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A Review on Veterinary Drug Residues in Foods of Animal Origin

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Abstract

Veterinary drugs may leave drug residues in foods like meat, milk, eggs, or honey because they are often used to improve animal development and prevent disease in animals that produce food. It, including antiparasitic, antibiotics, and growth promoters are crucial for preserving the wellbeing and production of agricultural animals, and the health of companion animals. However, excessive use of these drugs leads to harmful residues, such as metabolites and original drugs, which can be dangerous to both human and animal health. There is not enough information available in Ethiopia about the proper and reasonable use of veterinary medications and there is a clear lack of available information about antibiotic residues in animal derived foods. Therefore, the aim of this seminar paper is to review veterinary drug residues in foods of animal origin. A portion of drugs given to animals, such as hormones, growth promoters, antibiotics, or anticoccidials, may be metabolized and eliminated. However, edible tissues like meat, milk, eggs, seafood, or fish may still contain trace amounts of these drugs or their metabolites. Drug residues in animal-derived food can have a direct impact on human health, or they can have an indirect effect by spreading human pathogens through the selection of antibiotic resistance determinants. Drug residues in food samples are found and measured using analytical methods such as immunological methods, chromatography methods like liquid and gas chromatography, and biosensors. Therefore, Community awareness about veterinary drug residues in food of animal origin should be given by governmental bodies and other stockholders.

Keywords: Foods of animal origin • Drug residues • Veterinary drug

Introduction

Internationally, due to continued population expansion and a shift in diet toward meat eating, the demand for animal-derived food has significantly increased. Human health is related directly to the environment, and the nature and quality of the food. Animal productivity has increased quickly to maintain food security [1]. Veterinary drugs, including antiparasitic, antibiotics, and growth promoters, are crucial for preserving the wellbeing and production of agricultural animals, and the health of companion animals. Veterinary drugs may leave drug residues in foods like meat, milk, eggs, or honey because they are often used to improve animal development and prevent disease in animals that produce food.

Since veterinary drugs have been used extensively in the agro-industry and animal husbandry, the quality of food derived from animal products is a major concern for public health agencies worldwide. Additionally, the growing prevalence of residues and resistance has become interesting issues. Veterinary drug residues include impurities associated with veterinary drugs as well as the residues of parent compounds or metabolites of veterinary drugs found in any edible portion of animal products. They are one of the most important pollution sources from animal foods and are tightly connected with animal food safety.

Currently, veterinary drugs are still used to treat diseases in farmed animals and in aquaculture. Veterinary drugs are administered to animals in three ways: by injection, oral administration, or animal feed. Most of the medications are fed into the animal's diet. Animals metabolize veterinary medications; some of the medications stay in the animal's body while others are expelled into the environment. Veterinarian drugs typically find their way into fish, shrimp, and crabs, as well as other aquatic products and rivers, in aquaculture. Drug residues in animal products not only result in severe side effects like acute toxicity, allergic reactions, bacterial resistance, imbalanced human flora, carcinogenesis, teratogenicity, and mutagenicity, but they also cause massive economic losses for the country. Strictly regulating veterinary drugs residues and improving detection methods particularly rapid, sensitive, accurate, and simple testing methods are crucial for protecting ecological ecosystems and sustaining public health [2].

Animal medicines are found in fruit and vegetables that humans eat and drink. The re-entry of these drugs into the body poses a serious risk to human health. Maximum Residue Limits (MRLs) for veterinary drugs in animal-derived foods have been set by the European Union (EU), the United States, China, and other nations to safeguard the health and safety of consumers. Residues are defined as "pharmacologically active substances (whether active principles, recipients, or degradation products) and their metabolites which remain in foodstuffs obtained from animals to which the VMPs in question has been administered" by the European Union (EU) and the Center for Veterinary Medicine, an organization under the Food and Drug Administration (FDA/CVM) in the USA. Under the normal physiological conditions, following administration of a drug to an animal, most drugs are metabolized to facilitate elimination, and usually detoxification as well. In general, most of the parent product and its metabolites are excreted in urine and to a lesser extent *via* faeces.

Veterinarian drugs are now widely used, mostly in aquaculture and farm animal breeding, enabling the high-yield, high-quality production of foods derived from animals. However, excessive use of these drugs leads to harmful residues, such as metabolites and original drugs, which can be dangerous to both human and animal health. The veterinary profession is becoming more liberal due to current market economy developments. The issue is that distribution of phytosanitary products and veterinary medications is unregulated in most African nations. Even worse, there is currently no suitable legislation in place to ensure the caliber of the various goods that are introduced onto the African market.

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In addition to the health risk to local populations, the presence of residues from veterinary medicinal products in foods of animal origin could jeopardize international trade in the wake of the World Trade Organization (WTO) Agreement on the Application of Sanitary and Phytosanitary Measures (the 'SPS Agreement'), which underpins the globalization of markets, and of agreements by the West African Economic and Monetary Union (UEMOA) leading the West African market.

In Africa, agricultural sectors use a significant amount (50%) of antibiotics for animal farming, in addition to the negligent use of antibiotics in human medicine. But there isn't a precise law in place to prevent feedstuffs from being contaminated with antibiotics. There is not enough information available in Ethiopia about the proper and reasonable use of veterinary medications. Additionally, there is a clear lack of available information about antibiotic residues in animal derived foods [3].

Therefore, the objective of this seminar paper is:

- To review veterinary drug residues in foods of animal origin.

Literature Review

Veterinary drugs

Veterinary drugs are classified according to their use, source, and chemical structure and can be classified as semi-synthetic drugs, synthetic drugs, and natural drugs. Veterinarian drugs can be broadly categorized into four groups based on how they are used: growth-promoting drugs, internal and external parasitic disease control drugs, infectious disease control drugs, and general disease control drugs. Generally, researchers classify compounds according to their structure and function, such as antimicrobials, corticosteroids, analgesics, anti-parasitic and hormones [4].

The use of veterinary drugs has quickly increased, mainly in farm animal breeding and aquaculture, allowing high-yield and high-quality production of animal-derived foods.

It is against the law to use certain drugs on food animals. The drugs such as nitroimdazoles, clenbuterol, and chloramphenicol are not allowed to be given to animals that produce food. nitrofurans, Chloramphenicol is not used for any purpose that would result in the presence of residues in food animals for consumption by human beings. In veterinary medicine, Chloramphenicol is approved for use only in non-food producing animals [5].

Drugs used in poultry

The major drugs used in poultry such as chlortetracycline, sulfonamides, erythromycin, gentamicin, furazolidone, nitrofurazole, tylosine, lincomycin, ampicillin, doxycycline, neomycin, and other drugs are used for the treatment and prophylactic purposes. Sulfonamides in poultry are widely used for the treatment of infectious corynza, pullorum disease, fowl typhoid, and coccidiosis. The compounds roxarsone, carbarsone, and arsanilic acid have been used in drugs added to feed for chickens, and turkeys to prevent disease, increase feed efficiency, and promote growth.

Many farmers have treated most infectious diseases in chickens with drugs; regardless of the potential long-term health risks to humans if appropriate management practices are not followed [6].

Drugs used in dairy cattle

The most used drugs in dairy cattle are penicillin, tetracycline, amino glycosides, ceftiofur, chlorhexidine, povidone iodine, polymyxin B, macrolides, Sulfonamides, and other drugs. Dairy cattle that have been treated with antibiotics produce milk containing antibiotic residues for a period after treatment. Treated cows are therefore required to be excluded from the milk supply for a specific period to ensure that antibiotic residues no longer remain in their milk.

In dairy cattle, extra label intramasturial drug administration happens occasionally, when associated with mastitis (infections of the mammary glands) that does not improve with approved products. Ceftiofur sodium and ceftiofur hydrochloride are approved for intramuscular and subcutaneous use only and label use does not result in drug concentrations in milk greater than the tolerance limit level. Occasionally, these antimicrobials have been used in an extra labeled manner by bovine practitioners or dairy producers for the inframammary treatment of coliform mastitis [7].

Because povidone iodine is very effective eliminating all secretions from treated mammary gland quarter, it is likely a better choice for therapeutic cessation of lactation because the residues risk should be minimal if no secretion (milk) is produced. It is important to note that this is an instance of extra-label drug use, and that since adequate milk withdrawal data are unavailable, extra caution needs to be exercised to prevent milking treated mammary gland quarters, which may result in residues.

Major drugs used in beef cattle

Although numerous drugs are used on beef cattle, some of the most common ones are hormones, macrolides, penicillin, tetracycline, dihydrostreptomycin, and anti-helminthic.

Penicillin derivatives (β-lactam antibiotics) are widely used in beef cattle to treat infections and as feed or drinking water additives to prevent some diseases. To maximize their combined effects on pathogens, a mixture of benzathine penicillin, procaine penicillin, and dihydrostreptomycin is used in preparation.

In addition to treating a wide range of infections, oxytetracycline is also used to stimulate animal growth. Addition of tetracycline to animal feeds at 5-20ppm does not seem to produce residues in edible tissues. In addition to these, neomycin, gentamicin, flunixin, streptomycin, erythromycin, anti-helminthic, and other drugs are also used in beef cattle [4].

Feed additives have been used in animal nutrition over the past few years to enhance animal performance, health metrics, and nutrient utilization. Antibiotic resistance has been made possible using antibiotics as feed additives, though, and this could lead to an increase in the morbidity and mortality of diseases that were previously treatable with antibiotics.

There are important duties for the beef cattle feeder because some feed additives need to be removed from the diet prior to slaughter. The use of medicated feed additives is controlled by the Food and Drug Administration (FDA). The Environmental Protection Agency (EPA) regulates other feed additives like larvacides because they are not absorbed and do not directly affect the animal's physiology [4].

Drug residues in food

The term "drug residues in food" describes the existence of drug residues or their metabolites in consumables that come from crops or animals that have received pharmaceutical treatment. A portion of drugs given to animals, such as hormones, growth promoters, antibiotics, or anticoccidials, may be metabolized and eliminated. However, edible tissues like meat, milk, eggs, seafood, or fish may still contain trace amounts of these drugs or their metabolites. The amount of time needed for the drug to be eliminated from the animal's body, or the withdrawal period, may be used to assess the products' safety [8].

Discussion

Classification of drug residues in food

The classification of drug residues in food of animal origins is shown in Figure 1.

Antibiotics: A drug known as an antibiotic is used to treat or prevent bacterial infections that cause diseases in both humans and animals. Moreover, because of their significant therapeutic advantages, the widespread use of antibiotics as feed additives spreads among animal foods. The use of high doses of antibiotics in animals is the cause of this drug residue's presence in edible tissues. Quinolones and sulfonamides were the main drug residues

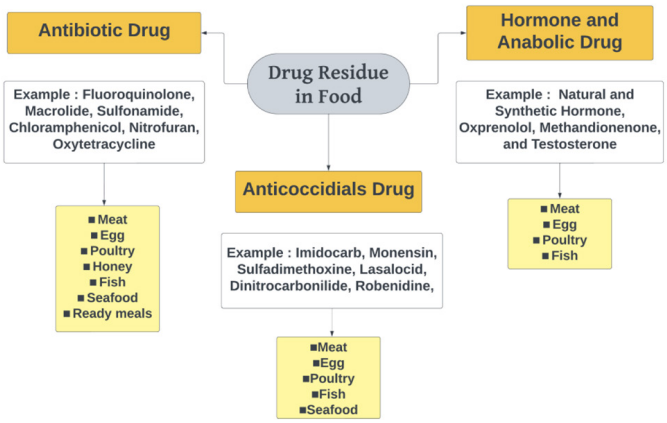

Figure 1. Drug residues in food.

found in the food; ciprofloxacin, norfloxacin, and sulfisoxazole were the specific compounds with the highest concentrations.

The extensive use of antimicrobial drugs in animals raised for food is a major factor in the development of antibiotic residues, which in turn leads to the worldwide issue of antimicrobial resistance, allergic reactions, mutagenic and carcinogenic effects, and even deaths [9].

Anticoccidial drugs: Antiprotozoal drugs, also known as anticoccidial drugs, are used to treat a variety of microscopic parasitic infections, most notably coccidiosis. The Eimeria genus of protozoa is the source of the disease coccidiosis. It primarily impacts poultry and ruminant animals. In poultry, anticoccidial drugs were given as prophylaxis because the losses from coccidiosis outweighed the expenses of giving preventive doses. Salinomycin, narasin, monensin, toltrazuril, robenidine, nicarbazin, dinitrocarbanilide, dimetridazole, decoquinate, and lasalocid are a few anticoccidial drugs that are frequently found in food. Anticoccidial residue in food exhibits undesirable toxicological effects, such as teratogenicity, hepatotoxicity, or neurotoxicity, at high doses in laboratory animals.

Hormones and anabolic drugs: In the production of livestock, hormones and anabolic steroids are used to promote growth, induce weight gain, and increase meat yield. Because of their use, these drugs results in active ingredient residues or their metabolites in the human food chain. Concerns regarding the increased use of these drugs have grown due to disturbances in the endocrine system's function. Hormonal drugs are synthetic compounds that mimic the actions of hormones, either as steroids or nonsteroidal products.

Growth promoters include beta-agonists like salbutamol, ractopamine, cimaterol, clenbuterol, and zilpaterol. Steroid hormones and non-steroidal hormones (protein hormones) are the two categories of hormones. It is possible to further categorize steroidal hormones into corticosteroids and anabolic steroids. Certain hormones, like estrogen, are recognized for their ability to cause cancer and damage to DNA, while other hormones, like diethylstilbestrol, have been linked to mutagenic, carcinogenic, immunotoxic, and teratogenic effects [10].

Type of food that usually contains drug residues

A variety of products derived from animals, including meat, poultry, fish, and prepared meals, contain veterinary drug residues. The use of hormones, growth promoters and antibiotics is indicated to ensure effective feeding and accelerated growth, and as treatment and prophylaxis of animal diseases. On the other hand, overdosing and inappropriate administration can have detrimental effects on humans, including resistance, carcinogenicity, organ dysfunction, and other adverse effects [11].

Meat: Meat samples are foods with a complex matrix that can form suspensions of different proteins and lipids along with other compounds. Nowadays, a lot of meat has drug residues from antibiotics, anticoccidials, and human anabolite medications from feed and water that build up in the bodies of the animals and their byproducts. As a result, knowledge of the contaminants is essential for consumer safety.

Drugs most likely to be detected in meat are penicillin (including ampicillin), tetracycline (including chlortetracycline, and oxytetracycline), neomycin, gentamicin, streptomycin, flunixin, arsenicals, and sulfonamides (including sulfadimethoxine and sulfamethazine and sulfamethoxazole). Penicillin and sulfonamide drugs were most detected at violative levels in swine and cattle. Neomycin and Gentamicin were also detected in several cattle, particularly calves. Other drugs detected in cattle and swine included tilmicosin, flunixin, and tetracycline.

Egg: When therapeutically used veterinary drugs or their metabolites reach the blood stream of hens, they are distributed over the whole body, especially the ovary with growing follicles and the oviduct, where the egg white is formed and secreted. Therefore, it may increase the incidence of unacceptable residues in eggs. Such residues are reduced by establishing and adhering to withdrawal periods before slaughter and by sometimes prohibiting the use of certain antibiotics in laying hens. Eggs are generally a commonly consumed food because of their complex matrix and high content of phospholipids, protein, cholesterol, and other nutrients. This could happen because of potential cross-contamination during food production, leading to the transfer of drug residues into the eggs.

Poultry: Poultry ranks as the second most consumed meat globally. Animals like chickens, turkeys, quails, and waterfowl like ducks and geese are all considered poultry. Because poultry farming is so common in developing nations, it is simple to obtain drugs that are dosed indiscriminately. In poultry, drugs are administered for growth promotion, prophylaxis, and therapy. This includes the frequent use of antiparasitic and antibiotic drugs in clinical medicine, which causes accumulation of residues in the tissues that are consumed.

Milk: Antibiotics are invariably administered to dairy cattle to control infectious diseases, but their indiscriminate use, without adequate technical and veterinary control, can lead to a series of negative consequences at all levels of the dairy productive chain. The use of antibiotics on dairy farms rarely results in antibiotic residues in milk and milk products. The use of intra-mammary antibiotics and mistakes regarding withholding periods of milk are the most frequently cited reasons for antibiotic residues. Antibiotic residues enter the milk supply when treated cows are returned to the milking herd early or when a cow retains antibiotic residues in the system for an extra ordinary length of period.

Before accepting each shipment of milk at the dairy plant, dairy processors can safeguard the milk supply by testing it for the presence of antibiotics such as penicillin and sulfa drugs. Moreover, initiatives are continuing to inform farmers and veterinary professionals about the necessity of removing drug residues from the milk supply. Processors play a crucial part in preventing dairy plants from accepting milk that contains drug residues and using it to create finished dairy products.

Fish: Due to the increased market demand, fish farming has significantly increased, making aquaculture a feasible alternative for fish breeding. Chemicals, including drugs, are frequently used in animal feeds in aquaculture to prevent and treat fish diseases. As a result, it's critical to identify contaminants in food safety analyses to reduce human exposure to unwanted veterinary drugs.

Risk factors for the development of residues

Veterinary drug residues are a significant cause of contaminated food. When applied as directed on the label, VMPs and agricultural chemicals shouldn't leave residues at the time of slaughter. But some explanations for these residues could be as follows: Not adhering to recommended withdrawal times; using equipment contaminated with drugs; failing to clean equipment used to mix or administer drugs; making mistakes in dosing, measuring, or mixing; letting animals access spilled chemicals or medicated feeds; not following recommended label directions or dosage (extra-label usage); Age, pregnancy, congenital conditions, diseases, allergies, drug interactions, changes in fish species' water temperatures, pollution of the environment, and inappropriate application of agricultural chemicals like pesticides are among the factors that have an impact on animals.

Residues from veterinary drugs, or VMPs, typically accumulated in the kidney or liver rather than other tissues. It has been observed that varying tissue positions, such as the site and route of administration, exhibit varying residue levels. The most likely cause of drug residues is human error, which includes incorrect use, such as applying drugs extra-label or illegally. Still, the most obvious cause of unacceptable residues could be failure to keep with the withdrawal period, including the use of long-acting and overdose drugs. Inadequate hygienic handling when transporting animals or goods, such as accidentally applying drugs to animal feed, contaminating animal feed supplies, and drug transfer from animal to animal, can also result in residues. Risk factors responsible for the development of residue are age of animal, feeding, disease status, Pharmacokinetics, and Improper withdrawal time.

Analysis of drug residues in food

To prevent the excessive and illegal use of veterinary drugs in the animal breeding industry, as well as to guarantee the safety of food derived from animals, both qualitative and quantitative analyses of these drugs are required. As a result, numerous detection methods have been created to find veterinary drug residues in foods derived from animals [4]. Regulatory bodies set Maximum Residue Limits (MRLs) for different drugs to guarantee food safety. Regulatory bodies put enforcement and monitoring programs in place to make sure MRLs are followed. Drug residues in food samples are found and measured using analytical methods such as immunological methods, chromatography methods like liquid and gas chromatography, and biosensors. A summary of the analytical methods used to look for drug residue in food is shown in Figure 2 [12].

Currently, the classic analysis methods commonly used for veterinary drugs include Enzyme-Linked Immunosorbent Assay (ELISA), Capillary Electrophoresis (CE), Liquid Chromatography (LC) and Gas Chromatography (GC) [4].

In general, these techniques detect foods derived from animals with a high degree of sensitivity and selectivity. Owing to the complexity of the matrix, sample pre-treatment is typically necessary prior to instrument testing. The methods for extracting veterinary drugs from animal-derived foods mainly include Liquid-Liquid Extraction (LLE); Solid-Phase Extraction (SPE); accelerated solvent extraction; quick, easy, cheap, effective, rugged and safe extraction; matrix solid-phase dispersion extraction; ultrasound-assisted extraction and solid-phase microextraction.

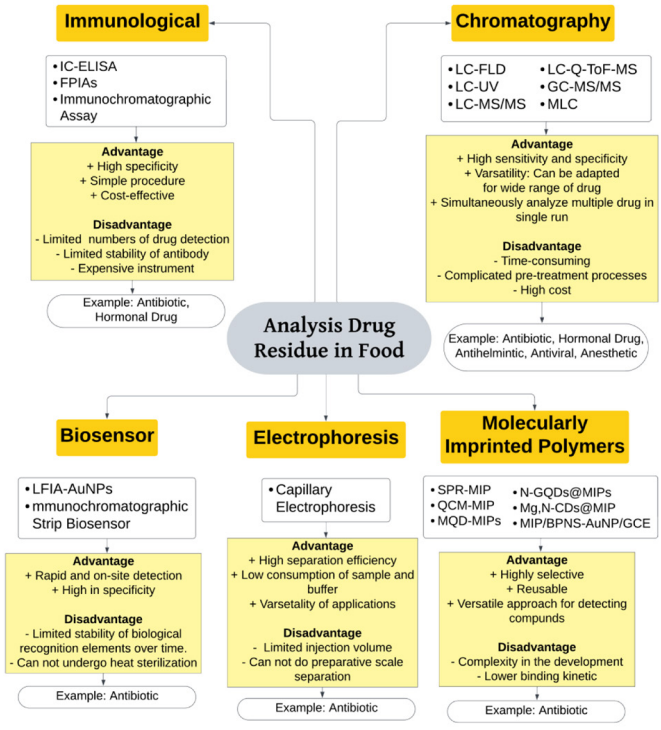

Figure 2. Analytical methods for the analysis of veterinary drug residues in food.

Nevertheless, the limitations of these sample pre-processing techniques along with the traditional detection methods include laborious operations, high time costs, and costly instruments. Using sophisticated devices based on sensing principles, such as electrochemical biosensors, piezoelectric biosensors, optical biosensors, and Molecularly Imprinted Polymer (MIP) biosensors, the second approach aims to detect veterinary drug residues in animal-derived foods.

The advantages of advanced methods over traditional detection techniques include speed, simplicity, low cost, high sensitivity, and high selectivity; however, the sensor's detection limit cannot be reached to the same extent, and the quantitative accuracy is not as good [4].

Potential effect of veterinary drug residues on public health

Low-level drug contamination typically doesn't pose a threat to public health. On the other hand, prolonged use of drugs may raise the possibility that a customer may experience negative side effects from residues, such as the development of antibiotic resistance and hypersensitivity reaction. Therefore, careful use of drugs in the manner of preventing feed contamination is necessary.

Development of drug resistance: Drug residues in animal-derived food can have a direct impact on human health, or they can have an indirect effect by spreading human pathogens through the selection of antibiotic resistance determinants. Resistant microorganisms can get access to humans, either through direct contact, or indirectly *via* milk, meat, and or egg. Due to their animal origin, these bacteria have the potential to either colonize human endogenous flora or add more resistance genes to the reservoir of genes already present in humans. There is a chance that humans could acquire resistance from animals.

Drug hypersensitivity reaction: Drug allergy is limited to a reaction mediated by IgE, whereas drug hypersensitivity is defined as an immune-mediated response to a drug agent in a sensitized patient. An allergic or hypersensitive effect following administration of a drug i.e., allergic drug is quite like that typified by allergic response to protein, carbohydrate, and lipid macromolecules. Anaphylaxis, serum sickness, cutaneous reactions, and a delayed hypersensitivity response to medications are examples of allergic reactions to drugs. Antibiotics, particularly penicillin, seem to be more frequently linked to these reactions than other drugs.

Carcinogenic effect: The term carcinogen refers to an effect produced by a substance having carcinogenic activity considerable confusion has existed because a carcinogen applies to substances that are so varied in their qualitative and quantitative characteristics. The interaction or covalent binding of carcinogenic residues to different intracellular components, including proteins, phospholipids, glutathione, Deoxyribonucleic Acid (DNA), Ribonucleic Acid (RNA), glycogen, and proteins, may pose a risk to health.

Disruption of normal intestinal flora: The bacteria that usually live in the intestine acts as a barrier to prevent incoming pathogens from being established and causing diseases. Antibiotics can kill specific important species of bacteria while reducing the overall number of bacteria. The broad-spectrum antimicrobials may adversely affect a wide range of intestinal flora and consequently cause gastrointestinal disturbance.

Reducing veterinary drug residues

Fresh and nutritious edible animal products may result from appropriate medication use and excellent veterinary care. Nevertheless, the unfavorable effects of drug use, like drug residues, persist in food contamination; these residue levels occasionally surpass safe consumer thresholds. However, several drug-related factors such as drug formulation type, site, and route of administration, dose, and animal-related factors such as breed, sex, age, and body condition, have potential effects on the pharmacokinetics and drug residue levels in milk, eggs, meat, and other edible tissues.

The physicochemical characteristics of the drug, such as its acidity or basicity and lipid solubility, which control the passive diffusion of drugs through cell membranes, determine the concentration of drug residue in tissues. Passive diffusion allows highly lipid-soluble medications to easily enter

the intra- and extracellular tissue compartments, while poorly lipid-soluble medications stay in the extracellular compartment.

Drug transport modulation delays bile or intestinal secretions, prolonging the macrocyclic lactone recycling period in the host, leading to transport protein (P-gp) efflux, which may be related to pharmacokinetic disposition and drug residue profiles. When this occurs, P-gp modulating agents shift tissue residue patterns [13]. Remarkably, drug administration through animal ears helps prevent drug residue accumulation in eatable animal tissues [14].

Conclusion and Recommendations

The use of veterinary drugs has quickly increased, mainly in farm animal which allows high-yield and high-quality production of animal-derived foods. Veterinary drug residues are the amount of the drug, its metabolites, and manufacturing impurities that remain in the products produced from treated animals. Edible tissues like meat, milk, eggs, seafood, or fish may still contain trace amounts of these drugs or their metabolites. The drugs such as nitroimdazoles, clenbuterol, and chloramphenicol are not allowed to be given to animals that produce food. To prevent the excessive and illegal use of veterinary drugs in the animal industry, as well as to guarantee the safety of food derived from animals, both qualitative and quantitative analyses of these drugs are required.

Therefore, based on the above given conclusions, the following recommendations are given:

- Community awareness about veterinary drug residues in food of animal origin should be given by governmental bodies and other stockholders,
- Veterinary drugs should be used as per veterinary prescription, and
- Strategies and policies about the use of veterinary drugs should be prepared by government to control drug residues in food on animal origin.

Acknowledgement

None.

Conflict of Interest

None.

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