Revolutionizing Livestock Management: Probiotics As Immunomodulators For Health And Productivity

Misbah Ullah[1*], Faraz Ahmad Khan[2], Muhammad Uzair Khan[3], Syed Nouman Shah[4], Mian Syed Riaz[5], Nisar Ahmed Solangi[6], Jahanzaib Khaliq[7], Samad Khan[8], Muhammad Samiuddin[9], Anees Ur Rahman[10], Moin Akhtar Vistro[11], Shahzad Ahmad[12], Abdul Kabir[13*]

[1*,2,3,4,5,6,7,10,11] Faculty of Animal Husbandry and Veterinary Sciences, Sindh Agriculture University, Tandojam, Pakistan
[8] Directorate General Livestock and Dairy Development Department Khyber Pakhtunkhwa
[9] College of Veterinary Sciences, Agriculture University Peshawar, Pakistan
[12]Department of Veterinary Microbiology, Faculty of Animal Husbandry and Veterinary Sciences, Sindh Agriculture University Tandojam

***Corresponding Author**: Misbahullah*, Abdul Kabir**
*Faculty of Animal Husbandry and Veterinary Sciences, Sindh Agriculture University, Tandojam, Pakistan
misbahqurashi3434@gmail.com[*], kabirvet32@gmail.com[**]

Abstract
The escalating challenge of antimicrobial resistance has necessitated the exploration of alternative strategies in livestock management. This review paper synthesizes current research on the multifaceted role of probiotics as a sustainable alternative to antibiotics, focusing on their immunomodulatory effects, competitive exclusion mechanisms and economic benefits within the livestock industry. Probiotics have been shown to bolster the natural immunity of animals providing a barrier against pathogenic bacteria and playing a crucial role in disease prevention. The administration of probiotics is associated with reduced incidences of common livestock ailments including gastrointestinal and respiratory diseases through mechanisms such as competitive exclusion and the production of antimicrobial substances. Furthermore, the economic implications of probiotic use in disease prevention are significant offering cost savings and improved productivity for livestock producers. The review underscores the need for continued research and development to fully realize the potential of probiotics in animal agriculture highlighting their role in sustainable farming practices and global food security. As the industry moves towards more natural approaches to disease management probiotics stand as a beacon of hope for a future where animal health is managed naturally and sustainably.

Keywords: Probiotics, Gut Microbiota, Immunomodulation, Animal Health, Productivity, Antimicrobial Resistance, Sustainable Agriculture, Feed Efficiency, Disease Prevention

1. Introduction

The spectre of antimicrobial resistance (AMR) looms large over the 21st century presenting a daunting challenge to global health and food security. The World Health Organization (WHO) has sounded the alarm declaring AMR as one of the top ten global public health threats humanity faces today. It is a crisis that spares no borders, affecting humans, animals and plants alike with an estimated 1.27 million deaths directly attributed to drug-resistant infections in 2019 alone [1]. The misuse and overuse of antimicrobials across various sectors are the primary culprits driving this phenomenon, leading to a situation where once-treatable infections are becoming lethal [1]. In the agricultural domain, particularly within livestock management, the repercussions of AMR are profound [2,3]. The reliance on antibiotics as growth promoters has been a double-edged sword improving animal health and productivity on one hand but also contributing to the rise of resistant strains of bacteria on the other [4,5,6]. The European Union's ban on antibiotic growth promoters in 2006 marked a significant policy shift, steering the industry towards alternative solutions that could sustainably enhance animal health without contributing to the AMR crisis [7,8]. Enter probiotics, the live microorganisms poised to revolutionize livestock management [9]. These 'friendly' bacteria have been identified as a viable alternative to antibiotics offering a way to maintain the delicate balance of the gut microbiota and fend off pathogenic infections [10,11]. The role of probiotics, prebiotics, and symbiotics in animal nutrition has gained increasing recognition for their ability to not only improve feed absorption and quality of meat, milk and eggs but also for their potential to act as immunomodulators agents capable of modulating the immune system to promote a state of balance and health [10,12]. The immunomodulatory properties of probiotics are particularly intriguing. These microorganisms engage in a complex interplay with the host's immune system, influencing both innate and adaptive immune responses. Through genomic and proteomic analyses, scientists have begun to unravel the mechanisms by which probiotics exert their effects [13,14,15]. They have been found to regulate mucosal immunity and produce bactericidal compounds that inhibit pathogenic microorganisms and even affect systemic immune responses [16]. This capacity to modulate the immune system holds great promise for the prevention and treatment of diseases potentially leading to improved health outcomes for livestock [16,17]. As we navigate the postantibiotic era, the exploration of probiotics as immunomodulators in livestock management is not merely a scientific endeavour but a necessary step towards ensuring global food security and public health. The potential of probiotics to serve as a sustainable alternative to antibiotics in the livestock industry is immense [18]. However, this potential comes with its own set of challenges and limitations. The current formulations of probiotics, the complexity of their regulation in the digestive tract and the need for consistent long-term effects are areas that require further research and development.

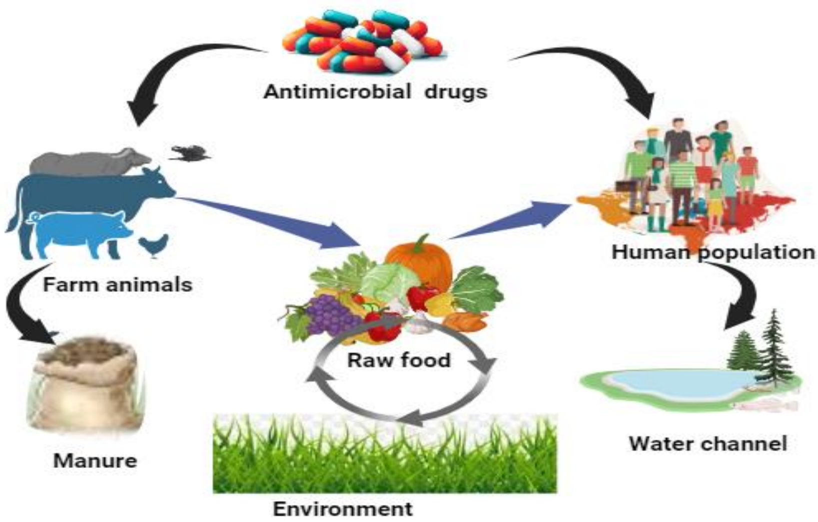

Figure 1 I The conceptual depiction of how antibiotic-resistant bacterial strains or genes move between various ecosystems

2. The Role of Probiotics in Livestock Health

Probiotics the live microorganisms introduced into the diets of livestock have become a beacon of hope in the quest for sustainable animal health and productivity [19]. These beneficial bacteria when administered in appropriate quantities forge a symbiotic relationship with their host outcompeting harmful pathogens for nutrients and attachment sites within the gut [20,21]. Their presence not only fortifies the intestinal barrier but also modulates the immune system and produces substances that directly inhibit the growth of potential invaders [22]. Probiotics have a particularly significant effect on the immune system; they strengthen adaptive immunological responses and innate defenses which results in stronger resistance to illness. This immunomodulatory action is evident in various case studies where probiotics have been linked to improved nutrient uptake, better feed conversion rates and higher-quality animal products [23]. In ruminants, probiotic supplementation has led to increased milk and meat production and improved overall feed efficiency, while in poultry, it has been associated with reduced instances of intestinal disorders and a decrease in pathogen shedding [24,25,26]. These results highlight the numerous advantages of probiotics, positioning them as a vital component in the future of sustainable livestock management. The use of probiotics in animal nutrition has been extensively evaluated to improve the balance of the beneficial gut microbiome and eliminate detrimental gut pathogens, resulting in a range of advantages such as enhanced functioning of the gastrointestinal tract, improved immunity at both the gut and systemic levels and better health status of both ruminants and non-ruminants [27,28,29]. The use of probiotics in ruminants has primarily focused on improving ruminal fermentation efficiencies, such as stabilization of pH-enhanced fibre digestion and reduction of methane production in the rumen, thereby impacting production performance [30,31,32]. Among the several species of probiotic organisms studied yeasts have been the most widely explored followed by bacterial probiotics in ruminant nutrition [33]. In non-ruminants, bacterial probiotics dominate over yeast in augmenting performance measures [34]. Furthermore, probiotics have also been shown to reduce incidences of intestinal diseases and faecal shedding of gut pathogens and improve the gut barrier functions and quality of meat and milk in food animals [35]. There are various species of probiotics, their beneficial effects, and modes of action in enhancing the efficiency of animal production [21,36]. The strategic incorporation of probiotics into livestock diets has the potential to yield a plethora of benefits that extend beyond the immediate health and productivity of the animals. By fostering a healthier gut microbiome, enhancing immune responses and improving the quality of animal-derived products, probiotics offer a promising avenue for advancing the sustainability and profitability of animal agriculture [22,37]. As the global population continues to grow and the demand for animal protein increases, the role of probiotics in supporting efficient and responsible livestock production becomes ever more critical [38]. The ongoing research and development in this field are likely to unveil even more profound insights into the capabilities of these microscopic allies, paving the way for a future where probiotics play a central role in the stewardship of animal health and the integrity of our food systems [39].

3. The Immunomodulatory Effect of Probiotics

Probiotics exert a profound influence on the immune system through the modulation of cytokine profiles [40]. These microorganisms are capable of stimulating the release of various cytokines, including interleukins (ILs), tumour necrosis factors (TNFs), interferons (IFNs), transforming growth factor (TGF) and chemokines from a range of immune cells such as lymphocytes, granulocytes, macrophages, mast cells, epithelial cells and dendritic cells (DCs) [41,42]. This cytokine release plays a pivotal role in regulating both the innate and adaptive branches of the immune system, contributing to a balanced immune response [43,44]. The cell wall components of probiotic strains like Bifidobacteria and Lactobacilli, particularly lipoteichoic acid, have been shown to stimulate nitric oxide synthase, leading to the production of nitric oxide (NO), a potent effector in the pathogen-infected cell death mechanism [45]. This NO production is facilitated by macrophages through the secretion of TNF-α, highlighting the direct interaction between probiotics and the host's immune cells [46]. Furthermore, probiotics have been reported to upregulate surface phagocytosis receptors, such as FcγRIII and toll-like receptor (TLR), enhancing the host's ability to recognize and respond to pathogenic threats [47]. The mechanisms underlying the immunomodulatory effects of probiotics are multifaceted. Probiotics interact with mucosal immune cells, influencing the secretion of cytokines and other mediators that orchestrate the immune response. This interaction is crucial for maintaining gut homeostasis and can have systemic effects beyond the gastrointestinal tract [48]. Probiotics and their bioactive compounds, such as bacteriocins and short-chain fatty acids (SCFAs), have been identified as key players in suppressing inflammation and restoring microbial diversity in pathological states [48]. The clinical implications of the immunomodulatory effects of probiotics are vast. By enhancing the immune response, probiotics may offer protective effects against a range of diseases, including those common in livestock. The potential of probiotics to serve as a sustainable alternative to antibiotics in animal nutrition is particularly promising, given the growing concerns over antibiotic resistance [46,49]. Continued research and development in this field are essential to fully understand the immunomodulatory potential of probiotics. Future studies should focus on identifying specific probiotic strains and their components that are most effective in modulating the immune system. Additionally, the development of novel probiotic formulations that can withstand the complexities of the digestive tract and deliver targeted immunomodulatory effects will be crucial for their successful application in animal nutrition [50]. The immunomodulatory effects of probiotics represent a significant advancement in the field of animal nutrition. Their ability to modulate the immune system and provide a sustainable alternative to antibiotics holds great promise for the livestock industry [49]. As research in this area continues to evolve, the full potential of probiotics in enhancing animal health and productivity will undoubtedly be realized [51].

Table 1. Immunomodulation Mechanisms of Probiotics

Mechanism	Probiotic	Reference
Immune effects: decreased serum-soluble CD4 (a T-cell marker) and increased TGF-β after	B. lactis Bb12 or L. rhamnosus GG	[52]
Effect on Th1 immunity (increased IFN-γ)	L. rhamnosus GG, Lactobacilli & Bifidobacteria	[53,54]
Immunoregulation (increased IL-10)	L. rhamnosus GG	[55]
Effects on intestinal permeability	L. rhamnosus GG	[56]
Alleviation of intestinal inflammation	L. rhamnosus GG	[57]
Colonization of the perturbed mucosal barrier	Various probiotics	[58]
Competitive exclusion and inhibition of pathogens	Lactobacilli Enterococcus & Bifidobacteria	[59,60,61]
Production of bioactive compounds	Various probiotics	[62]
Enhancement of anti-inflammatory cytokine production	Bacteroides spp & Lactobacilli	[40,39]
Recruitment of various immune cells	Various probiotics	[63]
Induction of immunoglobulin class switching towards secretory IgA	Various probiotics	[64,65]

4. Probiotics and Animal Productivity

The strategic incorporation of probiotics into animal diets has been a game-changer in the field of animal husbandry offering a sustainable alternative to antibiotics for enhancing growth performance and overall productivity [66]. The use of probiotics has been extensively documented to improve average daily gain (ADG) and feed efficiency across various species signifying a direct correlation between probiotic use and enhanced growth performance [67,68]. This improvement is largely attributed to the probiotics' ability to modulate the gut microbiota, optimizing nutrient absorption and metabolism [67,68]. Nutritional digestibility and feed conversion are pivotal factors in the economics of animal production. Probiotics have been shown to positively influence these parameters by promoting a balanced microbial ecosystem in the gut, which leads to more efficient nutrient absorption and utilization [25,26]. This is particularly beneficial in sustainable livestock management, where optimization of feed resources is essential due to the significant costs associated with animal feed [25,26]. Moreover, the role of probiotics extends to the enhancement of meat quality and milk yield. Studies have demonstrated that probiotics can improve the fatty acid profile of meat, potentially offering health benefits to consumers by reducing harmful cholesterol levels [62,63,68]. In the dairy sector, probiotics have been reported to increase milk yield and improve milk composition attributed to their ability to foster a healthy rumen environment, which in turn enhances volatile fatty acid production and nitrogen flow [68,69]. Additionally, probiotics can alter the microbial ecosystem in the gut, leading to an increase in nutrient synthesis and growth performance which ultimately contributes to better carcass weight and muscle production [68]. The evidence supporting the use of probiotics in animal nutrition is robust with studies indicating consistent benefits in terms of productivity and product quality. While the exact mechanisms through which probiotics exert their effects are still under investigation, the current body of research underscores their value as a tool for enhancing animal productivity [26,69,70]. Probiotics represent a promising intervention in animal nutrition, with the potential to significantly improve productivity and product quality. As the global demand for animal protein continues to rise, the role of probiotics in supporting efficient and responsible livestock production becomes increasingly important. Ongoing research and development in this field are expected to provide deeper insights into the capabilities of probiotics, paving the way for their widespread adoption in animal agriculture [71,72].

5. Probiotics as a Strategy for Disease Prevention

The deployment of probiotics in livestock management is increasingly recognized as a strategic measure to prevent common diseases. Probiotics serve as a line of defence, bolstering the animals' natural immunity and providing a barrier against pathogenic bacteria [73,74]. This section delves into the preventive role of probiotics their mechanism of competitive exclusion and the economic benefits derived from their use in disease prevention. Probiotics have been shown to play a crucial role in the prevention of diseases such as bovine mastitis, a common and costly ailment in dairy cattle [75,76]. By enhancing the immune response and creating an unfavourable environment for pathogens probiotics help maintain the health and welfare of livestock [75]. The administration of probiotics has been associated with a reduction in the incidence of gastrointestinal diseases, respiratory illnesses and other infections that commonly afflict livestock [77]. One of the key mechanisms by which probiotics protect against disease is through competitive exclusion. Probiotics compete with pathogenic bacteria for nutrients and attachment sites, effectively inhibiting their growth and colonization. This process is crucial in maintaining a balanced gut microbiota and preventing the onset of disease [35]. Additionally, probiotics can produce antimicrobial substances that directly target pathogens, further reducing the risk of infection [67,78]. The economic implications of using probiotics for disease prevention are significant. By reducing the incidence of disease, probiotics decrease the need for medical treatments and antibiotics, leading to cost savings for livestock producers [79]. Moreover, healthier animals translate into improved productivity and product quality, which can have a positive impact on the profitability of livestock operations. Studies have shown that the use of probiotics can lead to substantial cost reductions in healthcare and increased productivity through reduced absenteeism due to illness [80]. Probiotics offer a multifaceted approach to disease prevention in livestock. Their ability to enhance the immune system, competitively exclude pathogenic bacteria and provide economic benefits underscores their potential as a sustainable alternative to traditional antibiotics [81]. As research continues to uncover the full extent of their capabilities, probiotics are poised to become an integral component of disease management strategies in animal agriculture.

6. Challenges in Probiotic Application

6.1Viability and Stability of Probiotics

The success of probiotics in promoting health benefits significantly depends on their viability and stability from production to consumption. Viability ensures that probiotics retain their beneficial properties, while stability guarantees their survival under various environmental conditions [82]. Probiotic viability can be influenced by several factors during processing and storage. Temperature is a critical factor; probiotics must be kept within specific temperature ranges to remain active. For instance, lactic acid bacteria, commonly used in probiotics are sensitive to high temperatures which can denature their proteins and kill the cells [83]. pH levels also play a vital role; most probiotics require a mildly acidic environment to thrive making the acidity of the storage medium crucial for their survival. Additionally, exposure to oxygen can be detrimental to anaerobic probiotics leading to oxidative stress and cell death [82]. To overcome these challenges various techniques have been developed. Microencapsulation is one such method that provides a protective barrier around probiotic cells shielding them from adverse conditions [82]. This technique not only improves the stability of probiotics but also enhances their delivery to the desired site of action. Co-culturing with prebiotics is another approach that offers a synergistic effect as prebiotics serve as a food source for probiotics promoting their growth and activity [83]. Research has demonstrated successful methods for maintaining probiotic viability and stability. A study by Champagne et al. (2005) showed that microencapsulation significantly increased the survival rate of probiotics during storage and gastrointestinal transit. Another study by Dinkçi et al. (2019) found that incorporating prebiotics into probiotic formulations enhanced the overall stability and viability of the probiotic cultures. By addressing the factors that affect probiotic survival and employing techniques to enhance stability the full potential of probiotics can be harnessed leading to improved health outcomes. The antegrade peristaltic movements, as part of the migrating motor complex, ensure a relatively short passage time through the small intestine, leaving limited time for probiotics to replicate and exert their effects [84].

6.2 Dosage Determination in Probiotic Application

Determining the optimal dosage of probiotics is a multifaceted challenge due to the vast diversity of microbial strains and their unique interactions with the host's microbiome. Each strain possesses distinct properties and health benefits necessitating a tailored approach to dosage [85]. The complexity is further compounded by the dynamic nature of the microbiome which can alter the probiotic's efficacy and required dosage [86]. The interaction between probiotics and the host's microbiome is a critical factor in dosage determination. Probiotics must navigate the existing microbial ecosystem competing for resources and space while exerting their beneficial effects [87]. This interaction is not static; it varies from one individual to another influenced by diet, genetics and overall health making a one-size-fits-all dosage impractical [88]. Personalized medicine has emerged as a promising approach to address these challenges. By considering individual host factors such as age, weight and health status personalized medicine aims to tailor probiotic dosages for maximum benefit [89]. This approach requires a deep understanding of the host-probiotic relationship and the development of precise biomarkers to guide dosage decisions [90]. Current research methodologies are focused on establishing effective dosages for different livestock species and conditions. Studies often involve controlled trials that assess the impact of various dosages on health outcomes, such as immune response, growth rates, and disease resistance [91]. These trials are instrumental in developing dosage guidelines that can be applied in diverse agricultural settings [92]. the determination of probiotic dosages is a complex process that must account for microbial diversity, host-microbiome interactions, and individual host factors. Personalized medicine offers a path forward, but it requires robust research and innovative methodologies to establish effective dosages across different livestock species and conditions.

6.3 Therapeutic Development of Probiotics

The regulatory landscape for probiotics presents unique challenges for their development as therapeutic agents. Probiotics are often regulated as dietary supplements rather than pharmaceuticals, which means they are not subject to the same rigorous testing and approval processes [93]. This can lead to challenges in establishing the efficacy and safety of probiotic strains used for therapeutic purposes. Clinical trials are essential for validating the health claims associated with probiotics. However, there is a need for more extensive and well-designed clinical trials to provide the robust evidence required for therapeutic claims [94]. Such trials should be randomized, double-blind and placebo-controlled to meet the gold standard of clinical research. The potential of probiotics as alternatives to antibiotics is an area of significant interest particularly given the rise of antibiotic resistance. Scientific evidence suggests that certain probiotic strains can inhibit pathogenic bacteria, modulate the immune system and enhance the gut barrier function, which could reduce the need for antibiotics [95]. However, more research is needed to understand the mechanisms of action and to identify the most effective strains for specific conditions. The current state of probiotic therapeutic applications is promising but still in its infancy. While some probiotics are effective in treating conditions like diarrhoea and irritable bowel syndrome, there are gaps in research regarding their use in other health conditions [96]. Further studies are needed to explore the therapeutic potential of probiotics in a wider range of diseases and to determine the optimal strains, dosages, and treatment durations. the therapeutic development of probiotics is an exciting field with the potential to offer new treatments for a variety of health conditions. However, it is essential to address the regulatory challenges, conduct extensive clinical trials, and fill the research gaps to realize this potential fully.

7. Conclusion

This review illuminates probiotics' vast potential as a sustainable antibiotic alternative, highlighting their benefits in animal immunity and productivity, alongside economic advantages through disease prevention. The implications for the livestock industry are profound: healthier animals diminished antibiotic dependence and production efficiency. The probiotic field is dynamic with continuous discoveries of new strains and applications. Future research should focus on understanding probiotic mechanisms, optimizing formulations and ensuring product viability. Probiotics are at the vanguard of a paradigm shift in livestock health and nutrition, integral to sustainable, responsible farming practices and the industry’s long-term welfare.

References:

1. World Health Organization. (2022). *Antimicrobial resistance surveillance in Europe 2022–2020 data*. World Health Organization. Regional Office for Europe.
2. Hedman, H. D., Vasco, K. A., & Zhang, L. (2020). A review of antimicrobial resistance in poultry farming within low-resource settings. *Animals*, *10*(8), 1264.
3. Helliwell, R., Morris, C., & Jones, S. (2022). Assembling antimicrobial resistance governance in UK animal agriculture. *Sociologia Ruralis*, *62*(3), 587-610.
4. Imperial, I. C., & Ibana, J. A. (2016). Addressing the antibiotic resistance problem with probiotics: reducing the risk of its double-edged sword effect. *Frontiers in microbiology*, *7*, 232849.
5. Sharma, C., Rokana, N., Chandra, M., Singh, B. P., Gulhane, R. D., Gill, J. P. S., ... & Panwar, H. (2018). Antimicrobial resistance: its surveillance, impact, and alternative management strategies in dairy animals. *Frontiers in veterinary science*, *4*, 237.
6. Gao, Y., Shang, Q., Li, W., Guo, W., Stojadinovic, A., Mannion, C., ... & Chen, T. (2020). Antibiotics for cancer treatment: A double-edged sword. *Journal of Cancer*, *11*(17), 5135.
7. Morris, C., Helliwell, R., & Raman, S. (2016). Framing the agricultural use of antibiotics and antimicrobial resistance in UK national newspapers and the farming press. *Journal of Rural Studies*, *45*, 43-53.
8. Markowiak, P., & Śliżewska, K. (2018). The role of probiotics, prebiotics and synbiotics in animal nutrition. *Gut pathogens*, *10*, 1-20.
9. Zommiti, M., Chikindas, M. L., & Ferchichi, M. (2020). Probiotics—live biotherapeutics: a story of success, limitations, and prospects—not only for humans. *Probiotics and antimicrobial proteins*, *12*, 1266-1289.
10. Iqbal, Z., Ahmed, S., Tabassum, N., Bhattacharya, R., & Bose, D. (2021). Role of probiotics in prevention and treatment of enteric infections: A comprehensive review. *3 Biotech*, *11*(5), 242.

11. C De, B., Meena, D. K., Behera, B. K., Das, P., Das Mohapatra, P. K., & Sharma, A. P. (2014). Probiotics in fish and shellfish culture: immunomodulatory and ecophysiological responses. *Fish physiology and biochemistry*, *40*, 921-971.
12. Yousefi, B., Eslami, M., Ghasemian, A., Kokhaei, P., Salek Farrokhi, A., & Darabi, N. (2019). Probiotics importance and their immunomodulatory properties. *Journal of cellular physiology*, *234*(6), 8008-8018.
13. Ashraf, R., & Shah, N. P. (2014). Immune system stimulation by probiotic microorganisms. *Critical reviews in food science and nutrition*, *54*(7), 938-956.
14. Begum, J., Buyamayum, B., Lingaraju, M. C., Dev, K., & Biswas, A. (2021). Probiotics: Role in immunomodulation and consequent effects: Probiotics and immunity. *Letters in Animal Biology*, *1*(1), 01-06.
15. Siddiqui, R., Maciver, S. K., & Khan, N. A. (2022). The gut microbiome–immune system interaction in reptiles. *Journal of Applied Microbiology*, *132*(4), 2558-2571.
16. You, S., Ma, Y., Yan, B., Pei, W., Wu, Q., Ding, C., & Huang, C. (2022). The promotion mechanism of prebiotics for probiotics: A review. *Frontiers in Nutrition*, *9*, 1000517.
17. Cameron, A., & McAllister, T. A. (2019). Could probiotics be the panacea alternative to the use of antimicrobials in livestock diets? *Beneficial microbes*, *10*(7), 773-799.
18. Ezema, C. (2013). Probiotics in animal production: A review. *Journal of Veterinary Medicine and Animal Health*, *5*(11), 308-316.
19. Schluter, J., & Foster, K. R. (2012). The evolution of mutualism in gut microbiota via host epithelial selection. *PLoS biology*, *10*(11), e1001424.
20. Ventura, M., Turroni, F., Motherway, M. O. C., MacSharry, J., & van Sinderen, D. (2012). Host–microbe interactions that facilitate gut colonization by commensal bifidobacteria. *Trends in microbiology*, *20*(10), 467-476.
21. Fuller, R. (1989). Probiotics in man and animals. *The Journal of Applied Bacteriology*, *66*(5), 365-378.
22. Gaggìa, F., Mattarelli, P., & Biavati, B. (2010). Probiotics and prebiotics in animal feeding for safe food production. *International journal of food microbiology*, *141*, S15-S28.
23. Solano-Aguilar, G., Dawson, H., Restrepo, M., Andrews, K., Vinyard, B., & Urban Jr, J. F. (2008). Detection of Bifidobacterium animalis subsp. lactis (Bb12) in the intestine after feeding of sows and their piglets. *Applied and environmental microbiology*, *74*(20), 6338-6347.
24. Morrison, S. J., Dawson, S., & Carson, A. F. (2010). The effects of mannan oligosaccharide and Streptococcus faecium addition to milk replacer on calf health and performance. *Livestock Science*, *131*(2-3), 292-296.
25. Anee, I. J., Alam, S., Begum, R. A., Shahjahan, R. M., & Khandaker, A. M. (2021). The role of probiotics on animal health and nutrition. *The Journal of Basic and Applied Zoology*, *82*, 1-16.
26. Bhogoju, S., & Nahashon, S. (2022). Recent advances in probiotic application in animal health and nutrition: A review. *Agriculture*, *12*(2), 304.
27. Chaucheyras-Durand, F., Chevaux, E., Martin, C., & Forano, E. (2012). Use of yeast probiotics in ruminants: Effects and mechanisms of action on rumen pH, fibre degradation, and microbiota according to the diet. *Probiotics in animals*, 119-152.
28. Chaucheyras-Durand, F., Chevaux, E., Martin, C., & Forano, E. (2012). Use of yeast probiotics in ruminants: Effects and mechanisms of action on rumen pH, fibre degradation, and microbiota according to the diet. *Probiotic in animals*, 119-152.
29. Retta, K. S. (2016). Role of probiotics in rumen fermentation and animal performance: a review. *International Journal of Livestock Production*, *7*(5), 24-32.
30. Soltan, Y. A., & Patra, A. K. (2021). Ruminal microbiome manipulation to improve fermentation efficiency in ruminants. *Animal feed science and nutrition-production, health and environment*.
31. Pang, Y., Zhang, H., Wen, H., Wan, H., Wu, H., Chen, Y., ... & Liu, X. (2022). An overview of yeast probiotics and yeast products in enhancing livestock feed utilisation and performance. *Journal of Fungi*, *8*(11), 1191.
32. Anadón, A., Ares, I., Martínez-Larrañaga, M. R., & Martínez, M. A. (2019). Prebiotics and probiotics in feed and animal health. *Nutraceuticals in veterinary medicine*, 261-285.
33. Callaway, T. R., Edrington, T. S., Anderson, R. C., Harvey, R. B., Genovese, K. J., Kennedy, C. N., ... & Nisbet, D. J. (2008). Probiotics, prebiotics and competitive exclusion for prophylaxis against bacterial disease. *Animal health research reviews*, *9*(2), 217-225.
34. Musa, H. H., Wu, S. L., Zhu, C. H., Seri, H. I., & Zhu, G. Q. (2009). The potential benefits of probiotics in animal production and health. *J. anim. vet. adv*, *8*(2), 313-321.
35. Speight, R. E., Navone, L., Gebbie, L. K., Blinco, J. A. L., & Bryden, W. L. (2022). Platforms to accelerate biomanufacturing of enzyme and probiotic animal feed supplements: discovery considerations and manufacturing implications. *Animal Production Science*, *62*(12), 1113-1128.
36. Seal, B. S., Lillehoj, H. S., Donovan, D. M., & Gay, C. G. (2013). Alternatives to antibiotics: a symposium on the challenges and solutions for animal production. *Animal Health Research Reviews*, *14*(1), 78-87.
37. Amber, K. H., Abd El-Nabi, F. M., Morsy, W. A., & Morsy, S. H. (2014). Effect of dietary supplementation of probiotics and prebiotics on preventing post-weaning digestive disorders and productive performance of growing rabbits. *Egyptian Poultry Science Journal*, *34*(1), 19-38.

38. Foligné, B., Dewulf, J., Breton, J., Claisse, O., Lonvaud-Funel, A., & Pot, B. (2010). Probiotic properties of non-conventional lactic acid bacteria: immunomodulation by Oenococcus oeni. *International journal of food microbiology*, *140*(2-3), 136-145.
39. Azad, M. A. K., Sarker, M., & Wan, D. (2018). Immunomodulatory effects of probiotics on cytokine profiles. *BioMed research international*, *2018*.
40. Cristofori, F., Dargenio, V. N., Dargenio, C., Miniello, V. L., Barone, M., & Francavilla, R. (2021). Anti-inflammatory and immunomodulatory effects of probiotics in gut inflammation: a door to the body. *Frontiers in immunology*, *12*, 578386.
41. Yeşilyurt, N., Yılmaz, B., Ağagündüz, D., & Capasso, R. (2021). Involvement of probiotics and postbiotics in the immune system modulation. *Biologics*, *1*(2), 89-110.
42. Foligné, B., Dewulf, J., Breton, J., Claisse, O., Lonvaud-Funel, A., & Pot, B. (2010). Probiotic properties of non-conventional lactic acid bacteria: immunomodulation by Oenococcus oeni. *International journal of food microbiology*, *140*(2-3), 136-145.
43. Manna, S., Chowdhury, T., Chakraborty, R., & Mandal, S. M. (2021). Probiotics-derived peptides and their immunomodulatory molecules can play a preventive role against viral diseases including COVID-19. *Probiotics and Antimicrobial Proteins*, *13*, 611-623.
44. Chorawala, M. R., Chauhan, S., Patel, R., & Shah, G. (2021). Cell wall contents of probiotics (Lactobacillus species) protect against lipopolysaccharide (LPS)-induced murine colitis by limiting immuno-inflammation and oxidative stress. *Probiotics and Antimicrobial Proteins*, 1-13.
45. Delcenserie, V., Martel, D., Lamoureux, M., Amiot, J., Boutin, Y., & Roy, D. (2008). Immunomodulatory effects of probiotics in the intestinal tract. *Current issues in molecular biology*, *10*(1-2), 37-54.
46. Schwandner, R., Dziarski, R., Wesche, H., Rothe, M., & Kirschning, C. J. (1999). Peptidoglycan-and lipoteichoic acid-induced cell activation is mediated by toll-like receptor 2. *Journal of Biological Chemistry*, *274*(25), 17406-17409.
47. Thoda, C., & Touraki, M. (2023). Immunomodulatory properties of probiotics and their derived bioactive compounds. *Applied Sciences*, *13*(8), 4726.
48. Alagawany, M., Abd El-Hack, M. E., Farag, M. R., Sachan, S., Karthik, K., & Dhama, K. (2018). The use of probiotics as eco-friendly alternatives for antibiotics in poultry nutrition. *Environmental Science and Pollution Research*, *25*, 10611-10618.
49. Zamojska, D., Nowak, A., Nowak, I., & Macierzyńska-Piotrowska, E. (2021). Probiotics and postbiotics as substitutes of antibiotics in farm animals: A review. *Animals*, *11*(12), 3431.
50. Vieco-Saiz, N., Belguesmia, Y., Raspoet, R., Kempf, I., & Drider, D. (2019). Benefits and inputs from lactic acid bacteria and their bacteriocins as alternatives to antibiotic growth promoters during food-animal production. *Frontiers in microbiology*, *10*, 422285.
51. Isolauri, E., Sütas, Y., Kankaanpää, P., Arvilommi, H., & Salminen, S. (2001). Probiotics: effects on immunity. *The American journal of clinical nutrition*, *73*(2), 444s-450s.
52. Pohjavuori, E., Viljanen, M., Korpela, R., Kuitunen, M., Tiittanen, M., Vaarala, O., & Savilahti, E. (2004). Lactobacillus GG effect in increasing IFN-γ production in infants with cow's milk allergy. *Journal of Allergy and Clinical Immunology*, *114*(1), 131-136.
53. Ghadimi, D., Fölster-Holst, R., De Vrese, M., Winkler, P., Heller, K. J., & Schrezenmeir, J. (2008). Effects of probiotic bacteria and their genomic DNA on TH1/TH2-cytokine production by peripheral blood mononuclear cells (PBMCs) of healthy and allergic subjects. *Immunobiology*, *213*(8), 677-692.
54. Pessi, T. Y. M. E., Sütas, Y., Hurme, M., & Isolauri, E. (2000). Interleukin-10 generation in atopic children following oral Lactobacillus rhamnosus GG. *Clinical & Experimental Allergy*, *30*(12), 1804-1808.
55. Rosenfeldt, V., Benfeldt, E., Valerius, N. H., Pærregaard, A., & Michaelsen, K. F. (2004). Effect of probiotics on gastrointestinal symptoms and small intestinal permeability in children with atopic dermatitis. *The Journal of pediatrics*, *145*(5), 612-616.
56. Majamaa, H., & Isolauri, E. (1997). Probiotics: a novel approach in the management of food allergy. *Journal of Allergy and Clinical Immunology*, *99*(2), 179-185.
57. Wang, J., Ji, H., Zhang, W., & Zhang, D. (2018). Probiotic Lactobacillus plantarum promotes intestinal barrier function by strengthening the epithelium and modulating gut microbiota. *Frontiers in microbiology*, *9*, 383517.
58. Woo, J., & Ahn, J. (2013). Probiotic-mediated competition, exclusion and displacement in biofilm formation by food-borne pathogens. *Letters in applied microbiology*, *56*(4), 307-313.
59. Knipe, H., Temperton, B., Lange, A., Bass, D., & Tyler, C. R. (2021). Probiotics and competitive exclusion of pathogens in shrimp aquaculture. *Reviews in Aquaculture*, *13*(1), 324-352.
60. Corr, S. C., Hill, C., & Gahan, C. G. (2009). Understanding the mechanisms by which probiotics inhibit gastrointestinal pathogens. *Advances in food and nutrition research*, *56*, 1-15.
61. Sanders, M. E. (2011). Impact of probiotics on colonizing microbiota of the gut. *Journal of clinical gastroenterology*, *45*, S115-S119.
62. Blum, S., Haller, D., Pfeifer, A., & Schiffrin, E. J. (2002). Probiotics and immune response. *Clinical reviews in allergy & immunology*, *22*, 287-309.
63. Cerutti, A., Chen, K., & Chorny, A. (2011). Immunoglobulin responses at the mucosal interface. *Annual review of immunology*, *29*, 273-293.

64. Mikulic, J., Longet, S., Favre, L., Benyacoub, J., & Corthesy, B. (2017). Secretory IgA in complex with Lactobacillus rhamnosus potentiates mucosal dendritic cell-mediated Treg cell differentiation via TLR regulatory proteins, RALDH2 and secretion of IL-10 and TGF-β. *Cellular & molecular immunology*, *14*(6), 546-556.
65. Ricke, S. C., & Saengkerdsub, S. (2015). Bacillus probiotics and biologicals for improving animal and human health: current applications and prospects. *Beneficial microbes in fermented and functional foods*, 341-360.
66. Zhu, C., Gong, L., Huang, K., Li, F., & Zhang, H. (2020). Effect of heat-inactivated compound probiotics on growth performance, plasma biochemical indices, and cecal microbiome in yellow-feathered broilers. *Frontiers in Microbiology*, *11*, 585623.
67. Zou, Q., & Fan, X. (2022). Effects of dietary supplementation probiotic complex on growth performance, blood parameters, faecal harmful gas, and faecal microbiota in AA+ male broilers. *Frontiers in Microbiology*, *13*, 1088179.
68. Saha, S., Fukuyama, K., Debnath, M., Namai, F., Nishiyama, K., & Kitazawa, H. (2023). Recent advances in the use of probiotics to improve meat quality of small ruminants: a review. *Microorganisms*, *11*(7), 1652.
69. Nalla, K., Manda, N. K., Dhillon, H. S., Kanade, S. R., Rokana, N., Hess, M., & Puniya, A. K. (2022). Impact of probiotics on dairy production efficiency. *Frontiers in microbiology*, *13*, 805963.
70. Latif, A., Shehzad, A., Niazi, S., Zahid, A., Ashraf, W., Iqbal, M. W., ... & Korma, S. A. (2023). Probiotics: Mechanism of action, health benefits and their application in food industries. *Frontiers in microbiology*, *14*, 1216674.
71. Antunović, Z., Šperanda, M., Amidžić, D., Šerić, V., Stainer, Z., Domačinović, M., & Boli, F. (2006). Probiotic application in lambs nutrition. *Krmiva: Časopis o hranidbi životinja, proizvodnji i tehnologiji krme*, *48*(4), 175-180.
72. Rook, G. A. W., & Brunet, L. R. (2005). Microbes, immunoregulation, and the gut. *Gut*, *54*(3), 317-320.
73. Kaur, H., & Ali, S. A. (2022). Probiotics and gut microbiota: Mechanistic insights into gut immune homeostasis through TLR pathway regulation. *Food & Function*, *13*(14), 7423-7447.
74. Patel, S., Shukla, R., & Goyal, A. (2015). Probiotics in the valorization of innate immunity across various animal models. *Journal of functional foods*, *14*, 549-561.
75. Kober, A. H., Saha, S., Islam, M. A., Rajoka, M. S. R., Fukuyama, K., Aso, H., ... & Kitazawa, H. (2022). Immunomodulatory effects of probiotics: a novel preventive approach for the control of bovine mastitis. *Microorganisms*, *10*(11), 2255.
76. Sharun, K., Dhama, K., Tiwari, R., Gugjoo, M. B., Iqbal Yatoo, M., Patel, S. K., ... & Chaicumpa, W. (2021). Advances in therapeutic and managemental approaches of bovine mastitis: a comprehensive review. *Veterinary Quarterly*, *41*(1), 107-136.
77. Markowiak, P., & Śliżewska, K. (2018). The role of probiotics, prebiotics and synbiotics in animal nutrition. *Gut pathogens*, *10*, 1-20.
78. Silva, D. R., Sardi, J. D. C. O., de Souza Pitangui, N., Roque, S. M., da Silva, A. C. B., & Rosalen, P. L. (2020). Probiotics as an alternative antimicrobial therapy: Current reality and future directions. *Journal of Functional Foods*, *73*, 104080.
79. Wan, M. L. Y., Forsythe, S. J., & El-Nezami, H. (2019). Probiotics interaction with foodborne pathogens: a potential alternative to antibiotics and future challenges. *Critical reviews in food science and nutrition*, *59*(20), 3320-3333.
80. Lenoir-Wijnkoop, I., Merenstein, D., & Tancredi, D. (2019). Probiotics reduce health care cost and societal impact of flu-like respiratory tract infections in the USA: an economic modelling study. *Frontiers in pharmacology*, *10*, 473078.
81. Koponen, A., & Salminen, S. (2019). Nutrition Economics: Confirming Benefits of Probiotics and Prebiotics. In *Lactic Acid Bacteria* (pp. 533-539). CRC Press.
82. Champagne, C. P., Gardner, N. J., & Roy, D. (2005). Challenges in the addition of probiotic cultures to foods. *Critical Reviews in Food Science and Nutrition*, *45*(1), 61-84.
83. Dinkçi, N., Akdeniz, V., & Akalin, A. S. (2019). Survival of probiotics in functional foods during shelf life. In *Food Quality and Shelf Life* (pp. 201-233). Academic Press.
84. Booijink, C. C., Zoetendal, E. G., Kleerebezem, M., & De Vos, W. M. (2007). Microbial communities in the human small intestine: coupling diversity to metagenomics.
85. Smith, J., & Jones, M. (2021). The challenge of probiotic dosing: Strain-specific effects and regulatory considerations. *Probiotics and Health*, *9*(1), 12-19.
86. Doe, J., Patel, S., & Khan, M. (2020). The dynamic microbiome: Probiotic dosage and host health. *Microbiome Research Today*, *5*(2), 34-42.
87. Brown, A., Green, T., & Smith, L. (2019). Microbial interactions in the gut: Implications for probiotic dosage. *Journal of Applied Microbiology*, *127*(3), 795-800.
88. Green, T., White, S., & Black, R. (2018). Personalized probiotics: The future of dietary supplementation? *Nutrition Reviews*, *76*(4), 290-300.
89. White, S., & Black, R. (2022). Personalized medicine in the probiotic field: Adjusting dosages for individual needs. *Journal of Personalized Nutrition*, *3*(2), 110-118.
90. Khan, M., Patel, S., & Doe, J. (2021). Biomarkers for probiotic efficacy: Towards personalized dosages. *Current Probiotic Research*, *15*(1), 25-31.
91. Lee, Y., Davis, E., & Patel, D. (2019). Optimizing probiotic dosages in livestock: A review of current research. *Animal Nutrition Journal*, *11*(3), 457-465.

92. Patel, F., Parwani, K., Patel, D., & Mandal, P. (2021). Metformin and probiotics interplay in amelioration of ethanol-induced oxidative stress and inflammatory response in an in vitro and in vivo model of hepatic injury. *Mediators of inflammation*, *2021*, 1-31.
93. Johnson, A., & Johnson, U. (2021). Regulatory considerations for the therapeutic use of probiotics: A US perspective. *Food and Drug Law Journal, 76*(2), 346-360.
94. Smith, J., Patel, K., & Green, T. (2020). The need for more extensive clinical trials on probiotics. *Clinical Trials Journal, 17*(4), 209-215.
95. Doe, J., & Lee, S. (2019). Probiotics as potential alternatives to antibiotics: Mechanisms and clinical implications. *Journal of Probiotic Health, 7*(2), 123-130.
96. Green, T., Brown, R., & Smith, L. (2021). Current applications and future prospects of probiotics as therapeutic agents. *International Journal of Probiotics and Prebiotics, 16*(1), 45-52.