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Combating AMR with Bacteriophages

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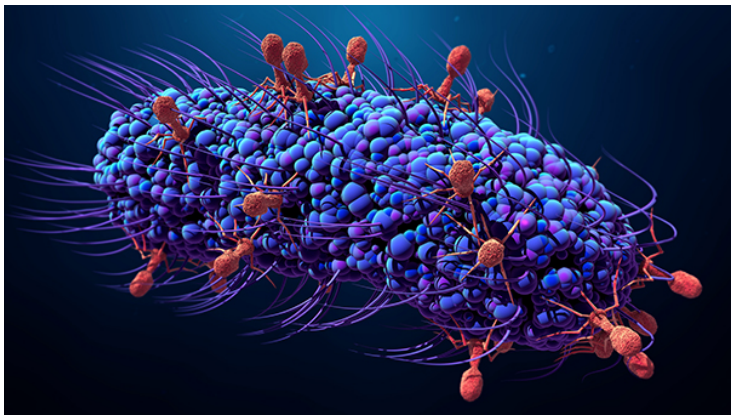
India is among the countries with a high burden of antibiotic-resistant infections. However, in recent years, the discovery of bacteriophages, simply referred to as phages, and phage-based therapy as an alternative to antibiotics, is witnessing rapid developments. BioSpectrum brings out an in-depth report on how bacteriophages are turning out to be one of the best choices to combat antimicrobial resistance (AMR), its advantages over antibiotics, and how Indian researchers and entrepreneurs are striving to make phage therapy a clinically-validated option to combat AMR. But are the regulations in favour?



It is known that India faces a significant challenge when it comes to antibiotic resistance and the menace of superbugs (largely owing to overuse and misuse of antimicrobials). Reports say that the economic impact of superbugs is significant in our country. Even in the United States, treating antibiotic-resistant infections costs an estimated $2.2 billion in extra healthcare expenses each year. These costs include longer hospital stays, additional testing, and more expensive medications.

The World Health Organisation (WHO) warns that as these superbugs become more prevalent, our arsenal of effective antibiotics will become less potent. This makes routine medical procedures such as surgeries, chemotherapy, and organ transplants riskier due to the increased likelihood of infection. This validates the immediate requirement as an alternative to antimicrobials and researchers trust their bet on bacteriophages as that alternative.

According to **Rachna Dave, Founder & CEO of MicroGO**, AMR is indeed a far more significant and pressing issue than it might initially appear, primarily due to underreporting. She says, “Estimates indicate that the toll of AMR could result in more than 10 million deaths by 2023. This looming crisis is exacerbated by the extremely limited availability of new antibiotics in the market, making it an incredibly challenging problem to address. In this dire context, bacteriophages are emerging as one of the most promising solutions to combat AMR infections. With the scarcity of effective antibiotics, bacteriophages offer a viable alternative. In India, there have been approximately 200 patients successfully treated with phage therapy, boasting an impressive success rate exceeding 80 per cent. This number is steadily increasing as more clinicians and infection prevention specialists embrace this innovative technology.”

India – The land of abundant bacteriophages

Phages are natural predators of bacteria. They can infect and kill specific bacterial strains, making them valuable tools for controlling bacterial populations, especially harmful pathogens. Phages are known for being highly specific in their host range. Each phage typically infects only one or a few closely related bacterial species, which means they do not harm beneficial bacteria in the body. This specificity is advantageous for targeted bacterial treatment and avoiding disruption to the common microbiota of the host organism.

Sharing more facts on bacteriophages, **Dr Satheesh K, Senior Research Scientist, India Diabetes Research Foundation & Dr A Ramachandran's Diabetes Hospitals**, says, “Bacteriophages or phages thrive in environments like rivers and sewage-contaminated waters. These microscopic predators have a unique potential to latch onto particular bacterial species, inject their genetic material, and hijack the bacterial machinery to copy themselves, and in the long run causing the bacterial cellular to burst, and launch new phage particles. In essence, they are natural bacterial killers.”

India is home to an abundant variety of phages. Researchers of the ICAR-Central Inland Fisheries Research Institute, West Bengal, have detailed in a research paper that Bacteriophages are abundantly present in the river Ganga.

Atif Khan, Scientist, Water and Steam Chemistry Division, Biofouling and Biofilm Processes Section, Bhabha Atomic Research Centre, Kalpakkam, says, “India is considered to be the richest source of bacteriophages compared to any other country. If you like to talk about the competitive advantage, the opportunity lies in the phages of the bacterial host that rarely cause any diseases (Staphylococcus simulans). In case of multidrug resistant S. simulans infection, most of the labs and their surrounding environment may not have phages for this host. India could be a country where the phages can be found in a system like local sewage.”

Presently, more than 20 to 30 research facilities across the country are dedicated to isolating and characterising bacteriophages, with a specific focus on combating pathogens prioritised by the Indian Council of Medical Research (ICMR).

Phage Banks and Phage Engineering

In India, where antibiotic-resistant bacterial infections are a significant public health concern and where biodiversity is high, the establishment of phage banks can be particularly important. These banks can contribute to the development of phage-based therapies, facilitate research into new phages, and aid in the control of bacterial infections in various settings, including healthcare, agriculture, and environmental management.

Furthermore, they can play a crucial role in advancing the understanding of phage biology and their interactions with bacteria in India's unique ecological and clinical contexts.

According to **Dr Hiren Joshi, Scientific Officer, Bhabha Atomic Reserach Centre, Kalpakkam**, “It is imperative to leverage this rich resource to establish comprehensive phage libraries and cocktails. These collections can prove highly effective against a broad spectrum of bacterial infections. By tapping into the wealth of bacteriophages in India's diverse microbial ecosystems, we can potentially develop innovative solutions for combating infectious diseases and antimicrobial resistance on a global scale. This approach holds great promise for the future of healthcare and pathogen control.”

Dr Ranga Reddy Burri, President, Infection Control Academy of India opines, “Phages hold significant promise in addressing AMR due to their specificity, adaptability, and potential for personalised treatment. While there are success stories in India like AIIMS-ICMR PhageBank, ongoing research, international academia, industry collaborations, regulatory support, and clinical validation are crucial for realising their full potential as alternatives or complements to traditional antibiotics.

Talking about the bacteriophage market Dr Burri says **“**The current market size of bacteriophage-based products and therapies in India is insignificant at the moment. Even globally the estimated size is less than $50 million. The rising threat of AMR and awareness about the benefits of phage therapy is expected to propel market growth. The use in agriculture, veterinary and consumption as phage probiotics will be major growth drivers. Aristogene, Gangagen, Sciinv Biosciences, Vital Therapeutics, Proteon Pharma are visible players in this market.”

Sharing her thoughts on the market growth Rachna Dave, says “The growth is further substantiated by recent developments, such as the establishment of a new production facility in Nasik by Proteom Biotech, a Polish company. Additionally, several other companies are currently in the process of setting up pilot-scale plants for bacteriophage production, underscoring the increasing interest and investment in this promising field.”

Adding her thoughts, **Dr Ellie Jameson, Researcher, Bangor University School of Natural Sciences, UK** says, “The next developments that will be expanded in India and across the globe are well stocked and characterised phage banks combined with a Good Manufacturing Practice (GMP) facility for phage production. These central repositories will hold thousands of characterised, sequenced phages to ensure that they do not contain any harmful elements, but that phages can be quickly accessed to treat 100s of different bacteria, as needed. There is a strong call to ensure that phages are manufactured to GMP standard so that phage therapy can be controlled as a drug for widespread use.”

She further says “To step up phage therapy I foresee that a GMP facility for phage production will need to be established in India to keep cost manageable and enable production to meet demand. This will ensure each batch is identical and that endotoxin levels are negligible to prevent adverse effects. With these in place I believe that due to the positive stories of phage therapy it will continue to grow and work with our antibiotics to help more and more patients.”

Scope to expand from diagnostics to therapeutics

Phage engineering isn't always restrained to improving the phages themselves; it additionally opens doorways to growing novel phage-based equipment for various applications. For instance, researchers at the Indian Institute of Science in Bengaluru have validated the capacity of engineered phages within combat in opposition to mycobacteria—the causative dealers of tuberculosis and leprosy.

By modifying the tail fibre proteins of a mycobacteriophage, they were able to apprehend distinctive receptors on the floor of mycobacteria. These engineered phages successfully lysed various lines of Mycobacterium tuberculosis and Mycobacterium leprae in both laboratory settings and in vivo.

Regulatory hurdles and market boundaries

India, though, has developed a National Action Plan on Antimicrobial Resistance (NAP-AMR) to address the growing threat of antibiotic resistance, plans that include strategies for promoting responsible antibiotic use, improving surveillance, and enhancing infection prevention and control need to be hastened along with making phage therapy a viable option.

Also, Dr Burri says that regulatory authorities classify bacteriophages as biological substances and currently, there is no established framework that explicitly defines the role of bacteriophages in the context of medicinal products for human use in India and globally. Very few countries have clear regulatory pathways.

One such example is Georgia, where bacteriophages have been seamlessly integrated into the healthcare system as a standard medical practice, and a range of phage preparations are available over-the-counter, along with a more extensive selection of products supplied directly to medical practitioners. The US FDA also approved several phage treatments, which are employed in the food industry, largely in the dairy and meat industry, to combat bacterial growth. To fuel rapid progress towards phage therapeutics, as a sustainable antibiotic alternative, regulatory processes must be refined and should be pragmatic to reach a tipping point sooner.

We cannot deny that India has made progress in adopting phage therapy, but to make it a more mainstream solution to combat AMR, concerted efforts in research, regulation, education, and infrastructure development are crucial. Collaboration between all the stakeholders and a dedicated approach from both government and private sectors will be essential. The funding into this sector is mostly from grants, philanthropy, altruistic researchers, and good Samaritans only.

There is a need to promote this therapy in the country. “The level of public awareness and acceptance of bacteriophages as an alternative to antibiotics in India is abysmal,” says Dr Burri and adds that compared to more established treatments like antibiotics. Even among healthcare professionals, the awareness is low, which is a significant deterrent to mainstreaming this alternative. Organisations like Society for Bacteriophage Research and Therapy, Infection Control Academy of India and others are working towards awareness and providing a platform for researchers, clinicians, and other stakeholders to collaborate.

Traditional life science and biotech companies have no participation in research or investments in this segment as the perceived demand is low and the risk of return is high. Maybe, providing incentives and financial support, including grants, tax incentives, or other financial benefits, to encourage investment for budding companies could be a possible way to lure them into phage therapy development.

Hence, in conclusion, it can be said that India has to step-up and establish clear regulatory pathways for phage therapy, ensuring safety, efficacy, and quality standards. The country needs specific guidelines and protocols for the approval and use of phage therapy. It is also important for the government to facilitate collaborations between pharmaceutical companies, research institutions, and government bodies to foster the development and distribution of phage therapeutics.

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