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REVIEW ARTICLE

Recent Biosensors for Detection of Antibiotics in Animal Derived Food

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ABSTRACT

Antibiotics are extensively employed as bacteriostatic agents for fighting against microbial infection in animals. However, inappropriate doses of antibiotic drugs may result in antibiotic residues in food of animal origin and may cause various side effects on human health. Moreover, the transferor of antibiotic-resistant bacteria to humans through the food chain may induce serious health hazards. Hence, it is vital to develop sensitive and selective methods for rapid screening and regular monitoring of antibiotic residues in animal-derived foods. The conventional different chromatographic and spectroscopic techniques are time-consuming, expensive and require skilled personnel. To overcome such limitations, biosensors have emerged as an innovative approach recently and integrated with nanotechnologies for sensitive, rapid and on-site monitoring of different antibiotic residues in animal origin foods. This mini-review aims to give an overview of the currently available biosensing techniques to detect antibiotic residue in foods.

KEYWORDS

Antibiotic residue; biosensor; animal-derived food; electrochemical detection

Introduction

Antibiotics are among the most important components used in the livestock industry and aquaculture worldwide for the treatment and prevention of diseases and growth promotion.[1] However, their misuse may result in antibiotic residues in foodstuffs such as meat, egg, fish and milk.[2] Residues of antibiotics may lead to various toxic effects in human and present a threat to health by spreading antibiotic-resistant bacterial infections.[3] In recent years, early detection of antibiotic residues has garnered significant attention worldwide due to its contamination and drug resistance.[4]

Various conventional approaches including chromatographic,[5] spectroscopic,[6] immunological,[7] etc. have already been reported for the detection of antibiotic residues in animal-derived foods. However, those methods are suffering from complex sample pretreatment, poor selectivity, high cost, and low sensitivity.[8] Last decades, biosensors have emerged as an alternative method which is a robust state-of-art for wide practical applications with advantages as portable, rapid, easy to handle, inexpensive, high sensitivity and real-time analysis.[9–11] Biosensors comprise two key elements in close proximity: a recognition element which recognizes the target molecule and a transducer for converting the recognition event into a measurable signal.[12,13] In recent years, electrochemical, optical and microbial biosensors have attracted great attention for the screening of antibiotic residues due to their high selectivity and become a hotspot. Numerous research papers have been published during this time to report different available biosensing techniques and their working principle.

Hereafter, this review aims to deliver an overview of the cutting-edge nano-bio technologies developed for very recently reported biosensors toward the detection of antibiotic residues in animal-derived foods.

Recent advancement in biosensors for detection of antibiotics

Compared to other detection techniques, biosensors are capable of performing residues screening relatively fast, accurately, and rapidly without the need for a specialist user. The selective and sensitive detection process of a biosensor depends on the most crucial component named biological recognition elements or bioreceptor whose signal is then detected with a suitable transducer. For fabricating a sensor, many bioreceptors such as enzyme, aptamer, antibody, DNA, microbial cell etc. have been most widely used. The basic working principle of a biosensor is illustrated in Figure 1.

On the basis of signal transduction, biosensors are generally divided into electrochemical, optical, and mass-based. Among them, electrochemical, colorimetric, surface plasmon resonance (SPR), and quartz crystal microbalance (QCM) techniques are the most commonly used for the screening of antibiotic residues and quality control of foods.[2,4,7,8,14–16] The following section offers a brief description and outlines of recently reported biosensors for the detection of antibiotic residues in animal foods and offers a brief description of their working principles.

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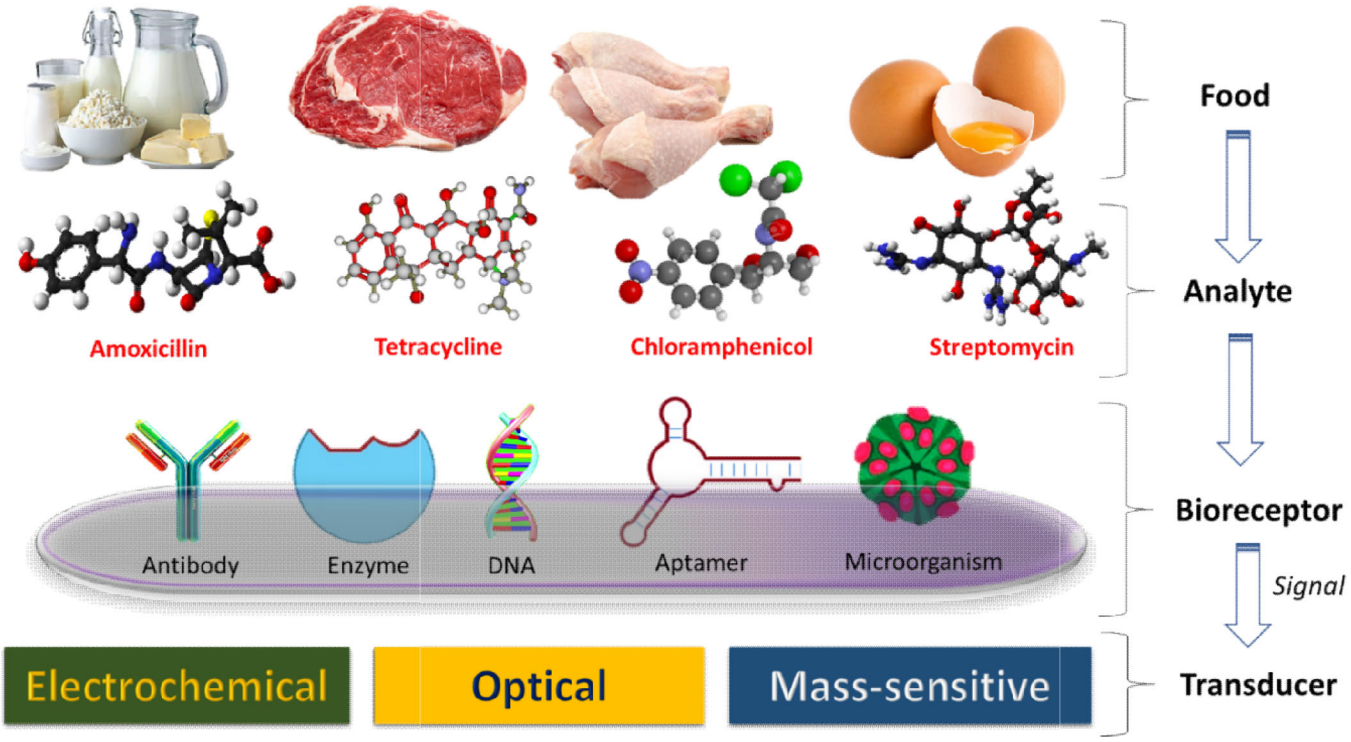

Figure 1. Schematic representation of the working principle of biosensors for the detection of antibiotic residues.

Electrochemical biosensors

Electrochemical biosensor (ECB) is one of the typical sensing devices based on the chemical reactions between immobilized biomolecules and target analytes that transform biochemical information into an analytically useful signal.[16] An electrochemical biosensor is generally designed with three electrodes such as a working electrode, reference electrode and counter electrode. These electrodes demand both chemical stability and conductivity to make electrode authentic.[17] Consequently, platinum, graphite, gold, and silicon compounds are widely used as electrode materials, depending on the analyte.[18,19] The working electrode performs as the biorecognition element at which biochemical reactions occur. The working principle of the reference electrode is to control a well-known and stable electrode potential by keeping it away from the reaction site. The counter electrode is employed to create a link with the electrolytic solution that causes the current to flow between the working electron and the counter electrode. The signal generated from the biological phenomenon is then converted into an electrical signal through a transducer.[20,21] Depending on the detection technique, there are four types of electrochemical biosensors namely potentiometric, amperometric, impedimetric and conductometric.[22–25] Owing to their unique properties compared to other methods, ECB has been widely used for the screening of antibiotic residues. A summary of the recent reports on ECB for antibiotic residue analysis is provided in Table 1.

Wang et al. have reported a highly sensitive electrochemical sensor based on dual recycling amplification strategy for antibiotic residues detection in milk samples.[28] They developed a homogeneous aptasensor for ampicillin detection using target-induced and T7 exonuclease-assisted dual recycling signal amplification strategy. The reported biosensing system exhibits a limit of detection (LOD) of 4 pM with the advantages of good selectivity. Recently, a simple and sensitive molecularly imprinted polymer (MIP) based electrochemical sensor was reported for the simultaneous determination of acetaminophen and sulfadiazine.[31] The authors have used a graphene oxide@covalent organic framework (GO@COF) nanocomposite for signal amplification. The observed high electroactive surface on glassy carbon electron was likely due to the proposed modification which facilitated electronic transfer. The reported sensor showed a strong current response to both acetaminophen and sulfadiazine spiked in beef, pork and chicken samples.

Mutharani et al. have demonstrated an efficient voltammetric sensor for sensitive detection of sulfamethazine (SFZ) in milk samples.[45] Very recently "signal-triggered" electrocatalyst has provoked immense interest in the growth of "stimulating-responsive" sensors. The constructed switchable ruthenium hybrid stimulating-responsive smart poly(N-isopropylacrylamide-co-methacrylic acid) microgel catalyst modified glassy carbon electrode (Ru@MGC/GCE) was used as a thermo-switch control (Figure 2A), which led to high electrocatalytic activity for the oxidation of sulfamethazine as shown in Figure 2B. The authors obtained satisfying results employing this switch control thermo-responsive voltammetric sensor for SFZ analysis in actual milk samples with a LOD value of 5 nM.

In 2018, El-Moghazy et al. have developed a label-free electrochemical immunosensor based on poly (vinyl alcohol-*co*-ethylene) (PVA-*co*-PE) nanofibrous membrane for the detection of chloramphenicol residues in milk.[29] The synthesized nanofibrous membrane was immobilized covalently

Table 1. An overview of recently reported biosensors for antibiotics detection in animal-derived foods.

Transducer	Bioreceptor	Analyte	Sample matrix	Linear range	LOD	References
Electrochemical	β-Lactamase	Benzylpenicillin	Milk	0.26-0.66 μmol/L	0.079 μmol/L	[26]
	Aptamer	Tetracycline	Milk	0.3–10 nM	266 pM	[27]
	Aptamer	Ampicillin	Milk	0.02 to 40 nM	4 pM	[28]
	Antibody	Chloramphenicol	Milk	0.01–10 ng/mL	0.0047 ng/mL	[29]
	Antibody	Ceftiofur	Chicken	0.01-100 ng/mL	0.01 ng/mL	[30]
	MIP	Sulfadiazine	Pork	0.5–200 μM	0.16 μM	[31]
		Acetaminophen	Chicken	0.05–20 μM	0.032 μM	
Colorimetric	Aptamer	Chloramphenicol Tetracycline	Milk/	0.05–1.8 μM	7.0	[32]
			Chicken	0.05–3.0 μM	32.9 nM	
	Aptamer	Tobramycin	Egg	40–200 nM	23.3 nM	[33]
	Aptamer	Streptomycin	Milk	0.003 – 20 ng/mL	1 pg/mL.	[34]
	Aptamer	Kanamycin	Milk	0.05 to 0.6 μg/mL	2.6 ng/mL.	[35]
	Aptamer	Chloramphenicol	Milk/Chicken	10–450 nM	7.65 nM	[36]
	Aptamer	Chloramphenicol	Milk	0.1–1000 pM	0.03 pM	[37]
SPR	Antibody	Enrofloxacin	Milk	–	0.07 uM	[38]
	MIP	Amoxicillin	Egg	0.1–2.0 ng/mL	0.022 ng/mL.	[39]
	MIP	Vancomycin	Milk	10-125 ng/mL	4.1 ng/mL	[40]
	MIP	Erythromycin	Milk	0.1-5 μM	1.62 nM	[41]
QCM	antibody	Streptomycin	Milk	0.3-50 ng/mL	0.3 ng/mL	[42]
	MIP	Tobramycin	Milk/Egg	1.7×10^{-11} to 1.5×10^{-10} M	5.7×10^{-12} M	[43]
	Antibody	Chloramphenicol	–	5-100 ng/mL	5 ng/mL	[44]

with a chloramphenicol antibody (Figure 3A) and the observed amperometric responses were based on the reduction of nitro groups of the captured chloramphenicol molecules on the antibody modified electrode. Furthermore, this new immunosensor accurately determine chloramphenicol residues without any pretreatment with good recovery. In another work, Stevenson and his coworkers have presented for the first time an affinity-based biosensor for the electrochemical detection of ceftiofur antibiotic residues within chicken meat.[30] The proposed sensor uses a self-assembled immunoassay to detect the ceftiofur biomarker by employing the electrochemical impedance spectroscopy (EIS) method as shown in Figure 3B.

Very recently, Zhang et al. have reported an exonuclease III-powered DNA walking machine for electrochemical detection of ampicillin in milk.[46] The authors claimed that the DNA walker has been integrated for the first time into electrochemical sensing for antibiotics detection. This label-free electrochemical sensor with a LOD of 0.76 pM indeed provides a useful tool for ampicillin residues detection. Recently, Liu and his coworkers have reported on-site detection of kanamycin in food samples with an aptamer and functionalized nanoparticles-based strip biosensor.[47] For the first time, they have used target-specific aptamer-modified nanoparticles as probe and oligonucleotide DNA1-modified silver nanoparticles as the signal amplification element. The lateral flow strip biosensor exhibited very high sensitivity with a LOD of 0.0778 nM and has been applied to detect kanamycin in various animal-derived food samples.

Optical biosensors

Optical based biosensors are extensively used for the detection of antibiotic residues in animal-derived foods because of their high sensitivity, quick response and specificity.[41,48–51] Optical methods can detect antibiotics by measuring the change in optical characteristics during the binding of the target analyte to bioreceptor. Based on the detection principle, optical sensors are mainly divided into several groups such as colorimetry, surface plasmon resonance (SPR), fluorescence, and surface-enhanced Raman scattering (SERS).[49] An optical biosensor is an analytical device that integrates a bioreceptor (antibodies, enzymes, or microbes) with a transducer system. The optical biosensor is used as an optical transduction unit for analyte detection and electrochemical biosensors for this mechanism are different from optical biosensors. A biological signal is generated by the bioreceptor with the target analyte through biochemical reactions which are converted to an optical signal by the optical transducer and this optical signal is proportional to the concentration of the measured target analyte. Physical or chemical changes in the events of the bioreceptor cause changes in light transmission, reflection, refraction, absorption, amplitude, phase, frequency or polarization and optical biosensors measure these changes as an operating principle.

Among different optical techniques, colorimetry is the simplest and most attractive sensing strategy owing to its simple optical features, practicality and low cost.[48] The key principle of the colorimetric method is to detect target analyte by the naked eye without complicated equipment. The unique physicochemical properties of metallic nanoparticles have received much attention for use in colorimetric sensors because of their distance/size-dependent optical properties. Antibodies and aptamers can be readily adsorbed on the surface of metal nanoparticles and have stronger binding affinity via nonspecific electrostatic interactions.[14]

Due to the extremely high extinction coefficient and unique optical properties, AuNPs based colorimetric aptasensors have attracted huge interest for the detection of antibiotic residues in foods.[52] To effectively prevent AuNPs aggregation in high ionic strength, several researchers used thiol groups of ssDNA covalently attached to AuNPs.[53] Very recently, Wu at al. have reported a label-free colorimetric aptasensor for the detection of multiplex antibiotics which is based on the controllable aggregation of AuNPs.[32] They have elaborately designed a multifunctional aptamer to be adsorbed on AuNPs surfaces and their reported sensor exhibited remarkable sensitivity for detection of chloramphenicol

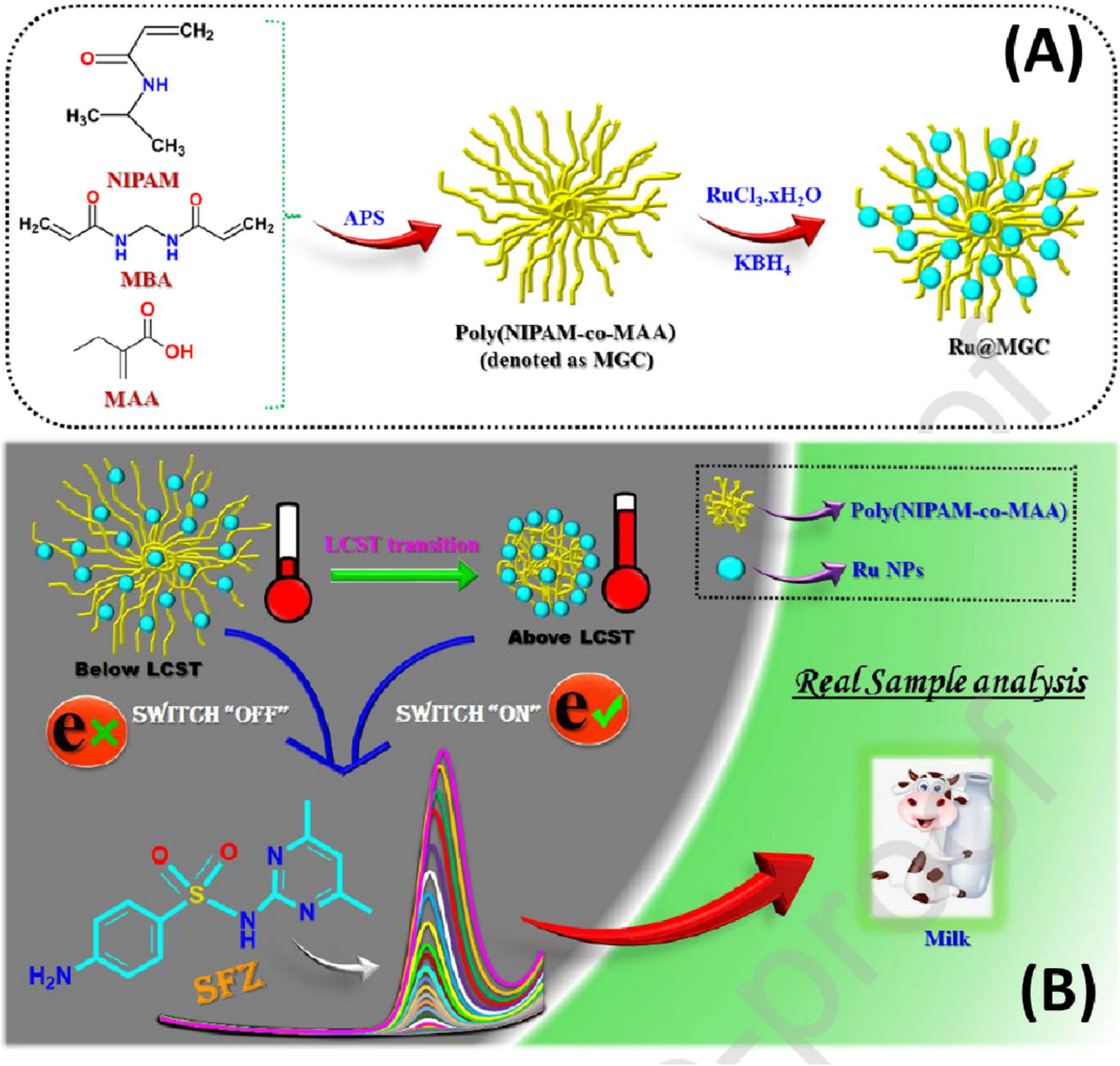

Figure 2. Schematic representation of (A) the preparation technique of ruthenium hybrid stimulating-responsive smart microgel catalyst Ru@MGC and (B) the thermo-reversible electro-oxidation of SFZ in real milk samples using Ru@MGC.[45] Reproduced with permission; copyright @ Elsevier.

and tetracycline with a LOD of 7.0 and 32.9 nM, respectively. Figure 4 represents the schematic illustration of the detection of chloramphenicol and tetracycline based on AuNPs colorimetric aptasensors.

Recently, several researchers reported the development of colorimetric aptasensor based on AuNPs toward the detection of antibiotic residues.[33,53–56] In another work, Ma et al. have developed a colorimetric aptasensors based on DNA and AuNPs for determination of tobramycin (TOB) in chicken eggs and milk.[33] Their observed high specificity and sensitivity was based on the aggregation of AuNPs and the special interactions between aptamer and TOB. The observed different colors with the naked eye due to the preventing aggregation ability of aptamer were finally quantified by UV–Vis absorption spectroscopy.

Several other colorimetric assays have also been widely exploited based on silver nanoparticles (AgNPs) and silica nanoparticles (SiO_2) due to their low cost, high surface area, and some unique advantages over AuNPs. In 2017, Luan et al. have developed a point of care testing colorimetric aptasensor using porous silica beads-enzyme linked polymer aptamer probes for streptomycin detection.[34] They have utilized the porous SiO_2 as a carrier to prepare sensitive probes to label more signal tracers as shown in Figure 5. Their obtained result clearly demonstrated the potential application of the developed aptasensor for streptomycin detection in milk samples with a LOD value of 1 pg mL^{-1}. On the other hand, Xu and his coworkers reported the colorimetric detection of kanamycin based on analyte-protected AgNPs and aptamer-selective sensing mechanism.[35] Their aptamer-selective sensing mechanism was

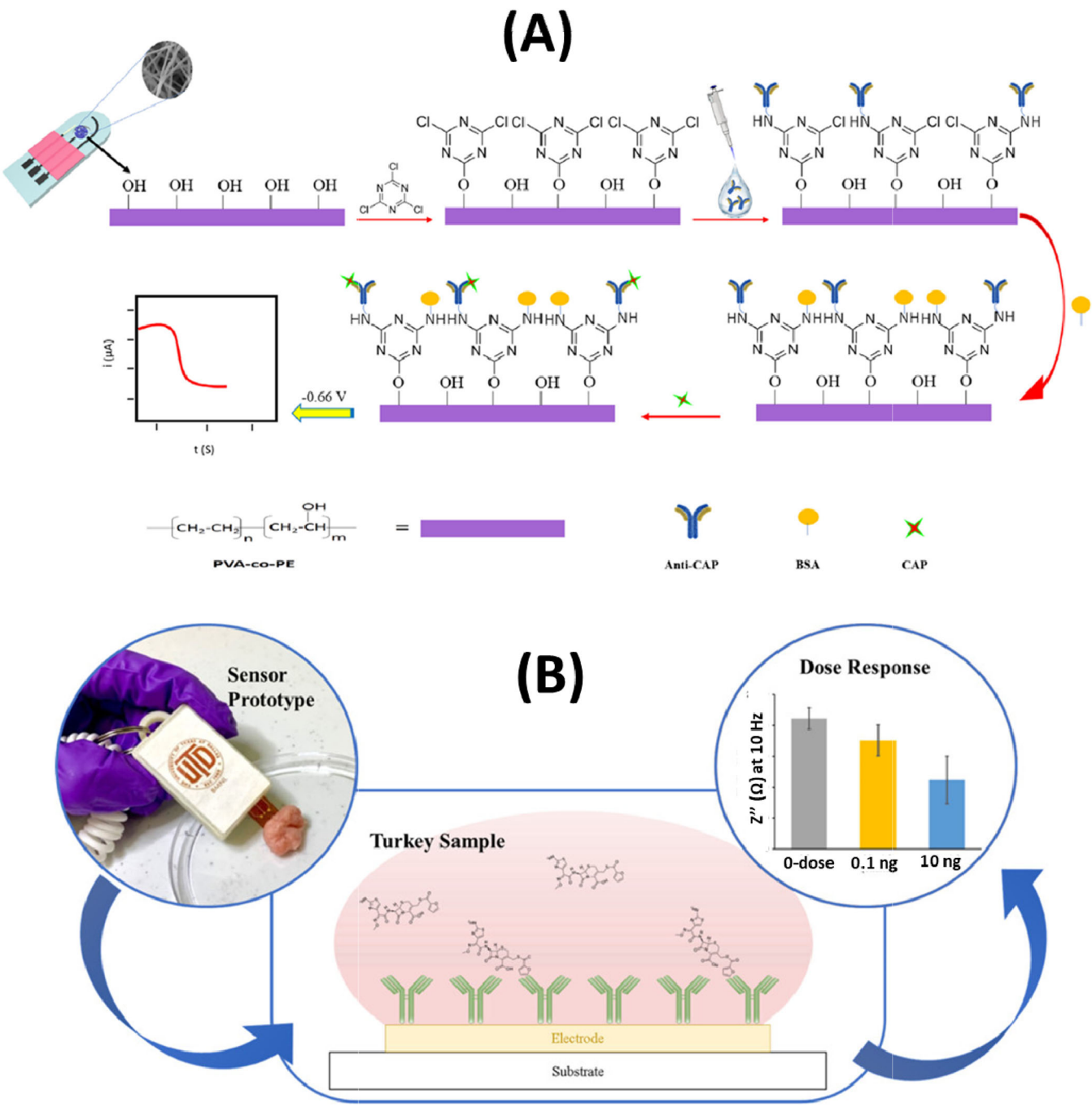

Figure 3. (A) Schematic illustration of chloramphenicol label-free immunosensor fabrication.[29] (B) Fabrication and detection principle of an affinity-based biosensor for the electrochemical detection of ceftiofur antibiotic residues in turkey chicken sample.[30] Reproduced with permission; copyright @ American Chemical Society.

based on the protection of AgNPs against salt-induced aggregation through antibiotic analyte which results a LOD of 2.6 ng mL^{-1} and demonstrated the applicability toward kanamycin detection in real milk samples.

Surface plasmon resonance (SPR) based optical biosensor has become an important biosensing technology due to its real-time, rapid, and ultra-sensitive detection of biological analytes. During the last two decades, biosensors based on SPR have attracted much attention in medical diagnostics, environmental monitoring and antibiotics detection due to their high sensitivity and fast detection technique.[51] SPR is widely used in biomolecular interaction analysis and belongs to label-free optical biosensing technologies. The basic principle of SPR based antibiotic sensors is real-time detection of refractive index changes and monitoring of biomolecular binding events during the recognition process.[57] This optical sensor uses an optical effect and special electromagnetic waves that can be utilized to measure the binding of molecules in real-time and to detect the interactions at the surface.[41] For the first time in 1995, Sternesjo and his coworkers introduced SPR-based biosensors for the detection of antibiotic.[58] Since then, many research works have been published based on the SPR technique and applied to the detection of antibiotic residues in foods.[40,51,59]

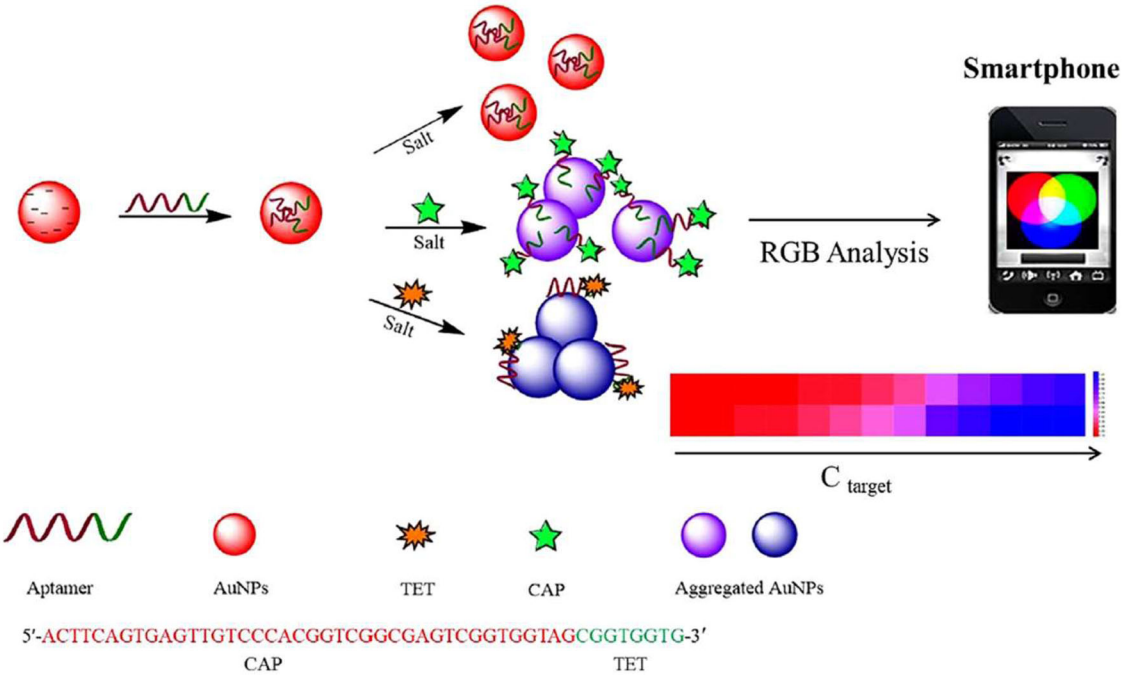

Figure 4. Schematic illustration of the detection of chloramphenicol/tetracycline based on AuNPs colorimetric aptasensors.[32] Reproduced with permission; copyright @ Springer.

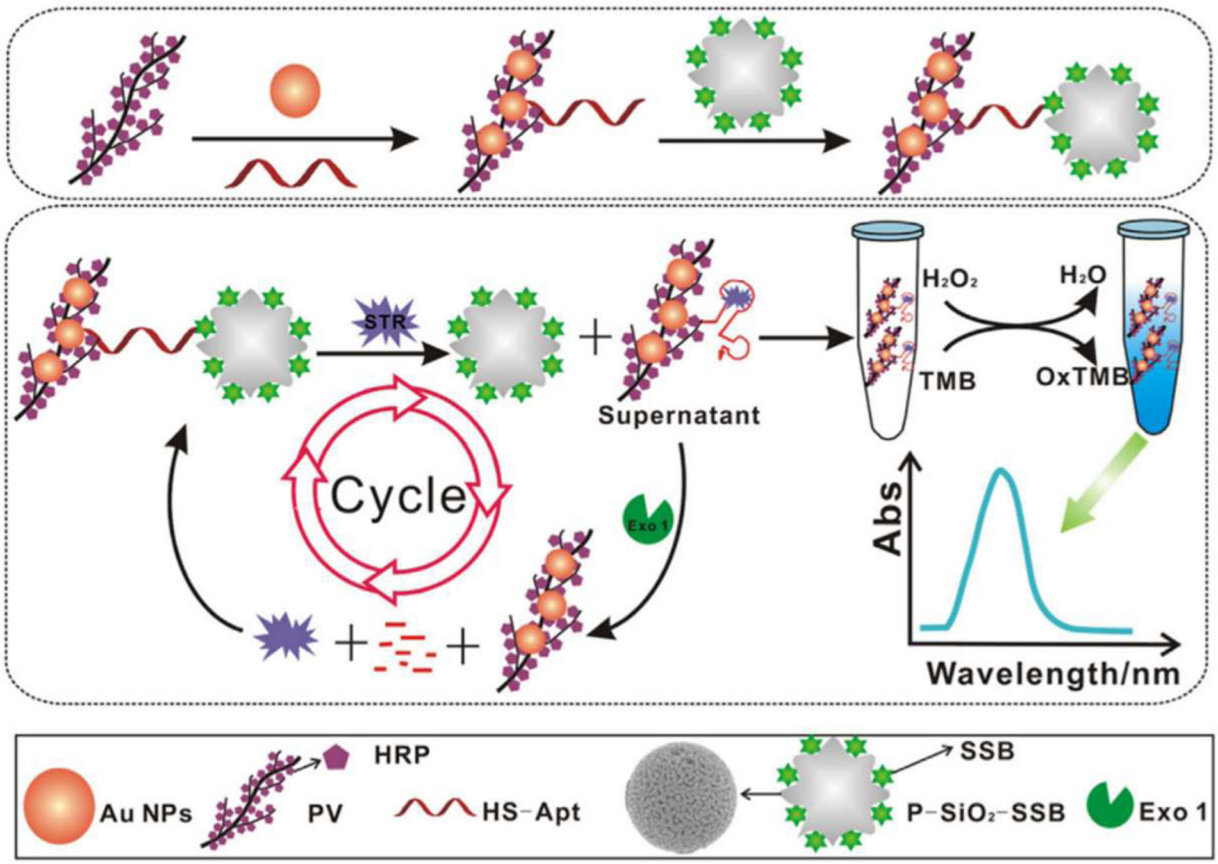

Figure 5. Scheme of depicting the proposed biosensing of streptomycin dependent on the developed colorimetric aptasensor.[34] Reproduced with permission; copyright @ Elsevier.

The integration of MIP as synthetic affinity receptors into SPR-based biosensors devices has made a significant contribution to the antibiotic residue analysis. Recently in 2018, Altintas has developed an SPR based sensor for the detection of vancomycin antibiotics in milk using rationally designed nano MIP.[40] For the first time, this work reported

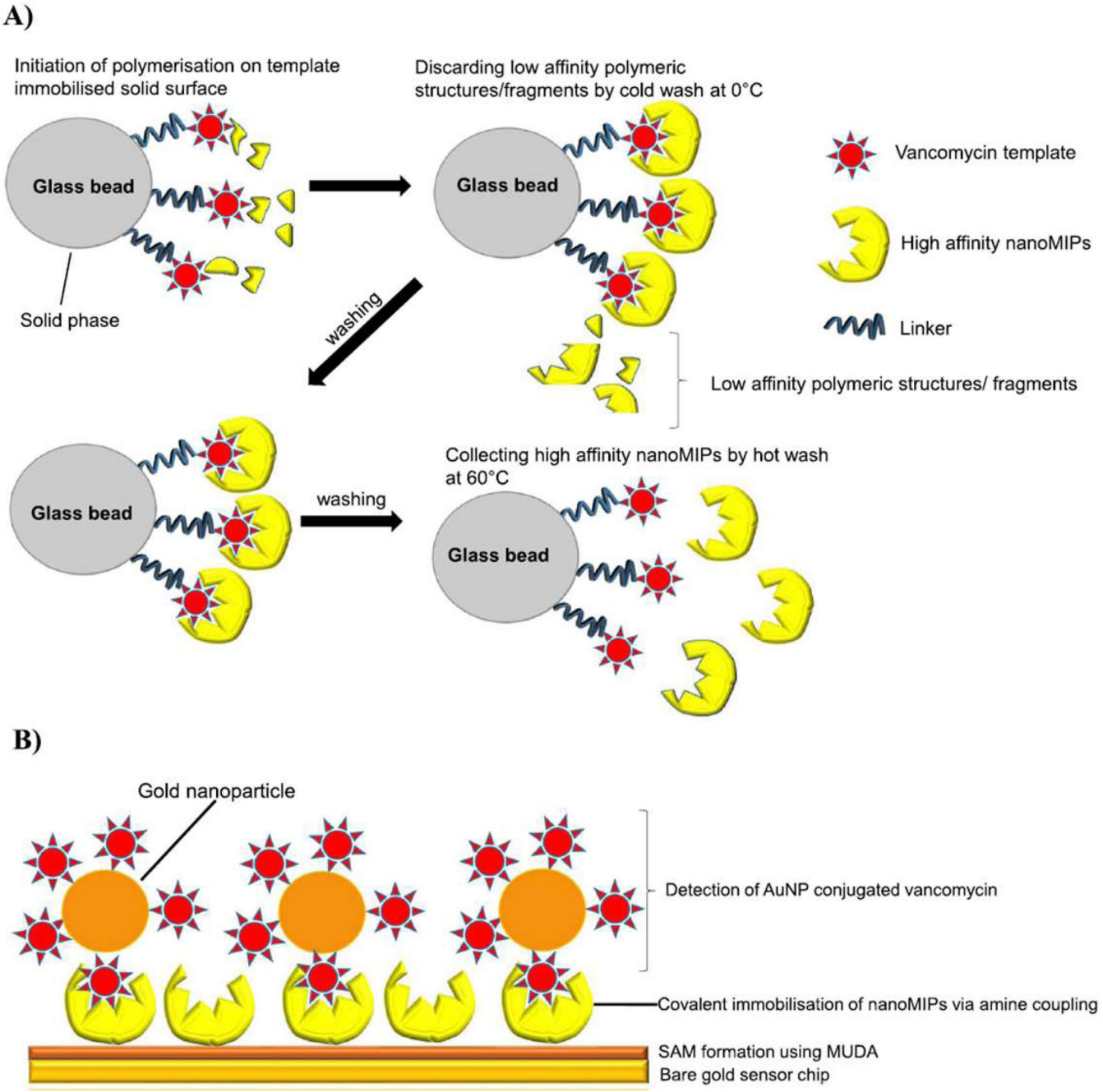

Figure 6. Schematic illustrations of the preparation of vancomycin nano MIP (A) and their use in sensor development as synthetic affinity receptors for vancomycin detection (B).[38] Reproduced with permission; copyright @ Elsevier.

nanomaterial-conjugated direct assay using the nano MIP receptors (Figure 6) for sensitive detection of vancomycin residue in milk samples. In another work, Fernández et al. have developed a nanogold probe enhanced SPR immunosensor for the detection of enrofloxacin residue in real milk samples.[38] The active ester method was used to covalently attach antibodies with AuNPs. The authors observed a significant increase in the detectability (LOD values own to 0.07 μg L^{-1}) through reducing the concentration of specific immunoreagents.

In 2017, Shrivastav and his coworkers have introduced a highly sensitive and selective erythromycin nanosensor employing fiber optic SPR/erythromycin imprinted nanostructure.[41] Moreover, the applicability of the proposed sensor was examined in real milk and honey samples analysis with a LOD value of a 1.62×10^{-3} μM which was found to be in good agreement for the industrial application. They have used fiber optic SPR configuration along with erythromycin imprinted nanoparticles.

Mass-sensitive biosensors

A mass-sensitive biosensor is another type of biosensor which works based on the piezoelectric effect. The sensing mechanism of this biosensor depends on the immobilization procedures and piezoelectric materials/crystals (transducer)

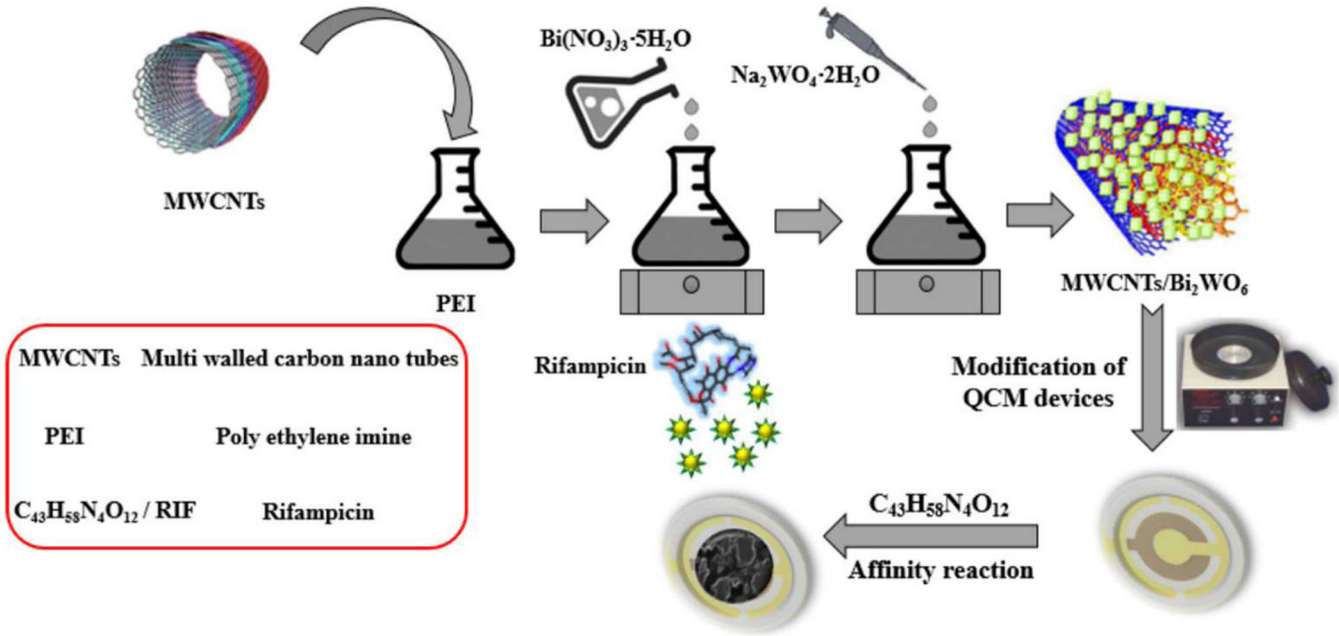

Figure 7. Schematic illustration for designing MWCNTs/Bi_2WO_6 nanocomposite based QCM sensor for the detection of rifampicin.[60] Reproduced with permission; copyright @ Elsevier.

used to evaluate the oscillation. All piezoelectric materials/crystals have a specific vibrational response for specific alternating current when applied with a fixed frequency. Adsorption of certain molecules or analyte on the sensing surface alters the resonance frequencies, which can be measured as an output signal.

The most common mass-based biosensing method is the quartz crystal microbalance (QCM). QCM has been gradually being used in diverse sensor applications due to the quick response, real-time output, easiness and practicality for large-scale use.[14] QCM is an operation that relies on the changes in the frequency of quartz crystal which is widely used for the detection of biomolecules without labeling.[4] QCM operates at its optimal level if used with a molecular recognition procedure where the polymerization occurs around the target molecule. Consequently, using a molecular imprinting approach a polymeric nanofilm was developed on the QCM sensor chip which results in an enhanced real-time sensing platform.

Compared with complicated and expensive optical instrumentation, the mass-sensitive QCM technique is more suitable due to its simplicity, real-time response, and convenience. The principle of QCM is based on an oscillating piezoelectric quartz crystal that inversely proportional to the mass change on the surface.[14] Sun and his coworkers have developed a three-dimensional sensing membrane functionalized QCM biosensor composed of antibody immobilization on electrospun polystyrene membranes for chloramphenicol detection in real-time.[44] They have observed increased sensitivity of their antibody-functionalized biosensor with increasing the specific surface area of the QCM. The resultant biosensors showed a LOD value of 5 ppb toward chloramphenicol detection with a very fast response. In another work, Mishra et al. have reported a flow injection analysis-electrochemical quartz crystal nanobalance (FIA-EQCN) biosensor for ultrasensitive detection of streptomycin residues in milk samples.[42] In the study, a monoclonal antibody specific to streptomycin (mAb- streptomycin) was successfully immobilized on to the thiol modified gold quartz crystal surface that facilitates ultra-sensitive detection with a LOD value of 0.3 ng/mL in real milk samples.

In 2019, Munawar et al. have introduced unconventional nanomaterials based QCM technique for the detection of rifampicin.[60] They have prepared multiwalled carbon nanotubes and bismuth tungstate nanocomposite and employed as a transducer layer onto the QCM sensor for selective detection of rifampicin. A LOD value of 0.16 µM was achieved toward rifampicin detection with the developed sensor with excellent specificity. Figure 7 represents the schematic illustration of MWCNTs/Bi_2WO_6 nanocomposite based QCM sensor for the detection of rifampicin.

Conclusions and perspectives

Antibiotic contamination and drug resistance have been recognized as a worldwide phenomenon. Recently, the monitoring of antibiotic residues in foods has become a prime concern in order to produce safe food. To date, various analytical approaches have been reported for the analysis of antibiotic residues in animal-derived foods. Although very innovative, many of the conventional and bioassay methods are impractical due to complex pretreatment, high cost and low sensitivity. However, biosensors are an extraordinary example that offers a high degree of automation, cost-effective, real-time measurements, high throughput, and highly selective monitoring. More importantly, biosensors have functional on-site monitoring and point of care diagnostics in screening antibiotic residues from animals-derived foods magnificently.

This review has provided a general overview of recently reported biosensing techniques toward the detection of different important antibiotic residues in animal-derived foods such as milk, egg and meat. In the development of biosensors, portability and miniaturization are the most challenging and realistic goals. Moreover, it appears that existing transduction methods suffer from reusability and on-site detection problem. Considering direct electron transfer between electrode and enzyme, the development of the third generation of enzymatic biosensors is also promising. This third-generation biosensor shows a prominent way to develop more sensitive and selective methods for detecting antibiotic residues in animal-derived foods.

Future efforts should concentrate on synergy for improved sensitivity and develop multiplex assays for use in the field. Further advance studies in microfluidic chips and lab-on-chip technique undoubtedly will improve the detection strategies of biosensors which will definitely allow a merger toward the detection of multiple analytes from a single sample source.

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