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A New Promising Target for Plant Extracts: Inhibition of Bacterial Quorum Sensing

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Abstract

Bacteria coordinate bacterium-bacterium interactions through a cell-to-cell communication mechanism known as quorum sensing (QS) systems. The QS-controlled behaviours occur when the bacterial population grows until a threshold concentration perceived by the bacteria is reached. There is an increasing need for the discovery of alternative antimicrobial therapies to control the bacterial pathogenicity; one of these is the herbal remedies. Besides their antibacterial properties, they can also target bacterial QS and thereby, interrupt bacterial communication. Crude plant extracts have anti-QS activities with inhibition of the expression of well-established specific induced gene(s). The quantitative real time PCR (qRT-PCR) assay had shown the down regulation of the QS-related genes.

Keywords: Quorum sensing; Plant extracts; qRT-PCR; QS-related genes

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Introduction

Quorum sensing (QS) systems are bacterial cell-to-cell communication systems involved in the regulation of virulence of many pathogenic bacteria. It has been suggested as a new target for the novel antimicrobial therapies. In Gram-negative bacteria, the studied QS systems use N-acyl homoserine lactones (AHLs) as signal molecules, but a thiolactone/lactone peptide-mediated quorum sensing (QS) system is commonly employed in the Gram-positive bacteria. Plant extracts with promoting effects owing to their antimicrobial prosperities have been gaining several research focuses in recent years. With respect to the treatment, a novel antimicrobial strategy is to interrupt bacterial quorum sensing by means of signal antagonists, the so-called QS inhibitors (QSIs). This review provides an overview of the new approaches targeting bacterial quorum sensing, highlighting the potential of the plant extracts on the inhibition of expression of specific QS-induced gene(s).

In the last few decades, bacteria regulate both bacterium-bacterium interactions and associations with higher organisms through a cell-to-cell communication mechanism recognized as quorum sensing (QS) systems. Quorum Sensing (QS) is a regulatory system that enables bacteria to make collective decisions regarding the expression of a specific set of genes [1]. It regulates bacterial pathogenesis by stimulating the expression of disease causing traits, such as motility, biofilm formation, sporulation, and expression of many virulence determinants [2].

It was evident that the QS is realized through the bacterial production of small diffusible chemical signaling molecules called as autoinducers (AI) or bacterial quoromone which allows bacteria to adjust their needs through alterations of the transcriptional program in a population density-dependent way. The QS-controlled behaviours occured only when the bacterial population grows until a threshold concentration of the bacteria is attained, will lead to activation or repression of specific genes. The accumulation of these molecules can occur only when the bacteria reach a specific cell density, termed as quorum [3].

The autoinducers can differ depending on the type of the bacteria. The AIs utilized by Gram-negative bacteria are known as N-acyl homoserine lactones (AHLs), while Gram-positive bacteria use the post-translationally modified oligopeptides as signaling molecules [4].

Gram-negative bacteria QS systems are based on LuxI/LuxR homologues. The LuxI homologues encode an AHL synthase involved in the synthesis of signal molecules, and the LuxR homologues encode the transcription regulatory protein which, upon binding of the cognate signal molecules, activates the transcription of the QS target genes [5].

In Gram-positive bacteria, the chemical signal is a modified oligopeptide or auto-inducing peptide (AIP). The peptide signal precursor locus is translated into a precursor protein which is cleaved to produce the processed peptide autoinducer signal. This signal is then transported across the membrane out of the cell. Extracellular accumulation of these signaling oligopeptides results in activation of a two-component signaling system resulting in altered gene expression [6].

There is an increasing need for the discovery of novel approaches such as alternative antimicrobial therapies those present novel or unexplored properties to efficiently control and manage bacterial infectious diseases. One such approach involves interrupting bacterial communication instead of killing the bacteria.

Since ancient times, plant food extracts and phytochemicals have been often used in nutrition and medicine because of their wide range of beneficial effects against chronic diseases as well as their antimicrobial activities.

In fact, crude plant extracts are found to be more effective than their isolated constituents at an equivalent dose attributing to positive interactions between components of the whole plant extracts. This synergy may include prevention of the active components from degradation by enzymes or facilitate transport across the cell barriers resulting in higher efficacy of the crude drug when compared with the purified components [7]. Hence, it is lately fulfilled that crude extracts are possibly the right strategy to treat the multi-drug resistant pathogenic bacteria comparing to the purified compounds isolated from the same extract.

Owing to the multi-component mechanisms used for plant-associated bacterial control and inhibition of pathogenic bacteria, further studies on the purification of active components and production of medicinal plant activities based on novel strategies are vital [8]. Moreover, a detailed chemistry of the active compounds and further evaluation of their mechanisms of actions and interaction with microbial processes are needed to be addressed [9].

Besides possessing several antibacterial properties, herbal remedies can also target the bacterial QS which have emerged as an attractive target to control their pathogenicity. In the last years, plant food extracts and phytochemicals have also been emphasized as quorum sensing inhibitors (QSI) [10]. One of the keys of success of plant food extracts and phytochemicals is attributed to their similarity to the ideal QSI, which involves being chemically stable and highly effective low-molecular-mass molecules with the added benefit that most of them are harmless for the human health [11].

Actually, the ability of plant extracts to interrupt QS systems may serve as a defense mechanism to combat against bacterial invasion. By targeting QS, an infective property of the bacteria, one can potentially impede the rate of resistance and infection. Many research studies have notified the ability of plant extracts and phytochemicals to interfere in the intra-and inter-species QS communication systems [12].

The plant components often target the bacterial QS system via different ways, by stopping the signaling molecules from being synthesized by the luxI encoded AHL synthase, degrading the signaling molecules and/or targeting the luxR signal receptor [13]. The most commonly identified mechanisms of action of plant food extracts and phytochemicals are related to their similitude in chemical structure to QS signals (AHL) and also their capacity to degrade signal receptors (LuxR/LasR) [14]. Some studies have shown the protective effects of the QSI compounds against pathogenic bacterial invasion. However, more *in vivo* studies are required to introduce appropriate results regarding bacterial pathogenesis and QS inhibition [15].

Interestingly, anti-QS compounds are important as they will unlikely cause resistance problems as they do not pose selection pressures. Most antagonists have narrow spectrum activities, which only target specific pathogens. This may be useful as they will specifically target a type of pathogen in a polymicrobial environment, but such a narrow antagonistic action has limited clinical values. Therefore, a cocktail therapy involving both antibiotics and anti-QS antagonists may provide synergistic effects [16].

Plant extracts comprise promising tools for the management of bacterial pathogenesis and microbial modulation. Earlier studies on anti-QS activities of plant extracts in bacteria have focused mainly on elucidating the inhibition of expression of well-established specific QS-induced gene(s) [17]. Reduction in QS gene expression will be correlated to the attenuation of bacterial virulence resulting in prevention of bacterial adverse effects [18]. The quantitative real time PCR (qRT-PCR) data and DNA microarray studies had shown the down regulation of the QS-related genes in various bacterial species, which is believed to be one of the major reasons responsible for the observed reduction in their virulence properties [19,20]. Finally, the reduction of QS gene expression and signaling molecule levels that affects the virulence factors production provides more insight into why these plant extracts were used in the past and how they can be used in the future to combat the bacterial infections [21].

Conclusion

Use of plant extracts is common in folk medicine for the treatment of bacterial infection. They have a great activity in inhibiting the bacterial QS systems and thereby mitigate bacterial pathogenesis. The mechanisms of action of these compounds as QSI are variable. Plant extracts constitute a promising tool for the management of bacterial pathogenesis through modulation of bacterial virulence genes. They have a vital role on the down regulation of the QS-related genes.

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