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Invited Review Article

Microbial harmony in peril? Identifying the impact of antibiotics on a healthy animal gut

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Abstract

The escalating threat of antibiotic resistance represents a global surge in public health. This phenomenon, characterized by the rapid proliferation of antibiotic-resistant strains, has been catalyzed by the extensive utilization of antibiotics over the decades. While antibiotics have undeniably saved countless lives, their pervasive impact extends to the intricate ecosystem of the gut commensals. The gut microbiota (GM), an assembly of diverse microbial communities residing within the intestinal tract, serves as an evolutionary battleground where host-microbe interactions have shaped the trajectory of both species. The GM, beyond its role in metabolic and immune functions, has co-evolved with the host, bestowing hindrance against pathogenic invaders. Overuse of antibiotics has however imparted perturbations upon this complex ecosystem, resulting in antibiotic-influenced dysbiosis. This phenomenon compromises the host's ability to withstand infections, underscoring the importance of understanding the co-evolutionary dynamics at play. In this review, I am going to take you on a journey through the annals of antibiotic history and elucidate the underlying mechanisms driving the emergence of resistance. We will further explore the long-term evolutionary consequences of antibiotic usage on the gut microbiome, shedding light on how the intricate interplay between microbes and their human hosts has been fundamentally altered. Our narrative will finally extend to the promising realm of alternative strategies, where evolutionary principles guide the quest for innovative solutions.

Keywords: AMR, Alternative medicine, Antibiotics, Gut microbiome, Phage therapy

Highlights

- Antibiotic misuse alters gut microbiota, weakening immunity.
- Co-evolution of gut microbes and induced dysbiosis.
- Explore long-term impacts of antibiotics on animal health.
- Evolutionary insights guide innovative alternatives.

INTRODUCTION

Antibiotics, the "wonder drugs" (Bud, 2007), initially celebrated for their role in suppressing bacterial infections (The World Health Organization, 2014), now face a formidable crisis: antimicrobial resistance (AMR), including multidrug resistance (MDR). The United States reports nearly 2 million cases of infections by resistant bacteria annually, costing $20 billion in healthcare (Lahsoune *et al*., 2007). In Europe, MDR infections claim 25,000 lives each year, with a financial toll of 1.5 billion euros (Uchil *et al*., 2014). AMR poses a significant threat to public health, challenging strategies against a spectrum of infectious diseases (Prestinaci *et al*., 2015). AMR's intricate web extends into our environment, linked to climatic shifts and human lifestyles like travel and dietary habits (MacFadden *et al*., 2018). Recent metagenomic analyses reveal commensal bacteria in healthy individuals as reservoirs of AMR (Hendriksen *et al.*, 2019b). The development of antibiotics faces challenges from formidable adversaries like methicillin-resistant *Staphylococcus aureus* (MRSA) and drug-resistant *Pseudomonas aeruginosa* (Davies and Davies, 2010). Moreover, the emergence of superbugs like New Delhi Metallo-β-lactamase 1 (NDM-1) adds to these concerns (Nazir *et al*., 2012).

Discovery of antibiotics and contemporary resistance development

In the early 20th century, Paul Ehrlich's discovery of "magic bullets" marked a turning point in medicine, with the discovery of Penicillin by Alexander Fleming in 1928 (Abraham and Chain, 1940). Effective

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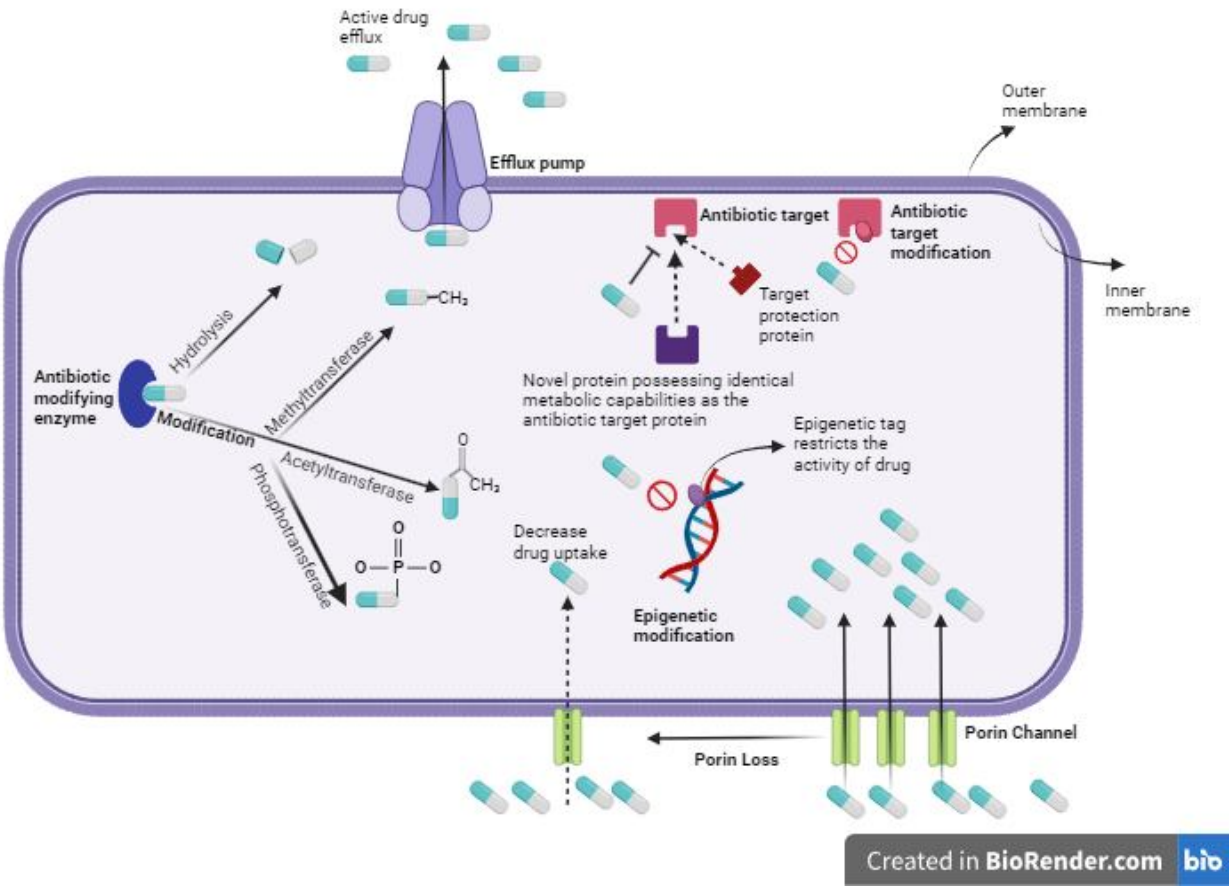
antibiotics underpin modern medicine, from cancer treatment to surgeries (Prestinaci *et al*., 2015). Antibiotics are classified based on their mechanisms of action, including interference with cell wall synthesis like β-lactam antibiotics and glycopeptides. Others bind to ribosomal subunits (macrolides, chloramphenicol), inhibit protein synthesis (quinupristin/dalfopristin), or target nucleic acid synthesis (fluoroquinolones, rifampin). Some disrupt metabolic pathways (sulphonamides) or bacterial membranes (polymyxins) (Tenover, 2006; Kapoor *et al*., 2017). Understanding the origins and diversity of resistance genes is crucial in addressing MDR (Aslam *et al*., 2018). Antibiotics continue to shape medicine while facing the challenge of microbial resistance. Now, in the enduring battle against antibiotics, bacteria have honed a repertoire of sophisticated defences over aeons of evolution (Kong *et al*., 2010). These defences encompass a multifaceted array. At the molecular level, bacteria employ intricate strategies for resistance (Fig. 1).

Enzymatic inactivation: Bacteria produce enzymes that deactivate antibiotics through processes like hydrolysis and redox reactions. Notable examples include β-lactamases, which neutralize penicillin-like antibiotics (Shaikh *et al*., 2015; Reygaert, 2018; Khameneh *et al*., 2019)

Chemical modification: Enzymes catalyse reactions like acetylation, phosphorylation, and adenylation, chemically altering antibiotics. These changes reduce the drug's affinity for its target, resulting in higher bacterial minimum inhibitory concentrations (MIC) (Ogawara, 2019).



[Antibiotic inactivation is achieved through enzymatic degradation or modification, rendering antibiotics ineffective. Target site alteration can involve gene mutations or enzymatic changes, reducing antibiotic binding. Target bypass occurs when a new protein performs the antibiotic target's function. Decreased influx is caused by membrane changes like porin downregulation, while active efflux utilizes transmembrane pumps to export antibiotics. Target protection involves a protein shielding the antibiotic target from inhibition.]

Fig. 1. Mechanisms of antibiotic resistance

Efflux pumps (EPs): Bacteria utilize EPs to expel antibiotics that have entered their cells. EP-mediated resistance is exceptionally versatile, encompassing diverse antibiotics (Spratt, 1994). These pumps exist in Gram-negative bacteria (GNB), Gram-positive bacteria (GPB), and even eukaryotic organisms (Webber and Piddock, 2003). EPs are categorized into five classes, each employing distinct energy sources for efficient expulsion (Paulsen *et al*., 1996; Piddock, 2006).

Outer membrane (OM): The OM's evolution stems from the need to shield bacteria from antibiotics, especially in intricate microbial communities (Hibbing *et al*., 2010). Beyond protection, the OM interprets signals from agents like antibiotics. This multifaceted defence is vital for bacterial survival (Beceiro *et al*., 2013). Remarkably, the OM facilitates nutrient exchange through specialized β-barrel protein channels known as "porin channels." Diminished porin levels hinder drug entry, leading to resistance (Fukuoka *et al*., 1993). This resistance isn't confined to specific species; it extends to various GNB, including *Acinetobacter baumannii* and MDR *Klebsiella pneumoniae* strains (Thomson and Bonomo, 2005).

Genetic and epigenetic modification: Pathogenic bacteria, with remarkable genetic adaptability, have evolved mechanisms to counter environmental threats, including antibiotics. They share niches with antibiotic-producing microbes, fostering resistance development. Early studies revealed intrinsic resistance properties, like gene mutations and horizontal gene transfer (HGT) via plasmids (Munita and Arias, 2016). While antibiotics revolutionized medicine by reducing bacterial infection mortality, their misuse has fuelled resistance. Epigenetic events, such as adenine and cytosine methylation, can introduce mutations, influencing antibiotic susceptibility (Ghosh *et al*., 2020). These multifaceted mechanisms underscore bacteria's capacity to develop robust AMR, illuminating the intricacies of this ongoing evolutionary arms race.

Overuse of antibiotics accelerates resistance development

Approximately 30-50% of antibiotics prescribed to clinical outpatients are unnecessary, and nearly 30% of hospital antibiotics are prescribed incorrectly (Pichichero, 2002; Shapiro *et al*., 2014; Fleming-Dutra *et al*., 2016). Local outpatient prescribing practices contribute to local resistance patterns, which can differ from global trends (Hicks *et al*., 2011). Azithromycin and amoxicillin, prescribed by healthcare professionals, particularly during the winter season, account for over 80% of antibiotic use (Hicks *et al*., 2011; Suda *et al*., 2013).

Overuse in human health sector: Antibiotic misuse, self-prescription, improper dosing, and prolonged usage, act as the driver of AMR (Prestinaci *et al*., 2015). Additionally, nosocomial pressures contribute to the spread of difficult-to-treat microbes (Mehrad *et al*., 2015).

Overuse in livestock and fishery sector: Antibiotics in the livestock sector are used as prophylactic or metaphylactic agents other than therapy to treat infections (Landers *et al*., 2012). Excessive use accelerates AMR development, creating conditions that favour the selection of resistant bacteria, which subsequently contaminate the environment (Manyi-Loh *et al*., 2018). On the contrary, antibiotics in aquaculture are overused, often added to fish and shrimp feed without full consumption (Marshall and Levy, 2011; Romero *et al*., 2012). Poor sanitation fosters pathogenic bacteria growth, especially in crowded fish populations, increasing the risk of antibiotic-resistant bacteria spreading (Cabral, 2010). Additionally, domestic use of various antibacterial chemical products may contribute to AMR (Davies and Davies, 2010).

AMR amongst the food chain: AMR can rapidly disseminate through the food chain (Founou *et al*., 2016). Direct contact with livestock, poultry, and their biological substances, like blood, faeces, and saliva, can transmit AMR from animals to humans (Manyi-Loh *et al*., 2018). Those in close contact with animals, such as veterinarians, farmers, and food handlers, are particularly susceptible to antimicrobial resistant bacteria (Manyi-Loh *et al*., 2013). Initially, this transmission didn't seem a major public health threat, but it's now clear that occupationally exposed workers and their families can serve as portals for AMR bacteria and antibiotic-resistant genes (ARGs) to enter the community and healthcare facilities (Beltrami *et al*., 2000; Dunstan *et al.,* 2008). Antibiotic residues can lead to serious health issues, including hepatotoxicity, carcinogenicity, allergic hypersensitivity reactions, mutagenicity, and nephropathy. HGT plays a crucial role in AMR development, allowing resistance genes to spread through plasmids (Bello-López *et al*., 2019). This concept is well-documented in environmental niches, like water, soil, and manure, leading to the proliferation of ARGs and resistant bacteria (Fletcher, 2015). Lower and middle-income countries often use untreated human and animal waste as fertilizer and fish and shellfish feed in aquaculture, contributing to environmental pollution

and AMR spread in the food chain (Kraemer *et al*., 2019). In the current scenario, various types of AMR bacteria have been increasingly found in food and animal products, affecting humans to varying degrees (Woolhouse *et al*., 2015; Hernando-Amado *et al*., 2019; Hendriksen *et al*., 2019a). Commensal and indicator organisms that carry ARGs can spread to foodborne and pathogenic bacteria. Genetic events like recombination across ecological niches can lead to the emergence of new AMR strains or genes (Schmutzer and Barraclough, 2019). Globally, AMR and ARGs of animal origin are reported, with varying incidence based on geography and resources. Examples include methicillin-resistant *Staphylococcus aureus* (MRSA) and extended-spectrum β-lactamase (ESBL) producing Enterobacteriaceae (e.g., *E. coli*, *Salmonella* spp., *Shigella* spp., *Enterobacter* spp., *K. pneumoniae*, etc.).

Link between microbiome and AMR

An animal's intestine houses a diverse GM, primarily composed of Firmicutes, Bacteroides, Actinobacteria, and a smaller population of Proteobacteria (Rinninella *et al*., 2019). This composition varies among individuals due to factors like age, antibiotic use, probiotics, prebiotics, drug abuse, environment, food habits, lifestyle, and geography (Conlon and Bird, 2014). The GM consortia influence the host immune cells and palliate the metabolic processes (Kau *et al*., 2011). It contributes to immune homeostasis, gastrointestinal development, nutrient acquisition, vitamin synthesis, and resistance against pathogens through a mechanism known as colonization resistance (Pickard *et al*., 2017). Colonization resistance involves two main mechanisms. Indirect mechanisms incite innate immune responses, resulting in the creation of mucosal secretions and the formation of protective elements like short-chain fatty acids (SCFAs) or peptides (Belkaid and Hand, 2014). Direct mechanisms include the production of bacteriocins, nutrient competition, and confrontation with invading pathogens (Lawley and Walker, 2013). Alterations in gut microflora can lead to changes in an individual's microbiome, contributing to various chronic disorders like inflammatory bowel disease (IBD), rheumatoid arthritis (RA), obesity, cardiovascular diseases, Alzheimer's disease (AD), multiple sclerosis (MS), Parkinson's disease (PD), autism spectrum disorder (ASD), and cancer (Diamanti *et al*., 2016; Kho and Lal, 2018; Khan *et al*., 2019). The imbalance in intestinal microbiota and its link to disease development is often mediated by factors like antibiotic misuse, psychophysical stress, and unhealthy dietary habits (DeGruttola *et al*., 2016). These factors disrupt the protective role of the microbiota, making individuals more susceptible to colonization by foreign pathogens (Table 1). Importantly, a healthy microbiome consortium can restore dysbiosis, a phenomenon known as

Table 1. The effects of antibiotics on the gut microbiome*

Antibiotics	Mechanism of resistance development	Effects of the gut microbiome	References
Amoxicillin	Alteration of drug target, Production of β-lactamase	Damages Enterobacteriaceae population	Gipponi *et al*., 1985
Ampicillin	Target alteration, β-lactamase	A decrease in bacterial diversity with a prevalence of *Enterobacter* spp.	Greenwood *et al*., 2014
Cefotaxime	Target alteration	A decrease in bacterial diversity and a decrease in abundance of anaerobic and *Enterobacter* spp.	Sunakawa *et al*., 1984; Lambert-Zechovsky *et al*., 1985
Chloramphenicol	Enzymatic inactivation by acetylation via acetyltransferases or phosphotransferases	Bactericidal microbiota disturbance$^{\varphi}$ and alteration in the skin microbiome	Drago, 2019; Holden *et al*., 2014
Ciprofloxacin	Target alteration, efflux pump	Reduction in Enterobacteriaceae and SCFAs producers, decrease in bacterial diversity	Brismar *et al*., 1990; Dethlefsen *et al*., 2008; Dethlefsen and Relman, 2011; Zaura *et al*., 2015

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Antibiotics	Mechanism of resistance development	Effects of the gut microbiome	References
Clarithromycin	Target alteration, Drug inactivation	Reduction in *Actinobacteria*	Jakobsson *et al*., 2010
Clindamycin	Target alteration	Reduction in *Staphylococci*, *Enterococci* anaerobic and SCFAs producing bacteria, decrease in *Bacteroides* spp.	Kager *et al*., 1981; Jernberg *et al*., 2007
Erythromycin	Efflux pump	Reduction in *Streptococci*, *Enterococci* and *Enterobacteria*, increase in *Staphylococci*, alteration in anaerobic bacteria	Brismar *et al*., 1991
Gentamycin	Drug modification and decreased uptake	A decrease in bacterial diversity with a prevalence of *Enterobacter* spp.	Greenwood *et al*., 2014
Meropenem	Target alteration, β -lactamase	Reduction in *Enterobacteria*, *Bacteroides* sp., *Clostridia*, *Streptococci* and Gram-negative cocci	Bergan *et al*., 1991
Metronidazole	Efflux pump	Reduction in *Actinobacteria*	Jakobsson *et al*., 2010
Streptomycin	Drug modification and decreased uptake	A decrease in overall bacterial diversity with a prevalence of Bacteroidaceae and Ruminococcaceae	Lichtman *et al*., 2016
Ticarcillin	Target alteration, β-lactamase	Reduction in *Enterococci*	Nord *et al*., 1989
Tigecycline	Target alteration, efflux pump	Reduction in Bacteroidetes Enterobacteriaceae, Bifidobacteria and *Lactobacilli* with an increase in *Proteobacteria*	Nord *et al*., 2006; Bassis *et al*., 2014
Vancomycin	Inhibition of Cell wall synthesis	A decrease in overall bacterial diversity	Vrieze *et al*., 2014

* Adapted and modified from Langdon *et al*., 2016

Microbiome resilience (MR).

Alternatives to antibiotics to curb antibiotic overuse

Overuse of antibiotics damages intestinal flora, causing collateral effects on GM, leading to AMR development. Numerous solutions exist to reduce the selection for the AMR variants or replace antibiotics, each with its benefits and costs.

Anti-quorum sensing molecule: Bacteria communicate via autoinducer (AI) molecules, N-acyl-homoserine lactones (AHLs) in GNB and small peptides in GPB, a process known as quorum sensing (QS) (Atkinson and Williams, 2009). QS serves as a crucial player, governing bacterial virulence (*P. aeruginosa* and *Vibrio cholera*) (Rutherford and Bassler, 2012). Inhibiting bacterial communication and virulence can be achieved through various means, including QS signal destruction (Rasmussen *et al*. 2000; Manefield *et al*. 2002) and competitive binding of quorum sensing inhibitors (QSIs) to AIs, which regulate cell surface receptor proteins (Yada *et al*. 2015; Vadakkan *et al*. 2018). Using QSIs as an alternative to antibiotics may offer robust antivirulence strategies to combat resistance.

Antitoxin production: Toxins, primarily protein-based, are potent virulence factors produced by various bacteria that manipulate host cell functions and take control of cellular machinery. They target specific cells within an organism and modify their cellular components. Antitoxins, in contrast, are antibodies that bind to toxins,

facilitating their rapid removal from the body by neutralizing their function. Learning from the host's defence mechanisms, there has been progressing in using antisera and antibodies against toxins like anthrax and Shiga toxin (Lu *et al*., 2018). While secretion systems like type 2, type 3, and type 4 collectively downregulate bacterial infections, the therapeutic use of antitoxins as an alternative strategy remains an underexplored area. Utilizing *in-vivo* model systems can provide insights into the effective use of this approach to combat bacterial infections (Langdon *et al*., 2016).

Gut microbiota restoration by probiotics: Probiotics offer a solution by promoting rebiosis, restoring an affected (dysbiotic) gut microbiome in individuals (Gagliardi *et al*., 2018). Probiotics are the live bacterial cells administered in sufficient amounts, provide health benefits to the host, and effectively treat intestinal diseases such as antibiotic-associated diarrhea, *Listeria* spp. and *C. difficile* infections (Hickson, 2011). With advancements in genetic engineering and microbiome research, scientists are increasingly exploring probiotics as an alternative treatment for complications associated with MDR bacteria and high-density infections. Studies have demonstrated that periodic administration of engineered *Lactobacillus lactis* can significantly reduce bacterial loads in *Enterococcus faecium* infections by approximately 10,000-fold (Geldart *et al*., 2015). Engineered probiotics, like *E. coli*, can detect specific signalling molecules, such as AHLs used in bacterial quorum sensing, to target *Pseudomonas aeruginosa* gut infections (Hwang *et al*., 2017). Probiotics activate a genetic program to eliminate their targets by sensing intracellular signals. While probiotics show promise as an effective treatment regimen, more specific research is needed to determine the most appropriate probiotic choices. The growing interest in enhancing the gut microbiome with engineered probiotics represents an evolving therapeutic approach to combat the AMR problem. However, addressing safety concerns, gaining consumer acceptance, and overcoming substantial challenges associated with engineered probiotics remain essential steps in this field.

Microbiota modulation using synbiotics: A synbiotic refers to a synergistic blend of probiotics and prebiotics designed to positively impact the host by enhancing the survival and functionality of beneficial microorganisms within the gut. Recent research has elucidated the mechanisms of action, favorable outcomes, and proven efficacy of synbiotics in diverse animal species, including poultry, cattle, pigs, and companion animals. While the majority of synbiotic studies have been concentrated in poultry, there is a growing body of research extending to other animal categories. The strategic administration of synbiotics in animals holds significance for nurturing a thriving intestinal microbiota, pivotal for various functions such as nutrient production, prevention of infections from intestinal pathogens, and modulation of the immunological response. Consequently, the deliberate modification of gastrointestinal microorganisms becomes imperative to achieve, reinstate, and sustain a harmonious balance in the ecosystem and activity of the intestinal microbiota, thereby promoting the overall health and performance of animals. Synbiotics, composed of carefully chosen probiotic microorganisms and complementary prebiotics, emerge as a promising avenue for optimizing animal health and production (Malik *et al*., 2019)

Phage therapy (PT): Bacteriophages (phages), viruses that selectively kill bacteria, are abundant in the gut microbiome (Principi *et al*., 2019). Phages, as natural bacterial predators, are increasingly employed to combat various bacterial infections (Divya and Hosseinidoust, 2019). The rising issue of AMR has reduced the effectiveness of antibiotics, making PT an attractive option due to its high specificity against bacteria. Phages have demonstrated significant activity against bacteria like *Pseudomonas aeruginosa*, *Bacillus cereus*, and *Enterococcus faecalis* (Taati Moghadam *et al*., 2020). Advancements in recombinant DNA technology have enabled the engineering of phages to enhance their function by influencing the gut microbiome (Khan *et al*., 2016). Engineered T7 phages, for instance, have shown improved activity in reducing bacterial virulence factors (Drulis-Kawa *et al*., 2012). Phages are often combined with low doses of antibiotics, effectively reducing AMR development in bacteria (Gordillo and Barr, 2019). Programmed phages specifically target pathogenic bacteria without harming host cells. Based on previous reports, PT holds promise as an alternative to empirical antibiotic use. Engineered phages and phage-antibiotic synergy offer significant potential in the fight against AMR and dysbiosis.

Endolysins and artilysins: Bacterial lysins or endolysins (ELs), enzymes encoded by bacteriophages, are tools extensively used by phages to selectively digest the bacterial cell wall component known as peptidoglycan (Schmelcher *et al*., 2012). Research on ELs has gained prominence since the early 20th century. ELs work rapidly and effectively, targeting

antimicrobial-resistant (AMR) and persistent bacteria in chronic infections while sparing the gut microbiome. One limitation of ELs is their effectiveness mainly against Gram-positive bacteria like *Staphylococcus aureus* and *Enterococcus* spp. To tackle this issue, researchers have developed artilysins (ALs), which are engineered antibacterial proteins designed to breach the outer membrane of GNB and target their cell walls (Briers *et al*., 2014). ALs possess a combination of the favourable characteristics of endolysins (ELs) and demonstrate significant effectiveness against both GNB and GPB bacteria that exhibit multidrug resistance (MDR). Experimental evidence underscores the potential of engineered ALs, such as Art-175, to degrade persistent AMR bacteria like *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (Defraine *et al*., 2016).

Currently, veterinary research is assessing the efficacy of ALs in treating bacterial infections like dermatitis and otitis (Seal *et al*., 2018).

Faecal microbiota transplantation: Microbiota manipulation can be achieved through probiotics, as previously discussed, or through faecal microbiota transplantation (FMT), an emerging field in modern microbiome research, yet to be validated that explores the role of beneficial bacteria in the gut ecosystem. FMT governs the transfer of faecal microbiota from a healthy individual to a patient as a therapy to treat various bacterial infections, for example, Clostridium infections (CI). This treatment is achieved by restoring colonization resistance and reducing the presence of antimicrobial resistance genes (Gupta *et al*., 2016). *In-vivo* models also support the use of FMT in treating conditions like diarrhoea (Kim and Gluck, 2019). FMT facilitates gut microbiome restoration and inhibits spore germination by producing bacteriocins, which are ribosomally synthesized antimicrobial peptides (Kim *et al*., 2017). FMT appears to be a comprehensive form of probiotic use and has shown potential in combating multidrug resistance (MDR) with increasing successful reports. However, larger studies are needed to establish its effectiveness, as most current research is limited by small sample sizes.

Conclusions

The intricate interplay between the GM and the host's immune system plays a pivotal role in sculpting host metabolism and influencing the development of various diseases. This bi-directional relationship is a fundamental aspect of overall health. When we consider microbiota manipulation methods such as FMT and probiotics, we see the potential to leverage this relationship to our advantage. FMT and probiotics act as agents of change within the GM landscape. They introduce beneficial microorganisms or their products, providing essential nutrients and growth factors that can help strengthen or restore a healthy balance of intestinal microbiota. These strategies hold immense promise as alternatives to traditional empirical treatments. One of the key mechanisms at play here is the reduction of bacterial virulence. As FMT and probiotics promote the growth of beneficial microorganisms, the virulence of pathogenic bacteria is naturally diminished. Ideally, this strategy could be implemented in a veterinary setup to treat bacterial infections. This reduction in virulence makes bacterial cells more susceptible to the action of antibiotics. Even small amounts of antibiotics can effectively target and eliminate these weakened bacterial cells, which would otherwise be resilient in the face of standard antibiotic treatments. However, it's important to note that while these strategies show great potential; further research is needed to fully understand the molecular and pharmacodynamics aspects involved.

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