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REVIEW

Detection of Antibiotic Residues in Food Using Biosensors

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Over the years, antibiotics and their implementation have been even more erratic and ambitious, considering their reputation and clinical relevance. In modern times, the medicinal use of antibiotics is important for the treatment of a wide variety of microbial infections. The misuse and overuse of antibiotics have contributed dramatically to the elicitation of antibiotic-resistant bacteria (ARB) that has become a global concern. Those immune to the medication live and reproduce as bacteria are repeatedly exposed to low doses of an antibiotic, while the remainder dies off, resulting in a new population of bacteria that avoids the use of antibiotics. Antibiotics residues in food products/byproducts are metabolites present in trace levels in any edible portion of animal product after administration of antibiotics. The antibiotics residues in food which lies in excess than that of acceptable range of maximum residue limit contribute in development of antibiotic resistances among animals/humans. In dairy industries, rapid advancements in technology are being made and food processing technology has started to focus on biosensors to assess the consistency of food products. Biosensors are instruments that contain a biochemical molecule that produces a tactile signal which is transformed into an indication to assess the consistency and protection of food. In recent years, when the devices began to grow constantly with their extensive deployment in the food industries, current traditional methods that have historically been introduced replaced them. The goal of the following review is to provide a thorough overview of biosensors and their forms that differ depending on the substrate involved and highlight the insights that rule the importance of biosensors in antibiotic residue detection.

Keywords: Antibiotic residues, Antibiotic Resistance, Biosensors, Animal products/byproducts.

INTRODUCTION

Antibiotics are naturally or synthetically derived metabolites derived from living organisms or under laboratory conditions, with potent ability to kill or facilitate inhibition of microbial growth. The compound is classified based on their ability *i.e.* bactericidal or bacteriostatic effect and also on the basis of their efficacy towards treatment against a broad spectrum of microbial species [1,2]. The application of antibiotics in the form of drugs in the treatment of animals, which is shortly followed by their treatment for humans against prevention of disease have become pivotal over the years and thus their usage has become indispensable and inevitable today [3,4]. The prevention of disease in animals can be attained by following proper hygienic principles, biosecurity measures and management practices so as to minimize the use of antibiotics in food animals. Use of antibiotics as growth promoters and feed additives can be avoided in order to control the antibiotic residues in food [5].

When considering the interference of veterinary medicine and particularly the implication of antibiotics as licensed chemicals for their use in food and feed products after their pre-marketing acceptance, the primary reasons for the toxicity of antibiotic residues present in food remain [6,7]. A major danger to both animal and human health is posed by antibiotic residues. The dire problem observed may be antibiotic resistance residues that, before their excessive use in animal husbandry, spread through microbial communities [8]. Food origin from an environment contaminated with antibiotics will eventually result in the antibiotic residues in different kinds of food. The elicitation of antibiotic-resistant bacteria (ARB) has become a global problem due to the abusive use and overuse of antibiotics. World Health Organization has issued antimicrobial

resistance to be a public health crisis and needs managerial implication to handle with utmost caution. Antibiotic resistance represents bacterial ability towards resisting against abiotic effects, for which they were sensitive previously *via* genetic mutations or through the development of antibiotic resistance genes (ARGs), bacterial species become resistant to antibiotics. The propagation of antibiotic resistance genes (ARGs) is, however, attributable to bacteria's ability to share genes across species boundaries. Mobile genetic components (MGEs), such as plasmids, integrons, transposons and genomic islands containing ARGs, are promoted actives [9-11]. Globally, environmental antibiotic resistance in India has increased significantly [12]. It is claimed that India and China are the world's leading producers of active pharmaceutical ingredients, among which Dr. Reddy's is one of the leading producers from India with more than six FDA approved plants followed by Sun Pharma manufacturing company [13].

Antibiotic pollutants used in aquaculture and effluent discharge from the pharmaceutical sector also contain antibiotic sediments. These antibiotics, encouraging selective antibiotic-resistant bacteria, exert selective pressure on the usual sediment flora [14,15]. The consumption of tainted food presents a significant danger to general public health owing to potential carcinogenic and poisonous properties dispelled by antibiotic residues and its allergic tendency. Furthermore, unnecessary antibiotics usage in food processing and animal husbandry makes it possible for pathogenic bacteria to be vulnerable to multi-drug antibiotics utilized as human medicine. These antibiotic residues posing deleterious impact to the protection over manufacturing process and resulting in economic risk, since they obstruct the processes of biotechnological processing involving microorganisms such as starter cultures in dairy industries [16]. In agricultural products of animal origin, there are trace amounts of antibiotics/antimicrobial drugs, and these are used for public administration of medication. Milk pollution has been the subject of a great deal of national discussion. For more than 20 years, the general debate concerning biological significance behind the presence of antibiotic/antimicrobial residues has been addressed and remains the focus for scientific community and also as attributing to political action over drug regulations [17]. However, there is a need to assess the biological value of antibiotic residues and antimicrobials. Similarly, the complete use of the antibiotics developed remains divided between human usage and the numerous applications of veterinary medicine and animal agriculture. Inactive agriculture, antibiotics, and antimicrobials have two common applications [18]:

- Therapy and prevention of illness
- For purposes of sub-therapeutic or diet.

Mode of antibiotic residues and their occurrences in food: The advent of veterinary antibiotics, which began shortly after the treatment of antibiotics for several human bacterial infections, may be traced to the indirect cause of food toxicity of the residues of antibiotics [19]. Antibiotics are mainly used for rearing disease-free animals that are used for food products and byproducts. Indeed, the utilization of antibiotics have become essential for the treatment against diseases namely mastitis, respiratory diseases, arthritis, gastrointestinal infections, as well as other forms of infectious bacterial diseases [4].

More recently, highly promising and improved yields have been shown by antibiotic use, especially in fatteners and broilers. Indeed, the enhancement of the growth rate of antibiotics often results in the following effects: thinning of the lining of the intestinal mucosal membrane, which is necessary, in particular, in order to promote better absorption; alteration of the motility of intestine, which is vital for improving assimilation; enhancement of production under favourable conditions for beneficial absorption; although only baby animals and poultry are receptive to the maintenance of antibiotic-mediated hygiene in most cases. This method is currently problematic since these feed additives are typically used in vast and small quantities and for very long stretches without permission, resulting in drug pollutants eating food obtained from animals. The handling of whole classes of livestock, such as chickens, fish or other species, is a common practice for livestock farmers, even if there are only a few infected individuals. This process unintentionally and inappropriately exposes stable individuals to antibiotics. Furthermore in order to avoid infections, many animal producers utilize sub-therapeutic doses on antibiotics, which led to entry of antibiotic residues into human food chain. Sometimes, viral infections, which are not responsive to such drugs/antibiotics also incorrectly administered. Both approved antibiotics are supposed to be used by animals. The harmful residual effects of antibiotics can be minimized with withdrawal periods for the drugs. This period is very essential to minimize and safeguard the human from antibiotics exposure in food substances [20].

The smaller intestines of chickens are fed with antibiotics, 30-50% less in weight compared with chicks not administered for antibiotics. Slimmer intestinal walls followed by shorter spans of the intestines and variations in histology contribute to narrower intestines. In addition, chicks raised under the administration of antibiotic controlled condition displayed intestinal characteristics equal to those of antibiotic-treated chicks. Antibiotics also altered the intestinal mucosa bacterial populations, allowing the development capacity observed in gnotobiotic birds to be approached by antibiotic-fed chicks. On the other hand, antibiotics like tetracyclines have similarity in their structural and it is difficult to quantify and identify their residues in the complex food matrix. In such cases an additional confirmatory analysis is essential to eliminate the false positive detection [21].

It is inevitable for residues to exist. Residues tend to emerge prominently based on the following conditions: lack on adherence over withdrawal dates, additional labelling use/inappropriate usage, lack of appropriate knowledge pertaining with withdrawal periods over medications usage from extra-label mode and also with regards to presently available analytical tools for evaluation/monitoring of residues that are much more sensitive compared with their application primarily for gaining clearances [22]. Predominantly this results in the occurrences of increased traces of antibiotic/antimicrobial residues; alongside with occurrence of certain violative residues somewhat less often, however in large traces. The highest propensity for violative antibiotic residues is typically displayed by cattle. In developing nations, the likelihood of residue from milk is greater compared to developed nations. This can be attributed

to the absence of testing facilities and regulatory bodies which regulate the number of drug residues from foods in terms from maximum residue limits [MRLs] [23]. MRL is categorized as being legally allowed or approved as permissible in or on fruit, agricultural product or animal feed, which results from the registered usage over agricultural/veterinary chemicals which poses to be the highest prescribed forms of residual concentrations [16].

The biggest possible residue issue for Bob veal calves (under 150 pounds) is that these animals can be killed before medications can be reduced to appropriate levels. Cows may also be an effective source of residue, as livestock with poor performance or chronic health conditions can be killed before drug withdrawal occurs. Regardless of species, all animals that are culled from herds face residue problems. Residues of sulfonamide face concerns close to those of antibiotics [24].

Several antibiotic classes like teteracyclines, aminoglycosides, sulphonamides, *etc.* are used extensively in majority of the food producing animals. Though they are used for disease prevention and growth promotion its utilization must always be monitored and regulated. Antibiotic residues pose a serious threat in the environment as significant amount of drug is released in the environment during the manufacturing process and other proportion through animal excrete. Monitoring of the antibiotic residues through proper detection methods is always necessary to protect the health of consumers and minimize the environmental contaminations [25]. Likewise, transfer of antibiotic resistant bacteria to humans is one of the major unde-sirable effects of antibiotics. The assessment of risk-benefit ratio is very important and it has to be done before the use of drug in living organisms [26]. A brief details of the analysis of different antibiotic residues in various kinds of food products are given in Table-1.

Conventional approaches on screening: It is appropriate, on the basis of the definition set out in the EC/2002/657 2002 Commission Decision to assign screening techniques concerned to the processes used to diagnose the presence of the analyte or to assess the type of analyte by reference to the degree of significance involved. Such strategies tend to illustrate the ability to sample a much larger sample throughout and are very much used to shift through the larger sample. Thus, it is important to evaluate the methodology or process involved in sample analysis for the screening of any specific target of interest. The goal of evaluating the presence/absence of antibiotic residue requires many approaches. Solvent extraction or solid phase extraction are commonly used approaches in the detection of antibiotic residues. Both quantitative and qualitative analysis of antibiotic residues in various food matrices requires simple, fast and inexpensive extraction and detection methods [51]. Of which, biosensors are considered to be the accurate and quicker, well-suited method used to evaluate antibiotic residues from food. The first approach used for sample analysis is the screening method, intending to evaluate the presence or absence of antibiotic residues. The screening approaches or methods can be generally categorized into traditional as well as creative methods involved to be even more precise. The former is considered to be the oldest conventional method-related technique, and the latter's innovative methods discuss the methodology governing the implementation of emerging technology with novel bio-recognition/detection components. The above method, which involves the creation and use of biosensors and in the evaluation of residues of antibodies in foods, is discussed in this article.

TABLE-1
ANTIBIOTIC RESIDUES IN DIFFERENT FOOD PRODUCTS

Antibiotic	Food product	Ref.
Chloramphenicol	Chicken	[27]
Ciprofloxacin and other drugs	Chicken	[28]
Chloramphenicol	Eggs	[29]
Tetracyclines, β-lactams, aminoglycosides and macrolides	Eggs	[30]
Doxycycline, tilmicosin, cloxacillin and ceftiofur	Poultry muscle	[31]
Enrofloxacin	Liver-poultry, Liver-cattle, Liver-sheep	[32]
Gentamicin, streptomycin, penicillin	Milk	[33]
Minocycline	Porcine muscle	[34]
Penicillin	Milk	[35]
Quinolone, enrofloxacin and tetracycline	Chicken, Beef	[36]
Quinolone, sulphonamides, tetracycline	Milk	[37]
Quinolones tetracyclines	Animal-derived foods	[38]
Sulfapyridine, sulfamethoxazole, lincomycin flumequine	Milk	[39]
Tetracycline	Eggs	[40]
Tetracycline	Fresh meat (Cattle tissue; Triceps muscle; Gluteal muscle; Diaphragm; Kidney; Liver)	[41]
Tetracycline	Milk	[42]
Tetracyclines	Eggs	[43]
Tetracyclines	Milk	[44]
Ciprofloxacin, streptomycin, sulphanilamide, tetracycline	Raw meat	[45]
Tetracyclines	Chicken meat	[46]
β-Lactams	Cattle meats	[47]
β-Lactams	Eggs	[48]
Ceftiofur	Ground turkey meat	[49]
Peptide antibiotics	Milk	[50]

Receptor based screening methods combined with various labelling techniques like quantum dots can increase the scope of multi-residue detection in food samples [52].

In many fields, such as the food industry, there is an increasing necessitation for developing biosensors with higher selectivity and reliability, and for rendering quick, easy and followed by inexpensive monitoring. This involves screening wider array of molecules that supersede disadvantages pertaining to traditional approaches. Biosensors met each criteria, involving speed, low cost, reliability, and moderate value over money which is quickly deployed by comparatively untrained workers. The first publications date from 1980 to 1990 for the identification of antibiotic residues in food [53]. It is time to discuss an up-to-date, systematic analysis of important observations of receptors/transducers over the decade [54]. This covers major advancements in the design and manufacturing of antibiotic residue detection biosensors for various food products (milk, beef, chicken, honey and sea foods). The optical, mass-sensitive and electrochemical methods are the three main methods used in the signal transducing mechanism and each methods has its own advantages and disadvantages. Incorporation of nanomaterials in the construction of electrochemical biosensors has wide range of quantitative and qualitative approaches. Silver nanoparticle is one such examples where it is used in commercial antibiotic kits and biosensors to enhance the rapid response and sensitivity [55]. A description of the various types of receptors used to detect veterinary drugs is given in the present article. While the first receptors to be used were antibodies, modern types of receptors are being gradually created and used for the production of biosensors. Often discussed are the various forms of transducers and their possible veterinary drug screening applications in food. In this report, the advan-tages and disadvantages of the various receptors and transducer forms are discussed. Finally, it highlights the future of veterinary drug regulation in foodstuffs and subsequent biosensor production.

Immunosensors: For the identification of antibiotic residues in milk, the largest biosensor group focuses on strengthening the immunochemical biorecognition reactions. The electrochemical and optical ones are the most commonly used immunosensors, the latter being prominently surface plasmon resonance (SPR) biosensor. While immunosensors appeared to be highly selective, and also examination speed depends on time needed for incubation of complex formed of antigen/antibody. Fully reviving the device can also be quite a moment in contrast.

Gaudin *et al.* [56] developed a surface plasmon resonance (SPR) biosensor on basis of commercially developed antibody anti-ampicillin (AMP) exhibiting far higher affinity for β-lactam (open rings) than for closed ones for the detection of β-L residues in milk. The chemical pre-treatment and post enzymatic treatment application allowed detection limits on AMP for 33 and 12.5 μg/L, respectively. Zhang *et al.* [57] identified a further SPR immunosensor for the AMP analysis. This assay involves with competitive binding that blended with monoclonal anti-AMP antibodies between the AMP that immobilizes covalently on sensor surface and AMP-in sample mixture. The sensor detected a number of free antibodies bound to the sensor's surface after the milk sample was injected. The limit for AMP detection was 2.5 μg/L with this sensor.

Fernandez *et al.* [58] suggested portable SPR for determination of fluoroquinolone ciprofloxacin, enrofloxacin and norfloxacin from milk. In simultaneous detection involving three antibiotic groups (sulfonamides, fluoroquinolones and phenols), with previous version involving portable SPR developed [59]. Similarly, competitive assay oriented format was built on the sensor. ENrofloxacin (ENRO) concentration limits were 1.7 μg/L, 2.1 μg/L of chloramphenicol (CAP) and 1.1 μg/L of sulfapyridine (SPY). By integrating seven different basic immunoassays, antibiotic recognition was performed on a sensor chip, which particularly functions based on inhibition of competitive antibody binding. If diluted milk samples were used 10 times, immunosensor demonstrated ppb level (μg/L) immunity over target components. Ferguson *et al.* [60] have suggested an SPR immunosensor on CAP residues of milk, also built as linking assay method. With this assay, the limit of detection of CAP of milk was very limited: 0.05 μg/L. Haasnoot *et al.* [61] evaluated both competitive as well as direct binding of SPR immunoassays on milk based on monoclonal anti-dihydro STR antibodies for STR (streptomycin screening) residues. For both the direct and competitive binding assays, the maximum detection for STR was 20 μg/L. Ferguson *et al.* [60] have released one more active STR immunosensor, using commercial Qflex™ antibodies. This assay made it possible to measure STRs in whole bovine milk at concentrations of 30 μg/L (3.5% fat content).

Knecht *et al.* [62] who proposed a parallel affinity immunosensor array (PASA) employing multi-analyte based assays incorporating indirect competitive ELISA study on 10 distinct antibiotics screened from milk samples. In order to prepare disposable microarrays, Hapten was then conjugated with several other antibiotics and was mounted on the modified grade of microscopic slides. The concurrent identification of individual analytes has been made possible by special monoclonal antibodies against each antibiotic. A secondary antibody, called HRP (horseradish peroxidise), which induces improved chemiluminescence, was observed for antibody binding. The thresholds for identification ranged 0.12-32 μg/L. Kloth *et al.* [63] proposed an improved PASA protocol, which also required 13 antibiotic residues in milk to be multiplexed for examination. Hapten-antibiotic conjugates have been combined with PEG (epoxy-activated polyethylene glycol) chip surfaces in these regenerable microarray chips. Simultaneous identification of 13 antibiotics was possible within 6 min in case of raw samples of milk similar with corresponding values of MRL.

Conzuelo *et al.* [64] who detects tetracyclines in milk, reported that disposable amperometric magneto immunosensor that employ polyclonal sheep anti-tetracycline antibody, which was immobilized on ProtG-MBs surface (protein G-functionalized magnetic beads) and SPCEs. Tetracycline tracking was achieved by directly binding for binding sites of captured antibodies between TC-HRP. The concentration limits on tetracycline estimated 8.9 μg/L, likewise oxytetracycline 1.2 μg/L, chlortetracycline 66.8 μg/L and doxycycline 0.7 μg/L. From the reports of Conzuelo *et al.* [65] suggested similar form of immunosensor for precise detection and quantification of sulfonamide

from milk residues. On the electrode surface, which involves with modification in 4-aminobenzoic acid, they utilized immobilized polyclonal rabbit antibodies with the reported value was 0.15 µg/L. The immobilized antibodies on surface on protein G-modified carbon plates based on immunoassay direct competitive on SPY determination. The detection limit for this immunosensor at a comparable dosage was 0.13 µg/L for SPY.

For fluroquinolones (FQs), tetracyclines (TCs), β-lactam antibodies (β-Ls) and wavelength interrogated optical sensor (WIOS) technology employed to develop biosensors. In 2009, Suarez *et al.* [66] identified competitive immunosensor on concomitant detection of three antibiotics-sulfapyridine (SPY), oxytetracycline (OTC) and ciprofloxacin (CIP) for raw milk. For indirect formats involving three different haptens, were subjected for experimentation. Multiple antiserum receptors in turn interacted specifically with different antibiotics which were further spiked upon presence of three different antibiotics at corresponding MRLs in ranges of 100 µg/mL that were in combination on raw milk samples. Excessive traces of antibodies which were not bounded with antibiotics were captured on sensing area (hapten-coated) during interaction with the sensing surface. The antibodies attached revealed from secondary antibody. WIOS immunosensors for sulfonamides identification and simultaneous sulfonamides screening and the other prominent classes antibiotics was developed by Adrian *et al.* [67] involving FQs, TCs and β-Ls. Sedimentation Event Sensor (SES) depended on competitive format in of immunoassay, of which SAs, β-Ls, FQs, haptenized proteins and TCs were then immobilized to chip surface forming various sensing zones. Milk extracts were combined and the bio-receptors were applied with special antibodies. For SES sensors, the detection limit was 0.5 µg/L for SPY, CIP: 1.3 µg/L, AMP: 3.1 µg/L followed by OTC: 34.2 µg/L.

With regards to CIP concentrations ranges as minimal as 10 pg/mL, the antibody/antigen affinity reaction contributed over unusually responsive as well as impedance response stability. For direct detection with regards to penicillin G residues in milk samples was achieved *via* immobilized forms of monoclonal anti-penicillin over self-assembled gold electrode monolayer thioctic acid, wherein flow injection impedimetric immuno-sensor developed as an effective approach as reported by Thavarungkul *et al.* [68]. The impedance is increased by combination with penicillin G (PEN) with anti-PEN to region of electrode side. As maximal detection achieved reported 1 pg/L for this immunosensor, which was significantly lower when on comparison with corresponding milk MRL, however for sensor preparation usually takes about two days.

The amperometric immunoassay developed by Merola *et al.* [69] for penicillin G (PEN) in milk. This immunosensor particularly was based on competitive binding on anti-PEN-biotin-avidin-peroxidase complex by the free BSA-PEN and conjugates of PEN immobilized with that of the sensor membrane. For that immunosensor, the detection limit was as low as 5 mg/L. Wu *et al.* [70] also documented another amperometric immunosensor in milk for PEN. The association between PEN and the traditional methylene blue covalently bound and HRP-PEN-Ab, on glass carbon electrode was based on this biosensor. Impedance spectroscopy and cyclic voltammetry made it possible to meet the detection limit of 0.6 µg/L. Pinacho *et al.* [71] reported the electrochemical magneto immunosensor for the identification of CIP. The technique involves the attachment of antibody-modified CIP (Ab171) and HRP-BSA and collected by magnetic electrode on the post-incubation of samples followed by electrochemical oxidation of H_2O_2 aided with HRP catalyzed reaction. CIP in limits of 9 ng/L detection limit appeared nearly poor as obtained in the resultant literature sources.

Jiang *et al.* [72] developed a nanogold RS (resonance-scattering) spectral test for PEN determination. Binding of PEN with anti-PEN, results in immobilization to gold nanoparticles surface, which further leads to cleavage of nanoparticles. Upon exposure, the nanoparticles aggregate, thus exhibiting residual presence of PEN, forming effect of resonance scattering evaluated at 560 nm. Quantifying a total rage of 0.78 µg/L, which was observed the maximum range determined from assay detection. Another immunosensor for kanamycin (KAN) detection in milk. Using nanoparticles of SPIO (superparamagnetic iron oxide), this sensor functions with a shift due to magnetic stimulation. Here, KAN being the target analyte competes with SPIO nanoparticles surface. This results with immobilized KAN, which subsequently hindered production of SPIO aggregates. The spin-spin relaxation time (T2) of the neighbouring water molecules, which differs as a consequence of target analyte and its effect, which further then modulated by the dispersed and aggregated SPIO states. The detection limit for KAN with this biosensor was 0.1 µg/L.

Karaseva *et al.* [73] have developed piezoelectric immunosensors to detect ampicillin (AMP), penicillin G (PEN) and the full penicillin G antibiotic residues. Through immobilization of PEN-/AMP-hapten based protein conjugates from the poly-pyrrole film *via* glutaraldehyde, wherein the receptor serves as adhesive for the sensors, which were formulated in accor-dance to their piezoelectric nature. The concentration limits obtained for PEN, AMP and PEN in ranges of 0.8 µg/L; 3.9 and 1.7 µg/L, respectively. Similarly, Kivirand *et al.* [74] reported the rapid identification of PEN residues from milk. Further-more, SAW (surface acoustic wave) based biosensor which involves with binding inhibition assay on sensor surface along-side with monoclonal anti-PEN contact *via* PEN residues presence in sample and thereby PEN epitopes were then immobilized. In case of binding of sensor's surface by antibodies was further then accompanied with acoustic (gravimetric) detection. Low levels of PEN have resulted in a greater binding load on the surface of free Abs and therefore results in production of strong signals. The identity limit was 2.2 µg/L for PEN in lower-fat milk.

Antibodies: Antigens are the bio-receptors utilized extensively in biosensor growth. In an extremely accurate way, antibodies correspond to a particular antigen. For biosensors, they usually are immobilized to substrate, which attributes as detector surface. These antibodies basically depend on selective properties followed by their mode of synthesis, likely monoclonal, polyclonal/recombinant. Application of conventional immunization protocols, polyclonal antibodies are made, especially in goats, rabbits, pigs, and dogs. In conjunction with

piezoelectric transducing materials, immunosensors dependent on antibodies, whether electrochemical or optical, are also defined [75]. In many areas of research, antibodies are the most widely used receptors for biosensor growth, especially for antibiotic residual screening. Different antibiotic antibodies followed by numerous forms of veterinary medications available on a commercial basis. Enzymes, usually used to act as markers rather than features of biorecognition as well, are part of biorecognition. Enzyme-based biosensors are primarily *via* two way detection mechanisms. The first approach/way concerns with catalytic transfer (usually from a shape that lies in undetected form to detectable form) of an analyte. Second approach involves analyte's determination that impede or otherwise moderates enzymatic activity. For catalytic production and detection on drug residues, enzymatic biosensors use various enzymes which are then precisely measured using transducer (optical or electrochemical). Today's most popular enzymatic biosensor is the blood glucose detection biosensor. To detect penicillin G, an enzyme based biosensor has been developed by Kiran & Kale [76]. Penicillinase produced as a result of transformed (*E. coli* JM109) bacteria was further then immobilized to pH meter electrode. No extension on this biosensor to more complex food matrices has taken place. Recent developments in the molecular detection technology have paved way in the identification of aminoglycoside antibiotics by using nucleic acid aptamers as recognition molecules. Aminoglycoside antibiotics are commonly found in animal derived food products and onsite detection is necessary. The use of aptamers has several advantages such as selectivity, specificity and is inexpensive [77].

Electrochemical biosensors: In several fields, electrochemical biosensors have been taken into accounts, *e.g.* disease control, food protection, environmental sustainability and importantly for biomedical uses [78,79]. In the field of electrochemical biosensors, because of their peculiar electrical and chemical properties, nanomaterials have gained considerable interest as a means of achieving improved performance. Also deploying nanomaterials could potentially increase response speed, susceptibility and selectivity for fulfilling requirements for contaminant detection on tested food samples, qualitative aspects [80,81]. Countless nanomaterials were employed for identification of antimicrobial based residues from that of animal derived foods, most significantly involving with application of Si, C, Me nanoparticles and other forms of functionalized nanoparticles. For identification on antibiotic residues from animal based foods, biosensors employ aptamer for identifying factor, which were subjected for application on a wider range. From recent development in the manufacture of electrochemical biosensors to identify the most commonly used antimicrobial drugs is illustrated.

The basic theory underlying electrochemical based biosensors involves with production of chemical reactions that comprises with the absorption of ions/electrons which subsequently influence observable electrical properties exhibited by solution, like electrical currents/potential, between immobilized biomolecules and target analytes [82,83]. Immobilization from electrochemical transduction agent such as an electrode *via* a biochemical receptor (like membrane/receptive surface or enzyme). Technology for electrochemical sensing started in the early 1950s. For the conversion of chemical information into a visible electric signal, there exist various electrochemical biosensors types [82,83].

Pencil graphite electrode modified with silver nanoparticles and reduced graphene oxide is used as an electrochemical biosensor in the detection of sulfadimethoxine antibiotics in meat products. Accuracy, reproducibility, stability and good range of selectivity was observed in this kind of aptasensor. This electrochemical biosensors exhibit good recovery ranges in meat samples with adequate sensitivity, thus aids in safety monitoring of food products [84]. Inclusion of carbon nanostructures and various other nanoparticles in the fabrication of electrochemical biosensors are the recent attraction to many researchers working to improve the response speed of detection. Biosensors incorporated with carbon nanotubes have enhanced chemical stability, electron transfer and mechanical strength. Likewise, carbon black and carbon dots are also used in the fabrication of electrochemical sensors to increase its conductivity [85].

Optical biosensors: As specific analytes bind to molecular receptors, the optical sensor is based upon a change in optical properties. There exists numerous array on subclasses on basis of individualized optical principles are included in optical based detection. Classical fluorescence as well as Time Resolved Fluoro Immuno Assay (TR-FIA), since 1990, numerous methods have been developed with the use of classical principle on fluorescence detection for antibiotic residues presence in milk namely: aminoglycosides [86], sulfadimethoxine from milk [87] and from tap water and milk [88]. Technology known as time-resolved fluoroimmunoassay (TR-FIA) developed various scree-ning processes that employs veterinary antibiotic residues (antibiotics, coccidiostats) [89-93]. Techniques can be used to identify particular antibiotic (*e.g.* chloramphenicol) and in various antibiotics group (*e.g.* fluoroquinolones). These biosensors functions *via* multiplexing technologies based on fluorescence detection. The fluorescence-based multiplex biosensor was generated by Chen *et al.* [94] for the detection of antibiotic traces in the chicken, liver and porcine muscle. The microarray was printed out of the modified glass chip at different positions. The experiment was conducted for screening and quantification of over eight different antibiotics from six samples within an overall duration of 3 h, with a slightly lesser degree of sample quantity, when on comparison to conventional ELISA approaches.

Surface plasmon resonance (SPR) based biosensors: Analyzing biomolecular behaviour remains as a contemporary form of optical analysis technology which employs biosensor. In 1990, Biacore Co. launched its first device which was commercially available. The BIA-core contains the findings of the sensor-chip, SPR detector, microfluidic chuck, control based program, and evaluation test. SPR-based optical sensors that functions *via* emitting specialized forms of electromagnetic waves for detection of surface based interactions [95]. It measures the variations in the surface of the liquid *via* determining refractive index *via* sensor chip and furthermore, the underlying variations appear relative to both the sensor chip' surface

and binding of biomolecule of mass. With mass changes from the sensor chip surface occurring during association/dissociation observed for biomolecular complexes, resulting in a transition of cause from the angle of the resonance position. With an intermolecular reactions analysis, which allows one of the reactants coupled with the sensor chip and another sample reactant to move through the sensor surface at a constant pace by a microfluidic chuck.

In addition, binding reactions between molecules can lead to a difference in the molecular concentration on the surface of the sensor chip; an SPR signal can quantify and perceive the difference as a resonance unit. In last two decades, applications of SPR-based biosensors have received considerable interest [96]. In real-time, these biosensors have been of greater utility with label-free surface techniques for molecular interaction tracking and inspection detection related to medical diagnostics, food protection, environmental monitoring and basic biological studies [97]. In the lipid membranes, the binding attributes on antimicrobial and antimicrobial agents calculated mainly *via* SPR-based biosensors. SPR-based biosensors are usually devices used to analyze the antibiotics-containing samples. In multiple animal tissues, such as β-lactamase, sulfonamides, aminoglycosides, and tetracyclines, these assays have been commonly used to test many types of antibiotics [98]. SPR-based biosensors are less stable with just one interaction measuring channel usable, instead of 2-8 based on various Biacore systems. Recently, in the technical advancement of the SPR method, which involved with the SPR sensing on the analytical applications is hindered *via* reduced performance on the complex samples, which could be attributed as serious limitations. In particular, however, SPR-based systems remain big, costly pieces of equipment, so it is important to formulate an acceptable strategy for the manufacture of a cost-effective biosensor for its disposal.

Diffractive optics technology (DOT): DOT integrates the format of multiplex immunoassay under real time observations that include protein-based interactions [99]. The photodiode, which can also be directly compared with that of the analyte concentration, measures the total magnitude of the diffraction order. A versatile trading framework is known as the dotLab® mX (Axela Biosensors, Canada) platform which, in turn, promotes the development of protein biomarker techniques and new methods of diagnostic testing [100]. In case of antibiotics, these devices could be adapted for screening for low molecular weight drugs. In such cases, there are no literary references that underline the device's screening of antibiotic residues.

Chemiluminescence immunoassay (CLIA): A bioreceptor (analyte) that happens to be specifically labelled with a chemiluminescent agent (*e.g.* luminol) covalently. Thus, light-emitting reactions appear to create a signal under the specified intensity (photons/s) by activating the luminescent symbol. Thus, it seemed to be relatively easy to quantify light intensity, so it only involves a photomultiplier/photodiode, along with related electronics that allow both conversion and recording signals. Most experiments were heterogeneous and so demanded isolation from the unbound mark. The assessments are much easier, but they are a little more complex to do. A homogeneous assay, however, requires a light emission reaction that has been compromised by some sort of association between the analyte and that of the bioreceptor. The chemiluminescence and bioluminescence technologies in numerous areas that effectively film contaminants *e.g.* bacterial contamination as well as other sources of inorganic environmental contaminants (heavy metals and their trace level/sample ranges derived from environment) were also reported from a thorough analysis [101]. There are two kinds of known chemiluminescent biosensors: intra-laboratory chemiluminescent biosensors and commercial chemilumine-scent biosensors.

Intra-laboratory chemiluminescent biosensors: In medicinal chemistry, environmental research and nutritional study, CLIA has various applications. A literature review identifies and examines advances from field on biosensors on basis of chemiluminescence detection which was then coupled alongside immunoassay based techniques [102]. These advancements further took place, for instance, in new luminescent markers development followed with enhancement by signal enhancers of 25 existing markers, as well as in the area of contact surfaces. The literature on food pollutants has documented reports governing with intra-laboratory based immunoassays (chemiluminescence-dependent) [103-105].

Commercial chemiluminescent biosensors: Since biosensors developed primarily for screening purpose on detection of antibiotic residues, there are only two types of commercial chemiluminescence. MCR 3 developed by research group which employed its application for screening against antibiotic residues from milk [63] and also honey [106], was commercially applied, as the biochip based semiautomated system aids for carrying out majorly for forensic and veterinary investigations [107]. Evaluation of several reported antibiotic residue screening kits in honey, muscle and aquaculture products [108-110]. A type of luminescence and the emission of 'cold light' by luminescent bacteria is bioluminescence. The luminescence gap may be affected by a luciferase enzyme that is programmed by lux gene simultaneously after the target analyte's response, indicating a dose-dependent interaction. In microorganisms, the Lux gene expression can either be constitutively/inducible regulated. The developed strains are in accordance to transcriptional response reporters using bioluminescence genes (lux). In the presence of specific molecules, light production increases. Conversely, like *Vibrio fischeri*, there are typically bioluminescent bacteria. In this case, the contaminant's presence tends to inhibit bacterial development, resulting in the reduced light production. The literature has identified biosensors based on application involving luminescent bacteria developed to screen several antibiotics from sample [111,112].

Microbial biosensors: Bioluminescence can be used as one of the most common approaches, where bioluminescence is a type of luminescence which can otherwise be referred to as 'cold light' pollution if various microbial species are used as an efficient biosensor for deciding antibiotics. This difference in luminescence may be triggered by the encoded luciferase enzyme which utilizes lux gene, which subsequently expresses based on a dose-dependent relationship reaction

TABLE-2
MICROBIAL BIOSENSORS EMPLOYED FOR SCREENING ANTIBIOTIC RESIDUES FROM MILK

Biosensor assay	Antibiotic res.	Bio-selective element	LOD	Principle of detection	Antibiotic residues	Ref.
Electrochemical assay	AMP, diCLOX, PEN, CLOX, OXA	*Bacillus stearothermophilus* var. *calidolactis*	~ 120 min	MRL level	CO_2 detection (microbial growth inhibition)	[113]
	CIPRO, CTC, DAN, ENRO, FLU, MAR, NALA, NOR, OTC, TC	*Escherichia coli*	≤ 25 µg/L	CO_2 detection (Evaluating growth inhibition of microbes)	OTC, TC, CTC, ENRO, MAR, NALA, CIPRO, DAN, FLU, NOR,	[114]
Iodometric assay	AMOX, AMP, CEFL, CFZ, CLOX, PEN	*Bacillus cereus*	AMOX, CLOX, AMP, PEN ≥ 100 mg/L; CFZ, CEFL 2.5-1000 mg/L	Detection *via* colour change	PEN, AMP, CLOX, AMOX, CEFL, CFZ	[117]

acquired by the target analyte based on the residual presence. This expression of lux gene could, in its essence, be regulated by microorganisms either constitutively or even inducibly. Bacterial strains, on the other hand, can be assembled from transcriptional responses using the bioluminescence gene (lux) in reporter types. In contrast, the mechanism regulated by light output reflects an improvement in the total existence of a given substance. Conversely, there are many groups of bacteria that are naturally bioluminescent, including *Vibrio fischeri*. In this case, as the presence of a contaminant inhibits the growth of bacteria, the production of light continues to decline.

To recognize antibiotic residues presence in case of milk sample was succeeded based on their application involving enzymatic behaviour exhibited by microorganisms, as there are a few biosensors designed in accordance to their characteristic nature [113,114]. The β-L regulation mechanisms are based on concepts similar to those of microbiological inhibition studies [115], with quantitative or semi-quantitative identification of the bio-recognition reaction signal. Due to the lack of antibiotics, microbial biosensors depend on the calculation of bacterial growth inhibition [116].

Ferrini *et al.* [113] performed an investigation involving a hybrid biosensor, which borrows the classic microbiological screening technique for antibacterial displaying electrochemical recognition and antibacterial reading. *Bacillus stearothermophilus* var., if this particular process is considered. As a research microorganism, *Calidolactis* was used and furthermore the growth control was determined electrochemically by measuring emitted volume of CO_2. The participation *via* such microbial inhibitors (involving antibiotics) presence in milk sample facilitates in prohibiting the need for microbial inhibitors in the test strain, thus decreasing the overall rate of CO_2 growth. Compared with a controlled milk sample, this difference in CO_2 output was reported during the initial 120 min. The limits of detection were at the levels of MRL. *Bacillus cereus* assay, a recent analysis involving a microbial sensor, was based on the β-lactamatic effect and uses iodine for the reaction predictor as suggested by Das *et al.* [117]. This method includes checking for their selectivity under varied β-Ls as well as for other antibiotics. In the absence of antibiotics in the food sample produced, the crops remain the same with no change in colour in the case of the ampoules examined, which, in turn, suggests the specific development necessary for the enzyme by microorganisms appeared to be lower than the appropriate amount, such that the mixture of starch iodine for the food sample could not be decreased. In the existence of traces of antibiotics in the sample examined, the biosensor undergoes a shift in colouration which was observed over a median period of 15-25 min. In addition, β-Ls below 100 mg/L were inhibited by *B. cereus*, which, on the other hand, should be much higher than approved MRL values in the case of β-Ls. They found that inhibitions varied from 2.5 to 1000 mg/L at very high doses, taking into account other forms of antibiotics and their tests, indicating a lower degree of system sensitivity. For the determination of antibiotic residues in milk, a condensed outline of microbial based biosensors is provided in Table-2.

Conclusion

The antimicrobial resistance bacteria and antimicrobial resistance genes are the serious global challenges and can be carried away *via* transportation to various nations. Similarly, antibiotic residues in food substances are also a serious concern to humans as well as environment. Usage of antibiotics to food animals must be strictly scrutinized and adequate holding period should be observed. Though detection of antibiotic residues in various food matrices seems to be complex, with the advent of biosensors its complexity has been reduced. Various biosensors incorporated with nanostructures and nanoparticles have wide range of industrial applications. Single step detection, sensitivity, selectivity are enhanced with the fabrication of biosensors with nanostructures and have opened a new area for scientific researchers. Appropriate use of antibiotics and accurate quantification of antibiotic residues in food products must go hand in hand to safeguard humans from increasing health concerns due to antibiotic residues.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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