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Mini Review

Aptamer-based Electrochemical Sensors for Rapid Detection of Veterinary Drug Residues

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Due to aptamer-based biosensors being simple to prepare and easy to modify, while having good stability and a wide range of binding targets, they have attracted the attention of many researchers. Based on the basic principles of aptamers and the latest research results in the field of electrochemical aptamer biosensors, this paper reviews and discusses the prospects for the latest development of electrochemical technology in the field of aptamer biosensors for detecting veterinary drug residues.

Keywords: Aptamer; Electrochemical sensor; Veterinary drug residues; β-agonist; Nitrofuran; Fluoroquinolone

1. INTRODUCTION

In recent years, food safety has become an important issue of wide concern to society as a whole. On the one hand, foodborne diseases have not been effectively controlled [1–4]. On the other hand, in international trade, due to the existence of drug residues in food and other factors, the technical barriers of the food trade in developed countries limit the export of food from developing countries. In addition, food safety is an important part of national security [5–7]. According to statistics, in the past decade, there have been serious outbreaks of foodborne diseases on all continents of the world. One-third of the world's people have experienced foodborne diseases [8–10].

Among them, the residues caused by the widespread use of agricultural and veterinary drugs, the addition of all kinds of contraband substances and the biological toxins produced in the storage and

transportation process due to improper management can all seriously affect the quality and safety of related food [11–13]. This is a threat to the life and health of consumers, and the food quality and safety problems caused by it are receiving increasing attention. Due to the disadvantages of time-consuming and laborious pretreatment processes and the high requirements for technicians and equipment, traditional instrument analysis methods are difficult to simplify. Thus, the traditional methods are only suitable for the confirmation of suspected samples and cannot meet the needs of rapid detection and screening of food quality for supervising the safety of the food [14–18]. Therefore, it is urgent to develop a simple, rapid, sensitive and accurate method for the rapid detection of chemical pollutants in agricultural products [19–21]. At present, the most widely used rapid detection method are immunoassays, but many pollutants are small molecules without immunogenicity or have biological toxicity, so it is difficult to prepare antibodies with high affinity. Therefore, at present, there is still a lack of corresponding rapid detection methods, there is still reliance on conventional instrumental analysis techniques such as chromatography and mass spectrometry [22–25].

As a new type of biometric molecule, aptamers with high affinity and high specificity for target molecules are sometimes called "chemical antibodies". In fact, aptamers have many unique advantages compared with commonly used antibodies as biological recognition elements [40–43]. For example, aptamers have a very wide range of targets. Theoretically, any molecule, including toxic substances, can be used as a target for aptamers. In addition, the size of an aptamer is smaller than that of an antibody, which makes it possible to get into areas that immunoglobulin has difficulty accessing; thus, the use of aptamers greatly increases the flexibility of building different types of biosensors [44,45]. Similar to antibodies, aptamers can be used to develop a variety of analytical methods based on the principle of specific recognition and binding [46–49]. In addition, different fast detection methods based on a molecular switch mode can be designed and developed according to a change in conformation of the aptamer when combined with the target. The sensitivity of these methods can reach the level of nM, pM or even fM.

Generally, the binding of aptamers to target molecules includes hydrogen bonding, shape complementation, electrostatic adsorption and base pair stacking. When a specific target is added to the system, the aptamer can undergo specific conformational changes, such as folding and bending, according to its structure and other characteristics to form hairpin, stem ring, pseudoknot, tetragonal ring and G-quadruple structures, which allows it to combine with different target specificities [50–52]. The binding mechanism of the aptamer to the target is similar to that of an antigen antibody. However, there are many kinds of aptamers, including small molecules such as metal ions, large molecules such as proteins and even cells and tissues [53–55]. Therefore, the specific binding mechanism varies according to the target. When targeting small molecules targets, the aptamers tend to be macromolecular substances, so the small molecular targets are usually embedded in the aptamers or wrapped up by the aptamers. In most cases, small molecular targets can only bind to a specific aptamer, such as with ATP and cocaine [56–59]. With macromolecular targets (such as proteins), their structures are more complex. Since aptamers are relatively small molecules, they will bind to multiple sites of macromolecular targets, which is similar to the antibody binding mechanism with "antigen epitopes", such as with IgG and thrombin. Because there are many macromolecular epitopes, such as proteins, in theory, macromolecular targets can be bound by multiple aptamers [60–64].

With the rapid development of aptamer technology, various detection methods based on aptamers have been widely used in the field of chemical analysis, especially in the field of food safety analysis, due to their advantages of simplicity, high sensitivity and low cost. At present, nearly 100 kinds of aptamers for toxic and harmful substances have been screened out. In recent years, based on these highly specific ligands, many rapid detection methods have been developed, such as colorimetry, fluorescence, electrochemistry and chemiluminescence. Table 1 shows examples of these methods and applications.

Table 1. Applications of aptamers in food safety analysis.

Target classification	Target molecules	Analysis method	Sample	Reference
Antibiotic	Penicillin	Fluorescence/colorimetry	Milk	[65]
	Streptomycin	Electrochemistry	Milk	[66]
		Fluorescence	Milk	[67]
		Colorimetry	Honey	[68]
		Fluorescence/colorimetry	Milk	[69]
	Oxytetracycline	Colorimetry	-	[70]
		Fluorescence	Milk	[71]
		Enzymic method	Milk	[72]
	Kanamycin	Colorimetry	Milk	[73]
		Electrochemistry	-	[74]
		Colorimetry	Milk	[75]
		Fluorescence	Milk	[76]
	Sulfamethoxide	Colorimetry	-	[77]
	Chloramphenicol	Electrochemistry	-	[78]
		Electrochemistry	Honey	[79]
		Electrochemistry	-	[80]
		Electrochemistry	Fish	[81]
Biotoxin	Aflatoxin M1	Electrochemistry	-	[82]
		Electrochemistry	Milk	[83]
	Aflatoxin B1	Fluorescence	Peanut oil	[84]
		Fluorescence	Corn/peanut	[85]
		Colorimetry	Corn	[86]
		Electrochemistry	Peanut	[87]
		Strip method	Corn	[88]
	Ochratoxin A	Electrochemistry	-	[89]
		Fluorescence	Wine	[90]
		Microfluidic Chip	Beer	[91]

2. APTAMER-BASED ELECTROCHEMICAL SENSOR

An electrochemical aptamer biosensor is composed of an electrode with a fixed aptamer and electrochemically active recognition elements. First, the aptamer is fixed on the electrode surface under appropriate conditions, and the target to be tested is added to interact with the aptamer. Due to the change in electrode surface structure, the target can be detected by detecting the change in the electrochemical signal. Based on the research work conducted on electrochemical immunosensors, many new electrochemical aptamer biosensors have been developed, including sandwich-type electrochemical aptamer biosensors, which are active in immune sensing technology, and electrochemical switches, which are based on the structural changes of target molecules before and after aptamer binding.

Depending on whether markers are used to generate detection signals, electrochemical aptamer sensors can be roughly divided into two categories: labeled and unlabeled.

Because the aptamer itself is not electrically active, the redox signal of G, A and C bases in a basic unit of an aptamer chain is low, and electrochemical modulation is not conducive to maintaining the affinity of the aptamer, so most electrochemical aptamer sensors have applied functional markers to obtain quantitative detection signals. According to the different markers, the labeled electrochemical aptamer sensors can be roughly divided into electroactive redox molecular markers, enzyme markers and [92,93]nanoparticle markers. The redox molecular marker with an electrochemical aptamer biosensor is mainly based on a change in conformation caused by the aptamer before and after recognition of the target analyte, which results in a change in the charge transfer efficiency of the electroactive substance on the DNA chain and a change in the detection signal. Commonly used electroactive materials for the modified electrodes are ferrocene, methylene blue and other small molecules. The signals of the above electrochemical aptamer biosensors are based on the attenuation degrees of the electrochemical signals that are caused by the binding of target molecules with the aptamers. Otherwise, these signals are called signals on the biosensor.

Plaxco et al. [94] self-assembled 32-base thrombin aptamers with thiol and methylene blue modified at both ends of a gold electrode surface. After thrombin binds with the aptamers, the distance between the methylene blue marker and the electrode increases, or the mass transfer of the electrolyte is blocked, and the electrochemical signal decreases, so a signal off-type electrochemical aptamer sensor is constructed. Li et al. [95] used the signal amplification effect of gold nanoparticles and ferrocene as an electroactive probe to construct a signal off-type sensor for the detection of lysozyme through a competitive reaction between lysozyme and a complementary DNA chain to an aptamer probe chain. The proposed electrochemical sensor can detect lysozyme to 0.1 pM. Some positively charged electroactive organic molecules, such as cationic dyes and cationic polyelectrolytes, can also be adsorbed on the aptamer chain with a negative phosphoric acid skeleton or embedded in a double chain gap through electrostatic action to generate electrochemical signals. Once an aptamer leaves the electrode surface, either the double chain opens or other competitive cations are introduced; thus, some of the markers will leave the electrode and directly lead to the attenuation of an electrochemical signal. Obviously, the electrostatic interaction of these electroactive "markers" with aptamers is a key link and an important factor affecting the reproducibility of the sensor. Based on this, Yu et al. [96] reported a lysozyme sensor based on this electrostatic adsorption. The redox signal of ruthenium is generated by the adsorption of a hexaammonia ruthenium cation as a marker on the negatively charged aptamer chain, which is fixed on the electrode. The aptamer binds to lysozyme at neutral pH. The aptamer chain entangles lysozyme, and some of the hexaammonia ruthenium cations adsorbed on the aptamer chain are bound to be rejected by the positive lysozyme and separate from the electrode, thus reducing the electrochemical signal. A similar principle has also been used in a system of polysulfide benzene cationic polymers modified with ferrocenyl groups and thrombin. In contrast, an enhancement of the electrochemical signal caused by the target molecules binding to aptamers is regarded as a quantitative analysis signal, which is called a signal on an electrochemical aptamer biosensor. The signal on an electrochemical aptamer sensor is generally based on decreasing the distance between the redox marker and the electrode, which is caused by the binding of target molecules. It is not difficult to see that there

are an increased number of requirements in the design and preparation of these probes, and the preparation process is more complex. Therefore, it is another research idea to develop a more sensitive but simple fluorescence analysis method based on the properties of aptamers, target molecules and fluorescent substances instead of nanomaterials.

Fan et al. [97] found that ATP aptamers with thiol and ferrocenyl modifications at both ends were hybridized with their complementary chains to form a double chain structure and then self-assembled to the gold electrode surface to construct a signal on-type ATP aptamer sensor. This kind of double chain structure is rigid enough, and its length exceeds the maximum electron tunneling distance (> 10 nm); additionally, ferrocene, unlike methylene blue molecules, can form a conjugated structure with a double chain nucleic acid structure to realize long-range electron transfer. Therefore, ferrocene, an electroactive marker, cannot exchange electrons with the electrode and can only detect very weak current signals. When the ATP target molecule is added, it binds to the aptamer. The original double chain is untied, and the aptamer is folded. The ferrocenyl group at the end of the aptamer is drawn to the electrode surface at the same time. This method realizes electron transfer or tunneling between the aptamer and the electrode. The redox current is significantly enhanced. This change can be sensitively detected by square wave voltammetry.

An enzyme-linked immunosorbent assay (ELISA) has been widely used to detect various proteins. An enzyme-labeled aptamer sensor combines the advantages of an aptamer and an enzyme label and has its own characteristics and advantages in the detection of disease-related proteins. Especially for some proteins with aptamer double binding sites, such as thrombin, the sandwich method of an "aptamer target protein enzyme-linked aptamer" can be used to construct enzyme-linked electrochemical aptamer sensors.

Because thrombin has two binding sites, two aptamer chains can be screened by SELEX technology, and a sandwich-type aptamer sensor can be constructed to detect thrombin. Katakis et al. [98] successively fixed mercapto antithrombin aptamer I, thrombin, biotin-labeled antithrombin aptamer II and affinity-labeled horseradish peroxidase (HRP) on the surface of gold electrodes to construct a classic "sandwich" structure. The catalytic oxidation of hydrogen peroxide by the labeled horseradish peroxidase can be detected by an osmium mediator, and thus, thrombin can be indirectly detected. To further reduce the detection limit, Zhang et al. [99] made use of the signal amplification effect of gold nanoparticles and the enrichment and separation effect of magnetic beads by labeling horseradish peroxidase on the magnetic beads modified with aptamer II to form an aptamer/gold nanoparticles/enzyme structure, and this sensor successfully realized an electrochemical measurement of coagulase. Similarly, Mascini et al. [100] fixed mercapto antithrombin aptamer, thrombin, biotin-labeled antithrombin aptamer and affinity-labeled alkaline phosphatase on the surface of gold shell magnetic nanoparticles. The magnetic particles are concentrated on the working electrode by a magnetic field, and thrombin can be detected with high sensitivity by detecting the current of the catalytic reaction product of alkaline phosphatase.

In addition to fixed-aptamer substrates for sensor sensitization, nanoparticles are also a good choice for signal amplification as a marker. Nanoparticles are widely used in various labeling methods because of their large specific surface area and strong catalytic ability. In addition, because the enzyme is also a kind of protein in nature, there are some unavoidable disadvantages of protein, such as

inactivation, or the activity is greatly affected by the mediator and environment. However, nanoparticles do not have these limitations, so they can obtain better detection performance and construct electrochemical aptamer sensors by detecting the components of nanoparticles. Quantum dots play an increasingly important role in the study of aptamers because of their special size effect, photoelectric properties and good biocompatibility. By labeling the QDs on the aptamer chain or target analyte, we can indirectly measure the target by measuring the metal content of the quantum dot components combined on the sensor [101–104]. By using different quantum dot markers for different ligands and measuring the positions of different redox peaks corresponding to different metal elements, a quantum dot-based ligand electrochemical biosensor can be constructed to achieve simultaneous analysis and detection of multiple targets.

When there is no marker, the electrochemical detection signal obtained by the sensor is usually based on the change of mass transfer or the electron transfer potential resistance before and after the aptamer probe combines with the target. At present, most of the unmarked electrochemical aptamer sensors are based on the change in Faradaic impedance, which is caused by the aptamers and target molecules combining. Proteins, such as thrombin and IgE, fixed on the surface of electrodes often hinder electrochemical reactions.

The mass transfer from the probe to the electrode surface increases the Faradaic impedance, so the detection of protein can be realized. Lee et al. [105] fixed an amino-modified thrombin aptamer on a carboxylated pyrolytic carbon electrode by amidation. By adjusting the pH value of the solution to make thrombin negatively charged, the probe with the same negative charge is effectively rejected, and an amplified Faradaic impedance signal is obtained.

Since the synthesis of aptamer DNA strands were reported, due to their easy preparation, easy modification and wide range of binding targets, they have attracted great attention from researchers. Electrochemical technology plays an increasingly important role in the field of aptamer biosensors due to its good selectivity and high sensitivity. In particular, the emergence of new materials has injected new vitality into the development of electrochemical aptamer biosensors. With more suitable ligands of different substrates being screened out, the application of new materials improves electrochemical detection technology. Electrochemical aptamer biosensors will be widely used in molecular diagnosis, food inspection, environmental monitoring and medical inspection.

3. APTAMER-BASED ELECTROCHEMICAL SENSOR FOR VETERINARY DRUG DETECTION

Animal-derived foods are all edible animal tissues, which include eggs and milk, meat and its products (including animal organs), aquatic products, etc. Veterinary drug residues refer to drug prototypes, metabolites and drug impurities accumulated or stored in cells, tissues and products after drug administration. Veterinary drugs mainly include the residues of antibiotics, hormones and other drugs, such as malachite green. Long-term consumption of animal-derived food with excessive veterinary drug residues will seriously affect health.

β-agonists are mainly composed of phenylethanolamine and tert-butyl or isopropyl groups. According to different substituents on the benzene ring, they are divided into three types: aniline type,

phenol type and resorcinol type. The representative compounds are clenbuterol, salbutamol and terbutaline. β-agonists can promote fat decomposition, increase protein synthesis and improve the lean meat rate of ketone bodies. However, the use of large doses easily causes residual accumulation in animals. Table 2 shows the recent development of aptamer-based electrochemical sensors for β-agonist detection.

Table 2. Applications of aptamers in β-agonist detection.

Target molecule	Sample	Reference
Ractopamine, clenbuterol, salbutamol, phenylethanolamine and procaterol	Pork	[106]
Ractopamine	Human urine	[107]
Ractopamine	Animal urine	[108]
Ractopamine	Pork	[109]
Ractopamine, clenbuterol and salbutamol	Pork	[110]
Ractopamine	Beef	[111]
Clenbuterol	Biological fluids	[112]

Chloramphenicol is a highly effective and broad-spectrum antibiotic that is widely used in the treatment of various infectious diseases in animals. However, chloramphenicol has serious side effects, which can cause aplastic anemia and granulocytopenia. In addition, it will cause an imbalance in the normal flora of the body and make people susceptible to various diseases. If chloramphenicol remains in edible animals, it can be transmitted to humans through the food chain. Therefore, chloramphenicol residues in animal food are a potential hazard to human health. Xiao et al. [113] designed an electrochemical sensor based on an aptamer. They applied it to the detection of thrombin. The device links methylene blue to one end of the aptamer sequence, while the other end is modified with a thiol group and fixed on the surface of the electric signal guide plate. When thrombin is not present, the aptamer sequence is in an extended state and has flexibility. The methylene blue is brought into contact with the surface of the electrode plate so that electrons are transferred between the methylene blue and the gold electrode.

Table 3. Applications of aptamer in chloramphenicol detection.

Target molecule	Sample	Reference
Chloramphenicol	Honey	[79]
Chloramphenicol and PCB72	-	[114]
Chloramphenicol	-	[115]
Chloramphenicol	Milk	[116]
Chloramphenicol/florfenicol/ thiamphenicol	-	[117]
Amoxicillin /florfenicol	-	[118]
Chloramphenicol	Urine, pharmaceutical samples	[119]

When the aptamer binds with thrombin, the aptamer folds into an inherent three-stage structure so that methylene blue cannot come into contact with the gold electrode, and thus, electron transfer is inhibited. Table 3 shows the recent development of aptamer-based electrochemical sensors for chloramphenicol detection.

Malachite green and crystal violet are both triphenylmethane dyes. They are used as disinfectants and parasiticides in aquaculture. However, malachite green, crystal violet and their metabolites are considered to have teratogenic, carcinogenic and mutagenic effects, and have been banned for the disinfection of edible aquatic products by many countries. Malachite green and crystal violet can inhibit the transformation of glutamate into peptides and related products when bacteria or fungi are in a period of division and proliferation, which hinders the division and reproduction of bacteria. Malachite green and crystal violet are used as fishing drugs because they are easy to operate and have remarkable curative effects. At the same time, as an industrial dye, it is convenient to purchase at a low price. The UK initially found that workers who produce malachite green are prone to bladder cancer. This phenomenon caused people to pay attention to the toxicity of triphenylmethane dyes such as malachite green and crystal violet. Since the 1990s, malachite green, crystal violet and other dyes easily accumulate as residues in organisms and have been known to have high toxicity, , teratogenicity, carcinogenicity and mutagenicity toward humans and animals. For example, Figure 1 shows an example of malachite green detection [120]. Kim et al. [121] invented an aptamer electrochemical sensor for the detection of oxytetracycline. In this device, single strand DNA is fixed on an electrode chip, and $Fe(CN)_6^{3-}$ is used as an energy transfer element. When oxytetracycline exists and changes with the concentration, currents of different sizes can be detected and used to quantify the concentration of oxytetracycline. Table 4 shows the recent development of aptamer-based electrochemical sensors for malachite green and crystal violet detection.

Table 4. Applications of aptamers in malachite green and crystal violet detection.

Target molecule	Sample	Reference
Malachite green	-	[122]
Malachite green	Fish	[123]
Malachite green	Fish	[124]
Malachite green	Fish	[120]
Crystal violet	-	[125]

Nitrofurans are synthetic broad-spectrum antibiotics, namely, furantone, furacilin, furazolidone and furantoin. Because these antibiotics have similar skeletal structures, their pharmacological actions are almost the same. However, their therapeutic effects are different in practical life. Unfortunately, this kind of drug has certain toxic effects on aquatic products, poultry and other animals. Long-term, large-scale or excessive use easily causes toxic reactions in the above animals, and considerable poisoning may cause the death of livestock and poultry. In recent years, many studies have shown that nitrofurans and their metabolites have adverse effects on human health. They are potential teratogenic, carcinogenic and mutagenic substances. Interestingly, graphene has been used for the determination of clenbuterol [126]. Table 5 shows the recent development of aptamer-based electrochemical sensors for nitrofuran detection.

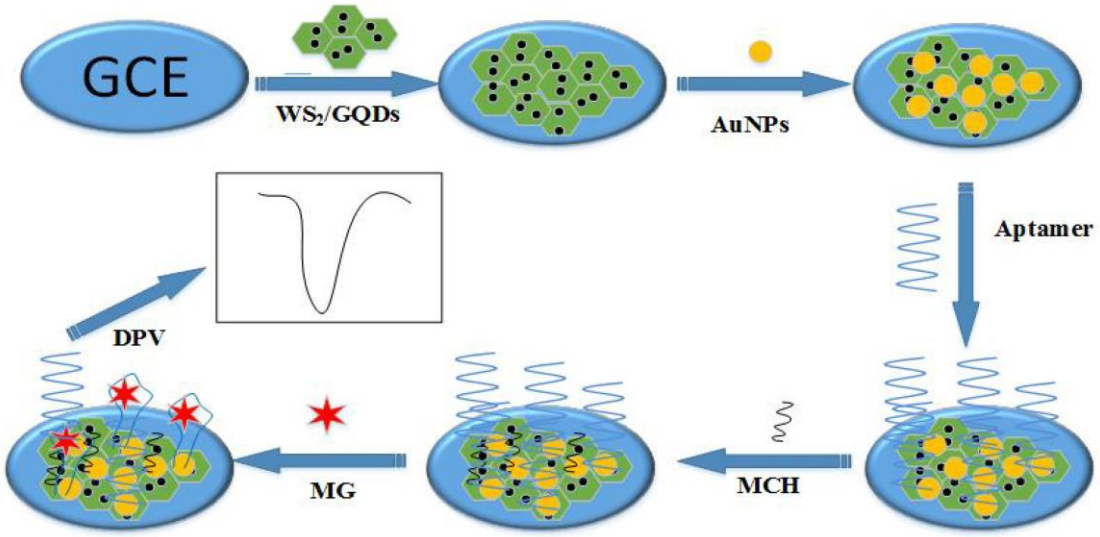

Figure 1. Fabrication process of the aptasensor for malachite green detection [120] (Copyright received from MDPI).

Table 5. Applications of aptamers in nitrofuran detection.

Target molecule	Sample	Reference
Nitrofuran	-	[127]
Nitrofuran	-	[128]
Sulfamethazine	-	[129]
Nitrofuran	-	[130]
Clenbuterol	-	[126]

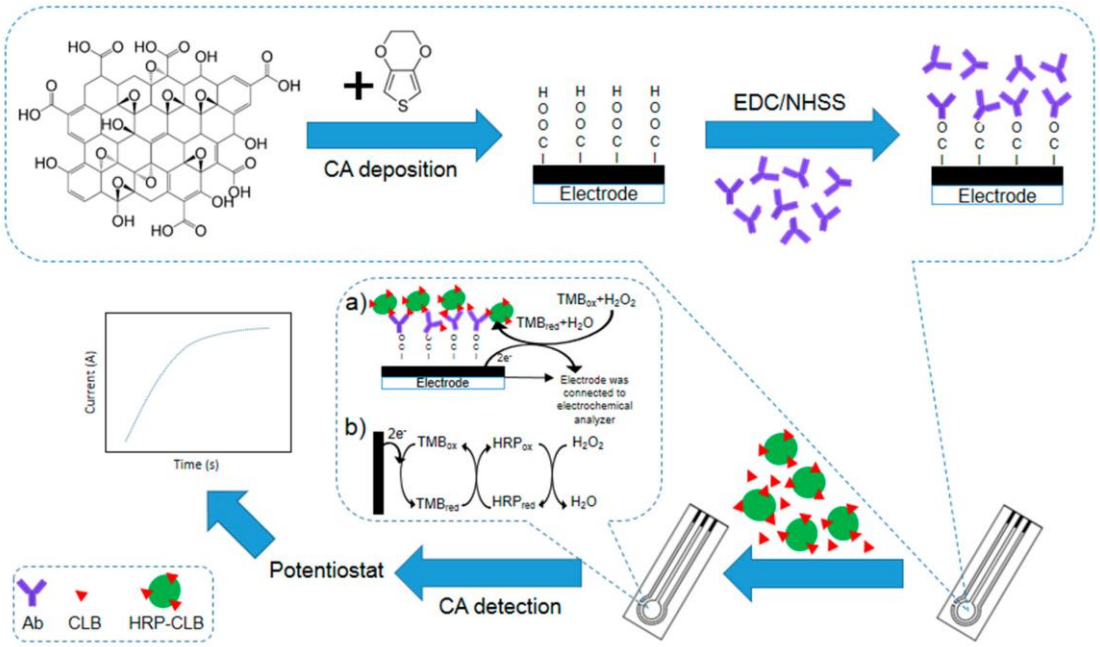

Figure 2. Schematic diagram of fabrication of clenbuterol hydrochloride immunosensor [126] (Copyright received from MDPI).

To promote the rapid growth of animals and improve lean meat rate and feed utilization, a large number of antibiotics, including fluoroquinolones, have been used. However, drug residues in animal food are caused by drug abuse, noncompliance with the drug off period and individual metabolic differences in animals; these residues are harmful to human health, especially when found in meat, eggs and dairy products. Quinolones are synthetic broad-spectrum antibiotics that have been studied the most and developed the fastest in the past decade. Quinolones are inhibitors of bacterial DNA. The target enzyme of quinolones is DNA gyrase (its function is to make DNA form a helix for rapid replication), which makes DNA replication impossible. Because bacteria are prokaryotes, their genomic DNA is not surrounded by a nuclear membrane, while the DNA of animal cells exists in a nucleus, surrounded by a nuclear membrane. Therefore, the drug cannot come into contact with the DNA in animal cells but can come into contact with the DNA in bacteria; therefore, the bacterial cells cannot divide, resulting in a rapid bactericidal effect. Ciprofloxacin, norfloxacin and enrofloxacin are the most widely used quinolones with the strongest antibacterial activity. Table 6 shows the recent development of aptamer-based electrochemical sensors for fluoroquinolone detection.

Table 6. Applications of aptamers in fluoroquinolone detection.

Target molecule	Sample	Reference
Ciprofloxacin	Milk	[131]
Tetracyclines	Milk and serum	[132]
Ciprofloxacin	-	[133]
Streptomycin	Serum	[134]
Ofloxacin	Effluent of sewage treatment plant	[135]
Streptomycin	Milk	[136]
Streptomycin	Milk and serum	[137]

4. CONCLUSION

Since the synthesis of aptamer DNA strands were reported, due to their easy preparation, easy modification and wide range of binding targets, they have attracted great attention from researchers. However, electrochemical technology plays an increasingly important role in the field of aptamer biosensors due to its good selectivity and high sensitivity. In particular, the emergence of new materials has injected new vitality into the development of electrochemical aptamer biosensors. With an increasing number of aptamers composed of different substrates being screened out, the application of new materials to electrochemical detection technology continues to improve, the detection limit of the constructed sensor continues to decrease, and the linear range continues to broaden. In the near future, electrochemical aptamer biosensors will have more extensive research and application prospects in the fields of molecular diagnosis, food inspection, environmental monitoring and medical inspection.

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