural components of the *Pseudomonas aeruginosa* biofilm matrix. *Journal of Bacteriology* **186**, 4457-4465

Fujimoto Y, Satoh M (1988) A new cytotoxic chlorine-containing polyacetylene from the callus of *Panax ginseng*. *Chemical and Pharmaceutical Bulletin* **36**, 4206-4208

Fujimoto Y, Satoh M, Takeuchi N, Kirisawa M (1990) Synthesis and absolute configurations of the cytotoxic polyacetylenes isolated from the callus of *Panax ginseng*. *Chemical and Pharmaceutical Bulletin* **38**, 1447-1450

Fuqua C, Winans SC, Greenberg EP (1996) Census and consensus in bacterial ecosystems: The LuxR-LuxI family of quorum-sensing transcriptional regulators. *Annual Review of Microbiology* **50**, 727-751

Garau J, Gomez L (2003) *Pseudomonas aeruginosa* pneumonia. *Current Opinion in Infectious Diseases* **16**, 135-143

Giske CG, Monnet DL, Cars O, Carmeli Y (2008) Clinical and economic impact of common multidrug-resistant Gram-negative bacilli. *Antimicrobial Agents and Chemotherapy* **52**, 813-821

Goldberg JB, Ohman DE (1987) Activation of an elastase precursor by the *lasA* gene product of *Pseudomonas aeruginosa*. *Journal of Bacteriology* **169**, 4532-4539

Goncalves S, Quintas C, Gaspar MN, Nogueira JMF, Romano A (2009) Antimicrobial activity of *Drosophyllum lusitanicum*, an endemic Mediterranean insectivorous plant. *Natural Product Research* **23**, 219-229

Greenberg EP, Hastings JW, Ulitzer S (1979) Induction of luciferase synthesis in *Beneckea harveyi* by other marine bacteria. *Archives of Microbiology* **120**, 87-91

Havarstein LS, Coomaraswamy G, Morrison DA (1995) An unmodified heptadecapeptide pheromone induces competence for genetic transformation in *Streptococcus pneumoniae*. *Proceedings of the National Academy of Sciences USA* **92**, 11140-11144

Hay ID, Gatland K, Campisano A, Jordens JZ, Rehm BH (2009) Impact of alginate overproduction on attachment and biofilm architecture of a supermucoid *Pseudomonas aeruginosa* strain. *Applied and Environmental Microbiology* **75**, 6022-6025

Henke JM, Bassler BL (2004) Three parallel quorum-sensing systems regulate gene expression in *Vibrio harveyi*. *Journal of Bacteriology* **186**, 6902-6914

Higgins DA, Pomianek ME, Kraml CM, Taylor RK, Semmelhack MF, Bassler BL (2007) The major *Vibrio cholerae* autoinducer and its role in virulence factor production. *Nature* **450**, 883-886

Hoiby N (1974) Epidemiological investigations of the respiratory tract bacteriology in patients with cystic fibrosis. *APMIS. Section B: Microbiology and Immunology* **82**, 541-550

Hoiby N, Flensborg EW, Beck B, Friis B, Jacobsen SV, Jacobsen L (1977) *Pseudomonas aeruginosa* infection in cystic fibrosis. Diagnostic and prognostic significance of *Pseudomonas aeruginosa* precipitins determined by means of crossed immunoelectrophoresis. *Scandinavian Journal of Respiratory Diseases* **58**, 65-79

Homma H, Yamanaka A, Tanimoto S, Tamura M, Chijimatsu Y, Kira S, Izumi T (1983) Diffuse panbronchiolitis. A disease of the transitional zone of the lung. *Chest* **83**, 63-69

Homma JY, Suzuki N (1961) A simple protein with pyocine activity isolated from the cell wall of *Pseudomonas aeruginosa* and its close relation to endotoxin. *Japanese Journal of Experimental Medicine* **31**, 209-213

Homma JY, Suzuki N, Ito F (1963) The surface structure of *Pseudomonas aeruginosa*. *Journal of Immunology* **90**, 819-828

Hood RD, Singh P, Hsu F, Guvener T, Carl MA, Trinidad RR, Silverman JM, Ohlson BB, Hicks KG, Plemel RL, Li M, Schwarz S, Wang WY, Merz AJ, Goodlett DR, Mougous JD (2010) A type VI secretion system of *Pseudomonas aeruginosa* targets a toxin to bacteria. *Cell Host and Microbe* **7**, 25-37

Hou JP (1977) The chemical constituents of ginseng plants. *Comparative Medicine East and West* **5**, 123-145

Huber B, Riedel K, Hentzer M, Heydorn A, Gotschlich A, Givskov M, Molin S, Eberl L (2001) The cep quorum-sensing system of *Burkholderia cepacia* H111 controls biofilm formation and swarming motility. *Microbiology* **147**, 2517-2528

Iglewski BH, Sadoff J, Bjorn MJ, Maxwell ES (1978) *Pseudomonas aeruginosa* exoenzyme S: an adenosine diphosphate ribosyltransferase distinct from toxin A. *Proceedings of the National Academy of Sciences USA* **75**, 3211-3215

Ivanova V, Kolarova M, Aleksieva K, Dornberger KJ, Haertl A, Moellmann U, Dahse HM, Chipev N (2007) Sanionins: Anti-inflammatory and antibacterial agents with weak cytotoxicity from the Antarctic moss *Sanionia georgico-uncinata*. *Preparative Biochemistry and Biotechnology* **37**, 343-352

Janeway CA Jr. (1989) Approaching the asymptote? Evolution and revolution in immunology. *Cold Spring Harbor Symposia on Quantitative Biology* **54 Pt 1**, 1-13

Ji G, Beavis RC, Novick RP (1995) Cell density control of staphylococcal virulence mediated by an octapeptide pheromone. *Proceedings of the National Academy of Sciences USA* **92**, 12055-12059

Jia L, Zhao Y, Liang XJ (2009) Current evaluation of the millennium phytomedicine- ginseng (II): Collected chemical entities, modern pharmacology, and clinical applications emanated from traditional Chinese medicine. *Current Medicinal Chemistry* **16**, 2924-2942

Jin SH, Park JK, Nam KY, Park SN, Jung NP (1999) Korean red ginseng saponins with low ratios of protopanaxadiol and protopanaxatriol saponin improve scopolamine-induced learning disability and spatial working memory in mice. *Journal of Ethnopharmacology* **66**, 123-129

Kaplan HB, Greenberg EP (1985) Diffusion of autoinducer is involved in regulation of the *Vibrio fischeri* luminescence system. *Journal of Bacteriology* **163**, 1210-1214

Kelly RC, Bolitho ME, Higgins DA, Lu W, Ng WL, Jeffrey PD, Rabinowitz JD, Semmelhack MF, Hughson FM, Bassler BL (2009) The *Vibrio cholerae* quorum-sensing autoinducer CAI-1: Analysis of the biosynthetic enzyme CqsA. *Nature Chemical Biology* **5**, 891-895

Kempner ES, Hanson FE (1968) Aspects of light production by *Photobacterium fischeri*. *Journal of Bacteriology* **95**, 975-979

Kendall MM, Rasko DA, Sperandio V (2007) Global effects of the cell-to-cell signaling molecules autoinducer-2, autoinducer-3, and epinephrine in a *luxS* mutant of enterohemorrhagic *Escherichia coli*. *Infection and Immunity* **75**, 4875-4884

Khafagi IK, Dewedar A (2000) The efficiency of random versus ethno-directed research in the evaluation of Sinai medicinal plants for bioactive compounds. *Journal of Ethnopharmacology* **71**, 365-376

Killar L, MacDonald G, West J, Woods A, Bottomly K (1987) Cloned, Ia-restricted T cells that do not produce interleukin 4(IL 4)/B cell stimulatory factor 1(BSF-1) fail to help antigen-specific B cells. *Journal of Immunology* **138**, 1674-1679

Kim JY, Lee KW, Kim SH, Wee JJ, Kim YS, Lee HJ (2002) Inhibitory effect of tumor cell proliferation and induction of G2/M cell cycle arrest by panaxytriol. *Planta Medica* **68**, 119-122

King SR, Tempesta MS (1994) From shaman to human clinical trials: The role of industry in ethnobotany, conservation and community reciprocity. *Ciba Foundation Symposium* **185**, 197-206; discussion 206-113

Klevens RM, Morrison MA, Nadle J, Petit S, Gershman K, Ray S, Harrison LH, Lynfield R, Dumyati G, Townes JM, Craig AS, Zell ER, Fosheim GE, McDougal LK, Carey RB, Fridkin SK (2007) Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. *JAMA: The Journal of the American Medical Association* **298**, 1763-1771

Koh KH, Tham FY (2011) Screening of traditional Chinese medicinal plants for quorum-sensing inhibitors activity. *Journal of Microbiology, Immunology, and Infection* **44**, 144-148

Kohler T, Curty LK, Barja F, van Delden C, Pechere JC (2000) Swarming of *Pseudomonas aeruginosa* is dependent on cell-to-cell signaling and requires flagella and pili. *Journal of Bacteriology* **182**, 5990-5996

Kong KF, Schneper L, Mathee K (2010) Beta-lactam antibiotics: From antibiosis to resistance and bacteriology. *APMIS* **118**, 1-36

Larsen MW, Moser C, Hoiby N, Song Z, Kharazmi A (2004) Ginseng modulates the immune response by induction of interleukin-12 production. *APMIS* **112**, 369-373

Latifi A, Foglino M, Tanaka K, Williams P, Lazdunski A (1996) A hierarchical quorum-sensing cascade in *Pseudomonas aeruginosa* links the transcriptional activators LasR and RhIR (VsmR) to expression of the stationary-phase sigma factor RpoS. *Molecular Microbiology* **21**, 1137-1146

Lechner D, Stavri M, Oluwatuyi M, Pereda-Miranda R, Gibbons S (2004) The anti-staphylococcal activity of *Angelica dahurica* (Bai Zhi). *Phytochemistry* **65**, 331-335

Lee JH, Lee JS, Chung MS, Kim KH (2004a) *In vitro* anti-adhesive activity of an acidic polysaccharide from *Panax ginseng* on *Porphyromonas gingivalis* binding to erythrocytes. *Planta Medica* **70**, 566-568

Lee JH, Park EK, Uhm CS, Chung MS, Kim KH (2004b) Inhibition of *Helicobacter pylori* adhesion to human gastric adenocarcinoma epithelial cells by acidic polysaccharides from *Artemisia capillaris* and *Panax ginseng*. *Planta Medica* **70**, 615-619

Lee JH, Shim JS, Chung MS, Lim ST, Kim KH (2009a) Inhibition of pathogen adhesion to host cells by polysaccharides from *Panax ginseng*. *Bioscience, Biotechnology, and Biochemistry* **73**, 209-212

Lee JH, Shim JS, Lee JS, Kim MK, Chung MS, Kim KH (2006) Pectin-like acidic polysaccharide from *Panax ginseng* with selective antiadhesive activity against pathogenic bacteria. *Carbohydrate Research* **341**, 1154-1163

Lee MS, Yang EJ, Kim JI, Ernst E (2009b) Ginseng for cognitive function in Alzheimer's disease: A systematic review. *Journal of Alzheimer's Disease* **18**, 339-344

Lee YS, Chung IS, Lee IR, Kim KH, Hong WS, Yun YS (1997) Activation of multiple effector pathways of immune system by the antineoplastic immunostimulator acidic polysaccharide ginsan isolated from *Panax ginseng*. *Anticancer Research* **17**, 323-331

Lepine F, Milot S, Deziel E, He J, Rahme LG (2004) Electrospray/mass spectrometric identification and analysis of 4-hydroxy-2-alkylquinolines (HAQs) produced by *Pseudomonas aeruginosa*. *Journal of the American Society for Mass Spectrometry* **15**, 862-869

Lequette Y, Lee JH, Ledgham F, Lazdunski A, Greenberg EP (2006) A distinct QscR regulon in the *Pseudomonas aeruginosa* quorum-sensing circuit. *Journal of Bacteriology* **188**, 3365-3370

Leung KW, Wong AS (2010) Pharmacology of ginsenosides: A literature review. *Chinese Medicine* **5**, 20

Lewenza S, Conway B, Greenberg EP, Sokol PA (1999) Quorum sensing in

Burkholderia cepacia: identification of the LuxRI homologs CepRI. *Journal of Bacteriology* **181**, 748-756

Lewenza S, Sokol PA (2001) Regulation of ornibactin biosynthesis and *N*-acyl-L-homoserine lactone production by CepR in *Burkholderia cepacia*. *Journal of Bacteriology* **183**, 2212-2218

Li W, Gu C, Zhang H, Awang DV, Fitzloff JF, Fong HH, van Breemen RB (2000) Use of high-performance liquid chromatography-tandem mass spectrometry to distinguish *Panax ginseng* C. A. Meyer (Asian ginseng) and *Panax quinquefolius* L. (North American ginseng). *Analytical Chemistry* **72**, 5417-5422

Liberti LE, Der Marderosian A (1978) Evaluation of commercial ginseng products. *Journal of Pharmaceutical Sciences* **67**, 1487-1489

Lim DS, Bae KG, Jung IS, Kim CH, Yun YS, Song JY (2002) Anti-septicaemic effect of polysaccharide from *Panax ginseng* by macrophage activation. *Journal of Infection* **45**, 32-38

Lindgren V, Wretlind B (1987) Characterization of a *Pseudomonas aeruginosa* transposon insertion mutant with defective release of exoenzymes. *Journal of General Microbiology* **133**, 675-681

Liu CX, Xiao PG (1992) Recent advances on ginseng research in China. *Journal of Ethnopharmacology* **36**, 27-38

Liu PV (1966) The roles of various fractions of *Pseudomonas aeruginosa* in its pathogenesis. II. Effects of lecithinase and protease. *Journal of Infectious Diseases* **116**, 112-116

Liu PV (1973) Exotoxins of *Pseudomonas aeruginosa*. I. Factors that influence the production of exotoxin A. *Journal of Infectious Diseases* **128**, 506-513

Liu PV, Hsieh H (1973) Exotoxins of *Pseudomonas aeruginosa*. 3. Characteristics of antitoxin A. *Journal of Infectious Diseases* **128**, 520-526

Liu PV, Yoshii S, Hsieh H (1973) Exotoxins of *Pseudomonas aeruginosa*. II. Concentration, purification, and characterization of exotoxin A. *Journal of Infectious Diseases* **128**, 514-519

Lord KA, Hoffman-Liebermann B, Liebermann DA (1990) Nucleotide sequence and expression of a cDNA encoding MyD88, a novel myeloid differentiation primary response gene induced by IL6. *Oncogene* **5**, 1095-1097

Ma Q, Zhai Y, Schneider JC, Ramseier TM, Saier MH Jr. (2003) Protein secretion systems of *Pseudomonas aeruginosa* and *Pseudomonas fluorescens*. *Biochimica et Biophysica Acta* **1611**, 223-233

Malott RJ, Sokol PA (2007) Expression of the *bviIR* and *cepIR* quorum-sensing systems of *Burkholderia vietnamiensis*. *Journal of Bacteriology* **189**, 3006-3016

Manefield M, de Nys R, Kumar N, Read R, Givskov M, Steinberg P, Kjelleberg S (1999) Evidence that halogenated furanones from *Delisea pulchra* inhibit acylated homoserine lactone (AHL)-mediated gene expression by displacing the AHL signal from its receptor protein. *Microbiology* **145 (Pt 2)**, 283-291

Manefield M, Rasmussen TB, Henzter M, Andersen JB, Steinberg P, Kjelleberg S, Givskov M (2002) Halogenated furanones inhibit quorum sensing through accelerated LuxR turnover. *Microbiology* **148**, 1119-1127

Matsunaga H, Katano M, Yamamoto H, Mori M, Takata K (1989) Studies on the panaxytriol of *Panax ginseng* C. A. Meyer. Isolation, determination and antitumor activity. *Chemical and Pharmaceutical Bulletin* **37**, 1279-1281

Mattiuzzo M, Bertani I, Ferluga S, Cabrio L, Bigirimana J, Guarnaccia C, Pongor S, Maraite H, Venturi V (2011) The plant pathogen *Pseudomonas fuscovaginae* contains two conserved quorum sensing systems involved in virulence and negatively regulated by RsaL and the novel regulator RsaM. *Environmental Microbiology* **13**, 145-162

McGaw LJ, Lall N, Meyer JJ, Eloff JN (2008) The potential of South African plants against *Mycobacterium* infections. *Journal of Ethnopharmacology* **119**, 482-500

McKnight SL, Iglewski BH, Pesci EC (2000) The *Pseudomonas* quinolone signal regulates Rhl quorum sensing in *Pseudomonas aeruginosa*. *Journal of Bacteriology* **182**, 2702-2708

Mearns MB, Hunt GH, Rushworth R (1972) Bacterial flora of respiratory tract in patients with cystic fibrosis, 1950-71. *Archives of Disease in Childhood* **47**, 902-907

Medzhitov R, Janeway CA Jr. (1999) Innate immune induction of the adaptive immune response. *Cold Spring Harbor Symposia on Quantitative Biology* **64**, 429-435

Medzhitov R, Preston-Hurlburt P, Janeway CA Jr. (1997) A human homologue of the *Drosophila* Toll protein signals activation of adaptive immunity. *Nature* **388**, 394-397

Medzhitov R, Preston-Hurlburt P, Kopp E, Stadlen A, Chen C, Ghosh S, Janeway CA Jr. (1998) MyD88 is an adaptor protein in the hToll/IL-1 receptor family signaling pathways. *Molecular Cell* **2**, 253-258

Meltzer MS, Benjamin WR, Farrar JJ (1982) Macrophage activation for tumor cytotoxicity: induction of macrophage tumoricidal activity by lymphokines from EL-4, a continuous T cell line. *Journal of Immunology* **129**, 2802-2807

Miller MB, Skorupski K, Lenz DH, Taylor RK, Bassler BL (2002) Parallel quorum sensing systems converge to regulate virulence in *Vibrio cholerae*. *Cell* **110**, 303-314

Miller ST, Xavier KB, Campagna SR, Taga ME, Semmelhack MF, Bassler BL, Hughson FM (2004) *Salmonella typhimurium* recognizes a chemically distinct form of the bacterial quorum-sensing signal AI-2. *Molecular Cell* **15**, 677-687

Moreira CG, Sperandio V (2010) The Epinephrine/ Norepinephrine/ Autoinducer-3 Interkingdom Signaling System in *Escherichia coli* O157:H7. In: Lyte M, Freestone PPE (Eds) *Microbial Endocrinology: Interkingdom Signaling in Infectious Disease and Health*, Springer, New York, pp 213-227

Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL (1986) Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *Journal of Immunology* **136**, 2348-2357

Mougous JD, Cuff ME, Raunser S, Shen A, Zhou M, Gifford CA, Goodman AL, Joachimiak G, Ordonez CL, Lory S, Walz T, Joachimiak A, Mekalanos JJ (2006) A virulence locus of *Pseudomonas aeruginosa* encodes a protein secretion apparatus. *Science* **312**, 1526-1530

National Institutes of Health, NIAID (2006) The problem of antimicrobial resistance. Available online: http://www.idph.state.ia.us/adper/common/pdf/abx/tab9_niaid_resistance.pdf

Nealson KH, Hastings JW (1979) Bacterial bioluminescence: Its control and ecological significance. *Microbiological Reviews* **43**, 496-518

Nealson KH, Platt T, Hastings JW (1970) Cellular control of the synthesis and activity of the bacterial luminescent system. *Journal of Bacteriology* **104**, 313-322

Ng WL, Bassler BL (2009) Bacterial quorum-sensing network architectures. *Annual Review of Genetics* **43**, 197-222

Nichols WW, Evans MJ, Slack MP, Walmsley HL (1989) The penetration of antibiotics into aggregates of mucoid and non-mucoid *Pseudomonas aeruginosa*. *Journal of General Microbiology* **135**, 1291-1303

Nickel JC, Ruseska I, Wright JB, Costerton JW (1985a) Tobramycin resistance of *Pseudomonas aeruginosa* cells growing as a biofilm on urinary catheter material. *Antimicrobial Agents and Chemotherapy* **27**, 619-624

Nickel JC, Wright JB, Ruseska I, Marrie TJ, Whitfield C, Costerton JW (1985b) Antibiotic resistance of *Pseudomonas aeruginosa* colonizing a urinary catheter *in vitro*. *European Journal of Clinical Microbiology* **4**, 213-218

Novick RP, Geisinger E (2008) Quorum sensing in *Staphylococci*. *Annual Review of Genetics* **42**, 541-564

Obritsch MD, Fish DN, MacLaren R, Jung R (2005) Nosocomial infections due to multidrug-resistant *Pseudomonas aeruginosa*: Epidemiology and treatment options. *Pharmacotherapy* **25**, 1353-1364

Ochsner UA, Snyder A, Vasil AI, Vasil ML (2002) Effects of the twin-arginine translocase on secretion of virulence factors, stress response, and pathogenesis. *Proceedings of the National Academy of Sciences USA* **99**, 8312-8317

Oinuma K, Greenberg EP (2011) Acyl-homoserine lactone binding to and stability of the orphan *Pseudomonas aeruginosa* quorum-sensing signal receptor QscR. *Journal of Bacteriology* **193**, 421-428

Oliveira DF, Pereira AC, Figueiredo HCP, Carvalho DA, Silva G, Nunes AS, Alves DS, Carvalho HWP (2007) Antibacterial activity of plant extracts from Brazilian southeast region. *Fitoterapia* **78**, 142-145

Peck-Palmer OM, Unsinger J, Chang KC, Davis CG, McDunn JE, Hotchkiss RS (2008) Deletion of MyD88 markedly attenuates sepsis-induced T and B lymphocyte apoptosis but worsens survival. *Journal of Leukocyte Biology* **83**, 1009-1018

Peres MT, Delle Monache F, Cruz AB, Pizzolatti MG, Yunes RA (1997) Chemical composition and antimicrobial activity of *Croton urucurana* Baillon (Euphorbiaceae). *Journal of Ethnopharmacology* **56**, 223-226

Perrett S, Whitfield PJ, Sanderson L, Bartlett A (1995) The plant molluscicide *Millettia thonningii* (Leguminosae) as a topical antischistosomal agent. *Journal of Ethnopharmacology* **47**, 49-54

Pesci E, Pearson J, Seed P, Iglewski B (1997) Regulation of *las* and *rhl* quorum sensing in *Pseudomonas aeruginosa*. *Journal of Bacteriology* **179**, 3127-3132

Pesci EC, Milbank JB, Pearson JP, McKnight S, Kende AS, Greenberg EP, Iglewski BH (1999) Quinolone signaling in the cell-to-cell communication system of *Pseudomonas aeruginosa*. *Proceedings of the National Academy of Sciences USA* **96**, 11229-11234

Petkov VD, Belcheva S, Konstantinova E, Kehayov R, Petkov VV, Hadjiivanova C (1994) Participation of the serotonergic system in the memory effects of *Ginkgo biloba* L. and *Panax ginseng* C. A. Meyer. *Phytotherapy Research* **8**, 470-477

Pfeifer Y, Cullik A, Witte W (2010) Resistance to cephalosporins and carbapenems in Gram-negative bacterial pathogens. *International Journal of Medical Microbiology* **300**, 371-379

Phair JP, Tan JS, Watanakunakorn C, Schwab L, Sanders LW (1970) Carbenicillin treatment of *Pseudomonas* pulmonary infection. Use in children with cystic fibrosis. *American Journal of Diseases of Children* **120**, 22-25

Pollack M (2000) *Pseudomonas aeruginosa*. In: Mandell, G, Benett J, Dolin R (Eds) *Principles and Practice of Infectious Diseases*, Churchill Livingstone, New York, pp 2310-2335

Radad K, Gille G, Liu L, Rausch WD (2006) Use of ginseng in medicine with emphasis on neurodegenerative disorders. *Journal of Pharmacological Sciences* **100**, 175-186

Rampioni G, Pustelny C, Fletcher MP, Wright VJ, Bruce M, Rumbaugh KP, Heeb S, Camara M, Williams P (2010) Transcriptomic analysis reveals a global alkyl-quinolone-independent regulatory role for PqsE in facilitating the environmental adaptation of *Pseudomonas aeruginosa* to plant and ani-

mal hosts. *Environmental Microbiology* **12**, 1659-1673

Rasmussen TB, Bjarnsholt T, Skindersoe ME, Hentzer M, Kristoffersen P, Kote M, Nielsen J, Eberl L, Givskov M (2005) Screening for quorum-sensing inhibitors (QSI) by use of a novel genetic system, the QSI selector. *Journal of Bacteriology* **187**, 1799-1814

Reading NC, Torres AG, Kendall MM, Hughes DT, Yamamoto K, Sperandio V (2007) A novel two-component signaling system that activates transcription of an enterohemorrhagic *Escherichia coli* effector involved in remodeling of host actin. *Journal of Bacteriology* **189**, 2468-2476

Ren D, Sims JJ, Wood TK (2001) Inhibition of biofilm formation and swarming of *Escherichia coli* by (5Z)-4-bromo-5-(bromomethylene)-3-butyl-2(5H)-furanone. *Environmental Microbiology* **3**, 731-736

Rezzonico F, Duffy B (2008) Lack of genomic evidence of AI-2 receptors suggests a non-quorum sensing role for *luxS* in most bacteria. *BMC Microbiology* **8**, 154

Romero CD, Chopin SF, Buck G, Martinez E, Garcia M, Bixby L (2005) Antibacterial properties of common herbal remedies of the southwest. *Journal of Ethnopharmacology* **99**, 253-257

Ryan RP, McCarthy Y, Watt SA, Niehaus K, Dow JM (2009) Intraspecies signaling involving the diffusible signal factor BDSF (*cis*-2-dodecenoic acid) influences virulence in *Burkholderia cenocepacia*. *Journal of Bacteriology* **191**, 5013-5019

Saier MH Jr. (2006) Protein secretion and membrane insertion systems in Gram-negative bacteria. *Journal of Membrane Biology* **214**, 75-90

Schaefer AL, Val DL, Hanzelka BL, Cronan JE Jr., Greenberg EP (1996) Generation of cell-to-cell signals in quorum sensing: acyl homoserine lactone synthase activity of a purified *Vibrio fischeri* LuxI protein. *Proceedings of the National Academy of Sciences USA* **93**, 9505-9509

Schauder S, Shokat K, Surette MG, Bassler BL (2001) The LuxS family of bacterial autoinducers: Biosynthesis of a novel quorum-sensing signal molecule. *Molecular Microbiology* **41**, 463-476

Schinkovitz A, Stavri M, Gibbons S, Bucar F (2008) Antimycobacterial polyacetylenes from *Levisticum officinale*. *Phytotherapy Research* **22**, 681-684

Schuster M, Greenberg EP (2006) A network of networks: quorum-sensing gene regulation in *Pseudomonas aeruginosa*. *International Journal of Medical Microbiology* **296**, 73-81

Smyth AR, Cifelli PM, Ortori CA, Righetti K, Lewis S, Erskine P, Holland ED, Givskov M, Williams P, Camara M, Barrett DA, Knox A (2010) Garlic as an inhibitor of *Pseudomonas aeruginosa* quorum sensing in cystic fibrosis - a pilot randomized controlled trial. *Pediatric Pulmonology* **45**, 356-362

Sokol PA, Darling P, Lewenza S, Corbett CR, Kooi CD (2000) Identification of a siderophore receptor required for ferric ornibactin uptake in *Burkholderia cepacia*. *Infection and Immunity* **68**, 6554-6560

Solomon JM, Lazazzera BA, Grossman AD (1996) Purification and characterization of an extracellular peptide factor that affects two different developmental pathways in *Bacillus subtilis*. *Genes and Development* **10**, 2014-2024

Solomon S, Horan T, Andrus M, Edwards J, Fridkin S, Koganti J, Peavy G, Tolson J, Syst N (2003) National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2003, issued August 2003. *American Journal of Infection Control* **31**, 481-498

Song Z, Johansen HK, Faber V, Moser C, Kharazmi A, Rygaard J, Hoiby N (1997a) Ginseng treatment reduces bacterial load and lung pathology in chronic *Pseudomonas aeruginosa* pneumonia in rats. *Antimicrobial Agents and Chemotherapy* **41**, 961-964

Song Z, Kharazmi A, Wu H, Faber V, Moser C, Krogh HK, Rygaard J, Hoiby N (1998) Effects of ginseng treatment on neutrophil chemiluminescence and immunoglobulin G subclasses in a rat model of chronic *Pseudomonas aeruginosa* pneumonia. *Clinical and Diagnostic Laboratory Immunology* **5**, 882-887

Song Z, Kong KF, Wu H, Maricic N, Ramalingam B, Priestap H, Schneper L, Quirke JME, Høiby N, Mathee K (2010) *Panax ginseng* has anti-infective activity against opportunistic pathogen *Pseudomonas aeruginosa* by inhibiting quorum sensing, a bacterial communication process critical for establishing infection. *Phytomedicine* **17**, 1040-1046

Song Z, Moser C, Wu H, Faber V, Kharazmi A, Hoiby N (2003) Cytokine modulating effect of ginseng treatment in a mouse model of *Pseudomonas aeruginosa* lung infection. *Journal of Cystic Fibrosis* **2**, 112-119

Song Z, Wu H, Mathee K, Hoiby N, Kharazmi A (2002) Gerimax ginseng regulates both humoral and cellular immunity during chronic *Pseudomonas aeruginosa* lung infection. *Journal of Alternative and Complementary Medicine* **8**, 459-466

Song ZJ, Johansen HK, Faber V, Hoiby N (1997b) Ginseng treatment enhances bacterial clearance and decreases lung pathology in athymic rats with chronic *Pseudomonas aeruginosa* pneumonia. *APMIS* **105**, 438-444

Spelman K, Burns J, Nichols D, Winters N, Ottersberg S, Tenborg M (2006) Modulation of cytokine expression by traditional medicines: A review of herbal immunomodulators. *Alternative Medicine Review* **11**, 128-150

Sperandio V, Torres AG, Jarvis B, Nataro JP, Kaper JB (2003) Bacteria-host communication: The language of hormones. *Proceedings of the National Academy of Sciences USA* **100**, 8951-8956

Stewart-Tull DE, Armstrong AV (1972) The effect of 1-hydroxyphenazine and pyocyanin from *Pseudomonas aeruginosa* on mammalian cell respiration. *Journal of Medical Microbiology* **5**, 67-73

Sung WS, Lee DG (2008) The combination effect of Korean red ginseng saponins with kanamycin and cefotaxime against methicillin-resistant *Staphylococcus aureus*. *Biological and Pharmaceutical Bulletin* **31**, 1614-1617

Surette MG, Bassler BL (1998) Quorum sensing in *Escherichia coli* and *Salmonella typhimurium*. *Proceedings of the National Academy of Sciences USA* **95**, 7046-7050

Surette MG, Miller MB, Bassler BL (1999) Quorum sensing in *Escherichia coli*, *Salmonella typhimurium*, and *Vibrio harveyi*: A new family of genes responsible for autoinducer production. *Proceedings of the National Academy of Sciences USA* **96**, 1639-1644

Swartzman A, Kapoor S, Graham AF, Meighen EA (1990) A new *Vibrio fischeri lux* gene precedes a bidirectional termination site for the *lux* operon. *Journal of Bacteriology* **172**, 6797-6802

Telford G, Wheeler D, Williams P, Tomkins PT, Appleby P, Sewell H, Stewart GSAB, Bycroft BW, Pritchard DI (1998) The *Pseudomonas aeruginosa* quorum-sensing signal molecule *N*-(3-oxododecanoyl)-1-homoserine lactone has immunomodulatory activity. *Infection and Immunity* **66**, 36-42

Tessema B, Mulu A, Kassu A, Yismaw G (2006) An *in vitro* assessment of the antibacterial effect of garlic (*Allium sativum*) on bacterial isolates from wound infections. *Ethiopian Medical Journal* **44**, 385-389

Toda M, Okubo S, Ikigai H, Suzuki T, Suzuki Y, Hara Y, Shimamura T (1992) The protective activity of tea catechins against experimental infection by *Vibrio cholerae* O1. *Microbiology and Immunology* **36**, 999-1001

Toder DS, Gambello MJ, Iglewski BH (1991) *Pseudomonas aeruginosa* LasA: A second elastase under the transcriptional control of *lasR*. *Molecular Microbiology* **5**, 2003-2010

Tredget EE, Shankowsky HA, Rennie R, Burrell RE, Logsetty S (2004) *Pseudomonas* infections in the thermally injured patient. *Burns* **30**, 3-26

Trinchieri G, Wysocka M, D'Andrea A, Rengaraju M, Aste-Amezaga M, Kubin M, Valiante NM, Chehimi J (1992) Natural killer cell stimulatory factor (NKSF) or interleukin-12 is a key regulator of immune response and inflammation. *Progress in Growth Factor Research* **4**, 355-368

Uematsu S, Akira S (2008) Toll-Like receptors (TLRs) and their ligands. In: Bauer S, Hartmann G (Eds) *Handbook of Experimental Pharmacology*, Springer, Berlin, pp 1-20

Ulrich RL, Deshazer D, Brueggemann EE, Hines HB, Oyston PC, Jeddeloh JA (2004a) Role of quorum sensing in the pathogenicity of *Burkholderia pseudomallei*. *Journal of Medical Microbiology* **53**, 1053-1064

Urbanowski ML, Lostroh CP, Greenberg EP (2004) Reversible acyl-homoserine lactone binding to purified *Vibrio fischeri* LuxR protein. *Journal of Bacteriology* **186**, 631-637

Valade E, Thibault FM, Gauthier YP, Palencia M, Popoff MY, Vidal DR (2004) The PmlI-PmlR quorum-sensing system in *Burkholderia pseudomallei* plays a key role in virulence and modulates production of the MprA protease. *Journal of Bacteriology* **186**, 2288-2294

Waters CM, Bassler BL (2005) Quorum sensing: cell-to-cell communication in bacteria. *Annual Review of Cell and Developmental Biology* **21**, 319-346

Weeks JN, Galindo CL, Drake KL, Adams GL, Garner HR, Ficht TA (2010) *Brucella melitensis* VjbR and C12-HSL regulons: contributions of the *N*-dodecanoyl homoserine lactone signaling molecule and LuxR homologue VjbR to gene expression. *BMC Microbiology* **10**, 167

Wei HL, Zhang LQ (2006) Quorum-sensing system influences root colonization and biological control ability in *Pseudomonas fluorescens* 2P24. *Antonie van Leeuwenhoek* **89**, 267-280

Weigel LM, Clewell DB, Gill SR, Clark NC, McDougal LK, Flannagan SE, Kolonay JF, Shetty J, Killgore GE, Tenover FC (2003) Genetic analysis of a high-level vancomycin-resistant isolate of *Staphylococcus aureus*. *Science* **302**, 1569-1571

Wilderman PJ, Vasil AI, Johnson Z, Wilson MJ, Cunliffe HE, Lamont IL, Vasil ML (2001) Characterization of an endoprotease (PrpL) encoded by a PvdS-regulated gene in *Pseudomonas aeruginosa*. *Infection and Immunity* **69**, 5385-5394

Williams P, Camara M (2009) Quorum sensing and environmental adaptation in *Pseudomonas aeruginosa*: A tale of regulatory networks and multifunctional signal molecules. *Current Opinion in Microbiology* **12**, 182-191

World Health Organization (2010) Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response. Available online: http://whqlibdoc.who.int/publications/2010/9789241599191_eng.pdf

Wretlind B, Pavlovskis OR (1984) Genetic mapping and characterization of *Pseudomonas aeruginosa* mutants defective in the formation of extracellular proteins. *Journal of Bacteriology* **158**, 801-808

Wu H, Lee B, Yang L, Wang H, Givskov M, Molin S, Hoiby N, Song Z (2011) Effects of ginseng on *Pseudomonas aeruginosa* motility and biofilm formation. *FEMS Immunology and Medical Microbiology* **62**, 49-56

Wu L, Estrada O, Zaborina O, Bains M, Shen L, Kohler JE, Patel N, Musch MW, Chang EB, Fu YX, Jacobs MA, Nishimura MI, Hancock RE, Turner JR, Alverdy JC (2005) Recognition of host immune activation by *Pseudomonas aeruginosa*. *Science* **309**, 774-777

Yahr TL, Goranson J, Frank DW (1996) Exoenzyme S of *Pseudomonas aeruginosa* is secreted by a type III pathway. *Molecular Microbiology* **22**, 991-1003

Yahr TL, Mende-Mueller LM, Friese MB, Frank DW (1997) Identification

of type III secreted products of the *Pseudomonas aeruginosa* exoenzyme S regulon. *Journal of Bacteriology* **179**, 7165-7168

Yun TK (2001) Brief introduction of *Panax ginseng* C.A. Meyer. *Journal of Korean Medical Science* **16**, 53-55

Zaborina O, Lepine F, Xiao G, Valuckaite V, Chen Y, Li T, Ciancio M, Zaborin A, Petrof EO, Turner JR, Rahme LG, Chang E, Alverdy JC (2007) Dynorphin activates quorum sensing quinolone signaling in *Pseudomonas aeruginosa*. *PLoS Pathogens* **3**, e35

Zhang Z, Pierson LS III (2001) A second quorum-sensing system regulates cell surface properties but not phenazine antibiotic production in *Pseudomonas aureofaciens*. *Applied and Environmental Microbiology* **67**, 4305-4315

Zhu J, Yamane H, Paul WE (2010) Differentiation of effector CD4 T cell populations (*). *Annual Review of Immunology* **28**, 445-489