

The rise of novel antimicrobials

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The need for solutions to combat new and existing infections has never been so topical. The current SARS-CoV-2 pandemic and the rise in antimicrobial resistance in previously treatable microbial diseases are two examples requiring antimicrobial solutions for systemic or topical treatment or as preventative measures, including empowering improved infection control measures. At the same time, the sustainability of ingredients, formulation excipients and the drive to use more natural ingredients in products have led to increased research outputs on natural products or novel compounds, and to a reflection on formulations and how these can improve the efficacy of antimicrobials.

Demonstration of the efficacy of novel antimicrobials, particularly of natural origin, is only the start of the journey towards the translational application of findings. Yet such studies are important for several reasons including (i) a better understanding of the sustainable exploitation of natural resources for their potential antimicrobial activity; (ii) gaining valuable knowledge of the interactions between the microbial targets and the novel antimicrobial; (iii) a better understanding of antimicrobial activity against microbial biofilms; and (iv) a better reflection on formulation and on antimicrobial test protocols. Understanding micro-organism–antimicrobial interactions may lead to the identification of novel target sites or/and potential synergistic applications for the antimicrobial.

This special issue on The Rise of Novel Antimicrobials aims to address the points made above and comprises a collection of state-of-the-art reviews and original articles. Two reviews focus on novel antimicrobial compounds derived from marine micro-organisms. These articles reflect on the limitations of culture-based methods, and how culture-independent methods including genome mining, proteomics profiling and the application of metagenomics, provide a novel but essential approach to maximize the discovery of novel metabolites (Abdelaleem et al. 2022; Sedeek et al. 2022). Another review by Owen et al. reflects on plant-derived novel antivirals, a highly relevant topic, particularly with the current COVID-19 pandemic. The authors highlight our poor understanding of the antiviral mechanism of action of many potential

phytochemicals and the paucity of clinical trials using such natural products.

Although there is a drive to develop new antimicrobial solutions for emerging diseases, one cannot forget current diseases for which treatment might be suboptimal. The review by Collins and Riley (2022) looks at the evidence of the novel antimicrobial ridinilazole for the treatment of *Clostridioides difficile* infection.

The search for novel antimicrobials is only the start of a journey to produce new effective antimicrobial solutions. Often missed is the impact of formulation and formulation excipients and antimicrobial efficacy. Al-Adham et al. (2022) reflect on the antimicrobial activity of thermodynamically stable microemulsions.

This special issue is also composed of several original research articles, some presenting evidence of the antimicrobial efficacy and mechanisms of bactericidal action of natural product extracts. For example, the antibacterial effect of acerola (*Malpighia emarginata* D.C.) and cashew apple (*Anacardium occidentale* L.) against enterotoxigenic *Escherichia coli* (Costa Lima et al. 2022) and the antibacterial and anti-quorum sensing of *Muntingia calabura* L. leaf extract against *Pseudomonas aeruginosa* (MosaChristas et al. 2022).

Other studies presented here focus on antimicrobial peptides (Yadav et al. 2022) and novel chemistry such as small molecules (Xu et al. 2022) and hydrazone analogues, highlighting the importance of combining *in vitro* with *in silico* investigations in the search for new antimicrobials (Azar et al. 2022). One study investigates the antimicrobial activity of natural deep eutectic solvents (NADES), a new class of green formulations, informing the concept that excipients may play an important role in the overall activity of a formulation (Al-Akayleh et al. 2022).

While the antibacterial efficacy of novel compounds is often evaluated against planktonic bacteria, exploring their efficacy against bacterial biofilms is also critical. Biofilms are the normal or preferred mode of growth of bacteria and can present additional challenges to the use of antimicrobials due to their nature, which include physical barriers to penetration with the presence of extracellular

polymeric substances, and slow metabolism, enhanced expression of resistance mechanisms and increased gene exchange.

Several articles presented here investigate the antibiogram activity of novel antimicrobials or novel antimicrobial combinations (Haines *et al.* 2022; MosaChristas *et al.* 2022; Shi and Shi 2022; Tosun *et al.* 2022; Zhang *et al.* 2022).

Novel antimicrobial compounds of natural origin may not have the desired antimicrobial activity to justify the massive financial investment necessary for the development of new chemotherapeutic agents yet their use as adjuncts to existing antimicrobials might be synergistic and beneficial. Hence, exploring synergistic combinations is a valid and promising approach that should be

encouraged, as demonstrated by the papers from Haines *et al.* (2002) and Xu *et al.* (2022).

Overall, this special issue aims to highlight several important principles in the search for novel antimicrobials and it presents manuscripts with different, valid, new and interesting approaches to combat microbial infection and contamination.

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