

Mannan-Rich Fractions in Poultry Nutrition: A Sustainable and Defensive Strategy Against Antimicrobial Resistance

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Abstract

*Antimicrobial resistance (AMR) has evolved to be a significant global threat, menacing worldwide health and food security. Its proliferation in poultry farming has spurred the search for sustainable, non-antibiotic alternatives. One promising alternative is Mannan-Rich Fractions (MRFs), which are derived from *Saccharomyces cerevisiae*. These bioactive compounds not only support poultry health but also aid in suppressing pathogenic bacteria without contributing to resistance. This review brings together current studies highlighting how MRFs exert heterogeneous actions, including competitive exclusion of pathogens, encouraging beneficial gut microbes, immunomodulation, and metabolic disruption in resistant bacteria. Research indicates that MRFs effectively lower the intestinal loads of *Escherichia coli*, *Salmonella enterica*, and *Campylobacter jejuni*, etc., while improving feed conversion ratio, villus height, and nutrient absorption. At the molecular level, MRFs influence many key enzymes involved in glycolysis and the TCA cycle, and induce reactive oxygen species (ROS) production in resistant *E. Coli*, thereby resensitizing them to antibiotics. When used alongside fermented feed ingredients or probiotics, MRFs further enhance immune gene expression, growth rate, and gut barrier integrity. Together, these findings position MRFs as a powerful, natural solution for minimizing antibiotic usage in poultry farming. The integration of MRFs into poultry diets presents a promising alternative to conventional antibiotic use, aligning with global efforts to contain AMR in poultry.*

Keyword: Antimicrobial resistance, yeast mannan fraction, poultry, reactive oxygen species, gut health

INTRODUCTION

AMR has emerged as one of the most pressing challenges of the 21st century, frequently described as the “silent pandemic” due to its gradual yet devastating impact on global health and food systems [1]. According to recent projections, AMR could cause up to 10 million deaths annually by 2050, surpassing cancer as a leading cause of mortality if unchecked [1–3]. Beyond the clinical burden, AMR also carries significant economic consequences, with potential global losses estimated at USD 100 trillion over the next three decades due to reduced productivity, higher healthcare costs, and food insecurity [1].

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The poultry sector plays a pivotal role in this crisis. Poultry meat represents one of the fastest-growing and most widely consumed sources of animal protein worldwide, with intensive production systems accounting for most of the supply [2]. To meet escalating consumer demand, poultry farming has historically relied heavily on antimicrobials not only for therapeutic purposes but also as growth promoters and prophylactics [4, 5]. This widespread and often indiscriminate usage has inadvertently increased the emergence of MDR pathogens such as *Campylobacter jejuni*, *Escherichia coli*, *Salmonella enterica*, and

methicillin-resistant *Staphylococcus aureus* (MRSA) [1, 6]. These pathogens colonize poultry flocks asymptomatically, yet they can enter the food chain and cause serious zoonotic infections in humans, thereby establishing poultry farming as a critical node in the global AMR network [7–11].

Despite increasing awareness and regulatory restrictions on AGPs, AMR continues to persist in poultry production systems. Contributing factors include high stocking densities, poor biosecurity in certain regions, and the persistence of AMR genes in environmental reservoirs such as soil, litter, and wastewater [9, 11]. The complexity of these transmission pathways makes it clear that simply reducing antibiotic usage is insufficient; alternative strategies must be developed to safeguard poultry health, maintain productivity, and reduce resistance dissemination [1].

In response, research has shifted toward identifying natural, non-antibiotic feed additives capable of sustaining growth performance while mitigating pathogen colonization. Among these, MRFs derived from the outer cell wall of *Saccharomyces cerevisiae* have emerged as a particularly promising intervention [6]. These bioactive polysaccharides exert multifactorial benefits: they mimic host cell receptors to competitively exclude pathogens [5], modulate the gut microbiota toward beneficial taxa [6], improve gut morphology and nutrient absorption [7], and enhance immune function through immunomodulatory pathways [8]. Similarly, recent mechanistic insights also suggest that MRFs may induce metabolic disruptions in resistant bacteria, such as increased ROS production and altered NAD⁺/NADH ratios, that resensitize them to conventional antibiotics [12–19].

Positioning MRFs within the broader One Health framework, their applications also offer benefits beyond the poultry farm. By lowering antibiotic dependence in livestock, MRFs contribute to reducing the environmental resistome and minimizing spillover risks to humans [1]. Moreover, their alignment with consumer demand for antibiotic-free poultry products and sustainable farming practices misleads the practical relevance to both global markets and public health agendas [3].

This review systematically evaluates the potential of MRFs as a natural solution to combat AMR in poultry farming. It examines their mechanisms of action, effects on pathogen load, and contributions to gut health and immunity, while also exploring novel insights into metabolic disruption, resistome modulation, and sustainable valorization strategies. Through this comprehensive lens, MRFs are positioned not only as feed additives but as strategic tools for advancing antimicrobial efficacy in poultry production systems.

ANTIMICROBIAL RESISTANCE IN POULTRY FARMING

Antibiotics have been extensively used in poultry farming as therapeutic, metaphylactic, or prophylactic agents in order to treat or prevent infections [2]. Since 1951, they have been employed as AGPs, administered at subtherapeutic doses to alter the intestinal microbiota of animals and to enhance their growth. However, the excessive and indiscriminate use of antibiotics, especially misuse and overuse, has led to the development of microbial reservoirs that harbor AMR genes in livestock, including poultry [1]. This dependence on AGPs has facilitated the rise and widespread dissemination of MDR organisms, including *Campylobacter* spp., *Staphylococcus aureus*, *Escherichia coli*, *Salmonella* spp., etc. These pathogenic microbes have been recognized as major contributors to AMR and zoonotic threats. Table 1 provides a thorough summary of these prominent pathogens, outlining the diseases they cause in poultry and humans, their mode of transmission, and antimicrobial resistance profiles. This comprehensive summary emphasizes the vital connections between poultry health, pathogen transmission, and the escalating problem of AMR.

The evolution of AMR in bacteria can occur through two main pathways: intrinsic (natural) resistance and acquired resistance. Intrinsic resistance results from preexisting phenotypes. During this process, bacteria accumulate genetic errors within preexisting genes on plasmids or chromosomes, which are then inherited by subsequent generations through VGT. On the other hand, acquired resistance develops either through genetic mutation or by incorporating resistance-encoding DNA fragments such as integrons, transposons, phages, or plasmids by HGT mechanisms [9].

Following their emergence, resistant bacteria and their associated genes disseminate throughout the poultry production system via multiple transmission routes. Direct spread occurs through bird-to-bird contact, especially in intensive farming setups where high stocking densities increase the probability of microbial exchange [1, 10]. Indirect transmission occurs through tainted water sources, feed, and farm equipment, as well as through ecological niches such as wastewater, soil, and litter. These environmental reservoirs accumulate antibiotic residues, active metabolites, and resistant strains via urine and fecal excretion [11, 12]. These residues have the potential to persist in the environment, which could further promote selection and spread of resistance genes [1]. Moreover, instead of using transmission modes, one can also use some calibrative indexes to measure certain parameters required for microbial exchange, such as:

- Normalized Horizontal Gene Transfer (HGT) Index ratio of plasmid-borne AMR genes to total microbial load (resistome mobility potential).
- Resistome Risk Index (RRI) integrates abundance of clinically relevant AMR genes with their mobility (plasmid/integron-linked vs. Chromosomal).
- Network Co-occurrence Index graph-based metrics (degree centrality, modularity) to quantify pathogen–commensal AMR gene sharing networks.
- ARG-Sharing Potential (ASP) proportion of AMR genes co-localized with mobile genetic elements (MGEs) across microbial communities.

Further, these antimicrobial resistance genes can transmit from poultry to humans, thereby increasing the global burden of AMR. Farmers, veterinary doctors, food handlers, and slaughterhouse workers are at highest risk due to their direct contact with poultry or their biological fluids and excreta, including saliva, blood, urine, and feces [1]. Furthermore, resistant microbes can also enter indirectly into the human ecosystem through the handling and intake of adulterated poultry products [11].

The sustained spread of AMR in poultry farming not only endangers animal health but also amplifies the threat. If the current trend persists, then it is projected that by 2050, the deaths caused by resistant bacterial infections will surpass the mortality rate caused by cancer [13]. Such an alarming trajectory underscores the need for urgent measures aimed at curbing the emergence and dissemination of AMR. Current efforts are focused on alternatives that could enhance antibiotic efficacy and reduce their overall use, thereby promoting animal health naturally. (Figure 1)

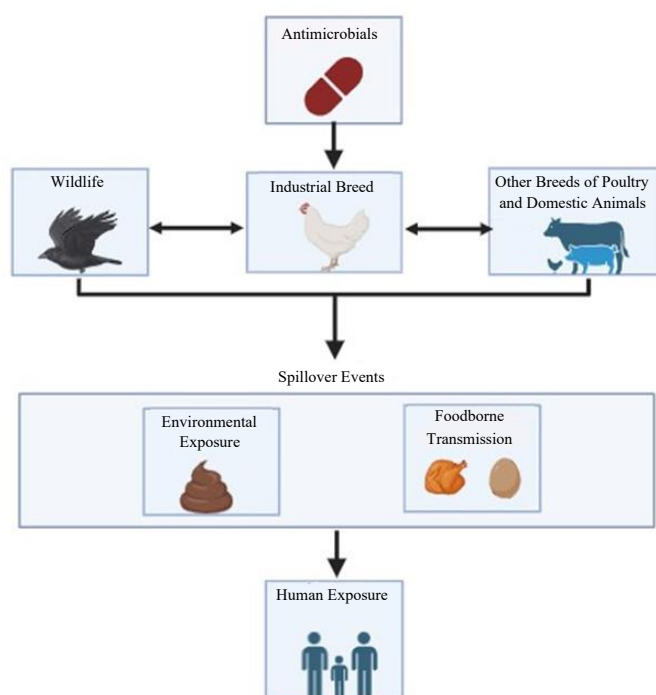


Figure 1. AMR spillover and transmission pathway in poultry systems.

MANNAN-RICH FRACTION: A PROMISING PREBIOTIC

MRFs represent a refined preparation of mannose-containing oligosaccharides (MOS), primarily isolated from the cell wall of *Saccharomyces cerevisiae* (Table 1). Commercial yeast cell wall products typically contain polysaccharides (30–60%), proteins (15–30%), lipids (5–20%), and trace chitin [3]. From this complex matrix, MRFs are purified through sequential fractionation, resulting in highly active mannooligosaccharides enriched with β -glucan residues [16]. Structurally, MRFs are characterized by α -(1, 2) and α -(1, 3) branched mannose chains attached to an α -(1, 6)-linked backbone, giving them their unique binding and immunomodulatory properties [17].

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Table 1. Key poultry pathogens: zoonotic risks, antimicrobial resistance profiles, and transmission dynamics.

Pathogen	Disease in poultry	Transmission	Disease in humans	AMR profile	Reference
<i>Enterococcus</i> spp. (<i>E. cecorum</i> , <i>E. faecalis</i>)	Free thoracic vertebra (FTV) osteomyelitis, septicemia, omphalitis, yolk sacculitis	Vertical & horizontal transfer	Endocarditis, UTIs; vancomycin resistant infection	Streptomycin, doxycycline, tetracycline, ciprofloxacin, enrofloxacin, vancomycin (variable)	[1].
<i>Escherichia coli</i> ; Avian pathogenic <i>E. coli</i> (APEC),	Colibacillosis, septicemia, coligranuloma respiratory infections,	Oral, vertical, inhalation	UTIs, neonatal meningitis, sepsis	Aminoglycosides, penicillin cephalosporins, fluoroquinolones	[1, 14].
<i>Extraintestinal E. coli</i> (ExPEC)	peritonitis, orchitis				
<i>Campylobacter</i> spp. (<i>C. jejuni</i> , <i>C. coli</i>)	Intestinal colonization, usually asymptomatic in poultry	Wild animals, pests or humans	Campylobacteriosis (Acute bacterial diarrhea, gastroenteritis)	Nalidixic acid, ampicillin, ciprofloxacin, erythromycin, gentamicin, tetracycline, cephalaxin	[1, 10, 14].
<i>Salmonella enterica</i>	Fowl typhoid, Pullorum disease, Avian paratyphoid	Vertical and Horizontal routes	Foodborne enteric disease (fever, diarrhea), septicemia	Nalidixic acid, amoxicillin, fluoroquinolones, macrolides, 3rd-generation cephalosporins	[1, 14, 15].
Methicillin resistant <i>Staphylococcus aureus</i> (MRSA)	Arthritis, synovitis, chondronecrosis, subdermal abscesses, gangrenous dermatitis, septicemia	Direct contact, meat contamination	Food poisoning, skin infections	Ampicillin, Amoxicillin, penicillin, cefoxitin, amoxicillin-clavulanic acid, tetracycline, kanamycin.	[1, 14].

When incorporated into poultry feed, MRFs enhance growth, improve feed conversion efficiency, and strengthen intestinal health [7, 18]. Their multifunctionality distinguishes them from conventional antibiotics, as they exert indirect effects such as receptor mimicry, prebiotic modulation of gut microbiota, and stimulation of host immune responses [4, 6]. The rising global demand for antibiotic-free production systems underscores the relevance of MRFs as natural, safe, and sustainable feed supplements.

Distinctiveness of MRFs Compared to Conventional MOS

Although MOS derived from yeast cell walls have been widely studied, MRFs represent a more targeted and potent fraction. Unlike crude MOS, which contain heterogeneous sugar residues and β -

glucan contamination, MRFs are selectively enriched to maximize biological activity [16]. This refinement allows stronger pathogen binding affinity, particularly against fimbrial adhesins of *Salmonella* and *E. Coli* [5]. Studies comparing MOS and MRF supplementation indicate that MRFs achieve more consistent outcomes in reducing pathogen load and improving intestinal morphology, likely due to their higher mannose density and standardized structure [6, 18].

From a nutritional perspective, MRFs also exert indirect benefits by lowering gut inflammation and oxidative stress, thereby improving the availability of nutrients for growth. For instance, supplementation trials in broilers demonstrated higher villus height, reduced crypt depth, and improved VH: CD ratio under MRF diets compared to standard MOS, correlating with better feed efficiency and body weight gain [7]. This distinction positions MRFs as the next-generation prebiotic supplement in antibiotic-free poultry farming.

Practical Applications and Industry Relevance

The application of MRFs extends beyond pathogen exclusion. In poultry exposed to heat stress or high stocking density, MRF supplementation has been reported to enhance intestinal tight junction expression, improve goblet cell density, and strengthen mucin secretion [7, 8]. These effects contribute to maintaining gut integrity under stressful conditions, where conventional antibiotics often fail to provide protection.

Moreover, MRFs have been shown to synergize with probiotics and fermented feed ingredients, resulting in stronger immunological and metabolic benefits [20–25]. By fostering an environment conducive to beneficial microbes such as *Lactobacillus* and *Bifidobacterium*, MRFs indirectly elevate the production of SCFAs, particularly butyrate, which supports epithelial cell proliferation and immune defense [21].

From an industry standpoint, the growing ban on AGPs in several regions has fueled the demand for natural feed additives. MRFs, being residue-free and consumer-safe, directly align with these regulatory shifts and consumer preferences for antibiotic-free poultry products [3, 6]. Additionally, their compatibility with other functional additives, such as organic acids and phytobiotics, makes them highly versatile for integrated feeding strategies aimed at sustainable production (Table 2).

Table 2. Symbiotic use of MRF/MOS with probiotics or fermented co-additives in poultry.

Probiotic / Co additive	MRF/ MOS dose	Probiotic dose (CFU)	Model & duration	Stressor/Context	Key outcomes (directional)	Novelty / notes	Ref.
<i>Lactobacillus plantarum</i> (in ovo or feed)	0.1–0.2%	10 ⁶ –10 ⁸ per g feed (or per chick in ovo)	Broiler, 35–42 d	Routine grow-out	↑ Performance (BWG), ↓ FCR; improved gut morphology (VH↑, VH:CD↑); favorable microbiota shift	Demonstrates true synbiotic effect with delivery flexibility (in ovo vs. feed)	[25]
<i>Bifidobacterium bifidum</i> + MOS	0.2%	10 ⁶ per g feed	Broiler, 35–42 d	Routine grow-out	↑ Growth vs. control and antibiotic (BMD) group; ↓ coliforms/ <i>E. coli</i> / <i>C. perfringens</i> ; ↑ <i>Lactobacillus</i> / <i>Bifidobacterium</i>	Head-to-head with antibiotic control strengthens antibiotic-sparing claim	[5]
Fermented soybean meal (FSBM) + MOS (dietary mix)	As per diet (FSBM inclusion with MOS)	– (fermented co-additive)	Broiler, full grow-out (~42 d)	Routine grow-out	Highest BWG among diets; ↓ harmful ileal/cecal pathogens; ↑ LAB	Cost-effective prebiotic + fermented feed combo for field use	[22]

<i>Multicomponent yeast cell wall (MOS + βglucan)[†]</i>	200 ppm	–	Broiler, 35–42 d	Routine grow-out	↑ Final BWG (~13%); ↓ FCR (~12%); ↑ beneficial microbes; ↓ pathogen adhesion	Useful baseline to benchmark added probiotic benefit	[3]
<i>MOS + Selenium nanoparticles (SeNPs)</i>	As per study	–	Broiler, 6 wks	High stocking density (HSD) stress	Weekly BW and FCR improved (wk 5–6); VH↑, VH:CD↑; goblet cells↑	Stress-mitigation angle; barrier function under HSD	[7]
<i>MRF (three formulations) ± background microbiota</i>	Productspecific	–	Broiler, 35 d	Fieldrelevant microbiota	Campylobacter caecal load ↓ by ~1.2–1.5 log ₁₀ (qPCR)	Public-health aligned endpoint; supports synbiotic stacking trials	[10]

MECHANISM OF ACTION OF MANNAN-RICH FRACTION (MRFs)

MRFs employ a variety of mechanisms by which they help to mitigate AMR. They work by both directly enhancing the efficacy of antibiotics against resistant microbes and indirectly reducing the reliance on antibiotics through improved animal health and a more resilient gut environment.

Metabolic Reprogramming and Induction of Reactive Oxygen Species (ROS) in Resistant Microorganisms

Proteomic analysis unveils that MRF supplementation influences translational regulation of key metabolic pathways within antibiotic-resistant *E. Coli* (Figure 2). It ameliorates protein expression of key enzymes involved in the TCA cycle, such as isocitrate dehydrogenase (ICD), aerobic respiration control protein (ARCA), citrate synthase (GLTA), and aconitate hydratase B (ACNB). This metabolic shift elevates cellular metabolism and triggers an increase in ROS production, which in turn enhances bacterial sensitivity to antibiotics [4, 19].

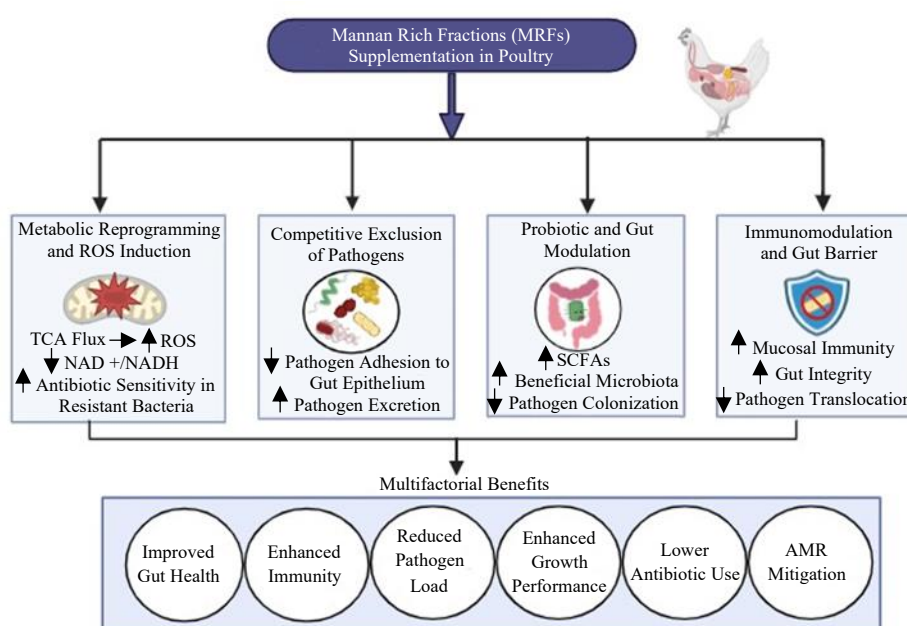


Figure 2. Mechanistic illustration of MRFs action in poultry.

Furthermore, by rapidly converting NAD⁺ to NADH and reducing the NAD⁺/NADH ratio, MRF elevates the overall concentration of NAD(H⁺). This cofactor modulation impacts bacterial physiology

and antibiotic susceptibility by promoting hydroxyl radical (OH) production through NADH-driven TCA cycle activity. Furthermore, MRF treatment upregulates the expression of oxidative phosphorylation proteins, primarily ATP synthase subunits γ , b , and β , suggesting an overactivation of the electron transport chain [4].

When used alongside bactericidal antibiotics like ampicillin, MRF significantly enhances the generation of intracellular ROS in *E. Coli* [4, 20]. These high levels of ROS likely overwhelm the resistant organism's protective and defense systems, evidenced by elevated expression of peroxide-scavenging enzyme alkyl hydroperoxide reductase (AHPF). Consequently, resistant *E. Coli* strains undergo oxidative damage, which may help them to restore their susceptibility to antibiotics [4]. (Figure 3)

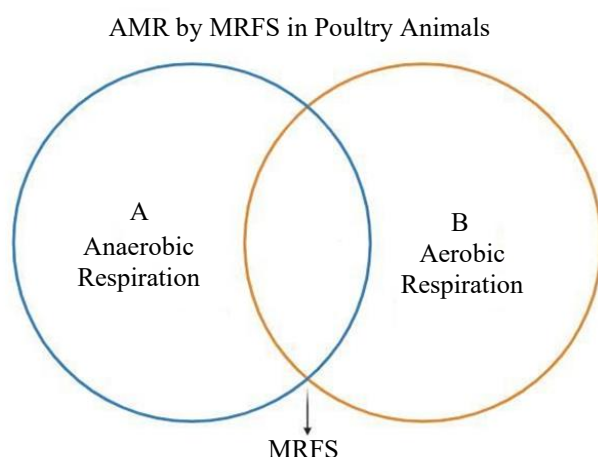


Figure 3. Venn diagram showing AMR between aerobic and anaerobic pathways in terms of MRFs.

Competitive Exclusion of Pathogens

MRFs dramatically reduce the count of pathogenic microbes in the gastrointestinal tract. They function by directly binding to pathogenic bacteria like *Campylobacter*, *Salmonella*, and *E. Coli*, etc., that possess type 1 fimbriae with mannose-sensitive lectins, restricting their attachment to the intestinal epithelial surface and facilitating their excretion [5].

Prebiotic Effect

MRF promotes the proliferation of beneficial gut microbes, such as *Bifidobacterium* and *Lactobacillus*, etc. [6]. These beneficial bacteria synthesize short-chain fatty acids, such as butyric acid, which serve as an energy source for intestinal epithelial cells and support their proliferation [21]. This prebiotic action fosters a more stable and competitive gut microbiota, making it harder for pathogenic microbes to establish dominance.

Immunomodulation and Gut Barrier Enhancement

MRFs have been found to markedly alter intestinal morphology in poultry, contributing to better gut health and nutrient absorption. Their supplementation showed increased villus height and reduced crypt depth in the jejunum and duodenum, thereby increasing the villus height to crypt depth (VH: CD) ratio, a key marker of enhanced nutrient digestibility and absorption efficiency [7]. This morphological enhancement is accompanied by improved enzymatic activity, including elevated levels of pancreatic and intestinal proteases and amylase, which collectively optimize nutrient utilization [7, 22].

At the molecular level, MRFs upregulate the expression of tight junction-related genes, which facilitate integrity and mucin synthesis. For instance, in heat-stressed broilers, MOS precursor of MRF supplementation upregulates the expression of genes such as occludin, mucin-2, zonula occludens-1, and claudin-3, critical for gut barrier integrity. They collectively reinforce the intestinal epithelium and reduce permeability that could otherwise facilitate pathogens to infiltrate and spread antimicrobial resistance [8].

MRFs also boost immune responses by increasing goblet cell density and lymphocyte infiltration within the intestinal mucosa, thereby strengthening the gut's primary defense mechanisms [7]. Mannan components derived from yeast function as pathogen-associated molecular patterns (PAMPs), which bind to pattern recognition receptors (PRRs) present on gut-associated immune cells. This interaction activates macrophages and modulates immune responses [24].

Additionally, MRF supplementation supports systemic humoral immunity. Research on laying hens reveals that MOS significantly elevates serum concentrations of immunoglobulins such as IgY (IgG) and IgM, while also enhancing antibody responses to vaccines, such as those against avian influenza [24]. These immunomodulatory effects highlight the potential of MRFs to improve poultry health, thereby minimizing reliance on antibiotics. (Table 3)

Table 3. MRF effect and mechanism against key poultry pathogens.

Pathogens	MRF mechanism	MRF effect	References
<i>Escherichia coli</i>	Induces oxidative stress, ↓ virulence genes, metabolic dysfunction (↑ TCA flux, ↓ NAD ⁺ /NADH ratio)	↑ antibiotic sensitivity; ↓ colonization, ↓ virulence expression	[4].
<i>Campylobacter spp.</i> (<i>C. jejuni</i> , <i>C. coli</i>)	Competitive exclusion, modulation of gut microbiota	↓ Cecal colonization by >1.5 log ₁₀ CFU/g	[10].
<i>Salmonella spp.</i>	Competitive exclusion via mannose receptor mimicry, ↑ mucosal immunity	Reduced gut colonization and shedding, ↑ immune function	[3].
<i>Clostridium perfringens</i>	Prebiotic effect; enrichment of beneficial microbes, immune stimulation	↓ <i>C. perfringens</i> load; improved gut microbiota profile, enhanced mucosal immunity	[22].
<i>Enterococcus spp.</i>	Immune modulation (↑ goblet cells, ↑ lymphocytes), enhanced gut morphology	Improved gut integrity, better resistance to enteric pathogens, potential reduction of AMR gene dissemination	[7].

EXPERIMENTAL INSIGHTS INTO THE BENEFITS OF MRF IN POULTRY PRODUCTION

Mannan-rich fractions (MRFs) have been widely researched for their multifaceted benefits in poultry farming. These functional feed additives, often overlapping with mannan oligosaccharide (MOS), offer several advantages ranging from growth enhancement and improved intestinal morphology to inhibiting pathogens and mitigating antibiotic resistance (AMR). The following subsection summarizes key findings from various studies assessing the effects of MRFs, either alone or in combination with prebiotics and fermented feed ingredients.

Enhanced Growth Performance and Feed Efficiency

Multiple studies have reported that supplementing the poultry diet with MRF can significantly improve nutrient uptake, body weight gain (BWG), and feed conversion ratio (FCR). A study involving 480 day-old male broiler chickens showed that combining mannan oligosaccharide (MOS) with fermented soybean meal (FSBM) has a stronger effect than either one alone. Compared to other dietary meals, this mixture resulted in the highest BWG for the total grow-out period [22]. Another study investigating yeast cell wall as a source of MOS and β -glucan (β -G) in broiler chickens demonstrated that dietary addition of 200 ppm MOS + β -G improved final live BWG by about 13% and FCR by approximately 12% in comparison to the control group [3]. Malini et al. (2024) also reported enhanced performance parameters in broiler chickens when MOS was administered with *Lactobacillus plantarum* both *in ovo* or through feed, indicating a beneficial synbiotic interaction [25]. Supplementation of 0.2% MOS along with *Bifidobacterium bifidum* (BFD) at a concentration of 10⁶ CFU per gram of feed exhibited a significantly better growth rate and efficiency in broilers compared to the control and antibiotic (bacitracin methylene disalicylate, BMD)-treated groups [5]. Furthermore, under high stocking density (HSD) stress, cosupplementation of MOS with selenium nanoparticles (SeNPs)

significantly boosted weekly body weight and FCR in broilers during the fifth and sixth weeks, effectively neutralizing the adverse effect of HSD stress on growth [7].

Enhanced Intestinal Health and Morphology

MRFs play a vital role in shaping gut microbiota. According to Soumeh et al. (2020), supplementing poultry diets with FSBM, MOS, and their combination (MIX) effectively suppressed harmful pathogens such as *Clostridium perfringens* and coliforms in the ileum and cecum, while simultaneously increasing the population of beneficial lactic acid bacteria (LAB) [22]. Similarly, another study showed that MOS and β -glucan (β -G) supplementation can enhance gut health by promoting beneficial microorganisms like *Lactobacilli* and yeast, preventing the adhesion of pathogens such as *Salmonella* and *E. Coli*, and enhancing gut morphology by increasing villi length, which further improves intestinal integrity and nutrient absorption capacity [3]. Likewise, research examining MOS and *Bifidobacterium bifidum* (BFD) supplementation observed a significant reduction of gut coliforms, *Escherichia coli*, *Clostridium perfringens*, and total plate count, while elevating *Lactobacillus* and *Bifidobacterium* counts [5]. These probiotic bacteria produce short-chain fatty acids (SCFAs), which serve as energy sources for intestinal cells and support gut health [22]. Moreover, at high stocking density, amalgamation of MOS and SeNPs led to an increase in duodenal villus height (VH), an improved VH: crypt depth (CD) ratio, and a higher total goblet cell (TGC) density in both the jejunum and ileum. These changes suggest stronger barrier protection and enhance the local immune response [7].

Pathogen Reduction and AMR Mitigation

A study examining dietary supplementation of three distinct yeast MRFs in 492 broiler chickens found that MRF-based supplements effectively reduced natural *Campylobacter* species colonization in the broiler cecum. After 35 days, quantitative polymerase chain reaction (qPCR) analysis showed statistically significant reductions, with supplement 2 achieving a 1.5-log reduction and supplement 3 showing a 1.2-log reduction in *Campylobacter* colonization levels. These findings are clinically significant since quantitative risk assessments indicate that a 2-log reduction in *Campylobacter* counts potentially decreases the incidence of human campylobacteriosis by up to 30-fold [10].

Although predominantly an in vitro study, research on MRF demonstrates its ability to influence antibiotic susceptibility in resistant microorganisms. The introduction of MRF to the growth medium of antibiotic-resistant *Escherichia coli* cultures resulted in a nearly 40% increase in reactive oxygen species (ROS) level compared to the control group. This effect became even more pronounced when MRF was combined with a bactericidal antibiotic, resulting in an approximate 60% increase in ROS production. Such observations suggest a synergistic or adjuvant interaction. This combination also resulted in a 73% reduction in bacterial growth, which was more effective than using antibiotics alone. These findings suggest that MRF may potentiate the efficacy of bactericidal antibiotics by inducing metabolic changes that enhance ROS production in resistant bacteria, thereby potentially rendering them more susceptible to antibiotics. This approach offers a promising strategy to improve antibiotic efficacy and potentially reduce reliance on antibiotic usage [4].

Case Study 1 Commercial Layers: MRFs Reshape the Cecal Resistome Under Farm Conditions

- **Objective:** To investigate how Mannan-Rich Fractions (MRFs) reshape the cecal resistome in commercial laying hens under real farm conditions.
- **Methods:** A 2024 field-based study included 120 layer hens across two farms. Birds were supplemented with dietary MRFs for 8 weeks. Cecal samples were analyzed using shotgun metagenomics to evaluate antimicrobial resistance gene (ARG) profiles.
- **Findings:** MRF-supplemented hens showed a significant reduction in ARG abundance, particularly tetracycline and sulfonamide resistance genes. Shifts in microbiome composition favored beneficial genera such as *Lactobacillus*, which contributed to a more balanced cecal ecology.
- **Implications:** This case highlights the potential of MRFs as a sustainable strategy to limit ARG dissemination in commercial poultry operations without compromising productivity.

Case Study 2 Layer Pullets: Yeast Cell Wall Lowers *Salmonella* Enteritidis in the Ceca and Ovaries

- **Objective:** To evaluate the efficacy of yeast cell wall-derived MRFs in reducing *Salmonella* Enteritidis colonization in layer pullets.
- **Methods:** A 2024 controlled trial was conducted on 200 layer pullets. MRFs were incorporated into feed from day 1 to 10 weeks. Microbiological assays and qPCR were performed on cecal and ovarian tissues to detect *Salmonella*.
- **Findings:** Birds receiving MRF supplementation exhibited a 65% reduction in cecal *Salmonella* loads and a 70% decline in ovarian colonization compared to the control group. Enhanced mucosal immunity and higher secretory IgA levels were also observed.
- **Implications:** Yeast-derived MRFs represent a natural alternative to antibiotics for controlling enteric pathogens in poultry, thereby reducing zoonotic transmission risks.

ADVANTAGES OF MRFS OVER CONVENTIONAL ANTIBIOTICS

MRFs offer a compelling substitute for conventional antibiotics in poultry farming, addressing AMR while simultaneously enhancing overall poultry health. Unlike antibiotics, which function by directly killing or inhibiting pathogens, often at the expense of gut microbial balance, MRFs work in a more balanced way. They employ a multifactorial approach that mitigates disease risks while preserving gut homeostasis.

The key advantages of MRFs include:

- **No Contribution to Antimicrobial Resistance:** MRFs, unlike antibiotics, do not exert selective pressure on bacterial populations. They work by imitating host epithelial receptors, preventing pathogens from attaching to the gut lining [6]. This approach helps to prevent infection without promoting horizontal gene transfer, a major factor in AMR spread [5].
- **Promotion of Gut Health and Immune Function;** Unlike antibiotics, which often disrupt beneficial gut microbes, MRFs actively promote the growth of *Lactobacillus*, *Bifidobacterium*, and other probiotics [5]. Simultaneously, they enhance gut morphology and upregulate immune markers, including goblet cell density and tight junction proteins, leading to enhanced mucosal defense [7].
- **Residue-Free and Consumer Safe:** Unlike conventional antibiotics, which may leave detectable drug residues in poultry meat or eggs, MRFs are natural, non-antibiotic compounds that do not accumulate in tissues [5]. This makes them a desirable alternative for poultry production, aligning with consumer demands for drug-free meat products [3].
- **Environmentally and Economically Sustainable:** MRFs align with the goal of sustainable and organic poultry farming by supporting higher nutrient digestibility and utilization, improving feed efficiency, and reducing pathogen shedding into the environment. Their compatibility with other natural additives like probiotics and fermented ingredients enables a holistic approach to flock health. Although the initial cost of MRFs may be higher than antibiotics, the long-term benefits in terms of animal welfare, improved performance, and product quality offer a compelling return on investment [22–26].

Comparison with Other Non-Antibiotic Alternatives

In poultry production, several non-antibiotic strategies have been explored to improve gut health and productivity, including organic acids, probiotics, prebiotics, phytochemicals (plant extracts), and bacteriophages [27–30].

- Organic acids such as formic, lactic, and butyric acids lower gut pH, which inhibits pathogens like *Salmonella*. However, their effectiveness can vary depending on feed composition and pH stability.
- Probiotics like *Lactobacillus* and *Bifidobacterium* help fortify gut microbial balance and immunity, though their colonization efficiency and stability in feed processing present challenges.
- Prebiotics, including FOS and MOS, selectively support beneficial microbes; MOS also serves as a decoy receptor for pathogens like *E. Coli* and *Salmonella*, reducing their attachment to the gut.
- Phytochemicals (herbal extracts and essential oils) exhibit antimicrobial and antioxidant properties and can enhance feed palatability and digestion, yet their efficacy may vary due to composition inconsistencies.

- Bacteriophages are highly target-specific and can lyse pathogenic bacteria effectively, but their narrow activity spectrum and regulatory constraints limit broad application.

In contrast, MRFs, derived from yeast cell walls, offer multiple advantages: they modulate the microbiome, block pathogen adhesion, enhance gut integrity, and can reduce pathogen prevalence.

Meta-analyses show that MRF supplementation improves broiler growth, feed conversion ratio (FCR), and survival rates, performing on par with antibiotic growth promoters. By combining microbiome support, immune benefits, and pathogen exclusion without the drawbacks of colonization or specificity issues, MRFs stand out as a versatile and effective natural intervention in antibiotic-free poultry production [31–35].

MRFS AND RESISTOME MODULATION: A GENOMIC PERSPECTIVE

The role of MRFs in shaping not only microbial populations but also the resistome of the poultry gut represents an emerging research frontier. The resistome encompasses all antimicrobial resistance (AMR) genes within the microbiota, many of which can be mobilized via plasmids, transposons, or bacteriophages, and subsequently disseminated through HGT [36]. Intensive poultry farming environments are known hotspots for resistome amplification, given the continuous exposure of gut microbiota to antimicrobial residues and stressors [9].

Suppression of Horizontal Gene Transfer (HGT)

Recent in vitro findings suggest that dietary MRF supplementation can reduce conjugative transfer of resistance plasmids in *E. Coli* and *Salmonella* by altering bacterial adhesion and quorum sensing dynamics [37]. By binding to fimbrial adhesins and interfering with cell-to-cell contact, MRFs may indirectly reduce the physical interactions required for plasmid conjugation. Moreover, MRF-induced metabolic reprogramming, particularly the elevation of ROS, can impose physiological stress that reduces bacterial competence for HGT [19]. These mechanisms highlight the possibility that MRFs function not only as pathogen suppressors but also as modulators of gene transfer within the gut ecosystem.

Insights from Metagenomic Approaches

Advances in shotgun metagenomics and resistome sequencing now allow precise monitoring of AMR gene abundance in poultry microbiomes [38]. Integrating these tools with MRF supplementation trials could reveal whether MRFs shift microbial community structure toward reduced prevalence of key resistance determinants, such as extended-spectrum β -lactamase (ESBL) genes or tetracycline resistance cassettes. Preliminary animal studies indicate that MRF supplementation decreases the abundance of multidrug efflux pump genes while promoting genes linked to SCFA synthesis [39]. Such resistome-level shifts may explain, at least in part, the observed re-sensitization of resistant *E. Coli* strains to antibiotics.

By targeting both the phenotypic level (pathogen exclusion, immune modulation) and the genotypic level (resistome suppression, reduced HGT), MRFs emerge as a uniquely positioned feed additive within antibiotic stewardship frameworks. Incorporating resistome analysis into poultry nutrition studies would provide stronger mechanistic evidence and accelerate regulatory acceptance of MRFs as a functional alternative to antimicrobials.

CHALLENGES AND LIMITATIONS

Biological Variability and Scientific Uncertainty

The response of poultry to MRF supplementation is not uniform. Outcomes are influenced by bird genetics, age, and husbandry conditions, with stronger benefits often observed in early growth stages when gut microbiota is still developing [28]. Differences among broiler breeds and production environments also suggest a genetic – environment interaction in MRF responsiveness [29].

Scientific findings are also mixed. Some trials report notable improvements in weight gain, feed conversion ratio, and pathogen suppression, while others show minimal or inconsistent effects. Many of

these studies are short-term or laboratory-based, raising concerns about how well results translate to large-scale commercial production. Additionally, under conditions of low pathogen load, MRF supplementation may have limited benefit, or even alter microbial balance in ways that are not always desirable [29].

Production, Economic, and Regulatory Barriers

Another challenge lies in the production and formulation of MRFs. Different extraction techniques – e.g., autolysis, enzymatic hydrolysis – produce variable oligosaccharide profiles, making it difficult to standardize formulations. Variability in mannoooligosaccharide chain length, β -glucan content, and batch-to-batch composition complicates dosage determination and feed integration [28].

Economically, MRFs remain more costly than antibiotics, which limits adoption by large producers. While their long-term benefits include improved poultry health and reduced antimicrobial resistance, the lack of immediate cost savings often discourages investment [29]. From a regulatory perspective, although MRFs are generally recognized as safe, approval processes differ across regions. The absence of harmonized guidelines, coupled with slow regulatory clearances, delays commercialization and global adoption. Addressing these regulatory inconsistencies and reducing production costs will be crucial to encourage broader use in poultry systems.

CIRCULAR BIOECONOMY AND SUSTAINABLE VALORIZATION OF MRFs

The integration of MRFs into poultry farming not only offers biological efficacy but also provides a unique opportunity to advance the goals of the circular bioeconomy. In recent years, the livestock industry has increasingly recognized that feed interventions must align with sustainability principles, particularly in the context of reducing agro-industrial waste and enhancing value recovery from underutilized biomass [31].

Valorization of Industrial Byproducts

One of the most promising sources of MRFs is the spent yeast biomass generated in large volumes by breweries, wineries, baking industries, and bioethanol plants. Traditionally, this biomass has been discarded as waste or used as low-value animal feed. However, modern biorefinery concepts allow the targeted extraction of functional compounds such as MRFs, β -glucans, and proteins from yeast cell walls [32]. By implementing enzymatic hydrolysis or autolysis-based extraction methods, mannan-oligosaccharides with high bioactivity can be produced at relatively low cost [33]. Importantly, coupling MRF recovery with the extraction of other co-products creates a multistream utilization strategy, enhancing overall process profitability and minimizing waste.

Economic and Environmental Benefits

The economic feasibility of MRF supplementation remains a barrier to widespread adoption, particularly in low- and middle-income poultry-producing countries. Valorization of industrial byproducts offers a pathway to reduce production costs and make MRF supplementation more accessible to small and medium-sized poultry producers [34]. From an environmental perspective, reusing yeast biomass prevents its disposal into landfills or wastewater, which can otherwise contribute to environmental pollution. Thus, MRF production contributes to reduced greenhouse gas emissions, supports responsible resource utilization, and aligns with Sustainable Development Goal 12: Responsible Consumption and Production [35].

Synergy with One Health and Policy Frameworks

Adopting circular bioeconomy strategies in MRF production also strengthens the One Health paradigm, which emphasizes the interconnectedness of human, animal, and environmental health. By lowering the cost of non-antibiotic feed interventions, valorization strategies can accelerate the transition away from antibiotic dependency in poultry systems, indirectly reducing the risk of AMR spillover to humans [31]. Furthermore, the integration of circular economy principles resonates with international policy frameworks such as the European Union's "Farm to Fork" strategy and India's push toward bio-based economies, making MRFs strategically relevant beyond poultry nutrition [32].

Future Innovations in Sustainable MRF Production

Emerging research suggests that advanced bioprocessing techniques, such as membrane ultrafiltration, green solvents, and microbial fermentation, can further improve yield and consistency of MRFs derived from industrial biomass [33]. Additionally, the encapsulation of valorized MRFs in biopolymeric carriers could enhance their stability during feed processing and storage, addressing one of the current limitations of direct supplementation [34]. When integrated into large-scale poultry production systems, these innovations will create a closed-loop model where industrial byproducts are recycled into high-value poultry feed additives, reducing environmental footprint while boosting poultry health.

FUTURE DIRECTIONS

To fully exploit the benefits of MRFs in mitigating AMR in poultry, both translational techniques and mechanistic understanding must be evolved. Future research should aim to elucidate the precise molecular processes by which MRFs influence host immunity, gut microbiota, and the resistome. The integration of multi-omics techniques – such as proteomics, metagenomics, and metabolomics – could offer comprehensive insights into how MRFs modify dynamics of microbial communities, improve mucosal immunity, and suppress resistance gene proliferation [26, 18].

Prioritizing the optimization of MRF types, dosage, and administration methods is essential. Discrepancies in efficacy across different studies may be attributable to variation in yeast strains used, extraction techniques, or level of polymerization. Standardizing MRF composition and identifying bioactive markers (e.g., mannose concentration or chain length) would help to ensure consistent results across poultry breeds, production phases, and environments [28, 7]. Furthermore, innovative feed formulations including encapsulation or slow-release of MRFs could improve gut-targeted delivery and functional stability.

To establish the real-world efficacy of MRFs in poultry farming, large-scale field trials on a commercial scale are essential. These investigations should examine long-term effects on growth, feed efficiency, and microbial ecology in both layers and broilers [21]. Next-generation MRF formulations hold significant potential, particularly when conjugated with targeted antimicrobial agents like bacteriocins or nanoparticles. Such hybrid formulations could suppress broad-spectrum pathogens and lower the risk of resistance development [29]. Additionally, integrating MRFs with other non-antibiotic interventions such as organic acids, probiotics, and phytochemicals may also yield synergistic effects on intestinal health and AMR mitigation [1, 25, 30].

Ultimately, well-defined regulatory guidelines and incentive-based policies are required. Together, these directions offer a roadmap for leveraging MRFs as a viable alternative in the global initiative to reduce antimicrobial usage in poultry farming.

CONCLUSION

Mannan-rich fractions (MRFs), derived from yeast cell walls, have demonstrated strong potential as a sustainable alternative to antibiotics in poultry farming. Their multifaceted biological roles – ranging from competitive exclusion of pathogens and modulation of beneficial microbiota to metabolic reprogramming of resistant bacteria – provide both direct and indirect means of tackling antimicrobial resistance (AMR). Unlike conventional antibiotics that impose selective pressure and accelerate resistance development, MRFs act in harmony with the gut ecosystem, improving intestinal integrity, nutrient absorption, and immune responses, while simultaneously weakening the persistence of resistant pathogens. This unique mode of action positions MRFs as a viable tool within the One Health framework, safeguarding animal welfare, human health, and environmental sustainability.

Importantly, evidence from field-based case studies has validated their applicability under commercial conditions. In one trial with commercial layer hens, dietary MRF supplementation for eight weeks led to a measurable reduction in antimicrobial resistance genes, particularly those conferring resistance to tetracyclines and sulfonamides. These hens also displayed beneficial shifts in gut

microbiota composition, favoring genera such as *Lactobacillus*, which enhanced overall intestinal resilience. Similarly, in a controlled study involving layer pullets, the inclusion of MRFs in feed resulted in a 65% reduction in cecal *Salmonella* Enteritidis loads and a 70% decrease in ovarian colonization. These effects were accompanied by heightened mucosal immunity and elevated secretory IgA levels, underscoring MRFs' role in reducing zoonotic risks and improving flock health without reliance on antibiotics. Together, these findings demonstrate not only the mechanistic promise of MRFs but also their real-world efficacy in reshaping the poultry resistome and curbing pathogen transmission.

Nonetheless, some challenges remain before MRFs can be universally adopted. Their efficacy may vary depending on bird genetics, age, and farm management practices, while production inconsistencies in molecular composition can influence outcomes. Economic considerations, including higher upfront costs compared to antibiotics, also present barriers to widespread adoption. However, when weighed against long-term benefits – enhanced growth, reduced disease burden, improved food safety, and decreased environmental contamination – the advantages of MRFs are compelling.

In summary, MRFs provide a scientifically validated, residue-free, and environmentally responsible approach to AMR mitigation in poultry production. Scaling up their integration into commercial feed strategies, supported by standardized formulations and policy incentives, could substantially reduce dependence on antibiotics and contribute to global efforts to control antimicrobial resistance.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

1	AMR	Antimicrobial Resistance.
2	MRF	Mannan-Rich Fraction.
3	ROS	Reactive Oxygen Species.
4	MDR	Multi – Drug Resistant.
5	MOS	Mannan Oligosaccharide.
6	AGP's	Antimicrobial Growth Promoters.
7	HGT	Horizontal Gene Transfer.
8	VGT	Vertical Gene Transfer.
9	SCFA	Short Chain Fatty Acid.
10	TCA	Tricarboxylic Acid Cycle.