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A review on probiotics for animals and their mode of action

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Abstract

Antimicrobials are used to treat illnesses like calf scour and maintain performance. Animals that receive antibiotics as nutritional modifiers may experience changes in the makeup of their gut bacteria due to the emergence of resistant strains or the spread of resistance genes to other bacteria. Since growing concern about antibiotic resistance, its impact on the environment and chemical residue persistence in animal products, probiotics as an alternative feed additive have been developed to improve animal health and productivity. FAO/WHO defines probiotics as live microorganisms which, when administered in adequate amounts, confer a health benefit on the host. Probiotics should improve the native microflora's attributes or the gut microbial balance, which will benefit the host animal. The status of these microorganisms is "generally recognised as safe" (GRAS). As lactic acid bacteria have the ability to significantly modify the microenvironment in the GIT through their metabolites and inhibitory compounds, they can be employed as helpful microorganisms, or probiotics. They have different modes of preventing pathogen colonisation and activity. This review paper provides a better understanding of Probiotic Concept, Characteristics, mode of action and benefits for farm animals.

Keywords: Probiotics, animals, mode of action

Introduction

The term "probiotic" is derived from two Greek words, "pro" and "bios", which refer to "for/or life". Metchnikoff, of the Pasteur Institute in 1907, who observed the positive effects of natural intestinal microbiota, is thought to be the first one to propose the probiotic concept (Miecznikow, 1907) [43]. Metchnikoff discovered that villagers in the Caucasus Mountains consumed a fermented yoghurt drink on a daily basis, and his research found that a probiotic called *Lactobacillus bulgaricus* improved their health and may have contributed to their longevity. Ferdinand Vergin was probably the first person to invent the term "probiotic" who, in his paper entitled "Anti- und Probiotika" (1954), compared the harmful effects of antibiotics and antimicrobial agents on intestinal microflora with the useful effects of selected bacteria "probiotica" (Vergin, 1954) [63]. Lilly and Stillwell in 1965 [37] described "substances secreted by one microorganism which stimulate the growth of another". Thus, it contrasted to the antibiotic concept (Lilly and Stillwell, 1965) [37]. Sperti described probiotics as tissue extracts which stimulate microbial growth (Sperti, 1971) [55]. Parker in 1974 [48] defined probiotics in the modern sense of what we use today. He described "organisms and substances which contribute to intestinal microbial balance" (Parker, 1974) [48]. Thus, probiotic definitions have changed over the years and modified accordingly. In 1989, Fuller redefined probiotics as a live microbial feed supplement which beneficially affects the host animal by improving microbial balance (Fuller, 1989) [22]. Currently, the FAO/WHO definition is most commonly adopted, which describes probiotics as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" (FAO/WHO, 2002) [21]. The International Scientific Association for Probiotics and Prebiotics (ISAPP) gave a definition in 2013 and the term was restricted to particular formulas or products which fit into a defined character. These include: the count of viable cells, a favourable influence on a host’s health and its alimentary tract.

Probiotics include micro-organisms such as lactic acid bacteria (LAB), and/or nonlactic acid bacteria (*Bacillus cereus*, *Bifidobacterium lactis*), yeast (*Saccharomyces*, *Candida*), fungi (*Aspergillus*), microalgae (*Tetraselmis)* etc. The idea of probiotics is a part of the human food chain and has been extended to the field of livestock by developing fortified feed, leading to direct benefit to the animals.

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The intestine of animals is home to diverse and dynamic microbes which include lactic acid bacteria as a resident microbiota serving a variety of purposes and maintaining normal intestinal health. Probiotics can be fed to animals via food (eg, milk), water containing a single culture or as a mixture of cultures. Probiotics should increase the intestinal microbial balance (Fuller, 1989) [22] or the properties of the indigenous microflora (Havenaar, 1992) [27] resulting in positive outcomes for the host animal.

Lactic acid bacteria

Lactic acid bacteria (LAB) are widespread in ecological niches like soil and water, which may be of plant or animal origin (dairy, meat) and are seen ubiquitously in the urogenital and gastrointestinal tracts of animals (Liu *et al*., 2014) [38]. LAB are known to produce lactic acid as a main end product of their metabolism and a wide variety of metabolites that have benefits for end users. Hence, LAB are being used as starter cultures, probiotics, and synthesis of special nutraceutical products (Emerenini *et al*., 2013; Ruiz Rodriguez *et al*., 2017) [17, 51]. The lactic acid bacteria occur as cocci (spherical) or bacilli (rod shaped) and can tolerate a low pH range. Through their carbohydrate fermentation, they produce lactic acid either homo-fermentatively (lactic acid) or hetero-fermentatively (acetic acid, ethanol, CO_2 along with lactic acid). LAB are basically Gram positive, non-spore forming, catalase negative and lack cytochromes. Having characteristics of anaerobic to aero-tolerant, they are fastidious and strictly fermentative (glucose source) in nature (Brandt and Alatossava, 2003; Anal and Singh, 2007) [9, 4]. They can tolerate a low pH range, higher salt concentration, and heat treatments. Lactic acid bacteria are widely distributed in dairy products, meat, cereal grains, etc. and are associated with the GIT of humans and animals (Brandt and Alatossava, 2003) [9]. These bacteria have been consumed over the centuries without any adverse effects and have "generally recognised as safe" (GRAS) status (Zhou *et al*., 2000) [68]. Lactic acid bacteria can be used as beneficial microbes, or probiotics, since they are able to modify the microenvironment in GIT on a larger scale through their metabolites and inhibitory substances (Bajagai *et al*., 2016) [6].

Characteristics of probiotics (FAO, 2002; EFSA, 2005) [21, 19]

Probiotics exhibit the following characteristics.

Safety profile

- Originated from human/animal.
- Isolated from healthy animals' alimentary track.
- Prior safe use history.
- Proper identification (phenotypic and genotypic characters).
- Not associated with any infective disease.
- Not a reservoir for any antibiotic resistance genes.

Functional attributes

- Better survivability and metabolic activity at the target site.
- Resistance to acidic conditions in the stomach, bile salts and intestinal enzymes.
- It must compete with the intestinal ecosystem inhabited by microbial species.
- Antimicrobial activity towards pathogens like *E. coli, Salmonella, Clostridium* spp etc.
- Ability to adhere, get colonised and better survivability at particular sites in the gastrointestinal system of the host.

Technical attributes

- Production ease with high biomass amounts and a highly productive culture.
- Maintaining viable and desired functional properties during processing (freeze–drying) and distribution as a product.
- Higher survival rate during storage as a finished product.
- Genetically stable and resistance to bacteriophages.

Probiotics may have the following favourable benefits for farm animals (Fuller 1989) [22].

- Better resistance to infectious diseases.
- Improved growth rate and feed conversion.
- Better digestion and absorption of nutrients.
- Improved milk quality and milk yield.
- Increased egg production and egg quality.
- Essential nutritional provision.
- Better carcass quality and decreased contamination.

Mode of action

Probiotics exhibit different modes of action as described.

Adhesion to the intestinal wall to inhibit colonization by pathogens

Adhesion of bacteria to the intestinal wall is mainly by nonspecific physical binding followed by adhesion by specific cell wall components (Haddaji *et al*., 2015) [26]. Once after established, pathogens start exerting their effect through various mechanisms. Probiotic addition is known to improve normal microflora establishment, which in turn inhibits adhesion of harmful bacteria to the intestinal wall (Cho *et al*., 2011) [10]. There is a competition between probiotics and pathogens for the receptors, and probiotics outdo the pathogens by blocking them. By this mechanism, probiotics eliminate pathogens (Hughes and Heritage 2002) [29]. Certain probiotic bacteria are known to influence glycol conjugate expression on the intestinal epithelial cells, which may serve as a receptor for pathogenic adhesion (Umesaki *et al*., 1997) [60].

Competitive exclusion

The Intestinal tract is characterised by a dense and diverse population of about 2000 known species and a population of about 10^{10} cells/digesta (Hungate,1966; Drasar and Barrow, 1985) [30, 15]. Competitive exclusion involves exploiting commensal organisms activities against invaders like *E. coli, Salmonella*, and *Clostridia* for the benefit of the native population. Competitive exclusion (CE) is an intestinal lumen phenomenon where colonization of probiotics on the mucosa prevents pathogen adhesion and proliferation (Soerjadi *et al*., 1982) [54], and modification of microbial communities (Hosoi *et al*., 2000; Jin *et al*., 2000) [28, 32]. It is the basic ability of the microflora of GIT to prevent the establishment and exertion of harmful effects by pathogens. A mature GIT ecosystem gets established and utilizes available nutrients while preventing the foothold of pathogens in the complex environment of the intestine.

Competition for nutrients with pathogenic bacteria in the gut

Probiotics are known to compete for nutrients and adhesion sites with harmful bacteria. Energy and nutrient competition between these bacteria may lead to suppression of later bacteria. Because of the high-density microbial population, higher competition is witnessed for nutrients in the intestinal niche at an intense rate (Steer *et al*., 2000) [56]. Because of the size of the intestinal environment, dietary variations and other stressors on the animal allow environmental fluctuations in the intestinal microbes to occur more quickly, requiring the bacterial occupants to be more adaptable to opportunities and obstacles. Iron is an essential element required by most bacteria, the exception is lactobacilli. Some spp of *Lactobacillus* are known to bind to ferric hydroxide at the cell surface, making it unavailable for pathogens to multiply (Elli *et al*., 2000) [16]. Probiotic supplementation causes better digestion and fermentation activity.

Adhesion action to modulate mucosal epithelium: Immune modulation

Gut epithelial cells have evolved, making the intestinal epithelium not only an anatomical barrier but also an immunological organ. The intestine and gut-associated lymphoid tissue (GALT) are vital components of whole-body immune defence. The GIT's native microflora stimulates the recruitment of immune cells into the lamina propria, hence inducing an appropriate immune response whenever needed. The sum of all mechanisms by which a bacteria (probiotics) inhibits colonisation of other bacterial strains is referred to as colonization resistance. Adhesion of probiotics to the gut mucosal epithelium is one of the selection criteria to check colonisation potential, leading to interaction and modulation of the host immune system (Collado *et al*., 2007) [11]. Probiotic products like metabolites, cell wall components, and DNA can have an impact on the immune system. Dead probiotic bacteria or probiotics-derived components like peptidoglycan fragments or DNA, for example, might obviously have immune modulatory effects. Adhesion of probiotics to the intestine and release of soluble factors itself trigger a cascade of signalling ending up in immune modulation. Many probiotic benefits are mediated through immunological modulation, namely a balance of pro-and anti-inflammatory cytokines (Neish *et al*., 2000) [46]. Activation of the immune system by probiotic bacteria increases surveillance by leukocytes, eliminating the threat from pathogens (Hughes and Heritage 2002) [29]. Stimulation of immune response is mainly by modulating dendritic cell, macrophage, T & B lymphocyte function (Vanderpool, 2008; Yan and Polk, 2010) [62, 66]. Few research points out that probiotic cells and their soluble factors prompt immunomodulation by activating APCs (antigen presenting cells) at the intestinal level and increasing total, helper and activated T lymphocytes. Other possible pathways include activating toll-like receptors (TLR) and regulating signalling pathways and gene expression. The overall immunostimulatory effects of probiotics are by increasing immunoglobulin production; activation of cell mediated immunity; interferon production; increasing lymphocyte, natural killer (NK) cell and lymphocyte activity; and oxidative burst regulation (Koenen *et al*., 2004) [30].

Bacterial antagonism and Bactericidal activity:

Probiotics suppress the pathogen count by producing antibacterial compounds, competing for both nutrients and adhesion sites, altering metabolites and stimulating immunity. Established probiotics in the gut are known to produce substances with bactericidal or bacteriostatic properties (Hughes and Heritage 2002; Steiner, 2009) [22, 57].

Table 1: Inhibitory substances produced by probiotics.

SL. No	Metabolites	Mode of action
1	Lactic acid and volatile acids	Reduction in the pH which disrupts the cellular metabolism.
2	Primary metabolites 1. Hydrogen peroxide	Activation of lactoperoxidase system and inactivation of biomolecules by superoxide anion chain reaction
	2. Diacetyl	Interfering in the utilization of arginine
	3. Carbon dioxide	Anaerobic environment and disruption of cell membrane
3	Bacteriocins	Disrupting cytoplasmic membrane

Lactic acid is the major metabolite produced by *Lactobacillus*. It shows good to average antimicrobial activity. Acetic acid is another volatile acid produced by *Lactobacillus* species. Both reduce pH, affecting cellular metabolism and retarding unwanted microbes. These penetrate the cell membrane, affecting transmembrane potential, which inhibits substrate transport and membrane bound ATPase activity (Maloney, 1990) [39]. Hydrogen peroxide has an inhibitory action on a few Gram-positive and negative bacteria. It gets accumulated in the surrounding medium, creating an anaerobic environment and major molecules are inactivated by super oxide chain reaction. The antimicrobial activity of carbon dioxide is due to cell membrane disruption as a gaseous layer accumulates in the lipid bilayer. Gram-negative and positive bacteria are inhibited by diacetyl, which LAB produce from pyruvate and which has no impact on other LAB, preventing utilization of arginine. Bacteriocins, like antibiotics, can be bactericidal or bacteriostatic, having a broad or restricted spectrum of activity. Nisin is one such example which causes nonspecific efflux of amino acids and cations leading to the death of sensitive cells (Ruhr and Sahl, 1985) [50]. Bacteriocins of LAB origin are proteins or antimicrobial peptides that are ribosomal synthesized and show action on Gram-positive bacteria and don’t show any effect on producer cells (Cotter, 2005; Klaenhammer, 1988) [12, 35].

Neutralization of enterotoxins produced by pathogenic bacteria

Probiotics are known to neutralise the enterotoxins produced by pathogens. *L. bulgaricus* produces a metabolite which neutralises the enterotoxin produced by pathogenic coliforms in pigs (Mitchell and Kenworthy, 1976) [44]. Organic acid, bacteriocins, and antioxidants are a variety of compounds produced by probiotic bacteria. These substances, along with reducing viable pathogens, also affect their metabolic activity and toxin production. The decarboxylation of amino acids by the coliforms leads to the production of amines, which are toxic and irritate the GIT, leading to diarrhoea. Probiotic supplementation inhibits coliform proliferation, causing no amine production (McDonald, 2010) [42]. *L. rhamnosus* GG can bind to mycotoxins including deoxynivalenol and restrict the bioavailability of a toxin (Turner *et al*., 2008) [58]. Gratz et al. (2006) [23] observed in rats that *L. rhamnosus* GG modulated intestinal absorption and hence higher faecal excretion of aflatoxins, leading to lower toxicity, which is credited to binding of probiotics to aflatoxin. In-*vitro* studies indicate aflatoxin B1 uptake is reduced by strain LGG, which also protects against membrane and DNA damage (Gratz *et al*., 2007) [24].

Increasing the digestion and absorption of nutrients

The gut flora of animals has a role in digestion and absorption of nutrients from the feed. It aids in the metabolism of feed components such as carbohydrates, protein, lipids, and minerals, as well as vitamin synthesis. Gut microflora enzymes improve food digestion, especially in the lower intestine, which is advantageous to the host's nutrition (March, 1979; Sissons, 1989) [40, 53]. Probiotics have been shown to increase the digestibility of dry matter, organic matter, energy, crude fibre, crude protein, and phosphorus in a number of studies. Improved digestibility of dietary nutrients on probiotic supplementation is due to better production and activities of digestive enzymes in the intestinal tract by way of better fermentation and gut digestion (Cho, *et al*., 2011; Upadhaya *et al*., 2015) [10, 61]. Some postulated beneficial effects on animal nutrition of probiotic supplementation are due to the interaction of probiotics with bile salts and vitamin production (Oelschlaeger, 2010; Yirga, 2015) [47, 67]. *Lactobacillus* spp. are known to secret amylase, and protease which improve the digestion and absorption of carbohydrates, proteins respectively and thus improve feed conversion efficiency. They also have shown a protein sparing effect, since probiotics use carbohydrates for their metabolism whereas pathogens depend upon protein. By inhibiting pathogen proliferation, protein is made available to the host. The increased enzyme activity in the GIT of animals fed probiotics could be attributed to either the probiotics' own production of enzymes or the induced change in the gut micro-ecosystem, which in turn increased enzyme production.

ACE inhibitory activity

Angiotensin converting enzyme is an integral component of the renin-angiotensin system (RAS), which is involved in regulating blood pressure and fluid volume in the body. It is involved in the conversation of angiotensin I to vasoconstrictor angiotensin II. Inhibition of ACE leads to a decrease in angiotensin II, and a subsequent increase in the vasodilator bradykinin, hence a reduction in blood pressure. Fermented milk products are a rich source of bioactive peptides, in addition to delivering energy and minerals. Antihypertensive peptides, also known as angiotensin converting enzyme inhibitors (ACE-I), are the best researched of the different bioactive peptides (Muguerza *et al*., 2006) [45]. Many *in vivo* studies showed ACE inhibitory peptides on oral/intravenous administration significantly reduced blood pressure (Erdmann *et al*., 2008) [18]. Inhibition of ACE leads to a decrease in angiotensin II, and a subsequent increase in the vasodilator bradykinin, hence a reduction in blood pressure.

Other possible ways of mechanism of action includes carbohydrate receptor degradation by the secreted proteins, biofilm formation, bio surfactant induction, receptor analogue creation. Thus, probiotics are involved in inhibiting the pathogen colonisation and disease prevention in the host.

Neonatal Calf health and probiotics: The calf's digestive system functions like a monogastric animal during early life due to underdeveloped rumen-reticulum, omasum, while the abomasum serves as a major site for digestion (Davis and Drackley,1998) [13]. Calves are initially offered milk or milk replacers which gradually changes to solid feed within a few weeks after birth (Khan *et al*., 2011) [34]. In neonates, maturation of the gastrointestinal tract (GIT) is a complex phenomenon influenced by genetic, nutrition, and environmental factors with simultaneous establishment of intestinal microbiota. Microbial establishment in the new born calves starts right from the beginning in the birth canal, dams' skin and udder microbiota exposure. Few research has pointed out in-utero establishment of gut microflora, but the rapid development happens during the first few weeks of life (Amin and Seifert, 2021) [3]. New-born calves are highly vulnerable to bacterial and viral diseases during the pre-weaning stage, leading to neonatal diarrhoea, hence high morbidity and mortality (Uetake, 2013) [59]. During calf hood, calves are susceptible to many diseases which affect the economic viability of farm operations and have long-term effects on their performance (Donovan *et al*., 1998) [14]. Antibiotics are being used to maintain calf performance and to treat calf scour (neonatal diarrhoea). Antimicrobials used as nutritional modifiers in animals may alter the gut microbial composition by way of resistant strains or transfer of resistant genes to other bacteria (Aust *et al*., 2013) [5]. Since growing concern about antibiotic resistance, its impact on the environment and chemical residue persistence in animal products (Martínez-Vaz, *et al*., 2014; Yamamoto *et al*., 2014) [41, 65], probiotics as an alternative feed additive have been developed to improve calf health and productivity (Allen *et al*., 2013; Berge *et al*., 2009) [2, 7]. The supply of probiotic organisms with feed (mainly milk in the early period) allows the establishment of health-promoting bacteria in GIT together with normal commensal organisms. This intern prevents the adherence and colonisation by pathogenic microbes (Isolauri *et al*., 2001) [31], In calves, lactic acid bacteria (LAB) species target the lower part of the GIT and stabilise the gut microbes, thus reducing colonization by pathogens. LAB are known probiotics that can be included in regular feeding practices. *Lactobacillus* and *Bifidobacteria* reduced diarrhoeal episodes and increased body weight and feed conversion (Abe *et al*., 1995) [1]. The feeding of *Lactobacillus* spp. to calves raised their IgG levels, indicating that host-microbe associations may play a role in calf health modulation.

Other animals: Probiotics can become an important tool in veterinary practice and animal husbandry due to their multifaceted functions and can be used as a gut ecosystem enhancer in animal nutrition (FAO, 2013) [20]. Probiotics modulate the microbial community and enhance immunity. Usage of probiotics, particularly LAB improved growth and reproduction performance, hence improving health status and survival rates in all kinds of livestock (Seal *et al*., 2018; Yirga 2015) [52, 67]. They are used for both prophylaxis and therapeutic measures in clinical and veterinary practice (Weese, 2008) [64]. Supplementation of probiotics increased milk yield in dairy cows (Yu *et al*., 1997), improved egg quality and production (Haddadin *et al*., 1996) [25], and carcass characteristics and output in pigs (Jukna and Simkus, 2005) [33]. These could become a possible option for enhancing immunity (Patel *et al*., 2014) [49] and reducing the shedding of zoonotic pathogens from food animals. Probiotics have been used to increase the efficiency of the utilisation of feed, to increase milk production, and to reduce diarrhoea both in pigs and cattle, and to control the colonisation of the intestinal tract by Salmonella (Bernardeau and Vernoux, 2013) [8]. Selection of probiotics is made based on their physiological and functional properties. Exploring the genome of probiotic culture helps significantly to understand phylogenetically its capabilities and risk safety assessment.

Conclusion

This review manuscript has showed concept of probiotics started in humans and gradually shifted to livestock feeding because of its beneficial effects. Lactic acid bacteria are widely used as a probiotic in both humans and animals, which normally reinstate intestinal ecological balance in various niches. Probiotic supplementation improved digestibility of nutrients, nutritive value and nutrient utilization and can reduce the incidence of diarrhoea in calves. Probiotics have the potential to influence the host's defences, including both the innate and acquired immune systems. Hence, the probiotics can be developed as alternative feed additive for improved animal health and productivity

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