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Review Article

Probiotics " Alternative to antibiotics resistance"

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ABSTRACT

Antibiotic resistance is of great concern for human and animal globally. New resistance mechanisms are emerging and can spread between food-producing animals and humans all parts of the world. Antibiotic resistance is threatening our ability to treat common infectious diseases. Antibiotic resistance is accelerated by the misuse and overuse of antibiotics, so there is great demand for researches to discover alternative substances to reduce the impact and limit the spread of resistance. Probiotics are considered to be favorable live microorganisms by the host organism by maintaining microbial homeostasis and healthy gut, moreover, probiotics have been suggested as viable alternates to antibiotics and subsequently overcome antibiotic resistance and reduce the excessive use of antibiotics. In addition, providing other growth-promoting properties in the animal health and nutrition industry.

INTRODUCTION

Probiotic in Greek language means for life' The first probiotic definition was reported in 1908 by Elie Metchnikoff who noticed that consumption of fermented dairy products enhance the health life. He then reported that the presence of lactic acid bacteria in fermented dairy products helps keep the defensive system activated, resulting in higher longevity of its consumers (Stambler,2017).WHO and FAO in 2002, mentioned that probiotics are live microorganisms that revealed health benefits to the host when ingested in adequate amounts. According to the latest definition of the WHO, probiotics are refer to active mi-

crobes that stimulate the growth of other probiotic bacteria in the gut and possess beneficial health effects to the host (Hill et al. 2014). Guarner and Malagelada, (2003) pointed out that Lactic acid bacteria and bifidobacteria are the most strains frequently used as probiotics. Several microorganisms, particularly bacteria and fungi, have harbored probiotic activities, species belonging to the genera *Lactobacillus*, *Streptococcus*, *Lactococcus*, and *Bifidobacterium* remain the most popular probiotic agents to date (Hoseinifar et al.,2018).

There are records showing that the use of bacterial probiotics are more effective in chickens, pigs, and young calves, however, probiotic

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yeast (*Saccharomyces cerevisiae*) and fungal strains (*Aspergillus oryzae*) reveals better results in adult ruminants (Markowiak and Ślizewska, 2018).

Probiotic Microorganisms:

There are many different microorganisms used as probiotics. Bacteria, bacteriophages, microalgae, and yeasts are all examples of probiotics (Llewellyn *et al.*, 2014). There are numerous specific types of bacteria which consider as common probiotics commonly used in the livestock to date, which are *Lactobacillus*, *Bifidobacterium*, *Streptococcus*, *Enterococcus*, and *Lactococcus* (Collado *et al.*, 2005; Llewellyn *et al.*, 2014; and Abdelqader *et al.*, 2013). Probiotics are also made up of good yeast. The most common types of yeast found in probiotics is *Saccharomyces* (*S. cerevisiae* and *S. burlardii*), *Candida pintolopesii*, and *Aspergillus oryzae* are typical non-bacterial probiotics (Abdelqader *et al.*, 2013, Mookiah *et al.*, 2014 and Pedroso *et al.* 2013).

- *Lactobacillus* species :

Lactobacillus species is a type of bacteria used therapeutically as probiotics. There are lots of different species of *Lactobacillus*. *Lactobacillus* species are Gram-positive rods, obligate and facultative anaerobes in the human gastrointestinal and genitourinary tracts (Fujisawa *et al.*, 1992 McGroarty, 1993 and Madsen *et al.*, 1999). lactic acid-producing as the major metabolic end product of carbohydrate fermentation. They also help in the breakdown of foods, therefore producing hydrogen peroxide, lactic acid, and other substances which create an acidic, unfavorable environment for harmful or pathogenic organisms. *Lactobacillus* bacteria are commonly found in the human gut, mouth and vagina. They are considered generally as “good bacteria”, and in fact may contribute to good health. *Lactobacillus* is important for gastrointestinal function, as they are involved in vitamin B complex and vitamin K synthesis, natural antibiotic production, enhance innate and acquired immune defense, digestion and metabolize proteins and carbohydrates, detoxification of pro-carcinogens.

Some researchers have demonstrated that *Lactobacillus* can produce antifungal substances, such as benzoic acid, methylhydantoin, mevalonolactone (Prema *et al.*, 2008 and Niku-Paavola *et al.*, 1999) and short-chain fatty acids (Sjogren *et al.*, 2003). Magnusson and Schnürer (2001) discovered that *Lactobacillus coryniformis* can produce proteinaeous compounds exhibiting antifungal properties. *Lactobacillus reuteri* is one of the well-documented probiotic species in lactic acid bacteria and is mainly found in Gram-positive bacterium in the gut flora of animals and birds (Bhogoju *et al.*, 2018). Lactic acid bacteria are generally recognized as safe due to their ubiquitous appearance in food and their contribution to the healthy microbiota of animal and human mucosal surfaces. Due to their beneficial and nonpathogenic effects, Lactic acid bacteria are considered to be potential probiotics.

- *Bifidobacterium* species:

Bifidobacterium is an anaerobic, Gram-positive, V- or Y-type branched, rod-shaped, immobile, non-spore-forming, Gram-positive, anaerobic, catalase-negative bacteria that belong to the family Bifidobacteriaceae and the phylum Actinobacteria. Bacteria in the *Bifidobacterium* genus can utilize glucose and produce lactic and acetic acids as by-products. *Bifidobacterium* are found in large numbers in the gut of animals and human. Many *Bifidobacterium* are generally used as probiotics in human food and in pharmaceutical formulations (Gaggia *et al.*, 2010). *Bifidobacterium pseudolongum* have shown significant results on a better food conversion ratio (FCR) in piglets with no differences in final weight, weight gain, and feed intake. Moreover many of these germs have “GRAS” (“Generally Regarded As Safe”) status (Afonso *et al.* 2013).

- *Bacillus* species:

Bacillus is a genus of Gram-positive, aerobic or facultative anaerobic, endospore-forming bacteria. The ability to form spores is useful and provides long-term storage without the loss of viability compared to those containing non spore-forming bacterium. In addition,

spores are able to survive the harsh, low pH of the gastric barrier and can reach the small intestine to perform their probiotic properties (Cutting, 2011). Now many strains of some *Bacillus* species are used as probiotic dietary supplements in animal feeds. Bacteria of the genus *Bacillus* already used as probiotics have real potential and can be used in safe production and as an alternative to conventional antibiotics. Several researchers showed that these species possess high potential for immunomodulation and protection against diseases in animal breeding, and recommend *Bacillus subtilis* as a beneficial agent for the biological control of the diseases (Hoseinifar et al. 2018). Animal model research mentioned that ingesting bacillus spores increases immune response (Duc et al. 2004).

- *Saccharomyces* species:

Saccharomyces is a genus of budding yeast; it is also part of the gut microbiota. *S. cerevisiae* var. *bouardii* is an eukaryotic organism that has been used in scientific investigations since the time of its discovery (Khaneghah et al., 2020). *Saccharomyces cerevisiae* var. *bouardii* is the most significant probiotic yeast species due to its ability to produce different bioactive compounds (Lazo-Vélez et al. 2018). It is a non pathogenic yeast strain that has been used for the treatment and prevention of diarrhea. *Saccharomyces cerevisiae* var. *bouardii* is best known for its role in treating gastrointestinal diseases (Batista et al. 2014 and Drozdova et al. 2016). Other species belonging to this genus such as *Saccharomyces carlsbergensis* are also used as probiotics in animal feeding (Gaggia et al. 2010).

- *Lactococcus* species:

Hoseinifar et al. (2018) reported that *Lactococcus lactis* was capable of protecting different fish species against bacterial pathogens. *Lactococcus* strains are commonly used in the manufacture of fermented dairy products. Although *Lactococcus lactis* is considered safe for human and animal use, some studies have also linked *Lactococcus* bacteria

(*Lactococcus lactis* and *Lactococcus garvieae*) to infection (Rodrigues et al. 2016).

- *Enterococcus* species:

Enterococcus is a common member of the endogenous intestinal microbiota of humans and animals (Araújo and Célia, 2013). Sometimes, these strains are involved in the production of substances such as β -hemolysin, gelatinase, and aggregation substance that have undesirable phenotypes in probiotic strains (Araújo and Célia, 2013). Although this genus is not considered “generally recognized as safe”, species from the genus *Enterococcus* have been used as probiotic for human or animals (Araújo and Célia, 2013) and (Sivieri et al. 2008). These bacteria may participate in transmission of resistance to antibiotics (Anadón et al. 2006).

- *Streptomyces* species:

Streptomyces is mainly used as a probiotic in aquaculture, because of its unique ability to produce several antimicrobial agents as secondary metabolites. Several promising results of the genus *Streptomyces* was reported as probiotics in aquaculture (Das et al. (2010) and Augustine et al. (2015)).

- *Microalgae*:

Recently, microalgae have more attention due to their wide range of nutritionally important compounds for humans and animals, including polysaccharides, polyunsaturated fatty acids (PUFA), proteins, and antioxidants, such as carotenoids and phenolic compounds (Sathasivam et al. 2019). The actual and prospective clinical applications of microalgae raise the possibility that they can be used as probiotics, due to their ability to normalize the functioning of the microbiota of humans and agricultural animals and its ability to produce biologically active substances, including hormones, neurotransmitters, and immunostimulators. Several research investigated the probiotic properties of microalgae have shown that aqueous algae extract from *Spirulina platensis*, *Chlorella*, *Dunaliella salina*, *Chlorococcum* are potential sources. In food and nutri-

tion biotechnology, algae are usually used as extracts that can improve probiotic performance. Recently, cultivation of live microalgae with probiotics has gained more attention because interspecies interactions can add more value to the final product.

* **Spirulina :**

Spirulina belongs to blue-green autotrophic microalgal, which contains about 70 % of protein, being also rich in unsaturated fatty acids and pigments, such as linolenic acid and linoleic acid, carotenoids and chlorophylls (Bezerra et al. 2020; Li et al. 2019). *Spirulina* is commonly present in many freshwater environments. *Spirulina* is produced on a large scale in outdoor pools for commercial purposes to be used as a nutritional supplement in some countries such as Thailand, China, the United States, and India. On the other hand,

Chlorella:

Chlorella is a single-celled green microalgae that can exist in fresh and sea water (Eckardt, 2010). *Chlorella* belongs to the "Generally Recognized As Safe" (GRAS) category of the US Food and Drug Administration being rated as a green and healthy food by the Food and Agriculture Organization of the United Nations (FAO) (Song et al. 2018). Recent studies have reported that the biologically active ingredients in *Chlorella* show positive effects as anti-hypertensive, anti-allergic, anti-asthmatic, anti-diabetic, anti-tumor and preventing heart disease (Barboriková et al. 2019; Horii et al. 2019).

From the perspective of anti-inflammatory and microbial growth curves, the aqueous extracts of *Spirulina*, *Chlorella* and *P. tricornutum* may be suggested as potential sources of natural anti-inflammatory agents and antimicrobials for the prevention, treatment and control of bacterial infections and stimulation of probiotic activity (Jianjun et al. 2023).

* **Dunaliella:**

Dunaliella, together with other microalgae, *Arthrospira* and *Chlorella*, have been approved by the Food and Drug Administra-

tion (FDA) as a food source with a Generally Recognized as Safe (GRAS) status (Sui et al. 2020). Although *Dunaliella salina* is not as popular as *Chlorella* and *Arthrospira*, it has many beneficial properties for the development of new functional foods with probiotics and novel therapeutics (Ivana et al. 2022).

* **Chlorococcum:**

Chlorococcum sp. are non-toxic microalgae, and they are found in poorly studied and isolated regions (Tanmay et al. 2021). *Chlorococcum* sp. can accumulate nutrients, especially carbohydrates, lipids, and bioactive compounds of interest (Clediana et al. 2016).

- **Bacteriophages:**

First discover of bacteriophages was by the British bacteriologist William Twort in 1915. In 1917 the French-Canadian microbiologist Felix d'Herelle, realized the presence of some biological entities having the ability to kill bacteria. D'Herelle named them "bacteriophages" to refer that these viruses were able to "eat" and "devour" bacteria (Sulakvelidze et al. 2001). Phages have been played a role in controlling infectious diseases in aquaculture, moreover control diseases associated with severe economic losses (Sieiro et al. 2020 and Nakai et al. 2002). Several studies have been showed the effective control of fish diseases caused by several species belonging to the genus *Aeromonas* species. (Akmal et al. and Kim et al. 2015) or *Vibrio* species (Matamp et al. 2020; Khatharios et al. 2017 and Chen et al. 2019), highlighting the effectiveness of phage treatment as an excellent alternative to antibiotic treatment. Phages have been mentioned as a feasible alternative for treatment and prophylaxis in cattle, where the most prevalent infectious diseases either clinical or subclinical mastitis, metritis or respiratory infections caused by bacterial agents (Gutierrez et al. 2019). *Dunaliella salina*, *Chlorococcum* are potential sources.

Pros effects of probiotics:

Probiotics have demonstrated several important effects as therapeutic options for a vari-

ety of diseases in addition to enhance nutritional value of food products, improve the immune system, prevent gut infections, suppress antibiotic-associated diarrhea, and reduce lactose intolerance symptoms, moreover, reduction of colon cancer risk. One of the most beneficial proposed mechanism of probiotics is the formation of antibacterial substance termed bacteriocins and production of organic acids such as lactic and acetic acids which consider as the main antimicrobial compounds responsible for the inhibitory activity of probiotics against pathogens. The action of organic acids of probiotics against pathogens occurred by entering of undissociated form of organic acids into the bacterial cell and then dissociates inside bacterial cytoplasm leading to lowering of the intracellular pH or the accumulation the ionized form of organic acid intracellular of the pathogen can lead to the death of the pathogen (Ouweland, 1998 and Russeland Gonzalez, 1998). Bacteriocin may enable the direct inhibition of pathogen growth within the gastrointestinal tract (O'Shea, 2014). Also, probiotic bacteria are able to produce de-conjugated bile acids, which are derivatives of bile salts. De-conjugated bile acids exhibit a stronger antimicrobial activity compared to that of the synthesized bile salts of the host organism, So probiotics protect themselves from their own bactericidal metabolites (Oelschlaeger, 2010). Moreover, some strains of probiotics have the ability to produce metabolites that inhibit fungi growth (Coloretti et al. 2007, Lindgren and Dobrogosz 1990).

Benefit of probiotics in animal:

There is an evidence that the use of probiotics instead of antibiotics is beneficial in promoting animal growth through increase digestive enzyme, increase feed intake, increase body weight gain and increase reproductive performance (Zhang et al. 2021 and Lokapirnasari et al. 2019). Some probiotic strains have the ability to inhibit bad effect of animal pathogens as they have the ability to reduce infection and disease, increase resistance to pathogen, enhance immune response, improve intestinal microbiota and enhance antioxidant status. and may be considered as antibiotic alternatives in poultry, swine, cattle farming

and others for enhancing immune function and disease prevention (Vieco-Saiz et al. 2019). Administration of probiotics has shown increased effect in the levels of immunoglobulins such as M and A along with the increased levels of total antioxidant capacity in serum (Wang et al. 2018) Few probiotic strains have anti-inflammatory properties which allow the balance between pro- and anti-inflammatory cytokines (Cristofori et al. 2021 and Pagnini et al. 2010), Along with the anti-inflammatory responses, probiotics also exhibit anti-viral properties in animals (Lehtoranta et al. 2020).

Probiotics have ability for the production of antimicrobial substances, such as bacteriocins, hydrogen peroxide, and volatile fatty acids (Vieco-Saiz et al. 2019). It was recorded that organic compounds produced by probiotic bacteria have proven to exhibit inhibitory effects against pathogenic bacteria such as *Helobacter pylori* (Rezaee et al. 2019). Ma et al. (2019) reported that probiotic microbes such as *Bacillus subtilis*, *Saccharomyces cerevisiae*, and *Enterococcus faecalis* can enrich milk secretion in cows. Mammary gland condition improved along with the improved functions of the teat sphincter were noticed by the effect of Lactobacillus base teat spray (Alawneh et al. 2020). Addition of *Rhodospseudomonas palustris* showed improved microbial fermentation and high rumen microbial growth performance (Chen et al. 2020).

Characters of antibiotic and probiotic:

Antibiotics	Probiotics
Antibiotic means “against life	Probiotic comes from the Latin “pro” and Greek “bios”, meaning “for life”.
Antibiotics are low-molecular-weight substances produced by live microorganisms and plants, capable of selectively killing or preventing the growth of other organisms at low concentrations. These include synthetic organic compounds with identical antimicrobial activities (Smith <i>et al.</i> , 1998).	Probiotics are live microorganism with beneficial effects when provided in appropriate conditions to a host (Hill <i>et al.</i> , 2014).
Antibiotics are used as drugs requiring medical prescription,	Probiotics are freely available and mainly consumed as diet supplements or through fermented products, even if some strains are prescribed as drugs, such as <i>S. boulardii</i> as an antidiarrheal drug (More <i>et al.</i> , 2018).
Antibiotics are active substances directly used to fight pathogens, in addition antibiotics are only intended to inhibit or destroy bacteria of (Etebu <i>et al.</i> , 2016).	Probiotics are live microorganisms that can act directly by producing antimicrobial metabolites and competing microbes for sites/nutrients, or/and indirectly by stimulating host immune systems. In addition, probiotics help to repopulate the gut with healthy microbiota and reduce dysbiosis caused by antibiotics. probiotic activities are multiple and may include antibacterial, antifungal, and antiviral effects (Kosgey <i>et al.</i> , 2019 and Rezaee <i>et al.</i> , 2019).
Antibiotics are currently used to treat infections and inhibit the growth of pathogenic microbes .	Probiotics as antimicrobials is not limited to bacteria but is also applicable to viruses. Many reports indicates their efficacy in inhibiting human and animal pathogens through experimental models and clinical trials and confirms their potential applications to prevent diseases, treat infections, and promote growth performance, immune systems, and nutrient efficiency.
The main antibiotic action mechanisms include cell wall synthesis inhibition, cell membrane structure or function breakdown, nucleic acid structure and function inhibition, protein synthesis inhibition, and key metabolic pathway blockage of folate synthesis (Dowling <i>et al.</i> , 2017).	Antibacterial effect of Probiotics may directly act through antibiosis by producing metabolites such as bacteriocins, organic acids, antioxidant compounds, and nutrient-space competition, or indirectly by modulating the host’s gut microbiota and immune system, and can in this way reduce dysbiosis and bacterial infections, respectively
An effective antibiotic is a short-time and low-dose-acting antimicrobial, but it might cause progressive antimicrobial resistance and host microbiota imbalance by inducing a pathogen’s defense mechanisms and killing also good microbes.	The positive effects of probiotics are often perceptible after long-term uptake, without the side effects observed after antibiotic treatment. In fact, probiotics can control pathogenic targets through competitive exclusion of nutrients and space, and ensure the host’s microbiota balance.
Excessive and inappropriate use of antibiotics have resulted in the increase of bacterial antimicrobial resistance (AMR) and host microbiota imbalance or dysbiosis phenomena. Dissemination of antibiotic resistance genes into pathogenic bacteria has raised concern about the effectiveness of the current antibiotic storage in the near future.	Among probiotics’ disadvantages are their sensitivity reduced under extreme stress conditions (e.g., temperature, acidity, moisture, etc.), therefore their survival rate and therefore capacity to colonize the gut can reduced also.

Safety of Probiotics:

A bacterial strain's safety, its source, antibiotic-resistant characteristics, and absolute lack of pathogenicity associated with virulent cultures all contribute to the safety profile's primary foundation; the rest is performance (Galdeano and Perdiagon, 2004). The majority of probiotics are safe. Nevertheless, adverse effects have been sporadically reported and caution of potential side effects should be taken. A demonstrative report about probiotics and their potential side effect has been published by WHO/FAO (2002). Probiotic strains should be characterized by the absence of their virulent profile and their low resistance to antibiotics. Probiotics have a long record of safety use during history, which relates primarily to the use of *Lactobacilli*, *Bifidobacteria*, and *Streptococcus* (Shanahan, 2012). New probiotic microbes should belong to genera and strains commonly found in the healthy human intestinal microflora or in dairy food products. Accurate bacterial identification represents a critical step in evaluation of the safety of new probiotic strains (Holzapfel et al. 2001). Andrighetto et al. 1998 recorded that microbial identification at the molecular level should be applied because physiological and/or biochemical characterization alone is insufficient to achieve a reliable identification.

Probiotic performance promotes a variety of pathways, including adhesion to epithelial cells, decrease in gastrointestinal permeability, and immunoregulatory impacts (Lee and Salminen 2008). Probiotics are not metabolized, have no potential for transference to animal-derived foods, and so do not result in the creation of residues. Due to the absence of their explicit and/or indirect transit from the gut into the animal body, they do not affect metabolic activities and therefore have no adverse effect (Fefana, 2021). The introduction of novel microbes needs an acute investigation and assessment of their safety and the risk-to-benefit ratio.

CONCLUSION

The excessive and uncontrolled use of antibiotics are associated with the emergence of antimicrobial resistance. Con-

tinuous rising in multidrug-resistant organisms is responsible for causing millions of deaths and economic loss all over the world annually. Spreading of antimicrobial resistance led scientists to search for alternative solutions to antibiotics to overcome the global problem of several pathogens' resistance for both human and animal infections. Although probiotics is one of these solutions that can inhibit pathogens by production of toxic compounds, modulation of the immune system or competition for a colonization sites or nutritional sources, in addition, several scientific studies report the potential use of several probiotics as an alternative to antibiotics and their results seem very promising, despite some technical issues that should be solved before implementation, so probiotics need more research to gain additional data on their mode of action to improve its efficacy and verified how they whether benefit or not to the host with a practical approach without impacting on environmental pollution or antimicrobial resistance ..

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