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ORIGINAL PAPER

Electrochemical Sensing of Anticancer Drug Using New Electrocatalytic Approach

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Abstract
Cancer is one of the leading causes of death worldwide. It is very important to regulate drug doses for cancer patients in the treatment of cancer with drugs. Determination of drugs used as anticancer at low concentrations and determination of them with high sensitivity is of great importance for the follow-up of these drugs. Electrochemical techniques offer a wide variety of detection techniques that provide user-friendly, low-cost, and real-time monitoring compared to other conventional methods and provide low sensitivity and detection limits. By modifying the electrode surfaces with various materials, their sensitivity and detection limits can be increased. This review focuses on new electrocatalytic approaches and current developments for the electrochemical determination of anticancer drugs. In addition, anticancer drugs are classified in detail. Electrochemical sensors used in studies in recent years and verification parameters such as detection limit, linear dynamic range, sensitivity are given in tables.

Keywords Electrocatalysis · Electrocatalytic analysis · Anticancer drug · Electrochemical sensor · Nanomaterials

Abbreviations

AdSDPV	Adsorptive stripping differential pulse voltammetry
Ag	Silver
AgNCs	Silver nanocubes
AuNPs	Gold nanoparticles
CNTs	Carbon nanotubes
CPE	Carbon paste electrode
CV	Cyclic voltammetry
DPV	Differential pulse voltammetry
EIS	Electrochemical impedance spectroscopy
FE-SEM	Field emission scanning electron microscopy
FLU	Flutamide
GC–MS	Mass spectrometry–dependent gas chromatography
LC–MS	Mass spectrometry–dependent liquid chromatography
LOD	Limit of detection
MIP	Molecularly imprinted polymer
MOFs	Metal–organic frameworks
MoS_2	Molybdenum disulfide
MWCNT	Multi-walled carbon nanotube
NSCLC	Non-small cell lung cancer
PGNR	Porous graphene nanoribbon
SCLC	Small cell lung cancer
SEM	Scanning electron microscopy
SPCE	Screen-printed carbon electrode
SWV	Square wave voltammetry
SWCNT	Single-walled carbon nanotube
$ZnMn_2O_4$-PGO	$ZnMn_2O_4$ nanoparticles decorated porous reduced graphene oxide nanocomposite

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1 Introduction

Cancer is a global pandemic that causes abnormal cell development and spreads to other organs or tissues of the body. It is one of the leading causes of death worldwide, causing an estimated 9.6 million deaths in 2018 [1]. Various treatment methods are used for cancer. Major modalities include

surgery, radiotherapy, and chemotherapy. Chemotherapy can be used alone or in combination with other therapies for fighting the tumor cells. The surgical method, which is accepted as the primary treatment, especially for solid tumors, is the process of removing the tumor from the tissue or organ during an operation. Radiation therapy, a local treatment method, is one of the essential methods applied to shrink tumors and kill cancer cells by using high-energy particles (gamma rays, X-rays, electron beams, or protons) [1, 2].

Researchers have determined the availability of a new generation of drugs for cancer treatments that have undergone advanced clinical trials. However, using more sensitive and selective analytical techniques will be important for qualitative and quantitative analysis of drugs. Correspondingly, researchers have used different analytical methods such as chromatography, capillary electrophoresis, spectroscopy, and electrochemical methods to detect cancer drugs [3–6]. Today, techniques such as mass spectrometry–dependent liquid chromatography (LC–MS), capillary electrophoresis, mass spectrometry–dependent gas chromatography (GC–MS) are still extensively preferred for analyzing anticancer drugs. These techniques are sensitive, specific, and precise. However, the devices generally have disadvantages such as expensiveness, overuse of organic solvents, and lengthy analysis time [7].

Contrary to these methods, electroanalytical methods have recently been used in the analysis of anticancer drugs due to their more sensitive, more selective, environmentally friendly, short analysis time, and low cost [8, 9]. Electroanalytical techniques are frequently used to determine anticancer drugs. Solid electrodes such as gold [10], platinum [11], and carbon electrode [12] are preferred in such studies. Modified electrodes have a considerably different electrode surface than unmodified ones, resulting in more sensitive and selective results. Nanomaterials as surface modifiers are very beneficial in electrochemical analyses because they give excellent conductivity and electrocatalytic effects. In addition, these electrodes have many advantages, such as widening the surface area of the electrode by using different modifications and making electron transfer easier afterward [13–15].

In terms of electrical conductivity and biocompatibility, materials with high electrocatalytic effects such as titanium, zinc, magnesium, and their magnetic compounds, metal oxide nanostructures made of various metals containing nickel, magnesium, and iron are highly preferred in electrochemical applications due to their electrocatalytic properties. In addition, the combination of carbon-based materials with magnetic spinel ferrite nanoparticles is frequently used in studies because it improves electrochemical properties [16]. Bimetal type nanomaterials and composites with nontoxic, chemically, and thermally more stable properties are other important structures that show electrocatalytic properties [17–19]. These materials are used in many fields, such as photodegradation, supercapacitors, solar cells, and electrocatalysis [20–22]. Furthermore, these nanomaterials with high surface area and active sites have recently been preferred as electrochemical sensors. In particular, metal titanate nanocomposites as electrode materials have been the focus [23].

Recently, MIP-based electrochemical sensors used with microporous structures are another method showing electrocatalytic activity. Although there are problems with using the MIP method as electrochemical sensors, these shortcomings are overcome by using new types of crystalline materials and microporous metal–organic frameworks (MOFs). Although MIPs have high selectivity for the target molecule, they are a limited method for fast and efficient detection of analytes due to low-speed mass transfer and poor site accessibility [24]. MOFs with high porosity and large surface area are predicted to form active sites for electrocatalysis on the MIP polymeric network surface [8, 25–28]. However, single-component MOFs are often used in combination with nanomaterials to enhance the electrocatalytic properties of MIP. This is due to the poor conductivity and low signal-passing capacity of single-component MOFs [29]. A different work with electrocatalytic properties is the development of a composite DNA biosensor containing Pt, Pd, CdO, and single-walled carbon nanotube (SWCNT) for cyanazine herbicide determination. Another recent study to improve electrochemical conductivity is the fabrication of an immunosensor containing gold nanoparticles/porous graphene nanoribbon (AuNPs/PGNR), silver nanocubes (AgNCs), and molybdenum disulfide (MoS_2) for the detection of aflatoxin B1 (AFB1) [30, 31].

This review aims to explain new electrocatalytic approaches and current developments to determine anticancer drugs (natural products, alkylating agents, antimetabolites, and hormones) using electrochemical methods. We also detail brief descriptions of anticancer medications, electrochemical sensors used in recent studies, and verification parameters such as limit of detection, linear dynamic range, sensitivity. This review focuses on new electrocatalytic approaches and the most recent developments for the electrochemical determination of anticancer drugs. Reviews in the literature have generally focused on drug delivery. In addition, detailed information about anticancer drugs is given in this review.

2 Classification of Anticancer Drugs

Cancer is a complex process that includes many steps such as prevention, diagnosis, treatment, and monitoring. It is predicted that cancer, which is considered to be the most

challenging health problem in the world today, will maintain its effect for many years to come [32]. However, thanks to advancements in biomedical research, these different processes associated with cancer are enlightened. Thus, it provides an opportunity for the development of new anticancer agents [33].

The drugs used against cancer, anticancer drugs, can be classified according to their target therapy, such as immunotherapeutic agents, chemotherapeutic agents, and hormonal therapy agents [34]. The classification is not limited to this, but anticancer drugs are also discussed according to their mechanism of action or chemical structure in different sources.

In the most general sense, anticancer drugs either focus on killing the proliferative cells or specifically target the cancer-related molecules [35]. The first group is cytotoxic agents, and most of them have been used since the early days of cancer therapy [36]. Their major drawback is the strong adverse effects caused by the interaction with healthy cells such as bone marrow and hair follicles. On the other hand, targeted therapy offers an innovative approach by focusing only on tumor cells and causing less harmful adverse effects [37]. Drug research and development studies on cancer continue at full speed around the world. New ones, including those whose clinical trials are ongoing and have received FDA approval, are joining anticancer drugs. Currently used anticancer drugs are summarized in Table 1.

3 Electrocatalytic Applications on Electrochemical Analysis of Anticancer Drugs

Determination of drugs used as anticancer at low concentrations and analysis with high-sensitivity techniques are of great importance in chemotherapy follow-up. Techniques such as high-performance liquid chromatography, liquid chromatography-mass spectrometry, spectrophotometry, and capillary electrophoresis techniques are used to determine the concentration of anticancer drugs. However, these techniques have several disadvantages, such as pre-concentration steps, costly and requiring expertise, including derivatization and sampling before analysis [59, 60]. In order to overcome these disadvantages, many advantages of electrochemical strategies such as fast, sensitive, selective, and wide linear concentration range can be exploited. For the detection of anticancer drugs, methods such as amperometry, voltammetry, and potentiometry are used to detect them electrochemically. Of these methods, voltammetry has the most applications for identifying anticancer agents. Glassy carbon, carbon paste, and modified electrodes were used as working electrodes for electroanalytical detection of anticancer drugs. One of the critical developments in electroanalytical chemistry is the modification of the surface of the electrodes. Recent studies on anticancer drugs using electrochemical methods are summarized in Table 2.

In recent years, it has focused on developing efficient heterogeneous electrocatalysts with higher electrochemical activity to detect many organic and inorganic compounds with selective, sensitive, and stable detection platforms. Nanostructured metal particles (Au, Pd, and Pt) show an important role in catalytic and electrocatalytic reactions, especially in sensing platforms. In recent studies, Au-supported metal oxides, polymers, graphene, and ceramic nanocomposites have been used as nanoscale electrocatalysts to construct catalytic nano-interfaces of electronic devices to obtain highly sensitive and selective electrochemical sensors [61]. In this section, research using electrochemical techniques for the sensitive and selective determination of anticancer drugs is discussed [62–66].

Dehdashtian et al. developed a sensor for the electrochemical detection of the anticancer drug dacarbazine using a multi-walled carbon nanotube (MWCNT) modified carbon paste electrode (CPE) [67]. Carbon nanotubes (CNTs) expose excellent electrocatalytic, electrical, and mechanical properties. The electrochemical behavior of dacarbazine was examined using cyclic voltammetry (CV) and differential pulse voltammetry (DPV) for quantification. The developed modified electrode significantly increased the oxidation peak current of dacarbazine. The electronic transfer property of the modified electrode was characterized by electrochemical impedance spectroscopy (EIS), and the morphology of the electrode was characterized by scanning electron microscopy (SEM). Under the optimum conditions, the modified electrode showed a linear response over concentration ranging from 0.4 to 40 nM and 40–2500 nM dacarbazine, with a detection limit of (LOD) 0.12 nM. The fabricated sensor showed high sensitivity, good stability and was performed for the detection of dacarbazine in the pharmaceutical sample with a good recovery percentage.

In another study, Shams, and Yari used a silver decorated multi-walled carbon nanotube (Ag-MWCNT) modified glassy carbon electrode for voltammetric detection of the anticancer drug Epirubicin [68]. Ag-MWCNT/GCE has well electrical conductivity and reasonable electrocatalytic activity. This sensor was applied to investigate Epirubicin by CV (Fig. 1) and square wave voltammetry (SWV) (Fig. 2). Field emission scanning electron microscopy (FE-SEM), TEM, EDX, and XRD methods were applied for the characterization of the proposed electrode. In addition, EIS was used to examine the electrochemical properties of the new electrode. With the proposed sensor, analysis of Epirubicin in pharmaceuticals, blood, or urine samples was performed with high sensitivity with a low detection limit in a wide linear dynamic range.

Table 1 Classification of the most frequently used anticancer drugs

Group	Drugs	Mechanism of action	Clinical use	Adverse effects	Refs
Antimetabolites	5-Fluorouracil, 6-Mercaptopurine, 6-Thioguanine, Capecitabine, Cladribine, Clofarabine, Cytarabine, Decitabine, Fludarabine, Gemcitabine, Methotrexate, Nelarabine, Nolatrexed, Pemetrexed, Pentostatin, Pralatrexate	Antimetabolites are effective on the S phase of DNA synthesis, and they interact with the metabolism of proliferating cells by taking advantage of the differences in the metabolism of healthy cells and cancer cells	Colorectal cancer, breast cancer, gastroesophageal cancer, leukemia, hepatocellular cancer, non-Hodgkin's lymphoma, pancreatic cancer, bladder cancer, non-small cell lung cancer (NSCLC), head and neck cancer, lymphoma, liver cancer, mesothelioma	Nausea, vomiting, diarrhea, bone marrow depression, myelosuppression, immunosuppression, fatigue	[38–41]
Topoisomerase-I Inhibitors	Irinotecan, Topotecan	Inhibition of topoisomerase-I enzyme and preventing the resealing of DNA strands during DNA synthesis of single-stranded DNA	Ovarian cancer, small cell lung cancer (SCLC), colorectal cancer, pancreatic cancer	Nausea, diarrhea, myelosuppression, neutropenia, thrombocytopenia, anemia	[38, 42–45]
Topoisomerase-II inhibitors	Etoposide, Teniposide	Inhibition of topoisomerase-II enzyme and preventing the resealing of DNA strands during DNA synthesis of double-stranded DNA	Lymphoma, non-Hodgkin's lymphoma, leukemia, lung cancer, testicular cancer	Nausea, vomiting, bone marrow suppression, hypotension, hypersensitivity	[38, 42–44]
Taxanes	Cabazitaxel, Docetaxel, Paclitaxel	Antimitotic activity on the M phase of DNA synthesis	Ovarian cancer, breast cancer, NSCLC, SCLC, head and neck cancer, esophageal cancer, prostate cancer, gastric cancer, melanoma, pancreatic cancer	Nausea, vomiting, hypersensitivity, neurotoxicity, myelosuppression, hypotension, arrhythmia, neutropenia, leukopenia	[38, 46–49]
Vinca alkaloids	Vinblastine, Vincristine, Vindesine, Vinflunine, Vinorelbine	Inhibition of tubulin polymerization and disruption of cell cycle	Lymphoma, breast cancer, rhabdomyosarcoma, neuroblastoma, ovarian cancer, NSCLC, testicular cancer, bladder cancer	Nausea, vomiting, alopecia, fatigue, low blood count, constipation, muscular weakness, loss of reflexes, neutropenia, leukopenia, anemia, thrombocytopenia, diarrhea	[38, 50–52]
Antimicrotubule inhibitors	Eribulin, Ixabepilone	Inhibition of microtubule dynamics	Breast cancer	Neutropenia, peripheral neuropathy	[38, 53, 54]
Antitumor antibiotics	Bleomycin, Dactinomycin, Mitomycin, Plicamycin	Inhibition of DNA synthesis and repair, inhibition of DNA-directed RNA synthesis, cross-linking with DNA by alkylation, inhibition of mRNA synthesis	Breast cancer, squamous cell carcinoma of the skin, anus, and cervix, pancreatic cancer, lymphoma, leukemia, head and neck cancer, ovarian cancer, testicular cancer	Nausea, vomiting, alopecia, fatigue, myelosuppression, mucositis, hemorrhagic syndrome, liver and kidney toxicity	[35, 36, 53–56]
Alkylating agents	Altretamine, Bendamustine, Busulfan, Carmustine, Chlorambucil, Cyclophosphamide, Dacarbazine, Lomustine, Mechlorethamine, Melphalan, Streptozocin, Temozolomide, Thiotepa	Formation of alkyl radicals and interaction with DNA, RNA and proteins	Lymphoma, leukemia, breast cancer, lung cancer, ovarian cancer, brain cancer, bladder cancer, prostate cancer, testicular cancer	Nausea, vomiting, fatigue, myelosuppression, peripheral neuropathy, nephrotoxicity, alopecia, hepatotoxicity, dermatoxicity, neurotoxicity, pulmonary toxicity	[37, 38, 57]

Table 1 (continued)

Group	Drugs	Mechanism of action	Clinical use	Adverse effects	Refs
Platinum analogs	Carboplatin, Cisplatin, Oxaliplatin	Formation of interstrand and intrastrand cross-links in DNA	NSCLC, SCLC, head and neck cancer, gastroesophageal cancer, colorectal cancer, pancreatic cancer, testicular cancer, prostate cancer, cervical cancer, ovarian cancer, bladder cancer, sarcoma	Nausea, vomiting, myelosuppression, nephrotoxicity, neurotoxicity, peripheral neuropathy, ototoxicity, diarrhea	[37, 38]
Anthracyclines	Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mitoxantrone	Intercalation between DNA and RNA base pairs and inhibition of DNA and RNA synthesis	Sarcoma, leukemia, myeloma, lymphoma, breast cancer, ovarian cancer, testicular cancer, lung cancer, thyroid cancer, bladder cancer, stomach cancer, liver cancer, gastroesophageal cancer	Nausea, vomiting, myelosuppression, neutropenia, thrombocytopenia, cardiotoxicity, dermatoxicity, mucositis, alopecia	[37, 38, 58]
Miscellaneous	Abiraterone, Ado-trastuzumab, Belinostat, Bevacizumab, Bicalutamide, Bortezomib, Bosutinib, Brentuximab, Carfilzomib, Cetuximab, Enzalutamide, Erlotinib, Everolimus, Flutamide, Ibrutinib, Idelalisib, Imatinib, Lapatinib, Olaparib, Palbociclib, Panitimumab, Panobinostat, Pazopanib, Pertuzumab, Raloxifene, Rituximab, Romidepsin, Ruxolitinib, Sorafenib, Sunitinib, Tamoxifen, Trastuzumab, Vorinostat, Ziv-aflibercept,	Targeted therapy based on specific pathways such as inhibition of tyrosine kinase, epidermal growth factor receptor and vascular endothelial growth factor etc	Leukemia, NSCLC, pancreatic cancer, colorectal cancer, head and neck cancer, cervical cancer, ovarian cancer, thyroid cancer, lymphoma, breast cancer, melanoma, renal cell cancer, multiple myeloma	Nausea, vomiting, fever, cough, diarrhea, fatigue, skin rash, myelosuppression, immunosuppression, peripheral neuropathy, hepatotoxicity, myalgia, mucositis, gastrointestinal perforations, cardiac toxicity, thrombocytopenia, hand-foot syndrome, venous thromboembolism	[37, 38]

Table 2 Selected recent electrochemical studies of analysis of the most frequently used anticancer drugs

Anticancer drug	Electrode	Method	Application media	Linear Range	LOD	References
Dacarbazine	MWCNT/CPE	DPV	Pharmaceutical sample	0.4 to 40 nM and 40 to 2500 nM	0.12 nM	[67]
Dasatinib	Pd@Pt/MWCNT/GCE	AdSSWV	Blood serum and urine samples	38–9880 nM	6.72 nM	[70]
Daunorubicin	c-NFs-PGE	DPV	-	5–20 µM	2.93 µM	[71]
	ga-NFs-PGE				2.06 µM	
Docetaxel	Au-MWCNTs/GCE	DPASV	Human urine and human serum	0.3 – 3.3 µmol L^{-1}	90 nmol L^{-1}	[72]
Doxorubicin	Pd@Pt/MWCNT/GCE	AdSSWV	Blood serum and urine samples	4.4–8580 nM	0.86 nM	[70]
Doxorubicin Hydrochloride	GQD/GCE	DPV	Human plasma samples	0.018–3.60 µM	0.016 µM	[73]
Epirubicin	Ag-MWCNT/GCE	SWV	Pharmaceuticals, blood or urine samples	0.003—0.25 µM	1.0×10^{-3} µM	[68]
Erlotinib	β-CD/GCE	AdSSWV	Pharmaceutical dosage form	1.0×10^{-8}—8.0×10^{-6} M	1.07×10^{-9} M	[74]
Etoposide	Au/Pd@rGO@p(L-Cys)/PGE	DPV	Biological samples and pharmaceutical compounds	0.01 to 40.0 µM	0.718 nM	[75]
Flutamide	N-CQD@Co_3O_4/MWCNTs/ GCE	DPV	Human urine sample	0.05–590 µM	0.0169 µM	[76]
Flutamide	AuE	DPV	0.1 M Phosphate buffer (pH. 7)	6 to 60 µM and 100–600 µM	1.8 µM	[77]
Gemcitabine	NH_2-MWCNTs/GCE	DPV	Acetate buffer of pH 4.70	10–40 µg mL^{-1}	–	[65]
Hydroxyurea	HEH/Ag@Pt-CNPE	DPV	Phosphate buffer (pH. 7)	0.05 µM to 1.0 mM	23.0 nM	[78]
Hydroxyurea	nano-TiO_2/CPE	DPV	Phosphate buffer pH 2.0	8–180 mg L^{-1}	0.16 mg L^{-1}	[79]
Idarubicin	Ru@VC/GCE	AdSDPV	Human serum sample	5×10^{-8}—1×10^{-6} M	9.25×10^{-9} M	[80]
Ifosfamide	Au/Pd@rGO@p(L-Cys)/PGE	DPV	Biological samples and pharmaceutical compounds	0.10 to 90.0 µM	9.210 nM	[75]
Lomustine	MF/GPE	SWCASV	Human blood and urine samples	1.92×10^{-7}–1.36×10^{-5} M	8.13×10^{-8} M	[81]
Methotrexate	$CuCr_2O_4$/CuO/IL/CPE	DPV	Blood and urine samples	0.1–300 µM	25 nM	[82]
Mitoxantrone	MWCNT-Ag-PT GCE	DPV	Urine and blood serum samples	0.05 to 100.0 µM	13 nM	[83]
Paclitaxel	PPy/MWCNTs/PGE	DPV	–	0.1 to 50 mg L^{-1}	1.55×10^{-8} M	[84]
Pemetrexed	MIP/CQD/SPCE	DPV	Synthetic serum sample	5×10^{-9}–1×10^{-7} M	1.60×10^{-9} M	[85]
Sorafenib	Chitosan/-COOH MWCNT/GCE	AdSDPV	Spiked serum	1×10^{-8}–8×10^{-8} M and 1×10^{-7}–8×10^{-7} M	9.6×10^{-10} M	[69]
Tamoxifen	CeO_2–MWCNTs/CCE	DPV	Real samples	0.2–40 nM	0.132 nM	[86]
5-Flurouracil	Pt-SWCNTs/nH3MHP/CPE	SWV	Real samples	1.0 nM–520 µM	0.4 nM	[87]
5-Flurouracil	MWCNTPE	DPV	Pharmaceutical and urine samples	0.1×10^{-6}–5.0×10^{-6} M	3.94×10^{-8} M	[88]
Flutamide	$ZnMn_2O_4$-PGO/SPCE	DPV	Human urine sample	0.05–3.5 µM	8 nM	[89]
Flutamide	Mn_2O_3@h-BN	DPV	Human urine sample	0.08–1940 µM	8.5 nM	[90]

AdSDPV adsorptive stripping differential pulse voltammetry, *AdSSWV* adsorptive stripping square wave voltammetry, *SWCASV* square wave cathodic adsorptive stripping voltammetry, *AuE* gold electrode, *BDDE* boron doped diamond electrode, *CNTs* carbon nanotubes, *CQD* carbon quantum dot, *CPE* carbon paste electrode, *DPV* differential pulse voltammetry, *GCE* glassy carbon electrode, *GPE* graphene paste electrode, *SPCE* screen-printed carbon electrode, *PGE* pencil graphite electrode, *MF/GPE* mercury film-coated graphite pencil electrode, *MWCNTPE* multi-walled carbon nanotubes-paraffin oil paste electrode, *GQD* graphene quantum dot, *Ag* silver nanoparticles, *IL* ionic liquid, *MIP* molecularly imprinted polymer, *MWCNTs* multiwall carbon nanotubes, *N-CQD* nitrogen-doped carbon quantum dots, *nH3MHP* n-hexyl-3-methylimidazolium hexafluorophosphate, *p(L-Cys)* poly (L-Cysteine), *PT* polythiophene, *rGO* reduce graphene oxide, *PGO* porous reduced graphene oxide, *h-BN* hexagonal boron nitride

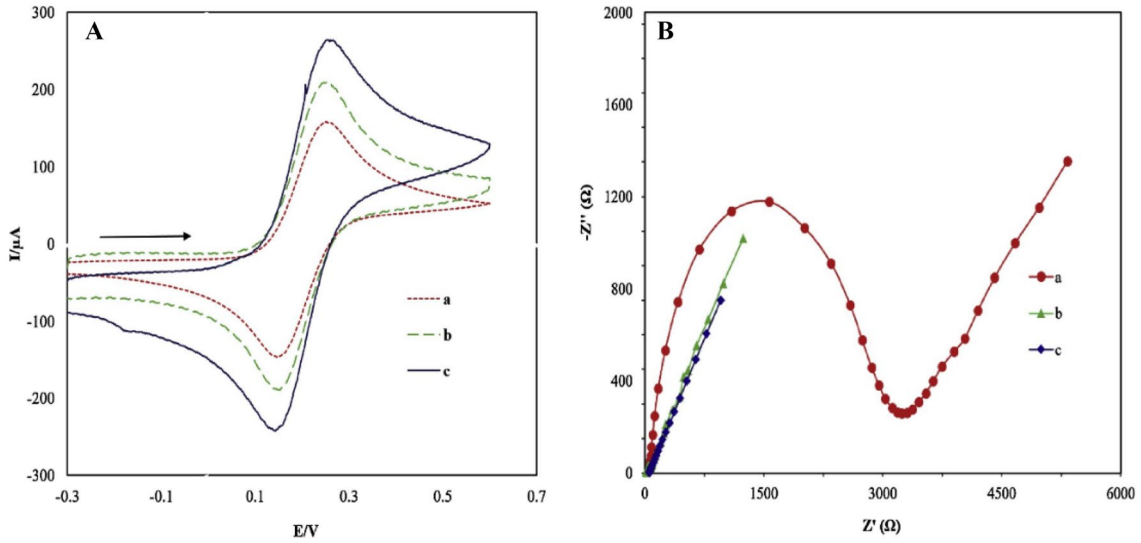


Fig. 1 Cyclic voltammograms (**A**) and EIS characteristics (**B**) of 5 mM $[Fe(CN)6]^{3-/4-}$ a solution containing 0.15 M KCl at a bare GCE (*a*), MWCNT/GCE (*b*) and Ag-MWCNT/GCE (c). Reprinted from ref [68] with permission from Elsevier

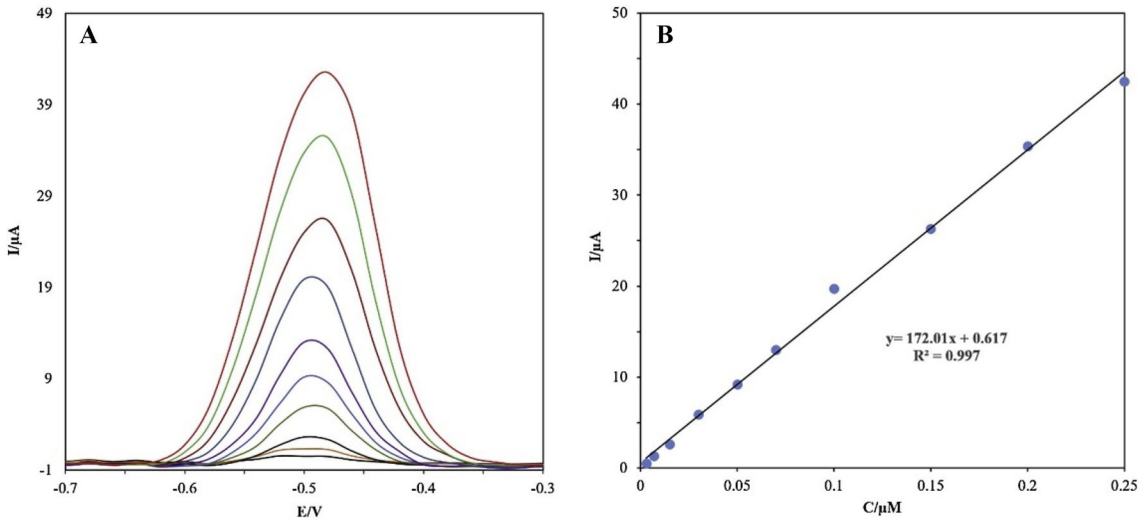


Fig. 2 SWV voltammograms of different concentrations of EP (**A**) and linear relationship between (Ip) and EP concentration (CEP) in the range 0.003–0.25 μM (**B**). Measurement conditions: pH 4.7, accumulation time = 23 min, pulse amplitude = 0.030 V, step width = 0.010 V, and frequency 25 Hz over the potential range of − 0.8 to − 0.2 V versus SCE, under open-circuit. Reprinted from ref [68]. with permission from Elsevier

A sensor was developed by Karadas-Bakirhan et al. for the detection of the anticancer drug sorafenib in serum by adsorptive stripping differential pulse voltammetry (AdS-DPV) using a chitosan/multi-walled carbon nanotube modified glassy carbon electrode (Chitosan/-COOH MWCNT/GCE) (Fig. 3) [69]. The proposed sensor provided a LOD 9.6×10^{-10} M in concentration ranges $1\times10^{-8}-8\times10^{-8}$ M and $1\times10^{-7}-8\times10^{-7}$ M. High recoveries were achieved for the spiked serum samples.

When the recent studies on the detection of anticancer drugs are reviewed, electrochemical sensors have been developed using nanomaterials, magnetic components, and various metal-containing materials. These materials, which provide increasing effects on electrical conductivity and electron transfer rate, have been used alone or in combination. This feature makes the sensor more selective and more sensitive. In electrochemical sensor applications, it is achieved through modified electrodes with higher sensitivity,

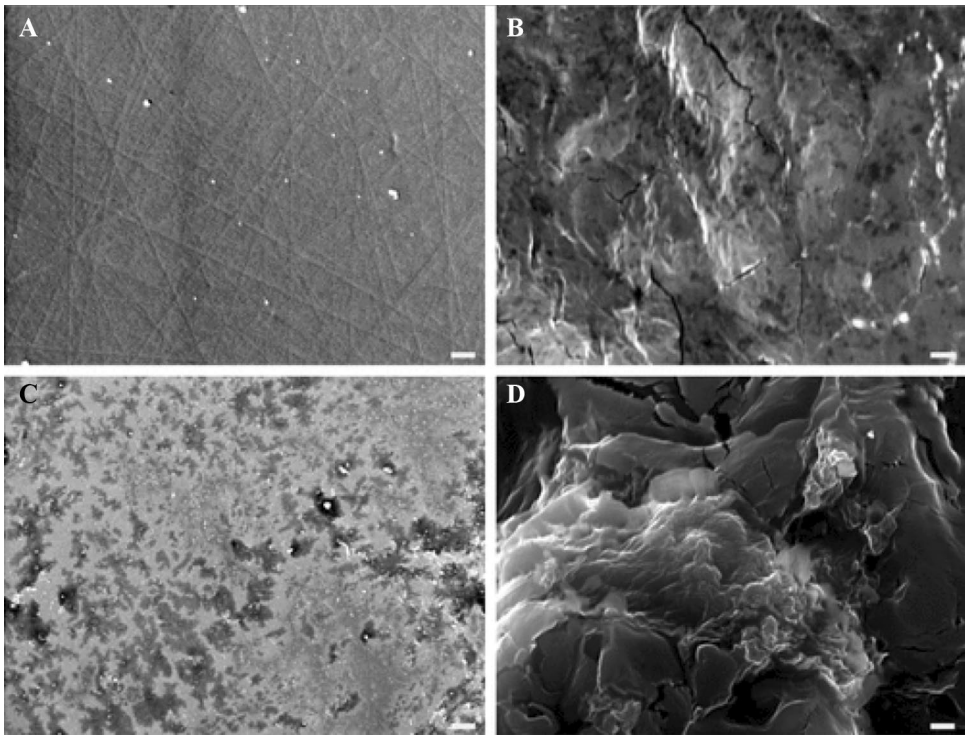


Fig. 3 SEM images of **a** bare GCE **b** Chitosan/GCE, **c**–COOH MWCNT/GCE and **d** Chitosan/-COOH MWCNT/GCE**.** Reprinted from ref [69]. with permission from Elsevier

better stability, and improved electrocatalytic activity to analyze anticancer drugs.

For example, in their study, Venkatesh et al. [89] utilized $ZnMn_2O_4$ nanoparticles decorated porous reduced graphene oxide nanocomposite ($ZnMn_2O_4$-PGO) based on anticancer drug flutamide (FLU) detection. Firstly, the new nanocomposite material, which occurred in a three-step synthesis process, consists of $ZnMn_2O_4$ nanoparticles and porous reduced graphene oxide nanolayers. The synthesized nanocomposite material was produced as disposable for the determination of anticancer FLU. The expected results of the nanocomposite material showed that the structure has a large surface area, and the electronic conductivity is relatively high. Moreover, $ZnMn_2O_4$-PGO nanocomposite modified screen-printed carbon electrode (SPCE) was found to exhibit electrocatalytic activity. Highly sensitive and selective results were obtained for the detection of FLU using DPV and EIS. The $ZnMn_2O_4$-PGO/SPCE composites electrochemical sensor exhibited a low LOD of 8.0 nM, and linear dynamic range vary from 0.05 to 3.5 µM under optimal experimental conditions. In addition, the $ZnMn_2O_4$-PGO/SPCE nanocomposite sensor was successfully applied to human urine samples and interfering compounds (Fig. 4).

In another work by Kesavan et al. [90], an electrochemical sensor was fabricated based on manganese oxide supported on hexagonal boron nitride (Mn_2O_3@h-BN) nanocomposite for the determination of flutamide (FLT). The characterizations of the Mn_2O_3@h-BN based nanocomposite material (XRD, FTIR, SEM, TEM, etc.) have been successfully completed (Fig. 5). The study revealed that Mn_2O_3@h-BN nanocomposite enhances the electrocatalytic performance for FLT detection. The developed electrochemical sensor exhibited a wide linear range between 0.08 and 1940.0 µM and a LOD of 8.5 nM for FLT. Furthermore, the developed Mn_2O_3@h-BN modified sensor has been applied to the determination of FLT in human urine samples. Furthermore, the suggested modified electrode's repeatability and reproducibility examination revealed an RSD of less than 1%, indicating that it may be used for sensing applications.

In summary, it showed that these two sensors, which were published in 2021 and developed for the detection of anticancer flutamide, do not have significant advantages over each other. The Mn_2O_3@h-BN/GCE-based nanocomposite modified sensor showed a wide linear range compared to the $ZnMn_2O_4$-PGO/SPCE nanocomposite modified sensor. The lowest detection limit of both electrochemical sensors was around 8.0 nM. It has been proven that metal ions in the nanocomposite increase electrocatalytic activity. In terms of sensitivity and selectivity, as well as recovery results, the proposed electrodes were satisfactory.

4 Conclusion

It is crucial to early treatment immediately after the diagnosis of cancer. The arrangement of drug doses is vital for cancer patients in drug therapy. The patient loses his life because of overdose; on the other hand, he cannot recover

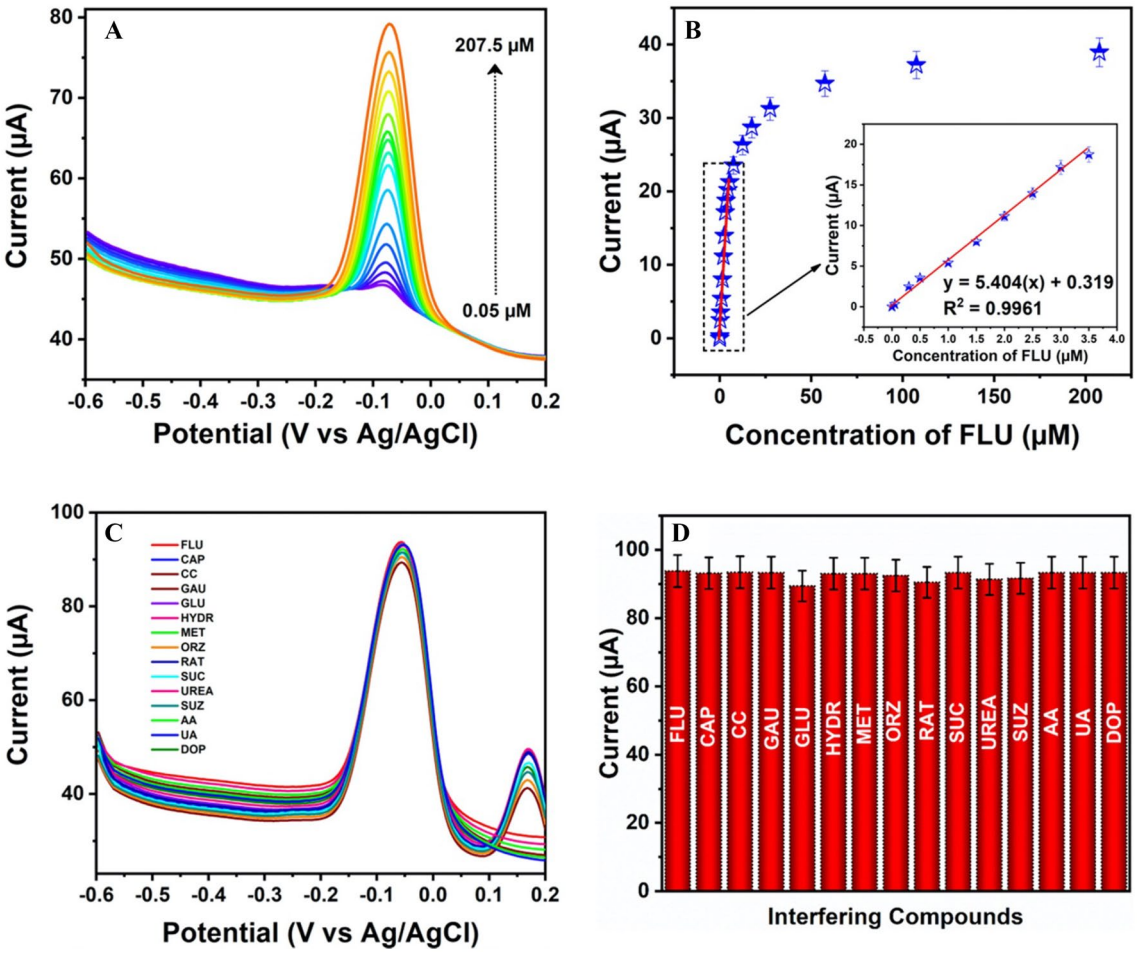


Fig. 4 **A** DPV response at different concentration of FLU (0.05–207.5 µM) in PBS (0.05 M, pH:7.0). **B** Corresponding linear calibration plot concentration of FLU (µM) vs current (µA). **C** Anodic current response for $ZnMn_2O_4$-PGO/SPCE with different interfering compounds. **D** corresponding bar diagram interfering compounds vs current. Reprinted from ref [89]. with permission from Elsevier

because of inadequate treatment. Many analytical methods have been developed, such as chromatography, spectrophotometry, electrochemistry, etc. Moreover, each of them has positive and negative attributes. Firstly, the analytical method should be fast, cheap, and user-friendly. Then, the developed technique should be accurate, sensitive, and selective. The electrochemical methods provide these opportunities to users.

The carbon-based or metallic nanomaterials have some electrocatalytic activity toward organic oxidizable drug active compounds in a suitable aqueous electrolyte solution. Electrode surface modifications exhibiting electrocatalytic activity can generate reducing equivalents (protons and electrons) through their reactions and transport them to an external electron acceptor. Based on the electrocatalytic activities of carbon-based or metallic nanomaterials and their performance for the direct application to the drug analysis by electrochemical methods, they have been proven to be a suitable electrode material for forming nanosensors. This study aims to collect the recently published related papers about nanomaterials-based sensors to determine anticancer drugs. The advancement of nanomaterials and electrochemical sensing methods were explained in detail. The nanomaterials have enhanced the performances of an electrochemical sensor in terms of sensitive, rapid and accurate, detection of anticancer drugs. Especially, the complex of various nanomaterials finds out the synergistic effect. Multi-walled carbon nanotubes combined with metal nanoparticles are widely utilized for the fabrication of anticancer drug nanosensors. Differential pulse voltammetry is extensively applied for the analysis of the anticancer drug.

5 Future Perspective

Further development in this research field should be focused on enlightening the relation between nanomaterials and transducers. The performance of carbon-based catalysts

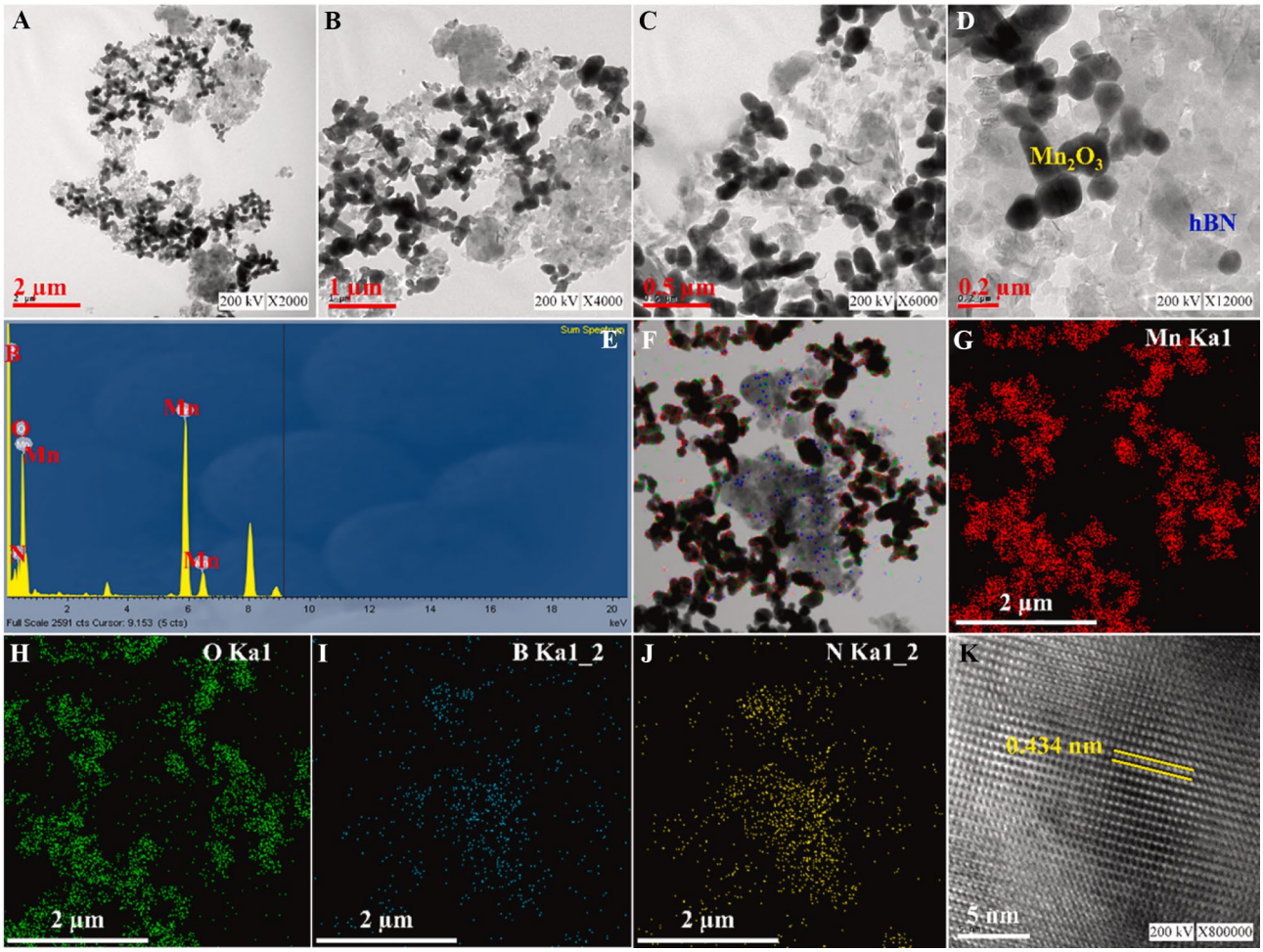


Fig. 5 **a**–**d** TEM image of Mn_2O_3@h-BN at different magnifications, **e** EDS analysis, **f**–**j** elemental mapping of Mn_2O_3@h-BN consists of elements like manganese (Mn), oxygen (O), boron (B), and nitrogen (N), **k** HRTEM image of Mn_2O_3. Reprinted from Ref [90] with permission from Elsevier

can surpass the performance metrics of conventional systems; high volume production at a low cost will be crucial to achieving commercial success. In recent years, significant progress has been realized towards scaling up the production quantities of carbon-based nanomaterials. Researchers and industry must team up to translate this success towards the best performing carbon-based electrocatalysts. Only then can these materials be integrated into practical devices for widespread application. Moreover, the nanomaterials-based electrochemical sensors are expected to offer highly reliable on-site analysis of anticancer in the biological sample. Furthermore, integrating electrochemical nanosensors and communication devices (e.g., smartphones and tablets) provides desirable, efficient portable devices for anticancer diagnostics.

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