Harnessing Probiotics for Controlling Salmonellosis

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Muhammad Sohail[1], Naseer Khan Momand[2], Amir Hamza Khan[3], Yabaiz Tahir[1], Abdul Qadir[4], Tuba Riaz[5], Muhammad Kashif Javaid [1,6], Mehran Asjad[7], Muhammad Sohail Irshad[8] and Abdul Raheem[9]

ABSTRACT

Numerous serotypes of the genus Salmonella may cause salmonellosis, which is still a major worldwide public health problem with enormous social and economic costs. Alternative tactics are typically required to successfully manage Salmonella infections, since conventional management measures are not always sufficient. This paper investigates the intriguing possibility of using probiotics as a workable and long-term method of managing salmonellosis. Probiotics, which are living microorganisms that provide health advantages when given in sufficient quantities, have shown significant promise in reducing the risk of Salmonella infections. This research comprehensively investigates the strategies that probiotics use to produce antimicrobial compounds against Salmonella. These processes include host immune response regulation, generation of antimicrobial chemicals, and competitive exclusion. The paper also explores the complex relationship between probiotics and the gut microbiota, providing insight into how probiotics may help restore the microbial equilibrium that Salmonella has upset. Additionally, this thorough investigation assesses how well different probiotic strains work to stop Salmonella from colonizing a variety of host species, such as people, animals, and poultry. The review summarizes the most important studies that have advanced our knowledge of the many ways that probiotics may be used to prevent Salmonella infections in a variety of settings. Additionally, covered are the difficulties and factors to be taken into account in the creation and use of probiotics as a salmonellosis management approach, such as strain selection, dose optimization, and the need for uniform regulatory frameworks. Probiotics and conventional therapies are investigated for possible synergies in order to provide an integrated strategy to managing salmonellosis from a holistic standpoint. This review concludes by offering a thorough summary of the status of research on using probiotics to manage salmonellosis. It provides important insights into the mechanics, uses, and difficulties of using probiotics as a long-term and successful tactic in the continuing fight against Salmonella infections by combining data from many research.

CITATION

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[1]Department of Pathology, University of Agriculture, Faisalabad, Pakistan
[2]Department of Poultry Science, University of Agriculture, Faisalabad, Pakistan
[3]Pak International Medical College, Peshawar, Pakistan

[4]Department of Plant Pathology, Balochistan Agriculture College, Quetta, Pakistan
[5]Department of Animal Nutrition, University of Veterinary and Animal Science, Lahore, Pakistan
[6]Hivet Animal Health Business, Lahore, Pakistan
[7]Department of Animal Nutrition, University of Agriculture, Faisalabad, Pakistan
[8]Department of Clinical Medicine and Surgery, University of Veterinary and Animal Science, Lahore, Pakistan
[9]Faculty of Veterinary Science, University of Agriculture, Faisalabad, Pakistan
***Corresponding author:** tuba.riaz@uavs.edu.pk

1. INTRODUCTION

The intestinal bacteria *Salmonella* still poses a serious threat to the world's public health. The bacteria that cause salmonellosis is known as *Salmonella* in honor of the study done by American bacteriologist D.E. Salmon. *Salmonella* is responsible for several diseases, including septicemia, enteric (typhoid) fever, and mild gastroenteritis. The Salmonella serovar involved, strain virulence, infective dose, host animal species, age and immune status of the host, and geographic region are just a few of the many variables that affect the nature and severity of infections in various animal species (Mastroeni & Maskell 2006). Only a small number of serovars, which can be divided into three groups based on how frequently they infect different hosts, are responsible for the majority of salmonellosis cases in humans and domestic animals. These serovars tend to cause subclinical intestinal infections or acute enteritis, while those with a narrow host range tend to cause severe systemic diseases. The serovars which are host-specific, are less able to trigger inflammatory reactions in the intestines. This could make immune de and tissue-wide spread easier. This pathogen feature may be attained either passively via the loss of effector proteins responsible for inducing pro-inflammatory responses or actively through the evolutionary acquisition of effector proteins responsible for immune suppression. *Salmonella* may spread among the animals, mostly via feces, which can lead to high levels of transmission and disease. Monitoring and attempting to manage these infections costs the agricultural sectors and public health authorities a lot of money each year. Finding ways to limit this transmission across animals would be made easier with knowledge of the pathophysiology of Salmonella infections in many animal species (Mastroeni and Maskell 2006).

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It is a strong foe due to its frequency in food and water sources, as well as its capacity to cause infections in the gastrointestinal system. Scientists have been looking for alternate approaches to reduce enteric infections since Salmonella is still a widespread disease in industrialized and developing nations, and because antibiotic treatments might have unintended side effects. Probiotics seem like a compelling option to address this issue. Live bacteria known as probiotics may help the host's health when given in sufficient doses (FAO/WHO 2001).
Antibiotics have been the mainstay of conventional methods for treating Salmonella infections, but the emergence of antibiotic-resistant forms has made it necessary to investigate other tactics. In the fight against salmonellosis. The WHO/FAO concentrated especially on probiotics as foods or nutritional supplements, although they may also be employed in medication applications (as live biotherapeutics), microbial feed additives (for animal usage), genetically modified organisms, and live vaccinations if given orally. The International Scientific Association for Probiotics and Prebiotics gave a more thorough insight into the appropriate usage of this word to improve clarity for probiotic terminology. The requirements for using probiotics in meals or medicines are among this definition's important features.
Probiotics—defined as living microorganisms that provide a health benefit when given in sufficient amounts—have emerged as a viable weapon. An in-depth discussion of probiotics' involvement in preventing and managing Salmonella infections is provided in this chapter.

2. UNDERSTANDING SALMONELLOSIS

Before delving into the potential of probiotics, it is crucial to comprehend the pathogenesis of Salmonella. The bacterium gains entry through contaminated food or water, and once inside the host, it employs an array of virulence factors to breach the intestinal epithelial barrier. This leads to symptoms ranging from mild gastroenteritis to severe systemic infections. Non-immune mechanisms, such as the stabilization of the gut mucosal barrier, increasing mucus secretion, and improving gut motility may prevent enteric pathogens from colonizing and infecting the mucosa. Other potential mechanisms include competing and struggling for nutrients and secreting specific low molecular weight antimicrobial secretions (bacteriocins). The effects of probiotic strains on non-immune defenses are mentioned in this chapter. Probiotic suspensions are effective in preventing several Salmonella serovars. According to Mountzouris et al.'s research, an oral probiotic (multi-strain) treatment decreased the amount of *S. enteritidis* in broilers (Mountzouris et al. 2009). They found that probiotic feeding substantially boosted intestinal and systemic levels of IgA and IgG antibodies against *S. enterica* and decreased the susceptibility of infected animals in treated groups (by 50%) as compared to untreated controls (by 100%). By enhancing specific anti-Salmonella antibodies in serum and the intestinal tract, increasing splenocyte proliferative responses to mitogens, and increasing phagocytic activity of peritoneal and blood cells, other probiotic strains, including *L. rhamnosus* HN001 and *B. lactis* HN019, demonstrated protective properties against S*. typhimurium* in mice (Gill et al. 2001; Shu et al. 2000). Mice infected with *S. typhimurium* and given the probiotic strain *L. helveticus* M92 were used in a study to demonstrate the significance of the lactobacillus S-layer protein in protecting the immune system. The authors hypothesized that the mice's intestinal tract's competitive exclusion and the increased immune protection provided by *L. helveticus* M92 and its S-layer protein were responsible for the decreased infection by *S. typhimurium* FP1 (Castillo et al. 2011).
The anti-inflammatory traits of some probiotic bacteria may also be linked to the pathogen defense offered by these microbes. The immune system's inflammatory response is triggered by the host defense against infection and may result in tissue damage (Fig. 1). In this regard, different research showed that probiotic bacteria of human origin, *Bifidobacterium infantis* 35624 when given to mice before they were exposed to *Salmonella typhimurium* or given an injection of LPS, had anti-

inflammatory and pathogen-protective effects. According to O'Mahony et al. (2008), the probiotic's positive impact was due to the production of Treg cells, which inhibited excessive NF-B activation in vivo. (Fig. 1), Using a mouse model, Gobbato et al. 2008) investigated the same LAB's efficacy against *S. typhimurium* in vivo. Particularly in mice given *L. bulgaricus*, they saw a considerable lowering of the number of apoptotic cells in the small intestinal tissue cells. The significant increase in Bcl-2+ anti-apoptotic protein cells seen in the small intestine of the mice who received this LAB may help to explain this outcome. *S. thermophilus* had no impact on apoptosis inhibition and failed to raise the number of Bcl-2+ cells in comparison to the untreated control. Instead, injection of *L. casei* increased the number of Bcl-2+ cells, albeit it had a comparable impact on apoptosis inhibition to *S. thermophilus*. It was also shown that mice administered L. *delbrueckii* subsp. *bulgaricus* had more IFN+ cells in their small intestines. The enhanced microbicidal activity seen in the macrophages isolated from the peritoneum and Peyer's patches after this LAB oral treatment was consistent with this finding. The number of IFN+ cells was similarly raised by *L. casei*, but this increase was insufficient to cause the peritoneal macrophages to become microbicidal. Fig. 2 shows some immune mechanisms generated by different probiotic strains against *Salmonella* infection.
Additionally, probiotics function as immunological adjuvants that affects systemic and mucosal immune responses. They can regulate NK cell activity, modulate the inflammatory response, stimulate the production of specific cytokines and the phagocytic activity of macrophages and neutrophils, and enhance specific antibody responses, particularly mucosal secretory IgA (Alvarez-Olmos & Oberhelman 2001; Galdeano de Moreno de LeBlanc et al. 2007). Given the diverse clinical manifestations, it is evident that a multi-faceted approach is required to combat this pathogen effectively.

3. PROBIOTIC'S MODE OF ACTION

Probiotics are expected to have a variety of different mechanisms of action. Some of these mechanisms influence the suppression of intestinal pathogenic microbes, while others are in charge of enhancing animal performance. Although the precise mechanisms of action by which probiotics perform biological activities are not entirely known, their mode of action is often described as competitive exclusion or colonization resistance (Fig. 3). Oelschlaeger describes three mechanisms in which probiotics function in the host system (Oelschlaeger 2010).
i. Probiotics may be useful in altering the host's innate and acquired immune systems. The direct action of probiotics on other microorganisms will prevent and serve to control infections and re-establish the microbial balance in the gut.
ii. Microbial products such as antimicrobials, toxins, and host metabolites may be the major components for probiotic actions. This will be efficient in preventing infectious diseases and ameliorating the inflammation of the host's digestive tract. The probiotics improve gastrointestinal digestion of meal components and nutrient absorption while also helping in the inactivation of toxins and detoxification of bile salt.
iii. probiotics compete with pathogenic bacteria to bind to mucus, since they may adhere to the mucosal wall and are beneficial in host immune responses (Galdeano et al. 2019).
By providing an additional source of nutrients and digestive enzymes, probiotics may also encourage the production of vitamins in the host (Markowiak 2017). In addition to producing inhibitory compounds such as volatile fatty acids and hydrogen peroxide to strengthen the host's tolerance to infections, these may stop the spread of dangerous bacteria (Plaza-Diaz et al. 2019).
According to research, yeast-based probiotics enhanced the amount of cellulolytic bacteria in ruminants, which demonstrates their impact on microbial fermentation and results in high cellulose breakdown and better microbial protein synthesis (Amin et al. 2021). By generating proteins or polypeptide bacteriocins, both Lactobacilli and Bifidobacteria promote the development of closely related bacterial species,

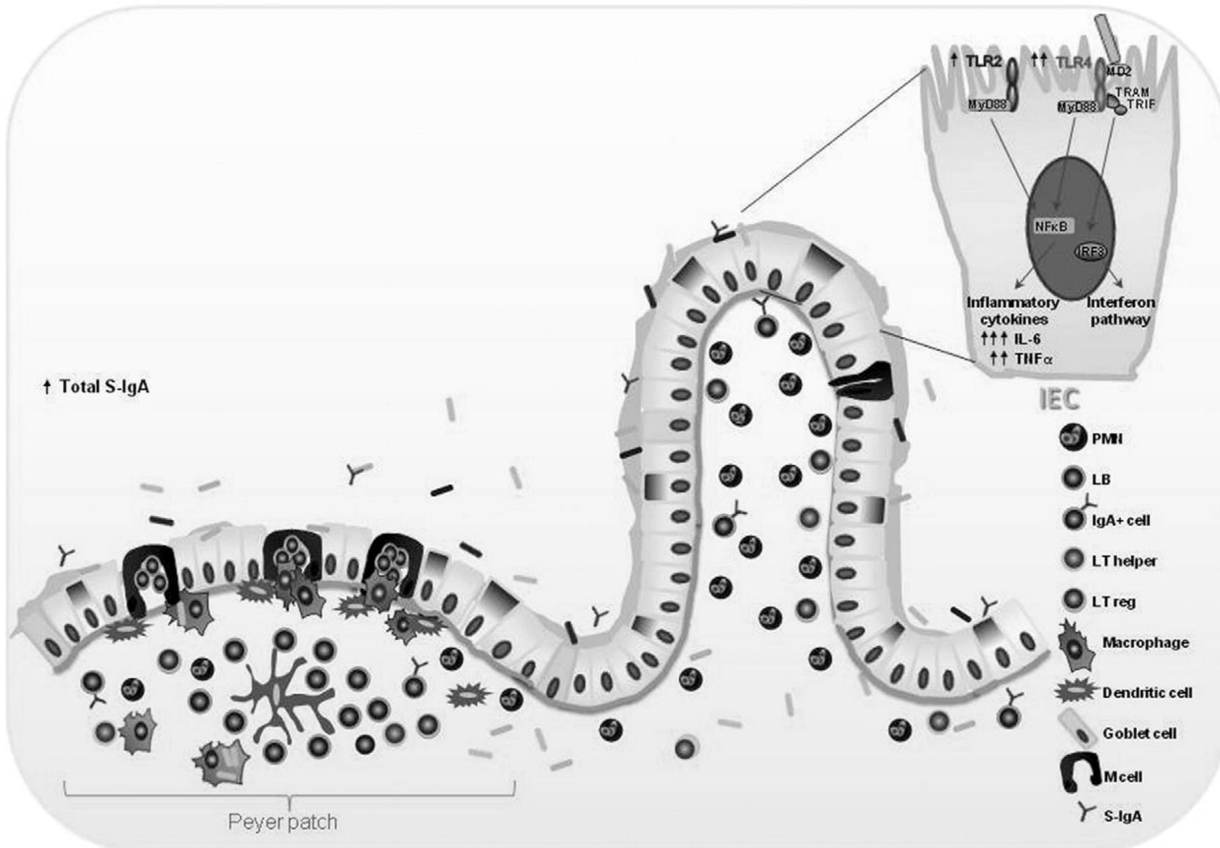

Fig. 1: Schematic diagram of the immune mechanisms generated against *Salmonella* infection in the inductor (Peyer's patches) and effector (lamina propria and epithelium) sites of the gut immune response. *Salmonella* enters through M cells or intestinal epithelial cells (IECs), then internalizes and replicates within phagocytic cells, and induces their cellular death, a mechanism used to disseminate to deeper tissues. The infection usually produces an inflammatory response with infiltration of polymorphonuclear cells, and the activation of inflammatory cascades into the immune cells and epithelial to produce pro-inflammatory cytokines and tissue damage (Castillo et al. 2011).

therefore, reducing the number of harmful germs in the gut. *Bacillus, Staphylococcus, Enterococcus, Listeria,* and *Salmonella* species are just a few of the pathogens that probiotic species like LAB, Bifidobacteria, and Bacillus can combat with the help of a few different types of thermostable bacteriocins (Piqué et al. 2019).

Havenaar et al. (2018) presented some specific characteristics of probiotics based on the various characteristics of a good microorganism, such as having a positive effect on the host, being nontoxic and nonpathogenic in nature, having the ability to survive for a long time with high cell counts, and their capacity to survive through the digestive system.

Some probiotic strains have been shown to exhibit anti-inflammatory qualities that support the equilibrium between pro- and anti-inflammatory cytokines (Cristofori et al. 2021; Pagnini et al. 2010), as well as the generation of antimicrobial compounds such as volatile fatty acids, hydrogen peroxide, and bacteriocins (Vieco-Saiz et al. 2019). According to studies, probiotic bacteria create organic chemicals that have been shown to have inhibitory action on pathogenic bacteria like *H. pylori* (Rezaee et al. 2019). Dai et al.'s investigations show that probiotics may improve tight junction protein expression by stimulating the p38 and ERK signaling pathways, which in turn can strengthen gut barrier integrity (Wang et al. 2018). Probiotics have antiviral activities in animals in addition to the anti-inflammatory effects (Lehtoranta et al. 2020).

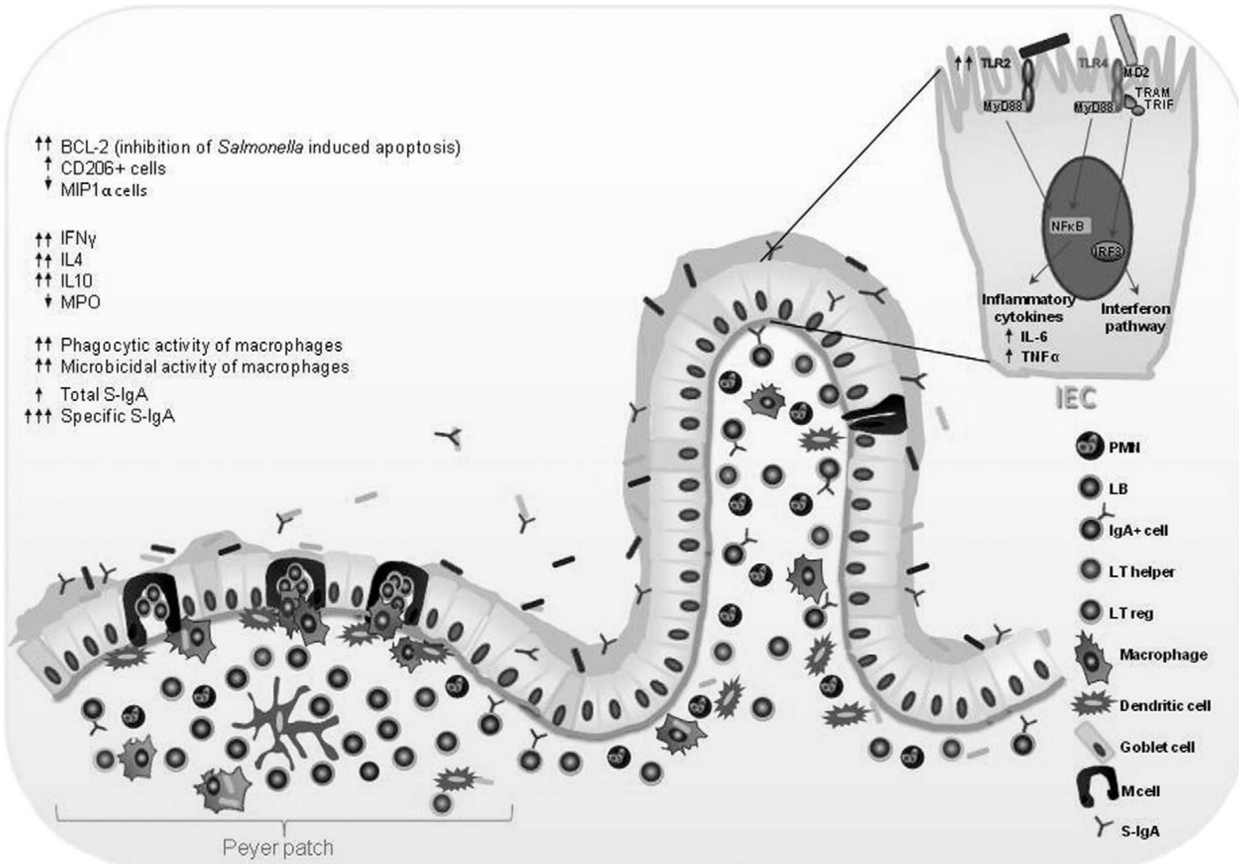

Fig. 2: Schematic diagram of some immune mechanisms generated by different probiotic strains against *Salmonella* infection. Probiotics produce an anti-inflammatory response, with increase of dendritic cells, macrophages, and Treg cells that produce regulatory cytokines such as IL-10. Probiotics also enhance IgA-secreting cells and mucus-producing cells that reinforce the intestinal defenses (Castillo et al. 2011).

Probiotic cultures were thought to have the potential to lessen exposure to chemical carcinogens in cancer studies. This can be performed by:
(i) detoxifying consumed carcinogens
(ii) modifying the intestinal environment which helps to minimize carcinogenic producing bacteria populations or metabolic activities
(iii) Producing metabolic products (e.g. butyrate) that start apoptosis
(iv) producing inhibitory substances to prevent tumor cell growth
(v) propagating the immune system in curtailing of cancer cell propagation for a better defense mechanism.

Probiotics may also boost the activity or synthesis of digestive enzymes in birds and shield them from the harmful effects of enzyme activity. Probiotics may also generate enzymes that hydrolyze or release nutrients in the host's digestive system. According to (Nahashon et al. 1994), layers given diets containing *L. acidophilus* showed a rise in phytase activity in the crop but not in their digestive systems. Additionally, enhanced P retention in layers was linked to higher phytase activity in the lactobacillus-fed birds.

All techniques must be carefully examined in each situation to have a comprehensive grasp of the probiotics' mechanism of action. Probiotic effects are the result of the probiotic bacteria' interaction with the host. Therefore, further research on the relationship between hosts and microorganisms is required

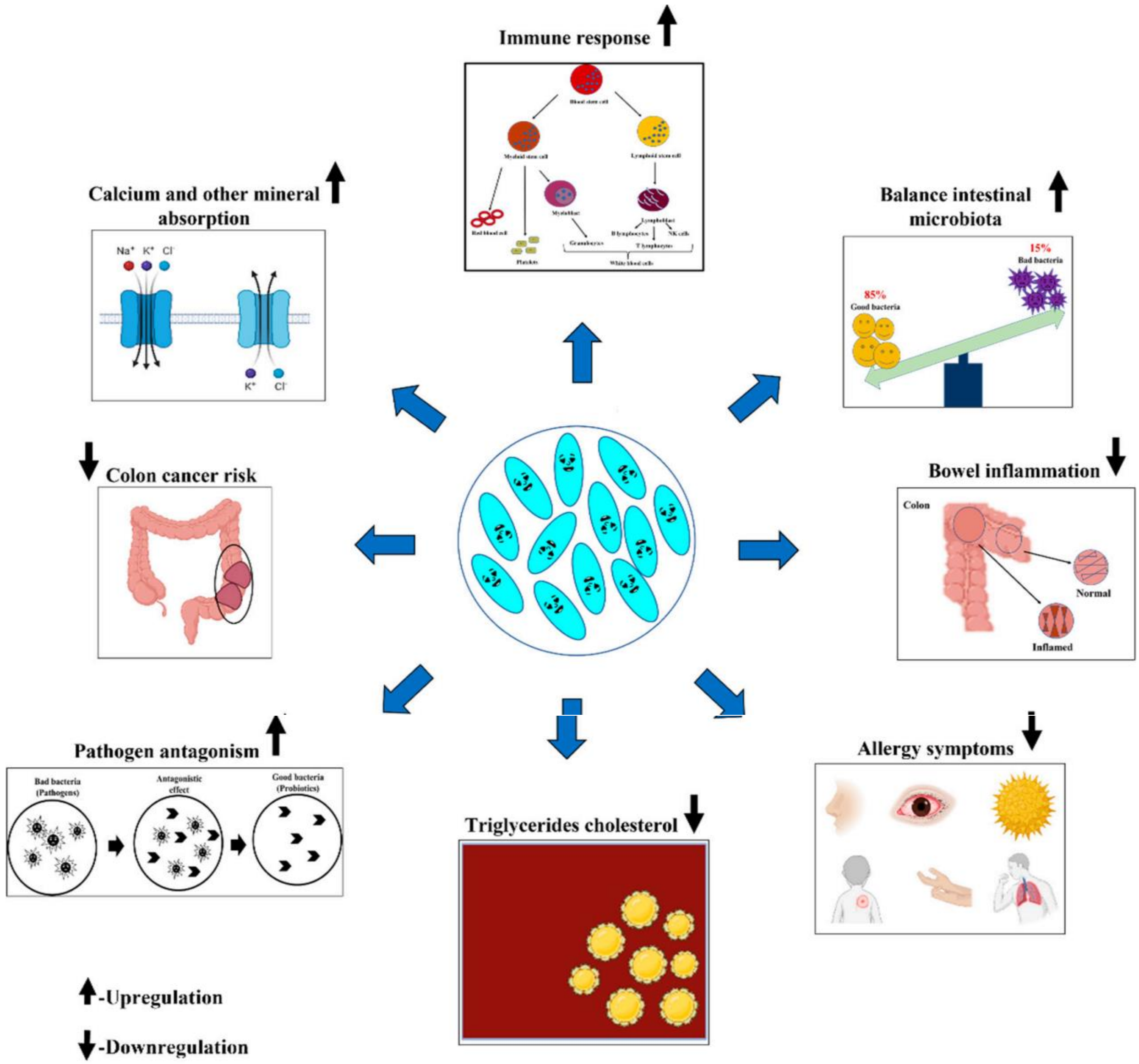

Fig. 3: Schematic view of Modes of action of probiotics (Galdeano et al. 2019)

to better understand how probiotics work. In the past, high research costs and underdeveloped molecular tools might have prevented in-depth examination of probiotic effects. The effects or mechanisms of action of probiotics may now be understood, however, thanks to several wonderful molecular approaches. Understanding microbial ecology and how probiotics function may be substantially facilitated by the rapid advancements in molecular techniques and DNA sequencing.

4. PROBIOTICS: A PRIMER

As per the definition given by the World Health Organization and the Food and Agriculture Organization, probiotics are live bacteria that, when properly provided, confer health benefits to the host and maintain health.

Decomposing bacteria and its components may also have probiotic-like qualities. The microorganism, which is commonly said to display the lactic acid bacteria and Bifidobacterium strains, has probiotic qualities and is employed in many healthful nutritional supplements and foods. Ideally, a genuine probiotic should be of safe human origin, in good health, and devoid of any pathogenic or toxic agents or vectors that might spread antibiotic resistance (Plaza-Diaz et al. 2019). Identification of the compounds one microbe produces that encourage another's development factors has updated the positive effects of symbiotic bacteria on mammals reaching the level of their intestinal fora (Bortoluzzi et al. 2020). Various investigations have shown a variety of potential theories surrounding probiotic classification according to evolutionary history. The development of genomic techniques has improved our ability to classify various probiotic species and mechanisms (Reid 2016). Several lactic acid bacteria (LAB) are regarded as probiotics as a result of the presence of these microorganisms when fermented with sugar-rich foods, the capacity to produce lactose (Plaza-Diaz et al. 2019). In line with their morphological and phenotypic features that are first lactic Termobacterium, Betacoccus, Streptobacterium, Tetracoccus, and Microbacterium were used to classify acid bacteria. Betabacterium. Currently, just Streptococcus is kept, whereas the remaining bacteria were given new names, including Bifidobacterium, Enterococcus species, and Lactobacillus species (Mohania et al. 2008). In terms of morphology, the *Lactobacillus* genus is a member of the *Firmicutes phylum,* class *Bacilli,* order *Lactobacillales,* and family *Lactobacillaceae*. It contains more than 170 species of Gram-positive, facultative, anaerobic, catalase-negative, rod-shaped bacteria. It is used in the creation of fermented foods that come from both plants and animals, including milk and meat (Zhang et al. 2018). *Bifidobacterium* is typically Gram-positive, non-motile, anaerobic, pleomorphic, non-sporting bacteria that result from the fermentation of carbohydrates into acetic, formic, and lactic acids (Vlkova et al. 2002). Because they are obligate anaerobes, *Bifidobacterium* cultivation is more difficult than *Lactobacillus* cultivation and frequently calls for more attention when it is used to make probiotic products and dairy products like yogurt (Abou-Kassem et al. 2020).

Today, encouraging an association of many probiotic species is a problem in probiotic analysis and production. This is due to research showing that it has a greater impact on a person's health than one probiotic usage. Eight different VSL, #3 probiotic substances were found to be effective in the treatment of a variety of conditions, including ulcerative colitis, boosting the immune system, improving diabetes patients' resistance to hepatic insulin, diarrhea, bowel disorders, and ulcerative colitis (Dong et al. 2016; Schlee et al. 2008). Additionally, combining *Bifidobacterium* strains with *Lactobacillus acidophilus* and (LA) has been proven to be effective in reducing the incidence of NEC (necrotizing enter colitis) and NEC-related deaths in infants with severe disorders (Nair and Soraisham 2013). When there is a mutual disruption between the probiotic consortia, the ability of the probiotic items will diminish. Therefore, it is important to guarantee that probiotic consortia won't interact with one another.

A single strain is insufficient; a combination of strains might be more beneficial, as shown by the basic research of probiotic products including bacteria, which indicated an effective improvement in the recovery of disorders (Nair and Soraisham 2013). On the other hand, although many microorganisms are regarded as probiotics, not all of them have the desired properties.

Before considering bacteria as a probiotic, numerous factors need to be considered, say researchers (Mitropoulou et al. 2013). To ensure the safety of probiotic products, the probiotic bacteria should be nonpathogenic and generally recognized as safe (GRAS) by the FDA Drug Administration and US Food.

There are living microorganisms in the gastrointestinal tract in addition to the beneficial bacteria that live in the human stomach. *Clostridium difficile* and *H. pylori* are the two most prevalent of these, but there are other types as well that might pose health risks.

By competing with supplements or adhering to the gastrointestinal region, probiotic use may prevent or minimize the growth of certain pathogens in the gastrointestinal system (Ohashi and Ushida 2009). In every circumstance, pathogens anticipate nutrients to multiply and either initiate or intensify diseases. The gastrointestinal system is noteworthy for its abundance of nutrients. It makes the environment suitable for the colonization of bacteria to begin. When compared to pathogens, the capacity of probiotics to win over the bacteria favors their growth (Khaneghah et al. 2020).

In the competition for nutrients, probiotics may create specific metabolites, such as unstable unsaturated lipids that disrupt the pH of the gastrointestinal system.

Because most pathogens cannot thrive at low pH, the pH lowering of the gastrointestinal system creates an unfavorable environment for bacteria and will inhibit pathogen development (Biswasroy et al. 2020). The digestive tract contains live bacteria, with *C. difficile* and *H. pylori* being the most prevalent. Other microbes are also present, and some of them pose health risks. Cocktail, a commercial probiotic, has been proven to significantly reduce salmonella infection in chicken tonsils and ceca (Moreno et al. 2010). Salmonella numbers included in the digestive system and further enteric dispersal are reduced by regular injection of Lactobacillus casei CRL, according to an in vivo study using a mouse model (Asahara et al. 2011). Probiotics, which predominantly encompass strains of *Lactobacillus, Bifidobacterium,* and other beneficial bacteria, play a pivotal role in maintaining gut homeostasis. They exert their influence through various mechanisms, including competitive exclusion, production of antimicrobial compounds, and modulation of the host immune response. These properties make probiotics an attractive candidate for preventing and mitigating Salmonella infections.

5. PROBIOTICS VS. SALMONELLA: A BATTLE FOR COLONIZATION

A key strategy employed by probiotics in combating Salmonella is competitive exclusion. By colonizing the gastrointestinal tract, probiotics create an environment that is less conducive for Salmonella to establish itself. This competition for resources and adhesion sites can significantly reduce the pathogen's ability to thrive. One of the most common causes of acute gastroenteritis, known as S. Typhimurium, is Salmonella enterica serovar typhimurium, which is characterized by inflammatory diarrhea. Inflammation facilitates in the making of colonization of S. Typhimurium and other Enterobacteriaceae, while the normal gut is mostly occupied by commensal microorganisms, namely Bacteroides and Firmicutes (Barman et al. 2008: Lawley et al. 2008: Lupp et al. 2007: Stecher et al. 2007). Recent research has demonstrated that *S. typhimurium* nourishes in the inflammatory gut because it can use particular carbon and energy reserves and is resistant to antimicrobial proteins produced by the host as part of the nutritional immune response (Thiennimitr et al. 2011; Liu et al. 2012; Raffatellu et al. 2009). The most significant micronutrient metal that S. Typhimurium uses is iron (Crouch et al. 2008; Raffatellu et al. 2009) which it acquires through specialized transporters (Liu et al. 2012; Raffatellu et al. 2009). Due to binding by host proteins such as heme, transferrin, ferritin, and lactoferrin, levels of free iron are very low in the host environment (Andrews and Schmidt, 2007). Hepcidin secretion, which stops the stomach from absorbing iron from the circulation by blocking the iron transporter ferroportin-1, is one of the additional strategies used by the host to further restrict iron availability during inflammation (Genz and Nemeth 2015).

Bacteria that lack iron produce and export siderophores, which are tiny, high-affinity iron chelators. All Enterobacteriaceae, including commensal E. coli and Salmonella, release enterochelin, a catecholate-type siderophore that is adequate to overcome the host's iron restriction in a normal (non-inflamed) environment (Raymond et al. 2003). However, when inflammatory responses happen, the host secretes antimicrobial peptide and lipocalin-2, which sequesters ferric enterochelin. As a result, strains of *E. coli,* such as *commensal E. coli,* that solely rely on enterochelin for siderophore-based iron acquisition are constrained in their growth (Berger et al. 2006). By producing extra siderophores that are not captured by lipocalin-2, certain infections can circumvent this response (Fischbach et al. 2006a). For instance, Salmochelin (Muller et al. 2009) a C-glucosylated enterochelin derivative that is too big to fit into the enterochelin-binding pocket of lipocalin-2 (Fischbach et al. 2006b; Hantke et al. 2003), may be produced and secreted by Salmonella.

Commensal bacteria known as probiotics are thought to have positive effects on the host. Probiotic strain *Escherichia coli Nissle* 1917 (*E. coli Nissle,* serotype O6:K5:H1) was first discovered in a soldier who seemed immune to a case of diarrhea *(Nissle*, 1959). Several intestinal disorders, including acute enteritis (Henker et al., 2007), have been treated or prevented with E. coli Nissle (Cukrowska et al. 2002; Kruis et al. 2004;; Mollenbrink and Bruckschen 1994; Nissle 1959), but it is unknown what mechanisms underlie these protective effects. According to Raffatellu et al. (2009), salmochelin-mediated iron acquisition during inflammation promotes *S. Typhimurium* colonization, therefore we reasoned that *E. coli Nissle* may defend the host by using comparable processes to compete with *S. typhimurium* for vital micronutrients.

The *E. coli* Nissle genome shared several fitness traits with strains of the same serotype of uropathogenic E. coli (UPEC), according to a snapshot study of the genome (Grozdanov et al., 2004). Contrary to popular belief, the *E. coli Nissle* genome seems to encode for as many iron uptake systems as UPEC (Martínez-García and Lorenzo 2011). Notable members of this arsenal include salmochelin, the hydroxamate-type siderophore aerobactin, the mixed-type siderophore yersiniabactin, and the hemin uptake transporter ChuA. It is hypothesized that redundancy in iron absorption, which encourages the development of UPEC in the bladder and kidney (Garcia et al. 2016) may also contribute to the colonization of the inflammation of the gut with *E. coli* Nissle.

6. IMMUNOMODULATION: STRENGTHENING THE HOST DEFENSE

Probiotics also play a vital role in modulating the host immune response. They enhance the activity of immune cells, such as macrophages and T cells, which are crucial in mounting an effective defense against Salmonella. Additionally, probiotics stimulate the production of antimicrobial peptides, reinforcing the innate immune system's capacity to combat the pathogen. First presented by Metchnikoff in 1907, the theory claims that intestinal bacteria cause "autointoxication," which is harmful to human and animal health. Additionally, he suggested that the prolongation of Bulgarian peasants was caused by their frequent consumption of fermented milk that contained living beneficial bacteria. As mentioned in previous sections, the gut microbiota has a significant influence on the host's immunology, biochemistry, physiology, and resistance to non-specific diseases (Gordon & Pesti, 1971). These findings have given rise to the hypothesis that altering the gut microbiota's makeup by dietary supplements may improve health (Goldin & Gorbach, 1992). According to Prasad et al. (1999), the two genera of probiotic bacteria that are most often utilized are Lactobacillus and Bifidobacterium. Gram-positive, non-spore-forming, catalase-negative, typically nonmotile rods, lactobacilli do not reduce nitrate and are not catalase-positive. According to Mikelsaar et al. (1998), the most often utilized lactobacilli species are *L. acidophilus*, *L. salivarius*, *L. casei*, *L. plantarum*, *L. fermentum*, and *L. brevis*. Bifidobacteria, on the other hand, are Gram-positive, non-spore-forming rods with unique cellular bifurcating or club-shaped morphologies. The species *B. animalis*, *B. longum*, *B. bifidum*, and *B. infantis* are the most often utilized ones.

It is widely accepted that at least 109 CFU/day of probiotics must be consumed (Ouwehand et al., 2002). The levels of lecithinase-negative clostridia in the feces were found to be much lower in research (Benno & Mitsuoka, 1992). Another research demonstrated that consumption of yogurt supplemented with *B. longum* substantially increased the number of Bifidobacteria in the treated participants' feces as compared to those who received control yogurt (Bartram et al. 1994).

In full-term newborns, Langhendries and colleagues (1995) studied the effects of drinking fermented baby formula containing live Bifidobacteria (106 CFU/g of *B. bifidum*), finding that there were significant increases in resident bifidobacteria. Human adult volunteers drank fermented milk containing Lb acidophilus LA2 for seven days; the number of resident *Lactobacilli* and *Bifidobacteria* rose noticeably in the excretions (Hosoda et al. 1996). The authors observed that the resident *Bifidobacteria* considerably increased and the clostridia counts dropped after examining the effects of ingestion of follow-up formula (NAN BF) containing *B. bifidum* strain Bb12 on fecal flora (Fukushima et al. 1997).

7. PROBIOTICS AND STIMULATION OF THE IMMUNE SYSTEM

Studies on both animals and people have shown that certain strains of lactic acid bacteria may trigger and control several features of acquired immune responses. Additionally, it has been shown that there are considerable variations in how well the immune system is modulated by various Bifidobacteria and lactobacilli strains and that these variations are dose-dependent. Readers are urged to study the outstanding reviews on the immunomodulatory effects of probiotics that have been published in recent years (Gill 1998).

Probiotics and probiotic-derived products are immunologically detected in the gut by specialized membranous cells (M cells), which are found on top of Payer's patches and epithelial cells. It has also been shown that dendritic cells, which are dispersed throughout the subepithelium, can directly sample lumenal antigens. Antigen-presenting cells (APCs) receive antigens that M cells have picked up, process, and offer them to naive T cells. Through the production of pattern-recognition receptors (such as TLRs and CD14) that identify pathogen-associated molecular patterns (PRRs), APCs can distinguish between closely similar bacteria and their byproducts. Whether T cells develop into T helper 1 (Th1), T helper 2 (Th2), or T regulatory (Treg) cells depends on the kind of cytokine release, phenotype, and level of activation of APCs. Th1 cells are subsequently activated, producing IFN-g, TNF-a, and IL-2, which is linked to the emergence of cell-mediated and cytotoxic immunity. Activated Th2 cells primarily secrete IL-4, IL-5, and IL-13, which promote the production of antibodies and are linked to atopy. Treg cells secrete IL-10 and TGF-b, which suppress both Th1 and Th2 cell activity.

8. ANTI-SALMONELLA COMPOUNDS: NATURE'S ARSENAL

Certain probiotic strains secrete antimicrobial compounds, such as bacteriocins and organic acids, which can directly inhibit the growth of *Salmonella*. This chemical warfare, waged by probiotics in the gut ecosystem, further diminishes the pathogen's ability to proliferate. Many probiotic strains have the capacity to synthesize a range of antibacterial compounds. The most frequent ones are carbon dioxide, hydrogen peroxide and antibacterial compounds like bacteriocins and non-bacteriocin, non-lactic acid molecules (Fayol-Messaoudi et al. 2005; Marianelli et al. 2010). These organic acids (lactic acid and acetic acid) cause a reduction in fecal pH. The ability of six Lactobacillus strains, including probiotic ones, to prevent the invasion of *S. Typhimurium* SL1344 into Caco-2/TC7 cells in culture was examined. Some of them produced just lactic acid, whereas other strains produced both lactic acid and one or more additional inhibitory substances, which were responsible for their antibacterial action (Makras et al. 2006). Another in vitro investigation revealed that the buildup of lactic acid was the cause of *L. rhamnosus* GG's antibacterial action against *S. typhimurium* (De Keersmaecker et al. 2006). In their investigation of the antibacterial properties of *L. plantarum* ACA-DC287, which they isolated from a Greek cheese. Fayol-Messaoudi et al. (2009) found that non-lactic acid molecules present in the probiotic strain's cell-free culture supernatant were responsible for killing the pathogen when it was co-cultured with S. Typhimurium. Additionally, *S. Typhimurium* was prevented from penetrating cultured human enterocytes like Caco-2TC7 cells by L. plantarum. According to Lin et al. (2008), a probiotic strain may prevent Salmonella choleraesuis from invading the human Caco-2 cell line via a variety of processes, including the generation of organic acids and bacteriocins.

There are several cases where bacteriocins produced by probiotic LAB influencing the health of the gastrointestinal (GI) tract (Gillor et al. 2008). Bacteriocins produced by lactic acid bacteria (LAB) have been thoroughly described (Castro et al. 2011: Cintas et al. 2000). However, due to their seldom inhibition of frequently encountered enteropathogenic bacteria as *Klebsiella, Enterobacter, Salmonella* or bacteriocins produced by Gram-positive bacteria have limited probiotic uses in the gastrointestinal tract.

9. STRAIN-SPECIFIC EFFICACY

It is important to note that not all probiotic strains possess equal efficacy against Salmonella. The choice of probiotic strain(s) is critical, as each may have distinct mechanisms of action and affinities for specific Salmonella serotypes. Thus, a tailored approach is necessary to select the most appropriate probiotic(s) for a given scenario.

10. CHALLENGES AND FUTURE PROSPECTS

Despite the promise of probiotics, challenges remain. These include strain stability, host-specific responses, and the need for standardized protocols for administration. Additionally, further research is warranted to better understand the complex interactions between probiotics and Salmonella.

11. CHALLENGES OF PROBIOTICS IN ANIMAL FEEDING

Animal feed products often include probiotic microbes, which are typically thought to be safe. The likelihood of propagating antibiotic resistance is increased by the presence of communicable antibiotic resistance genes in a few probiotic bacteria, and contagions from probiotic microorganisms as well as the occurrence of entero and emetic toxins are the main risks attached to probiotic microbes used in animal feed. most studies on probiotics. In papers, efficiency is more often discussed than safety. The most comprehensive information on probiotics' health is solely based on *Lactobacillus* and *Bifidobacterium.* Therefore, more studies about the safety and usage of probiotics. Probiotics used in animal feed are generally safe for animal protection, although when dealing with dangerous or unfavorable microorganisms, measures for people and the environment should be followed. Threats related to the use of probiotics in animal feed, hypothetically are listed below. the probiotic-eating animal contracting a GIT infection;
ii. GIT infection in customers who consumed animal products made by animals given probiotics;
iii. Transmission of antibiotic resistance to other pathogenic microorganisms through probiotics;
iv. Animal and human food handler infections;
v. Skin or eye sensitivity or discomfort in probiotic administrators;
vi. Probiotics' production of toxins that have negative metabolic or toxic effects on humans
vii. Hyperstimulated immune systems in susceptible hosts.

Animal feed containing probiotics must be considered before recognizing microorganisms as probiotics. should be compared to the dangers listed above. It's necessary to identify microbes down to the strain level to assess the specificity of a certain bacterium and to comprehend its advantageous attributes. When determining whether or not to utilize microorganisms as probiotics in animal feed, as seen in Fig. 4, there are a few issues that need to be resolved. Probiotics are primarily utilized The most secure bacteria are often *Lactobacillus* and *Bifidobacterium.* Numerous fermented foods have exploited microbes widely and historically for quite lengthy (Shortt et al. 1994). The GIT of people often contains a significant amount of these microorganisms. and animals, and diseases caused by these microbes are quite uncommon. According to the US Food and Drug Administration, *Lactobacillus bulgaricus* and *L. acidophilus* are "Generally Regarded as Safe" (GRS). The European Food Safety Authority (EFSA) has determined that a

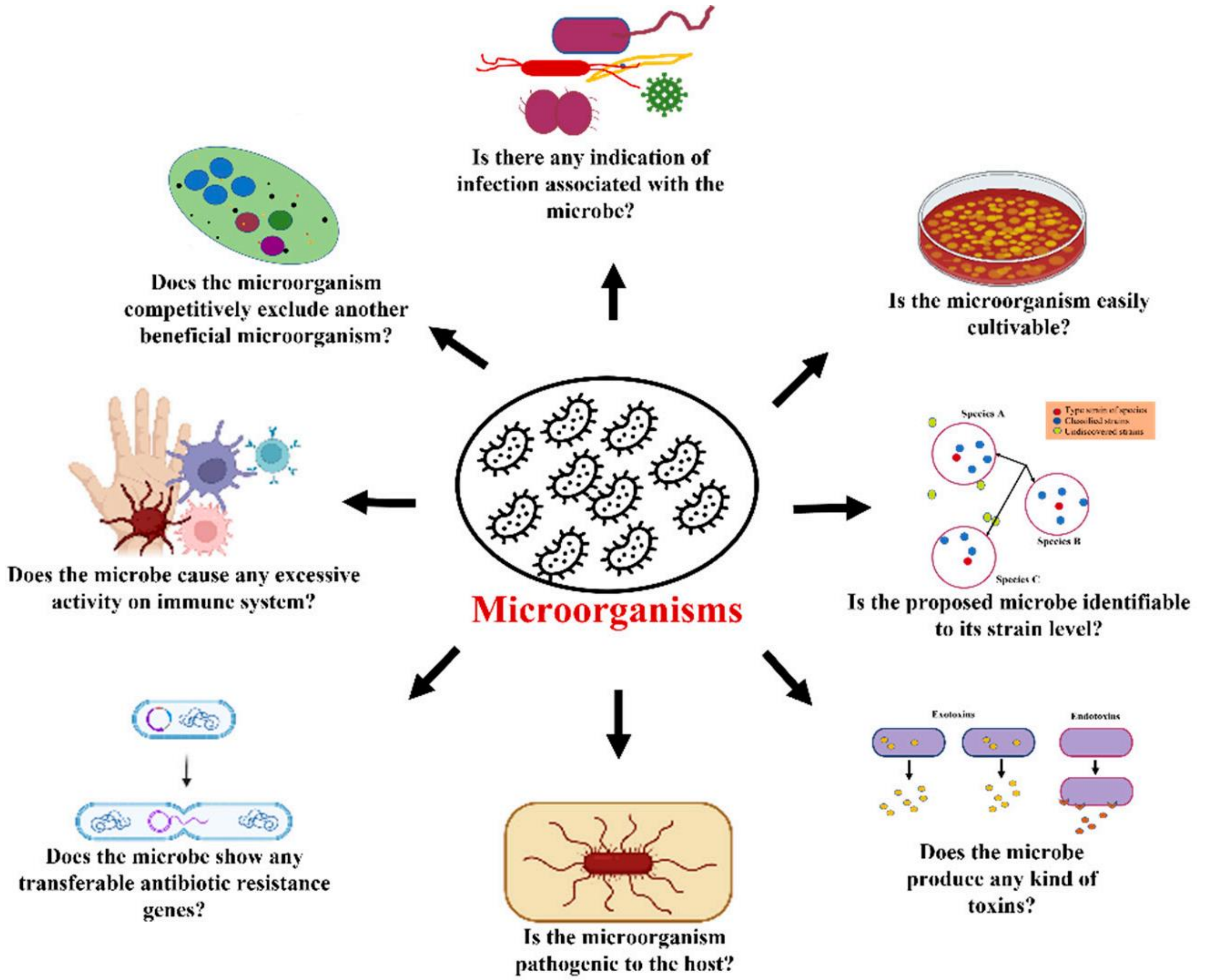

Fig. 4: Evaluation of potential probiotics in animal feeding.

select Bacillus species, such as *B. subtilis, B. megaterium, B. licheniformis*, and *B. coagulans*, are safe since they don't contain any toxins. Even while Enterococcus bacteria have many positive benefits, they have been linked to only a small number of human diseases, such as those that are acquired in public places and hospitals. Therefore, before using *Enterococcus* bacteria as probiotics, rigorous safety assessments are required (Arias et al. 2012).

12. FUTURE DIRECTIONS

According to research, probiotics are a major source of antimicrobials that promote good health and are used as a source of nutrients in the production of animals.

Probiotics may replace antibiotics that promote growth, strengthening the animals' immune systems in the process. Even with the existing understanding of how probiotics affect organisms, research is still being done to better understand some of their mechanisms of action. In the future, it will be crucial to understand how probiotics work in order to combat a certain element of growth or animal performance. Numerous applications of probiotics and their distinct diagnostic and therapeutic functions may be revealed by further study on certain gene expression pathways or metabolic pathways connected to the impact of probiotics. Targeted probiotic applications may also address a number of disease-related issues in both people and animals. Transcriptome and metabolomics, two cutting-edge molecular approaches, provide detailed information on the mechanisms of action of probiotics, illuminating their positive impacts and how they enhance bird performance. Additional investigation into certain gene expression pathways, such as those identified using metabolomics assays linked to the impact of probiotics, reveals multiple probiotic applications as well as their distinct diagnostic and therapeutic purposes. Probiotics may be used in very particular ways to address problems with a variety of diseases that affect both people and animals. Although probiotics have been praised for improving animal performance, including health, there are drawbacks to giving them to animals. Some probiotic species, like enterococci, may carry genes for drug resistance that are transmissible, while others, like Bacillus cereus, may create enterotoxins that might be hazardous to the host. Lack of knowledge about the probiotics' potential interactions with host cells and their appropriate safe dosages is another major obstacle to their utilization. Therefore, research must be improved to show that probiotics may be used appropriately and efficiently based on the circumstances of the target individuals or host organisms.

13. CONCLUSION

Probiotics represent a compelling avenue in the fight against Salmonella infections. Their multifaceted approach, encompassing competitive exclusion, immunomodulation, and the production of antimicrobial compounds, makes them invaluable allies in this battle. With continued research and a refined understanding of strain-specific efficacy, probiotics hold great promise for controlling salmonellosis and potentially revolutionizing our approach to infectious diseases.

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