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Review—Electrochemical Approaches and Advances towards the Detection of Drug Resistance

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Drug resistance in bacteria and cancer is a growing problem that decreases drug treatment effectiveness and increases the severity of bacterial infections as well as cancer mortality. Due to their high sensitivity, low cost, and rapid analysis time, electrochemical methods have been increasingly employed to tackle this challenge throughout the last decade. This review covers literature on the electrochemical characterization of antibiotics and chemotherapeutic drugs, as well as advances in analyzing interactions between drug compounds and biological cells. Recent developments towards the quantitative detection of drug resistance in bacteria and cancer by electrochemistry are discussed, and the use of specialized electrochemical instrumentation, such as scanning electrochemical microscopy, is highlighted.

The rapid spread of drug resistance in bacteria as well as cancer has developed into a significant threat to the global public health. According to the World Health Organization (WHO), antibiotic resistance is present in every country, and various national and international health organizations, including the United Nations, the Infectious Diseases Society of America, as well as the Public Health Agency of Canada, have called for the urgent development of new treatment and diagnostic strategies. The Centers for Disease Control and Prevention reports approximately 10 million deaths worldwide each year in connection with antibiotic resistance. Similarly, drug resistance in cancer is believed to be responsible for treatment failure in up to 90% of metastatic cancer patients. Cellular resistance mechanisms in both bacteria and cancer include cell membrane protein modifications, intracellular drug target alterations, and the over-expression of efflux pumps. The latter are the result of an over-expression of efflux pump proteins, which enable cells to expel drugs rapidly from the cell interior, before these compounds can take effective action. Drug compounds and efflux pump proteins have recently caught the attention by the electrochemical community to develop new methodologies to understand and detect drug resistance in both bacteria and cancer by electrochemistry.

In recent years, the innovation of electrochemical sensors has attracted immense attention, due to their high sensitivity, rapid analysis and ability to analyze complex samples, such as urine and blood. Although no sensor for the point-of-care detection of antibiotic resistance has been proposed so far, electrochemical sensors have become a powerful tool in various fields, such as environmental monitoring, biotechnology, and industrial process control. The advantages are clear: Electrochemical sensors are sensitive, inexpensive, and offer the detection of an analyte within the stand and detect drug resistance in both bacteria and cancer by electrochemistry.

In order to study drug resistance electrochemically, the redox properties of drug compounds must be well understood. Based on their chemical structure, FDA approved antibiotics are commonly categorized into eight different classes, as summarized in Table I. Due to the rapid spread of drug resistance, the development of novel antibiotic drug candidates is a preference focus of organizations such as the Infectious Diseases Society of America, as well as the Public Health Agency of Canada, have called for the urgent development of new treatment and diagnostic strategies.

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study, differential pulse voltammetry (DPV) and square wave voltammetry (SWV) revealed a limit of detection (LOD) of $1.87 \times 10^{-9}$ M and $1.55 \times 10^{-8}$ M, respectively. No interferences were reported in this publication.

**Ampicillin.** An interesting strategy to detect ampicillin has been proposed by Wang et al. using aptamer based differential pulse voltammetry. In this approach, a GCE was modified with double stranded DNA (dsDNA) containing an ampicillin aptamer sequence (Fig. 1a). Differential pulse voltammograms showed a pronounced reduction peak. This method resulted in an impressive detection limit of $3.2 \times 10^{-11}$ M and ampicillin was detected in real samples of milk and water.

**Ciprofloxacin (CIP).** Belonging to the second generation of fluoroquinolones, CIP is used worldwide as an antimicrobial agent

| Class Name          | Structure | Mechanism of Action                     |
|---------------------|-----------|-----------------------------------------|
| β-Lactam            | ![Structure](image1) | Inhibit bacterial cell wall biosynthesis |
| Aminoglycosides     | ![Structure](image2) | Inhibit bacterial protein synthesis leading to cell death |
| Glycopeptides       | ![Structure](image3) | Inhibit bacterial cell wall biosynthesis |
| Quinolones          | ![Structure](image4) | Inhibit bacterial DNA replication        |
| Oxazolidinones      | ![Structure](image5) | Inhibit bacterial protein synthesis      |
| Tetracyclines       | ![Structure](image6) | Inhibit bacterial protein synthesis      |
| Macrolides          | ![Structure](image7) | Inhibit bacterial protein synthesis      |
| Lipopeptides        | ![Structure](image8) | Disrupt bacterial cell membrane          |

**Table I. Classes of antibiotics reported in literature.**

| Class Name | Structure | Mechanism of Action |
|------------|-----------|---------------------|
| β-Lactam   | ![Structure](image1) | Inhibit bacterial cell wall biosynthesis |
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| Macrolides | ![Structure](image7) | Inhibit bacterial protein synthesis |
| Lipopeptides | ![Structure](image8) | Disrupt bacterial cell membrane |
Some antibiotics, such as CIP, can react with metal ions to form stable complexes. Several studies have been conducted to electrochemically characterize CIP. Its detection through the complexation of CIP with Cd$^{2+}$ was reported by Jun et al. A well-defined electrochemical signal was recorded at graphene modified GCEs as a result of the complexation of Cd$^{2+}$ by CIP. The concentration of CIP was found inversely proportional to the electrochemical signal and an irreversible oxidation peak of CIP in various electrolyte solutions, including acetate buffer solution (ABS), phosphate buffer saline (PBS) and sulphuric acid, was observed. GCE modifications using graphene resulted in a significantly enhanced anodic peak in the presence of Cd$^{2+}$ ions. Overall, this method showed good reproducibility and high selectivity with a detection limit of $5.9 \times 10^{-8}$ M. The main advantage of this approach is that the electrode did not suffer from electrode fouling which is commonly observed during the direct determination of CIP at bare GCEs. This method successfully detected CIP rapidly and sensitively in pharmaceuticals and urine samples.

Norfloxacin (NFX). This fluoroquinolone is commonly used to treat gastrointestinal, urinary and respiratory tract infections. As shown by Ke-Jing et al., NFX was detected at multi-wall carbon nanotube (MWCNT)/nafton film-coated GCEs during voltammetry. NFX was determined by linear sweep voltammetry at a potential range of 0.3 to 1.4 V vs Ag/AgCl, which resulted in a well-defined irreversible oxidation peak current at a peak potential of 1.11 V vs Ag/AgCl. The relationship between the peak current and the scan rate at a range of 10–250 mV s$^{-1}$ demonstrated that mass transfer occurs through an adsorption controlled process and that the pH of the supporting electrolyte solution has an important influence on the electrochemical reaction. The highest oxidation peak was recorded in HAc–NH$_4$Ac buffer solution at a pH value of 4.4. This method has been used in pharmaceuticals and urine samples with an excellent detection limit of $5 \times 10^{-8}$ M. Only minimal fouling effects were observed during this procedure.

Tobramycin. Tobramycin (TOB) is an aminoglycoside, which is effective against both Gram-positive and Gram-negative bacterial infections. A modified GCE was prepared by electropolymerization of pyrrole (Py) in the presence of tobramycin to form a molecularly imprinted polymer film on the GCE surface (PPy/GCE). The general approach of fabricating cavities in a polymer matrix based on a specific template molecule is known as Molecularly Imprinted Polymer (MIP) technique and has found useful application in a variety of research fields including electrochemistry, analytical chemistry and biology. In the work of Gupta et al., mass transfer occurs through a diffusion controlled process where TOB interacts with pyrrole and results in an oxidation peak at 0.72 V vs Ag/AgCl. Modified TOB imprinted PPy/GCEs were electrochemically characterized by cyclic voltammetry in the presence of potassium ferricyanide in KCl and compared to a bare GCE. The reversible redox peak of potassium ferricyanide, which is observed on the bare GCE, is not shown on the modified GCE due to
the presence of the polymer. Square wave voltammetry was performed revealing a favorable detection limit of 1.4 × 10⁻¹⁰ M.

**Neomycin.** Another example for the electrochemical characterization of aminoglycosides is neomycin, which has gained considerable attention due to its effectiveness against Gram-negative and Gram-positive bacteria to treat gastrointestinal infections and mastitis in livestock animals.

Neomycin exhibits a well-defined reduction peak at a potential of −0.2 V vs Ag/AgCl as shown by Hamnca et al. Square wave voltammetry was carried out at the surface of a polyamic acid/graphene oxide (GO)/screen-printed carbon electrode (SPCE) for the electrochemical detection of neomycin in aqueous solutions. The reduction peak current was shown to increase with increasing concentration of neomycin until the catalytic current enhancement effect at the electrode surface reached a saturation level. The limit of detection was found to be 1.07 × 10⁻⁶ M. This approach was applied to detect neomycin in urine samples, which presents a reliable and rapid alternative to common chromatography techniques.

**Azithromycin.** An interesting molecule of the macrolides class is azithromycin (AZM), which is effective against Gram-negative and Gram-positive bacterial infections. AZM is highly effective against upper and lower respiratory acute tract infections such as bronchitis, pneumonia, sinusitis, pharyngitis, tonsillitis and otitis, sexually transmitted diseases, skin and soft tissue infections.

The electrochemical behavior of AZM has been investigated by cyclic voltammetry on MIP modified carbon paste (CP) electrodes (MIP/CPs) and non-molecularly imprinted polymer (NIP) modified CP electrode (NIP/CPs). Voltamograms show an irreversible oxidation peak at 0.8 V vs Ag/AgCl due to the oxidation of one dimethyl-amino group on the desosamine sugar part of the molecule. This work gives the lowest detection limit of 2.3 × 10⁻¹¹ M, which compares favorably over any other voltammetry methods.

Other existing electrochemical studies on antibiotics not discussed in detail, are summarized in Table II.

**Electrochemical studies on cancer drugs.—Anticancer drugs that were electrochemically characterized in the last decade are categorized into four groups: alkylating agents, antimetabolites, cytokotoxic antibiotics, and inhibitors.** While alkylating agents, such as cisplatin lead to cell death in cancer by binding to DNA, antitumor activities. These antibiotics have many mechanisms of action. The subgroup of anthracyclines has been studied in the literature and contains antibiotics, doxorubicin and daunorubicin, extracted from Streptomyces bacteria. Doxorubicin (DOX) was detected using voltammetry as well as electrochemical impedance spectroscopy (EIS).

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Cytotoxic antibiotics are antibiotics that are found to have anti-tumor activities. These antibiotics have many mechanisms of action. The subgroup of anthracyclines has been studied in the literature and contains antibiotics, doxorubicin and daunorubicin, extracted from Streptomyces bacteria. Doxorubicin (DOX) was detected using voltammetry as well as electrochemical impedance spectroscopy (EIS).

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theme in these three studies is the combination of carbon nanotubes with nanoparticles and other components to detect drugs. Shams et al. introduce a GCE modified with silver decorated MWCNT composite (Ag-MWCNT/GCE). By using square wave voltammetry, this work detects epirubicin with a LOD of $1.0 \times 10^{-9}$ M. Kong et al. 2019 prepared a nanocomposite from nitrogen decorated carbon nanotubes. This nanocomposite is loaded with platinum nanoparticles (PtNP) and is then used to modify a GCE (N-rGO-SWCNTs-Pt/GCE). At optimized conditions, this method achieved an LOD of $5.7 \times 10^{-9}$ M for daunorubicin. In 2015, Hajian et al. fabricated an electrochemical sensor based on gold electrode modified with gold nanoparticles/ethyleneediamine (EDA)/multi-walled carbon nanotubes (AuNPs/EDA/MWCNTs/AuE). This sensor can detect valrubicin with an LOD of $1.8 \times 10^{-9}$ M in citrate buffer (pH 4.0) and 0.1 M KCl.

Alkylating agents include temodal, ifosfamide, and cisplatin. Temodal was recently detected by the authors Jahandari et al. in 2019, who propose the use of gold nanoparticles (AuNP) and dsDNA to modify a pencil graphite electrode. One unique feature of this work is the use of computational chemistry to study the intercalations between temodal and guanine in dsDNA structure, which is used to detect the drug. In particular, this interaction between drug and dsDNA decreases the current of the oxidation peak of the guanine base. This method achieved an LOD of $1.0 \times 10^{-9}$ M.

Other chemotherapeutic drugs that have been electrochemical studied in the past, but are not reviewed in detail here are etoposide and the tyrosine kinase inhibitor erlotinib. A summary of anticancer drugs investigated by electrochemistry is presented in Table III.

### Drug interactions studies

Drug interactions studies have been of significant interest to understand the mechanism of drug-cell interactions, which is crucial for the design of novel and effective pharmaceutical drugs. Most of the proposed drug interactions studies in literature focus on the interaction of a drug with DNA molecules. Triggered by an effective drug, DNA often times is susceptible to various intracellular redox reactions, which lead to DNA damage and cause pathological changes in cells. Drug molecules bind with DNA either covalently or non-covalently. Non-covalent interactions with DNA occurs primarily in three modes which include groove binding interactions, electrostatic interaction from the exterior sugar phosphate backbone and intercalations between the stacked base pairs of the ds DNA. Non-electrochemical interactions lead to the formation of a complex between the drug and DNA.

### Table II. Summary of the recent literature on antibiotics, characterized by electrochemistry. Articles denoted with a star symbol are discussed in detail in this review. RGO = reduced graphine oxide; POT (SDS) = poly(o-toluidine) (sodium dodecyl sulphate); CB = carno black; DHP = dihexadecylphosphate; CTAB = cetyltrimethylammonium bromide; BDD = boron doped diamond; GCP = glassy carbon paste; PoAP = poly(acridine orange)-poly(styrenesulfonate); G = graphene; ATP = 4-aminothiophenol; ABA = 4-amino benzoic acid (4-ABA); IL-G = ionic liquid-graphene; ZSM = mesoporous zeolitic material.

| Classes | Antibiotics | Method of Analysis | LOD [M] | Electrode modification | References |
|---------|-------------|--------------------|---------|------------------------|------------|
| B-Lactams | Ampicillin | DPV | $3.2 \times 10^{-11}$ | dsDNA/AMP aptamer | 55 |
| penicillin | CV | $8.0 \times 10^{-16}$ | RGO/AuNP | 55 |
| Amoxicillin | CV | $1.1 \times 10^{-5}$ | multisection nanoparticles | 56 |
| CV | $6.0 \times 10^{-7}$ | POT(SDS) | 20 |
| SWV | $9.0 \times 10^{-6}$ | AuNP-PdNP-RGO | 28 |
| SWV | $1.2 \times 10^{-7}$ | CB DHP | 25 |
| CV | $1.9 \times 10^{-9}$ | poly acridine orange | 26 |
| Aminoglycosides | Neomycin | SWV | $1.1 \times 10^{-6}$ | Polyamid acid/GO | 30 |
| Tobramycin | CV | $1.4 \times 10^{-10}$ | Polypyrrole | 28 |
| Quinolones | Ciprofloxacin | CV, ASV | $5.9 \times 10^{-8}$ | Graphene | 28 |
| CV, DPV | $5.0 \times 10^{-8}$ | CTAB | 12 |
| CV | $1.2 \times 10^{-8}$ | MgFe$_2$O$_4$/MWCNT | 11 |
| CV, LSV | $9.0 \times 10^{-7}$ | MWCNT | 39 |
| CV | $3.3 \times 10^{-6}$ | BDD | 38 |
| SWV | $3.3 \times 10^{-8}$ | GCP | 37 |
| CV | $6.0 \times 10^{-6}$ | MWCNT | 13 |
| Levofoxcacin | DPV | $1.0 \times 10^{-6}$ | PoAP/MWCNT | 43 |
| CV, SWV | $1.4 \times 10^{-8}$ | AgNPs-CB-PEDOT:PSS | 42 |
| CV, DPV | $5.3 \times 10^{-7}$ | MIP/AuNPs | 41 |
| CV, SWV | $2.9 \times 10^{-6}$ | BDD | 34 |
| CV | $1.0 \times 10^{-8}$ | AgNP | 33 |
| Norfloxacin | SWV | $3.4 \times 10^{-8}$ | Polyamid acid/GO | 30 |
| LSV | $5.0 \times 10^{-8}$ | MWCNT | 36 |
| Etrofoxcacin | LSV | $5.0 \times 10^{-7}$ | MWCNT | 39 |
| Ofloxacin | CV, SW-AdAsV | $1.8 \times 10^{-10}, 2.4 \times 10^{-10}$ | MWCNT | 32 |
| CV, DPV | $1.0 \times 10^{-9}$ | AuNP/ATP/ABA | 35 |
| Oxazolidonones | Linezolid | DPV | $1.5 \times 10^{-7}$ | bare GCE | 57 |
| Tetracyclines | Tetracycline | CV | $1.5 \times 10^{-5}$ | multisection nanoparticles | 56 |
| Macrolides | Azithromycin | CV | $7.0 \times 10^{-8}$ | bare AuE | 50 |
| CV | $7.0 \times 10^{-8}$ | MgCr$_2$O$_4$/MWCNT | 49 |
| CV | $1.3 \times 10^{-9}$ | MWCNT-DHP | 46 |
| CV | $1.9 \times 10^{-7}$ | bare GCE | 47 |
| CV | $1.9 \times 10^{-7}$ | Ru(bpy)$_3$/ZSM-5/Nafion | 48 |
| CV | $2.3 \times 10^{-11}$ | IL-G | 45 |

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**References**

1. Alkylating agents include temodal, ifosfamide, and cisplatin. Temodal was recently detected by the authors Jahandari et al. in 2019, who propose the use of gold nanoparticles (AuNP) and dsDNA to modify a pencil graphite electrode.
2. One unique feature of this work is the use of computational chemistry to study the intercalations between temodal and guanine in dsDNA structure, which is used to detect the drug. In particular, this interaction between drug and dsDNA decreases the current of the oxidation peak of the guanine base. This method achieved an LOD of $1.0 \times 10^{-9}$ M.
3. Other chemotherapeutic drugs that have been electrochemical studied in the past, but are not reviewed in detail here are etoposide and the tyrosine kinase inhibitor erlotinib. A summary of anticancer drugs investigated by electrochemistry is presented in Table III.
4. **Drug interactions studies.**—Drug interactions studies have been of significant interest to understand the mechanism of drug-cell interactions, which is crucial for the design of novel and effective pharmaceutical drugs. Most of the proposed drug interactions studies in literature focus on the interaction of a drug with DNA molecules. Triggered by an effective drug, DNA often times is susceptible to various intracellular redox reactions, which lead to DNA damage and cause pathological changes in cells. Drug molecules bind with DNA either covalently or non-covalently. Non-covalent interactions with DNA occurs primarily in three modes which include groove binding interactions, electrostatic interaction from the exterior sugar phosphate backbone and intercalations between the stacked base pairs of the ds DNA. Non-electrochemical interactions lead to the formation of a complex between the drug and DNA.
Table III. Recent electrochemical work on anti-cancer drugs detection by electrochemistry. Articles denoted with a star symbol are discussed in detail in this review. ($[\text{Co(phen)}_3]^3+$ = cobalt (III) trisphenanthroline complex; BMPA = biopolymer from babassu mesocarp modified with phthalic anhydride; PFR = porpyran; PANINT = polyaniline nanotube; CuSe = Copper solid amalgam electrode; AdSLSV = adsorptive stripping linear sweep voltammetry; Pd@PNP = mesoporous Palladium and Platinum core–shell nanoparticles; AdSSWV = adsorptive stripping square wave voltammetry; PTF = polythiophene; N-rGO = nitrogen-doped reduced graphene oxide; GST = Glutathione-s-transferase; Au-Pd@rGO = gold, palladium and reduced graphene oxide nanocomposite; PFUFX = polyurethane; PPHF = polypropylene hollow fiber).

| Classes          | Drug                       | Electrode modification              | Method of analysis | LOD [M]    | References |
|------------------|----------------------------|------------------------------------|--------------------|------------|------------|
| **Antimetabolite** | 6-Mercaptopurine           | MWCNT Paste electrode              | LSV                | $1.0 \times 10^{-7}$ | 76         |
|                  |                            | [Co(phen)]$_3^{1.5-}$-GO-dsDNA/GCE  | DPV                | $1.5 \times 10^{-8}$ | 72         |
|                  |                            | N-HCNs-Pd-MIP/IL-PGE               | DPASV              | $7.2 \times 10^{-10}$ |            |
|                  | 5-Fluorouracil             | Glucose/CPE                        | CV, DPV            | $5.2 \times 10^{-9}$ | 62         |
|                  |                            | BMPA/Flexible AuE                  | CV, SWV            | $3.4 \times 10^{-7}$ | 65         |
|                  |                            | Reduced GO-CS/GCE                  | CV, SCV, SWV       | $1.2 \times 10^{-9}$ |            |
|                  |                            | AuNP-MWCNT-CS/GCE                  | CV, DPV            | $2.0 \times 10^{-8}$ | 75         |
|                  |                            | AuNP-PFR/CPE                       | CV, DPV            | $6.7 \times 10^{-7}$ | 66         |
|                  |                            | PANINT-AgNP/PGE                    | DPV                | $6.0 \times 10^{-8}$ | 61         |
|                  |                            | IL/CEP                            | CV, DPV            | $1.3 \times 10^{-8}$ | 63         |
|                  |                            | GO-MWCNT/GCE and SPCE              | CV, SWV            | $1.6 \times 10^{-8}$ |            |
|                  |                            | CuSe                              | CV, AdSLSV         | $1.2 \times 10^{-9}$ | 77         |
|                  |                            | MTB/CPE                           | CV, DPV            | $2.0 \times 10^{-9}$ | 67         |
| **Cytotoxic antibiotic** | Gemcitabine             | AuE                                | DPV                | $6.0 \times 10^{-8}$ | 73         |
|                  |                            | MMOF-AuNP/AuE                      | LSV                | $3.0 \times 10^{-15}$ |            |
|                  | Doxorubicin                | MAB-AuNP-TBSol-Gel/AuE             | EIS                | $1.7 \times 10^{-13}$ |            |
|                  |                            | Mab-AuNP-APTES/SSE                 | EIS                | $3.1 \times 10^{-12}$ |            |
|                  |                            | Pd@PtNP-MWCNT/GCE                  | AdSSWV             | $8.6 \times 10^{-10}$ | 81         |
| **Mitoxantrone**  | dsDNA-MWCNT-AgNP-PTP/GCE  | Epirubicin                         | Ag-MWCNT/GCE       | SWV, CV     | $1.0 \times 10^{-9}$ |            |
|                  |                            | Daunorubicin                       | N-rGO-SWCNT-Pt/GCE  | DPV         | $5.7 \times 10^{-9}$ |            |
|                  |                            | Valnubicin                         | AuNP-EDA-MWCNT/AuE | CV          | $1.8 \times 10^{-8}$ |            |
| **Alkylating agents** | Cisplatin                | GST/CPE                           | CV, SWV            | $8.8 \times 10^{-6}$ | 87         |
|                  |                            | MWCNT/SPCE                        | CV, DPV            | $4.6 \times 10^{-6}$ | 86         |
|                  | Temodal                    | dsDNA-AuNP/PGE                     | DPV                | $1.0 \times 10^{-9}$ |            |
| **Inhibitors**    | Etoposide                  | Au-Pd@rGO-L-Cysteine/PGF           | DPV                | $7.2 \times 10^{-10}$ |            |
|                  | Erlotinib                  | MWCNT/P-FIX-PH/PF/PGF             | DPV                | $2.0 \times 10^{-8}$ | 74         |
|                  | Irinotecan                 | GCE                                | CV                 | $1.1 \times 10^{-10}$ | 89         |
|                  | Roscovitine                | PGE or SPCE                       | SWV                | $2.0 \times 10^{-7}$ | 90         |
|                  |                            |                                   | SPCE               | $1.5 \times 10^{-7}$ |            |
authors used Indium Tin Oxide (ITO) as working electrode which was modified by gold nanoparticles and silver nanoparticles (AgNP) to enhance the electrocatalytic surface, which is further treated with cysteine-containing branched arginyl-glycyl-aspartic acid (RGD-MAP-C) peptides to increase cell adhesion property and growth. Differential pulse voltammetry and cell viability assays were performed after 2 days of curcumin treatment at various concentrations. The result showed a clear decrease in cell viability with increasing curcumin concentration. Voltammograms of DPV experiments revealed a decrease of the oxidation peak indicating an anticancer effect of curcumin in U87MG cells. The authors concluded that the proposed electrochemical method is more sensitive, accurate, and free from optical interferences compared to traditional colorimetric methods.

Ganciclovir (GCV) is used as an antiviral drug against herpes viruses, varicella-zoster virus, cytomegalovirus and Epstein-Barr virus. In the literature it is reported that GCV is intracellularly converted to its triphosphate form, which inhibits DNA polymerase to elongate the viral DNA during replication by inhibiting the incorporation of deoxyguanosine triphosphate into growing viral DNA. Once the pyrophosphate is released, GCV monophosphate causes a slower replication process of viral DNA by incorporating into the end of a growing chain. Paimard et al. investigated the drug-DNA interaction of GCV on the surface of GCEs, modified with Fe₃O₄/cMWNTs/GCE using cyclic voltammetry. Voltammograms show an oxidation peak of GCV at 0.93 V vs Ag/AgCl at the Fe₃O₄/cMWNTs/GCE. The authors observed a decrease in the GCV anodic peak current and a positive shift in the peak potential at the surface of the modified electrode in the presence of DNA. This decrease in the oxidation peak current can be attributed to a drug-DNA interaction, which is thought to cause a decrease of equilibrium concentration of the free GCV due to GCV-DNA interaction. The positive shift in the GCV oxidation peak potential was explained as an intercalative binding of GCV with DNA molecules.

Investigation of drug resistance by electrochemistry.—Over the last decade, electrochemical research in the area of drug resistance has gone far beyond the characterization of drug compounds, which is nonetheless a crucial first step in recognizing drug resistance electrochemically. The following section discusses approaches based on redox mediators as drug resistance indicators, employed during standard electrochemical methods, such as voltammetry, and specialized instrumentation, such as Scanning Electrochemical Microscopy (SECM).

One of the most recent strategies to detect drug resistance in bacteria was reported by Sun et al. in 2019, who employed p-Benzoquinone (BQ) as a redox mediator and indicator for drug resistance in Escherichia coli (Fig. 4). BQ acts as an electron mediator during bacterial respiration events. Thereby, BQ is enzymatically reduced to hydroquinone (HQ), which diffuses from the cell towards an electrode, where BQ is regenerated at the electrode surface. Monitored by cyclic voltammetry, this mechanism was revealed as a reversible electron transfer reaction. For the quantitative detection of antibiotic resistance, the authors employed bacteria, resistant to trimethoprim, a folic acid synthesis inhibitor, which is known to inhibit the reduction of dihydrofolic acid to
tetrahydrofolic acid through binding with dihydrofolate reductase, which leads to the blockage bacterial DNA biosynthesis. During cyclic voltammetry, an increase in peak current was observed with increased resistance phenotype in E. coli. The authors concluded that this method is potentially capable of differentiating between wild type E. coli and antibiotic resistant E. coli with the same concentration, but more studies are needed for the detection in real and complex samples.

The detection of drug resistance in cancer cells has been approached by studying proteins, which are responsible for an increased number of drug efflux pumps when over expressed. Approaches in recent years include impedance spectroscopy and voltammetry, mostly through antigen/antibody modifications of electrodes and specialized instrumentation, such as SECM to monitor drug resistance activity in living cells. The most recent quantitative electrochemical approaches to measure drug resistance in living cells are discussed in the following section.

In 2015, Chen et al. assessed the expression of Bcl-2 proteins using an electrochemical immunoassay as outlined in Fig. 3. In this approach, GCEs were modified with L-Lysine through electro-polymerization (PLL/GCE). Functionalyzed electrodes were then immersed in a glutaraldehyde aqueous solution for 1 h. Finally, these electrodes were further modified with a Bcl-2 antigen (Bcl-2Ag) and BSA to block nonspecific binding sites. To detect the expression of Bcl-2 proteins, this modified electrode (Bcl-2Ag/BSA/PLL/GCE) is exposed to a solution containing gold nanoparticles (AuNP) coated with BSA and Bcl-2 antibody (Bcl-2Ab) in the absence of cells (blank), or in the present of drug resistance or drug sensitive cells for 3 h. The use of an antibody ensures the specificity of the proposed method. Electrochemical impedance spectroscopy (EIS) revealed changes in charge-transfer resistance between samples. In the absence of cells, the Bcl-2Ab/BSA/AuNP is able to bind to the Bcl-2Ag/BSA/PLL/GCE as it is modified with the antibody. Hence, the charge transfer resistance is lower than in samples containing cells, because of a competition between the electrode surface and the cells as both have Bcl-2Ag. The more the Bcl-2 proteins are expressed, the more Bcl-2Ab/BSA/AuNP bind to cells and hence, the fewer Bcl-2Ab/BSA/AuNP bind to the electrode. Impedance measurements revealed a decrease of charge transfer resistance as the expression of Bcl-2 proteins increases. Sincedrug resistant cells express more Bcl-2 proteins than drug sensitive cells, the charge transfer resistance measured in the former is smaller than that of the latter.

To investigate drug resistance activity rather than protein expression, cellular drug uptake was monitored in leukemia cells K562 and its multidrug resistant variant K562/A02.107 This approach by Zhang et al. in 2011 used carbon nanotube-modified GCEs (CNTs/GCE) to detect daunorubicin resistance caused by an over-expression of P-glycoprotein (MDR). This modified electrode is immersed in daunorubicin solutions containing cells. The authors hypothesize that sensitive cells have a higher drug uptake than resistant cells, which leads to a lower concentration of daunorubicin in suspensions of drug sensitive cells compared to daunorubicin suspensions of drug resistant cells. The results show a decrease in peak current with increasing concentrations of sensitive cells.

To study cells under physiological conditions and as close to their natural environment as possible, specialized electrochemical instrumentation, such as SECM, has been advanced and customized specifically for the analysis of living cells. In 2011, Kuss et al. reported a differential electrochemical response during SECM measurements between wild type cells and cells overexpressing the multidrug resistance associated protein 1 (MRP1) in the presence of the redox mediator ferrocenemethanol (FcCH2OH) (Figs. 4a–4b). MRP1 efflux pumps have the ability to expel drugs, and drugs in conjugation with the reduced form of glutathione (GSH), from the cell interior. In the literature MRP1 is known as an independent prognostic indicator and its expression is strongly predictive of the survival rate of cancer patients, which makes it an interesting target for drug resistance detection. Using flow cytometry, the authors showed that FcCH2OH increases the intracellular concentration of GSH and propose a mechanism (Fig. 4a) of action in which GSH is expelled from the cells at a higher concentration and reacts with ferrocenemethanol, the oxidized form of FcCH2OH ([FcCH2OH]+), regenerating FcCH2OH in solution. As a result, during SECM studies, an increase in electrochemical current was recorded when the microelectrode passes cells due to the enhanced oxidation of FcCH2OH at the microelectrode (Fig. 4b).

Adenocarcinoma cervical cancer (HeLa) cells over expressing MRP1 showed a lower electrochemical current signal. The importance of glutathione as an antioxidant suggests that it is possible to monitor the redox state of cells through this FcCH2OH-glutathione relationship.

Building on their previous work, Kuss et al. successfully extracted an apparent heterogeneous rate constant for drug resistant and nonresistant HeLa cells from experimental SECM data using cell permeable and impermeable redox mediators. This work determined the samples’ apparent heterogeneous rate constant, independent from their topography, which until this point remained a challenge to the SECM community, and presents the first step towards a quantification of multidrug resistance on the single cell level in human cancer cells by SECM. Further publications by the authors in 2015 demonstrated the application of SECM to cancer cells exposed to green tea catechins (GTC), which are known for their antioxidant properties, and the sensitive monitoring of the cells’ electrochemical response over time. In this work, the authors report a simulation model based on the electrode scan velocity during SECM studies for high scan rates and slow scan rates, which enables the determination of the apparent heterogeneous rate constant for cells within minutes. This presents a significant advantage over previous works as results will be more reliable, because cells can be imaged faster and before environmental changes potentially affect the cells metabolism during the experiment. Employing the established relationship between FcCH2OH and GSH, the authors reported an increase in current when HeLa cells were exposed to GTC. The authors suggested this behavior is due to an enhanced efflux of GTC and GSH as a potential defense mechanism to prevent cell death. The electrochemical current signal re-adjusted to a control value after the removal of GTC from the solution. Although no drug resistant cells were monitored during this study, this work represents an interesting approach to potentially monitor the initiation of drug resistance in cancer in the future by SECM.

The correlation between over-expression of proteins related to efflux pumps, such as MRP1, and functional activity of cells was investigated in 2017 by Polcari et al. By exposing wild type and drug resistant HeLa cells to a doxorubicin drug challenge (Fig. 4c), the authors monitored the apparent heterogeneous rate constant by SECM and obtained information about the expression of MRP1 by flow cytometry. Comparison of data from both instrumental approaches showed that functional activity and expression do not directly correlate.

**Discussion, Conclusions and Future Prospects**

The development of antibiotics and chemotherapeutics is one of the greatest scientific achievements of the 20th century, enabling the treatment of various infectious diseases and saving many lives of cancer patients. Unfortunately, the emergence of drug resistance due to overuse of antibiotics or ineffective treatment strategies has evolved to one of the greatest medical obstacles. To date no electrochemical sensor for the accurate determination of antibiotics in the environment, or the food industry has reached the commercial market and no chemical sensor for the routine detection of antibiotic resistance in patients has been proposed.

As outlined in this review, many common antibiotics, such as amoxicillin, ciprofloxacin, azithromycin, ampicillin have been successfully characterized using electrochemical techniques, such as cyclic voltammetry, in various buffer solutions.
Figure 6 presents an illustrative summary of detailed electrode modifications and instrumental approaches towards the electrochemical detection of analytes, such as cell metabolites and drug compounds. These techniques reach incredibly low detection limits, down to the sub-nanomolar range. However, analyses in buffer solutions do not accurately represent conditions in environmental samples or biological fluids. Inorganic and organic species present in pharmaceutical and biological samples can interfere with the detection of target drug compounds. A few studies considered such interferences with antibiotics, such as CIP. Interferences by various species such as Sr\(^{2+}\), Cd\(^{2+}\), Ba\(^{2+}\), Cr, Ni, Ca, Cu, acetate, lysine, L-glutamic acid, L-serine, conditions in environmental samples or biological fluids. Inorganic and organic species present in pharmaceutical and biological samples can interfere with the detection of target drug compounds. A few studies considered such interferences with antibiotics, such as CIP. Interferences by various species such as Sr\(^{2+}\), Cd\(^{2+}\), Ba\(^{2+}\), Cr, Ni, Ca, Cu, acetate, lysine, L-glutamic acid, L-serine,
L-histidine were studied by Lida et al. and results show influences on the electrochemical signal of CIP of about 5%, which demonstrates the importance of interference studies in quantitative analytical electrochemistry. The analysis of real samples, such as urine and blood is important to exclude interferences by common biomolecules present in samples of such highly complex composition. Interference studies become unavoidable especially when detecting multiple drugs simultaneously. Furthermore, although excellent detection limits have been achieved by electrochemistry during in vitro studies, no relationship to expected concentrations in vivo has been made in the literature. Potential application of electrochemical techniques for in vivo studies of drug detection should address the applicability of the proposed methods to therapeutic concentrations, which usually lie at the order of 1–7 mg·kg⁻¹ for individual dosages.  

Combined administration of several chemotherapeutics is considered to increase the effectiveness of the treatment, to minimize side effects, and prevent drug resistance to a specific drug. However, this strategy can lead to multidrug resistance in tumor cells with different drug-unspecific resistance mechanisms, such as MRP1 efflux pumps. 81,85 Hence, it is helpful to develop methods for the simultaneous detection of common drug combinations. Out of the literature reviewed in this work, only three studies have focused on the simultaneous detection of drug compounds. Hatamly et al. in 2018 85 detected ifosfamide, an alkylating agent, and etoposide, a topoisomerase II inhibitor, simultaneously. The achieved detection limit of ifosfamide and etoposide are 9.210 × 10⁻⁹ M and 0.718 × 10⁻⁹ M, respectively. Figure 5 demonstrates the simultaneous detection of these two drugs. Furthermore, Es’haghi et al. presented a method to monitor concentrations of capecitabine, an antimetabolite, and erlotinib, a tyrosine kinase inhibitor, in 2019. Kalambate et al. detected doxorubicin, an anthracycline antibiotics, and dasatinib, a tyrosine kinase inhibitor, simultaneously. 81 These studies are great examples for the analysis of mixtures of drugs by relatively simple electrode modifications and many similar studies on new investigational drug compounds, such as antibiotic hybrids, are expected to follow.

The increase of drug resistance in Gram-negative bacteria in particular is a major cause of concern, as many Gram-negatives cause serious infections, such as pneumonia, and few antibiotics effective against Gram-negatives have been developed due to their innate defense mechanisms including low outer membrane permeability and high number of efflux pumps. Thus, with the rise of drug resistance, many infections caused by Gram-negative bacteria have become untreatable. The development of antibiotic hybrids has gained significant attention, because reports show that some antibiotic hybrids have the ability to increase the efficacy of other antibiotics, which are unable to cross the cell membrane on their own in Gram-negative bacteria. These hybrid molecules represent interesting future targets for the quantitative detection of drug compounds by electrochemistry.

Although the presented review focuses on the direct detection of drug compounds at electrodes, it should be noted that other strategies have emerged to test the efficiency and antimicrobial properties of alternative treatment strategies by electrochemistry. The use of nanomaterials, such as silver nanoparticles, is one example. Arrassi et al. in 2017 proposed a holistic approach to release a desired amount of silver ions into human cells. Thereby, linear sweep
Voltammetry was performed to determine the precise amount of silver ions on conductive surfaces. Unfortunately, the low selectivity of silver was found to affect the growth of human cells surrounding the implants and ineffective antibacterial effects leads to the formation of a bacterial biofilm, which was reported immune to antibacterial drugs.

Drug resistance is a complex phenomenon associated with different cellular mechanisms, such as intracellular drug inactivation, drug target alteration, drug efflux pumps, cell death inhibition, and DNA damage repair. Targeting single mechanism to combat this issue is therefore often unsuccessful. Efflux pumps mediated resistance is one of the most electrochemically studied mechanisms, because electrochemistry can easily quantify the flux of electrochemically active species. However, literature shows that efflux pump protein expression is not directly correlated to a profound drug resistance phenotype. Hence, more studies are expected to focus on other drug resistance mechanism rather than drug efflux. The detection of metabolic molecules released from cells by electrochemistry therefore presents an excellent approach to tackle the phenomenon of drug resistance. Combinatorial approaches that incorporate electrochemical methods into the biochemistry toolbox are needed to address both multi-mechanism drug resistance and the analysis of complex samples.

In summary, electrochemistry with its high sensitivity, rapid data output and cost-efficient procedures represents an immense potential to aid in both the detection of resistance and to further the understanding of underlying cellular mechanisms that ultimately lead to a drug resistant phenotype in cells. The development of devices able to detect drug compounds and drug resistance rapidly, sensitively and inexpensively would be of major benefit for clinical diagnoses, disease control, environmental monitoring and food safety. Although no immediate device for the detection of drug resistance has been developed yet, the last decade has provided fundamental steps towards the understanding of electroactive drug compounds and the recognition of drug resistance activity by electrochemistry.

Figure 5. Simultaneous electrochemical detection of both anti-cancer drugs IFO and ETO as developed by B. Hatamluyi et al. 

![Voltammetry Graphs](image)
Figure 6. Schematic summary of commonly used electrode modifications and techniques to detect analytes, such as cell metabolites or drug compounds. R = reduced species; O = oxidized species.

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