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Editorial

Dry Antibiotic Pipeline: Are Nontraditional Anti-infective Strategies the Answer?

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The World Health Organisation (WHO) and allied agencies have time and again expressed grave concern over the worsening state of the silent pandemic of "antibiotic resistance" (ABR), virtually drying antibiotic pipeline and, in the wake of conducive scot-free environs due to the uncontrolled COVID-19 pandemic (currently in the midst of its third wave dominated by the variant "Omicron"), likelihood of enhanced proliferation of lethal infectious illnesses [1,2].

Admittedly, in order to combat the ABR, the crying need of the time is discovery, research and development of new antibiotics from new classes on ongoing basis. Paradoxically, that does not seem to be happening in the near future notwithstanding endeavours of the scientists, pharma industry, philanthropist bodies and the WHO and its allied agencies. Hence, evolving alternative strategies that are effective against the bacterial pathogens should be in place [3]. These approaches need to be safe too for humans and livestock.

Nonconventional strategies include commonly used food items such as garlic, ginger, onion, honey, etc. These food items are believed to be gifted with anti-infective and other medicinal properties since ancient times. Honey, for instance, has been observed to have a broad spectrum inhibitory activity against both Gram positive and Gram negative pathogens [4]. The precise usefulness of food items in combating infections remains to undergo stringent evaluation scientifically.

The prospective agents for the so-called "alternatives" include antibodies, immunotherapeutics, bacteriophages, antimicrobial peptides (AMPs), especially antibacterial peptides (ABP), bacteriocins, faecal microbiota transplant (FMT), probiotics, phage therapy, and oligonucleotides, etc. for competitive exclusion of pathogens through genetical modification.

Antibodies: Monoclonal antibodies (mAbs) merit use in severe infections for which other therapies are not available. Their prohibitive cost factor does not favour their routine use.

Immunotherapeutics: These involve molecules that boost the host's internal immune system to generally prevent illness during the infection-prone times. Some examples of forthcoming vaccines in midstage development are *Clostridium difficile* (Phase III), *Mycobacterium tuberculosis* (Phase II), Group B *Streptococcus* (Phase II), and *Staphylococcus aureus* (Phase II) [5].

Bacteriophages: These, basically viruses that infect the bacteria, carry the potential for therapeutic purposes. This therapy (also termed "phage" therapy) ranks among the most actively researched alternatives to antibiotics. However, there are numerous roadblocks that need to be circumvented before this therapy could substitute antibiotics.

Probiotics: Probiotics *(*also prebiotics and synbiotics) are good bacteria that are supposed to modulate the gut microbial community

toward health. There is a reasonable evidence favouring their usefulness as adjuvant therapy in bacterial infections. However, some reports indicate lack of consistent efficacy. As yet there is hardly any convincing evidence of their usefulness as an alternative to antibiotics. Clearly, more work is required to demonstrate their role as an alternative to antibiotics.

Fecal microbiota transplantion (FMT): This is an effective option for therapy of recurrent infection with *Clostridium difficile,* the commonest cause of pseudomembranous colitis. Presently, its use in other indications merits clinical trials.

Antibacterial peptides (ABPs): ABPs have broad activity to directly kill pathogens with a broad inhibitory effect on such pathogenic bacteria as VRE, *Acinetobacter baumannii* and MRSA in clinical medicine, *S. aureus, Listeria monocytogenes* and *E. coli* in food and *Salmonella, Vibrio parahaemolyticus* in aquatic products.

Oligonucleotide therapy: This is in the process of research trials as a new approach for the treatment of MDR pathogens. Recently, there is evidence of the powerful antimicrobial activity of this lipid oligonucleotide (LON) on the ß-lactamase activity in clinical and laboratory studies. The self-delivery of oligonucleotide sequences via lipid conjugation may be extended to several antibiotics, opening up novel ways to tackle the nasty problem of ABR.

Additionally, a word about the nanoantibiotics. The metal and metal oxide-based nanoparticles are known to have less toxicity and enhanced antimicrobial efficacy. Hence, these are regarded as promising therapeutic candidates for future applications in biomedical sciences. Their unique properties such as an increased surface area to volume ratio render them efficient drug carriers with enhancement of their solubility.

As suggested by Kumar and associates [5], in this context, it is desirable to carry out research be carried out for detecting ideal targets for new inhibitory molecules such as bacterial secretion system and two component system. Bacterial secretion system is a highly specialized nano-mechanical system analogous to "nano-syringes". These syringes directly deliver substances in eukaryotic cells, thereby causing a desirable effect.

It is felt that the nontraditional strategies may well be useful as complementary therapy or as adjuvants in combating the bacterial infections and ABR. However, there is no convincing evidence as yet towards their being absolute alternatives for antibiotics.

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