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Review article
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METHODS OF DETECTING THE VETERINARY DRUGS RESIDUES AND THE WAYS OF REDUCING THEIR CONTENT IN FOOD PRODUCTS. REVIEW

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Abstract
The review was prepared in order to systematize the knowledge obtained in the recent years by the scientists from all over the world in the field of veterinary drugs application in the animal husbandry and the ways of management of their content in food products. It includes information on almost all currently known groups of antibiotics applied in animal husbandry, it considers the ways to reduce their amount in raw materials and / or the finished products, and describes the methods and procedures used to detect the residues of the veterinary drugs in raw materials and food products. It is not possible to run modern animal husbandry without the veterinary drugs. The global application of the veterinary drugs in animal husbandry exceeds 12 thousand tons, most of which are antibiotics for the infectious diseases treatment or prevention. Using the antibiotics in rearing the farm animals has led to the problem of their residues and / or metabolites in the raw materials and finished food products, which is why these food products cannot be considered safe for human consumption. The build-up of antibiotics in animal tissues depends on the group of the veterinary drug being used, and on the type of an animal. The content of residual amounts of some groups of antibiotics can be reduced by heat treatment of the meat. However, heat treatment can lead to the formation of new compounds that are potentially dangerous for the human health. Various analytical methods are used to determine the content of residual amounts of veterinary drugs in the food products, including enzyme immunoassay, chromatographic methods, biosensors and microbiological methods. The methods reviewed here for detecting the residual amounts of antibiotics in food products have their own advantages and disadvantages. In general, modern methods can currently detect the residues in food products of all known groups of antibiotics, used in animal husbandry, but it is necessary to keep on working on their improvement.

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Introduction

The application of veterinary drugs is an integral part of modern animal husbandry. Without the veterinary drugs the industry just would not produce the required volumes today. The research [1] conducted approximately 70 years ago put the start for the large-scale application of antibiotics. Since its beginning, this practice has become a backbone of animal husbandry, thus causing a transformational shift in the agricultural practices all over the world. The arising of antibiotic therapy has caused the dramatic increase in livestock quantity and a made revolution in animal nutrition. Growing global demand for animal protein has driven a shift to more intensive livestock production systems. These systems rely heavily on antimicrobial drugs designed to maintain animal health, to sustain relatively high levels of efficiency, and to ensure the economic viability of the industry. Thus, the historical progression of antibiotics application in animal nutrition underlines its key role in satisfying the growing needs of modern agriculture.

Every year around the world about 12 thousand tons of antibiotics are used in animal husbandry, about 75% of which are used to cure the infectious diseases, for preventive purposes or for growth stimulation [2]. It has led to numerous problems in the food production system, one of which is the residual amounts of antibiotics, as well as their possible metabolites. The issue of residual amounts of antibiotics is stated in almost all countries of the world. The degree of this issue depends on the legislation of the country and the prohibition to use of certain veterinary drugs, valid in its territory. However, no matter how strict the legislation is on application of antibiotics, no country is able solve the issue of residual amounts of antibiotics in the food products. And the antibiotics are also detected in almost all types of food products of animal origin: antibiotics are found in milk, meat of productive animals and poultry, eggs. The worst-case scenario (with antibiotic residues from animal products and microbial resistance genes) is assumed in many low-income and middle-income countries where there is either little or no relevant health regulation and supervision, and where there is disordered marketing and intense use of veterinary antimicrobials [3].

EU ban on using the antibiotic growth promoters due to microbial resistance genes became a turning point in the livestock industry. Since then, other countries have followed this example, including China that did the same in 2020. This is caused with the positive correlation between the intensity of antibiotics application and all the associated consequences of antibiotics use in animal products and their circulation the environment. Despite this ban, many farmers in many countries keep on using antibiotics, often in breach of any rules, regulations and permissions for their use. The excessive using of antibiotics in animal husbandry is the reason of the issue of antibiotic residues in the animal products, which is often impossible to get rid off completely. The nutritional value of animal products plays a key role in maintaining human health and well-being. But application of veterinary drugs can lead to antibiotics traces in the food products, which can negatively affect the consumers' health.

The authors set several purposes in this review of the scientific literature devoted to the methods for detecting residues of veterinary drugs, which purposes are caused by several important factors.

First, control of veterinary drug residues in food is critical to ensure its safety for the consumers. Veterinary drugs can be used to treat animals and improve their productivity. However, some of these drugs substances may persist in meat, milk, eggs, and other animal products even after slaughter or harvesting. These residues may pose a threat to human health via allergic reactions, toxic effects, or other adverse actions.

Second, food preparation methods can significantly affect the concentration and the form of veterinary drug residues. For example, cooking is able to decompose some compounds, while other processing methods, such as marinating or smoking, can change the chemical composition of the drug contained. The understanding of the way that various cooking processes affect veterinary drug residues is essential to develop efficient methods of food quality assurance.

Third, there is necessity to develop new and improved analytical methods for detection and quantification of veterinary drugs residues. The traditional analytical approaches pretty often require expensive equipment and highly qualified personnel, which demands limit their application in everyday practice. The development of the simpler, faster and more cost-saving methods will improve monitoring of food safety and will reduce risks for the consumers. Thus, the review of literature on this topic will contribute to a better understanding of the existing challenges and opportunities encountered in the field of monitoring of veterinary drug residue in food, and will help to define the directions for further research and development in this important area.

Objects and methods

In order to understand the scope of the issue and to define the ways to cope with it, an extensive analysis of peer-reviewed scientific papers written in English, Arabic, Turkish and Spanish was conducted. The articles selected from the initial search were manually screened by their abstracts and by extracting information from the full text. Initial search key words included "antibiotic residues", "antibiotics and poultry", "antibiotic residues and milk", "antibiotics and animal products", "antibiotics in ruminants" and "antibiotic residues effects". Scopus, Science Direct, Google Scholar, Academia, ResearchGate and Wiley Online were used to search for literature.

Groups of antibiotics used in animal husbandry

Antibiotics belong to several classes: β-lactams, cephalosporins, chloramphenicol, sulfonamides, macrolides, aminoglycosides, quinolones, fluoroquinolones, lincosamides, tetracyclines (Figure 1). The important β-lactam antibiotics include ampicillin, penicillin G, cloxacillin,

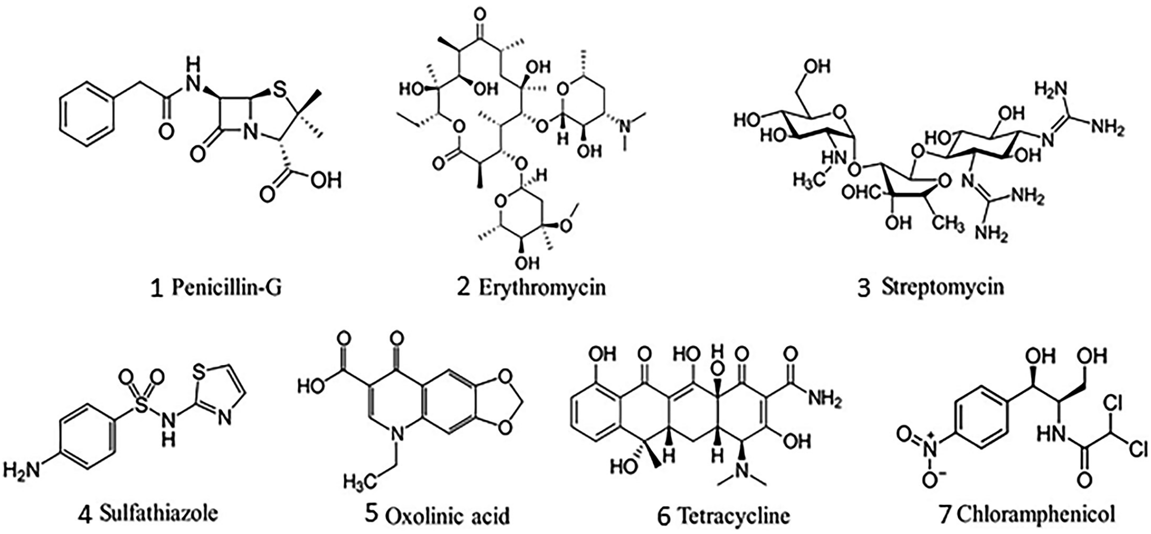

Figure 1. Chemical structure of the typical antibiotics from various families: 1 — penicillin G from β-lactams, 2 — erythromycin from macrolides, 3 — streptomycin from aminoglycosides, 4 — sulfathiazole from sulfonamides, 5 — oxolinic acid from quinolones, 6 — tetracycline from tetracyclines and 7 — chloramphenicol from amphenicols

dicloxacillin, and cephalexin. The variety of quinolones have been approved for their application in animal husbandry, including ciprofloxacin, enrofloxacin, marbofloxacin, danofloxacin, difloxacin, sarafloxacin, flumequine, norfloxacin, flumequine, oxalic acid and oxolinic acid [4].

Other antibiotics, like oxytetracycline, chlortetracycline, gentamicin, neomycin, streptomycin, sulfadimethoxine, erythromycin and bacitracin, amoxicillin, sulfamethazine, are approved for use in poultry, swine, ruminants and pseudoruminants, and can be administered orally (via water or feed), by injection or transfusion.

One more issue related to the use of antibiotics is the frequent use of broad-spectrum drugs, which include several antibacterial components. They are wide-spread in the developing countries and are available in various forms such as liquids, powders, packaged in sachets, plastic bottles, and glass bottles. Despite the various brand names, the commercial antibiotics are based on common active agents, and their formula consists of a combination of several antibiotics (Table 1).

Table 1. Antibiotics/antibiotic groups used in livestock farms

Group	Antibiotic
Quinolones	Ciprofloxacin, Enrofloxacin, Marbofloxacin, Danofloxacin, Difloxacin, Sarafloxacin, Norfloxacin, Flumequin,
Penicillins	Amoxicillin and Penicillin G
Cephalosporins	Cephalexin, Ceftiofur
Tetracyclines	Doxycycline, Oxytetracycline, Chlortetracycline, Tetracycline
Aminoglycosides	Streptomycin, Gentamicin, Amikacin
Macrolides	Tylosin, Erythromycin
Sulfonamides	Sulfadiazine, trimethoprim-sulfamethoxazole
Lincosamides	Lincomycin
Levomycetin	Chloramphenicol
Bacitracin	In the form of zinc bacitracin

Distribution of antibiotics in the animal products

According to the analyzed literature, the antibiotics distribute unevenly in animal tissues and, accordingly, in the animal products, which is explained by the animal's metabolism. This fact influences the subsequent use of obtained raw materials for the food production, as well as it influences the food processing methods. The distribution of antibiotics can vary significantly among various components of animal products. Depending on the group of antibiotics, their "migration" among the animal tissues, their accumulation and excretion occurs differently. For example, a study [5] showed that the amount of oxytetracycline and tetracycline found in the sheep kidneys was greater in comparison with their amount found in the sheep liver and muscles. The analysis of the residual content of amoxicillin and tylosin showed the similar differences between muscle tissue, liver and kidneys [6]. It was found that liver and kidneys contain a large volume of antibiotic residues in comparison with other organs, which is logical, since liver and kidneys belong to the excretory organs. The residual amount of veterinary drugs also greatly depends on the animal species and on the duration of the rearing period. However, the antibiotics of the same group accumulate in various parts of the muscle tissue of the same animal species [6]. However, antibiotics accumulate to the greatest extent in the internal organs of the animal, not in the muscle tissue. The philic or phobic nature of antibiotics can influence their distribution in various areas of the muscles, liver and kidneys due to the different metabolic roles of these organs. For example, Yang et al. [7] when analyzing poultry found higher levels of antibiotics in chicken giblets than in chicken meat and eggs. Khattab et al [8] demonstrated that the percentage of egg whites samples positive for amoxicillin residues was higher than the percentage of egg yolks samples.

The content of antibiotics in animal tissues depends on the specific type of antibiotics administered and their clearance rate, which is influenced by the factors like the interval between the drug administration and the animal slaughter. The prevalence of antibiotic residues varies among livestock species and is formed by regional practices of antibiotic applications [9]. It is necessary to note, that broilers were found to feature the higher rates of antibiotic residues detection than the farm egg-layers and the locally-raised chickens [10]. Understanding the route of drug administration (oral, intramuscular, parenteral, intramammary) and drug concentration is crucial to interpreting antibiotic residue levels in the animal products [11]. Differences in antibiotic levels among the livestock species may also be related with the antibiotics properties and the animals' physiology or structure. For example, Huong et al. al. [12] found high levels of tetracycline residues in chicken, and sulfonamide residues in pork. The lipophilic nature of sulfonamides may result in higher retention in pork in comparison with chicken, thus indicating the influence of animal developmental processes on elimination of antibiotics.

Data on content of veterinary drugs residues in products of animal origin depending on the type of production.

The literature review showed that meat sold in the suburban shops contains more antibiotic residues than meat sold in city stores [13,14]. The study [15] found that pork from animals slaughtered in city slaughterhouses contains less veterinary drug residues than pork obtained from the local slaughterhouses. In their study, Zhang et al. al. [16] found that total antibiotics concentration in pasture-raised cattle and sheep was very low.

Although only a few cases of acute toxicity in humans caused by the antibiotic residues have been documented [17], it is essential to raise awareness of the potential risks related with the consumption of food products that contain antibiotics. The average consumer is generally unaware of the dangers of antibiotic residues contained in food products. However, the absorption of antibiotics from food products and their accumulation in the human body may pose a threat to human health [18]. The diseases caused by exposure to toxic substances, including drug residues, are classified as the diseases of toxicological origin [19]. Antibiotic residues may serve as potential toxicological agents, the exposure to which may be potentially dangerous for humans, especially for the children. Their presence in animal products may cause pathogens resistance to the effect of antimicrobial drugs [20]. Long-term consumption of the food products with excessive residues of veterinary drugs may lead to chronic poisoning, as well as teratogenic, carcinogenic and mutagenic aftermaths. Food products contaminated with antibiotic residues are able to cause bone marrow dysfunction, disrupt intestinal flora, and cause skin allergies to sulfonamides when found in high concentrations in the food. It was found that the products of decomposition resulting from heat treatment of the antibiotics like oxytetracycline and ceftiofur provide cytotoxic effects on human lung, liver, and kidney cells [21].

Ways for reducing veterinary drugs residual amounts in the food products

The absence of antibiotics in a food product is one of the main indicators of its safety. As it was already noted, the issue of the content of veterinary drug residues in food products is of concern for the governments of most countries worldwide. In the developed countries, this issue is addressed for safety and public health reasons, but in many low-income and middle-income countries, food safety issues are addressed for reasons of economic benefit, because the unsafe food products cannot be sold on international markets [22]. During the production of food, various methods of processing raw materials are used, which provide different effects onto all groups of antibiotics. In most cases, the technological process leads to the significant reducing of antibiotics content in the finished food product, which makes it safer for consumption. Table 2 below sums up the results of studies devoted to analyzing the effect of certain technological processes on the concentration of antibiotics in the food products.

Heat treatment

The various processing steps during cheese production (pressing, salting, boiling of cheeses, whey acidification) and various types of heat treatment like pasteurization (72 °C for 15 sec and 63 °C for 30 min) resulted in a 52% to 99% reduction in enrofloxacin. In general enrofloxacin is very sensitive to high temperatures and is prone to strong decomposition. For example, frying and grilling reduced oxytetracycline content by 91–95%, whereas the reducing of enrofloxacin residues was lower, ranging from 25.6% to 33.3% within the same methods of heating [23]. Temperature, method and time of cooking play an important role in the reducing of antibiotic residues. Slow cooking of broiler carcasses led to significant reducing of tetracycline antibiotic concentrations, reaching 86–89%. This ensures that the meat becomes safe for human consumption [24]. Long cooking times at low temperatures, such as braising / simmering, are considered to be an efficient method for reducing antibiotic residues in chicken meat before its consumption. Microwave cooking for 1 minute has proven to reduce tetracycline residues in pork by up to 67% [25]. However, not only the method of heat treatment affects the "behavior" of the antibiotic during heat treatment of the raw materials; the type of animal also matters [27]. In addition, the decomposition of veterinary drug residues is also affected by the pre-heat treatment of raw materials; for example, a greater degree of antibiotic decomposition is observed during heat treatment of minced meat in comparison with heat treatment of whole raw materials [28].

Table 2. Brief review of ways of reducing antibiotics content by the food products processing.

Way of processing	Product	Achieved result	Antibiotics	Sources
Heat treatment/ Pasteurization	Dairy products	Various processing steps (pressing, salting, boiling cheeses, whey acidification) and pasteurization (72 °C for 15 sec and 63 °C for 30 min) resulted in a 52–99% reduction in the amount of the veterinary drug	Enrofloxacin	[6]
Boiling and frying	Meat and offal	Boiling reduces the amount of veterinary drug residues in muscle tissue and has greatly reduced the residual amount in the liver.	Oxytetracycline	[23]
Frying and grilling	Meat	Frying and grilling reduced oxytetracycline levels by 91–95%, while reductions in enrofloxacin residues were less expressed, ranging from 25.6% to 33.3% under the same heating conditions.	Oxytetracycline; Enrofloxacin	[23]
Long-term heat treatment	Broiler chicken meat	Braising / simmering reduces the content of tetracycline antibiotics by 86–89% in broiler carcasses.	Tetracycline	[24]
Microwave irradiation	Pork	Microwaving for 1 minute reduces tetracycline residues in pork by 67%.	Tetracycline	[25]
Freezing	Meat	Freezing at –10 °C for 9 days provided no profound effect on the concentration of antibiotic residues.	Oxytetracycline	[23]
	Meat	Chilling meat at 4 °C for 3 days resulted into a small reduction in antibiotic residues of approximately 16%, whereas freezing meat at –18 °C for six weeks had minimal effect.		[23]
Food processing	Milk	Drug content increases 5 times in cottage cheese in comparison with the original raw material, while only a small amount of drug is lost in the whey	Monesin	[26]
Food processing	Milk	Milk skimming reduced enrofloxacin content by 95%	Enrofloxacin	[6]

Notwithstanding many studies that demonstrate the benefits of heat treatment for reducing antibiotic residues in animal products, it is important to note that heat treatment is able not only to decompose antibiotics, but also to form the new compounds on their bas, or to convert them into another form. Side-products of veterinary drug decomposition are able to provide a detrimental effect on the human body, like it does oxytetracycline decomposition product — 4-epioxytetracycline, or the ceftriofur decomposition product — cephalhyde, which products provide cytotoxic effect on lung, liver and kidney cells. Veterinary drug decomposition products can also react with food components. For example, the products of ciprofloxacin decomposition, formed as a result of heat treatment, react with lactose during heat treatment of milk. Planche (2022) showed that sulfamethoxazole lost its antimicrobial activity by 45%, but six sulfamethoxazole decomposition products were found in the cooked meat [29].

In relation to that, heat treatment of raw materials is not a panacea in the issue of reducing the veterinary drugs content. For sure, in general it is wrong to use raw materials with antibiotics for its further processing, and in many countries of the world this is prohibited, as, for example, in the Russian Federation the presence of antibiotics in food raw materials is not allowed according to the TR CU 021/2011[1]. But in countries where the legislation is still not so strict in relation to the veterinary drugs content, it is important to choose the right modes of processing raw materials, as it will reduce the amount of antibiotics in the finished product, but at the same time it will not lead to the formation of other compounds that can be potentially dangerous for the human health.

Methods for detecting antibiotic residues in food products

To ensure food safety, the regulatory authorities have set maximum residues levels (MRLs) for various medicines.

In the Russian Federation, MRLs for the content of veterinary drugs in food products are defined in the TR CU 021/2011[1]. To conduct testing of products, first of all it is necessary to use the methods presented in the List enclosed to the TR CU 021/2011[2]. This List contains methods for detecting the antibiotics based on HPLC–MS/MS and ELISA [30] methods. It is also necessary to note that previously the content of veterinary drugs in meat products was regulated by the TR CU 034/2013[3], but according to the adopted Decision of the EEC No. 70[4] all groups and classes of the antibiotics previously regulated in the TR CU 034/2013[3] have been included into the TR CU 021/2011[1].

In global practice antibiotics in food products are detected by various analytical methods, like chromatography and by biosensors. These methods allow qualitative and quantitative controlling of the veterinary drugs content in almost any food matrix. It should also be noted that other methods, such as electrophoresis [31], Raman spectroscopy [32], and voltammetric methods [33] are also applicable for detecting the antibiotics in meat tissues, but their use for this purpose is not as widespread. Biosensors are used as a screening methodology for detecting the antibiotics animal products [34]. Biosensors are mainly used to detect the presence of antibiotics in milk and honey, but nevertheless, some published articles devoted to using the biosensors have shown the possibility of their using for the antibiotic's detection in meat.

Figure 2 shows a diagram of the analytical methods, used in analyzing the presence of veterinary drug residues in the food products, and also lists their advantages and disadvantages.

Iimmunoassay methods

One of the types of enzyme immunoassay used to detecrmine the content of veterinary drug residues in food products is the indirect enzyme-linked immunosorbent assay (ic-ELISA). The difference between the direct and indirect ELISA method is that in direct ELISA an enzyme-conjugated primary detection antibody is added that binds to the antigen coating the well, while in indirect ELISA, after immobilization of the antigen, a primary antibody is added that binds to the antigen, followed by the addition of an enzyme-conjugated secondary antibody. Direct ELISA is a faster diagnostic method, but it cannot amplify signals, which inability results to poor sensitivity. The amplification step in indirect ELISA is able to increase sensitivity, so ic-ELISA can be more sensitive than direct ELISA. In [35], ic-ELISA was used to detect the presence of residues of quinoxaline-based antimicrobials. Quinoxaline is a semi-finished product widely used for the production of pharmaceuticals, it posesses anti-inflammatory, antimalarial, and antibacterial action. When using quinoxaline-based preparations, a large amount of its deoxymetabolites with toxic properties may remain in the raw material. As a result of the work, the limits of detection (LOD), limits of quantification (LOQ), and recovery rates of quinoxalines determined with the help of ic-ELISA for analyzing pork, pork liver, pork kidneys, chicken meat, and chicken liver

[1] TR CU 021/2011. "Technical Regulations of the Customs Union "On food safety" (as amended as of July 14, 2021)" Retrieved from https://docs.cntd.ru/document/902320560#8Q20M0. Accessed December 4, 2024 (In Russian)

[2] EFES (2019). List of international and regional (interstate) standards, and in case of their absence — the national (state) standards containing rules and methods of analyzing (testing) and measuring, including rules for sampling, necessary for the application and implementation of the requirements of the technical regulations of the Customs Union and the implementation of technical regulation objects conformity assessment. Approved by the Decision of the Board of the Eurasian Economic Commission of December 24, 2019 N 236. Retrieved from https://www.gostinfo.ru/trts/List/45 Accessed on December 4, 2024 (In Russian)

[3] TR CU034/2013 Technical Regulations of the Customs Union "On the safety of meat and meat products" Retrieved from http://docs.cntd.ru/document/499050564. Accessed on December 4, 2024 (In Russian)

[4] EAEU (2023). "On Amending Certain Decisions of the Customs Union Commission and the Council of the Eurasian Economic Commission" Decision No. 70 of 23.06.2023. Retrieved from https://docs.eaeunion.org/documents/418/7522/ Accessed on December 4, 2024 (In Russian)

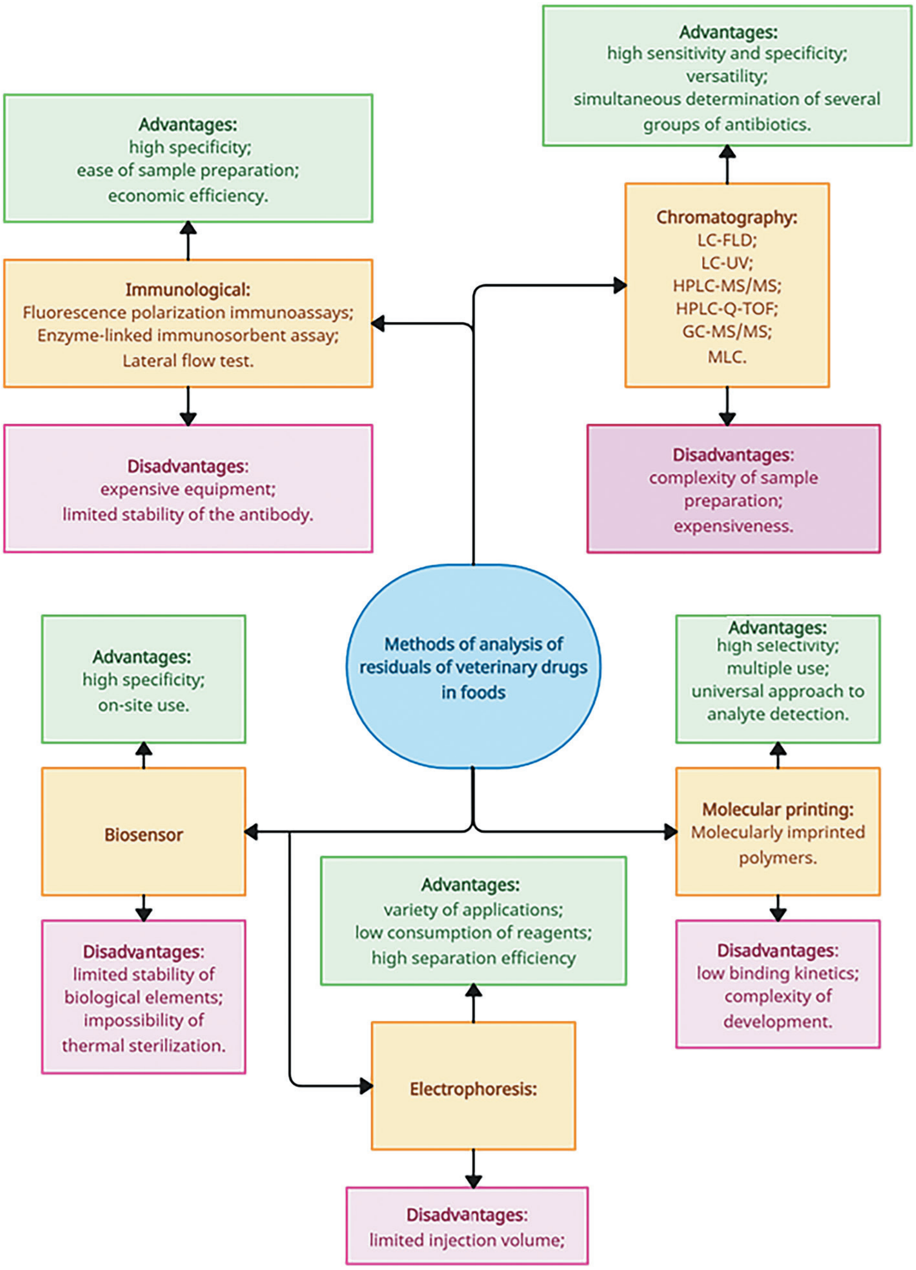

Figure 2. The most widely used methods for analyzing the content of veterinary drug residues in food (created with app.creately.com)

were 0.48–0.58 μg/kg, 0.61–0.90 μg/kg, and 73.7–107.8%, respectively. These results show that the ic-ELISA-based technique can effectively detect quinoxaline residues. The simplicity of this analytical method reduces the time required for the sample pre-treatment, improves efficiency, and complies with the requirements for quinoxaline residue analysis. This is the difference between the immunochemical methods and instrumental methods of detection like HPLC or LC–MS/MS, which require expensive equipment, complex technology and long process of testing.

Another immunoassay for detecting the presence of veterinary drugs residues in food products is fluorescence polarization immunoassay (FPIA). FPIA has gained wide application in laboratory practice due to its high sensitivity, good reliability and fast implementation [36]. The basic principle of FPIA for the small molecules is the interaction between a tracer (a chemical conjugate of an antigen with a fluorophore) and the competing antigens. As the concentration of analytes in the reaction solution grows up, the analytes occupy the antibody binding sites, thus preventing the binding of the tracer to the antibody, which leads to the formation of free tracer molecules. When the reaction mixture is irradiated with plane-polarized light, the presence of such free molecules is demonstrated as fluorescence depolarization. In view of this, the FPIA method is promising for detecting various low-molecular compounds, including veterinary drugs in food products. For example, this method was used to determine erythromycin in dairy products [37]. Extraction of erythromycin from milk for FPIA is quite simple and consists in protein precipitation with organic solvents. The LOD of erythromycin was 14.08 μg/L, and the detection rate was 96.08–107.77%.

Another type of immunoassay, the immunochromatographic assay (ICA) (or lateral flow test), due to its execution simplicity and portability of the necessary equipment, has also found wide application in the management of veterinary drugs residues in the areas like biomedicine, agriculture, and the food industry [38].

Moreover, test systems based on the ICA method using gold nanoparticles for the ultra-sensitive detection of antibiotic residues are now being actively developed.

Chromatographic methods

Probably the chromatographic methods are the most frequently used methods for determining the content of veterinary drugs residues in food products. Despite the active growth in popularity of the other methods (ELISA, biosensors, etc.) due to their simplicity and high speed of their use, chromatographic methods still remain the arbitration technique in tasks of determining the content of antibiotics in products, i. e. in the cases when the antibiotics were already detected by some other methods, the obtained results get confirmation from chromatographic methods.

Today, there are methods for determining antibiotics content in food products via chromatography for almost all groups of antimicrobial drugs (quinolones, sulfonamides, nitrofurans and their metabolites, penicillins, amphenicols, etc.) in all types of food products of animal origin. In the Russian Federation the majority of these methods have passed the state standardization procedure.

From among all currently existing chromatographic methods, the most preferable one for testing food products for presence of veterinary drugs residues is the method HPLC–MS/MS. This method is used because of its high sensitivity, while the multiple reaction monitoring (MRM) technology eliminates false positive or false negative results. The HPLC–MS/MS equipment itself is quite expensive, but is not a rarity anymore. Instrumental settings for determining antibiotics are not very complicated and often allow determining several groups of antibiotics in one test run, moreover the tests do not require some rare and/or specific reagents. The biggest disadvantage of determining antibiotics with the help of HPLC–MS/MS is, perhaps, the process of the sample preparation. In majority of cases, it is necessary to use solid-phase extraction to extract the necessary analytes from the sample, which action significantly increases the total time of one analysis and increases its final cost [39].

Biosensors

The concept of biosensors is the combination of a biological component with a physicochemical detector. Biosensors are user-friendly and economically advantageous means of detecting the antibiotics residues due to their low cost [40]. Enzymes, antibodies, nucleic acids or whole cells that can react with the analyte of interest can be used as a biological component (or bioreceptor) in biosensors, and the physicochemical detector, in its turn, "reads" this reaction and converts it into a measured signal [41]. Today, the biosensor techniques are actively developing with involvement of more complex devices based on sensing principles, like piezoelectric biosensors, optical biosensors, molecularly imprinted polymer biosensors, fluorescent biosensors or electrochemical biosensors due to their high speed, sensitivity and selectivity [42].

Today one of the most promising biosensor methods is the analysis based on using the biochips. To detect veterinary drugs in this way, a set of micro matrices arranged on a solid substrate is used, which allows for multiple tests to be conducted simultaneously. Analysis using biochips is focused on the precise recognition of analyte binding to biological receptors on an ordered substrate, which allows for quantitative or semi-quantitative recording of the content of the corresponding analyte. Analysis based on the use of biochips allows simultaneous monitoring of significant number of several tens of analytes [43].

The paper [44] provides a review of widely used biosensors for testing food products for antibiotics residues. It reviews various types of sensors that involve enzymes, antibodies and nanobodies, aptamers, DNAzymes, molecularly imprinted polymers (MIPs) and cells as selective antibiotic-binding reagents. Various groups of nanostructures including carbon-based nanomaterials, metallic nanomaterials, quantum dots, luminescent upconversion nanoparticles (UCNPs), and magnetic nanoparticles integrated into biosensor detection platforms are discussed, as well as different detection methods including optical methods (colorimetry, fluorescence, chemiluminescence, and surface plasmon resonance). The authors review the pluses and minuses of each type of biosensors. Fluorescent biosensors, for example, can serve an excellent option for quantitative and semi-quantitative detection due to their high sensitivity and reproducibility. Using nanomaterials such as UCNPs, sensitivity at the pg/mL level has been achieved. The minus is that to read the result a fluorometer is needed. Another option is colorimetric biosensors with fairly high sensitivity. The sensitivity of colorimetric biosensors can be further increased by signals amplifying and by using DNAzymes, but the duration of analysis can be significantly increased. In general, most authors who are involved in the use of biosensors for analyzing food products for residual antibiotic content agree that it is necessary to carry out work to improve their performance. Improvement of the electrode material, metal nanoparticles, metal oxides, and carbon nanostructures for creating electrochemical biosensors will significantly increase sensitivity and reduce analysis time. In general, the use of nanomaterials improves the characteristics of almost all types of biosensors. Nanomaterials are able to improve optical and magnetic properties in optical biosensors, thus providing higher sensitivity and accuracy of detection [44]. Due to their high stability in various reaction environments, long shelf life, ease of synthesis, low production costs, and *in vitro* development, MIPs are also the promising tools for their use in biosensors. Yue et al. [45] reviewed the latest developments and using the aptamer-based sensors, oligonucleotide receptor molecules, for detection of aminoglycoside antibiotics. They selected nine methods of signals detection used in aptamer biosensors for detection of aminoglycosides: optical fluorescence, colorimetric, chemiluminescence, surface-enhanced Raman scattering, electrochemical impedance, voltammetric, potentiometric, electrochemiluminescent and photoelectrochemical. The authors came to the conclusion that each aptasensor has its own distinctive properties and that the choice of the instrument for detection of aminoglycosides depends on certain conditions and purposes. It is important to note that aptomer-based sensors have been accepted for their application for detection of other veterinary drugs and pesticides as well [46,47].

Microbiological methods

Microbiological methods are usually used as the initial screening tools for the qualitative or semi-quantitative detection of veterinary drug residues. Microbiological methods are based on the microbial growth inhibition and the use of receptor molecules that bind antibiotics [48–50]. Microbial inhibition test detects drug residues based on their ability to inhibit the growth of microorganisms. For example, the strain of *Escherichia coli* was used to screen the fluoroquinolones and quinolones residues in the animal products [48,49].

Discussion

The main part of the modern food production is based on the processing of the ingredients purchased from various suppliers. It is necessary to inspect and control pretty long list of safety parameters in the raw materials delivered for the production, including the content of veterinary drugs residues in raw materials of animal origin. But not all manufacturers, especially the small-scale ones, have the opportunity and the necessary funds to transport raw materials for testing to some third-party laboratories, and even more so to maintain their own laboratory for the purposes of incoming and production control. In this regard, control methods that can be used "on site" will be promising and attractive, providing the opportunity to at least qualitatively determine the presence of standardized substances in raw materials.

However, there are only a few methods for the simultaneous extraction and detection of antibiotics residues of various classes in animal products due to their unique physicochemical properties. One of the potential reasons that put obstacles for the integrated detection is the difficulty of simultaneous extraction of several antibiotics. Although antibiotics have different structures, still they feature certain common physicochemical properties, like polarity and solubility [51]. Therefore, the development of a unified pretreatment using the common properties of these antibiotics is a promising direction to overcome this limitation. Low acceptable levels of antibiotics in animal products require high-throughput methods of detection with high sensitivity. Over the past few decades, many analytical methods have been developed for antibiotics detection, including instrumental analysis methods, microbiological methods, immunoassays, etc. [32]. Highly sensitive instrumental analysis methods, like HPLC–MS/MS (which is the basis for almost all methods included in the List of methods in the TR CU 021/2011[5]), are not suitable for continuous monitoring of the samples within production due to the high cost of equipment, the complexity of sample preparation and the need for professional personnel. Therefore, the development of highly effective and sensitive methods for monitoring the antibiotics residues of various classes in the products of animal origin is very important.

Over the recent time the developing of rapid methods based on immunochromatography for the purpose of detecting veterinary drugs in food products has gained particular popularity. However, in the same List of methods in the TR CU 021/2011[5], there are practically no express analysis methods. Partially, the methods based on the ELISA method can be attributed to the express determination of antibiotics. The List contains about 30 such methods. Basically, they use the test systems RIDASCREEN and MaxSignal. Nowadays their use is a big challenge due to western sanctions imposed onto the Russian Federation due to the absence of official representations or headquarters, the withdrawal of the manufacturers from the Russian market and the extension of delivery terms and, accordingly, prices increase. Only one method included in the List is related to the express testing, but its scope of application applies only to milk — MVI.MN 5930-2018[6] and is applied till the relevant interstate standard is included into the list of standards.

Conclusion

Summing up the conducted review, it can be concluded that at present the field of control of residual quantities of veterinary drugs in food products is very well developed. Almost all groups of antibiotics used today in the animal husbandry are supported with a methodological basis for their detecting in raw materials and finished food products. Moreover, almost any group of antibiotics can be determined using various methods. The further development of this field is necessary for the development and improvement of already existing methods and techniques, for example, in the development of a unique method for the samples preparation, with the help of which it will be possible to extract absolutely all known groups of antibiotics for HPLC, thus increasing the sensitivity of immunoanalytical methods or reducing the time of analysis with the help of biosensors.

[5] TR CU 021/2011. "Technical Regulations of the Customs Union On food safety (as amended as of July 14, 2021)" Retrieved from https://docs.cntd.ru/document/902320560#8Q20M0. Accessed on December 4, 2024 (In Russian)

[6] MVI.MN 5930–2018 "Methodology for measuring the content of lincomycin in dairy products using test systems manufactured by Beijing Kwinbon Biotechnology Co., Ltd, China". Certificate of Attestation No. 1086/2018 dated 03.01.2018 (In Russian)

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