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APPLICATION OF MEDICINAL PLANTS, PROBIOTICS AND SYNBIOTIC PRODUCTS IN PREVENTIVE CARE AND ALTERNATIVE THERAPY FOR FARM ANIMALS IN MODERN VETERINARY MEDICINE. A REVIEW

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Abstract

Sustainable production of high-quality animal and plant production for feeding the growing world population of consumers is a key challenge for the future industry. New animal farming methods are introduced, focusing on enhancing meat and milk quality and safety, in parallel taking into account welfare and preservation of natural environment. Selection conducted towards high growth rate results in breeds and hybrids characterized by fast growth but in the same time by delayed morphological and functional maturity and by an underdeveloped immune system. Antibiotics and other medicinal products are widely used, mainly to modify the digestive microbiota, to increase the productivity and growth of animals and to compensate for low immunological activity. The long-term use of these substances has led to the development of drug-resistant microorganisms, posing a threat to consumer health and having a negative impact on the environment. This review studies the ways of limiting the use of antibiotics in animal husbandry, alternative strategies to improve production and animal health - the use of probiotic, prebiotic and symbiotic preparations, as an effective treatment against pathogens.

***Key words**: antibiotic resistance, farm animals, medicinal plants, prebiotics.*

INTRODUCTION

Antimicrobial resistance (AMR) poses a significant risk to global health and development. One of the primary factors contributing to the rise of resistance in pathogens is the excessive use of antimicrobials. Synthetic drugs have residual effects in animal production (Dowarah, 2017). Reducing their use in animal husbandry is important to maintain antibiotic effectiveness in the future (Lalouckova et al., 2021). The World Health Association has identified AMR as one of the ten major threats to public health, based on the fact that an estimated 1.27 million deaths worldwide in 2019 can be attributed to it (Murray et al., 2022). In 2021, The European Centre for Disease Prevention and Control (ECDC), the European Food Safety Authority (EFSA) and the European Medicines Agency (EMA) have published the third joint report on an integrated analysis of antimicrobial consumption and the emergence of antimicrobial resistance. The links between antimicrobial use (AMU) and the development of AMR in commensal *E. coli* in animals are analysed (ECDC, EFSA & EMA, 2021). In Canada, a study based on data from studies in broiler chickens, pigs and turkeys found associations between increasing AMU and decreasing susceptibility of *E. coli* to several antimicrobials (Agunos et al., 2021). Their use was found to be associated with resistant *E. coli* isolates in pig farms in the United Kingdom (Abuoun et al., 2020). Fonseca et al. (2023) examined *E. coli* in calves and found that those treated with sulfonamides, tetracycline, and fluoroquinolones exhibited a higher prevalence of antimicrobial resistance (AMR) and an increased expression of virulence genes in these isolates compared to untreated animals. Similarly, Formenti et al. (2021) reported a greater occurrence of resistant *E. coli* in calves that received treatment. Furthermore, Pires et al. (2022) analyzed public databases from 1980 to 2018, which indicated a notable rise in AMR in commensal *E. coli* in animals, with significant increases for various antimicrobials, notably penicillin combined with β-lactamase inhibitors and cephalosporins, alongside a doubling of multidrug resistance (MDR). In a different investigation in Quebec, Canada, researchers assessed AMR in *E. coli* from fecal samples of

healthy dairy cattle and discovered elevated resistance levels to tetracycline, sulfisoxazole, and streptomycin (Massé et al., 2021). The incidence of antimicrobial resistance in *Salmonella* spp. has been found to be increasing over the past few decades and has caused concern in both human and veterinary medicine (Besser et al., 2000; Fey et al., 2000).
This review examines ways to limit the use of antibiotics in livestock production, alternative strategies to improve production and animal health - the use of probiotic, prebiotic and symbiotic preparations as effective treatments against pathogens.

MATERIALS AND METHODS

In the present review was used information from publications obtained on the Internet - Google Scholar but mostly Research Gate, PubMed, Scopus and Web of Science - as well as journal editions worldwide and also editions in Bulgaria.

RESULTS AND DISCUSSIONS

The use of antibiotics in farming practices is adding to the growing challenge of antimicrobial resistance worldwide (Chang et al., 2015). Animals are treated with significant amounts of drugs, making them reservoirs of bacterial antimicrobial resistance genes. They can transmit to humans via the food chain, through direct contact, and from the environment (Laxminarayan et al., 2013; Lalouckova et al., 2021). This necessitates the search for alternative strategies to improve animal production and health, and in recent years, research has been conducted using probiotic, prebiotic and synbiotic preparations as an effective model in the fight against pathogens. They influence a number of metabolic processes, support the body's immunological response and suppress inflammatory processes. The primary motivation behind their application is the aim to obtain positive outcomes akin to those produced by antibiotic treatments (Markowiak & Śliżewska, 2018).
The term "probiotic" was first introduced in an article by Vergin in 1954. Lilly & Stillwell (1965) defined probiotics as microorganisms that promote the growth of other microorganisms. Fuller (1989) added that for substances to be considered probiotics, they must be viable and exert beneficial effects on the host. Guarner & Schaafsma (1998) further clarified that the dosage of these probiotic organisms is crucial to achieving a positive outcome. Their main function is that they have an effect on the development of the microbiota and ensure a balance between pathogens and bacteria. In *in vitro* studies, it has been demonstrated that low molecular weight compounds, such as hydroperoxides and short-chain fatty acids produced by probiotic microorganisms, play a role in inhibiting the growth of harmful pathogens (Oelschlaeger, 2010). Probiotic products may contain one or more microbial strains, such as Gram-positive bacteria: *Bacillus*, *Lactobacillus*, *Enterococcus*, *Streptococcus*, *Pediococcus*, some species of fungi and yeasts of *Saccharomyces cerevisiae* and *Kluyveromyces*, spores of the genus *Bacillus* and strains *Lactobacillus farciminis* and *Pediococcus acidilactici* (Simon, 2005). A number of scientists have established an effect on feed intake, body weight gain and general health in different animal species (Torres-Rodriquez et al., 2007; Samli et al., 2007; Casey et al., 2007; Chiofalo et al., 2004; de Rezende et al., 2012). Numerous scientific publications conclude that their addition to feed leads to improved quantity and quality of milk, meat and eggs and reduces the effect of weak limbs in broiler chickens (Musa et al., 2009; Plavnik & Scott, 1980). The lack of side effects is a significant benefit of probiotics (Markowiak & Śliżewska, 2018).
Weaning is a stressful time for piglets in pig farming, the feeding pattern changes and this leads to a disruption of immunological functions and a negative effect on the balance of the intestinal microbiota (Modesto et al., 2009). In their study, Böhmer et al. (2006) added the probiotic strain. From the 90th day of pregnancy until the 28th day of lactation, the addition of *Enterococcus faecium* DSM 7134 to the sow's feed significantly enhanced feed intake, increased the size of the offspring, and boosted the weight of the experimental animals. Kyriakis et al. (1999) found a positive effect when studying the effect of a probiotic with *Bacillus licheniformis* spores in piglets

from 5 to 10 days old. The study of the literature data shows that probiotics can be successfully used to prevent diseases such as salmonellosis, campylobacteriosis or coccidiosis.

Mountzouris et al. (2007) conducted research on the impact of probiotics in broiler chickens. Their study featured a supplement that included two strains from the *Lactobacillus* genus, along with one strain each of *Bifidobacterium*, *Enterococcus*, and *Pediococcus*. The result of the application of the probiotic leads to the stimulation of the growth of the birds and modulates the composition of the intestinal microbiota (Mountzouris et al., 2007). Recent research has highlighted the benefits of using feed enriched with the probiotic YEA-SACC-1026, which includes the bacterial strains *Bacillus licheniformis* and *Bacillus subtilis*, for sheep. This supplementation was shown to positively impact the fat and protein content of their milk, while also contributing to increased body weight in lambs (Kritas et al., 2006). Additionally, a study by Yu et al. (1997) explored the effects of incorporating *Aspergillus oryzae* into cattle diets, revealing enhancements in milk productivity, specifically in terms of higher protein levels and an increase in dry non-fat solids in the milk. A number of studies indicate that these feed additives contribute to increasing egg production and quality (Haddadin et al., 1996; Kurtoglu et al., 2004) and to reducing their contamination with *Salmonella* (Van Immerseel et al., 2006). In the studies of Haddadin et al. (1996), birds were fed feed supplemented with *Lactobacillus acidophilus*, higher feed conversion rates and increased egg production were found. In addition to probiotics, in recent years the attention of scientists has been attracted by natural products of plant origin - prebiotics or so-called medicinal plants. Prebiotics are types of oligosaccharides that our bodies can't digest but are crucial for the health of our gut microbiota. They play a key role in promoting the growth and activity of beneficial bacteria in the intestines while also positively influencing overall health (Rioux et al., 2005). Research shows that prebiotics can reduce the presence of harmful bacteria in both animal studies and clinical trials involving humans. They eliminate the need for competition with bacteria (Sivieri et al., 2014). In recent years, their use in animal nutrition has received increasing attention, with the effect on overall health being studied (Markowiak & Śliżewska, 2017). Medicinal plants can provide host resistance to colonization by pathogenic bacteria by inhibiting their adhesion to the intestinal epithelium. Indigestible oligosaccharides have been shown to limit intestinal colonization by *Clostridium difficile in vitro* (Hopkins & Macfarlane, 2003). The makeup of gut microbiota is intricately linked to the overall health of an individual. Changes in this composition can lead to local dysbiosis and a range of metabolic disorders. This underscores the importance of investigating new protective and therapeutic approaches to prevent intestinal dysbiosis (Allaw et al., 2020; Lalouckova et al., 2021).

Smiricky-Tjardes et al. (2003) investigated the effect of a prebiotic on the gastrointestinal microbiota in pigs and found a significant increase in the number of *Bifidobacterium* and *Lactobacillus* in feces.

Scientific studies by Shivanna et al. (2013) indicate that in rats fed stevia, a decrease in blood glucose, ALT and AST was found, which is also confirmed by a study by Nenova & Enchev (2022) in pigs. It reduces the concentration of MDA (malondialdehyde) in the liver and improves its antioxidant status. A study by Pirgozliev et al. (2021a) proves that the addition of stevia improves the hepatic antioxidant status in broilers, by increasing hepatic vitamin E and carotenoidite, respectively. Other scientific experiments have found that adding stevia and sea buckthorn to poultry feed can improve their antioxidant status (Pirgozliev et al., 2021b; Pirgozliev et al., 2023). The antibacterial effect of stevia extracts against *Staphylococcus aureus*, *Bacillus cereus* and *Escherichia coli* was investigated by Pól et al. (2007) and Lalouckova et al. (2021). Nilson et al. (2023) investigated the effect of stevia extract as a substitute for antimicrobial drugs in broiler chickens. Their studies found improved immunological maturity in primary lymphoid organs and a balanced gut microbiota.

Gęgotek et al. (2018) found that when fibroblasts were incubated with sea buckthorn oil, there was a notable decrease in the production of reactive oxygen species (ROS). Sea buckthorn supplementation can be used as a natural source of antioxidants for the prevention and treatment of diseases associated with oxidative stress (Zhen et al., 2022). In vivo experiments in mice showed that it has antihyperlipidemic effects. A study by Zhen et al. (2022) showed that a 70% methanol extract effectively reduced leg swelling and inflammation in rats. Similarly, Verma et al. (2011) reported that an extract from sea buckthorn leaves was remarkably effective against 67 different Gram-positive bacteria, managing to inhibit the growth of strains like *S. aureus*, *S. epidermidis*, *S. intermedius*, and *S. pyogenes* by nearly 50%. Carotenoids such as β-carotene, lutein, lycopene, and β-cryptoxanthin exhibit hepatoprotective activity by reducing oxidative stress and regulating lipid metabolism in hepatocytes (Elvira-Torales et al., 2019).

Derbakova et al. (2016) investigated the effect of sea buckthorn extract on *Cryptosporidium* spp. in calves. They reported that it has anti-inflammatory, anthelmintic and antibacterial effects. Its addition to the feed ration leads to improved body weight in pigs, milk production in goats and egg laying in poultry (Shaker et al., 2018).

Recent studies indicate that various plant extracts can enhance the antibacterial effects of conventional medications when tackling mastitis. In their research, Srichok et al. (2022) explored the antibacterial properties of *O. tenuiflorum* extract and its potential interactions with standard antibacterial treatments aimed at mastitis-causing pathogens such as *Staphylococcus aureus*, coagulase-negative staphylococci (CNS), *Streptococcus agalactiae*, and *Escherichia coli*. Antibacterial drugs in combination with plant extracts broadened the antibacterial spectrum while reducing the antibacterial doses (Srichok et al., 2022). Maocheng et al. (2022) investigated the effect of quercetin on induced inflammation of mammary epithelial cells in cattle and investigated its possible mechanism. Yusrizal & Chen (2003) explored how feeding broiler chickens fructan sourced from chicory led to improvements in their weight gain, better feed conversion rates, and lower cholesterol levels. Similarly, Thitaram et al. (2005) verified the beneficial impact of isomalto-oligosaccharide (IMO) supplementation on the gut microbiota of broiler chickens infected with *Salmonella typhimurium*. In another study, Biggs et al. (2007) examined the effects of a diet enriched with five different oligosaccharides, including inulin, TOS, oligofructose, short-chain oligosaccharides, and MOS, on chicken health. Baurhoo et al. (2007) found that excessively high doses of prebiotics can have a negative impact on the gastrointestinal system and slow down the growth of animals (Baurhoo et al., 2007). A review of the literature indicates that studies examining the impact of prebiotics on animal health often yield conflicting results. This inconsistency arises from the unique characteristics of specific compounds, varying dosages, and different administration times. These factors highlight the importance of exploring and utilizing a range of biologically active components as natural strategies to enhance animal performance (Pandey & Rizvi, 2009). The development and use of effective antioxidants of natural origin is a priority nowadays. Medicinal plants can protect animals from free radicals and prevent oxidative damage, which causes degenerative and pathological processes (Tadhani et al., 2007).

In 1995, Gibson & Roberfroid coined the term "synbiotic" to highlight the combined benefits of probiotics and prebiotics working together. They ensure the survival of beneficial microorganisms and stimulate the proliferation of specific local bacterial strains (Markowiak & Śliżewska, 2018). Synbiotics combine the benefits of probiotics and prebiotics, working together to promote the survival of probiotics in our digestive system (Rioux et al., 2005). Nemcová et al. (1999) confirmed the synergistic effect of the bacteria *Lactobacillus paracasei* combined with FOS in the intestinal microbiota of piglets. The researchers observed an increase in the total number of beneficial bacteria of the genus *Lactobacillus* and *Bifidobacterium* in the group of animals fed with the synbiotic. At the same time, the number of bacteria of the genera *Escherichia coli*, Enterobacteriaceae and *Clostridium* decreased in the feces of the studied piglets (Nemcová et al., 1999). Li et al. (2008)

investigated the impact of certain factors on the growth, nutrient digestibility, gas production, and intestinal microbiota composition in weaning pigs. Mohnl et al. (2007) found that the tested product exhibited growth-promoting abilities similar to those of avilamycin in broiler chickens. Meanwhile, Vicente et al. (2007) validated the beneficial effects of a synbiotic product that included *Lactobacillus* spp. alongside lactose. Their research on *Salmonella*-infected turkeys highlighted the positive impact of this symbiotic on both feed conversion and body weight gain. Additionally, Li et al. (2008) explored how administering FOS and the *Bacillus subtilis* bacteria affected broiler chickens, noting enhancements in average daily gain and feed conversion ratios, along with a decrease in the rates of diarrhea and mortality when compared to those treated with tetracycline. Awad et al. (2009) studied the effect of a symbiotic product containing *Enterococcus faecium* bacteria and FOS as a prebiotic, and immunomodulatory substances from seaweed (phycophytes) on the health status of broiler chickens. An increase in the average daily body weight gain, slaughter ratio and feed conversion ratio were found.

In summary, researchers agree that symbiotic products provide better efficacy compared to the separate administration of probiotics and prebiotics (Markowiak & Śliżewska, 2017).

CONCLUSIONS

The use of feed additives, including probiotics, prebiotics, and synbiotics, is both safe and environmentally friendly, while also reducing reliance on antibiotics. However, further investigation is still needed to fully understand the mechanisms behind the actions of these probiotic organisms and their combinations in synbiotics. A wealth of scientific research supports the beneficial effects of probiotics on animal health, including their role in protecting against pathogens, enhancing the immune response, and improving the overall quality of animal production. Additionally, prebiotics can serve as an alternative or complementary approach to boost the benefits of probiotics. The use of a combination of these additives shows a synergistic effect, and can be even more effective in stimulating the intestinal microbiota and improving health. A difficulty in creating synbiotic products is the choice of the appropriate probiotic and prebiotic. Scientific research and development of innovative technologies are needed, which will lead to better production effects and higher quality of animal production.

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