Effects of plant sesquiterpene lactones on quorum sensing-regulated bacterial phenotypes

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Introduction

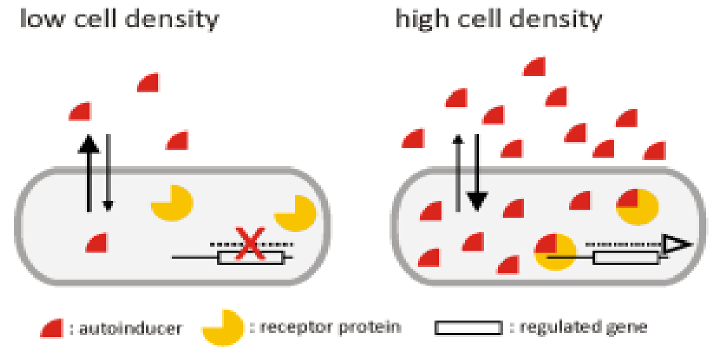


Fig. 1 QS system
https://schaechter.asmblog.org/schaechter/2016/10/quorum-sensing-for-the-mutes.html

A significant number of virulence-related phenotypes such as biofilm formation, secretion of virulence factors (synthesis of pyocyanin and violacein), etc, are regulated by the **quorum sensing (QS) system**. QS represents the cell to cell communication within the bacterial world that allows bacteria to share information about cell density and adjust gene expression accordingly (Fig.1).

Inhibition of this bacterial communication will lead to disability of initiating most of the virulence activity which will help the host for an effective immunological clearance. Thus, the QS system has lately been recognised as an important target for novel antibacterials. Among the substances that are expected to interfere with QS, important group are some low mwt metabolites of different medicinal plants. High are the expectations to **sesquiterpene lactones** that have structural similarities with the homoserine lactone signals of bacterial QS (Fig. 2).

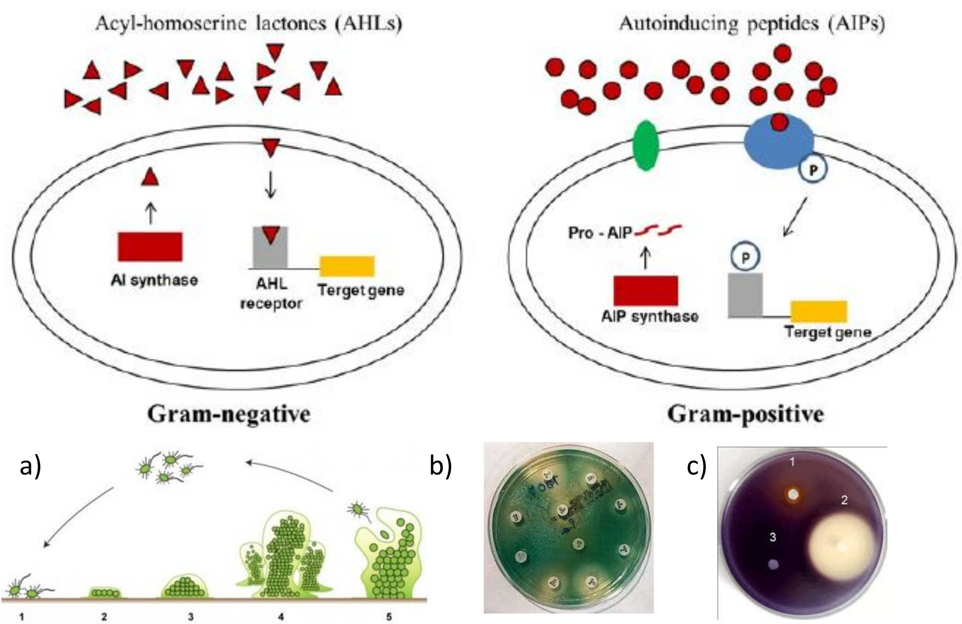


Fig. 2 Biofilm formation (a) and synthesis of pyocyanin (b) and violacein (c).
http://www.formatex.info/microbiology4/vol1/322-336.pdf

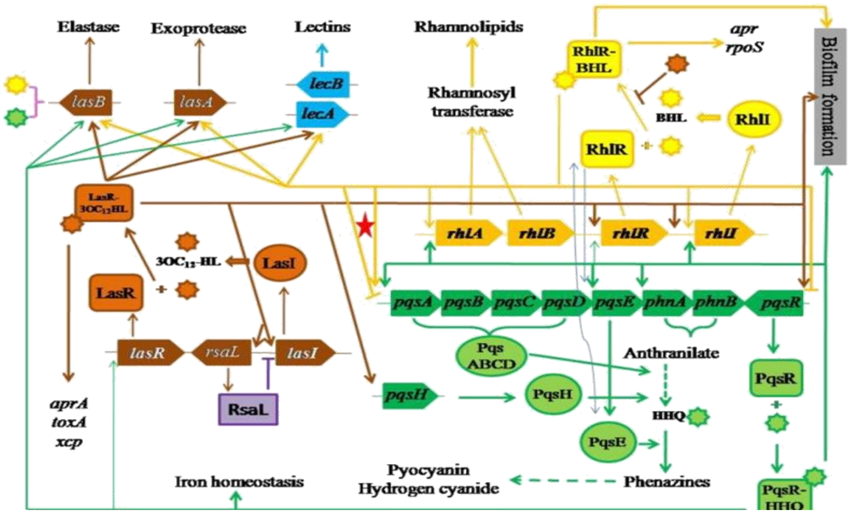
Objectives of the study

To test the capacity of **10 purified sesquiterpene lactones isolated from Bulgarian medicinal plants** to influence the development of QS-regulated phenotypes - production of the pigments **violacein** (*C. violaceum*) and **pyocyanin** (*P. aeruginosa*) and **biofilm** formation in two Gram-positive (*S. aureus, B. subtilis*) and two Gram-negative (*P. aeruginosa, E. coli*) model strains.

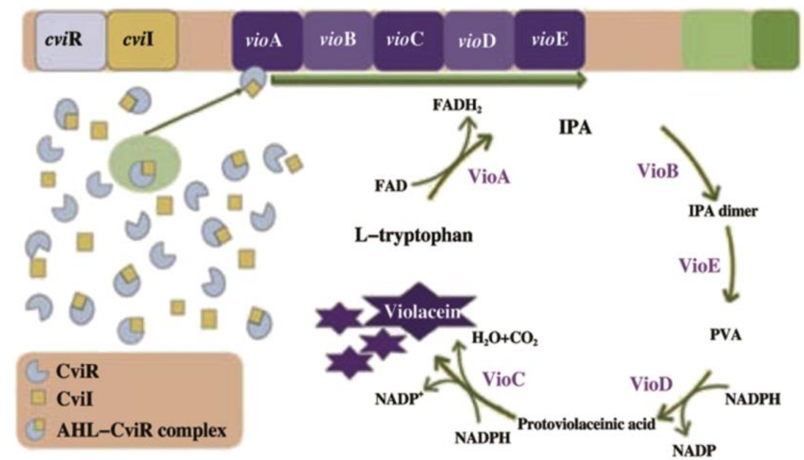
Materials and Methods

Strains: *P. aeruginosa* PAO1, *E. coli* 25922, *S. aureus* 29213, *B. subtilis* 168, *C. violaceum* 30191. ***Biofilm*** production was evaluated as described by Paunova-Krasteva et al. (Biofouling ,2020, 36, 679-695). ***Pyocyanin*** production was determines by the method of Önem et al. (Fresenius Environmental Bulletin, 2018, 27, 9906-9913). ***Violacein*** synthesis was quantified by the method of Choo et al. (Appl Microbiol., 2006, 42, 637-41)

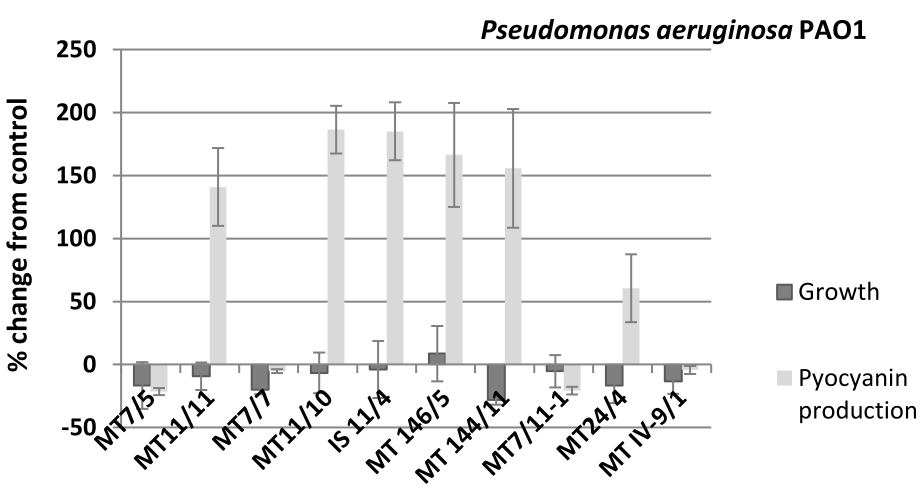
Effects on growth and the release of QS-regulated pigments

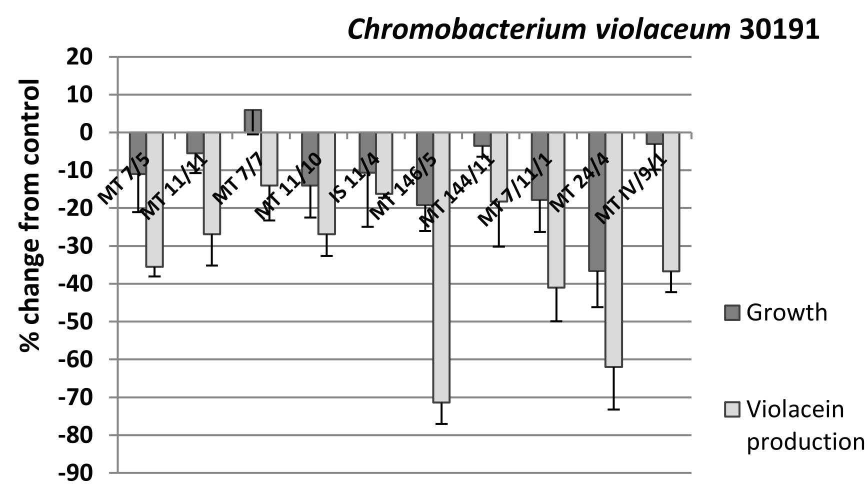


Three QS systems with their effects and regulatory pathways in *P. aeruginosa*. *Adapted from Yan et al.* (*Front. Microbiol.*, 2019, 10, 1582)



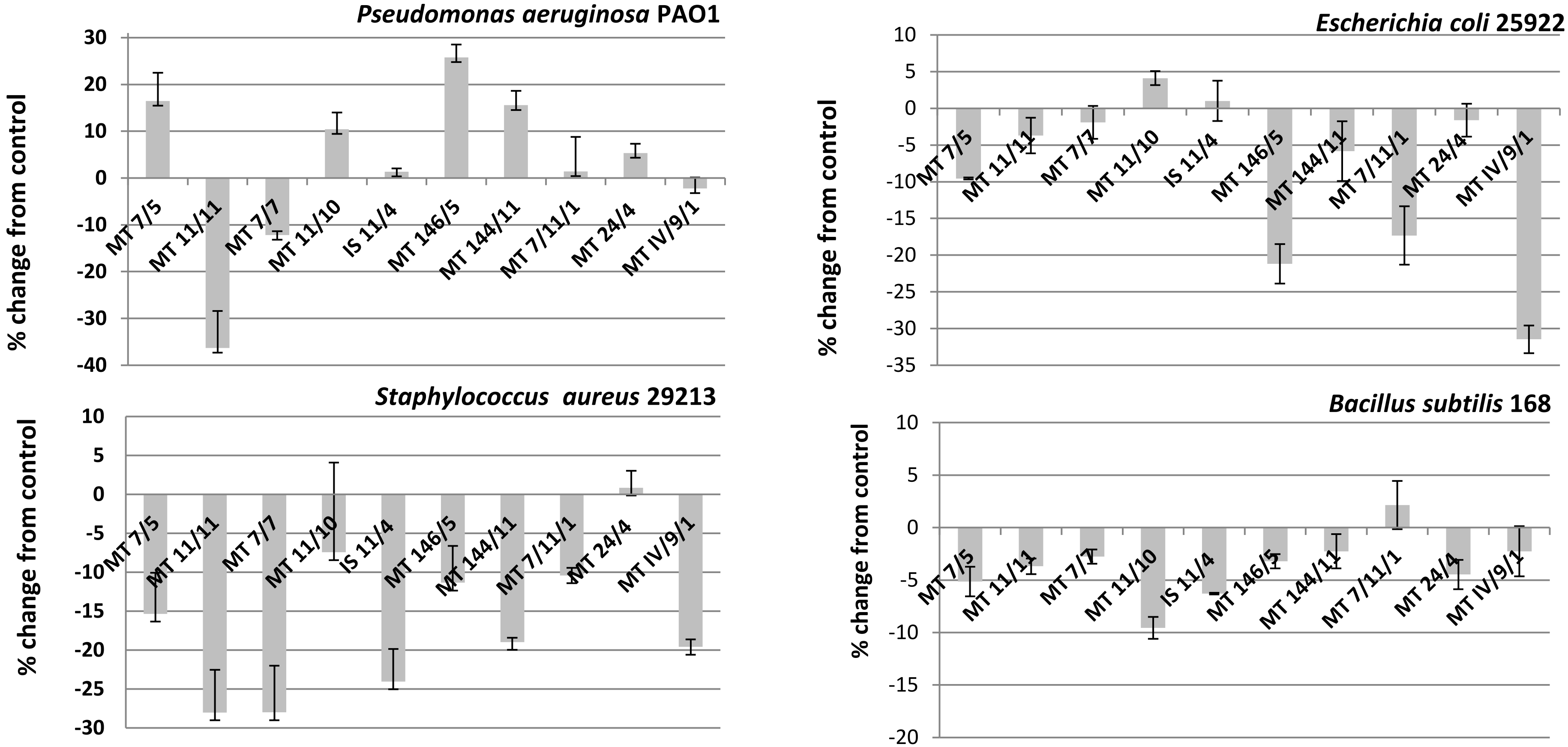
Schematic of violacein byosynthesis. Adapted from Kothari et al. (*Asian Pacific Journal of Tropical Medicine*, 2017, 10, 744-752)





Strong suppression of the production of the pigment violacein by *C. violaceum* was observed. However, pyocyanin release was stimulated or was not affected by the presence of the sesquiterpene lactones .

Effects on biofilm growth



The tested lactones tended to suppress the biofilm growth of the Gram-positive model strains. In Gram-negative bacteria the effects are variable, mostly in *P. aeruginosa*.

Conclusion

All of the tested sesquiterpene lactones were shown to influence the phenotypes in focus, however the effects differed between the bacterial species. Probably, this is due to the difference QS mechanism in Gram – positive and Gram - negative bacteria. It is known that *P. aeruginosa* has more complex QS mechanism than *C. violaceum* thus regulation is more complicated. The observed species-specific responses to plant substances should be taken into account and studied in further detail in order to develop successful approaches to the suppression of bacterial virulence.