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PREDATORY BACTERIA: AN NOVEL APPROACH TO THERAPEUTIC USES

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Abstract:

Parallel to the predator's increasing understanding, it became clear that the remarkable predatory capability of human pathogenic bacteria represents a feature that could be exploited to potentially use *B. bacteriovorus* as a "Biocontrol agent". Because it could be used as a probiotic and antibiotic agent, research on this particular "predatory bacterium" has received attention in response to the growing problem of antibiotic resistance. In this paper, we highlight the important aspects of the study of *B. bacteriovorus*, including discovery, predation mechanisms, predation resistance, and potential applications. Furthermore, this review discusses the studies that pave the way for *B. bacteriovorus* to be used as a "living antibiotic" in human therapy, with a focus on its interaction with biofilms, the host immune response, predation susceptibility, and in vivo applications. The available data suggest that this predator bacterium can be transformed from a purely academic curiosity into a tool for combating antibiotic-resistant infections.

Key words- Predatory bacteria, Biocontrol agents, predation resistance, living antibiotic, antibiotic resistant infections.

I. INTRODUCTION

Pathogenic organisms are the greatest concern from the point of view of human health. Pathogenic organisms may belong to many groups, including bacteria, fungi, protozoa, viruses, etc (Sharma et al, 2017). Bacterial infections have become the crown of most problems as it develops antibiotic-resistant organisms due to their enhanced survival ability (Piddock, 2016). Antibiotics are used to treat microbiological illnesses caused by bacteria or fungi. Infectious diseases were assumed to be extinct after the discovery of antibiotics. The widespread and often excessive use of conventional antimicrobials has dramatically increased multi-drug resistance bacteria. If the infection cannot be treated with primary antibiotics, more expensive drugs should be used. In many cases, longer hospital illnesses and treatments increase medical costs and increase the financial burden on families and society.

In the middle of this global concern, a promising solution was found by investigating one of nature's fundamental rules, prey-predator interaction. Predator-prey relationships exist worldwide, and predatory strategies used by microorganisms vary widely. These interactions are not new to the microbial world, and it has even been proposed that bacterial predation is one of the forces that drive bacterial form and size (Young, 2006). Predation occurs at all levels of life, in all sectors of life, and in all situations. Bacterial predation has been recognized for a long time.

Predatory bacteria are getting popular as bio-control agents, with several recent studies highlighting their therapeutic potential, particularly because of their capacity to continue predation against multidrug-resistant (MDR) Gram-negative pathogens despite antibiotic resistance(Randall et al, 2013). The study of bacterial defense against predation has gained traction in recent decades and has developed as a fascinating topic that crosses multiple scientific domains. This paper aims to give an interdisciplinary overview of these recent developments using predatory bacteria.

II. Discovery of Predatory bacteria:

Stolp and Petzold in 1962 uncovered the Gram-negative predatory bacteria *Bdellovibrio bacteriovorus* accidentally while isolating bacteriophages of the phytopathogen from soil suspension. They were termed *Bdellovibrio bacteriovorus*, which describes the bacteria's shape and presumed method of life; they were curled and seemed to attach to their target and absorb the prey cell material, resembling a leech ("bdella" in Greek). The term B. bacteriovorus was coined by Robert E. Buzzzchanan.

The genus Bdellovibrio is a member of the Bdellovibrionaceae family and is divided into two members: *Bdellovibrio bacteriovorus* (*B. bacteriovorus*), a periplasmic predator, and *Bdellovibrio exovorus* (B. exovorus), an epibiotic predator. Periplasmic invasion is one of the predatory strategies utilized by bacteria. The predator cell invades and grows within the periplasm, a compartment seen in Gram-negative cells. For e.g., *Bdellovibrio* like organisms (BALOs).

Prey – Predator relationship has been studied in different biotic terrain, including different flora and fauna but numerous aspects of this interaction are still unclear concerning microorganisms. All three crucial groups of micro-predators include protists,

Predatory bacteria, and bacteriophages. They greatly differ in size, prey particularity, hunting strategies, and in performing population dynamics (Johnke et al, 2014).
In the case of Predatory prokaryotes, it's difficult to interpret whether these organisms are truly predatory by ecological definition or they are parasites.

There are a few basic parameters of predation which includes the following:

1. Predator must be able to locate the prey cell.
2. Association between Predator and Prey cells must be irreversible.
3. Predator cells must feed on the cells or products of cells.
4. Assimilation of the released nutrients by the predatory cell.

III. Taxonomy and predation mechanisms:

In nature, predation has been documented as an integral part of the food chain in an ecosystem. Thus, bacteria are predated by bacteriophages, protists, and other prokaryotes. Unlike bacteriophages, protists and predatory prokaryotes are cellular organisms. In contrast with protists, predatory prokaryotes are smaller than their prey and have evolved distinct strategies for predation. Parasitic bacteria are from the diverse clades of the Proteobacteria, a major group of Gram-negative bacteria. For example, *Micavibrio* spp. is grouped in alpha-proteobacteria. *Lysobacter* spp. in gamma-proteobacteria. *Myxococcus* spp., *Bdellovibrio* spp., *Bacteriovorax* spp., and *Daptobacter* are grouped in deltaproteobacteria (Esteve et al, 1992). The phylogenetic analysis of *Vampirococcus* is not known (Berleman and Kirby, 2009), although Vampirococcus may be related to Deltaproteobacteria due to their predation type and other taxonomic characteristics. The δ – proteobacteria includes three families – the Bdellovibrionaceae (Seidler and Starr, 2021), the Bacteriovoracaceae (Pineiro et al, 2007) and the Peridibacteriaceae.

Bacterial predation can be classified broadly into the following categories:

(i) **Wolfpack:** In this type of predation, a variety of hydrolytic enzymes are produced by several Predator cells. These enzymes degrade nearby bacteria. This leads to the availability of host cell-derived nutrients. *Myxococcus* (Burham, Collart, Highison, 1981) and *Lysobacter* (Lin and McBride, 1996) are examples of this kind of Predation.

(ii) **Epibiotic:** Epibiotic predation requires cell-to-cell contact. Predator cells possess specialized structures through which it attaches host cell and begins to degrade and assimilate host molecules. An example of these includes *Vampirococcus* which preys on the various species of *Chromatium* (Esteve et al, 1992). *Micavibrio aeruginosa* and *Bdellovibrio exovorus* exhibit an Epibiotic predation strategy (Koval et al, 2013, Davidov et al, 2006).

(iii) **Direct invasion:** This strategy was also called diacytosis by Moulder (2003). Here, the Predator cells directly enter the host cytoplasm. *Daptobacter* which preys on Genus *Chromatiaceae* organisms exhibits a direct invasion predation mechanism(Guerrero et al, 1986).

(iv) **Periplasmic:** This type of predation is exhibited by the *Bdellovibrio* organism. It preys on mostly Gram-negative organisms. They invade and grow within the periplasmic space. Periplasm has osmolarity same as the cytoplasm. The periplasmic space contains solutes, enzymes, and oligosaccharides(Stolp and Starr, 1983).

IV. BALOs and other predatory bacteria as biocontrol agents:

Emerging antibiotic resistance caused by pathogenic bacteria is viewed as a global issue, accounting for thousands of casualties and millions of dollars spent on health care each year (Carlet et al, 2014). With the development of a few new antibiotic classes, newer approaches for treating bacterial infections are becoming important (Projan, S 2008). Alternative approaches, such as bacteriophage therapy, show promise but are limited by a restricted host range and the rapid development of bacterial resistance. Bacteriophages and Predatory bacteria, such as *Bdellovibrio bacteriovorus*, may be effective as a treatment. Predatory bacteria have a wider host range than phages (Atterbury, R. J. et al, 2011).

O. O. Oyedara et al (2016) isolated two different strains of *Bdellovibrio* designated SKB1291214 and SSB218315 from soil underneath a banana (Musa paradisiaca L) plant. *Bdellovibrio* strain SKB1291214 could form plaque with 36.11% of bacterial isolates considered for prey range analysis, whereas *Bdellovibrio* strain SSB218315 could prey on 61.11% of bacterial isolates. None of the *Bdellovibrio* strains formed plaque on the six gram-positive bacteria studied, which included the genera *Staphylococcus* and *Bacillus*. This study has revealed the remarkable potential of the two *Bdellovibrio* strains isolated from soil and showed the ability to prey on different types of gram-negative bacteria, which could be used in the future to control pathogenic gram-negative bacteria.

Micavibrio aeruginosa exhibits diverse specificity for the host range. They can prey on many bacteria that have been added as a boon to treat many infections caused by these pathogens. A profound effect is observed against bacteria from the genus *Burkholderia, Escherichia, Klebsiella, Pseudomonas, and Shigella.* Moderate predation effects are seen for bacteria in Genus *Acinetobacter, Enterobacter, Proteus,* and *Yersinia* (Kadouri et al, 2013).
Bdellovibrio bacteriovorus has exhibited broad host range specificity. It is found to reduce the number of bacteria which includes the Genus *Acinetobacter, Aeromonas, Bordetella, Burkholderia, Citrobacter, Enterobacter, Klebsiella, Listonella, Proteus, Pseudomonas, Salmonella, Shigella, Vibrio,* and *Yersinia* (Dashiff et al, 2011).
Vibrio parahaemolyticus is found in marine environments and it can cause food poisoning outbreaks. The parasitic bacterium *Bdellovibrio* is found to keep a check on the *Vibrio parahaemolyticus* in a marine environment, especially during the winter seasons (Miyamoto and Kuroda, 1975).

Viable but Non-culturable [VNBC] is one of the survival strategies of microorganisms under stress conditions. They lose their ability to grow and multiply VNBC cells have been a concern to public health as it is very difficult to detect in samples but are capable of causing disease (Moulder J W, 1985). *Helicobacter pylori* are found to grow actively as well as VNBC cells. *Bdellovibrio* can attack these cells and act as a biocontrol agent (Markelova, 2010). *Bdellovibrio bacteriovorus* strains which

parasitize *Rhizobium meliloti, R. trifolii, Agrobacterium tumefaciens,* and *A. radiobacter* have been found in Western Australian soils. Rhizobium lupini was not lysed by any strain. The *Bdellovibrio* strains are capable of destroying large numbers of rhizobia in the laboratory (Parker and Grove, 1970).

V. The ability of predatory bacteria to reduce biofilm formation:

BALOs adapt to biofilms by expressing a "biofilm mode," which includes increased expression of genes involved in flagellar biosynthesis, gliding motility, chemotaxis, and proteolysis. Furthermore, specific, highly active serine proteases and a mild DNase activity that impacted S. aureus biofilms were discovered (Monnappa et al, 2014, Im, Dwidar and Mitchell, 2018). Many clinically significant bacteria are capable of producing extracellular polymeric substances (EPS) that construct complex structures known as biofilms. The biofilm provides a favorable environment for the resident bacteria (Francis et al, 2011).

Staphylococcus aureus is one of the most frequent nosocomial infection-associated multidrug-resistant pathogens isolated from patients. *S.aureus* can easily colonize the skin or nasal passage of humans. It can also inhabit and form biofilms on a variety of abiotic surfaces. These include catheters, medical equipment, and implants and prosthetics. These Biofilms are composed of bacterial cells embedded within a matrix called extracellular polymeric substances (EPS). This EPS matrix is formed using extracellular DNA, polysaccharides, and proteins and anchors the cells to the surface, making it difficult to eradicate the organism once it establishes itself. Predatory bacteria like *Bdellovibrios* are well known for their action on gram-negative bacteria. *B. bacteriovorus* produces two types of proteases that can be effective on the Gram-positive organism like *Staphylococcus aureus* biofilm. The action of extracellular proteases provides this predatory bacterium source of energy and amino acids from the Biofilm. Although *B. bacteriovorus* does not predate on Gram-positive bacterial strains but can thrive in a natural environment with non-prey Gram-positive organisms(Im, Dwidar and Mitchell, 2018). This results in effective inhibition of the formation of *S.aureus* biofilm and reduces its virulence (Monnappa et al, 2014).

VI. Predatory bacteria *In vivo* antibacterial therapy:

Bdellovibrio bacteriovorus was the first successfully used Predatory bacteria *in vivo* as an injected antibacterial therapy using zebrafish (*Danio rerio*) larvae infected with an antibiotic-resistant strain of the human pathogen *Shigella flexneri*. *Shigella*-dependent replication of *Bdellovibrio* was captured inside the zebrafish larvae, indicating active predation *in vivo*. *Bdellovibrio* can be engulfed and ultimately eliminated by host neutrophils and macrophages, yet have a sufficient dwell time to prey on pathogens.

Experiments in immune-compromised zebrafish reveal that maximal therapeutic benefits of *Bdellovibrio* result from the synergy of both bacterial predation and host immunity, but that *in vivo* predation contributes significantly to the survival outcome. This successful antibacterial therapy can be achieved via the host immune system working together with bacterial predation by *Bdellovibrio*. Such cooperation may be important to consider in the fight against antibiotic-resistant infections *in vivo*. This represents key milestones in the future use of *Bdellovibrio* as a "living antibiotic" *in vivo*, and they warrant further research into the development of predatory bacteria as an antibacterial agent for infected sites or wounds in higher vertebrates and, ultimately, humans. The strength of such prokaryotic-predator: eukaryotic-leukocyte combinations is an important therapeutic consideration as we move forward in responding to new Gram-negative bacterial threats (Willis et al, 2016).

Antibiotics, despite being an efficient method of treatment for infection, it has off-target effects. These effects can cause dysbiosis within the gut microbiome which in turn often leads to significant decrease in bacterial diversity. This may last for up to a year to return to normal. Predatory bacteria like *B. bacteriovorus* when introduced into the gut of rats mostly associated with health benefits and result in limited population shifts in the gut microbiota. Predatory bacteria favor against the off-target effects of antibiotics and can be used as novel antimicrobial agents (Shatzkes et al, 2017).

Keratitis is the inflammation of the Cornea. Both Gram-positive and Gram-negative pathogens can be the causative agent of Bacterial keratitis. It is a localized infection whereas a particular area of the Cornea is infected by mostly Gram-negative pathogens like *Pseudomonas aeruginosa* and *Serratia marcescens*. Predatory bacterial spp *Bdellovibrio bacteriovorus* and *Micavibrio aeruginosa* can kill the Keratitis isolates *Pseudomonas aeruginosa* and *Serratia marcescens in vitro*. These predators were noncytotoxic and non-inflammatory to human corneal-limbal epithelial cells (HCLE) *in vitro*. They do not enhance proinflammatory cytokine production in Human cell lines which contributes to the safe use of Predatory bacteria in *vivo* clinical therapy of Ocular infections (Shanks et al, 2013).

Salmonella is a gram-negative foodborne pathogen that has been associated with fish outbreaks all over the world. Currently, the use of antibiotics in fish farming as growth promoters or for treatment and prevention of fish diseases raises the risk of antibiotic-resistant bacteria developing in the fish gut microbiome and/or fishing water. Many studies have shown that antibiotic-resistant bacteria from fish or aquatic environments are widely transmitted to humans (Francis et al, 2011). Salmonellosis risk of fish consumption is often caused by *Salmonella enterica spp. Enterica serovar typhimurium*. In imported Seafood *S.typhimurium* ranked 12th of all the serotypes detected (Heinitz et al, 2000). *Peredibacter* sp strain BD2GS and *B. bacteriovorus* strains showed powerful lysing ability for Salmonella. These abilities of BALOs were characteristics of strain and not species. The lytic ability of BALO to reduce contamination by the foodborne pathogen is advantageous over chemical sanitizers i.e very specific in action and prey resistance is extremely rare (Sockett and Lambert, 2004). The direct exposure of *B. bacteriovorus* and *M. aeruginosavorus* on human cell lines did not elicit any measurable cytotoxic or inflammatory response and are anti-toxic to human cells. The therapeutic effects seen by predatory *Bdellovibrio* treatment may be due to competition for resources, including nutrients and the limited available oxygen. This gives the way for clinical trials in the future using predatory bacteria as a means of safe biological control agents against human pathogens. *Bdellovibrio* species do not have a detrimental effect on the health and well-being of noninfected birds, although some changes are seen in the commensal gut flora.

Bdellovibrio can be used effectively to remove bacteria such as *Escherichia coli* and *Salmonella* strains from the surfaces of food processing equipment. These techniques can control pathogenic organisms in foods (Fratamico and Cooke, 1996).

VI. Future investigations: (Dashiff et al, 2011)

A few of the queries are stated below:

a) **Will the presence of a host immune system affect the efficiency of predation?**
b) **Will there be any elicitation of an aggressive immune response?**
c) **Will only the action of predation will be sufficient to clear the site from the infection** or at least result in a reduction of the microbial load to levels that will allow the host immune system to clear the system from the infection?
d) **What will happen to the commensal Gram-negative microbial population in presence of Predatory bacteria?**

Before the use of predatory bacteria could be considered all these queries need to be thoroughly investigated in in-vivo model systems. This may be probably the focus of future investigations.

VII. Practically is it safe?

It's easy to imagine using these organisms to treat pathogens in aquatic and industrial settings; however, using these predators to treat human and animal infections is a different story. Are these organisms dangerous? The strongest evidence for human safety comes from the findings of Iebba et al, (2013) who discovered B. bacteriovorus in the guts of healthy people (Iebba V et al, 2013). Previous research revealed that Bdellovibrio had a distinct lipid A portion of its lipopolysaccharide structure that was far less immunogenic than typical lipopolysaccharide (Schwudke D et al, 2003). A recent review by the Mitchell group explains what is known about the safety of these predatory bacteria (Dwidar M et al, 2012), demonstrating that multiple studies failed to detect harmful effects after topical application, ingestion, or injection of B. bacteriovorus into vertebrates. This includes a recent study conducted at the University of Nottingham (UK) that found no negative health effects in chickens given oral B. bacteriovorus treatments (Atterbury RJ et al, 2011). While these studies are limited, they do extend support to the theory that predatory bacteria could be used in future therapeutic strategies.

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