Invited Editorial

Is 'quorum quenching' a promising tool to combat antibiotic-resistant bacteria?

Naga Raju Maddela
Department of Biological Sciences, Faculty of Health Science, Universidad Técnica de Manabí, Portoviejo, Ecuador

In the present-day world, 'antibiotic-resistance' is one of the hot topics concerning global health, food security, and development. Antibiotics have proved to be less effective in the treatment of several infections, e.g. pneumonia, tuberculosis, gonorrhea, and salmonellosis.[1] Several pathogens are resistant to the known antibiotics, and per WHO, there is a priority pathogens list for research and development (R&D) of emerging therapeutic agents. It is no secret that antibiotic-resistance can affect anyone irrespective of age and geographical origin by increasing hospital stays, medical costs and mortality. The development of antibiotic resistance in pathogens can be attributed to misuse of antibiotics in humans and animals. In addition, the use of antibiotics has been greatly enhanced by the global outbreak of coronavirus. In a very recent investigation, it has been reported that the concentration of antibiotics, so called 'emerging contaminants', was found to have increased to >90% in wastewaters after the COVID-19 pandemic.[2] Thus, the present situation pressurizes pathogens evolutionarily in developing resistance against several existing therapeutic agents; the result is the emergence of 'antibiotic resistance genes' (ARGs). Now, ARGs are everywhere in the environment, similar to other chemical pollutants, and threaten human health. Thus, ARGs are considered to be one of the 'emerging contaminants', which implies a global concern about ARGs. It is noteworthy that ARGs are not just confined to wastewater settings and pathogens; ARGs have also been identified in human gut biota.[3] There is an enormous potential for horizontal gene transfer (HGT) of ARGs from gut microbiota to human pathogens. Likewise, human biota is considered to be a newly emerged source of ARGs spreading to pathogens; literally, this situation is one of "good microbes with bad genes". In a nutshell, in the era of global change, finding alternative therapeutics to traditional antibiotics could have a huge impact not only in the control of antibiotic-resistant pathogens but also in the mitigation of future emerging diseases.

Eighty percent of global chronic recurrent microbial infections in humans are attributed to bacterial biofilms, as the pathogens in biofilm form acquire 10-100 times the antibiotic resistance of the planktonic stage.[4] Several bacterial pathogens (e.g. *Escherichia coli*, *Klebsiella* sp., *Pseudomonas* sp., and *Staphylococcus* sp.) have a strong capacity to produce biofilms either in pure or in mixed form,[5] and the inhibition of these biofilms is one of the promising approaches to the control of pathogens and the infections that they cause. Biofilm formation is a behavior of quorum sensing (QS), which is regulated by several signaling molecules, such as N-acyl-homoserine lactones (AHLs), autoinducer 2 (AI-2), autoinducing peptides (AIP), autoinducer 3 (AI-3), and pseudomonas quinolone signal (PQS). Fortunately, there are several enzymes (from microorganisms and human cells) and synthetic agents that have the capacity to interrupt the

*Email: raju.maddela@utm.edu.ec
ORCID ID: 0000-0002-7893-0844

activities of QS agents, which inhibition of QS behaviors by means of chemicals and/or enzymes is called quorum quenching (QQ).[6] There is a significant interference by QQ of the microbial activities under *in vivo* and *in vitro* conditions.[7] Quorum quenching has been successfully used to mitigate the biofilms of pure and mixed cultures of model bacteria, and the QQ strategy has also been implicated at field-level in different environmental settings (e.g. health care facilities, wastewater treatment settings, aquaculture, food industries, agriculture, etc.). The characteristics and crystalline properties of several QQ enzymes are available. These insights clearly open the doors for designing QQ-based therapeutic agents for the control of biofilm-based health issues. As QQ agents do not kill the bacteria, a novel approach is to use QQ agents in combination with antibiotics to treat the microbial infections.[8] However, the actual scenario about the progress of the QQ strategy is slow, and the QQ strategy is still far from its commercialization. The principal reasons for the delay in the implications of QQ strategy in the therapeutic field are as follows: (i) QQ has been tested only against biofilms of model bacteria and moreover in single species cultures in most investigations; and (ii) there is an inconsistency in the activity of the QQ strategy in biofilm inhibition.[9] Therefore, future studies are greatly warranted in the following areas – (i) QQ activities should be tested against the biofilms of various environmental isolates rather than placing the emphasis only on the biofilms of model organisms; and (ii) mitigation of pure and mixed-species biofilms should be tested using QQ organisms and QQ agents under *in vivo* and *in vitro* conditions. Such studies may reduce the gap between laboratory investigations and commercialization of the QQ strategy in the emergence of QQ-based therapeutics. Hopefully, even with rising antibiotic resistance, QQ compounds may be used in combination with other antimicrobials. However, the exaggerated claims by many authors about the benefits of these compounds should be tempered.

CONFLICT OF INTEREST

None.

FUNDING

None.

DATA AVAILABILITY STATEMENT

Not applicable.

REFERENCES

1. World Health Organization. Antibiotic resistance. Geneva: World Health Organization;2020.
2. Jiménez-Bambague EM, Madera-Parra CA, Machuca-Martinez F. The occurrence of emerging compounds in real urban wastewater before and after the COVID-19 pandemic in Cali, Colombia. Curr Opin Environ Sci Health 2023;33:100457. doi: 10.1016/j.coesh.2023.100457.
3. Crits-Christoph A, Hallowell HA, Koutouvalis K, Suez J. Good microbes, bad genes? The dissemination of antimicrobial resistance in the human microbiome. Gut Microbes 2022;14: 2055944. doi: 10.1080/19490976.2022.2055944.
4. Mah TF. Biofilm-specific antibiotic resistance. Future Microbiol 2012;7:1061-72. doi: 10.2217/fmb.12.76.
5. Schettini Alava MB, Maddela NR. Influence of interspecies interactions on biomass and extracellular polymeric substances of bacterial biofilms. Univ Med 2023;42:84–93. https://doi.org/10.18051/UnivMed.2023.v42.84-93.
6. Grandclément C, Tannières M, Moréra S, Dessaux Y, Faure D. Quorum quenching: role in nature and applied developments. FEMS Microbiol Rev 2016;40:86-116. doi: 10.1093/femsre/fuv038.
7. Sikdar R, Elias M. Quorum quenching enzymes and their effects on virulence, biofilm, and microbiomes: a review of recent advances. Expert Rev Anti Infect Ther 2020;18:1221-33. doi: 10.1080/14787210.2020.1794815.
8. Paluch E, Rewak-Soroczyńska J, Jędrusik I, Mazurkiewicz E, Jermakow K. Prevention of biofilm formation by quorum quenching. Appl Microbiol Biotechnol 2020;104:1871-81. doi: 10.1007/s00253-020-10349-w.
9. Maddela NR, Meng F. Discrepant roles of a quorum quenching bacterium (*Rhodococcus* sp. BH4) in growing dual-species biofilms. Sci Total Environ 2020;713:136402. doi: 10.1016/j.scitotenv.2019.136402.