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Monitoring of drug resistance towards reducing the toxicity of pharmaceutical compounds: Past, present and future

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Highlights

- Various types of rapid and sensitive techniques for the screening of drug resistance were discussed.
- The roles of nanomaterials on development of novel methods for the monitoring of drug resistance were presented.
- Key issues in the rapid detection of drug resistance was discused.

Abstract

Drug resistance is worldwide health care crisis which decrease drug efficacy and developing toxicities. Effective resistance detection techniques could alleviate treatment cost and mortality associated with this crisis. In this review, the conventional and modern analysis methods for monitoring of drug resistance are presented. Also, various types of emerging rapid and sensitive techniques including electrochemical, electrical, optical and nano-based methods for the screening of drug resistance were discussed. Applications of various methods for the sensitive and rapid detection of drug resistance are investigated. The review outlines existing key issues in the determination which must be overcome before any of these techniques becomes a feasible method for the rapid detection of drug resistance. In this review, the roles of nanomaterials on development of novel methods for the monitoring of drug resistance were presented. Also, limitations and challenges of conventional and modern methods were discussed.

Keywords; Drug resistance, bioanalysis, advanced nanomaterials, toxicity, pharmaceutical compounds.

1. Introduction

Drug resistance as an emerging health concern reducing the efficiency and potency of a drug to produce effective treatment of pathogenic microorganisms or cancer and decrease overall patient survival [1]. During the cancer invasion and metastasis, large number of failures in the chemotherapy is related with the resistance of tumor cells to anticancer agents [2]. Consequently, resistance to drugs led to many other problems including toxicity and huge costs for development of new drugs [3].

In contemporary clinical practice, resistance to anticancer drugs can only be detected after long treatment periods [3]. Various mechanisms including reduced influx or enhanced efflux of drug, drug detoxification, glutathione conjugation, disrupt in DNA repair introduced for resistance against some anticancer agents like cisplatin [4].

It is important to point out that resistant to anticancer agents already exists before of chemotherapy in about half of cancer cases [3]. Thus, diagnostic tests for drug resistance in individual prior to commencing treatment with chemotherapy agents are required to predict the efficacy of chemotherapy and avoid any toxicity in normal tissues [3].

Several *in vitro* test analysis methods have been developed to assessment of resistance or sensitivity [5-7]. Unfortunately, none of these prognostic tests have been recognized for routine

clinical diagnostics [5-7]. Therefore, novel methods should be used for the monitoring of drug resistance.

Resistance to antibiotics is another well-known problem in the treatment of infections, with alarming trend [8]. Management of bacterial infections related to antibiotic resistance is requiring intensive care units with large amounts of money, which impose substantial socioeconomic and healthcare burdens [8]. Also, the use of some antibiotics has various toxicities for patient, which can cause disorders and complications, depending on the dosage and duration of drug. According to estimations a large number of pathogenic bacteria are resistant to at least one antibiotic in both inherent or acquired resistance types [9]. The presence of antibiotic induces stress and SOS system in bacteria and subsequently upsurge the rate of mutation and resistance [10]. In addition to design new effective antibiotics to overcome drug resistant which is costly and time consuming, it is clear that development of new, and rapid, reliable tests are also desperately required to tackle the difficulties in traditional microbiological techniques. Existing detection methods for drug resistance require high period for analysis and are limited specificity in pathogen identification. In this review, the conventional analysis methods for the diagnosis of drug resistance are presented. Moreover, the role of emerging automated techniques including electrochemical, electrical, optical, and nanosensor and their pros and cons has been reviewed and the remaining challenges for future development were discussed.

2. Mechanisms and conventional methods towards monitoring of drug resistance:

Drug resistance is a major global concern in medicine and it happened in consequence of disease tolerant to pharmaceutical treatments. Resistance to antimicrobial and anticancer drugs compared to other drugs causes more challenging and life threading situations [2, 11-15].

Generally, drug resistance is divided into intrinsic or acquired types and is developed through different mechanisms including drug inactivation, drug target alternation, drug efflux, drug metabolism alteration, and cell death inhibition [2, 13, 16-19]. The early and accurate detection of drug resistance due to mentioned their mechanisms is required not only for therapeutic purposes but also to monitor the prevalence and epidemic speared of drug resistance in the community [20].

The conventional laboratory methods for drug resistance have been used for years. Phenotypic detection of antimicrobial resistance (AMR) traditionally was evaluated with antimicrobial tests [21]. These techniques are based on cultural methods includes drug susceptibility tests (DST) like disk diffusion, broth dilution, agar dilution, double disk synergy test (DDST) and gradient diffusion [22]. But, culture-based methods are time-consuming, inconclusive, requiring high technical skills for sample preparation and could have a high risk of exposure to contamination during tests [15, 23, 24].

The molecular-based laboratory tests for the detection of antimicrobial and anticancer drugs were used to overcome cultural methods' drawbacks. These traditional laboratory methods in drug resistance detection briefly includes but are not limited to these methods: Enzyme-linked immune-sorbent assay (ELISA), hybridization system, Polymerase chain reaction (PCR) assay, microarrays, Radioimmunoassay (RIA), Northern blot, western blot, mass spectrometry, and flow cytometry [11, 25-28].

ELISA is a traditional colorimetric method using poly or monoclonal antibodies [29]. The multiple steps and long incubation period were made it inaccurate and time-consuming method in the clinical analysis [30].

Hybridization system is one of the oldest techniques, based on nucleic acid detection. This method was replaced by recent PCR methods[20].

PCR technique was introduced by Kary Mullisres in 1980. This method application in drug resistance is the identification of involved DNA sequences in this phenomenon [22, 23, 31]. Simple PCR, Real-Time PCR (TaqMan Assay), Restriction fragment length polymorphism (RFLP) PCR and multiplex PCR are commonly used to detect genetic mutations leads to drug resistance. Hybridization system and different types of PCR were used in the genetic assessment of drug resistance [24, 32].

Simple PCR method base on agarose gel electrophoresis with three steps (DNA denaturation, annealing of primers and extension of DNA) needs trained laboratory technician and 6-8 hours analysis time [20, 31]. Other limitations of this method are the risk of contamination and false positive or negative results. Also, this method needs exact isolation of the work environment [33]. Unlike simple PCR method, Real-Time PCR determines the amount of genome. Besides, the real-time PCR is safer than simple PCR due to omitting of ethidium bromide. However, this method is expensive and need an expert operator [31, 34]. Multiplex PCR uses multiple primers to detect different target gens. Also, it is more accurate and reliable. But, the primer design and optimization tests for microbial species should be processed carefully by an expert technician [35]. RFLP PCR is another agarose gel-based method used for mutation analysis associated with drug resistance

[22]. This method could detect amplified forms of DNA and needs complex laboratory procedures [36]. The high risk of contamination in this method could limit its application like other fingerprinting techniques besides high expenses and long-time procedures [24, 33].

The other detection methods of drug resistance are microarray and Radioimmunoassay (RIA)[12, 37]. Microarray method used arranged DNA sequences in rows and each sequence is identified with its position [38]. Microarray method could analysis expression levels of several genes contributing to multidrug resistance [16, 39]. In this method, gene expression in cells could be evaluated by measurement of gene expression levels or their RNA products[40]. The RIA method was based on measurement of radiolabeled agents and traditionally was used for the monitoring of anticancer drug resistance [31, 37]. Both of these methods need a well-trained staff and complex instrumentations. High costs, long-time procedures, and accessibility for clinical situations are other drawbacks in these methods [25].

Northern blot and Western blot test are also used for drug resistance detection based on gel electrophoresis. RNA molecules were separated in Northern blot test whereas proteins were detected in Western blot analysis [41, 42]. Because of the instability of RNA molecules and slow detection procedures, sensitivity and reliability of Northern blot test are less than Western blot[43]. On the other hand, high expenses and time-consuming procedures lead to the reduction of these methods application in drug resistance detection [43, 44].

Generally, genomic-based methods in detection of specific resistance genes, which does not always indicate the existence of drug resistance phenomenon, are available only for limited defined genes participated in drug resistance [26, 29]. Also, in drug resistance, different mechanisms were

associated with different mutations in genes; therefore the lack of defined genomic process to detect new mutations causes false negative results [22].

Mass spectrometry is another analytical method, which detects cellular proteomes as an indicator of gene expression and metabolism [45]. This method is based on analysis of large molecules and mass spectral proteins [45]. Flow cytometry method is also based on the detection of proteins associated with drug resistance [31]. This method could detect the quantity of cellular fluorescent drug retention and fluorescent cellular markers involved in drug resistance [19]. The high risk of contamination, long time procedure, and high expenses are drawbacks of these methods like other mentioned methods [45].

Due to the importance of early detection of drug resistance and necessity of fast replaced accurate treatment in patients with resistant infections or cancers, the reliable and accurate detection methods should be developed for the analysis of drug resistance.

3. Electrochemical and Electrochemiluminescent (ECL) sensing

Electrochemical techniques have traditionally played a critical role for the development of biosensing devices because of their potential for achieving specific, sensitive and low-cost detection of biomolecules. A typical electrochemical biosensor is made from biological sensing molecules and a signal transformer. The potential difference between the electrode surface and electrolyte solution changes when the electrochemical reactions of the chemical elements in the base electrolyte solution changes. The ultimate change in the sensor's signal transforms into a

signal output related to the analyte concentration, which is then analyzed and displayed using a data acquisition and signal analysis system [46].

The multidrug resistance (MDR) is the main obstacle in cancer therapy, which renders the most of conventional chemotherapeutic drugs ineffective and for which there is currently no appropriate technique to screen it's *in vitro* activity. Therefore, diagnosis of MDR can facilitate the early diagnosis and effective treatment of tumors. One of the initial biggest challenges for development of effective biosensors in cancer detection is to design a low-cost and selective probe that can be applied to identify cancer cells. Han and co-workers proposed a label-free cytosensor based on the electrochemical impedance spectroscopy (EIS) and phage display technology for the recognition of cancer cells, without complicated purification prior to detection. This platform demonstrated high specificity for tumor diagnosis with a low limit of detection (79 cells mL^{-1}) [47]. The overexpression of transmembrane proteins such as P-glycoprotein (P-gp) and MDR-related protein 1 (MRP1) can confer MDR which are from a special family of 5′-triphosphate-binding cassette transporters. Although, the role of ATP-binding cassette transporters has been identified so far, there is no method available for *in situ* screening the resistance related to these transporters without interfering with normal cytoplasmic activities or metabolic environment. For this purpose, Kuss et al. proposed a scanning electrochemical microscopy (SECM) assay for the quantitative analysis of MRP1-mediated MDR at the single-cell level in patterned adenocarcinoma cervical cancer cells. In a SECM, the electrochemical current is recorded with high spatial and temporal resolution by scanning a microelectrode across a surface. Here, the redox mediator ferrocenemethanol ($FcCH_2OH$) was utilized to detect MRP1 activity in HeLa and HeLa-R cells based on its efficient

interaction with glutathione involved in MRP1-related transport. They demonstrated that there is a clear difference in electrochemical signal intensities between HeLa and HeLa-R cells [48]. Similarly, it was reported that the redox state of cancer cells can be affected by ferrocenemethanol and its oxidized form ($[FcCH_{(2)}OH]^{(+)}$). In this study, SECM technique confirmed the interaction between $FcCH_{(2)}OH$ and human cancer cells and investigated that the differential response to FcCH(2)OH in multidrug-resistant cells is in part due to MRP1's overexpression [49].

The relevant spectroscopic studies and electrochemical data have reported the selective binding behavior of tetrathiafulvalene (TTF) derivative (TTF-$(COONBu_4)_2$) with P-gp overexpressed on the plasma membranes of drug resistant leukemia cells. Zhang and co-workers have exhibited a multi-signal responsive strategy for distinguishability of relevant cancer cells using TTF derivative as a probe molecule and indium tin oxide electrode as a biosensing interface without the need for target amplification and labeling cells [50].

The types of tumor cells can also be classified according to the transporter activities in given cell membrane by directly characterizing the corresponding electrochemical behaviors of the daunorubicin residues as an electrochemical probe in the medium containing different cancer cells. This method suggests a novel strategy for diagnosis and sensing of MDR in cancers. Zhang et al. have designed a novel label-free strategy for early detection of the MDR in cancer cells by an electrochemical cytosensor through the supramolecular interaction between the carbon nanotubes modified glassy carbon electrodes and drug. Obtain results demonstrated that this sensing method can directly examine the function of transporters present in cell membranes, detect the cell phenotype in sensitive leukemia cells K562 and its MDR ones K562/A02 [51].

A wide variety of sensitive ECL assays have been fabricated for monitoring of nucleotide sequences and proteins, especially ECL sensing with tris (2, 2′-bipyridyl) ruthenium (ii) ($Ru(bpy)_3^{2+}$) in the presence of its derivatives as ECL indicators [52]. The techniques that allow detection of a single target are now very good to simultaneously measure the expression of P-gp in cells owing to the problems in obtaining single-cell protein and estimating the cell numbers. Therefore, another stably expressed protein, such as glyceraldehyde 3-phosphate dehydrogenase (GAPDH) or β-actin, was important to be applied in the available P-gp screening techniques as a control [53]. Therefore, a competitive method-based ECL assay with a single indicator was used to simultaneously determine the concentration of GAPDH and P-gp in cancer cells by converting these proteins to partially coincident nucleotide sequences using a sandwich type immunoassay on magnetic beads. The competitive nucleotide hybridization on the electrode surface was then detected to estimate the concentration ratio related to the ECL signals. This approach can be helpful to overcome the inevitable limitations from the cross reactions among the multiple ECL indicators [54].

At the present time, the alarming increase of MDR instantly threatens the efficiency of conventional antibiotics and requests the rapid clinical diagnosis method. It is necessary to design new point-of-care biosensors capable of differentiating between Gram-negative and Gram-positive bacteria, as well as quantifying molecular resistant markers in the different types of bacteria due to minimize infectious outbreaks. LIU's group have reported a rapid antimicrobial susceptibility testing (AST) technique based on an electrokinetic enhanced biosensor platform to directly determine the antibiotic resistance profile without prior purification which combines

electrochemical sensing of bacterial 16S rRNA and phenotypic bacterial growth under several antibiotic conditions [55]. In another study, a novel electrochemical biosensor was prepared for the marker-free screening and treatment of the drug-resistance gene blaNDM-1 (metallo-b-lactamase New Delhi metallo-b-lactamase-1 (blaNDM-1) in multidrug-resistant organisms (MDROs) in complex clinical specimens. In the present study, highly specific locked nucleic acid (LNA) -modified Au-electrodes were designed as working probes. This technique did not need DNA isolation or PCR amplification and allowed for the sensitive detection of drug resistance gene blaNDM-1 in MDROs where the limit of detection was about 1 pg L^{-1} [56]. Similarly, Obaje et al. fabricated a carbon impedimetric electrochemical sensor based on a ceramic substrate performing a low-cost detection of blaNDM, a major antimicrobial resistance concern in carbapenem-resistant Enterobacteriaceae. This proposed sensor was used as an EIS technique for detecting synthetic blaNDM targets with a low limit of detection 200 nM [57].

OXA type β-lactamases are commonly found in Gram negative bacteria, and their prevalence can confer resistance to β-lactam based antibiotics through cleavage of the active β-lactam motif. In this regard, a highly simplified potentiostat circuit, named SimpleStat, was developed to perform Differential Pulse Voltammetry measurements and to detect the presence of OXA-1 DNA sequences for oxacillin resistance using two electrode systems including polycrystalline Au electrodes and Au electrodes integrated onto the board. Here, the electrode surface was fabricated single stranded DNA probe monolayer due to specifically detection of the OXA-1 gene [58].

Most current detection technologies used for the identification of microbial pathogens in biological samples, like PCR and ELISA are generally time-consuming, expensive and require skilled

technicians. According to literatures review, electrochemical sensing of antibiotic resistance has been considered to be useful because of its high specificity and sensitivity, short analysis time and low limits of detection [59]. Electrochemical biosensors in combination with AST of the physiological samples may offer an excellent alternative to the conventional methods of bacterial infectious diseases diagnostics. ECL assay has a high potential for the simultaneous measurement of multiple biomarker proteins. However, recent data have indicated that cross reactions among different indicators is a major limitation for ECL assay [60].

4. Electrical sensing

Electrical sensing has been proven as a label-free, rapid, robust and easy-to-use method for a wide variety of biosensing applications like cell growth, necrosis pattern, and bacteria detection on the surface of the electrodes in various media [26, 31].

Cell-based impedance sensing has received a great deal of attention, suggesting a potential for the prediction of therapeutic outcomes in more detail using patient-derived cells/tissues as a basis. It is a probe free, highly sensitive, and versatile technology platform. In this regard, Real Time Cell Electronic Sensing (RT-CES) can provide additional information to select personalized anti-cancer medicine [61] . This strategy can be useful when applications of a certain drug require to be assessed on particular types of cancers, or on different stages of a cancer. In this regard, Audrey et al. developed a useful analytical approach using RT-CES for the monitoring of drug resistance against docetaxel, mitoxantrone, abiraterone acetate, sunitinib malate, and carboplatin in three

prostate cancer cell lines while no such resistance was detected by endpoint cell viability assays [61].

Taxanes are first- and second-line chemotherapeutic agents used to many human cancers. In the course of cancer therapy, hypersensitivity or resistance to one form of taxane can develop and patients may need a different class of taxane to rescue the pharmaceutical advantage of the drug. Currently, there is no validated technique for predicting tumor responses to taxanes before treatment or when hypersensitivity or resistance begins to develop. Hence, a recent attempt was made to design a quartz crystal microbalance biosensor due to study responses of human mammary epithelial tumor cells treated with taxanes and to predict therapy outcome prior to treatment. The remarkable shifts in frequency and resistance levels reflected apoptosis or resistance to taxanes [62].

During recent years, microfluidics has attracted a great attention in developing tools for cancer diagnosis. More importantly, microfluidic systems are potential candidates for *in vitro* experiments owing to their high capability to manipulate individual cells, and small number of cells required for each endpoint. This strategy can allow high content research and also help to handle scarce material derived from patients [63]. Currently, the development of a bio-functional model to measure cancer resistance *in vitro* is of great interest as a significant problem in clinical cancer treatment. Such versatile models need an acceptable simulation of drug diffusion and a microenvironment, allowing cell-matrix and cell-cell interactions. For this, Wang and co-workers built a bilayer hydrogel-based 3D microfluidic chip to address the problem of drug resistance of

different loci in tumor mass with the hydrogel acting as native extracellular matrices in which supports long-time cell proliferation and survival, metabolism of cancer drugs and also interaction between different types of cells. It was reported that both sensitive and resistant tumor cells cultured in the microenvironment respond differently to the drug and can be recognized under the same chemical environment [64]. A microfluidic platform was also fabricated based on the integration of microfluidics and electrical sensing modality in a 3D extra cellular matrix that enables screening drug susceptible cells, drug tolerant, and drug resistant cells in less than 12 h. Here, interdigitated Au electrodes were able to examine the change in the electrical response of cancer cells seeded in a 3D gel matrix through a dynamic delivery of chemotherapeutic drug next to the matrix [65].

Antibiotic resistance has been attempted to be resolved by the development of point-of-care platform technologies to rapidly detect pathogens, identify the right antibiotics, and make efficient therapeutic decisions. Notably, molecular sensing assays of target DNA and genetic mutations involved in drug resistance require profound professional knowledge about the genetic basis of antibiotic resistance found in target pathogenic bacteria [66, 67]. Staphylococcus aureus (*S. aureus*), a Gram-positive bacterium, is the major cause of a number of infections ranging from cellulitis to severe diseases like septicaemia and septic arthritis. Recently a chip sensor based on interdigitated electrodes was developed for rapid detection of *S. aureus* and its resistance to flucloxacillin in a cost effective manner [68]. In another study, a 3D microfluidic platform was fabricated based on the synthetic antimicrobial peptides (AMP)-coated microsensors with species-

specific binding capabilities due to detect multiple pathogens in less than 12 h [69]. Safavieh's group reported the ability of the plastic microchips involving interdigitated electrodes to selectively capture and isolate bacteria from whole blood using antibody and evaluated their electrical response against gentamicin antibiotic. This technology depends on the potential impact of antibiotics on the growth of captured microorganisms on-chip in different media [70]. A sensitive and simple technique was also proposed based on the electrochemical sensors and real-time sensing of a rolling-circle amplification for recognizing antibiotic resistance genes in different strains of β-lactamases [71].

Electrical sensing gives real-time kinetic data of the cell growth and necrosis pattern on the electrodes surface which is a simple, low-priced, label-free, rapid, and sensitive technique [72-74]. For rapidly and precisely monitor the cancer cells response to the different drugs, the combination of microfluidics and electrical biosensing modality in a 3D tumour microenvironment may provide a powerful platform [75].

Microfluidic systems can be promising candidates for the next generation of in vitro cancer models because of their ability of manipulating single cells, and decreased number of cells needed for each endpoint [76, 77].

5. Optical sensing

5. 1. Antibiotic susceptibility test:

Optical sensing process and imaging for evaluating antibiotic susceptibility detect changes in the cell morphology, size [78, 79] and cell number [80] in the presence of an antibiotic. Some methods

capture the growth of individual cells that attached to an inert surface [79, 81] but in some like oCelloScope method take pictures from a population of cells in liquid fluids [82].

Imaging tools provide rapid methods for antibiotic susceptibility test. The most important limitations of imaging-based antibiotic susceptibility test tools are that they are not appropriate for slowly-growing pathogens, such as Mycobacterium tuberculosis [83].

Multiplexed automated digital microscopy (MADM) developed to provide 1-hour identification and 5-hour antimicrobial susceptibility testing directly from patient samples. However, conventional antimicrobial susceptibility test longs 2 to 4 days. This rapid antimicrobial susceptibility test as opposed to the conventional method increases the chance of appropriate therapy as soon as possible and decreases the spread of MDR miroorganisms. In this method, at first clinical specimens are automatically run an agarose gel to separate sample impurities such as debrides and lysed blood cells. Then, the purified sample is pipetted into single flow cells of a multichannel test cassette. In this cassette, purified sample cells are immobilized via electrokinetic concentration. The top and bottom surface of each flow cell are coated with indium tin oxide and considered cell electrodes. Additionally, the bottom surface has a skin of poly L-lysine as capture layer. Applying a low voltage results in a negative charge on the purified cell sample, their migration toward the bottom surface, their capturing and immobilization. Then, immobilized cells are identified by fluorescence *in situ* hybridization (FISH) assay. A mixture of fluorescently labeled dyes, ATTO-532 (target probe, green) bind to rRNA of each identified targets and ATTO-647 (universal probe, red) binds for identifying bacterial or yeast targets from debrides, is added to flow cells. Images were captured from each flow cell by an epifluorescence dark field

microscope in at 532 nm and 647 nm. The target bacteria/yeast are identified after colocalization of universal and target probes. Furthermore, a universal nucleic acid stain is added to a separated flow cell to quantify the total number of organisms. Comparing the number of the presented organism in this later assay with the number of each labeled organism determine non-target microorganisms and polymicrobial samples. To evaluate antimicrobial susceptibility testing, antibiotic with a specific concentration in a Mueller Hinton agar is dispensed into flow cells with appropriate concentration of immobilized organisms. Mueller Hinton agar makes daughter cells from a progenitor cell be localized in a colon. A dark-field microscope and a camera take time-lapse pictures every 10 minutes from immobilized progenitor cells that are growing to daughter cells. Time-lapse images of each colon are compared with their first images and are used as a metric of growth of each clone. Minimum inhibitory concentration can be extracted from these data with special software. Susceptible clones lyse or their growth stopped where the resistance clones grow [81]. Furthermore, phenotypic resistance mechanisms can be detected by this technique [81, 84]. (Figure 1) [85]

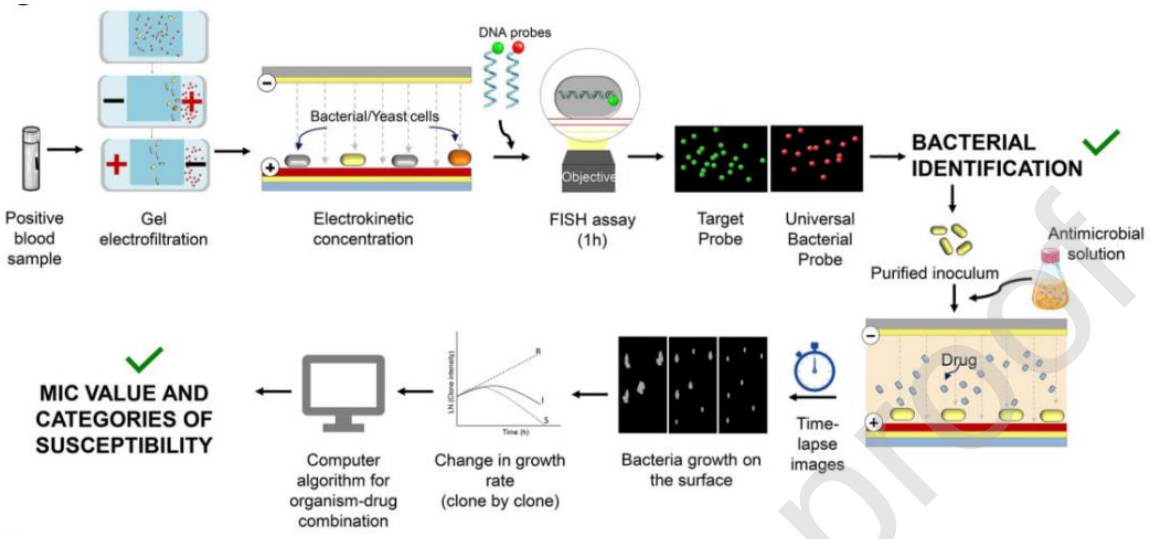

Figure 1. The basic principle of multiplexed automated digital microscopy. Adopted from [85] with permission.

Single-cell morphological analysis (SCMA) is the other rapid antimicrobial susceptibility test that the results are obtained in less than 4 hours. This assay utilizes a microfluidic agarose channel (MAC) system (figure 2). Cell bacteria is immobilized in the agar medium (1.5%) in the well inlet. The nutrients and various concentrations of different antibiotics in the liquid Mueller-Hinton-Broth (MHB) media are added to different wells of MAC system and diffused toward the bacterial well in MAC. The rate of this diffusion, <5 min, is less than the bacterial dividing times, about 20 min. The image of bacterial cells growing, in the region closest to the antibiotic well, was captured by time-lapse bright-field microscopy to monitor the change in the bacterial morphology. Each image field contains ten cell bacteria. Time-lapse imaging for AST continued 3 hours after drug administration for Gram-negative strains and 4 hours after drug administration for Gram-positive

strains. After time-lapse imaging, susceptibility determination and morphological pattern of single cells against antibiotics are classified to typical antibiotic-resistant in which the bacterial cells divided into two cells; typical antibiotic-susceptible condition in which the bacteria do not grow, filamentary or swelling formation may happen but the bacterial cells do not divide; and antibiotic-resistant condition in which filamentary or swelling formation coexist with the bacterial cell dividing. Swelling or filament formation is special for Gram-negative bacterial cells that are not considered as growth. So, bacterial area measuring method that evaluates the cell area in the images do not determine the correct MIC value in swelling or filamentary conditions. In the SCMA method for overcoming this problem, the antibiotic responses of bacteria are classified based on morphology and cell mass. This method compared with a bacterial area measuring method reduces antibiotic susceptibility test errors for both B-lactam and non-B-lactam antibiotics against Gram-negative strains *E. coli*, *P. aeruginosa,* and *K. pneumonia*. The results in comparison with gold standard broth microdilution test have 91.5% categorical agreement and less than 6.51% discrepancies [79].

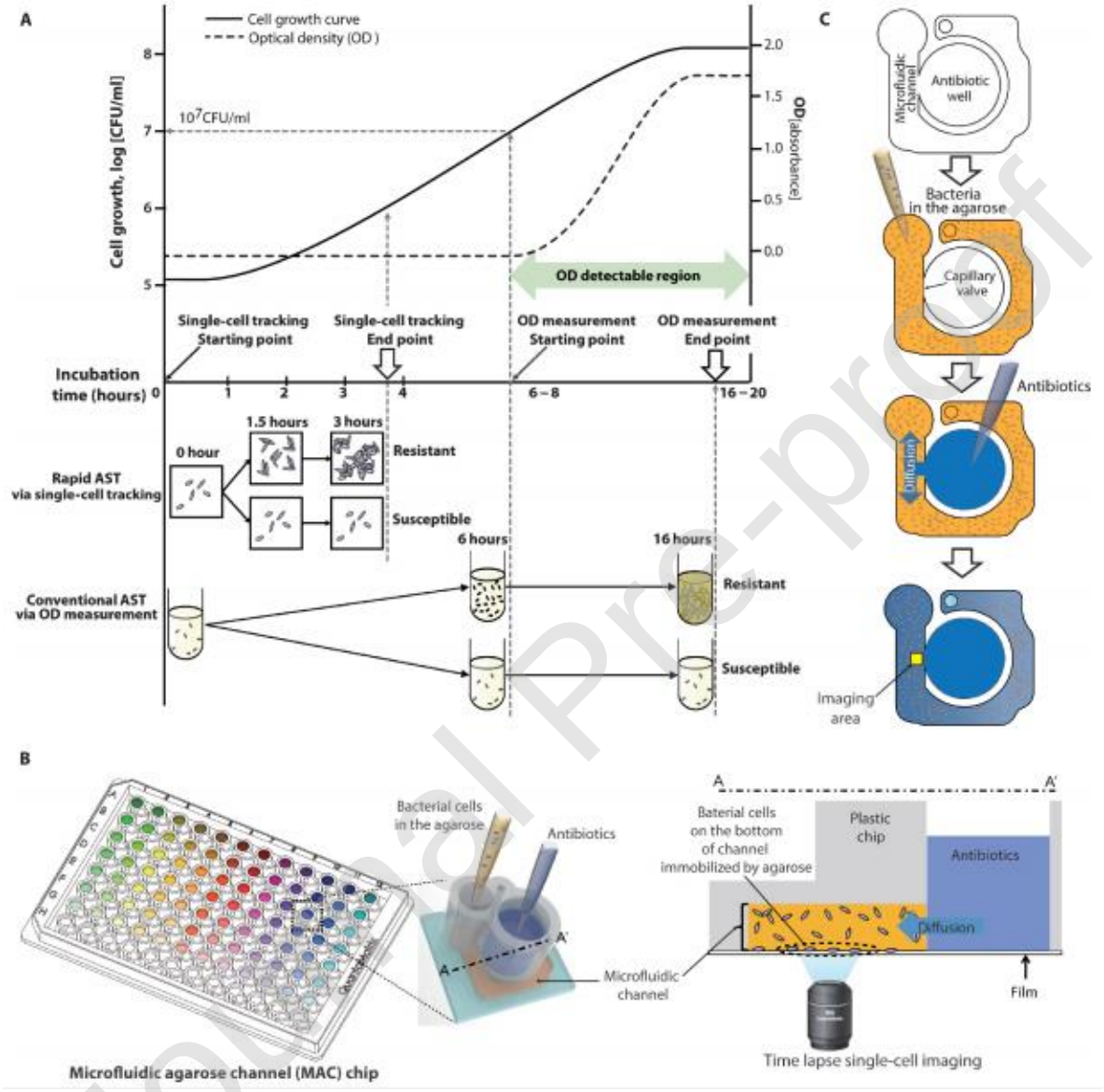

Figure 2. The rapid antibiotic susceptibility test uses single bacterial cell morphology tracking in microfluidic agarose channels. (A) Comparison of an antibiotic susceptibility test based on SCMA with the conventional method using OD measurements. (B) Schematic of the microfluidic agarose

channel (MAC) chip. (C) Experimental procedure for the MAC chip. Adapted from [79] with permission.

5.2. Anticancer resistance test:

Early diagnosis of drug resistance is crucially important to decrease healthcare costs and improve public health. Nowadays, positron emission tomography (PET) is used to diagnosis of cancer drug resistance when cancer therapy has been started [86]. However, it could not distinguish between intrinsic and acquired drug resistance. By the PET method, the metabolic activity of neoplastic tissue is estimated by dynamic cancer imaging. Radiopharmacon 18-fluorodeoxyglucose (^{18}F-FDG) is employed herein and used to evaluate tumor glycolysis as a marker of cell viability. Furthermore, utilizing a combination of PET camera with computed tomography (PET/CT) establish a good method to detect anatomical localization of very small tumor mass. Malignant lymphoma, breast cancer, lung cancer, cancer of the cervix and ovaries, colorectal cancer, head and neck carcinoma and esophageal cancer are tumor types for which FDG-PET assays have been utilized to evaluate tumor response during drug treatment [87].

6. The role of nanomaterials for the screening of drug resistance

During last decades, researches were conducted to investigate the adversary effects of pharmaceuticals particularly antibacterial agents regarding to the high and unwanted consumption of such therapeutic agents [88]. Indeed, excessive consumption of such drugs may lead to create critical issues, for instance significant negative impact on human health (antibacterial resistance),

liver damage, allergic reactions, jaundice and digestive disorders and so on. The various parameters like dose, personal sensitivity, usage duration and also maximum residue are involved in manifestation of side effects of these agents. Accordingly, employment of exact quantitative analysis for detection of antibiotics in different environments is very important due to widespread use of these drugs to circumvent various diseases [89].

To date, various techniques are applied to monitor antibacterial residues in different conditions. With regard to some of complexities of these conventional methods including long times, high cost, and pretreatment steps that have been restricted their utilization, design of effective biosensors is essential [90]. With reference to scientific progresses during recent decades, fabrication of nanoparticle-based biosensors is one of promising fields that has been received the attention of researchers [91, 92]. In general, a sensor is comprised of two main components: a recognition element and a transducer. To date, versatile recognition element was employed for fabrication of sensors with different applicability like antibodies, aptamers, mesoporous structures, nanomaterials and so on. Among all of them, nanomaterials are appropriate candidates for this purpose. Rapidity and simplicity of use accompanied with inexpensive monitoring of the broad spectrum of molecules are advantages of nanosensors [93-95]. Some of nano/biosensors types for monitoring various antibiotics residual was listed in table 1.

As mentioned in previous section, there are various novel techniques for generation of diagnostic sensors; in the following sections, application of nanomaterial-based sensors for the screening and monitoring of drug resistance will be discussed.

7. Electrochemical nanosensor for the monitoring of drug resistance

Production and or consumption ions/electrons arising from the chemical reactions between immobilized biomolecules and target analytes is the basic principle for electrochemical sensors, which in turn can have impact on the measurable electrical properties like potential or electrical current. Metal nanoparticles are promising candidates to improve the sensitivity of electrochemical sensors owing to large surface area as well as high catalytic efficiencies [105]. Gold nanoparticles have received more attention, which is contributed to their exceptional features such as remarkable conductivity, size-dependent electrochemistry, excellent optical properties, appropriate biocompatibility and also chemical stability [106, 107]. Another prominent example from metal nanoparticles class is iron oxide nanoparticles; although high reactivity of these materials can constrain their applicability as biosensor [108]. In this regard, employment of magnetic core-shell nanoparticles is one of appropriate solutions to circumvent such critical issue. For this purpose, magnetic materials as the core and metal/metal oxides (e.g. *Au, silica*) as the shell have been applied [109, 110]. Among the investigated core-shell platforms, magnetic core-gold shell nanostructures are introduced for construction of effective biosensors because of their simplicity, cost-effective, suitable stability as well as great conductivity of both Fe_3O_4 and Au nanoparticles [111].

Radek Zborˇil *et.al.*, proposed an effective nanoprobe based magnetic gold nanocomposite (Fe_3O_4-Carboxymethyl cellulose (CMC) @Au) for determination of chloramphenicol in human urine samples with an approximate value of recovery around 97%. In this investigation, CMC as a stabilizing agent for prohibition of the Fe_3O_4 nanoparticles aggregation in order to overcome the

kinetic barrier for electron transport. Gold nanoparticles in this nanocomposite play a vital role as an electron-conducting tunnel for better electron transport [96]. Obtained results of this report suggested that constructed nanosensor can be used as an efficient nanoprobe for monitoring of chloramphenicol with higher sensitivity, repeatability, and reproducibility.

Recently, a gold nanocomposite (gold-graphene oxide-molecularly imprinted polymer (MIP)) proposed as a substrate to construction of electrochemical nanosensor for detection of cloxacillin (CLO) residual in milk samples [112]. In the optimum condition (pH=8.5, time contact= 89 min, 0.79 g MIP), removal of cloxacillin was reported 92% with the linear range s from 110 to 750 nM with detection limit of 36 nM. Therefore, Jafari and coworkers were stated that this fabricate nanocomposite are able to accurate quantification cloxacillin in dairy products to prevent consequences of excessive consumption of this antibiotic in human foods.

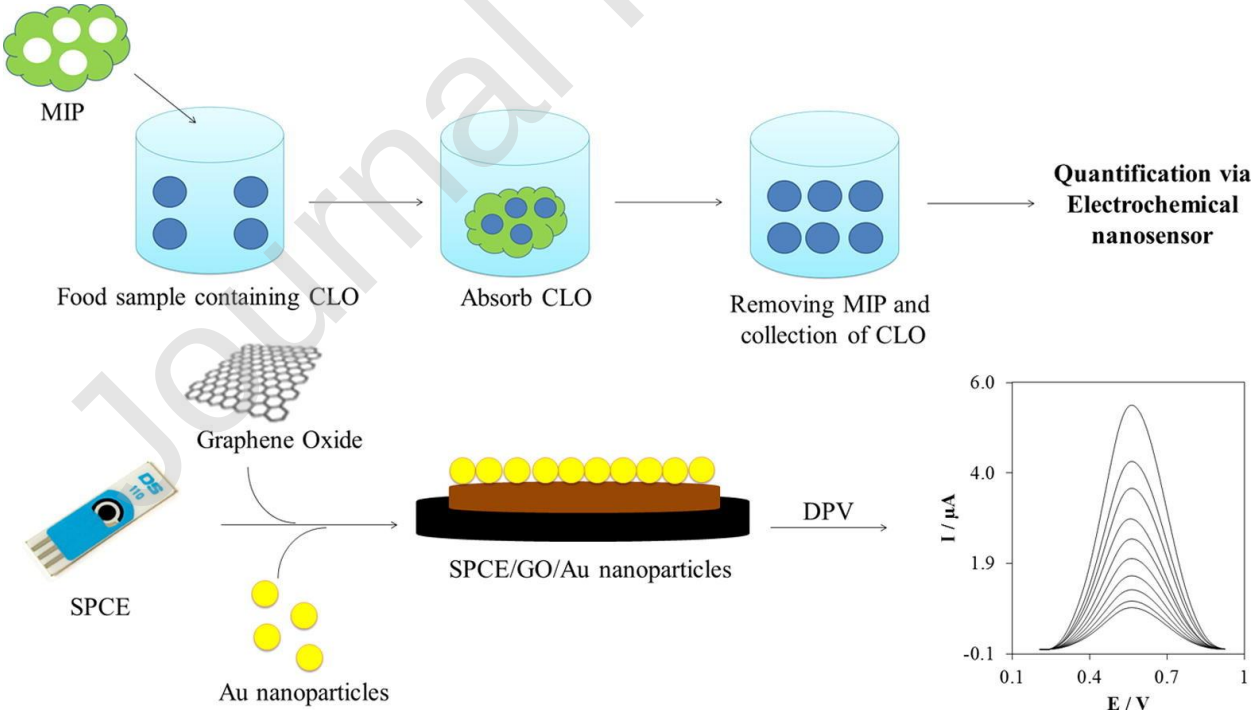

Figure. 3: Fabrication of MIP, pre-concentration and detection of the cloxacillin by means of the electrochemical nanosensor. Adopted from [112] with permission.

As the request for faster, smaller, low-priced, and ultrasensitive quantification and qualification of samples rapidly increases, these techniques provide a viable path toward the next generation of electrochemical sensors. More developments in the preparation of nanomaterials and the production of discrete nanoelectrodes has the high potential to benefit society in a broad scope of areas, with the prospective for real-time point of care detection of analytes slowly being realized. The main challenge of such applications is commercial development which is the requirement for a low cost, reproducible fabrication procedure for nanomaterial based sensors on an economically beneficial scale while keeping the accuracy obtained within a laboratory environment [113].

8. Optical nanosensors for the monitoring of drug resistance

In the case of optical sensors, binding specific analytes to molecular receptors results in the change in their optical properties and consequently record an output signal that is light. Briefly, this group of nanosensors transform a chemical/biological incident into a readable optical signal [114]. The first optical nanosensor that constructed from polyacrylamide (PAA) nanoparticles loading with a fluorescein dye to detect the pH changes, reported by Sasaki et al [115].

According to the literature review, optical nanobiosensors can be used as probe for determination of the environment in order to quantify biochemical species as well as their pharmacokinetics that are necessary for understanding the cellular functions and inter/intracellular processes that could be utilized for biomedical applications [116, 117]. Fluorescent nanomaterials rather than other

nanostructures, are considered as a suitable candidate for utilization in designing optical sensing platforms [118]. Among of them, quantum dots are one of the attractive fluorescent nanoparticles that are employed to create the novel nanoprobes for quantification of some analytes with the high sensitive. In this context, it is important to consider that their outstanding optical properties like such as high optical quantum yield, narrow and symmetrical spectra, wide excitation spectra and photo-stability make them as appropriate candidate for the sensing purpose [119].

Recently, an optical sensor based on xidized starch polysaccharide biopolymer-capped CdTe/ZnS quantum dots for determination of tetracycline in biological samples was presented by Soleimani and et al. The reported detection limit for this nanobiosensor in complex matrixes (pharmaceutical formulations, urine, saline and glucose serums) was 2.74nM in the concentration range from 9.14nM to $7.23 \times 10^{-}$μM [101].

In a similar research study, nitrogen and sulfur co-doped carbon dots were designed through one-step hydrothermal route as an optical sensing agent for detection of tetracycline in real milk samples. The presence of heteroatoms nitrogen and sulfur can enhance the optical and electrical properties of carbon dots [102]. A wide linear range of 0.1–65 μM (R^2 = 0.9916) and detection limit of 0.04 μM are provided by this fabricated nanosensor.

Optical signal detection by nanosensors provides high sensitivity as a result of the distinctive connections of active sites of nanomaterials with light signals. However, detection mode of the optical phenomena strongly affects on sensitivity [120]. Optical sensors are utilized for numerous

types of spectrographic analysis, like fluorescence, absorption, Raman, surface enhanced Raman scattering (SERS), refraction, visible radiation, and qualitative analysis using dispersion [121]. SERS based nanosensors have high potential capabilities to address many aspects for high-resolution and ultrasensitive optical probing in biomedicine. SERS nanosensors offer numerous advantages over other optical sensors with respect to sensitivity and molecular specificity, versatility and multifunctionality, biocompatibility, mobility, have the exiting potential to become the next-generation sensing method for enhancing our understanding of cellular processes on the molecular level [118].

9. Electrochemiluminescence nanosensors for the monitoring of drug resistance

Another effective monitoring technique is electrochemiluminescence (ECL), combination of the electrochemical and chemiluminescent methods. In this method, occurred electron transfer reaction at the electrode surface can generate chemiluminescent reaction, which in turn causes an excited state of photon emission; through the applied potential, this process is manageable. Simplicity, rapidity, high sensitivity, cost-effective and also low background are benefits of this approach [122]. Despite the considerable advantages of ECL, this method suffers from the lack of enough selectivity. To date, various type of nanomaterials such as quantum dots, carbon nanotubes, silica nanoparticles, metal nanoparticles are reported for enhancement of ECL sensors performance as well as improvement of their selectivity [123]. Therefore, ECL can be introduced as a promising candidate for the sensing of antibiotics. For instance, an ECL aptasensor based on luminol-gold nanoparticles was constructed for detection of chloramphenicol.

In this work, an ultrasensitive ECL sensor was designed based on AuNPs-labeled coating antigen modified glassy carbon electrode and CdSe quantom dots/ poly (diallyldimethylammonium chloride)-graphene/gold nanoparticle (CdSe QDs/PDDA-GN/AuNPs)-labeled antibody as bioprobe for ractopamine monitoring. Based on obtained results in this study, the fabricated probe was indicated good electronic conductivity, fast response as well as satisfactory stability which are prerequisite for designing ECL sensors with high sensitivity. Besides, the authors of this articles declared that acceleration of electron conduction for achievement of dual signal amplification as well as supplying a large surface area could be contributed to presence of AuNPs and PDDA-GN in the prepared sensor [124].

For the detection of tetracyclines, Chen and coworkers designed an ECL biosensor based on a $Ru(bpy)_3^{2+}$-doped silica nanoparticles (Ru-SiNPs)/Nafion film modified electrode [125]. Ru-SiNPs produced by a water-in-oil microemulsion process, it were then immobilized on the glassy carbon electrode (GCE) by means of Nafion film. It was showed that the presence of tetracyclines can improve the ECL response of the modified electrode. The results displayed that the LODs are 0.1 μM for oxytetracycline, 0.23 μM for tetracycline, and 0.16 μM for chlortetracycline, respectively. The linear range is 0.1–100 μM for oxytetracycline, 1–100 μM for tetracycline, and 1–100 μM for chlortetracycline. Furthermore, this ECL biosensor also displayed great stability and repeatability, which cause its application in evaluating the content of antibiotics in drugs.

For enhancing the performance of the ECL biosensors, various factors can be helpful such as choosing reliable recognition elements, developing a highly efficient ECL probe, and utilizing

appropriate nanomaterials to serve as carriers for signal molecules or as ECL signal tags, as well as to modify electrodes to increase ECL efficiency.

Especially, paper-based ECL detection platforms enable portable and sensitive point of care detection. In addition, impurities, test cost, sample volume, and reproducibility of the test results should be considered in the biosensors [126].

10. Photoelectrochemical (PEC) Nanosensors for the monitoring of drug resistance

Photoelectrochemical (PEC) is a novel sensing pathway for detection of various antibiotics with high sensitivity as well as rapid response. The performance of PEC is based on the combination of the PEC oxidation and specific biorecognition. PEC-based sensors possess greater efficacy rather than traditional optical and electrochemical biosensors with regard to they have benefits both optical and electrochemical sensors. According to literature review, approaches analytical based on PEC sensors have been received more attention owing to their excellent features including simple apparatus, easy miniaturization, rapid response accompanied with high accuracy, reduced background signal and so on [122, 127].

Currently, with the purpose of improve the PEC performance, incorporating functional nanostructures is employed in their design. In this regard, Liu *et al.,* proposed a biosensor based on graphitic carbon nitride (g-C_3N_4) sensitized with CdS QDs for the construction of PEC aptasensor for sensing of tetracycline. In this research, g-C_3N_4 coupled with CdS QDs (g-C_3N_4-CdS) nanocomposites as highly efficient photoactive structures and the free tetracycline-binding aptamer as the special bio-recognition element were suggested. π-π stacking interaction can

immobilize this biosensing agent on the surface of g-C_3N_4-CdS composites. The finding of this article indicated that the g-C_3N_4-CdS composites highly sensitive photocurrent signal responding in comparison to either CdS QDs or pristine g-C_3N_4. In the presence of tetracycline, a boosted photocurrent signal was generated because of the specific capture of tetracycline by tetracycline-binding aptamer. In the optimum states, this nanosensor displayed a linear range from 0.01 μM to 0.25 μM with a detection limit of 5.3 nM [128].

In another study, Verdian and coworker reported a PEC nanosensor comprised of a label-free liquid crystal (LC) based aptasensor for the monitoring of tetracycline in dairy products. In this biosensor, through an amide chemical-bonding aptamer can immobilize on a modified glass substrate as the recognize element. With binding of aptamer to tetracycline, a considerable disruption was occurred in orientation of LCs bar-shape molecules, which lead to visible color images. The authors reported the recoveries of the spiked samples for this nanobiosensor were between 95.6% and 108.7% with a linear range from 0.5 to 500 pM and detection limit of 0.5 pM [129].

Photoelectrochemical-based nanosensors have received a great deal of attention in nanotechnology related analytical devices, for which they are strong alternatives to other related sensors for pharmaceuticals and drug analysis. Photoelectrochemical-based nanosensors are superior to conventional electrochemical sensors. These sensors consist of quantum dots immobilized on the surface of electrode using a linker (linking agents are different depending on the quantum dots, nature of electrodes, and experimental conditions) for detection even for subtle. Upon illumination these photoelectrochemical nanosensors produce photocurrent, which depends upon several

factors such as the nature of the material, the quantity of analyte, and the environment (temperature, pH of medium, pressure, etc.) [130-135]. With improved fabrication techniques and the ability to address numerous sensing challenges, the efficiency of photoelectrochemical-based nanosensors has improved many-fold [136].

11. Conclusion

Resistance to antimicrobial and anticancer drugs compared to other drugs causes more challenging and life threading situations. To date, various techniques are applied to monitor resistance to antimicrobial and anticancer in different conditions. With regard to some of complexities of conventional methods including long times, high cost, and pretreatment steps that have been restricted their utilization, design of effective biosensors is essential. Electrochemical techniques have traditionally played a critical role for the development of biosensing devices because of their potential for achieving specific, sensitive and low-cost detection of biomolecules. ECL based assay has a high potential for the simultaneous measurement of multiple biomarker proteins. However, recent data have indicated that cross reactions among different indicators is a major limitation for ECL assay. Nanomaterial-based sensors are novel sensing tools for the screening and monitoring of drug resistance. Rapidity and simplicity of use accompanied with inexpensive monitoring of the broad spectrum of molecules are advantages of nanosensors.

For commercial fabrication of such applications, there are some challenges such as the requirement for a low cost and reproducible production method for nanomaterial based sensors while maintaining the accuracy obtained within a laboratory environment. Optical signal detection by nanosensors such as SERS nanosensors have great potential capabilities to address many aspects

for high-resolution and ultrasensitive optical probing in biomedicine such as drug resistance detection, and have the potential to become the next-generation sensing technology. Furthermore, ECL detection platforms enable portable and sensitive point of care detection. Photoelectrochemical-based nanosensors are powerful alternatives to other related sensors for pharmaceuticals and drug analysis, for which they are quite popular in nanotechnology related sensing techniques. These electrochemical sensors are superior to conventional electrochemical sensors.

Conflict of interest

There is no conflict of interest.

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Table 1. Some nano/biosensors types for monitoring various antibiotics residual along with their status.

Applied technique	Nanosensor type	Status/Action	Ref.
Electrochemical	Magnetic Gold Nanocomposite (Au- Fe_3O_4)	Detection of **C**hloramphenicol in human urine samples	[96]
	Gold nanourchin/graphene oxid	Detection of Azithromycin in human serum	[97]
	Gold nanowires/graphene oxide/electropolymerized molecular imprinted polymer	Detection of Cefixime traces in human serum and urine	[98]
Photoelectrochemical	Aptasensor based on cerium doped CdS modified graphene	Detection of Tetracycline in human urine samples	[99]
	Aptasensor based on graphitic carbon nitride/ CdS quantum dots aptasensing of tetracycline	Detection of Tetracycline in human urine samples	[100]
Optical	Oxidized starch polysaccharide biopolymer-capped CdTe/ZnS quantum dots	Detection of tetracycline in pharmaceutical formulations, saline, urine and glucose serums	[101]
	Nitrogen and sulfur co-doped carbon dots	Detection of tetracycline in real milk samples	[102]
Electrochemiluminescence	Fluorescent Carbon Dot	Detection of Cefixime in human urine specimens and raw milk	[103]
	bispyrene/AgNP-based ratiometric nanoprobe	Detection of Etimicin in human urine	[104]
	Molecularly imprinted nanoparticles	Detection of Ciprofloxacin in aqueous solution	[94]