Recent perspectives of growth promoters in livestock: an overview

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Abstract

Growth promoters are substances that are added to the feed as supplements or injections to improve feed conversion ratio and growth in livestock. They mainly help improve the distribution of fat and protein and increase the conversion rate of feed into muscle. The growth promoting effect of antimicrobials was discovered in the 1940s when animals fed with dry Streptomyces aureofaciens mycelium containing residual chlortetracycline exhibited improvement in growth. Its benefits include prevention and treatment of animal diseases, improved production of edible animals, increased milk and egg production and improved environmental and rumen health. Antimicrobial peptides are used in place of antibiotic growth promoters. It promotes the digestibility of nutrients, the gut microbiota, and the morphology of the intestine and the activity of immune function. Phytochemicals are cheap and ready-to-use alternatives which leave no toxic residues in milk and meat. They pose a risk of public health concerns such as antibiotic resistance, side effects, and residual risk. The use of alternative growth promoters should minimize the use of traditional antibiotics. Research in this area is still needed and the ultimate goal would be safe, clean and hygienic milk and meat production.

Key words: Antimicrobial; feed; public health; growth promoters; livestock

Introduction

Growth promoters are substances that are added to the feed as supplements or injections to improve feed conversion ratio and growth in livestock. Performance enhancers are substances used to increase animal feed conversion, average daily profit, carcass quality or milk yield. The benefits and risks of growth promoters remain a complex and controversial issue. (Herago & Agonafir, 2017; Gobezie, 2022).

All non-nutrient feed additives such as antibiotics and exogenous enzymes that improve animal growth can be described as growth promoters. The most commonly used growth promoters are feed additives, anabolic implants, bovine growth hormone and repartitioning agents (Kennedy et al., 1999; Getabalew et al., 2020).

Growth promoters are primarily used in livestock to promote growth, improve fat and protein distribution, and increase feed-to-muscle conversion. Most growth promoters are orally active and can be given either in food or drinking water, while other active hormones can be given in the form of small implants to the subcutaneous tissue of the ear. (Toldra and Reig, 2014) The growth-promoting effect of antimicrobials was discovered in the 1940s when it was observed that animals fed dry Streptomyces aureofaciens mycelium containing residual chlortetracycline improved growth. The United States Food and Drug Administration approved the use of antibiotics as animal additives without veterinary prescription in 1951. Also, in the 1950's and 1960's each European state approved its own national regulations about the use of antibiotics in animal feeds (Al-Dobaib & Mousa, 2009).

The mechanism of action of antibiotics as growth promoters is related to interactions with intestinal microbial population. Both genetics and nutrition are the two most important factors affecting animal productivity. Meat animal producers are concerned with the amount of protein fed that is converted into muscle deposition. Protein formation can be estimated by comparing the amount of nitrogen fed to the amount of nitrogen in the animal's waste. However, growth promoters can improve the efficiency of animals to use nitrogen of their ration to form amino acids and build their own protein. Most growth promoters accelerate nitrogen retention in the body (Herago & Agonafir, 2017).

Classification of growth promoters

1. Antibiotics

Different classes of antibacterials used as growth promoters have been presented in the table no.1. Antibiotics used as feed additives exert their effects in the digestive tract of animals by controlling unwanted competing microorganisms. It utilizes nutrients to produce unwanted or toxic substances and creates an optimal environment for the intestinal mucosa that allows efficient absorption of nutrients. Therefore, nutrition utilization, feed conversion ratio, and growth rate have improved. Also note that growing animals derive their greatest benefit from antibiotic growth promoters (Jones et al., 2003).

Mechanism of action includes improving the absorption of nutrients protect nutrients against the destruction by bacteria, reducing the production of toxins by gut bacteria and decreasing the incidence of asymptomatic intestinal infections (Al-Dobaib & Mousa, 2009). In ruminants, they act primarily on rumen microflora and alter rumen fermentation. They enhance the microbial production of gluconeogenic fatty acid propionate. The altered rumen fermentation also decreases production of methane with less loss of high-energy in rumen. The beneficial effect on growth may also be achieved by suppression of pathogenic organisms and harmful bacterial metabolites (Sandhu, 2013).

Ionophore antibiotics - e.g., Monensin, lasalocid and salinomycin. Monensin acts on bacteria by promoting the transport of sodium ions to cells and accelerating the sodium / potassium pump in the cell membrane, causing an ion imbalance. As the transport mechanism requires energy in the form of Adenosine Triphosphate (ATP). Continuous exposure to Monensin could lead the cell to exhaust energy supplies, resulting death by osmotic disruption of the cell (Getabalew et al., 2020).

Non-ionophore antibiotics - e.g., Zinc bacitracin, flavomycin, virginiamycinavilamycin, spiramycin and avoparcin. Non-ionophore antibiotics selectively modify the microbial population of animals to improve production efficiency. Non-ionophore antibiotics can be administered in milk replacers for young animals or in supplementary concentrates (Sandhu, 2013).

Synthetic antimicrobials - e.g., Carbadox and olaquindox. Carbadox and olaquindox are two widely available antibacterial synthetic quinoxaline compounds with growth promoting activity. (Al-Dobaib and Mousa, 2009). The growth-promoting effect of both compounds should be provided primarily by stabilizing the gut microbiota, which improves feed conversion ratio and reduces toxin formation. Carbadox is both mutagenic and carcinogenic in animals, and olaquindox is highly mutagenic. So, they are withdrawn.(Courtheyn et al., 2002)

Table 1: Classification of Antibacterial Growth promoters

Class	Antibiotic	Spectrum	Growth promotion (Species)
Aminoglycosides	Neomycin, Gentamicin	Narrow spectrum Broad spectrum	Cattle, Swine and sheep Swine
Pencillins	Pencillin G potassium Pencillin G Procaine	Broad spectrum	Swine and Swine
Ionophores	Lasalosid, salinomycin, Monensin	Broad spectrum	Swine and cattle
Macrolides	Erythromycin Tylosin, Tilmicosin	Broad spectrum	Chicken and Swine
Streptogramins	Virginiamycin	Broad spectrum	Chicken and Swine
Tetracyclines	Oxytetracycline, chlortetracycline	Broad spectrum	Cattle, Sheep,Chicken and Swine
Beta lactams	Ampicillin, amoxycillin	Broad spectrum	Cattle, Sheep, Chicken and Swine
Polypeptides	Bacitracin	Narrow spectrum	Cattle

Source: Al-Dobaib and Mousa, 2009.

2. **Hormones**

Hormones promote unnatural fast growth in farm animals. Mode of action of growth promoting hormones is to help to improve meat quality by decreasing the deposition of fat, producing the lean meat. They increase feed efficiency, thereby allowing more growth with less feed. They increase lactation period in cows when injected with bovine growth hormone (rBGH). This hormone interacts with other hormones in cows bodies to increase the amount of milk they produce. Growth promoting hormones enhance endogenous estrogen production and growth. (Bloss et al., 1966).

Steroidal sex hormones such as estradiol, progesterone and testosterone have been used for anabolic purposes in animals. Sex steroids produced in testes have important anabolic properties causing increased protein synthesis, enhanced muscle development and better feed efficiency resulting in net-weight gain. However naturally occurring sex steroids are not orally active, require relatively large doses to be administered and can transiently affect behavior of treated animals. Zeranol (a-Zearalanol) is a synthetic analogue of naturally occurring plant oestrogenzearalenone. Its mechanism of action is similar to that of oestrogen. It binds to cytosolic receptors for estradiol-17ß and modulates protein synthesis. It increases nitrogen retention, feed conversion efficiency, protein synthesis and body weight. The increase in growth rate is by 12-15% and feed conversion by 6-10% in steers (Sandhu, 2013).

Bovine somatotropin (BST) is a bovine growth hormone produced by the pituitary gland of cattle. During lactation, BST mobilizes body fat and uses it as energy, directing feed energy to milk production rather than tissue synthesis.In fact, BST increases efficiency in milk production by 10% to 15%. Though the use of BST is primarily concentrated on increasing milk product its effects on beef cattle are increased growth rates, improved feed conversion and carcass lean, while decreasing carcass fat.

These hormonal implants can promote growth during lactation, growth, and the final stages of meat production. They are implanted in the form of depot capsules and release certain doses of hormone over a period of time. The types of hormones most commonly used in the production of cattle in the form of implants include the natural hormones, estradiol, testosterone and progesterone, and the synthetic hormones (trenbolone acetate and geranol). Estradiolis responsible for female characteristics, testosterone is responsible for male characteristics, and progesterone is responsible for maintaining pregnancy. The other two hormones mimic the biological activity of the natural hormones: trenbolone acetate mimics the action of testosterone and zeranol mimics.Testosterone or testosterone propionate, alone or in combination with other hormonally active substances, used primarily to improve the rate of weight gain and feed efficiency by anabolic action of androgens. Trenbolone Acetate assumed to exert its anabolic action via interaction with androgen and glucocorticoid receptors including bile (Platter et al., 2003; Takemura et al., 2007)

3. **Repartitioning agents (Beta 2-Agonists)**

Beta-adrenergic agonists increase growth efficiency by stimulating beta-adrenergic receptors on the cell surface. They act as redistribution agents that alter carcass composition by altering nutrient distribution to reduce fat deposition by up to 40% and increase muscle protein content by up to 40%. Increased protein acquisition is mediated by agonist binding to muscle beta 1 and beta 2 receptors, resulting in increased muscle protein synthesis. In muscle tissue, beta agonists promote protein synthesis and cell hypertrophy by inhibiting proteolysis.

In adipose tissue, beta -agonists promote lipolysis. They may have a secondarymechanism mediated by other hormones by increasing blood flow. A wide range of compounds has been investigated as beta-agonists including Cimaterol, clenbuterol, fenoterol, isoprena_line, mabuterol, ractopamine, salbutamol, terbutaline and zilpaterol. Zilpaterol, present as an active beta2-agonist in Zilmax, is one of the new beta agonists officially registered for fattening purposes in cattle in Mexico and South Africa. Zilpaterol hydrochloride is a powerful beta agonist, which is more effective than ractopamine, but only about one-tenth effective as clenbuterol. Mexico reported that zilpaterol supplementation can have a marked beneficial effect on growth performance and carcass yield of feedlot steers. The most effective use of a repartitioning agent is in the finishing period in the one to two months prior to slaughter. (Mazzanti et al., 2003; Yang andMcElligott, 1989).

4. Probiotics

Probiotics are mono or mixed culture of living microorganisms, which induce beneficial effect on the host by improving the properties of the indigenous microflora. Several microorganisms have been considered as probiotics including fungi particularly mushroom and yeast, bacteria and mixed cultures comprising of various microbes (Tsugkieva et al 2021). The microorganisms used as probiotics are indicated in Genera Lactobacillus and Bifidobacterium are mostly reported (Ovcharova et al, 2022). Other bacteria that have been used, to a lesser extent in poultry and animal probiotics include Bacillus, Enterococcus, Streptococcus, Lactococcus, Pediococcus (Dawson et al., 1990).

Lactobacillus stimulates the rapid growth of beneficial microorganisms within GIT by occupying binding sites in the intestinal mucosa or by competing with pathogens for nutrients and absorption sites. Probiotics Lactic acid bacteria have the ability to attach to the intestinal epithelium and therefore compete with pathogens for adherent receptors. Probiotic bacteria produce organic acids, hydrogen peroxide, lactoferrin, and bacteriocins. These can be either bactericidal or bacteriostatic. Lactobacillus has been shown to be an immunomodulator by enhancing macrophage activity, increasing local antibody levels, inducing interferon production, and activating killer cells. They prevent the growth of coliforms and thereby reduce the amine production caused by decarboxylation of amino acids by coliforms (Dowarah et al., 2016).

5. Prebiotics

Prebiotics are indigestible feed components that selectively stimulate the growth of limited number of beneficial gut microbiota such as Bifidobacteria and Lactobacillus species. They have a mechanism of action similar to that of probiotics. One approach for future research is to study the combination of probiotics and prebiotics as synbiotics. It is a mixture of probiotics and prebiotics that has beneficial effects on the host. These effects include enhancing the survival and persistence of live microbial dietary supplements in the gastrointestinal tract by selectively stimulating growth and metabolism of beneficial microbes (Huyghebaert et al., 2011).

Prebiotics mainly consist of oligosaccharides (carbohydrates) and also include some non-carbohydrates. Some oligosaccharides prebiotics commonly in human food supplements are fructo-oligosaccharides (FOS), xylo-oligosaccharides (XOS), polydextrose and galacto-oligosaccharides (GOS). Mannooligosaccharides are used as prebiotics in pet foods. (Sandhu, 2013).

6. Metals

Certain copper salts such as copper sulphate, copper carbonate and cupric oxide are occasionally incorporated in excess of nutritional requirements in the animal feed for production enhancing and growth promoting effects. These effects of copper salts have been related to their antibacterial activity and also to correction of copper deficiency. Combination of a copper salt and an antibacterial agent shows additive effect on growth rate and feed-conversion efficiency. Arsenical compounds such as arsanilic acid and sodium arsanilate have been used in the past as growth promoters in pigs and poultry diets. These compounds are no longer recommended in animal production due to the risk of potential adverse effects (Sandhu, 2013). The positive impact of hydroxy mineral in animal feed i.e. better stability of feed components as well as in animals' i.e. higher bioavailability as compared with other form of trace minerals has also been studied (Reddy et al 2021).

7. Enzymes

The enzymes enhance production and feed conversion efficiency mainly by converting food into easily digestible molecules. Some of the important enzyme products approved for use in diets include amylases, lipases, phytases, galactosidasesglucanases, xylanases, proteases, pepsin, methionine and polygalacturonase (Bhutyal et al 2021). All are fermentation products of either bacteria or fungi and are available as liquids, solids, powders, coated preparation granulates or micro granulates (Sandhu, 2013).

Benefits of animal growth promoters

Prevention and treatment of animal diseases

With intensive animal production, bacterial and parasitic diseases became more and more frequent. According to an estimate, 80 types of bacteria, such as Escherichia coli, Salmonella, and Clostridium are involved. Due to unique advantages, such as exact targeting of pathogens, well-known mechanisms of activity and desired stability, antimicrobials justified their usage in livestock and poultry, and played important part for prevention and treatment of bacterial and parasite diseases reduction (Shi et al., 2011).

Enhancement of animal production

These could reduce the colonization of intestinal bacteria and inhibit the growth of pathogenic microorganisms. By decreasing the thickness of mucous membrane, lead to more absorption of nutrients and reduced fermentation. They directly neutralized the host immune response. In short, antimicrobials could affect the host intestinal flora, intestinal physiology, and immune system, and consequently, prevent disease, improve feed conversion, and enhance the growth of animals (Getabalew et al., 2020)

Improvement of environment

Livestock waste is one of the major sources of greenhouse gases, as the abnormal fermentation of gastrointestinal tract contents can produce lots of methane, ammonia, carbon dioxide, as well as stench gases Nitrogen and phosphorus in waste lead to environmental pollution, aquatic eutrophication and ecosystem imbalances. Some antibacterial agents in the feed may suppress abnormal fermentation and, as a result, reduce greenhouse gas emissions, primarily methane. Ionophore antibiotics have been widely used as feed additives in ruminants due to their favourable effects on rumen fermentation and methane reduction (Kobayashi,2010).

Improvement of rumen health

Ionophores decrease protein deamination in the rumen. This increases the effectiveness of bypass protein in cattle. Bypass protein has been demonstrated to increase from 22 to 55% in various experiments. Bypass protein is protein that is not broken down in the rumen but instead it is digested in the ileum of the small intestines. The basic effect of ionophores is to alter the flow of cations across cell membranes.

This leads to a reduction in Gram-positive bacteriaknown to cause bloat and other digestive problems associated with high carbohydrate diets.Ionophores are able to improve feed conversions and enable cattle to get more metabolizable energy from feed. One study indicates ionophores feed in combination with fat supplementation caused increased lipid flow to the small intestines. This can lead to potentially better utilization of fats in the diet of ruminants (Perry et al., 1976).

Risks by growth promoters

Antimicrobial Resistance Concerns

Antibiotic-resistant microorganisms are estimated to kill more people than cancer by 2050 (Bacanli and Basaran, 2019). Concerns on misuse and overuse of antimicrobial may end in the development of drug-resistant pathogens resulting in poor response to treatment. Long-term and low-level exposure to antibiotics may be more selective than short-term and complete therapeutic use. In one study, it was observed that the proportion of tetracycline resistance genes in the faecal flora of steers fed traditionally was significantly higher than in faecal samples of cattle without antibiotics.In addition, the use of a single antimicrobial agent can induce cross-resistance to antimicrobial agents used in veterinary and human treatment. For example, the use of chlortetracycline in growth rates is associated with ampicillin and tetracycline resistance in common faecal E. coli. Therefore, the use of antibiotics to avoid the development of resistance has become the most important issue in the effective treatment of bacterial and parasitic infections in food-producing animals.

The resistant bacteria may also be released into the environment by humans and then transferred into new hosts in the environment (Gassner and Wuethrich, 1994).

Administration of AGPs has been increasingly scrutinized due to concerns over selection for AMR and potential transmission of antimicrobial-resistant bacteria to human beings. The risk posed depends on whether the AMA registered for use in livestock belongs to the same class as AMAs registered for use in human medicine. Importantly, certain classes of AMAs used in livestock as growth promoters are also administered therapeutically in humans (e.g., tetracyclines, penicillins, aminoglycosides), whilst others (e.g., ionophores) are used only in livestock. To reduce the risk of losing AMA efficacy in humans, most regulatory agencies are currently focused on controlling the non-therapeutic administration of HAMAs(human anti-microbial agents) to livestock. (Brown et al., 2016).

Ionophores toxicity

The use of ionophores as coccidiostats and growth promotants has resulted in the occurrence of toxicoses in target and nontarget species. Clinical and pathologic effects of ionophore poisoning are caused by bioactivity and damage to excitable tissues such as cardiac muscle, skeletal muscle, smooth muscle and the nervous system. Because ionophore poisoning is often associated with feed mixing errors, practitioners should prioritize tests to confirm suspicious feed removal and overexposure.

Ionophores toxicosis was reported in cattle, horses, ostriches and camels. However, camels were found to be particularly sensitive to ionophores compared with other animals. Toxic effects of ionophores are directed mainly against skeletal and/or cardiac muscle as a result of disturbances in muscle cell calcium homeostasis followed by increased intracellular Na+ concentration. Equines are much more susceptible to cardiac muscle damage than other species and the effects are reported to be persistent.

Ionophore should not be used in birds that lay eggs for human consumption, as residues can enter the food chain and be toxic to humans. Ionophore is not used in human medicine due to its strong cardiovascular effects (Baird et al., 1997).

Hormonal adverse effects

The use of six growth hormones 17ß-oestradiol, progesterone, testosterone, zeranol, trenbolone and melengestrol acetate (MGA) for growth promotion in cattle poses a risk to the consumers but with different levels of conclusive evidence. This is the main finding of the Scientific Committee for Veterinary Measures relating to Public Health which has unanimously adopted an opinion on potential risks to human health from hormone residues in meat and meat products.

The adverse effects include developmental, neurobiological, genotoxic and carcinogenic effects. These effects can be attributed to either the parent compound or the metabolites. There is substantial recent evidence that the natural hormone 17ß-oestradiol has to be considered as a complete carcinogen. It exerts both tumour initiating and tumour promoting effects. Estrogens bind to the estrogen receptor (ER) and subsequently stimulate cancer cell growth by transcriptional regulation of genes involved in cell proliferation. Cancers linked to the presence of estrogen include breast, endometrial and ovarian cancer (Morito et al., 2001).

Residual problem

Many of the drugs and antibiotics can elicit allergic reactions. Most of the information is related to hypersensitivity to penicillins, aminoglycosides and tetracyclines. Idiosyncratic reactions such as allergies, rashes and phototoxic dermatitis have been reported associated with the use of tetracycline. The most important side effect of antibiotic residues is the transmission of antibiotic-resistant bacteria to humans due to mobility resistance. More and more people are dying from antibiotic-resistant bacterial infections. Pathological effects include Autoimmunity, Carcinogenicity due to Sulphamethazine, Oxytetracycline, Furazolidone, Mutagenicity, Nephropathy due to Gentamicin, Hepatotoxicity, Reproductive disorders, Bone marrow toxicity due to Chloramphenicol, Allergy due to Penicillin (Campagnolo et al., 2002).

Public health impact of growth promoters

Human health is directly affected by antibiotic residues in the meat that can cause side effects, or indirectly by the choice of antibiotic resistance determinants that can spread to human pathogens. Antibiotics are illegally used in many countries to promote the growth of food agriculture. These conditions favor the selection and spread of antibiotic resistant bacteria among animals, to the environment and eventually to humans, where they cause infections that are more difficult to treat, last longer or are more severe than antibiotic sensitive infections.

Recent research suggests that food animals (Particularly pigs) may also be a reservoir of some strains of methicillin resistant Staphylococcus aureus (MRSA) for humans although it appears that people are the major reservoir for most epidemiologically important strains of MRSA. While the major public health impact from food animals is normally attributed to food borne Salmonella and Campylobacter. Recent research is making it increasingly apparent that food animals are also an important reservoir of antibiotic resistant E. coli urinary tract and probably blood stream infections of humans (Marshall and Levy, 2011). However, ingestion of animal foods containing ractopamine residues increases the toxicological risk to human health and also causes cardiovascular disease. Probiotic manufacturers, healthcare professionals, and public health authorities are looking at some form of system for monitoring the health effects of long-term probiotic administration. Characterization of each microbial strain used in the production of probiotics should be based on guidelines jointly submitted by FAO and WHO developed by the Working Group on the Safety of Probiotic Products for Human Health. There is improper application of probiotic production guidelines leads to the development of pathogenic microorganisms for human and animal health. The FDA, WHO, American dietetic association and national institutes of health have independently stated that dairy products and meat from Bovine somatotropin (BST) treated cow are safe for human consumption (FAO and WHO).

Table 2. Maximum Residual Limit (µg/kg) for veterinary residues

Antibiotics	MRL
Benzyl penicillin	4
Ampicillin	4
Amoxycillin	4
Oxacillin	30
Cloxacillin	30
Dicloxacillin	30
Tetracycline	100
Oxytetracycline	100
Chlortetracycline	100
Streptomycin	200
Dihydrostreptomycine	200
Gentamycine	200
Neomycin	100
Sulphonamides	100
Trimethoprime	50
Spiramycin	200
Tylosine	50
Erythromycine	40
Quinalones	75
Polymyxine	50
Ceftiofur	100
Cefquinome	20

Source: Nisha, 2008

Global policies on growth promoters

On a global level, a recent joint workshop was held involving the WHO, Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health (OIE) on non-human antimicrobial usage and antimicrobial resistance on 15–18 March 2004 Oslo, Norway. The resulting report recommends the implementation of WHO's global principles for controlling antimicrobial resistance in food animals. These principles include the withdrawal of AGP from food animal production when and until a risk assessment is performed, which is also in a class that is also used to treat human illness. In addition, the report recommends conducting risk assessment studies at the national level and establishing a monitoring program to monitor the use of antimicrobial growth promoters and antimicrobial resistance in livestock bacteria.

Denmark was among the first countries to ban the use of hormones for growth promotion in meat animals, banning them in 1963. Concern about growth-promoting hormones became widespread in Europe in 1977 after the discovery that a number of young boys in Italy had begun to develop breast cancer. Researchers suggested that estrogen in poultry or meat might have been related to the incident (Yuri et al., 2006). Whereas the EU has banned the use of all hormones other countries do allow the use of steroid hormones and hormone-like substances in various combinations with the aim to improve weight gain and feed efficiency in livestock farming. In the United States, Canada, Australia, New Zealand and in some countries in South America, Asia and Africa the natural hormones - testosterone, 17ß-oestradiol and progesterone - and the synthetic hormones trenbolone, zeranol and melengestrol acetate can be used to promote growth. Currently, five hormones (Progesterone, testosterone estradiol-17, and zeranol and trenbolone acetate) are approved for implants in cattle in the U.S.A. But these implants have been officially prohibited in Europe since 1989 (Cogliani et al.,2011) The focus of bans in Sweden has been on antibiotics for growth promotion, rather than hormones. In 1986 Sweden banned all use of antibiotics for the purposes of growth promotion. Sweden was among the first countries to implement the recommendations of the United Kingdom’s 1969 Swann Commission, which recommended restricting the use of antibiotics and prohibiting specific drugs in animal feed.

Denmark introduced its first antibiotic ban in May 1995 when it banned the use of avoparcin in the country. This followed the release of a 1993 report that linked the emergence of the antibiotic-resistant bacteria. After avoparcin ban, the total use of antimicrobials for growth promotion continued to increase until January 1998 when Denmark banned a second growth promoter, virginiamycin. Following the actions in European countries such as Sweden and Denmark, the Commission of the European Union banned the use of avoparcin as a growth promoter in all EU member states in 1997. In the EU, feed additives cannot be placed on the market unless they are authorized based on scientific evaluation of their efficacy, effect on animal and human health and on the environment. There are currently no beta agonists registered in the EU for use in cattle as growth promoters, indeed in the EU this class of compound is specifically prohibited under EU Directive 96/22/EC. There is one product registered as a growth promoter in cattle in South Africa and Mexico zilpaterol (Zilmax, Hoechst Roussel Vet) – and one in pigs in the USA, Mexico, Brazil, Philippines and Korea ractopamine (Herago and Agonafir, 2017).

Legal framework for use of antibiotics in food-producing animals in India

In India, Ministry of Health and Family Welfare, Government of India, has framed a comprehensive policy, namely, National Policy for Containment of Antimicrobial Resistance, 2011, to address the growing problem of multi-drug resistance. It covers a wide range of aspects such as review of current situation regarding manufacture, use, and abuse of antibiotics. It also includes a national surveillance system for monitoring antibiotic resistance and conducting infection surveillance in hospitals, developing rapid diagnostic tools for antimicrobial-resistant pathogens. Reducing antibiotic selection pressures by advocating alternative control measures, establishing monitoring systems, and promoting rational drug use through education and supervision (Moudgil et al., 2018).

In India, until 2013 there were no official regulations on the use of antibiotics in food animals reared for domestic consumption when the amendment was made in Drugs and Cosmetics Rules by the Ministry of Health and Family, Government of India. The amendment states that the container of the medicine meant for treatment of food producing animals should be labelled with the withdrawal period of the drug for the species on which it is intended to be used. If the withdrawal period is not specified, it should be at least 7 days for eggs or milk, 28 days for meat including fat and offal, and 500-degree days for fish flesh. But still there is no legislation on restricting/banning the use of antibiotics as AGPs in India which have been now banned in many developed countries. In India, the manufacture and sale of antibiotics for human and veterinary purposes are regulated by the Central Drug Standard Control Organization (CDSCO) under the Drugs and Cosmetics Act, 1940.

It is revised at times based on the advice of the drugs technical advisory board which is a part of the CDSCO in the Ministry of Health and Family Welfare, India. The most recent is the introduction of Schedule H, a class of prescription drugs in India. These are drugs which cannot be purchased over the counter without the prescription of a qualified doctor. The Food Safety and Standards Authority of India (FSSAI), 2011, under the Food Safety and Standard Act (2006) is the main authority under the Ministry of Health and Family Welfare for implementing science-based standards for food articles.

It also regulates manufacturing, storage, distribution, sale and import to ensure theavailability of safe and healthy food for human consumption. FSSAI's main task is to implement good manufacturing practices, good hygiene standards, key controls for hazard analysis, and new practices established by regulations. (Moudgil et al., 2018) Currently, FSSAI is only for seafood, including shrimp and all other types of fish and marine products, under food safety and standards (contaminants, toxins, residues), has a level of resistance to antibiotics and other pharmacologically active substances) Regulations, 2011. Tolerances for antibiotics and other pharmacologically active substances in milk, meat and eggs have not yet been established.

On 19th July, 2019 Ministry of health and family welfare Government of India amended section 26A of the Drugs and Cosmetics Act, 1940 which prohibits the manufacture, sale and distribution of the Colistin and its formulations for food producing animals, poultry, aqua farming and animal feed supplements. It directs the manufacturer of Colistin and its formulations to label the container of the drug and mention the words “NOT TO BE USED IN FOOD PRODUCING ANIMALS, POULTRY, AQUA FARMING AND ANIMAL FEED SUPPLEMENTS” in conspicuous manner on the package insert and promotional literature of the said drug and its formulations (CDSCO).

The Export Inspection Council of India (EIC), under Export (quality control and inspection) Act, 1963, was set up by the Ministry of Commerce and Industry, Government of India, with mandate of sustained development for the export trade of India through acquiring quality control and inspection. The act has also setup rules stipulating the upper permissible limits for certain antibiotics and anthelmintics like albendazole and fenbendazole in milk and milk products. Moreover, MRLs for antibiotics in eggs and prohibition on the use of chloramphenicol, dimetridazole, metronidazole, nitofuran metabolites and anticoccidials in feed and medication of poultry intended for export or in any stage of production of egg powder is advocated. EIC has a residue monitoring plan for the export of fresh poultry meat and poultry meat products to the European Union to ensure food safety and quality of the exported products. EIC has also adopted the EU standards for exported products, but there are no regulations for domestic consumption of chicken (Moudgil et al., 2018)

Important websites for legal and regulatory institutions

https://cdsco.gov.in.
https://www.fda.gov.in

https://european-union.europa.eu/index_en
https://www.fda.gov.in
https://www.fao.org.in
https://www.fssai.gov.in
www.centerforfoodsafety.org/issues/307/animal-factories/animal-factories-and-environmental-pollution

Alternatives to antimicrobial agents for growth promotion use

Antimicrobial peptides (AMPs) display a broad spectrum of activity against bacteria, fungi, viruses, and cancer. Examples include Lactoferrin (bLf), Plectasin and Pediocin A. Normally, the activity of AMPs can be related to bacterial membrane interaction. This interaction can occur associated with ion channel/ pore formation and/or detergent-like effect, indicating the molecular basis of their attraction to membranes. In addition, AMP exhibits a variety of mechanisms of action, including membrane disruption, increased membrane permeability, and / or disruption of important cellular processes by interacting with intracellular targets. Besides, the use of AMPs as a growth promoter has demonstrated beneficial effects on nutrient digestibility, the intestinal microbiota, intestinal morphology, and immune function activities. (Rodrigues et al., 2021).

Clay minerals include molecules of silicon, aluminium and oxygen. The best known clay minerals are montmorillonite, smectite, kaolinite, biotic and clinoptilolite. Clays added to the diet can bind and immobilize toxic materials in the gastrointestinal tract of animals and thereby reduce their biological availability and toxicity. Clay minerals can bind aflatoxins, plant metabolites, heavy metals, and toxins. The extent of adsorption is determined by the chemistry of the clay minerals, exchangeable ions, surface properties and the fine structure of the clay particles. An important role is played by pH, dosage and exposure time. As a result of their binding properties, clays have been widely used in swine diets to improve pig performance when diets containing mycotoxins are fed. Clays have also been shown to prevent diarrhoea in weaned pigs. (Liu et al.,2021)

Egg yolk antibodies (IgY) can be administered as feed in a variety of forms, including whole egg powder, whole egg yolk powder, water-soluble fraction powder, or purified IgY. Details concerning IgY production including choice of adjuvant, route of immunization, dose, immunization frequency and techniques for IgY extraction from the yolk including agglutination of bacteria, inhibition of adhesion, opsonization followed by phagocytosis and toxin neutralization. Further research is necessary to determine the exact mechanism for the growth promoting activity of IgY. Unfortunately, there are several reports where egg yolk antibody failed to improve pig performance. The most likely reason why egg yolk antibodies failed to improve performance was that they did not survive through the gastrointestinal tract (Thacker, 2013).

Phytochemicals can also be classified as essential oils and oleoresin, depending on the process used to obtain the active ingredient. Essential oils especially those that contain phenol and aldehydes, for example cinnamaldehyde, citral, thymol and eugenol as major components could show considerable antibacterial activity. Plant extracts consists mainly of proteins, peptides, oligosaccharides, fatty acids, vitamins, micro minerals. Plant extracts have a wide range of activities, and their active secondary plant metabolites usually belong to the class of isoprene derivatives and flavonoids. Numerous plant extracts contain compounds with antibacterial, anti-inflammatory, anticoccidial, and anthelmintic properties.These properties of plant extract are mainly due to the bioactive compounds such as flavonoids and glucosinolates isoprene derivatives found in nature. Additionally, the properties probably are the major mechanisms by which plant exert positive effects on the growth performance and health of animals. They can exhibit their effects by stimulating feed intake and endogenous secretions or having antioxidant, antimicrobial activities. Various plant or herbal extracts are commonly included in poultry diets for promoting growth performance and animal health especially when there are health challenging conditions. The supplementation of plant extracts or oils in to diets increased the body weight gain, feed intake and improved feed conversion rate in poultry.

Essential oils are aromatic oily liquids obtained from plant material and usually have the characteristic odour or flavour of the plant from which they are obtained. They are typically mixtures of secondary plant metabolites and contain phenolic compounds (i.e. thymol, carvacrol and eugenol), terpenes (i.e. citric and pineapple extracts), alkaloids (capsaicin), lectins, aldehydes (i.e.cinnamaldehyde), polypeptides or polyacetylenes. They can be extracted from plants with organic solvents or steam distillation. The cinnamaldehyde, carvacrol, eugenol, and thymol have received the greatest interest for use in pig production. Use of essential oils as a potential alternative to antibiotics in pig feed as a result of in vitro studies showing that essential oils have antibacterial activity against the microbial flora commonly present in pig intestines. The exact mechanism of action of essential oils is unknown, but activity may be associated with changes in lipid solubility on the bacterial surface.

The hydrophobic component of the essential oil dissolves the outer membrane of E. coli and Salmonella and makes it possible to inactivate these pathogens. Weight gain, feed conversion ratio, and fecal consistency in pigs fed essential oils were essentially comparable to those in antibiotic-fed pigs. The improved performance appeared to be mediated by improved dry matter and protein digestibility due to improved intestinal morphology. In addition, total antioxidant capacity and levels of the cytokine's interleukin-6 and tumour necrosis factor were altered by inclusion of essential oils.

Rare earth elements comprise of elements scandium, yttrium, lanthanum and the 14 chemical elements following lanthanum in the periodic table called lanthanides. The application of rare earth elements as feed additives for livestock especially in swine has been practiced in China for decades. It has been suggested that rare earth elements may promote growth by influencing the development of undesirable bacterial species within the gastrointestinal tract. For example, lanthanum has been shown to bind to the surface of bacteria. This reduces the surface charge and retards electrophoretic migration. When the surface charge is completely neutralized, flocculation occurs. In addition, bacterial respiration has been shown to be strongly inhibited by lantanides. Another explanation for the growth promoting effects of rare earth elements is due to improvements in nutrient digestibility and availability. It has been suggested that rare earth elements may influence the permeability of the intestines thereby enhancing the absorption of different nutrients. Enhanced secretion of digestive fluids and increased gastrointestinal motility have also been proposed as explanations for the enhanced digestibility of nutrients following dietary inclusion of rare earth elements (Oluwafemi et al., 2020).

Tannins are water-soluble polyphenolic compounds of variable molecular weights which precipitate proteins. Tannins can be classified into condensed and hydrolysable. Chestnut tannins may change the droppings consistency, resulting in firmer droppings in treated groups which positively affect the litter status and thus improving the overall health status and welfare of chickens in intensive production systems. A recent work reported that chestnut extracts exhibited a surprising effect in improving the tolerance to gastric transit of Lactobacilli, also improved the tolerance to bile juice and reduced the number of gastrointestinal parasites in mammals and birds. Many works report the antiviral activity of some tannin against animal viruses. Tested condensed and hydrolysable tannins showed an unspecific neutralizing effect on enveloped virus by binding to cell receptor like glycoproteins or CD_4, also induced aggregation of purified virions or BSA through association of tannins with proteins. In one of the studies, they reported that the quebracho extract reduced intracellular viral activity by inhibition of viral enzymes. The higher intracellular activity of quebracho extract could be due to the smaller size of tannins extracted from this plant that could penetrate the cells (Redondo et al., 2014).

Conclusion

Antimicrobial agents and hormones are potent growth promoters provided that the target animals receive recommended dosage levels and side effects, especially antibiotic resistance, are avoided by using growth promoter antibiotics not designed for human use. However, different approaches for the use of probiotics and prebiotics have been suggested and promising non-risky application is achieved. Countries should develop policy on the use of different animal growth promoters and monitor the regulations. Unfortunately, the vast majority of alternatives produce inconsistent results and rarely equal antibiotics in their effectiveness. Therefore, it would appear that research is still needed in this area and that the perfect alternative does not exist as yet.

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