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Microbial Predators: A New Frontier in Disease Management

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Abstract Microbial predators play a critical role in disease management by naturally targeting and eliminating pathogenic microorganisms. This study comprehensively examines various types of microbial predators, including bacterial, fungal, and protist predators, and their mechanisms of predation, such as attachment and invasion, secretion of lytic enzymes, and consumption and digestion of prey. It emphasizes the significant impact of microbial predators in targeting pathogenic bacteria, controlling fungal infections, and their applications in agriculture and medicine. This study also discusses the advantages of microbial predators over traditional methods, potential challenges, and strategies to overcome these limitations. By showcasing successful case studies in agriculture, medicine, and environmental fields, it illustrates the practical benefits and effectiveness of microbial predators. This study outlines future research and development needs, technological innovations, and the integration of microbial predators with other disease management strategies. The findings underscore the importance of microbial predators in disease management and provide recommendations for future research to enhance their efficacy and application.

Keywords Microbial predators; Disease management; Bacterial predation; Fungal control; Agricultural applications

1 Introduction

Microbial predators, encompassing a diverse array of organisms such as protists, predatory bacteria, and bacteriophages, play a crucial role in shaping microbial communities and influencing ecological dynamics. These predators exhibit a variety of hunting strategies and prey specificities, which significantly impact the population dynamics and community structure of their prey (Johnke et al., 2014). Despite their importance, the role of microbial predators in disease management has only recently begun to be explored, presenting a new frontier in the field of microbiology and disease control.

Microbial predators are integral to the functioning of ecosystems, influencing nutrient cycling, energy flow, and the structure of microbial food webs (Hungate et al., 2021). For instance, predatory bacteria such as *Bdellovibrio* and *Myxococcus xanthus* exhibit high growth and carbon assimilation rates, which can enhance their control over lower trophic levels in microbial communities (Sydney et al., 2021). These interactions are not only fundamental to ecological theory but also have practical implications for managing bacterial populations in various environments, including wastewater treatment plants and agricultural soils (Geisen and Quist, 2020).

The potential of microbial predators in disease management is vast. Predatory bacteria and other microbial predators can be harnessed to control pathogenic bacteria, offering an alternative to traditional antibiotics, which are increasingly becoming ineffective due to rising antibiotic resistance. Additionally, microbial predators can influence the community structure of pathogens, thereby reducing their prevalence and virulence (Chen et al., 2011). For example, the presence of toxin-producing endosymbionts in fungi can protect the host from micropredators, highlighting the complex interactions that can be leveraged for disease control (Richter et al., 2022).

The objectives of this study are to synthesize current knowledge on microbial predators, explore their ecological roles, and evaluate their potential applications in disease management. By integrating findings from various studies, this study aims to provide a comprehensive understanding of how microbial predators can be utilized to develop innovative strategies for controlling diseases, thereby contributing to the advancement of sustainable and effective disease management practices.

2 Types of Microbial Predators

Microbial predators play a crucial role in regulating microbial communities and maintaining ecological balance. They can be broadly categorized into bacterial predators, fungal predators, and protist predators. Each group exhibits unique predatory mechanisms and ecological impacts.

2.1 Bacterial predators

Bacterial predators are a diverse group of microorganisms that prey on other bacteria. Among the most well-studied bacterial predators are the myxobacteria, such as *Myxococcus xanthus*, which utilize a broad range of prey through the secretion of antibiotic metabolites and hydrolytic enzymes (Morgan et al., 2010). Another notable group is the *Bdellovibrio* and like organisms (BALOs), which are obligate predators that invade and consume Gram-negative bacteria. Recent studies have also identified novel bacterial predators like *Bradymonabacteria*, which exhibit versatile survival strategies and a preference for Bacteroidetes (Mu et al., 2020). These bacterial predators can significantly influence microbial community structure and dynamics by reducing bacterial biomass and altering prey populations (Johnke et al., 2014).

2.2 Fungal predators

Fungal predators, though less studied than bacterial predators, play a significant role in microbial predation. They often target other fungi and bacteria, employing various mechanisms such as the production of lytic enzymes and secondary metabolites. For instance, the exposure of the non-pathogenic yeast *Sporobolomyces primogenomicus* to predation by the amoeba *Acanthamoeba castellanii* led to the emergence of resistant strains with altered morphology, suggesting that fungal predators can exert selective pressures on their prey (Idnurm, 2023). This interaction highlights the potential of fungal predators to influence microbial community composition and drive evolutionary changes in their prey.

2.3 Protist predators

Protist predators are key players in microbial ecosystems, primarily preying on bacteria and fungi. They are integral components of the soil microbiome and can significantly impact microbial community structure and function. For example, the introduction of beneficial bacteria like Bacillus can alter protist community structures, indicating that protist predators respond dynamically to changes in their environment (Xiong et al., 2019). Protists such as *Cercozoa* and *Ciliophora* have been shown to increase in abundance in response to pathogen invasion, suggesting their role in top-down regulation of microbial communities under pathogenic stress (Gao et al., 2023). Additionally, protists are sensitive to environmental changes, such as antibiotic exposure, which can alter their community composition and ecological functions (Nguyen et al., 2020). In summary, microbial predators, including bacterial, fungal, and protist predators, are essential for maintaining microbial diversity and ecosystem stability. Their predatory activities shape microbial community structures and drive evolutionary adaptations in their prey, highlighting their importance in disease management and ecological research.

3 Mechanisms of Predation

Microbial predators employ a variety of mechanisms to attack, kill, and consume their prey. These mechanisms can be broadly categorized into attachment and invasion, secretion of lytic enzymes, and consumption and digestion. Understanding these processes is crucial for leveraging microbial predators in disease management.

3.1 Attachment and invasion

Attachment and invasion are the initial steps in microbial predation. Predatory bacteria such as *Myxococcus xanthus* and *Bdellovibrio bacteriovorus* exhibit sophisticated mechanisms to attach to and invade their prey. *M. xanthus* uses a type IV filament-like machinery known as Kil, which promotes motility arrest and prey cell plasmolysis, facilitating tight contact with prey cells for their intoxication (Seef et al., 2021). This contact-dependent mechanism is central to effective prey colony invasion and consumption. Similarly, *B. bacteriovorus* invades the periplasm of Gram-negative bacteria, where it replicates and eventually lyses the prey (Dörr, 2023).

3.2 Secretion of lytic enzymes

Once attached, microbial predators secrete a variety of lytic enzymes to break down the cell walls of their prey. *M. xanthus* secretes hydrolytic enzymes, including a family 19 glycoside hydrolase, which display bacteriolytic activity (Arend et al., 2020). These enzymes are particularly effective against Gram-positive bacteria, while cell-associated mechanisms are more crucial for killing Gram-negative bacteria. Streptomyces species also produce numerous lytic enzymes, such as glucanases, mannosidases, and chitinases, to digest the cell walls of yeast (Yamada et al., 2023). Additionally, *B. bacteriovorus* secretes specialized lytic transglycosylases to clear prey cell septum obstructions, enhancing its ability to consume prey.

3.3 Consumption and digestion

After the prey cell wall is breached, microbial predators proceed to consume and digest the prey's cellular contents. *M. xanthus* induces prey lysis from the outside and feeds on the released biomass, a process facilitated by its gliding motility and induced cell reversals (Thiery and Kaimer, 2020). This allows *M. xanthus* to remain within the prey area and efficiently consume the available nutrients. *B. bacteriovorus* digests the prey within the periplasmic space, utilizing the prey's cellular components as nutrients (Negus et al., 2017). The production of antifungal polyenes and cholesterol oxidase by *Streptomyces* further destabilizes the prey cell membrane, aiding in the assimilation of yeast cells. In summary, microbial predators utilize a combination of attachment and invasion, secretion of lytic enzymes, and consumption and digestion to effectively kill and consume their prey. These mechanisms highlight the potential of microbial predators in disease management by targeting pathogenic bacteria and fungi.

4 Role in Disease Management

4.1 Targeting pathogenic bacteria

Microbial predators have shown significant potential in targeting pathogenic bacteria, offering a promising alternative to traditional chemical treatments. For instance, the predatory myxobacterium *Citreicoccus inhibens* has demonstrated bacteriolytic properties against both Gram-negative and Gram-positive phytopathogenic bacteria, making it a versatile biocontrol agent (Zhou et al., 2021). Additionally, the interactions between bacteria and fungi within the human microbiota can influence bacterial pathogenesis, with certain fungi regulating bacterial growth and virulence, thereby impacting human health.

4.2 Controlling fungal infections

Microbial predators also play a crucial role in controlling fungal infections. The use of microbial antagonists, such as certain bacteria and fungi, has been explored for postharvest disease suppression in fruits and vegetables. These antagonists can inhibit fungal growth through various mechanisms, including competition for nutrients, mycoparasitism, and the secretion of antifungal metabolites (Dukare et al., 2019). Furthermore, the entomopathogenic fungi, which have been used as biocontrol agents for over 150 years, not only kill insect pests but also exhibit antifungal properties, contributing to plant pathogen antagonism (Bamisile et al., 2021).

4.3 Applications in agriculture and medicine

The applications of microbial predators extend to both agriculture and medicine. In agriculture, microbial predators like the endosymbiotic bacteria *Mycoavidus* in *Mortierella* fungi protect their host from nematode attacks, promoting plant growth and soil health (Figure 1) (Büttner et al., 2021). Similarly, the *Rhizopus-Mycetohabitans* symbiosis produces rhizoxin, a toxin that defends the fungal host against protozoan and metazoan predators, highlighting the ecological role of microbial predators in maintaining soil health (Richter et al., 2022). In medicine, the potential of microbial predators is being explored for developing new antimicrobials and antivirulence factors, leveraging the interactions within the human microbiota to discover novel therapeutic agents (MacAlpine et al., 2022). In summary, microbial predators offer a multifaceted approach to disease management by targeting pathogenic bacteria, controlling fungal infections, and providing applications in both agriculture and medicine. Their ability to interact with and regulate other microorganisms presents a new frontier in sustainable disease management strategies.

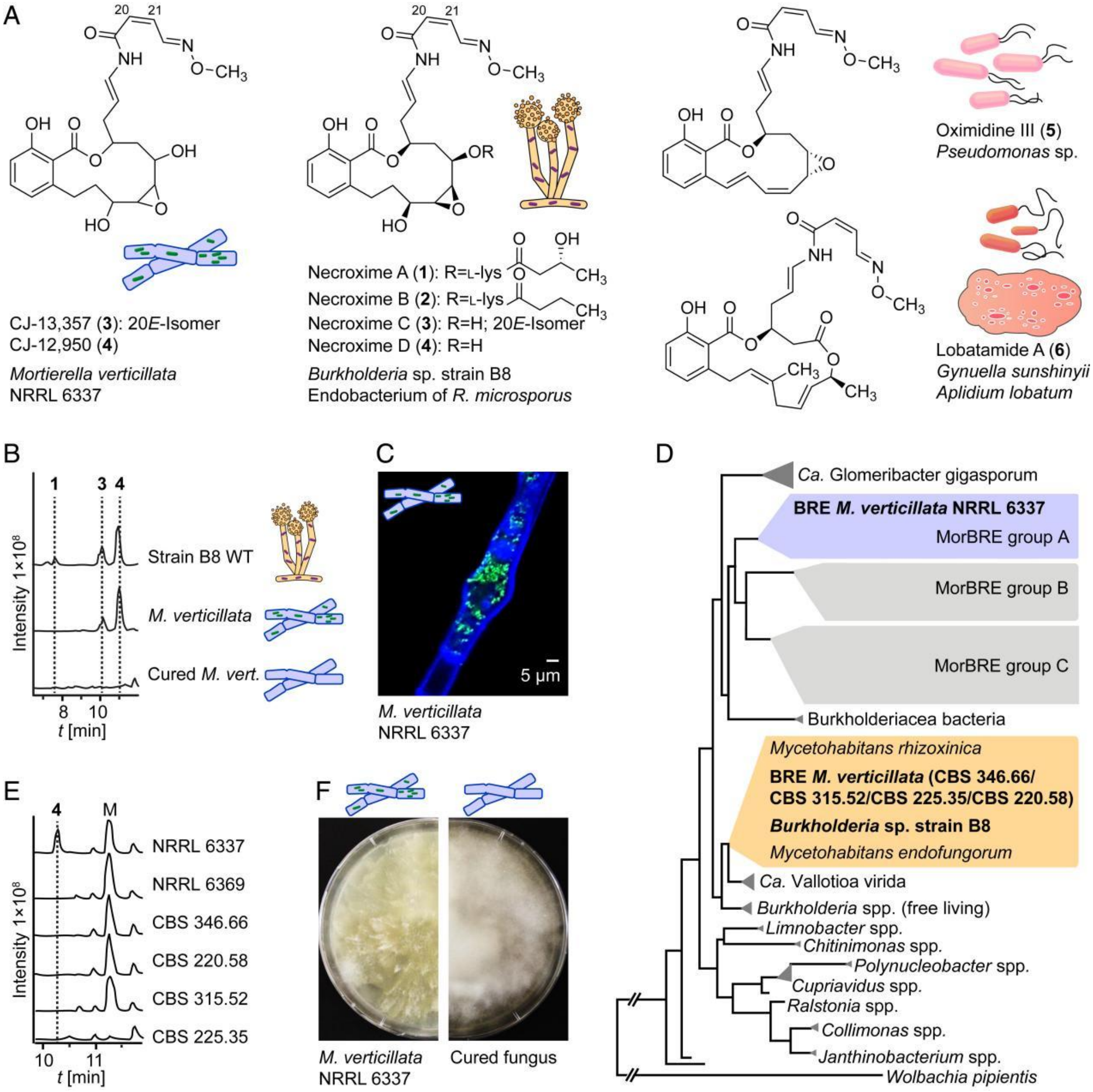

Figure 1 Bacterial origin of cytotoxic benzolactones from *M. verticillata* cultures (Adopted from Büttner et al., 2021)

Image caption: (A) *Cytotoxic lactone* compounds assigned to endofungal symbionts from the fungus *R. microsporus* (1–4), *M. verticillata* (3–4), *Pseudomonas* sp. (5), and a tunicate and the bacterium *Gynuella sunshinyii* (6). (B) Metabolic profiles of extracts from *Burkholderia* sp. strain B8 and *M. verticillata* NRRL 6337 as symbiont or cured strain as total ion chromatograms in the negative mode. (C) Fluorescence micrograph depicting endosymbionts living in the fungal hyphae; staining with Calcofluor White and Syto9 Green. (D) Phylogenetic relationships of *Mortierella symbionts*, *Burkholderia* sp. strain B8, and other bacteria based on 16S rDNA. BRE, Burkholderia-related endosymbiont of *Mortierella* spp. (E) Metabolic profiles of extracts from *M. verticillata* NRRL 6337 and other necroxime-negative *M. verticillata* strains analyzed for endosymbionts in this study as total ion chromatograms in the negative mode. M, medium component. (F) Growth of symbiotic *M. verticillata* NRRL 6337 in comparison to the cured strain (Adopted from Büttner et al., 2021)

Büttner et al. (2022) found that the cytotoxic benzolactones identified in *Mortierella verticillata* cultures are attributed to bacterial endosymbionts. They observed distinct metabolic profiles in extracts from both *Burkholderia* sp. strain B8 and *M. verticillata*, which contain these endosymbionts, compared to the cured strain without the symbionts. Fluorescence microscopy revealed these endosymbionts within the fungal hyphae, further supporting their integral role. Additionally, phylogenetic analysis demonstrated the close relationships between *Mortierella symbionts* and other bacteria, emphasizing the specific association with Burkholderia-related endosymbionts. The growth comparison highlighted that symbiotic *M. verticillata* exhibited distinct characteristics compared to the cured strain, showcasing the influence of these bacterial symbionts on the host fungus.

5 Advantages and Limitations

5.1 Benefits over traditional methods

Microbial predators, such as *Bdellovibrio bacteriovorus* and *Micavibrio aeruginosavorus*, offer several advantages over traditional antibiotic treatments. One significant benefit is their ability to target and kill antibiotic-resistant bacteria, which is increasingly important in the face of rising multidrug-resistant (MDR) infections (Shatzkes et al., 2016). Unlike antibiotics, which often have a broad-spectrum effect and can disrupt beneficial microbiota, predatory bacteria are more selective, preying specifically on pathogenic bacteria and thereby preserving the host's beneficial microbial communities (Mosca et al., 2016). Additionally, predatory bacteria do not replicate outside their prey, reducing the risk of developing resistance. This specificity and reduced likelihood of resistance make microbial predators a promising alternative to conventional antibiotics.

5.2 Potential challenges

Despite their promising benefits, the use of microbial predators in disease management faces several challenges. One major concern is the safety and potential side effects of introducing predatory bacteria into the human body. Although initial studies have shown that predatory bacteria do not cause adverse effects or significant immune responses in animal models, comprehensive safety assessments in humans are still needed. Another challenge is the variability in predatory efficiency across different environments and host conditions. For instance, the effectiveness of predatory bacteria can be influenced by the presence of other microbial communities and the specific conditions of the infection site (Summers and Kreft, 2022). Additionally, the potential for prey bacteria to develop resistance mechanisms against predation, although less likely than antibiotic resistance, remains a concern (Sydney et al., 2021).

5.3 Strategies to overcome limitations

To address these challenges, several strategies can be employed. Extensive clinical trials are necessary to thoroughly evaluate the safety and efficacy of predatory bacteria in humans. These trials should include diverse patient populations and infection types to ensure comprehensive safety data. Combining predatory bacteria with other therapeutic approaches, such as antibiotics or phage therapy, could enhance their effectiveness and reduce the likelihood of resistance development (Fernández et al., 2018). Additionally, genetic engineering of predatory bacteria to enhance their predatory capabilities and adaptability to different environments could improve their therapeutic potential. Finally, mathematical modeling and in vitro studies can help predict the dynamics of predator-prey interactions and optimize treatment protocols. By addressing these challenges through rigorous research and innovative strategies, microbial predators can become a viable and effective tool in the fight against antibiotic-resistant infections and other microbial diseases.

6 Case Studies

6.1 Successful applications in agriculture

Microbial predators have shown significant promise in agricultural applications, particularly in enhancing crop yields and managing plant diseases. For instance, microbiome research has led to the development of various products and methodologies that have positively impacted the agrifood system. These include the use of microorganisms as soil fertilizers and plant strengtheners, as well as tools to manage diseases and pathogens in crops. Such applications have not only improved crop productivity but also contributed to economic and societal benefits. Additionally, biocontrol strategies utilizing microbial agents have been effective in modulating plant defense mechanisms and controlling plant pathogens, offering a sustainable alternative to chemical pesticides (Rahman et al., 2018). The use of augmentative biological control (ABC) has also been successful, with microbial agents being released to reduce pests, leading to healthier crops and reduced pesticide residues (Lenteren et al., 2018).

6.2 Medical case studies

In the medical field, microbial predators such as *Bdellovibrio bacteriovorus* have been explored for their potential to combat drug-resistant pathogens. These predatory bacteria can reduce populations of harmful bacteria, including those in biofilms, which are often resistant to conventional antibiotics. The ecological role of these predators extends beyond simple predation, as they can also impact biofilm structures and prey resistance, making them a promising tool in the fight against antimicrobial resistance (Figure 2) (Mookherjee and Jurkevitch, 2021). Mathematical modeling has further supported the potential of these predators in medical applications by predicting their effectiveness in various scenarios, including the removal of prey species and shaping microbial ecosystems (Summers and Kreft, 2022).

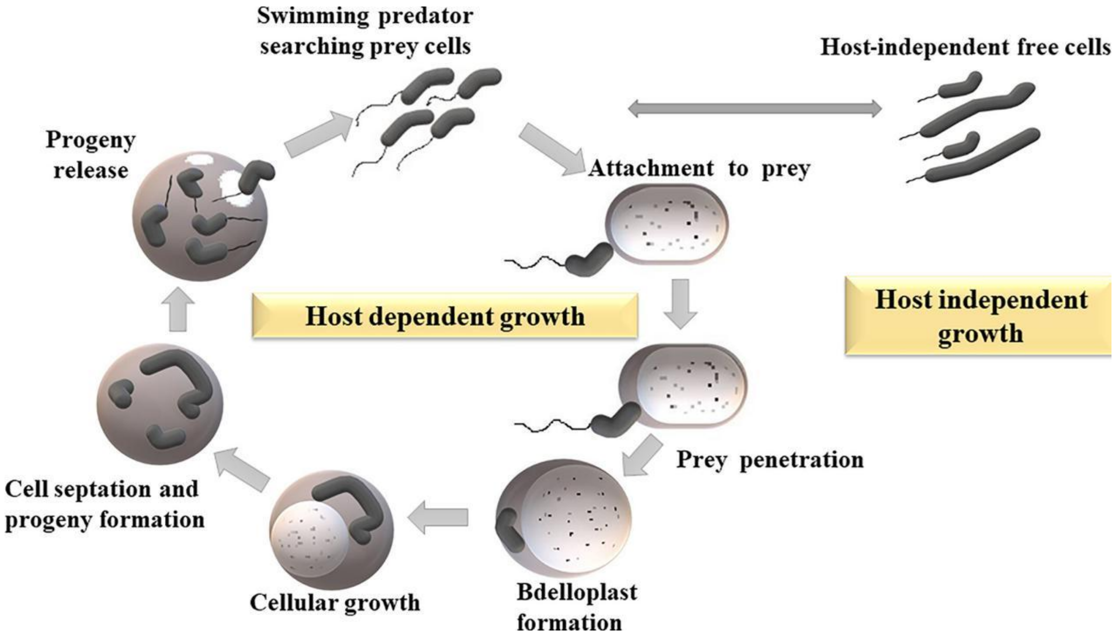

Figure 2 Host-dependent and host-independent lifecycle of periplasmic *Bdellovibrio* and like organisms (*Bdellovibrio bacteriovorus*, *Bacteriovorax stolpii*, *Bacteriovorax* sp., *Peredibacter starrii*, *Halobacteriovorax litoralis*, *Halobacteriovorax marinus*, *Halobacteriovorax vibrionivorans*) (Adopted from Mookherjee and Jurkevitch, 2021)

Image caption: The diagram is based on scanning electron micrographs of *B. bacteriovorus* by several researchers (Adopted from Mookherjee and Jurkevitch, 2021)

Mookherjee and Jurkevitch (2021) found that the lifecycle of periplasmic *Bdellovibrio* and similar organisms involves both host-dependent and host-independent phases. In the host-dependent phase, the swimming predator cells attach to and penetrate prey cells, where they undergo cellular growth, bdelloplast formation, cell septation, and progeny formation. The progeny are then released to continue the cycle. In contrast, during the host-independent phase, the free cells can grow and proliferate without a host, maintaining the population until they encounter new prey. This dual lifestyle allows these organisms to adapt to varying environmental conditions and ensures their survival and propagation through both parasitic and free-living strategies.

6.3 Environmental applications

Microbial predators also hold potential for environmental applications, particularly in bioremediation and biosensing. Engineered microbes with microbial biocontainment systems (MBSs) can be deployed in diverse environments to execute biological processes in situ without harming the target system. These systems have been used in agriculture, medicine, and industrial applications, demonstrating their versatility and effectiveness in responding to environmental stimuli (Figure 3) (Angles et al., 2022). Additionally, insect symbionts have been identified as valuable sources of biotechnological applications, including the control of agricultural pests and vectors of human diseases. The manipulation of these symbionts or their associations with hosts can lead to innovative solutions for pest and disease management (Berasategui et al., 2015).

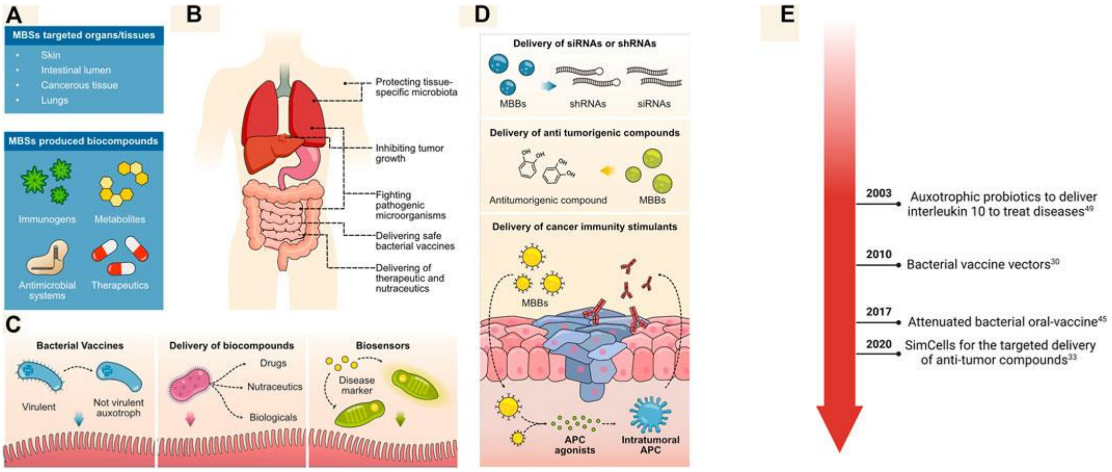

Figure 3 MBSs for clinical applications (Adopted from Angles et al., 2022)

Image caption: (A, B) MBSs can be used to deliver a range of bio-compounds to different organs and tissues for diverse bacterial therapies. (C) The intestinal lumen is an attractive target for the delivery of non-replicative attenuated bacteria as vaccines (left-most panel, bio compounds (middle panel) and to test for the presence of diseases using available biomarkers (right-most panel). (D) Strategies used to treat tumorigenic tissues with MBSs, including the delivery of RNAs, drugs, and immune stimulants. MBBs are used for targeted delivery of shRNAs and siRNAs to tumors as a mean to knock down drug-resistance genes (top panel); MBBs can also be used as a direct biomanufacturing machinery for synthesis of antitumorigenic compounds (middle panel) or even for the delivery of agonists that will induce the development of an immunity response against the tumor (lower panel). (E) Timeline for major medical applications (Adopted from Angles et al., 2022)

Angles et al. (2022) found that microbial-based systems (MBSs) offer significant potential for clinical applications by delivering various bio-compounds to targeted organs and tissues. These systems can be utilized to protect tissue-specific microbiota, inhibit tumor growth, combat pathogenic microorganisms, and deliver safe bacterial vaccines, therapeutics, and nutraceuticals. Specifically, the intestinal lumen is a promising target for the delivery of non-replicative attenuated bacteria as vaccines and biocompounds, as well as for biosensors to detect disease markers. MBSs can treat tumorigenic tissues by delivering RNAs, drugs, and immune stimulants, thus knocking down drug-resistance genes, synthesizing antitumorigenic compounds, and inducing immunity responses against tumors. The development timeline highlights significant milestones, such as the use of auxotrophic probiotics to deliver interleukin 10 in 2003, bacterial vaccine vectors in 2010, attenuated bacterial oral vaccines in 2017, and SimCells for targeted anti-tumor compound delivery in 2020.

7 Future Directions

7.1 Research and development needs

The future of microbial predators in disease management hinges on addressing several key research and development needs. One primary area is the comprehensive understanding of microbial predator-prey dynamics within the human microbiome. The reintroduction of bacterial predators to restore gut microbiota diversity, as suggested by Mosca (2016), requires extensive research to identify the specific predators that can thrive and effectively control pathogenic populations without disrupting beneficial microbes. Additionally, the safety and efficacy of predatory bacteria in vivo, as demonstrated in the reduction of *Klebsiella pneumoniae* burden in rat lungs (Shatzkes et al., 2016), need further validation across different pathogens and host systems. Moreover, the development of novel antimicrobial compounds and biocontrol strategies, as highlighted in Mantravadi et al.

(2019) and Rahman et al. (2018), should be prioritized. This includes exploring the potential of engineered phages, CRISPR-based genome editing, and other innovative approaches to enhance the effectiveness of microbial predators. The integration of high-throughput sequencing technologies to study microbial communities, as discussed in Massart et al. (2015), will also be crucial in understanding the complex interactions within the microbiome and optimizing biocontrol methods.

7.2 Technological innovations

Technological advancements will play a pivotal role in the future of microbial predator-based disease management. The application of nanomedicine, as explored in Mehrabi et al. (2023), offers promising avenues for the delivery and enhancement of microbial predators. Nanotechnology can facilitate the targeted delivery of predatory bacteria to infection sites, improving their efficacy and reducing potential side effects. Additionally, the development of rapid diagnostic tools using micro-engineering and informatics, as mentioned in Massart et al. (2015), will enable the timely identification of infections and the appropriate deployment of microbial predators. Furthermore, the use of next-generation sequencing (NGS) technologies, as emphasized in Massart et al. (2015), will revolutionize our understanding of microbial ecosystems and their manipulation for disease control. These technologies can help identify key microbial interactions and guide the development of prebiotic approaches to steer the microbiome towards a pathogen-resistant state.

7.3 Integration with other disease management strategies

For microbial predators to be effectively integrated into broader disease management strategies, a multi-faceted approach is necessary. Combining microbial predators with traditional methods, such as antibiotics and immunizations, can enhance overall treatment efficacy and mitigate the risk of resistance development. The concept of "One Health," which emphasizes the interconnectedness of human, animal, and environmental health, should be embraced to develop holistic disease management strategies. In agriculture, the integration of microbial predators with biocontrol agents and plant-optimized microbiomes, as discussed in Rahman et al. (2018), can lead to more sustainable and effective pest and disease management practices. This approach not only improves crop yields but also reduces the reliance on chemical pesticides, benefiting both human health and the environment. In conclusion, the future of microbial predators in disease management is promising, with significant potential for innovation and integration with existing strategies. Continued research and technological advancements will be essential to fully realize their potential and address the growing challenges of antibiotic resistance and emerging infectious diseases.

8 Concluding Remarks

Microbial predators represent a promising frontier in disease management, offering novel approaches to combat bacterial infections, particularly in the face of rising antibiotic resistance. This section synthesizes the key findings from recent research, underscores the importance of microbial predators in disease management, and provides recommendations for future research.

Recent studies have highlighted the significant role of microbial predators in various ecosystems and their potential applications in disease management. Predatory bacteria such as *Bdellovibrio bacteriovorus* and *Micavibrio aeruginosavorus* have demonstrated the ability to reduce bacterial burdens in vivo, showcasing their potential as biocontrol agents against Gram-negative pathogens. Additionally, *Bradymonabacteria*, a novel group of bacterial predators, have shown versatile survival strategies and a broad prey range, particularly in saline environments, indicating their ecological significance and potential utility in diverse settings. The dual predation by bacteriophages and predatory bacteria has been shown to be more effective in eradicating bacterial prey than single predation, suggesting a synergistic approach to microbial control. Furthermore, studies have demonstrated that predatory bacteria can significantly contribute to bacterial mortality and nutrient cycling in microbial food webs, rivaling the impact of bacteriophages.

The importance of microbial predators in disease management cannot be overstated. As antibiotic resistance continues to pose a global health threat, the need for alternative antimicrobial strategies becomes increasingly urgent. Predatory bacteria offer a unique mechanism of action, preying on pathogenic bacteria and reducing their populations without the risk of developing resistance that is commonly associated with traditional antibiotics. Their ability to target a broad range of Gram-negative bacteria makes them particularly valuable in treating infections caused by multidrug-resistant organisms. Moreover, the ecological role of predatory bacteria in nutrient cycling and maintaining microbial community structure further underscores their potential in both environmental and clinical applications.

Future research should focus on several key areas to fully capitalize on the potential of microbial predators in disease management, more in-depth studies are needed to understand the mechanisms of predation and the interactions between predatory bacteria and their prey at the molecular level, including exploring genetic and biochemical pathways involved in the mechanisms of predation and resistance, and it is important to comprehensively assess, through extensive in vivo studies and clinical trials, the predatory bacteria's clinical settings' safety and efficacy, and the development of combination therapies utilizing predatory bacteria and phages should be pursued, as this approach has shown enhanced efficacy in controlling bacterial populations. Future studies should also evaluate the ecological impact of introducing predatory bacteria into different environments to ensure that their use does not disrupt existing microbial communities or lead to unintended consequences. In conclusion, microbial predators have great potential as a new frontier in disease management. By deepening the understanding of their biology and optimizing their application, innovative strategies can be developed to combat bacterial infections and address the growing challenge of antibiotic resistance.

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Conflict of Interest Disclosure

The author affirms that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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