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REVIEW ARTICLE

Probiotics as an Alternative Approach to Antibiotics for Safe Poultry Meat Production

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A B S T R A C T

Poultry industry is growing at large scale being good source of animal origin protein for the humans. To have optimum output in terms of meat and eggs many practices are being applied to the commercial flocks. Different types of the growth promoters including phytochemicals, amino acids, organic acids and antibiotics at sub-therapeutic dosages are used. This use of antibiotics as growth promoter led to the antimicrobial resistance which is big challenge for the poultry industry in terms of infection control and residues in the meat. It also has concerns in terms of One Health Triad. Because this sub-therapeutic use of antibiotics leads to the emergence of superbugs for the birds as well for humans. There is a dire need to find out some alternative approaches those not only improve the growth performance as well as boost the immune system of the birds that prevents the outbreaks of the infections. Many prebiotics and probiotics are being identified those can be used in poultry to improve the efficiency of flocks, quality of meat and also enhance the profit margins of the framers. Probiotics have many advantages over the other growth promoters as per the published literature. So, in this article a comprehensive review of the probiotics, types, how they affect the bird's physiology and immune system that can make them a safer choice, has been done so that they can pave the way about future of the probiotics for the poultry scientists and farmers.

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INTRODUCTION

Food safety is always a top most priority in terms of public health and becomes more significant while considering animal origin protein including eggs and meat. Many of the food borne pathogens can cause illness to the poultry birds starting from the initial hatch to the meal preparations. Two most common causes of foodborne illness in humans are campylobacter and salmonella and efforts are made to control these infections in poultry either through prevention or eliminations (Ricke, 2021). Antibiotics remain the only choice to control such infections and used at sub-therapeutic level in feed. This practice ultimately results in development of microbial resistance in birds as well as in humans consuming these birds as meat (Elalamy *et al*., 2020). Now-a-days, poultry industry is under continuous pressure to control the use of antibiotics as feed additives (Cox and Dalloul, 2015).

Poultry industry based upon its size and production is vertically integrated animal industry and is continuously expanding due to high demands of meat and eggs (Dittoe *et al.,* 2020; Jeni *et al.,* 2021). Poultry has become an established industry around the globe and the poultry sector has strengthened its position in agri-food production. However, the demand for the poultry meat is increasing tremendously being the cheap source of animal protein, so the utilizations of the antibiotics as a therapeutic agent to combat many pathogens associated problems as well as a feed additive to enhance the production efficiency is there. The perception is that by 2050, the human population will be 9.3 billion and production and consumption will be 60% higher than today (Krysiak *et al.,* 2021). As per FAO (Food and Agriculture Organization) report, it has been estimated that the global poultry meat consumption will increase by 52% and egg consumption will be around 39% in 2050 (Krysiak *et al.,* 2021; Susanti *et al.,* 2021). So, this increasing demand has put a pressure on industry to improve the efficiency in terms of meat and egg production and it can be achieved through preventing the outbreaks of infections. Previously, antibiotics including streptomycin, tetracycline, avoparacin etc. have been used as growth promoters to improve the performance of the birds in terms of body weight gain (Dibner and Richards, 2005; Krysiak *et al.,* 2021) and as well as to control the outbreaks which now-a-days is of significant concern due to harmful effects on consumers in terms of residues (Kabir, 2009; Alkhalf *et al*., 2010; Krysiak *et al.,* 2021). In 2006, the restrictions from the EU (European Union) regulatory bodies were introduced on AGPs (antibiotics as growth promoter) and prophylactic and this policy has also been adopted by the other countries including Mexico, South Korea and New Zealand. On the other hand, the USA, Australia, Japan and Canada have partially banned the derivatives of antibiotics and excluded some as growth promoter. As per these policies, this is big challenge for the poultry industry (Salim *et al.,* 2018; Ramlucken *et al.,* 2019; Susanti *et al.,* 2021; Krysiak *et al.,* 2021).

This overall scenario of the challenging demand and food safety concerns have stressed the scientists and researchers to find some alternative approaches to control the pathogens, improving the efficiency of birds in terms of FCR and being safer for the human population (Haung *et al*., 2004; Panda *et al*., 2006; Rashid *et al*., 2022). The producer and consumer both are interested in alternative approaches to the antibiotics. Many alternatives are being developed like antibodies, bacteriophages, vaccines, antimicrobial peptides, organic acids, enzymes, plant derivatives, essential oils, prebiotics and probiotics (Abbas *et al*., 2011a,b; Abbas *et al*., 2012; Idris *et al*., 2017; Yasmin *et al*., 2020; Hussain *et al*., 2021; Rani *et al*., 2021; Sharif *et al*., 2021; Rashid *et al*., 2022). Most of the studies have emphasized the use of prebiotics, probiotics and combination of both to have maximum output from the poultry (Hussein *et al.* 2020a; Abd El-Hack *et al.,* 2020; Susanti *et al.,* 2021; Krysiak *et al.,* 2021; Popov *et al.,* 2021; Rashid *et al*., 2022). Many of these alternatives have proved themselves in the last years but not cost effective (Ramlucken *et al.,* 2019) and probiotics proven to be more beneficial as compared to all other available options (Shewita and Taha, 2018; Arif *et al.,* 2019, 2020; Abd El-Hack *et al.,* 2017, 2020; Khan *et al*., 2020). So, in this review, the information regarding these alternative approaches particularly probiotics and their beneficial effects have been reported and how they can be a game changer for the poultry meat industry.

Probiotics history: Probiotics have also been defined as feed supplement which consist of useful microbes and substances those have been defined as a live microbial feed supplement that beneficially affect the intestinal microbial balance resulting in enhanced FCR and improved body weight gain and decrease mortality in broiler birds (Haung *et al*., 2004; Panda *et al*., 2006; Kabir, 2009; Krysiak *et al.,* 2021) and also have no negative correlation with the profit margins **(**Cox and Dalloul, 2015). Probiotics has been explored as an option mainly to reduce the enteric infection and also to reduce the meat contaminations in terms of public health. These are non-pathogenic, live microorganisms having potential beneficial effects on gut microbiota, immunomodulators, and as an additive enhances the early colonization of beneficial bacteria (Cox and Dalloul, 2015; Kumar *et al.,* 2016; Jamal *et al.,* 2019).

Elie Metchnikoff was the first investigator in the area of probiotics who reported in Bulgarian peasants that the human consuming large amounts of soured milk enjoy long life span that strengthen the belief of the scientist that the soured milk improves the lower gut health and overall microflora. Later on, he tested milk samples cultures fermented by Lactobacillus spp, and that *Lactobacillus bulgaricus* became the popular strain for yoghurt fermentation (Fuller, 1992; Forkus *et al.,* 2017, Ran *et al.,* 2019; Abd El-Hack *et al.,* 2020).

The word "probiotic" has been used differently in past, originally meant for the products produced by a protozoa that stimulate production of other substances (Kabir, 2009; Azad *et al.,* 2018). Later on, used for the animal feed supplements description which had beneficial effects on gut microflora of the host. Various researchers defined it as per their own findings. For example, Fuller defined it as "a live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance" (Fuller, 1989; Jamal *et al.,* 2019). Crawford (1979) has explained it as "a culture of specific living micro-organisms (primarily Lactobacillus spp.) which implants in the animal to ensure the effective establishment of intestinal populations of both beneficial and pathogenic organisms" (Kabir, 2009). Verschuere *et al.* (2000) proposed a detailed definition of the probiotics as "a live microbial audit which has beneficial effect on the host by modifying the host-associated, ambient microbial community through improvement of its feed or enhancing its nutritional value and also by enhancing the host response toward diseases or by improving the quality of its ambient environment" (Jamal *et al.,* 2019).

The meaning and terminology of the probiotics have been changed over the years. For example, in 1953, the term "probiotika" was introduced for the scientific community by Werner Kollath (1953) and defined the term as the live microorganisms being essential for the healthy development of the gut. Later in 1965, the same term was redefined as "the microorganisms that would aid in the growth of the beneficial microflora in the gut" (Vila *et al.,* 2010; Azad *et al.,* 2018) that is still credit the todays meaning of the word Probiotic but opposite to the meanings of word "antibiotic" where the antibiotics represent that inhibit the growth of microorganism through chemical substance (Fuller, 1992; Wang *et al.,* 2019; Abd El-Hack *et al.,* 2020). A comprehensive definition of the probiotics has been approved by the FAO and WHO as "living microorganisms which when administered in adequate amount confer a health benefit on the host" (Azad *et al.,* 2018; Krysiak *et al.,* 2021).

Characteristics of probiotics: The criteria to a probiotics has been defined by the US National Food Ingredient Association is that it should be living microorganism including bacteria, fungi and yeast (Kabir, 2009) , nonpathogenic, non-toxic, favorable to the host health when administered through digestive route (Guillot, 1998; Kabir, 2009), resistant to the acidic environment of digestive system, can adhere to the intestinal epithelium and maintain the microflora present physiologically in intestine (Mottet and Tempio 2017; Krysiak *et al.,* 2021).

Specific strains of probiotics have this unique ability to survive in host during extreme environments. When they pass through the acidic environment of GIT due to the stomach acids and bile salts, still they are viable (Smith, 2014; Abd El-Hack *et al.,* 2020). This is mainly a big challenge, as the pH of simple stomach species ranges from 1.5-3.0, addition to that the many of the gastric enzymes and bile salts in intestines lead to breakdown of these organisms (Fontana *et al.,* 2013; Abd El-Hack *et al.,* 2020). In these conditions, spore forming species mostly germinate and survive. Another school of thought is that after germinating, these bacteria adhere to the food particles that prevent them from degradation in GIT and they can safely transit through re-sporulation mechanisms. It is totally dependent on the feed of the animals or birds because microorganisms require plenty of nutrients for the germination and proliferations (Johnson *et al.,* 2019; Abd El-Hack *et al.,* 2020).

Mechanism of action of Probiotics in poultry: Probiotics when ingested by the birds induce the physiological changes in the intestinal tissue structures that lead to immunological alterations in the whole GIT. This immunomodulation enhances the bird's resistance to the pathogens. It has been suggested that probiotics produce the short organic fatty acids along with other metabolites those have antimicrobial activities through the stimulation of receptor sites that lead to immune system activation and enhancement (Sherman *et al.,* 2009; Abd El-Hack *et al.,* 2020). Four major factors have been reported that prefer the development of beneficial microflora including (1) optimization of intestinal ecosystem and its antagonistic to other bacterial populations, (2) removal of the existing receptor sites for the pathogenic species, (3) secretion of antimicrobial metabolites and (4) competing for the nutrients (Rolfe, 1991; Abd El-Hack *et al.,* 2020).

Ideally these probiotics in poultry alter the microflora of the GIT tract and also enhance the mucin production through altered synthesis mechanism and its degradation that affects the capability of microflora for the nutrient's uptake (Patterson and Burkholder, 2003; Reid, 2006). Another structural effect on the intestine has been reported that the probiotics lead to the development of the villi and lead to increase in their size ultimately increasing surface area for the nutrient's absorption (Gunal *et al*., 2006; Panda *et al*., 2006). Beneficial effects on goblet cells, pyer's patches from M cells, and follicles for the gut associated lymphoid tissue (GALT) have also been reported. Their growth has positive correlation with the immune system of the birds through the production of IgA and IgM (mucosal antibodies) along with release of various cytokines like IL-10, IL-12 and tumor necrosis factor-alpha (TNF-α) that ultimately prevent the outbreak of GIT infections (Otutumi *et al*., 2012).

Intestinal mucosal modification also has been attributed to the changes produced by the probiotics through enhanced enzymes and metabolites activities that lead to change in flora and pH of intestine making it more favorable for the digestion and absorption of feed nutrients. These enzymes also have synergistic effects on the endogenous GIT enzymes those are responsible for the digestion and improve the wight gain in the flocks. These alterations in the intestine ultimately reduce the ammonia production in birds that improves the overall health status of the birds (Kabir, 2009; Rahman *et al*., 2009).

Promising effects of probiotics on Feed conversion ratio (FCR) have been reported in the poultry birds. It has been reported that the FCR becomes efficient through the increased growth of beneficial intestinal microflora, that ultimately leads to the more consumption and digestion of feed nutrients and inhibition of pathogenic strains. It has been stated that many factors can affect the efficiency of the probiotics like the strains selected, dose, route of administration, GIT environment and age of the birds (Kabir, 2009; Vineetha *et al*., 2017).

As the yeast is also being used as probiotics because it fulfills the criteria to be a probiotic, hence the mechanism of action how it improves the performance of poultry birds has not yet defined completely. First school of thought is that it probably supports the growth of beneficial microflora in the intestinal tract and second is more concerned with the elimination of pathogenic ones and their adverse metabolites (Gheisari and Kholeghipour, 2006). The metabolites produced by the yeasts are very similar to those produced by the bacterial strains including organic acids, amino acids, peptides and oligosaccharides having positive effects on the physiological performance of the birds (Gao *et al*., 2008; Muthusamy *et al*. 2011). Yeast also contains organic acids that increases the protein metabolism and vitamins absorption in poultry birds. Morphological alteration in the intestinal structures, that is having potential effects on FCR and weight gain, has also been attributed to the yeast supplementation just like that of bacterial strains (Nilson *et al*., 2004; Ghosh *et al*., 2012).

Effects of probiotics on immune system: As it has been mentioned in the section mechanism of action of probiotics, how they affect the intestinal immunity to have better outcome in terms of bird's physiological response on overall health status, weight gain, FCR etc., a brief description on overall immune has been mentioned in this section.

In poultry, probiotics also stimulate the systemic immune responses to some pathogens through enhanced secretion of antibodies form B-1 cells including IgA, IgG and IgM. Majority of these IgM participates in inmate immune responses against many invading pathogens prior to the stage when adaptive immune response overcome (Haghighi *et al*., 2005; Haghighi *et al*., 2006; Kumar *et al.,* 2013). It shows the overall immune stimulatory effects on avian immune system (Salim *et al*., 2013).

This immunostimulatory effect is attributed in two different ways. Firstly, all the viable microflora start to move and multiply in the intestine, and secondly the dead microflora secrete antigens and these are absorbed which ultimately boost the immune system (Otutumi *et al*., 2012). Among these, antigens like lipopolysaccharides and peptidoglycans are continuously releasing in intestinal lumen and during the infection their production is enhanced manifolds. This leads to the change in the intestinal epithelium of the host having chemotactic effects on mucosal cells responsible for immunity through the release of mediators like metalloproteins (Elastase and Cathepsin), cytokines, reactive oxygen and nitrogen metabolites which ultimately stimulates the synthesis of immunoglobulins (IgM, IgA and IgG) along with enhanced T lymphocyte migration and interferon production. In non-pathogenic bacteria (already present in the intestinal microflora) probiotic supplementation leads to the activation of dendritic cells that mediates the T-helper cells responses and stimulates the interleukin release particularly Il-4 & 10, those are important for the immunoglobulin production (Di Giacinto *et al*., 2005).

It has been reported that all the probiotic supplemented birds have increased antibodies production against Newcastle disease virus 10 days after post immunization as compared to the groups not supplemented with probiotics (Khaksefidi and Ghoorchi, 2006). Similarly, it has been documented that probiotic supplementation in newly hatched chicken stimulates the immune system (Qubih and Amin, 2011).

Effects of probiotics on poultry meat: As the probiotics have beneficial effects on the general physiological and immunological parameters of the birds. They also have proven to improve the overall carcass properties of the poultry birds along with chemical composition of meat, however depending upon the type of probiotic, composition and concentration being fed to the birds. Probiotics improved the carcass weight alongwith reduction in abdominal fat that improves the carcass quality (Hidayat *et al.,* 2016; Krysiak *et al.,* 2021) thus resulting in improved economic impact. As the probiotics increase the absorption of nutrients particularly amino acids so they help in muscle mass development and other body tissues (Hidayat *et al.,* 2016; Aziz *et al.,* 2020). These amino acids also improve the protein content of the thigh and breast muscles. In an experiment, it has been observed that if the probiotic @ 0.16 g/L is offered to the birds in drinking water, it improves the water absorption particularly in pectoral and thigh muscles. Many studies have reported the positive effects on microstructure of meat, like decrease in myofibril destruction in probiotic fed birds. Moderate effects on cooked breast meat have also been reported like elasticity, firmness, chewniness and cohesiveness (Ali and Abdelaziz 2018; Hussein *et al.,* 2020b; Krysiak *et al.,* 2021).

Commonly used probiotics in poultry: About thirty probiotics products are registered with EU currently and combinations of several strains of bacteria are also allowed as per regulation. Mainly available probiotics are *Bacillus* spp., *Bifidobacterium* spp., *Enterococcus* spp., *Lactobacillus* spp., *Lactococcus* spp., *Saccharomyces* spp., *Streptococcus* spp., *Aspergillus* spp. and *Candida* spp. (Jin *et al*., 1996; Kabir, 2009; Parker *et al.,* 2016; Ramlucken *et al.,* 2019; Krysiak *et al.,* 2021). These isolates from bacteria as probiotics produce enzymes or the enzyme activating products which activate the xylanases, phytases or cellulose proteases. In the modern era, the probiotics have processed through granulation process and changed into the spores and being used as feed additives.

Mainly probiotics are being administered through feed on poultry farms, while other routes or methods are also practiced including sprays, granules, coated capsules, tablets, powder sachets and gavages in the form of vaccines or drops. Some water formulations are also being practiced at grower level in poultry flocks (Jiang *et al.,* 2017; Hargis *et al.,* 2018; Krysiak *et al.,* 2021). In all these, the strategy remains the same that is to tackle the pathogen.

Among these, *Saccharomyces cerevisiae* known as baker yeast is used as probiotic in broiler feed both in starter and finisher. Already yeast products have been used as growth promoter in poultry feed. Mostly yeast added in the feed as yeast by products, commercial formulations or fermented mash of yeast that is produced on the farms (Saied *et al*., 2011). The cell wall of the *Saccharomyces cerevisiae* has positive developmental effects on the intestinal mucosa (Santin *et al*., 2001; Zhang *et al*., 2005). β-glucan and mannan oligosaccharides in this yeast also have positive effects like increased feed intake and body weight gain in commercial flocks (Adebiyi *et al*., 2012). Additionally, it also decreases the vaccine failure and boost the immune parameters including increase in lymphocyte proliferative responses and phagocytic cell activities. *Saccharomyces cerevisiae* also contains vitamin B complex, minerals and proteins (Ahmed *et al*., 2019).

Bacillus is another available option for the poultry and it is a spore forming bacterium hence having more potential to be used as probiotic. Three strains are commonly used including *B. subtilis, B. licheniformis* and *B. cereus* (Larsen *et al.,* 2014; Popov *et al.,* 2021). Addition to these, another strain of bacillus (*B. amylolique faciens* B-1895) has also shown positive effects on physiological performance and meat quality of birds. This strain also has potential effects on the degradation of non-starch polysaccharides, phytates in the feed and the enzymes secreted help in nutrients absorption (Chen *et al.,* 2014; Chistyakov *et al.,* 2015; Farhat-Khemakhem *et al.,* 2018; Popov *et al.,* 2021). Bacilli strains also maintain the intestinal homeostasis through the production of antimicrobial and xenobiotics. In cocks fed with probiotic, an additional effect, decrease in cholesterol level in hepatic tissue and serum has been documented (Endo *et al.,* 1999; Jandhyala *et al.,* 2015; Rowland *et al.,* 2018).

Bifidobacterium spp. are also being used as probiotic alone or in combination to other bacterial strains. The commonly used strains of the *Bifidobacterium* spp. are *B. bifidum*, *B. longum*, *B. animalis* and *B. infantis* have been administered through in-ovo inoculation that altered the ileal environment by increasing the lactic acid producing bacterial population along with decrease in the total coliform counts. However, it has been documented that *Bifidobacterium* has caused meningitis in a child, so should be selected carefully as probiotic due to its zoonotic potential (Abd El-Moneim and Sabic 2019; Abd El-Hack *et al.,* 2020). Some commercially available probiotics for different poultry birds (broilers, layers and ducks) in the market have been summarized in Table 1 along with the strains used for the formulation (Data has been collected from various sources on internet).

Conclusions: As the market for the probiotics have surpassed nearly 44.2 Billion US$ in the recent years around the globe and expectation is that it will cross 74.3 Billion US$ by 2025 at a growth rate of about 7.7%. For this tremendous demand for the probiotics, there is dire need to find out more efficient and economical species and technologies. Though a little knowledge is available regarding the zoonotic implication of already available options so more work should be done to make the poultry products safer for the consumers.

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Table 1: Commercially available Probiotics for Poultry

Bacterial Species used for Formulation	Bacterial Strain	Commercial Product	Reference
Lactobacillus acidophilus	Not available	Acid-Pak-4-Way	Krysiak *et al.* (2021)
Enterococcus faecium			
Bifidobacterium bifidum	Not available	Biogen D	Krysiak *et al.* (2021)
Lactobacillus acidophilus			
Pediococcus faecium			
Pediococcus acidlactici	CNCM MA 18/5M	Bactocil®	
Bacillus subtilis	DSM 5749	Bioplus 2B®	Bogere *et al.* (2019)
Bacillus licheniformis	DSM 5750		
Enterococcus faecium	NCIMB 10415	Cylactin LBC®	
Enterococcus faecium	M-74	Lactiferm	Krysiak *et al.* (2021)
Lactobacillus acidophilus	CECT 4529	*Lactobacillus acidophilus* D2/CSL®	Savvidou (2009)
Enterococcus faecium	DSM 5464	Microferm®	Savvidou (2009)
Enterococcus faecium	DSM 10663/NCIMB10415	Oralin	Krysiak *et al.* (2021)
Bifidobacterium bifidum	Not available	Probiomix	Krysiak *et al.* (2021)
Lactobacillus amylovorus			
Enterococcus faecium			
Lactobacillus acidophilus	Not available	Primalac®	Bogere *et al.* (2019)
Lactobacillus casei,			
Bifidobacterium thermophilum			
Enterococcus faecium			
Enterococcus faecium	DSM 4788/ATCC 53519	Probios PDFM Granular®	Savvidou (2009)
Enterococcus faecium	DSM 4789/ATCC 55593		
Lactobacillus acidophilus	Not available	Probios	Krysiak *et al.* (2021)
Lactobacillus casei			
Lactobacillus plantarum			
Enterococcus faecium			
Bacillus subtilis	DSM 32315	GutCare® PY1	Krysiak *et al.* (2021)

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