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Eubiotics as modern feasibility in Veterinary Medicine

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Review Article

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Abstract

Lately, antimicrobial resistance evolution (AMR) in bacteria has become a universal disaster for animal health. AMR is a result of the unethical and uncontrolled use of antibiotics in veterinary and medical medicine. The gut microbiome is considered to be the defining organ for a number of gastrointestinal and extra-gastrointestinal disorders, but it also serves as a reservoir for genes resistant to antibiotics, which can spread to pathogens and contribute to the development of drug-resistant bacteria. Within this context, Eubiotics, which involve probiotics, prebiotics, synbiotics, essential oils, and organic acids, have beneficial effects due to their modulatory roles on the gut microbiome, representing a potential nutritional strategy for mitigating AMR.

In addition to highlighting the complexities of the relationship that can be attributed to a number of intrinsic and extrinsic factors, this brief review aims to emphasize the use of eubiotics and related products to moderate AMR by clarifying their role in health promotion and disease prevention. The primary purpose of nutrition is to provide the body with the necessary nutrients for growth and development, but it now also serves other functions, such as maintaining health and preventing disease. Food bioscience research has shown that nutrition set a crucial role in the development (and subsequent treatment) of many health issues, primarily improving overall performance.

Ultimately, Eubiotics are ideal alternatives to antibiotic growth promoters that support animal health, performance, and the economics of livestock.

Keywords: *Eubiotics, Probiotics, Prebiotics, organic acid, Synbiotics, Animal health*

Introduction

Antimicrobial resistance (AMR) has become a serious global trepidation in the 21st century, affecting humans, animals, and the environment **O'Neill, (2014) and Kogut and Arsenault (2016)** emphasized the importance of optimal gut health for animal production performance, which is synonymous with animal health in the industry.

Animal performance and a healthy gastrointestinal tract (GIT) are directly correlated. While it has long been known that better gut health can improve animal health and wellbeing in food-producing animals, research on the role of intestinal microbiota in enhancing performance has only recently begun to take shape **Ballou *et al.*, (2016)**. Maintaining the intestinal barrier is essential for animal health and wellbeing, as it ensures nutrient absorption and protects the immune system by producing mucus and keeping pathogens and toxins out of the blood **Gaggia *et al.*, (2010)**.

In order to increase lactic acid bacteria (eubiosis) and decrease pathogenic bacteria (dysbiosis) in the animals' digestive tracts, a healthy intestinal microbial flora is promoted, an integrated strategy known as "eubiotic nutrition" combines various feed additives such as prebiotics, probiotics, essential oils, and organic acids **Elala and Ragaa, (2015)**. The Greek word "Eubiosis," which refers to an ideal microbial balance in the gastrointestinal tract, is associated with the term "Eubiotics" **Miniello *et al.*, (2017)**. Eubiotics, including organic acids, herbs, essential oils, prebiotics, probiotics, and exogenous enzymes, are becoming increasingly popular in animal production **Nowak *et al.*, (2017)**.

Types of Eubiotics

Probiotics

Probiotics, whether expressed as supplements or food products, have become the most significant element in the functional foods field. Probiotics considered as an essential ingredient and a business goal due to their potential health benefits **Sanz *et al.*, (2016)**. The term "probiotic" was coined by Werner Kollath in 1953, combining the Latin word "pro" and the Greek word "βιο," meaning "for life." According to Kollath, probiotics are living organisms that play vital roles in enhancing various aspects of health **Gasbarrini *et al.*, (2016)**.

The term "probiotics" refers to "live strains of carefully chosen microorganisms which, when given in sufficient quantities, confer a health benefit on the host" **Schrezenmeir and de Vrese, (2002)**, according to the current definition established in 2002 by experts from the FAO and WHO working group. According to **Valdes *et al.* (2018)**, probiotics are live microorganisms primarily used to balance the gastrointestinal system's microflora, benefiting the hosts by promoting growth and overall health. Lactic acid bacteria (Lactobacillus spp.) have been recognized as "healthy bacteria" since the early 20th century, with certain Gram-negative bacteria like E. coli also identified more recently **Marco *et al.*, (2006)**.

Modes of action of probiotics

There are various anticipated modes of action of probiotics. Some of these pathways improve animal performance, while others are linked to the inhibition of intestinal pathogenic microorganisms. Probiotics work in the host system in three ways, as described by **Oelschlaeger (2010)**. The first way involves successfully altering the host's innate and acquired immune systems, which can stop infectious illnesses from spreading and lessen intestinal tract inflammation. The second way involves taking direct action against other bacteria to regulate and prevent infections, restoring the gut's microbial balance to normal. The third way utilizes microbial compounds, which may be essential for probiotic effects and include toxins, antimicrobials, and host metabolites. Probiotics aid in toxin inactivation, bile salt detoxification, and improved meal digestion.

In the innate and adaptive immune response, **Petruzziello *et al.* (2023)** demonstrated that probiotics also regulate dendritic cells (DC), macrophages, B and T lymphocytes. Probiotics interact with intestinal epithelial cells, attract macrophages and mononuclear cells, and enhance the synthesis of anti-inflammatory cytokines. Probiotics help maintain microbial equilibrium in the gut by competing with pathogens for nutrients and receptor-binding sites, making it difficult for them to survive in the gut **Plaza-Diaz *et al.*, (2019)**.

Moreover, probiotics work as antimicrobial agents by generating compounds such as short-chain fatty acids (SCFA), organic acids, hydrogen peroxide **Ahire *et al.*, (2021)**, and bacteriocins **Fantinato *et al.*, (2019)**, thereby reducing harmful microorganisms in the gut. Probiotics additionally improve the intestinal barrier activity by motivation of the mucin proteins synthesis **Chang *et al.*, (2021)**, controlling the expression of tight junction proteins such as occludin and claudin 1, and modifying the immunological response within the gut **Bu *et al.*,**

(2022) and Ma *et al.*, (2022).

Probiotics health impact

Probiotics applied as dietary supplements can aid in the management of intestinal disorders. Certain probiotics inhibit the growth and colonization of harmful microbes in the digestive system, forming a barrier against them **Vanderpool *et al.*, (2008)**. **Kulkarni *et al.* (2022)** revealed that probiotics can also inhibit the growth and colonization of harmful pathogens in the intestines, such as Salmonella spp and *Clostridium perfringens*, through competitive exclusion mechanisms. Additionally, **El Khder *et al.* (2023)** concluded that calves suffering from unthriftiness experience many adverse effects on body performance and hematobiochemical variables. The probiotic taken alone or in conjunction with a mineral mixture induced an ameliorative effect on unthriftiness, improving body performance and hematobiochemical parameters. **Halder *et al.* (2024)** pointed out that probiotics have a positive effect on chicken health and immunity, demonstrating their efficacy as a substitute for commercial antibiotics.

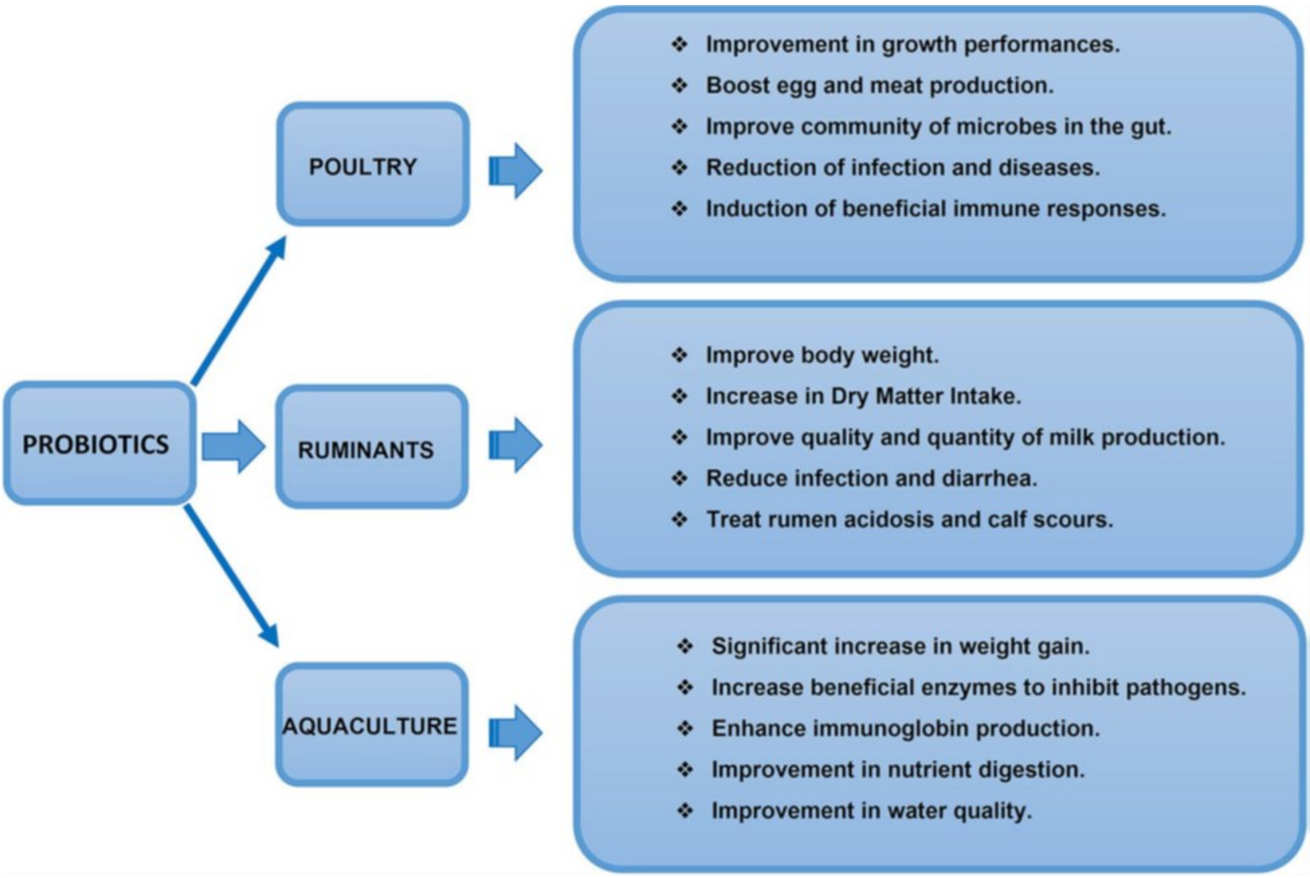

Fig. (1). Advantageous effects of probiotics on animal health (poultry, ruminants, and aquaculture) **Anee *et al.*, (2021)**

Prebiotic

Prebiotics are substances in food that promote the development or efficiency of beneficial microorganisms, including bacteria and fungi. They can change the composition of organisms in the gut microbiome, which is the most prevalent environment. As non-digestible fiber molecules that pass through the upper gastrointestinal system undigested, dietary prebiotics help in the growth or activity of beneficial bacteria in the colon by serving as their substrates **Hutkins *et al.*, (2016)**.

The definition of prebiotics and the food ingredients included in this classification have evolved since their initial description in 1995 by Glenn Gibson and Marcel Roberfroid **Glenn and Roberfroid (1995)**. In its earliest definition, prebiotics are non-digestible food ingredients that have been shown to benefit the host by selectively promoting certain bacteria in the colon **Gibson *et al.*, (2017)**. Further research has suggested that selective stimulation has not been scientifically demonstrated **Bindels *et al.*, (2015)**. The International Scientific Association for Probiotics and Prebiotics (ISAPP) defined prebiotics in 2016 in response to research that suggested prebiotics might have an effect on microbes outside of the colon: a substrate that a host microbe uses specifically to generate health benefits **Gibson *et al.*, (2017)**.

According to FAO/WHO, prebiotics are non-viable food ingredients that improve host health by modifying the microbiota. They are a collection of various carbohydrate components whose source, fermentation characteristics, and necessary dosages for health benefits are poorly understood. Prebiotics can be found in breast milk, soybeans, and foods high in inulin (such as chicory roots, Jerusalem artichokes, etc.). Raw oats, unrefined barley, wheat, yacon, and non-digestible carbohydrates, in particular, non-digestible oligosaccharides, are examples of non-digestible carbohydrates. However, only bifidogenic, non-digestible oligosaccharides me***et al*** the requirements for being classified as prebiotics. These include inulin, oligofructose, which is the product of inulin's hydrolysis, and (trans) galacto-oligosaccharides (GOS) **Pandey *et al.*, (2015)**.

Slavin (2013) stated that the following requirements must also be fulfilled by substances in order to be categorized as prebiotics:

I. Non-digestible and resistant to the gastrointestinal tract's mammalian enzymes and stomach acid breakdown
II. Fermented by gut microbiota
III. Promoting growth and activity of beneficial bacteria, improving the host's health

Yang *et al.* (2009) and You *et al.* (2022) noted that prebiotics are more useful than probiotics since they are intended to specifically support the beneficial bacteria that are already present in the intestines, as opposed to probiotics.

Modes of action of prebiotics

Prebiotics are primarily used by beneficiary microbiota in the colon through the process of fermentation **Slavin, (2013)**. Bacterial communities that use saccharolytic metabolism to break down substrates include *Lactobacillus* and *Bifidobacterium*. Many genes encoding carbohydrate-modifying enzymes and carbohydrate uptake proteins are found in the bifidobacterial genome. These genes denotes that *Bifidobacteria* include unique metabolic pathways, especially for prebiotics, which are oligosaccharides derived from plants, and their metabolism and fermentation. Short-chain fatty acids are the end product of these Bifidobacteria pathways, and they play a variety of physiological roles in body functions **Gibson *et al.* (2017)**.

Health impact of prebiotics

Enhanced feed turnover, decreased blood cholesterol, and improved body weight gain. Additionally, in the gastrointestinal tract of broiler chickens, the addition of fructans to feed resulted in a decrease in the number of potential pathogens like Salmonella and Campylobacter and an increase in the number of Lactobacillus genus bacteria **Yusrizal and Chen (2003)**. According to **Jung *et al.* (2008)**, adding the prebiotic increased the amount of Bifidobacterium bacteria in the study hens' intestines and decreased the amount of harmful bacteria that colonized those guts. Several studies on prebiotics in chickens show that oligosaccharides of mannose or fructose can effectively prevent the growth of *Salmonella* and *E. Coli* **Chambers and Gong 2011; Stanley *et al.* 2014).**

Xu *et al.* (2009) demonstrated that mannan-oligosaccharide as a prebiotic enhance growth and increases the activity of digestive enzymes including amylase and protease.

The beneficial effect of prebiotics in farmed aquatic fish was studied by **Song *et al.* (2014)**, who found that its role directly improves innate immune responses, such as enhanced lysozyme activity, neutrophil activation, phagocytic activation, and alternative complement system activation.

Synbiotics

Synbiotics supplements are a synergistic combination of probiotics and prebiotics. Prebiotics have the potential to boost the growth-promoting activity of the host's endogenous bacteria (intestinal flora) and increase the survival of probiotic strains. **Alloui *et al.*, (2013)**.

Mode of action of synbiotics

The mechanism of synbiotic effects is through modulation of metabolic activity in the intestine, preservation of the intestinal biostructure, growth of the beneficial microbiota, and simultaneous suppression of any possible pathogens in the GI tract.

Synbiotic formulations employ probiotic strains such as*, Bifidobacteria spp., Lactobacilli., B. Coagulans and S. boulardii,* etc. Oligosaccharides such as fructooligosaccharide (FOS), galactooligosaccharide (GOS), xylooligosaccharide (XOS), inulin, and prebiotics derived from natural sources like chicory and yacon roots, among others, are the main prebiotics that are utilized **Pandey *et al.*, (2015)**.

Health impacts of synbiotics

The effect of synbiotics on broiler chicken performance was recorded in a few trials according to **Awad *et al.* (2009)**, who discovered that, in comparison to basal diets supplemented with probiotics (homofermentative and heterofermentative Lactobacillus sp.), adding a synbiotic product to diets resulted in notable improvements in average daily gain, body weight, feed efficiency, and carcass yield percentage of synbiotic products or broiler chickens fed probiotics. In conclusion, scientists concur that using synbiotic products is more effective than applying probiotics and prebiotics separately **Awad *et al.*, (2009); Vandeplas *et al.*, (2009); Revolledo *et al.*, (2009)**. **Pawar *et al.* (2023)** affirmed the potential of supplemented fructooligosaccharide (FOS) and *B. subtilis* on immune attributes, growth performance, hemostatic and serological markers, and survival following pathogen infection of *Labeo fimbriatus* fingerlings in fish.

Essential oil compounds

Terpenoids and phenols are complex mixtures of volatile, lipophilic compounds that make up essential oils (EOs). **Windisch *et al.*, (2008); Brenes and Roura, (2010)**, making them one of the most fascinating categories of phytobiotic compounds **Diaz-Sanchez *et al.*, (2015)**.

Mode of action of essential oils

The hydrophobicity of essential oils appears to be linked to their antibacterial activity, as it disrupts the bacterial cell membrane's structure and function **Nazzaro *et al.*, (2013)**.

Additionally, essential oils can be used in conjunction with conventional antibiotic medications like tetracycline, doxycycline, and tilmicosin as adjuvants to lower the effective dosage and lessen bacterial resistance **Kissels *et al.*, (2017)**. These essential oils can be utilized as a feed additive as a novel therapeutic against multi-drug resistant bacteria since carvacrol and thymol have additive and synergistic effects when paired with each other or with doxycycline or tilmicosin against *P. multocida* and *M. haemolytica* **Kissels *et al.*, (2017)**.

Health impacts of essential oils

Many essential oils have the potential to be used as therapeutic agents against mastitis both in vitro and in vivo because of their lipophilicity, which is crucial for allowing the lipid layer of the bacterial cell membrane to penetrate and cause structural organization and integrity to be lost **Aiemsaard *et al.*, (2011); Dal Pozzo *et al.*, (2012)**. In vivo tests using a 10% combination of Lavandula angustifolia (lavender) and Thymus vulgaris (thyme) applied externally and through mammary infusions dramatically reduced the number of germs **Abboud *et al.*, (2015)**. Numerous essential oils' biological effects on economically significant production variables, including ruminant species' growth performance, milk yield, and reproduction, have been investigated **Oh *et al.*, (2017); Belanche *et al.*, (2020).**

Organic acid

Organic acids (OAs), both individually and as a combination of numerous acids, offer potential as feed additives in animal production **Nguyen and Kim, (2020)**. Organic acids support improved digestion and the preservation of the gut lining's cellular integrity by maintaining the normal gut flora **Sultan *et al.*, (2015)**.

Mode of action of organic acid

Organic acids added to feed can lower the pH of the stomach, which speeds up the conversion of pepsinogen to pepsin, therefore enhancing the rate at which minerals, proteins, and amino acids are absorbed **Park *et al.*, (2009)**. This could help reduce excretion of phosphorus and nitrogen, which would lessen pollution in the environment in addition to increasing performance **Lei *et al.*, (2017)**. Furthermore, due to their lipophilic undissociated form that allows them to cross cell membranes and change the concentrations of protons and related anion in the cytoplasm, organic acids have antimicrobial properties **Dibner and Buttin, (2002).** As a result, purine bases and vital enzymes suffer, and the viability of the bacteria decreases **Warnecke and Gill, (2005).** In order to reduce volatility and odor and to make manufacturing processes easier, examples and forms of acids are usually available as calcium, potassium, or sodium salts. **Huyghebaert *et al.*, (2011)**. Acidifiers as feed additives show the acidic character by the carboxyl functional group, -COOH, of the organic acids, involving the fatty and amino acids. Either simple monocarboxylic acids (formic, acetic, propionic, and butyric acids) or carboxylic acids with the hydroxyl group (lactic, malic, tartaric, and citric acids) or short-chain carboxylic acids comprising double bonds (fumaric and sorbic acids) are included **Shahidi *et al.*, (2014)**.

Health impacts of Organic acid

Broilers fed diets enriched with organic acids demonstrated a decline in *E. coli* inhabitants and an increase in *Lactobacillus* inhabitants, whereas marked increase of egg production in layer chickens with acidifiers **Nguyen *et al.*, (2018)**. In the case of heat stress, **Awaad *et al.* (2018)** demonstrated that broilers drunk acidified water with sodium butyrate alleviated the bad effects of heat stress on the immune system and liver histology, growth, and haematological and biochemical characteristics as well as oxidative stability, inflammatory markers, and carcass quality. It has also been demonstrated that mixes of acidifiers and sodium butyrate work as antioxidants to prevent damage from free radicals caused by heat stress. The beneficial influence of organic acids on immunological responses was evaluated by **Chowdhury *et al.* (2009)**, who discovered that feeding broiler chickens 0–5 % citric acid improved their immunological wellbeing. In addition, **Lee *et al.* (2017)** evaluated the effects of organic acids on broiler chickens' immune responses to viral antigens (H9N2) and found that the CD4+ CD25+ T-cell percentage was higher in the OV group (diet with organic acid supplements and administered an H9N2 vaccine [OV]) than in the control group, suggesting potential benefits. Many active ingredients (organic acid, probiotics, enzymes, antioxidants, vitamins, and in some cases essential oil plants) were combined to create these novel eubiotic mixtures for better animal performance **Yaşar *et al.*, (2017)**.

Conclusion

Probiotics play a well-documented vital role in physiology, with specific mechanisms that enhance health in various aspects. Prebiotics have the power to change the bacterial gut microbiome composition. Therefore, prebiotics and probiotics can be applied as substitutes for antibiotics to enhance function and reduce pathogenic load in animals' intestines. Synbiotic products have been shown to be more effective than using probiotics and prebiotics separately.
Essential oils (EOs) are phytobiotic compounds that, along with organic acids, have several biological functions that benefit animal health. Ultimately, the gut health of animals raised for production is crucial to their overall performance. In the animal production industry, factors such as economic aspects, animal health, and gut health are closely intertwined. The use of eubiotics supports this concept.

Recommendation

It is recommended to use a mixture of eubiotics as it has a significant impact on animal health, leading to positive benefits for livestock.

Eubiotics are able to prevent or treat digestive problems, especially in animals experiencing stress, dietary changes, or antibiotic therapy. After antibiotic treatment, eubiotics can help restore the gut microbiome and prevent secondary infections.

It is important to ensure proper dosage is used and monitor the animal's response, as the effectiveness of eubiotics may vary among animals.

It should be taken into consideration to ensure that the eubiotic products used contain high-quality, viable strains of probiotics and prebiotics.

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