Review

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Probiotics, Prebiotics and Synbiotics for Combating Antimicrobial Resistance in the Food Chain

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Abstract

The increasing prevalence of antimicrobial resistance (AMR) among foodborne pathogens has emerged as a critical global health concern, undermining the efficacy of conventional antimicrobial agents and threatening the safety and integrity of the food supply chain. In response, probiotics, prebiotics, and their combinations as synbiotics are increasingly recognised as sustainable, health-oriented strategies to mitigate AMR across the food chain. Probiotics—live microorganisms that, when administered in adequate amounts, confer health benefits to the host—contribute to AMR mitigation through multiple mechanisms, including competitive exclusion of resistant pathogens, production of antimicrobial metabolites (e.g., bacteriocins and organic acids), modulation of host immunity, and restoration of gut microbial balance. Prebiotics, defined as non-digestible food ingredients, selectively stimulate the growth and/or metabolic activity of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* spp., thereby reinforcing colonisation resistance. When combined as synbiotics, these agents may exert synergistic effects, enhancing microbial resilience, promoting gut health, and reducing the colonisation and persistence of AMR-related pathogens. The integration of these bio-based approaches into food systems—particularly in the development of fermented and functional foods—supports broader One Health objectives by reducing the need for antibiotics and contributing to global AMR containment efforts. This review summarises current scientific insights, explores practical applications, and outlines future perspectives on the role of probiotics, prebiotics, and synbiotics in combating AMR throughout the food chain.

Keywords: antimicrobial resistance; food safety; foodborne pathogens; probiotics; prebiotics; synbiotics; One Health

1. Introduction

The escalating crisis of antimicrobial resistance (AMR) has become one of the most pressing global health challenges of the 21st century. Over the past decades, the widespread and often inappropriate use of antimicrobial agents in human medicine, veterinary practice, and food production systems has accelerated the emergence and dissemination of resistant pathogens. AMR arises when microorganisms evolve and acquire the ability to withstand treatments that were previously effective, rendering infections significantly harder—or even impossible—to treat [1,2].

According to the latest global estimates, 4.95 million deaths in 2019 were associated with infections caused by resistant bacteria, of which 1.27 million were directly attributable to AMR [2]. In the European Union (EU), AMR accounts for more than 35,000 deaths annually, with economic losses exceeding EUR 11.7 billion [3]. Without effective countermeasures, projections suggest that AMR-related mortality could surpass 10 million deaths annually by 2050—overtaking cancer—and result in cumulative global economic losses approaching USD 100 trillion [4,5].

Among the most critical AMR-associated pathogens are *Campylobacter* spp., *Salmonella* spp., *Staphylococcus aureus*, *Escherichia coli*, *Listeria monocytogenes*, and *Clostridioides* difficile—microorganisms that frequently cause zoonoses and foodborne infections and often exhibit multidrug-resistant phenotypes [2]. In livestock production, bacteria such as *Mannheimia haemolytica*, *Pasteurella multocida*, *Moraxella bovis*, and *Histophilus somni* cause severe respiratory and systemic infections, reducing productivity and driving increased reliance on antimicrobial treatments [6,7]. These pathogens are major agents of gastrointestinal, respiratory, and systemic diseases that are often difficult to treat with standard therapies, especially in the context of zoonotic transmission through the food chain via contaminated meat, milk, or water.

The food chain plays a pivotal role in the dissemination of AMR. Although the use of antibiotics as growth promoters has been banned in the EU since 1 January 2006 [8], and the prophylactic use of antimicrobials was further restricted under Regulation (EU) 2019/6—enforced as of 28 January 2022—such practices remain widespread in many regions globally [9,10]. Resistant bacteria and resistance genes can be transmitted along the food chain through contaminated animal products, water, and environmental reservoirs. This alarming trend underscores the urgent need for integrated, cross-sectoral strategies based on the One Health approach, which recognises the interconnectedness of human, animal, and environmental health [11].

In this context, increasing scientific and regulatory attention is being directed toward sustainable, biological alternatives to conventional antimicrobials. Among the most promising are probiotics—live microorganisms that confer health benefits to the host—and prebiotics, non-digestible food compounds that selectively stimulate the growth and activity of beneficial gut microbes [12,13]. These agents exert antimicrobial effects via multiple mechanisms, including competitive exclusion of pathogens, production of antimicrobial metabolites (e.g., bacteriocins, organic acids, hydrogen peroxide), and modulation of host immune responses [14]. Prebiotics serve as selectively fermentable substrates that restore and enhance beneficial bacterial populations—particularly *Lactobacillus* and *Bifidobacterium* spp.—which may be disrupted by prior antibiotic use [15,16]. Unlike conventional antimicrobials, probiotics and prebiotics offer multifaceted, eco-friendly, and safe approaches to microbial control, making them attractive tools in combating AMR [17,18]. When used in combination, probiotics and prebiotics form synbiotics—formulations designed to enhance the survival, colonisation, and activity of beneficial microorganisms in the host. Synbiotics may exert synergistic effects by coupling the selective stimulation of host microbiota with the direct introduction of viable probiotic strains, thereby offering enhanced protection against pathogens and improved modulation of gut ecology [19,20].

This review provides an in-depth analysis of the scientific evidence supporting the use of probiotics, prebiotics, and synbiotics as sustainable strategies for combating antimicrobial resistance across the food chain and related production systems, including livestock and aquaculture. The aim is to examine their mechanisms of action, practical applications in different sectors, and potential contributions to AMR mitigation within the One Health framework.

2. Materials and Methods

A comprehensive narrative literature review was conducted to evaluate the current state of knowledge on the use of probiotics, prebiotics, and synbiotics as sustainable alternatives to antimicrobial agents in the food chain. The review emphasised their mechanisms of action, practical applications, and potential contributions to AMR mitigation within the broader framework of food safety and One Health.

Peer-reviewed publications, review articles, technical reports, and international guidelines were retrieved from multiple databases, including Web of Science, Scopus, PubMed, Academic Search Complete, CAB Abstracts, and EBSCO. In addition, the official websites of international organisations such as the WHO, FAO, and EFSA were consulted to obtain up-to-date data and expert opinions.

A structured search strategy was applied using predefined keywords and Boolean operators (AND, OR, NOT) to maximise relevance and coverage. Search terms included combinations such as "probiotics AND food safety", "prebiotics AND antimicrobial resistance", "synbiotics AND foodborne pathogens", "alternatives to antibiotics in food", "biological control AND fermented foods", "probiotics AND Listeria", "antimicrobial resistance AND natural antimicrobials", "probiotics AND One Health", and "gut microbiota AND pathogen exclusion".

The literature search covered papers published in the period from 2015 to 2025 and identified more than 150 relevant publications, of which 139, after relevance assessment, were included in the manuscript. A limited number of high-impact articles published before 2015 were also included when they provided foundational or widely cited insights into the historical context of antibiotic use and AMR development. Relevance was assessed through title, abstract, and full-text screening, while a snowballing approach was employed to identify additional sources cited within selected studies. The inclusion criteria were as follows: (i) relevance to the use of probiotics, prebiotics, and/or synbiotics in the control of foodborne pathogens; (ii) a clear focus on microbiological safety, health promotion, or AMR mitigation; and (iii) applicability to food systems and/or the One Health context. The evidence synthesised through this process provides the foundation for subsequent discussion on the feasibility, challenges, and benefits of these bio-based interventions.

3. Antimicrobial Resistance and the Food Chain

3.1. Historical Context of Antibiotic Discovery and AMR Emergence

The application of antibiotics in medicine and veterinary practice stands among the greatest achievements of modern science, having enabled the safe execution of complex medical procedures—including surgery, organ transplantation, and immunosuppressive therapies—and drastically reducing mortality from infectious diseases [21,22]. The discovery of penicillin from *Penicillium rubens* by Alexander Fleming in 1928 ushered in the so-called "Golden Age" of antibiotic discovery, spanning the 1940s to 1960s [23]. Most antibiotics in clinical use today originate from that period. Since then, however, antibiotic discovery has sharply declined, while the emergence of drug-resistant pathogens has accelerated [21]. The global rise of AMR, combined with stagnation in the development of new antimicrobial classes, has raised widespread concern about a potential return to a pre-antibiotic era. Consequently, antibiotics are now increasingly referred to as an "endangered therapeutic resource" [5,24]. Treatment failures caused by multidrug-resistant (MDR), extensively drug-resistant (XDR), and even pan-drug-resistant (PDR) bacteria are no longer isolated clinical events but are becoming increasingly common [21]. Infections once easily treatable now often require the use of last-resort antibiotics such as colistin or carbapenems, which are more toxic, less accessible, and not always effective [25,26].

3.2. Drivers of AMR in Medicine and Animal Agriculture

While the misuse and overuse of antibiotics in human medicine remain the primary drivers of AMR, the role of antimicrobial use in animal agriculture is increasingly recognised as a major contributor to the emergence and dissemination of resistance [27,28]. In livestock and aquaculture systems, antibiotics are administered not only for therapeutic purposes but also for metaphylaxis, prophylaxis, and, in some countries, as growth promoters to improve production efficiency [29,30]. These practices exert selective pressure that facilitates the emergence of resistant bacterial populations along the food production continuum.

Antibiotic-resistant bacteria (ARB) and antimicrobial resistance genes (ARGs) have been isolated from a variety of food-producing animals and animal-derived products. Examples include methicillin-resistant *S. aureus* (MRSA) [31,32], fluoroquinolone-resistant *Campylobacter* spp. [33,34], and extended-spectrum β-lactamase (ESBL)-producing *Salmonella* spp., *E. coli*, and *Klebsiella* spp. [35,36]. Transmission of ARB and ARGs from animals to humans can occur through multiple routes: (a) indirect transmission via contaminated animal-derived products such as meat, milk, and eggs [37]; (b) direct contact with colonised animals or biological materials (e.g. faeces, blood, milk) [38]; (c) environmental pathways, including exposure to contaminated water, soil, or air in areas where animal waste is used or released [39]; (d) occupational exposure affecting farmers, veterinarians, slaughterhouse workers, and food handlers, potentially facilitating the spread of AMR into the general population [40].

In both human and veterinary medicine, the widespread and often parallel use of antimicrobial agents has contributed to the emergence and spread of resistant pathogens across sectors. While public health professionals emphasise inappropriate antibiotic prescribing and poor patient compliance as key drivers of AMR, representatives of the animal production sector highlight responsible veterinary use and point to the overuse of antibiotics in human medicine. These differing perspectives have slowed the adoption of joint regulatory solutions to combat AMR [27,41]. Nevertheless, there is growing consensus that the use of medically important antimicrobials in livestock production—particularly for prophylactic purposes and growth promotion—poses a significant challenge [41,42], especially given that over 73% of antimicrobials sold globally are used in food-producing animals [41]

3.3. Global Trends and One Health Challenges

Recent data from the World Organisation for Animal Health [43] provide a mixed picture. Globally, antimicrobial use in animals decreased by 5% between 2020 and 2022, from 102 mg/kg to 97 mg/kg of animal biomass. However, regional disparities are substantial: while Europe and Africa recorded reductions, the Middle East reported a 43% increase during the same period. This report is particularly significant as it covered 71% of global animal biomass and included data from 157 countries, 111 of which submitted detailed quantitative reports.

The EU stands out as one of the few regions to achieve sustained progress. According to the thirteenth ESVAC report on the sales of veterinary antimicrobials in 31 European countries [42], total sales of veterinary antimicrobials decreased by 53% between 2011 and 2022, reaching the lowest level since systematic monitoring began. This success is attributed to consistent implementation of policies, including the 2006 ban on antibiotic growth promoters and, from 2022, additional restrictions on prophylactic use [10,42]. Similar measures are being introduced or considered in other high-income countries, such as the United States (US). According to FDA data from 2023, the sale and distribution of medically important antimicrobials for animals in the US decreased by 2% compared with the previous year, representing a total reduction of 37% since 2015 [44,45].

In contrast, many low- and middle-income countries continue to face challenges. Van Boeckel et al. [46] reported that China remains the largest consumer of veterinary antimicrobials, both in absolute quantities and per unit of animal biomass. In 2013, consumption in China reached 318 mg per population correction unit (PCU), significantly exceeding averages in most other countries. Global consumption that year was estimated at 131,000 tons, with projections suggesting it could reach 200,000 tons by 2030 [46]. Nonetheless, China had already introduced restrictions on the use of last-resort antimicrobials for human infections—setting a precedent by banning substances still in use in European animal farming at the time.

Despite encouraging steps in certain regions, the global picture remains uneven. In many parts of the world—particularly where regulatory oversight is limited—antibiotics continue to be used in animal farming without meaningful restrictions. These disparities highlight the urgent need for a coordinated One Health approach that recognises the interconnectedness of human, animal, and environmental health. Reducing unnecessary antibiotic use, improving biosecurity measures, and promoting alternative approaches—such as probiotics, prebiotics, and synbiotics—are essential to safeguard the efficacy of antimicrobials and mitigate the global threat of resistance.

4. Probiotics, Prebiotics and Synbiotics for Combating Antimicrobial Resistance in the Food Chain

4.1. Probiotics for Combating AMR in the Food Chain

4.1.1. Definition, Diversity, and Health Effects

Probiotics are defined as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host” [47]. This definition, endorsed by both the Food and Agriculture

Organization (FAO) and the World Health Organization (WHO), represents the most widely accepted standard in scientific literature and regulatory frameworks [48]. The concept of probiotics is ancient, with fermented foods such as sour milk and fermented cereals likely consumed since the Neolithic era and nations across early civilizations relying on microbial fermentation for preservation and nutrition. A modern, human-health–focused understanding emerged in 1891, when German gynecologist Albert Döderlein described lactic acid–producing Lactobacilli in the vaginal microbiota and their protective role against pathogens [49].

The probiotic genera most commonly used in food and supplements include Lactobacillus (including its reclassified subgroups such as *Lacticaseibacillus* and *Lactiplantibacillus*), *Bifidobacterium*, *Heyndrickxia* (formerly *Bacillus*), and the yeast *Saccharomyces* [48]. Other microorganisms, such as *E. coli* (e.g., strain Nissle 1917), *Enterococcus*, and *Weissell*a spp., are also being explored for their probiotic potential. While not all strains currently have formal safety approval, selected ones—such as *Lacticaseibacillus rhamnosus* GG and *Lactiplantibacillus plantarum*—have demonstrated promising effects and are being evaluated for targeted clinical or food-related applications [50]. Probiotic strains exhibit substantial diversity in phenotypic traits, genomic architecture, and functional properties, influencing their effectiveness in specific contexts [51].

They are widely incorporated into fermented foods (e.g., yoghurt, kefir, sauerkraut, kimchi, and other dairy and plant-based products), dietary supplements, and therapeutic formulations [52]. Such applications position probiotics as a cornerstone of functional foods, combining microbial safety and extended shelf life with health-promoting benefits. By reducing the reliance on chemical preservatives in food systems and lowering the risk of foodborne infections, probiotic-based functional foods may also contribute indirectly to AMR mitigation [53]. Reported health effects include modulation of gut microbiota, enhancement of immune function, improvement of nutrient bioavailability, and potential roles in reducing cholesterol, oxidative stress, and inflammation, as well as in alleviating lactose intolerance and supporting gastrointestinal health [47,54]. In addition, probiotics have emerged as a safer and more effective alternative to antibiotics in controlling pathogenic microorganisms. However, unlike antibiotics, they promote health by enhancing the composition and function of the gut microbiota, reducing the risk of infections, and supporting overall well-being [47,55].

From a regulatory perspective, the safety of probiotic strains is assessed differently across regions. In the US, the Food and Drug Administration (FDA) applies the *Generally Recognized as Safe* (GRAS) concept, which refers to taxonomically well-defined microorganisms with a documented history of safe use in food. In Europe, the European Food Safety Authority (EFSA) employs the *Qualified Presumption of Safety* (QPS) approach, which similarly grants a generic safety status but at the level of defined microbial groups. Both frameworks aim to ensure that only strains without pathogenic potential and with proven safety records are used in foods and supplements. For instance, within the genus *Lactobacillus*—today comprising over 260 recognized species—EFSA has granted QPS status to 37 species following the reclassification of this genus [53,56,57]. An overview of lactic acid bacteria species currently holding QPS status, based on the latest EFSA update [58], is presented in Table 1.

Table 1. List of LAB species with QPS status [58].

Carnobacterium divergens	*Lactobacillus johnsonii*	*Ligilactobacillus* (formerly *Lactobacillus*) *animalis*
Companilactobacillus (formerly *Lactobacillus*) *alimentarius*	*Lactobacillus kefiranofaciens*	*Ligilactobacillus* (formerly *Lactobacillus*) *aviarius*

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Companilactobacillus (formerly *Lactobacillus*) *farciminis*	*Lactococcus lactis*	*Ligilactobacillus* (formerly *Lactobacillus*) *salivarius*
Fructilactobacillus (formerly *Lactobacillus*) *sanfranciscensis*	*Lapidilactobacillus* (formerly *Pediococcus*) *dextrinicus*	*Limosilactobacillus* (formerly *Lactobacillus*) *fermentum*
Lacticaseibacillus (formerly *Lactobacillus*) *casei*	*Latilactobacillus* (formerly *Lactobacillus*) *curvatus*	*Limosilactobacillus* (formerly *Lactobacillus*) *mucosae*
Lacticaseibacillus (formerly *Lactobacillus*) *paracasei*	*Latilactobacillus* (formerly *Lactobacillus*) *sakei*	*Limosilactobacillus* (formerly *Lactobacillus*) *panis*
Lacticaseibacillus (formerly *Lactobacillus*) *rhamnosus*	*Lentilactobacillus* (formerly *Lactobacillus*) *buchneri*	*Limosilactobacillus* (formerly *Lactobacillus*) *pontis*
Lactiplantibacillus (formerly *Lactobacillus*) *pentosus*	*Lentilactobacillus* (formerly *Lactobacillus*) *diolivorans*	*Limosilactobacillus* (formerly *Lactobacillus*) *reuteri*
Lactiplantibacillus (formerly *Lactobacillus*) *plantarum*	*Lentilactobacillus* (formerly *Lactobacillus*) *hilgardii*	*Loigolactobacillus* (formerly *Lactobacillus*) *coryniformis*
Lactobacillus acidophilus	*Lentilactobacillus* (formerly *Lactobacillus*) *kefiri*	*Oenococcus oeni*
Lactobacillus amylolyticus	*Lentilactobacillus* (formerly *Lactobacillus*) *parafarraginis*	*Pediococcus acidilactici*
Lactobacillus amylovorus	*Lentilactobacillus* (formerly *Lactobacillus*) *paraplantarum*	*Pediococcus parvulus*
Lactobacillus crispatus	*Leuconostoc citreum*	*Pediococcus pentosaceus*

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Lactobacillus delbrueckii	*Leuconostoc lactis*	*Secundilactobacillus* (formerly *Lactobacillus*) *collinoides*
Lactobacillus gallinarum	*Leuconostoc mesenteroides*	*Streptococcus thermophilus*
Lactobacillus gasseri	*Leuconostoc pseudomesenteroides*	
Lactobacillus helveticus	*Levilactobacillus* (formerly *Lactobacillus*) *brevis*	

While regulatory frameworks ensure the safety of probiotic strains, understanding their mechanisms of action is essential for optimising their application in food systems. Probiotics exert their beneficial effects through multiple mechanisms, including: (i) competitive exclusion of pathogenic microorganisms, (ii) secretion of antimicrobial compounds such as bacteriocins, hydrogen peroxide, and organic acids, (iii) reinforcement of the epithelial barrier, (iv) immunomodulation, and (v) inhibition of pathogen adhesion and invasion [52,59,60]. These mechanisms can broadly be classified as bactericidal actions, involving direct pathogen killing, or bacteriostatic actions, which suppress pathogen growth by competing for nutrients, adhesion sites, or altering environmental conditions such as pH [61].

Furthermore, probiotics enhance the physiological activity of gut microbiota by improving the bioavailability of short-chain fatty acids, peptides, and vitamins, and stimulating anti-inflammatory and immune responses [62]. Moreover, certain probiotic strains and their fermentates can interfere with quorum sensing systems, inhibit biofilm formation, and attenuate virulence factor expression in pathogenic bacteria—thereby strengthening their role in foodborne pathogen control [63–66]. Collectively, these mechanisms contribute to improved feed conversion rates, mitigation of food intolerances, and enhanced resilience of livestock against environmental and pathogenic stressors, aligning probiotic use with sustainable farming practices and reduced reliance on antibiotics [67]. Table 2 provides representative examples of probiotic strains and their fermentates, highlighting their antimicrobial activity against major foodborne pathogens and the corresponding mechanisms of action.

Table 2. Antimicrobial effects of probiotics.

Probiotic strains	**Target foodborne pathogens**	**Reported effects**	**Mechanisms of action**	**References**
L. rhamnosus GG	*C. jejuni*	Reduced adhesion and invasion	Competitive exclusion, immunomodulation	[68]
L. plantarum strains	*Salmonella* spp., *E. coli*, *C. jejuni*	Growth inhibition, reduced adhesion	Organic acids, bacteriocins, competition for nutrients	[69,70]
Bifidobacterium longum	*S. enterica*, *E. coli*	Reduced colonisation	SCFA production, epithelial barrier enhancement	[71,72]

Saccharomyces boulardii	*C. difficile*, *E. coli*, *Salmonella* spp.	Protection from diarhoea; modulation of inflammation	Toxin neutralisation, anti-inflammatory activity	[73,74]
L. acidophilus	*L. monocytogenes*, *E. coli*	In vitro and in vivo pathogen reduction	Bacteriocin production, inhibition of quorum sensing	[50,75]
Heyndrickxia coagulans (formerly *B. coagulans*)	*E. coli*, *Salmonella* spp.	Growth inhibition; gut barrier enhancement	Spore formation, SCFA production	[76]
Fermented *Woodfordia fruticosa* (with *L. plantarum* and *L. rhamnosus*)	*L. monocytogenes*, *Vibrio parahaemolyticus*	Reduced epithelial adhesion; immunostimulation	Interference with adhesion; ↑ IL-6 production (immunomodulation)	[77]
L. fermentum and *L. salivarius*	*S. Typhi*	Reduced virulence gene expression	Quorum sensing interfeence, inhibition of biofilm formation	[77]

4.1.2. Sustainable Strategies for Combating AMR

Within the framework of sustainable food production, probiotics are most commonly applied as natural and effective alternatives to antibiotics in livestock (particularly cattle and swine), poultry, and aquaculture. Their targeted use has been linked to improved animal health, enhanced growth performance, and a reduced incidence of gastrointestinal infections, thereby lowering the need for prophylactic or therapeutic antimicrobial treatments [44,78]. In addition, by reducing pathogen carriage and shedding in animals, probiotics lower the risk of contamination during slaughter and processing, thereby directly contributing to food safety and public health.

Beyond their recognised health benefits, certain probiotic strains may contribute to AMR mitigation indirectly, through the production of bioactive metabolites—such as organic acids, short-chain fatty acids, hydrogen peroxide, bacteriocins, and antioxidants—that inhibit or eliminate pathogenic microorganisms [53,79–82]. These metabolites, particularly bacteriocins, help maintain mucosal barrier integrity and promote "colonisation resistance" by preventing pathogen establishment in the gut [83]. Additional effects include stimulating mucus production, inducing antimicrobial peptide secretion, and modulating host immune responses, all of which strengthen the host's resistance to infection [84,85].

Probiotics combat pathogens primarily through competitive exclusion, antimicrobial metabolite production, and modulation of host immunity [20]. For example, *Lactobacillus* spp. exert competitive exclusion by occupying adhesion sites on the intestinal mucosa, thereby limiting colonisation by pathogens such as *E. coli* and *Salmonella* spp. They also produce lactic acid, bacteriocins, and hydrogen peroxide, which inhibit pathogen growth and reduce the need for a strong host immune response to infection. By lowering the incidence and severity of infections, probiotics not only improve growth and performance but also contribute to reducing reliance on antibiotics, thereby supporting AMR mitigation [50,67]. Postbiotics—non-viable microbial products such as bacteriocins, biosurfactants, cell wall fragments, and organic acids—are also gaining attention in food preservation, providing antimicrobial protection without the drawbacks of chemical preservatives or antibiotics [60,86–89]. Their incorporation into food systems extends shelf life, improves microbial

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safety, and aligns with One Health objectives by reducing selective pressure for resistance development.

Beyond pathogen suppression, probiotics enhance nutrient utilisation, improve gut integrity, reduce oxidative stress, and modulate inflammatory responses [50,90]. They also influence growth-related hormonal pathways, such as insulin-like growth factor 1 (IGF-1) signalling, thereby promoting resilience and growth performance [91,92]. This multifunctionality—combining pathogen control, immune modulation, and enhanced productivity—distinguishes probiotics from antibiotics, which mainly act through direct pathogen elimination. Moreover, consumer demand for "natural" and "antibiotic-free" products underlines the socio-economic relevance of probiotic applications in food systems.

Field studies highlight sector-specific benefits of probiotics. In poultry, targeted supplementation with *L. plantarum* and *B. subtilis* has been shown to lower *Salmonella* colonisation rates and improve feed conversion efficiency. In swine, *E. faecium* NCIMB 11181 improved gut microbiota composition and reduced faecal pathogenic bacterial loads, while in cattle, daily feeding of *L. acidophilus* NP51 at 10^9 colony-forming units (CFU) per head for 126 days reduced *E. coli* O157:H7 shedding by 37% [93–95]. These results highlight the importance of selecting probiotic strains based on host compatibility, environmental factors, and defined functional objectives.

In aquaculture, probiotics derived from bacterial, yeast, and algal sources have been successfully applied since the mid-1980s, delivering benefits such as modulation of gut microbiota, production of antimicrobial compounds (e.g., bacteriocins and organic acids), enhancement of immune responses, stress reduction, and improvement of water quality [96–98]. These effects directly contribute to AMR mitigation by reducing pathogen loads in aquatic environments, decreasing the need for antibiotic treatments, and limiting the dissemination of ARGs through water systems. Specific examples include *B. subtilis* improving growth performance and lowering ammonia levels in tilapia and shrimp [99], *P. acidilactici* reducing ammonia levels in shrimp ponds [100], and *E. faecium* excluding pathogenic bacteria in shrimp [101]. Yeast-based probiotics such as *S. cerevisiae* have stimulated immunity in tilapia [102], while more recent studies demonstrated that *Staphylococcus edaphicus* enhances immune parameters and survival in Kelabau fish following pathogen exposure [103], and recent reviews highlight the emerging probiotic potential of non-traditional genera, including *Staphylococcus* spp., in tilapia aquaculture [104].

From an environmental perspective, lowering antibiotic use minimises the release of antimicrobial residues and resistant bacteria into soil and aquatic ecosystems, supporting healthier microbial communities [105]. Advances such as microencapsulation have improved probiotic stability during storage and delivery, while combining probiotics with prebiotics in synbiotic formulations provides synergistic benefits for gut health and pathogen suppression [106]. A schematic overview is provided in Figure 1, highlighting the domains of probiotic application across food systems and their role in AMR mitigation.

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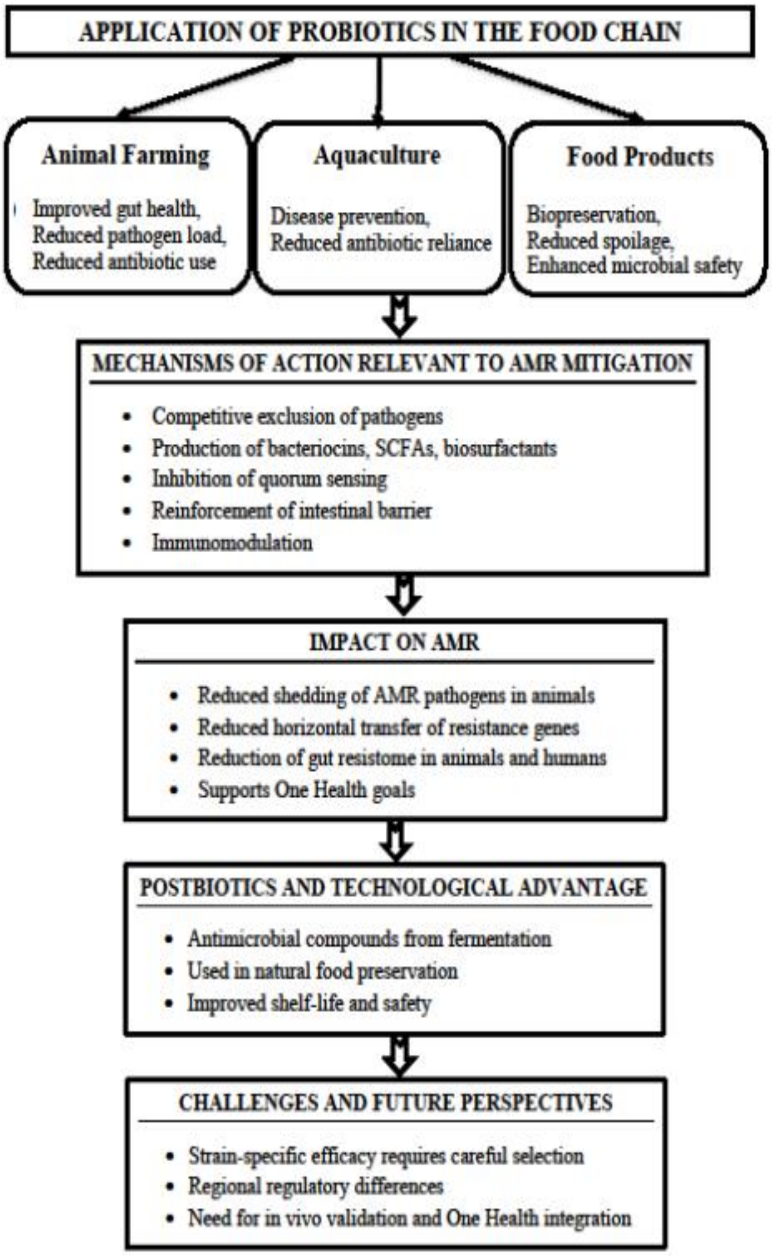

This schematic representation summarises the key domains of probiotic application—animal farming, aquaculture, and food products—and their associated benefits, such as improved gut health, reduced pathogen load, and decreased antibiotic use. Mechanisms of action include competitive exclusion of pathogens, production of antimicrobial compounds, and immunomodulatory effects, all contributing to the mitigation of antimicrobial resistance (AMR). The figure also highlights the role of postbiotics in food safety and preservation, and concludes with the main challenges and future perspectives for probiotic use within One Health frameworks.

Figure 1. Schematic overview of the role of probiotics as sustainable alternatives to antimicrobial agents in the food chain.

4.2. Prebiotics for Combating AMR in the Food Chain

4.2.1. Definition, Types, and Health Effects

The concept of prebiotics has undergone significant evolution since its introduction. Initially defined by Gibson and Roberfroid in 1995 as "a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health," the definition emphasized selective stimulation of beneficial gut bacteria, particularly bifidobacteria [107]. In 2017, the International Scientific Association for Probiotics and Prebiotics (ISAPP) revised this to: "substrates that are selectively utilized by host microorganisms conferring a health benefit" [13]. This broadened perspective now includes not only traditional carbohydrate-based prebiotics (e.g., inulin, fructooligosaccharides - FOS, galactooligosaccharides - GOS), but also emerging non-carbohydrate substrates such as phenolic compounds, human milk oligosaccharides, conjugated linoleic acid, and polyunsaturated fatty acids, expanding potential applications beyond the gut ecosystem [13,108].

More recently, the Global Prebiotic Association (GPA) proposed further refinement, removing the strict criterion of "selectivity" and defining a prebiotic as "a compound or ingredient that is utilized by the microbiota producing a health or performance benefit," while introducing the complementary term "prebiotic effect" to describe the specific outcomes arising from microbiota-mediated utilization [109]. Table 3 summarizes both well-established and emerging prebiotic candidates, highlighting their natural sources and representative evidence supporting their health-promoting effects.

Table 3. Established and emerging prebiotics, their natural sources, and reported health effects.

Class	Examples	Sources	Reported effects	References
Carbohydrate-based (traditional)	Inulin, GOS, FOS	Chicory root, onion, garlic, banana, legumes, human milk	Selective stimulation of bifidobacteria and lactobacilli; improved gut health; enhanced mineral absorption	[13,107]
Human milk oligosaccharides	2′-fucosyllactose, lacto-N-neotetraose	Human milk	Bifidogenic effect; immune modulation; pathogen protection	[110,111]
Non-carbohydrate substrates	Conjugated linoleic acid, polyunsaturated fatty acids	Dairy, meat, plant oils	Anti-inflammatory activity; immunomodulation; microbiota modulation	[108]
Plant-derived polyphenols	Flavonoids (catechins, anthocyanins), stibenes (resveratrol)	Berries, grapes, tea, cocoa	Fermentation by gut microbiota; antioxidant and anti-inflammatory effects; modulation of microbial composition	[108,112]
Marine- and fungal-derived polysaccharides	Fucoidan, laminarin, alginate oligosaccharides, chitosan oligosaccharides, β-glucans	Seaweeds, shellfish, yeast, mushrooms	Immunomodulation; antioxidant activity; stimulation of beneficial bacteria	[113–115]
Proteins and peptides	Bioactive peptides (milk- and soy-derived)	Dairy, legumes, cereals	Microbiota modulation; enhanced mineral	[116]

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			bioavailability; immune stimulation	
Minerals as prebiotic co-factors	Calcium, magnesium, zinc	Dairy products, cereals, vegetables	Synergistic effects with fibers; support for microbiota and host health	[109,117]
Carbohydrate-based oligosaccharides with antiviral activity	GOS, FOS, lactosucrose	Infant formula, human milk, synthetic oligosaccharides	GOS+FOS: reduced rotavirus shedding; improved stool consistency; alleviated gastroenteritis symptoms; improved immune responses. Lactosucrose: enhanced innate immune responses; increased survival against influenza A virus infection	[17,118,119]

Alongside these scientific developments, regulatory definitions remain fragmented across jurisdictions, reflecting the absence of a globally unified framework. The FAO's 2008 definition emphasized three pillars—component, health benefit, and microbiota modulation—while removing gastrointestinal selectivity and allowing for broader applications beyond the gut [120]. However, national and regional approaches continue to diverge: the US FDA does not provide an official definition, but regulates prebiotics within the general framework for food ingredients and dietary supplements [109]. Canada limits pre-cleared health claims to inulin [121], Australia and New Zealand permit self-substantiated general claims [122], Brazil requires pre-clearance and clinical evidence for nutrition or health claims linked to prebiotic ingredients, as established in Resolution in 2012 [123], and EFSA evaluates claims case by case without adopting a harmonized definition [109,117]. Such regulatory inconsistencies complicate the classification, marketing, and substantiation of prebiotic products, underscoring the need for internationally harmonized standards.

Beyond regulatory considerations, the recognized health effects of prebiotics have significantly expanded — from modulating gut microbiota to improving cardiometabolic and bone health, enhancing mineral absorption, supporting cognitive and mental well-being, and delivering antioxidant and neurovegetative benefits [108]. The expanded definition acknowledges prebiotics as diverse substrates that support host–microbiome interactions and systemic health, providing a basis for considering their role in sustainable strategies for AMR mitigation. Taken together, these scientific, regulatory, and clinical perspectives highlight the growing importance of prebiotics as versatile bioactive substrates. Their mechanisms of action will be further discussed in the following section on their role in AMR mitigation.

4.2.2. Mechanisms of Prebiotic Action in AMR Mitigation

Prebiotics exert health benefits, including the mitigation of antimicrobial resistance, through selective fermentation by beneficial gut microorganisms [124]. Fermentation by *Bifidobacterium* and *Lactobacillus* spp. produces short-chain fatty acids (SCFAs) such as acetate, propionate, butyrate, and lactate, which lower colonic pH, suppress pathogenic and resistant bacteria, and provide metabolic energy that reinforces epithelial cell function and intestinal barrier integrity [15,16]. This acidic environment enhances colonisation resistance by promoting beneficial microbes that outcompete pathogens for nutrients and adhesion sites. In addition, SCFAs and other metabolites modulate immunity by stimulating mucosal IgA responses, enhancing antimicrobial peptide secretion, and reducing inflammation, thereby strengthening host defence against resistant microorganisms [14,87]. Prebiotics also improve calcium and mineral absorption under acidic conditions, contributing to host physiology and further limiting the growth of opportunistic fungi and yeasts [16]. These effects reduce colonisation and persistence of major foodborne pathogens, including *Salmonella* spp., *E. coli* [125], *C. perfringens* and *Campylobacter* spp. [126], as well as viral agents such as rotavirus [118] and influenza A virus [119]. By limiting pathogen survival and transmission, prebiotics indirectly contribute to lowering the risk of AMR strains entering the food chain [17]. Despite these benefits, the rate and extent of microbial shifts in response to different prebiotic types and doses remain incompletely understood, and further clinical studies are required to exclude the risk of promoting pathogenic populations [127]. These limitations highlight the rationale for combining prebiotics with probiotics in synbiotic formulations, which will be discussed in the following section.

4.3. Synbiotics for Combating AMR in the Food Chain

4.3.1. Definition and Relevance in AMR Mitigation

The concept of synbiotics originates from the Greek words syn ("together") and biotic ("life"), reflecting their dual nature. Gibson and Roberfroid first introduced the term in 1995, defining synbiotics as combinations of probiotics and prebiotics that enhance host health by improving the survival and implantation of beneficial microorganisms in the gastrointestinal tract, while simultaneously stimulating the growth or metabolic activity of indigenous beneficial bacteria [107]. To refine and unify the terminology, the ISAPP revisited the concept in 2019, establishing a definition of a synbiotic as "a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host" [19]. ISAPP also introduced a classification into complementary synbiotics, which aim to stimulate the growth of resident microbiota, and synergistic synbiotics, where the prebiotic is selectively metabolised by the co-administered probiotic strain, thereby amplifying its functional impact [19].

To date, numerous reviews and clinical studies have highlighted the role of synbiotics in infection control and antimicrobial stewardship. In practice, synbiotic formulations typically combine strains of *Lactobacillus*, *Bifidobacterium*, or *Streptococcus* with prebiotic substrates such as inulin, FOS, GOS, xylooligosaccharides (XOS), or lactulose [128,129]. Such combinations overcome limitations of probiotic viability during processing, storage, and gastrointestinal passage, while also enhancing fermentation efficiency and nutrient bioavailability [19,20].

Unlike probiotics and prebiotics, synbiotics currently lack a harmonized regulatory framework, and their evaluation is generally based on the safety and efficacy of individual components rather than the combined formulation. This regulatory gap complicates standardized assessment, but also highlights the need for clearer guidelines as synbiotics gain importance in clinical and food-related applications.

Clinical and experimental studies consistently demonstrate the health benefits of synbiotics. Evidence indicates their efficacy in eradicating *Helicobacter pylori* infections [130,131], as well as in preventing surgical site infections, reducing sepsis risk, and lowering the incidence of postoperative complications such as diarrhea, pneumonia, and urinary tract infections [132,133]. Furthermore, meta-analyses confirm their role in shortening hospitalization, decreasing the need for antimicrobial therapy, and improving overall recovery outcomes [30,134,135].

By combining probiotics and prebiotics, synbiotics exert multifaceted mechanisms of action that surpass the effects of their individual components. These include enhancing probiotic survival and implantation, promoting synergistic fermentation with increased SCFA production, strengthening immune responses, and suppressing resistant pathogens. Fermentation-derived metabolites such as SCFAs lower colonic pH, inhibit pathogen persistence, and modulate host immunity through mechanisms including enhanced IgA responses and toxin neutralization [14,19]. Table 4 summarises the principal mechanisms through which synbiotics exert health-promoting effects, with emphasis on their relevance to AMR mitigation.

Table 4. Mechanisms and health effects of synbiotics relevant to AMR mitigation.

Mechanism of Action	Effects	References
Enhanced probiotic survival and implantation	Improved viability and colonisation of *Lactobacillus* and *Bifidobacterium* during gastrointestinal transit	[136,137]
Synergistic fermentation of prebiotics by co-administered probiotics	Higher SCFA production (acetate, butyrate, propionate); reduced colonic pH; inhibition of pathogens	[19,128]
Immune modulation	Increased IgA secretion, enhanced antimicrobial peptide production, reduced systemic inflammation	[14,129]
Suppression of resistant pathogens	Reduced colonisation by *Salmonella* spp., *E. coli*, *C. perfringens*, *Campylobacter* spp.	[126,131]
Antiviral protection	Attenuated rotavirus gastroenteritis and influenza A infection in vivo	[118,119]
Reduction of clinical infections and antimicrobial use	Decreased incidence of surgical site infections, sepsis, diarrhea, pneumonia; shortened hospital stay and reduced antibiotic therapy	[132–134]

From an AMR perspective, synbiotics contribute by providing favourable conditions for probiotic strains to thrive, outcompeting resistant pathogens, supporting intestinal homeostasis, and modulating host immunity. Most importantly, by reducing infection incidence and the need for antibiotic therapy, synbiotics indirectly decrease selective pressure for the emergence and dissemination of resistant strains. Their combined effects are increasingly recognised in both experimental and clinical contexts. Table 5 compiles representative in vivo and clinical studies demonstrating the antimicrobial and clinical benefits of synbiotics, highlighting their effects against foodborne pathogens, viral infections, and complications linked to AMR. These interactions are summarised schematically in Figure 2.

Table 5. Synbiotics: Evidence of antimicrobial and clinical effects.

Synbiotic composition	Target pathogens / conditions	Effects	References
L. fermentum CECT5716 + GOS	Rotavirus, respiratory infections	Inhibition of rotavirus; fewer gastrointestinal infections in infants	[106,130]
B. lactis B94 + inulin	*Salmonella*, *Shigella*, *C. difficile*, adenovirus, *Campylobacter*	Reduced duration of diarrhea; protection against multiple enteric pathogens	[138]

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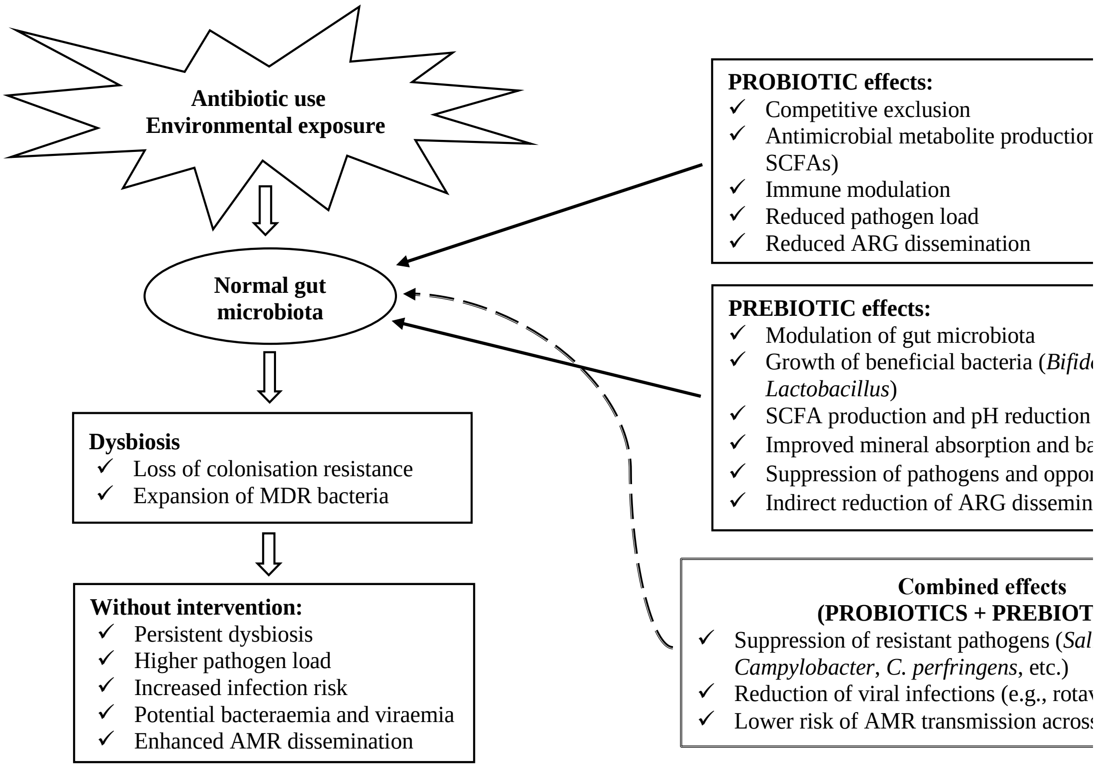
L. rhamnosus + inulin / FOS	Vancomycin-resistant *Enterococcus*	Significant inhibition of VRE growth	[20]
L. plantarum ATCC-202195 + FOS	Infant sepsis, respiratory infections	Reduced sepsis incidence and respiratory tract infections	[139]
Multi-strain mix (e.g., *L. acidophilus*, *L. rhamnosus*, *B. bifidum* + FOS)	Surgical site infections	Reduced postoperative infections and shortened antibiotic therapy	[133,134]



Probiotics and prebiotics, alone or as synbiotics, support gut health by modulating microbiota, competitively excluding pathogens, and producing antimicrobial metabolites. These effects reduce pathogen load and limit dissemination of resistance genes. In contrast, lack of intervention promotes dysbiosis, higher infection risk, and AMR spread.

Figure 2. Synergistic roles of probiotics and prebiotics in the mitigation of AMR.

5. Conclusions and Future Directions

The escalating global crisis of AMR calls for innovative, sustainable, and cross-sectoral strategies. Probiotics, prebiotics, and synbiotics collectively offer promising bio-based alternatives to conventional antimicrobials, with significant implications for food safety, public health, and One Health systems. Their complementary roles—probiotics through competitive exclusion, antimicrobial metabolite production, and immune modulation; prebiotics by selectively stimulating beneficial microbiota; and synbiotics by combining these mechanisms into synergistic formulations—position them as versatile tools for AMR mitigation across the food chain.

The benefits of probiotics, prebiotics, and synbiotics extend beyond individual hosts to broader ecosystems. In humans, they reduce infection risk and antibiotic reliance. In animals, including livestock, poultry, and aquaculture species, they improve growth, resilience, and disease resistance while lowering antimicrobial usage. In the environment, reduced antibiotic application decreases selective pressure for resistant bacteria and limits the release of antimicrobial residues. Thus, these interventions align with One Health objectives by simultaneously protecting human, animal, and environmental health within an integrated framework. Integration of probiotics and prebiotics into animal diets has demonstrated reduced shedding of resistant pathogens such as *Salmonella*, *Campylobacter*, and pathogenic *E. coli*, directly decreasing the risk of foodborne transmission. In aquaculture, supplementation improves water quality, reduces pathogen load, and minimises antimicrobial treatments. In fermented foods, probiotic and synbiotic incorporation enhances microbial safety, prolongs shelf life, and delivers functional health benefits to consumers. By reducing the need for synthetic preservatives and lowering the risk of foodborne infections, functional foods enriched with probiotics and synbiotics may also indirectly support AMR mitigation, bridging consumer demand for natural products with global public health priorities. These applications illustrate the feasibility of scaling biological interventions into diverse food systems, bridging laboratory discoveries with real-world applications.

Nevertheless, several challenges remain. Probiotic efficacy is highly strain-specific and influenced by host, environmental, and management factors. Survival during feed processing and consistent colonisation in different hosts remain limiting factors. Prebiotic responses are heterogeneous and depend on substrate type, microbiota composition, and dosage, with risks of unintended microbial shifts. Synbiotic formulations, although promising, require rigorous validation of strain–substrate compatibility to ensure reproducible outcomes. Regulatory requirements for safety and authorisation vary across regions, and the absence of harmonised international standards complicates their global adoption. Further in vivo studies are essential to confirm long-term benefits, ecological safety, and effects on AMR transmission.

Advances in genomics, systems biology, and synthetic biology offer opportunities to overcome current limitations. These tools enable the identification of robust strains with tailored functionalities, improved survival, and precise host–microbe interactions. Multi-omics approaches combined with computational modelling can unravel microbiota dynamics, predict prebiotic utilisation, and optimise synbiotic design. Encapsulation technologies and next-generation delivery systems will further enhance stability and efficacy. At the policy level, integrating probiotics, prebiotics, and synbiotics into AMR control strategies demands harmonised regulatory frameworks and sustained investment in translational research. Interdisciplinary collaboration among microbiologists, food technologists, veterinarians, clinicians, and policymakers will be critical to achieving their full potential. In conclusion, probiotics, prebiotics, and synbiotics hold substantial promise as sustainable alternatives to antimicrobials across the food chain. By reducing pathogen load, enhancing host resilience, and lowering antimicrobial dependence, they contribute directly to AMR mitigation and reinforce One Health strategies, while simultaneously supporting global food safety. To fully harness their potential, future efforts must focus on standardisation, validation, and innovation—transforming scientific insights into practical, safe, and globally accessible interventions.

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