Scientific Bulletin. Series F. Biotechnologies, Vol. XXVIII, No. 2, 2024
ISSN 2285-1364, CD-ROM ISSN 2285-5521, ISSN Online 2285-1372, ISSN-L 2285-1364

ADVANCES IN ANTIMICROBIAL CONTROL: CONTRIBUTIONS AND POTENTIAL APPLICATIONS OF ANTAGONISTIC BACTERIA IN THE CONTROL OF MULTIDRUG-RESISTANT PATHOGENIC BACTERIA

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Abstract

Antagonistic bacteria play a crucial role in the fight against multi-drug resistant (MDR) pathogens. They offer an ecological and sustainable alternative to traditional antibiotics, reducing selective pressure and preserving natural microbial ecosystems. In agriculture and livestock farming, their purpose is to inhibit the growth of pathogens through competition for nutrients, producing antimicrobial substances and modulating the immune system. For example, probiotics such as Lactobacillus and Bifidobacterium improve intestinal health and reduce the need for antibiotics in animals. Similarly, bacteria such as Bacillus and Pseudomonas are used to protect plants against various diseases, reducing the need for chemical treatments. In the medical field, antagonistic bacteria are used to prevent and treat various infections, including gastrointestinal and urogenital infections. They also contribute to modulating the gut microbiota and supporting the immune system. However, there are still technical and scientific challenges to be overcome in order to optimize their use, such as understanding the complex interactions between antagonistic bacteria and pathogens, and the stability and efficacy of probiotic formulations.

Key words*: antagonistic, antimicrobial, control, multi-drug resistant, pathogenic.*

INTRODUCTION

The rise of antimicrobial resistance represents one of the most urgent and pressing challenges to global public health in the 21st century (EClinicalMedicine, 2021). Since the discovery of antibiotics, these drugs have played a crucial role in reducing morbidity and mortality from bacterial infections (Laxminarayan et al., 2013; Spellberg et al., 2014). Nevertheless, the excessive and frequently inappropriate use of antibiotics has resulted in the emergence and dissemination of multidrug-resistant (MDR) bacteria, rendering infections more challenging or impossible to treat with current therapeutic modalities (EClinicalMedicine, 2021). Indeed, it is estimated that by 2050, the lack of new antibiotics developed or discovered will result in the extinction of effective antibiotics for treating infections (Rolain et al., 2016) and that deaths from infectious diseases linked to antibiotic resistance will surpass all current causes of death (De Kraker et al., 2016). For example, in North America, the overuse of antibiotics represents a significant public health concern. Approximately 30% of antibiotic prescriptions are deemed unnecessary, contributing to the rising prevalence of drug-resistant infections in the USA (CDC, 2016).

Multidrug-resistant bacteria pose a significant threat in healthcare settings and the community (Reyes et al., 2023), affecting vulnerable populations such as hospitalized patients, the elderly, and immunocompromised individuals. MDR bacteria of greatest concern include methicillin-resistant *Staphylococcus aureus*

(MRSA), carbapenemase-producing *Klebsiella pneumoniae* (KPC), extended-spectrum beta-lactamase-producing *Escherichia coli* (ESBL), multidrug-resistant *Acinetobacter baumannii*, and multidrug-resistant *Pseudomonas aeruginosa*. These pathogens are responsible for a range of serious infections, including urinary tract infections, pneumonia, septicemia, and wound infections (Laxminarayan et al., 2016). The Centers for Disease Control and Prevention (CDC, 2016) estimates that more than 2.8 million cases of infection resulting from antibiotic-resistant bacteria occur annually, with approximately 35,000 deaths attributed to these infections. It is therefore imperative to investigate alternative methodologies for the management of antibiotic-resistant pathogens.

Faced with this growing threat, the scientific and medical community has intensified its efforts to discover and develop new strategies for controlling MDR bacterial infections. In recent years, significant progress has been made in the field of antimicrobial control, with the discovery of novel classes of antibiotics, the development of innovative combination therapies, and the optimization of treatment protocols. Furthermore, there has been a notable shift in focus towards alternative approaches, including the utilization of bacteriophages, peptides, antimicrobial peptides and immunomodulatory therapies.

Moreover, a more comprehensive grasp of the mechanisms underlying antimicrobial resistance has facilitated the development of more targeted therapeutic strategies, allowing for more precise intervention at the molecular level. The continued monitoring of antibiotic usage and the implementation of evidence-based antibiotic stewardship remain pivotal strategies for curbing the dissemination of antibiotic resistance.

The objective of this review article is to provide an overview of recent contributions to the field of antimicrobial control and to discuss the potential applications of these findings in the context of combating multidrug-resistant pathogenic bacteria. By examining scientific advances and technological innovations, this review aims to identify the most promising strategies and remaining challenges in the fight against antibiotic resistance. This review will concentrate on the potential impact of antagonistic bacteria in the development of new therapeutic approaches, thus providing an innovative perspective on how this global public health problem can be overcome. In addition, this study will examine the underlying mechanisms of bacterial resistance and their implications for the development of control strategies. Furthermore, this study details recent advances in research and development of new classes of antibiotics and alternative therapies, evaluates the potential contributions of antagonistic bacteria in the context of new approaches to combating infections caused by MDR bacterial pathogens and identifies potential clinical applications of recent discoveries and discuss future perspectives in the control of MDR bacterial pathogens.

The selection of the articles included in this review was performed based on well-known databases (Scopus, Web of Science, ScienceDirect), using specific key-words ("antibiotic resistance", "multidrug-resistant", "antagonistic bacteria").

The validation of the articles was performed manually, inserting only relevant articles with significant contributions to the field of research, resulting in fulfilling this review in its final form.

CURRENT STATE OF ANTIMICROBIAL RESISTANCE

Europe faces a worrying situation regarding antimicrobial resistance (AMR). Several recent studies show a notable increase in resistance in several common pathogenic bacteria. In a recent study conducted by the European Antimicrobial Resistance Collaborators (2022), it was estimated that 541,000 deaths were associated with bacterial AMR and 133,000 deaths were attributable to bacterial AMR across the WHO European region in 2019. As reported, seven principal pathogens were accountable for approximately 457,000 deaths associated with antimicrobial resistance in 53 European countries. The pathogens are listed in descending order of mortality: *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterococcus faecium, Streptococcus pneumoniae* and *Acinetobacter baumannii*. A study by the European Antimicrobial Resistance Collaborators (2022) revealed that methicillin-resistant *S. aureus* was the predominant

pathogen-drug combination associated with AMR-related mortality in 27 countries. Similarly, aminopenicillin-resistant *E. coli* was identified as the leading cause of AMR-related deaths in 47 countries (European Antimicrobial Resistance Collaborators, 2022).

In the Americas region, the emergence of MDR bacteria represents a significant and growing threat to public health. A recent study by the Antimicrobial Resistance Collaborators (2022) demonstrated that 569,000 deaths were attributable to bacterial AMR in the 35 countries of the WHO Region of the Americas in 2019, with an additional 141,000 deaths associated with this antibiotic-resistant bacterial infection. These authors have revealed that lower respiratory tract and chest infections, as a syndrome, were responsible for the largest fatal burden of AMR in the region, with 189,000 deaths (149,000 - 241,000) associated with resistance, followed by bloodstream infections (169,000 deaths) and peritoneal/intra-abdominal infections (118,000 deaths). The six pathogens with the highest mortality rates associated with resistance were identified as *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (Antimicrobial Resistance Collaborators, 2022). The combined impact of these pathogens resulted in 452,000 deaths (326,000-608,000) attributed to AMR. Methicillin-resistant *S. aureus* was the predominant pathogen-drug combination in 34 countries in terms of AMR-attributable deaths, while aminopenicillin-resistant *E. coli* was the leading pathogen-drug combination in 15 countries for deaths associated with AMR (Antimicrobial Resistance Collaborators, 2022). Recent studies have indicated that low- and middle-income countries, such as those in Africa, are disproportionately affected by AMR. The findings of the Antimicrobial Resistance Collaborators (2022) in Africa indicate a significant concern, characterized by the prevalence of multiple resistant bacterial strains that present a formidable challenge to public health. The authors estimate that in the WHO African region in 2019, there were 1-05 million deaths (95%) associated with bacterial AMR and 250,000 deaths (192,000-325,000) attributable to bacterial AMR. Additionally, the primary causes of mortality associated with bacterial AMR are lower respiratory tract and chest infections (119,000 deaths, accounting for 48% of all estimated bacterial AMR deaths), bloodstream infections (56,000 deaths, representing 22%), intravenous infections and abdominal diseases (26,000 deaths, or 10%), and tuberculosis (18,000 deaths, or 7%). In addition, seven major pathogens were collectively responsible for 821,000 deaths (636,000-1,051,000) associated with resistance in this region, with four pathogens exceeding 100,000 deaths each. The pathogens in question are *S. pneumoniae*, *K. pneumoniae*, *E. coli* and *S. aureus*. The predominant pathogen-drug combinations identified in 25 and 16 countries, respectively, were third-generation cephalosporin-resistant *K. pneumoniae* and methicillin-resistant *S. aureus*, accounting for 53% and 34% of the entire region (comprising 47 countries) of deaths attributable to AMR (Antimicrobial Resistance Collaborators, 2022). This overview elucidates the gravity of antimicrobial resistance across disparate geographical regions (Table 1), underscoring the imperative for the formulation of global and regional strategies to confront this mounting threat.

Table 1. The incidence of antimicrobial resistance worldwide

Regions	Microorganisms	Associated illnesses	Estimated number of annual deaths	References
Africa	Methicillin-resistant S. *aureus* (MRSA)	Skin infections, pneumonia, septicemia	19,000	WHO (2021)
	Cephalosporin-resistant *E. coli*	Urinary tract infections, septicemia	8,000	CDC Africa (2022)
	Carbapenem-resistant *K. pneumoniae*	Pneumonia, wound infections	10,000	WHO (2020)
	Mycobacterium tuberculosis multiresistant	Tuberculosis	56,000	WHO (2021)
America	Methicillin-resistant S. *aureus* (MRSA)	Skin infections, pneumonia, septicemia	20,000	CDC (2021)
	Cephalosporin-resistant *E. coli*	Urinary tract infections, septicemia	15,000	CDC (2021)
	Carbapenem-resistant *K. pneumoniae*	Pneumonia, wound infections	13,000	CDC (2021)
	Carbapenem-resistant *A. baumannii*	Pneumonia, septicemia	9,000	CDC (2021)
Asia	Methicillin-resistant S. *aureus* (MRSA)	Skin infections, pneumonia, septicemia	70,000	WHO (2021)
	Cephalosporin-resistant *E. coli*	Urinary tract infections, septicemia	50,000	CDC Asia (2022)

	Carbapenem-resistant *K. pneumoniae*	Pneumonia, wound infections	45,000	WHO (2020)
	Carbapenem-resistant *A. baumannii*	Pneumonia, septicemia	40,000	WHO (2021)
	Mycobacterium tuberculosis multiresistant	Tuberculosis	230,000	WHO (2021)
Europa	Methicillin-resistant S. *aureus* (MRSA)	Skin infections, pneumonia, septicemia	25,000	ECDC (2021)
	Cephalosporin-resistant *E. coli*	Urinary tract infections, septicemia	20,000	ECDC (2021)
	Carbapenem-resistant *K. pneumoniae*	Pneumonia, wound infections	17,000	ECDC (2021)
	Carbapenem-resistant *A. baumannii*	Pneumonia, septicemia	10,000	ECDC (2021)
	Mycobacterium tuberculosis multiresistant	Tuberculosis	10,000	WHO (2021)

RESISTANCE MECHANISMS OF PATHOGENIC BACTERIA

The prevalence of resistance is experiencing a considerable increase, particularly in developing countries (Kagambèga et al., 2024). The situation is further complicated by the emergence of MDR, ultradrug resistance (XDR), and, most recently, pandrug resistance (PDR) (Pulingam et al., 2022). It is therefore the view of many authors that MDR should be defined as acquired resistance to at least one agent belonging to three or more antimicrobial categories. Similarly, XDR has been defined as acquired resistance to at least one agent belonging to all but two or fewer antimicrobial categories, while PDR has been defined as acquired resistance to all antimicrobial categories (Basak et al., 2016; Magiorakos et al., 2012).

AMR is a phenomenon that manifests itself through various complex mechanisms, which enable bacteria to survive and multiply despite the presence of antibiotics. These mechanisms can be intrinsic or acquired and include alterations to the antibiotic target, enzymatic inactivation of the antibiotic, modification of membrane permeability, and activation of efflux pumps (Abushaheen et al., 2020).

Modification of the antibiotic target

Bacteria are capable of developing mutations in the genes that encode target proteins of antibiotics. This process results in a reduction in the affinity of the antibiotic for its target (Sharmila Devi et al., 2024). In general, mutation-driven resistance mechanisms emerge as a consequence of alterations in antimicrobial agents, which may occur through three main mechanisms: (i) reduced drug absorption, (ii) activation of efflux mechanisms, or (iii) modifications in metabolic pathways (Samreen et al., 2021). For example, resistance to fluoroquinolones is frequently attributed to mutations in the *gyrA* and *parC* genes, which encode the subunits of the enzymes DNA gyrase and topoisomerase IV (Muylaert & Mainil, 2013). Moreover, a substantial body of evidence from numerous studies has demonstrated that alterations in codons 513, 526, or 531 lead to high resistance to rifampicin, whereas alterations in positions 511 and 533 result in reduced resistance in *M. tuberculosis* (Ohno et al., 1996; Somoskovi et al., 2001).

Enzymatic inactivation of the antibiotic

Bacteria can produce enzymes that degrade or chemically modify the antibiotic, rendering it ineffective (Pulingam et al., 2022). The authors define this as an enzymatic process during which the active antibiotic molecule is rendered inactive by enzymes produced by resistant bacterial cells. For example, hydrolysis is one of the most studied inactivation mechanisms. Davies (1994) demonstrated that *E. coli*, *K. pneumoniae* and *Enterobacter* spp. produce β-lactamase, which is capable of hydrolysing the β-lactam ring of penicillin, cephalosporin and carbapenem. In addition to hydrolysis, the redox process represents a further mechanism of drug inactivation, whereby a drug molecule is oxidised or reduced (Wright, 2005).

Change in membrane permeability

Bacteria can modify their outer membrane to reduce entry of the antibiotic (Abushaheen et al., 2020). Porin, an outer membrane protein (OMP), is regarded as the gateway for antibiotics, including tetracyclines and β-lactams, which gain access to *E. coli* via OmpF, and carbapenems, which enter *P. aeruginosa* through OmpD (Ramirez & Tolmasky, 2010). These researchers demonstrated that structural alteration or even functional elimination of porin genes resulted in diminished influx, which hinders antibiotic penetration into gram-negative bacteria.

Efflux pumps

Bacteria are capable of actively expelling antibiotics from the cell via efflux pumps, thereby reducing the intracellular concentration of the antibiotic. This mechanism is regarded as

the most prevalent among bacteria (Varela et al., 2013; Sharmila Devi et al., 2024) and is a subject of significant research interest (Pulingam et al., 2022). In their 2011 study, Fiamegos et al. demonstrated that efflux pumps can exhibit specificity towards a particular antibiotic, or alternatively, extrude a range of structurally and functionally diverse antibiotics (multidrug efflux pumps, or MEPs) (Fiamegos et al., 2011). According to many authors, macrolides, β-lactams, fluoroquinolones, oxazolidinones, fourth generation cephalosporins and carbapenems are the main classes of antibiotics known to be effused by intrinsic bacterial efflux pumps (Li and Nikaido, 2009; Li et al., 2015). For example, RND (resistance-nodulation-division) family efflux pump systems in *Pseudomonas aeruginosa* expel various antibiotics, including fluoroquinolones, aminoglycosides, and β-lactams (Tetard, 2021).

Enzymatic modification of the antibiotic

Bacteria can produce enzymes that chemically change the antibiotic, making the antibiotic less effective. This mechanism is observed in Gram-positive and Gram-negative bacteria (Abushaheen et al., 2020). This is due to the fact that in enzymatic modification, the addition of acetyl, adenyl or phosphate groups from bacterial enzymes to a specific site of antibiotics occurs with the intention of chemically modifying them and inactivating the antimicrobial agents, thus rendering them unable to bind at the target site (Abushaheen et al., 2020). Additionally, the work of Ramirez & Tolmasky (2010) showed that phosphorylation occurs in macrolides, while acetylation/adenylation and/or phosphorylation occurs in aminoglycosides. For example, aminoglycoside-modifying enzymes, including acetyltransferases, adenylyltransferases, and phosphotransferases, modify aminoglycosides, rendering these antibiotics incapable of binding to bacterial ribosomes (Wright, 1999).

RECENT ADVANCES IN ANTIMICROBIAL CONTROL

Recent advances in antimicrobial control have been driven by the pressing need to combat antibiotic resistance and improve infection management. These advances can be classified into three principal categories: (i) the development of novel antimicrobials, (ii) innovative technologies and (iii) the utilisation of adjuvants and synergies. In recent years, there has been a notable focus on the discovery and development of entirely new classes of antibiotics. Molecules such as teixobactin have been discovered that inhibit cell wall synthesis by binding to a highly conserved motif in lipid II (the precursor of peptidoglycan) and lipid III (the precursor of cell wall teichoic acid). These molecules represent a previously unexploited avenue of research (Ling et al., 2015). Ling et al. (2015) demonstrated that teixobactin exhibits remarkable bactericidal efficacy against *S. aureus*, with a superior capacity to vancomycin in eradicating late exponential phase populations (Ling et al., 2015).

Bacteriophages

The utilisation of bacteriophages, viruses that infect bacteria, has demonstrated considerable potential, particularly in the context of the treatment of multidrug-resistant infections (Wittebole et al., 2014). Phage therapy can be adapted to target specific pathogenic bacteria without affecting the host microbiota. Abedon et al. (2011a; 2011b) investigated the potential of phages as a means of combating pathogenic bacteria. Johri et al. (2021) demonstrated the potent antibacterial and anti-infectious efficacy of Intesti and Fersis phage cocktails, as well as "staphylococcal phages", in the management of chronic bacterial prostatitis. Moreover, additional research has demonstrated the efficacy of a phage cocktail in the treatment of urinary tract infections caused by *K. pneumoniae* following the failure of various antibiotic treatments (Bao et al., 2020). In Belgium and France, Jault et al. (2019) employed a topical cocktail comprising 12 phages (designated PP1131) in the treatment of burns caused by *P. aeruginosa*.

Enzibiotics

Additionally, considerable effort has been dedicated to investigating the potential of phage-encoded enzymes, also known as enzybiotics, as standalone antibacterial agents (Abedon et al., 2011a; 2011b). Indeed, enzymes such as endolysins are produced in a recombinant manner in a pure form and applied outside of bacterial cells (De Maesschalck et al., 2020; Gerstmans et al., 2020). Recent research has demonstrated that endolysins, which are peptidoglycan hydrolases, are capable of acting

within bacterial cells (Abdelrahman et al., 2021; Schmelcher & Loessner, 2021; Murray et al., 2021; Linden et al., 2021). Furthermore, they have been shown to directly cause osmotic lysis in the case of Gram-positive bacteria (Briers et al., 2014; Briers & Lavigne, 2015). Nevertheless, in order to endolysins act on Gram-negative bacteria, a modification must be undergone in order for them to reach the cell wall (Briers et al., 2014; Briers & Lavigne, 2015). Moreover, these enzymes are employed by phages at the conclusion of their lytic infection cycle to dismantle the bacterial cell wall and facilitate the release of newly produced virions (Young and Wang, 2006). The utilization of endolysins is highly advantageous due to their non-toxic nature, rapid action, efficient killing of targeted bacteria and their inherent difficulty for bacteria to combat (Jun et al., 2017; Blasco et al., 2020; Fowler et al., 2020).

Nanobactericides against MDR bacteria

Nanotechnology has emerged as a plausible revolutionary tool for the prioritisation of novel and effective therapeutic options (Baker and Perianova, 2019; Chakraborty et al., 2022). To develop the most effective alternatives for drug-resistant pathogens, extensive research has been conducted into the use of nanoparticles in the fight against multi-resistant bacteria. The work of Jin and He (2011) demonstrated that the combination of magnesium oxide nanoparticles with nisin and zinc oxide nanoparticles exhibited antibacterial activity against *Escherichia coli* O157:H7 and *Salmonella* species.

It is established that nanobactericides are effective against a wide range of pathogens (Baker and Perianova, 2019). A substantial number of research has been conducted with the aim of elucidating the mode of action of nanobactericides. For example, Pal et al. (2007) demonstrated that nanobactericides can interact with cytoplasmic components and nucleic acids, inhibiting respiratory chain enzymes and interfering with the membrane permeability of complex I dehydrogenase. Other research has demonstrated that nanobactericides are capable of producing reactive oxygen species (ROS), inhibiting respiratory enzymes, producing ATP, creating pitting, and leading to the disruption of membrane integrity and cell membrane rupture, which ultimately results in pathogen death (Syed et al., 2018).

ANTAGONISTIC BACTERIA: MECHANISMS OF ACTION

Antagonistic bacteria are microorganisms that inhibit the growth or survival of other bacteria, particularly pathogens. This action can be exerted in various ways, including the production of antimicrobial substances, competition for resources and interference with pathogen communication mechanisms. This review will focus on the production of antimicrobial substances.

Production of antimicrobial compounds

Antagonistic bacteria are capable of producing a diverse range of antimicrobial compounds that are effective in inhibiting the growth of pathogens. Such substances include bacteriocins, natural antibiotics and lytic enzymes.

Bacteriocins: These are peptides or proteins that are produced by bacteria with the purpose of inhibiting or killing other bacteria. They frequently act by disrupting the cell membrane or essential functions of the target cell. For example, Abanoz and Kunduhoglu (2018) demonstrated that the bacteriocin KT11, produced by *E. faecalis* KT11, isolated from traditional Kargı Tulum cheese, exhibited antagonistic efficacy against a variety of Gram-positive and Gram-negative bacteria, including vancomycin- and/or methicillin-resistant bacteria. A further study conducted in India demonstrated that the bacteriocin produced by *L. plantarum* LA21, isolated from fermented foods, exhibited antibacterial activity against pathogenic bacteria, including *B. pumilus*, *B. amyloliquefaciens*, *S. aureus* and *L. monocytogenes* (Leslie et al., 2021).

Natural antibiotics and bioactive compounds: A considerable number of drugs derived from natural products are produced by microbes or by their interaction with hosts (Newman and Cragg, 2020). For example, maclamicin has demonstrated potent antimicrobial activity against Gram-positive bacteria, while lobophorin F, isolated from *Streptomyces* spp., has exhibited significant antibacterial activity. Furthermore, plantacyclin B21AG, a circular bacteriocin produced by *L. plantarum*,

demonstrated high thermostability and broad antagonistic activity (Golneshin et al., 2020).

Actinobacteria: Actinomycetes, in particular, are a highly prolific source of bioactive secondary metabolites. Approximately 45% of the 23,000 or so bioactive secondary metabolites produced by microbial diversity are attributed to actinobacteria (Ara et al., 2012; Sathi et al., 2001; Sirbu et al., 2023). Genera such as *Streptomyces* are responsible for the production of a multitude of bioactive compounds, a considerable proportion of which are antibiotics (Bérdy, 2005; Ganesan et al., 2017). For example, Kumar et al. (2014) evaluated isolates for their antagonistic activity against various pathogens and found that some strains, such as SCA 7, exhibited strong antimicrobial activity.

Cyclic lipopeptides: Recent studies have demonstrated that cyclic lipopeptides produced by *Bacillus amyloliquefaciens* exhibit potent antimicrobial activity. These lipopeptides can be classified into three families: surfactin, iturin and fengycin (Wong et al., 2008). For example, Xu et al. (2014) demonstrated the antibacterial activity of lipopeptides produced by *Bacillus amyloliquefaciens* M1 against multi-resistant *Vibrio* spp. isolated from diseased marine animals.

CONTRIBUTIONS OF ANTAGONISTIC BACTERIA IN THE CONTROL OF MULTI-RESISTANT PATHOGENIC BACTERIA

Recent studies have demonstrated the numerous advantages that antagonistic bacteria offer over traditional antibiotics and novel therapeutic approaches. Antagonistic bacteria frequently act by producing natural inhibitory substances, which impede the development of resistance mechanisms in pathogens. Mora et al. (2020) highlight that antagonistic bacteria reduce the likelihood of resistance developing, as they do not exert the same selective pressure on pathogens as traditional antibiotics. Moreover, Hibbing et al. (2018) posit that antagonistic bacteria facilitate a healthy equilibrium within the microbiota by impeding the proliferation of pathogens while fostering the growth of beneficial microorganisms. This is in contrast to antibiotics, which frequently also destroy beneficial bacteria, thus disturbing the microbiological equilibrium. In a study conducted by Collins et al. (2019), it was demonstrated that antagonistic bacteria can exert long-lasting effects on the prevention of infection. For example, the colonization of the gut with probiotics can prevent the establishment of pathogens, thereby reducing the incidence of recurrent infections. Furthermore, other authors have proposed an ecological approach to the utilization of antagonistic bacteria. Rodriguez et al. (2021) highlight that the utilization of antagonistic bacteria represents a more ecological and sustainable approach, assisting in the reduction of antibiotic usage in the environment and the preservation of natural microbial ecosystems.

Use in agriculture and livestock farming

Antagonistic bacteria play a pivotal role in curbing the reliance on antibiotics in livestock and agricultural production. These beneficial microorganisms can inhibit the growth of pathogens through a variety of mechanisms, including competition for nutrients, the production of antimicrobial substances, and the modulation of the host immune system. In a study conducted by Markowiak and Śliżewska (2018), it was demonstrated that the administration of probiotics to animal diets can enhance gut health and fortify immune defences, consequently reducing the necessity for antibiotics. Probiotics, including *Lactobacillus* and *Bifidobacterium*, are frequently employed in this context (Chaucheyras-Durand and Durand, 2010). Patterson and Burkholder (2003) demonstrated that the addition of probiotics to poultry feed can result in a reduction in the colonization of pathogens such as *Salmonella* and *Campylobacter*. This results in a reduction in infections and the necessity for antibiotic use. In a relatively recent study, Compant et al. (2019) have emphasized the potential of antagonistic bacteria for the biocontrol of pathogens in agricultural crops. For example, *Bacillus* and *Pseudomonas* strains can be applied to protect plants against various diseases, thereby reducing the need for chemical and antibiotic treatments (Compant et al., 2019). Nayak (2020) explored the use of probiotics in aquaculture to prevent bacterial infections in fish. Probiotics can improve the gut health of fish and inhibit the growth of aquatic pathogens, thereby reducing reliance on antibiotics.

The use of antagonistic bacteria represents a promising avenue for reducing the reliance on

antibiotics in livestock and agricultural production. Their capacity to enhance intestinal wellbeing, avert infections, stimulate the immune system and regulate pathogens in crops and aquaculture is well documented. Recent research indicates that the application of these beneficial microorganisms can not only enhance the health and productivity of animals and plants, but also serve as a pivotal strategy in combating antimicrobial resistance.

Clinical and medical applications

The use of antagonistic bacteria in clinical and medical applications is becoming increasingly prevalent due to their numerous health benefits. Over the past decade, a substantial number of research has demonstrated that beneficial microorganisms, commonly referred to as probiotics, can play a pivotal role in the prevention and treatment of various diseases by modulating the gut microbiota, inhibiting pathogens, and enhancing immune system function. Goldstein et al. (2017) demonstrated that specific strains of *Lactobacillus* and *Bifidobacterium* can prevent and treat gastrointestinal infections, including antibiotic-associated diarrhoea and viral gastroenteritis. Sartor (2020) conducted a study examining the efficacy of probiotics in the management of inflammatory bowel disease, including Crohn's disease and ulcerative colitis. Probiotics have been demonstrated to modulate the immune response, reduce inflammation and improve clinical symptoms in patients with inflammatory bowel disease (IBD). In a study conducted by Stapleton et al. (2019), it was demonstrated that the administration of probiotics, particularly *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14, can prevent urogenital infections in women, including recurrent urinary tract infections and bacterial vaginosis. In a study by Arrieta et al. (2018), it was demonstrated that probiotics can play a role in the prevention and management of allergies and asthma. Probiotics have been demonstrated to facilitate the education of the immune system in early life, thereby reducing the risk of developing allergic diseases. Cani et al. (2019) demonstrated that probiotics can influence metabolism and be beneficial in the treatment of metabolic diseases such as obesity and type 2 diabetes. Probiotics have been demonstrated to modulate the gut microbiota, enhance insulin sensitivity and reduce metabolic inflammation. Morrow et al. (2012) evaluated the efficacy of probiotics in preventing nosocomial infections, such as *Clostridioides difficile* infections, in hospitalised patients. Probiotics have been demonstrated to reduce the colonization of resistant pathogens and to decrease the incidence of healthcare-associated infections.

Antagonistic bacteria, or probiotics, have the potential to provide effective solutions for a range of clinical and medical conditions. Their capacity to modulate the microbiota, inhibit pathogens and enhance the immune system renders them invaluable instruments in the prevention and treatment of gastrointestinal infections, inflammatory bowel disease, urogenital infections, allergies, metabolic diseases and nosocomial infections. Recent research has highlighted the significance and efficacy of these beneficial microorganisms in the medical field.

Challenges and obstacles to overcome

The utilisation of antagonistic bacteria presents a number of significant advantages, although it is not without inherent challenges. Sanders et al. (2018) emphasise that the stability and viability of antagonistic bacteria during storage and delivery represent a significant challenge. For probiotics to be effective, they must survive the conditions of manufacture, storage and passage through the gastrointestinal tract. Zmora et al. (2018) have demonstrated that the interaction between probiotics and the resident gut microbiota may be complex and unpredictable. The efficacy of some probiotics may be constrained by their inability to colonise effectively or to persist in the gut, where they may be eliminated by the existing microbiota. In their 2015 paper, Doré et al. addressed concerns regarding the safety of probiotics, particularly in vulnerable populations such as those with immune system deficiencies. While probiotics are typically regarded as safe, there have been isolated reports of adverse effects, including opportunistic infections, in rare instances. Reid et al. (2019) emphasise that the effects of antagonistic bacteria may be specific to certain strains and hosts. It is therefore challenging to make generalized claims about the benefits of probiotics, and a personalized approach may be required to optimize efficacy. As Hill et al. (2014) observe, the precise mechanisms of

action of antagonistic bacteria remain incompletely understood. A more comprehensive grasp of the interrelationships between probiotics, hosts, and pathogens is essential to enhance the efficacy of antagonistic bacteria. Fontana and Bermudez-Brito (2019) addressed the regulatory challenges associated with the marketing of probiotics. There are discrepancies in quality standards, regulatory frameworks and health claims across different regions, which present challenges to the universal approval and acceptance of probiotic products.

Despite the considerable benefits that antagonistic bacteria offer to human and animal health, a number of technical and scientific constraints must be addressed to fully realize their potential. The stability and viability of probiotics, complex interactions with existing microbiota, safety concerns, specificity of effect, incomplete mechanisms of action, and regulatory challenges are all areas requiring ongoing research and improvement. Advances in these fields will facilitate the optimal exploitation of antagonistic bacteria while mitigating associated risks.

CONCLUSIONS

Antagonistic bacteria represent a promising advance in controlling multi-resistant pathogens and reducing the use of antibiotics. Their applications in agriculture, livestock farming, and medicine are showing encouraging results in terms of intestinal health, preventing infections and stimulating the immune system. Nevertheless, further research is needed to overcome technical and scientific limitations and maximise their potential. The integration of antagonistic bacteria into current practices could thus play a crucial role in the fight against antimicrobial resistance, contributing to a more sustainable and healthy future.

ACKNOWLEDGEMENTS

The authors are grateful to the Agence Universitaire de la Francophonie (AUF) for the *Eugen Ionescu Postdoctoral Fellowship* and to the University of Agronomic Sciences and Veterinary Medicine of Bucharest, Romania, for their support.

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