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Mini Review

Predatory Bacteria: A Novel Approach to Combat Antibiotic Resistance-A Review

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Abstract
Infections caused by multidrug-resistant bacteria have become one of the leading causes of morbidity and mortality worldwide, with approximately 700,000 deaths each year. Likewise, the discovery and development of new antibiotics have decreased resulting in increasingly complex clinical management of bacterial infections. For these reasons, there is an urgent need to look for alternatives for patients for whom conventional therapy is ineffective. Different antimicrobial alternatives such as phage therapy and nanoparticles have been reported. This study aimed to review what predatory bacteria are, their mechanism of action, safety and efficacy concerns, and also how the idea of injecting live bacteria into human and animal hosts has advanced over the years. Predatory bacteria, specifically *Bdellovibrio bacteriovorus*, offer a novel and intriguing approach to addressing this crisis. These bacteria exhibit natural predatory behavior, targeting and killing specific prey bacteria, including multidrug-resistant strains. Research into *Bdellovibrio* and like organisms (BALOs) has the potential to unlock new therapeutic strategies, providing a much-needed adjunct or alternative to traditional antibiotics. However, there are some concerns with their efficacies and toxicity. Therefore, there is a need for extensive research on predatory bacteria, BALOs.
Keywords: Multi-Drug Resistant, Antibiotics, Predatory Bacteria, BALOs.

1. Introduction

For more than 80 years since the discovery of Penicillin by Alexander Fleming, antibiotics have been used to treat bacterial infections. With the discovery of antibiotics came antibiotic resistance, the number of infections caused by multidrug-resistant (MDR) bacteria is increasing across the world, and the threat of untreatable infections has been looming since the beginning of the 21st century (Gajdács and Albericio, 2019). In a systematic analysis carried out by Murray *et al.,* (2022) to determine the global burden of bacterial antimicrobial resistance (AMR), they reported 4.95 million deaths associated with bacterial AMR, including 1.27 million deaths attributable to bacterial AMR. At the regional level, they estimated the all-age death rate attributable to resistance to be highest in western sub-Saharan Africa, at 27.3 deaths per 100,000, and lowest in Australasia, at 6.5 deaths per 100,000. The situation has been shown to be worse in developing countries where poverty, indiscriminate use and abuse of drugs; and purchasing of drug over the counter pose serious threat.

Over the last few years, there has been fundamental scientific research to find alternatives to antibiotics. These include 'living antibiotics'; live agents such as bacteriophage or their components (Lukacik *et al.,* 2012), predatory bacteria, and probiotics (Ghosh *et al.,* 2019). The predatory bacteria, the *Bdellovibrio* and like organisms (BALOs), are seen as viable alternatives to tackle the multidrug-resistant bacteria. The predation strategies employed by predatory bacteria are classified into two main categories: endobiotic (direct invasion) strategy and epibiotic strategy, depending on how the predators interact with their prey (Pérez *et al.*, 2016). There have been questions about the safety of BALOs in humans and animals and several studies have addressed this question including a review carried out by Dwidar *et al*., (2012) which demonstrated that multiple studies failed to detect deleterious effects following topical application, ingestion, or injection of *Bdellovibrio bacteriovorus* into vertebrates. This review aimed to highlight what predatory bacteria are, their mechanism of action, safety and efficacy concerns, and also how the idea of injecting live bacteria into human and animal hosts has advanced over the years.

2. BALOs: The Living Antibiotics

Predatory bacteria are those bacteria that specifically target and prey on Gram-negative bacteria (Dashiff *et al*., 2011). Predatory bacteria that are known to prey on other bacteria include *B. bacteriovorus*, *Micavibrio aeruginosavorus*, *Myxococcus xanthus*, *Vampirovibrio chlorellavorus* and are collectively known as, *Bdellovibrio* and like organisms (BALOs). BALOs can naturally invade, develop in, or on other unwanted bacteria, thus inhibiting and killing them both specifically and non-specifically. They are microscopic (0.5-1.5μm), mostly Gram-negative bacteria, found ubiquitously in aquatic environments, and soil. Some of them even belong to normal healthy gut microbiota of the intestines of animals and human beings (Mhase *et al*., 2022). According to Bratanis *et al.,* (2020), based on the feeding habits of preparatory bacteria, they are found within a vast taxonomic group that includes both facultative and obligate predators. While obligate predators survive by digesting prey cells, facultative predators can easily transition to a saprophytic state, ingesting a diverse range of substrates in the absence of suitable prey. To date, an obligatory predatory lifestyle is limited to α-proteobacteria (genus *Micavibrio*) and δ-proteobacteria (families: Bdellovibrionaceae, Bacteriovoraceae, Peredibacteraceae, Halobacteriovoraceae, and Pseudobacteriovoracaceae) (Bratanis *et al.,* 2020).

B. bacteriovorus is the most studied predatory bacterium to date (Shanks and Kadouri, 2014). It is the prototype of predatory bacteria; it was discovered nearly 60 years ago, giving rise to a broad field of inquiry in which a large and diverse group of organisms was found, and many individual species were characterized. The genome and lifecycle of *B. bacteriovorus* have several features that make it a promising therapeutic agent against Gram-negative bacterial pathogens. During the predatory lifecycle, the cell of the prey is killed within a short time (<30 min) which means, for the prey to survive, it would need to express defense mechanisms quickly enough to resist predation, something that has not happened yet. *B. bacteriovorus* predation does not result in the initial lysis of the prey, as the prey contents are ingested from within a stable bdelloplast structure before lysis, and this is in contrast to some antibiotics, which can cause a cascade of events that lead to bacterial autolysis and release of inflammatory molecules. Furthermore, there is no single receptor for prey recognition and attachment. There is upregulation after prey invasion, both in number and functional diversity, of prey-destructive enzymes with potential genetic redundancy. This suggests that simple prey resistance to predation by *B. bacteriovorus* is unlikely to occur (Atterbury and Tyson, 2021).

3. Predatory Mechanism of BALOs

Predator-prey interactions are a common phenomenon not limited to animals but also exist between microorganisms. These predatory bacteria aggressively hunt and kill other bacteria and yeast cells as food sources (Johnke *et al.,* 2014; Oyedara *et al.,* 2016). This predatory bacteria group *Bdellovibrio* and like organisms (BALOs) have strategies that they employ to feed on their prey (Gram-negative bacteria). These strategies are divided into three groups: wolf pack/group attack mechanism, epibiotic predation mechanism, and endobiotic predation mechanism. In wolf pack/group attack mechanism, they typically attack in packs, irrespective of this predatory bacteria's ability to hunt solely. Examples include *Lysobacter* species, *M. xanthus*, and other members of Myxobacteria (slime bacteria). These predators exhibit non-specificity to their prey and can feed on any bacteria that they encounter in proximity, which is an exception to the usual Gram-negative prey of BALOs (Velicer and Mendes-Soares 2009; Mhase *et al.,* 2022). Pérez Torres *et al.*, (2020) revealed that BALOs achieve this predatory mechanism by secreting diffusible chemical substances such as siderophores, bacteriocins, pigments, and antibiotics by the predator bacteria. Examples include the antibacterial compounds Myxovirescin A and Myxoprincomide observed from *M. xanthus*.

BALOs that exhibit an epibiotic mechanism of predation are highly motile and attach themselves to the cell surfaces of their prey similar to exo-parasitism, releasing some hydrolytic enzymes via the type iv secretion system (T4SS) into the prey cell and then consuming it externally by sucking out all the lysed cell component before rapidly dividing into daughter cells by binary fission. Examples of BALOs that exhibit epibiotic mode of predation include *Bdellovibrio exovorus, Vampirococcus micavibrio, Vampirococcus aeruginosavorus, M. aeruginosavorus, and V. chlorellavorus* (Pasternak *et al.,* 2014; Pérez *et al.,* 2016; Pérez Torres *et al.,* 2020). In the endobiotic mechanism, solitary predatory bacteria actively search for their prey, adhere to their exterior, penetrate and alter the target cell wall by secreting hydrolytic enzymes. They then enter the periplasmic or cytoplasmic space to consume it from within. The daughter cells produced then attack adjacent cells after the cycle is complete. *B. bacteriovorus* is a characteristic species in this group and the most studied (Sockett, 2009; Rotem *et al.,* 2015). *B. bacteriovorus* usually takes approximately three to four hours to complete an endobiotic predatory cycle. Although *B. bacteriovorus* is an obligatory predatory bacterium, it is however also capable of host-independent (HI) existence by exhibiting either saprophytic growth or axenic growth on culture media (Capeness *et al.,* 2013; Lambert *et al.,* 2016).

4. Efficacy of the BALOs

Several studies have determined the efficacy of the BALOs. The in vitro and in vivo studies investigated the potential of BALOs as a safe and effective alternative to conventional antibiotics. Monnappa *et al.*, (2016) examined the effects of BALOs on human cell lines, including the colon, airway, and mouse macrophage. They found that compared to *Escherichia coli,* BALOs triggered a significantly weaker inflammatory response in both the immune cells and epithelial cells (Monnappa *et al.,* 2016). Atterbury *et al*., (2011) examined the effect of *B. bacteriovorus* (strain HD100) on healthy chicks. The bacteria had no adverse impact on the animals' health or growth after introduction, but they did change the diversity of the gut bacteria. When 100µl of a 1.9×10^7 PFU/ml suspension of *B. bacteriovorus* HD100 was injected into chickens pre-infected with *Salmonella enteritidis*, the pathogens in the ceca were dramatically reduced, improving caecal morphology and indicating a reduction in inflammatory activity (Atterbury *et al*., 2011).

5. BALOs, Superior Alternatives?

There are several strategies to either limit the selection for antibiotic resistance or completely substitute the antibiotic entirely. These include phage therapy and nanoparticles. Superficially, *B. bacteriovorus* and bacteriophage share many characteristics as potential biological control agents. They both exhibit predatory or parasitic lifecycles, are self-replicating and self-limiting, and only survive as long as susceptible hosts or prey are around. When introduced into the bodies of animals and humans, they also appear to have little or no adverse impact. However, there are some notable distinctions between the BALOs and Phages, which may restrict their application in certain situations (Atterbury and Tyson, 2021). Maintaining the population of a bacteriophage is more complex than that of *B. bacteriovorus* because the host range of an individual phage is restricted to a few strains within a species or one or two closely related species of bacteria (Atterbury and Tyson, 2021). Most Gram-negative species are susceptible to predatory bacteria, and acquiring resistance, which can be a concern with phage therapy, is unlikely because predatory bacteria's broad-ranging killing mechanisms don't target specific prey proteins that can evolve resistance. But that also means *Bdellovibrio* could consume beneficial microflora (Madhusoodanan, 2019). Nanoparticles can be picked up by mitochondria and cell nuclei which may cause DNA mutations (Singh *et al.,* 2008). In contrast, BALOs are non-toxic and non-immunogenic (Gupta *et al.,* 2016). Unlike metallic nanoparticles that can accumulate in the body and be highly toxic, predatory bacteria target specific pathogens and leave the host cells unharmed (Kakasis and Panitsa, 2019).

6. Potential Limitations of the Use of BALOs as Biocontrol Agents

Although promising, there are downsides to the use of *BALOs.* These include the limited host range, environmental conditions, and chemical factors. Although very effective against Gram-negative bacteria, they are not capable of predating Gram-positive organisms like *Staphylococcus aureus,* which is one of the most frequently associated with multidrug resistance (Van Essche *et al.,* 2011). It can also not predate Gram-negative bacteria with the S layer (Dwidar *et al.,* 2012). That is, the predation of these organisms is highly dependent on the morphological makeup of the host bacteria. The presence and activity of these organisms are also highly dependent on the presence or absence of prey in the environment, therefore making the isolation difficult (Mhase *et al.,* 2022). They are also dependent on environmental factors such as temperature, oxygen availability, and pH. Studies have shown that they perform poorly in oxygen-limited environments such as the gut, which reduces the efficiency of application in such areas (Harini *et al.,* 2013). Although BALOs are insusceptible to B-lactams (Harini *et al.,* 2013), their activity is greatly affected by some chemicals such as detergent and the secondary metabolites produced by *Chromobacterium piscinae*, violacein, and cyanide (Mun *et al*., 2017). Cho *et al.*, (2019) demonstrated the effectiveness of detergent components, sodium dodecyl sulfate (SDS) and Triton X-100 against *B. bacteriovorus* by showing that SDS can kill the bacteria at 0.02% concentration (Cho *et al*., 2019).

7. Conclusion

BALOs are a promising tool for combating antibiotic resistance. Their unique predatory behavior offers potential advantages over conventional antibiotics. Researchers should look into combination with traditional antibiotics to enhance the effectiveness of treatment which could help reduce the development of antibiotic resistance. More studies are needed to evaluate the dissemination of predatory bacteria from the administration site, along with determining any long-term effects of exposure on the host or their resident microbiota.

Animal models and the ability to recover and count live predators in cellular models are essential milestones in assessing the effect of predatory bacterial treatment on the host, its bioavailability, and its dissemination. Extensive research is required to guarantee the safety of using *B. bacteriovorus* in humans.

Declarations

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