Recent Advances in Applications of Voltammetric Sensors Modified with Ferrocene and Its Derivatives

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ABSTRACT: This study is on current developments concerning ferrocene (FC) and its derivatives on the basis of electrochemical biosensors and sensors. The distinct physiochemical characteristics of FC have enabled the development of new sensor devices, specifically electrochemical sensors. Several articles have focused on the implementation of FC as an electrode constituent while discussing its electrochemical behavior. Furthermore, typical FC-design-based biosensors and sensors are considered as well as practical examples. The favorable design of FC-based biosensors and general sensors needs adequate control of their chemical and physical characteristics in addition to their surface immobilization and functionalization.

1. INTRODUCTION

Ferrocene was discovered in 1951,¹ and its formation was clarified by Wilkinson et al.² The common features of ferrocene reactivity to benzene were the reason scientists named this novel iron sandwiched compound ferrocene.² Ferrocene structure disclosure was an advancement in the field of chemistry and led to the emergence of organometallic chemistry. Ferrocene quickly became the focus of scientists and technical communities due to its unique chemistry. Scientists began to develop synthetic methods based on ferrocene derivatives and determined its use in a wide range of scientific zones.³

Air- and water-stable, ferrocene (FC) is subjected to reversible oxidation to FC⁺; hence, it is a favorable internal standard in electrochemistry. The stability of ferrocene enables its rings as derivatives via typical reactions in organic chemistry, providing access to numerous organometallic compounds. In general, ferrocene chemical and physical characteristics including its derivatives may be applied in an extensive range of subject areas including sensing, materials science, and catalysis.³ Herein, the current progress in electrode modification by ferrocene is reviewed along with its advancements in detecting various analytes. Ferrocene as a type of metalocene exhibited metallic and nonmetallic features. Their special electronic configuration allows them to have attractive electrochemical properties. The unique bonding between the metallic species (d-orbital) and nonmetallic species (π bond) provided a smooth electronic transfer pathway, suggesting interesting sensing applications.

2. FERROCENE AND FERROCENE DERIVATIVE MODIFIED ELECTRODES FOR BIOSENSING APPLICATIONS

The design of sensitive and user-friendly analytical processes to determine contaminants such as metal ions, drugs, toxins, and pesticides is vital in environmental analysis and food safety. Traditional analytical approaches in such an analysis are on the basis of chromatographic methods that enable selective and sensitive detection.⁴a In spite of these advantages, chromatographic methods necessitate skilled technicians for operation and are not sufficient for screening assessment. Thus, there are continuous advancements in expeditious and low-cost devices for environmental monitoring such as in situ analysis. Electrochemical biosensors are typically robust analytical tools enabling multiplexed analysis, prompt response, specificity, and sensitivity and are cost-efficient.³

Tajik et al. incorporated a ferrocene−derivative composite, 1-(4-bromobenzyl)-4-ferrocenyl-1H-[1,2,3]-triazole (1,4-BBFT), to create an adjusted graphene past electrode. Hydrophilic ionic liquid (n-hexyl-3-methylimidazolium hexafluorophosphate) was binded to assemble the adjusted electrode. At the modified electrode surface, the electro-oxidation of isoproterenol was examined by using square wave
voltammetry (SWV), chronoamperometry (CHA), and cyclic voltammetry (CV). At optimal conditions, the SWV peak current of isoproterenol linearly increased with isoproterenol concentrations within the $6.0 \times 10^{-8}$ to $7.0 \times 10^{-4}$ M range and at a 12.0 nM detection limit. This modified electrode demonstrates favorable resolution among the voltammetric peaks of theophylline, acaminophen, and isoproterenol, making it adequate for isoproterenol determination with the existence of theophylline and acaminophen within real samples.

The evaluation of electrochemical activity and methyldopa determination was conducted by Salaminpour et al. for a carbon nanotube (CNT) adjusted carbon paste electrode (CPE) and FC acting as an electrocatalyst. The outcome of CV showed that the FC and CNT scheme can significantly increase electrocatalytic behavior toward methyldopa oxidation. This improvement led to a substantial enhancement of methyldopa anodic peak current and enables the creation of an extremely sensitive voltammetric sensor to detect methyldopa within real samples. At optimal conditions, the sensor has a wider dynamic range of 0.1–500 μM at a 0.08 ± 0.002 μM detection limit. The suggested approach enabled the detection of methyldopa in the proximity of folic acid.

Beitolli at al. synthesized Au–ZnO nanoparticles and 2-chlorobenzoyl ferrocene (2CBF) and applied it for glutathione electro-oxidation at the exterior of the adjusted electrode. At optimal conditions, the SWV peak current of glutathione linearly increased with concentrations of glutathione with the $5.0 \times 10^{-8}$ to $2.0 \times 10^{-7}$ M range with 0.659 μA μM$^{-1}$ sensitivity and a 20.0 nM method detection limit. The modified electrode demonstrated a favorable clarification among the voltammetric peaks of tryptophan and glutathione, making it adequate to detect glutathione with the existence of tryptophan within real samples.

Karimi-Maleh et al. designed a ferrocene-adjusted carbon nanotube paste electrode which was applied as a sensitive means of determining N-acetylcysteine at trace levels. The use of a highly conductive carbon nanotube can significantly improve the sensitivity. It was proven by double step chronamperometry and direct current voltammetry that the modified sensor is able to catalyze N-acetylcysteine oxidation in phosphate buffer solution (PBS) which exhibits a sharp oxidation peak current. The linear calibration range was 1.0–400.0 μM at a 0.6 μM detection limit for DPV. This modified sensor was evaluated as a selective electrochemical sensor to determine N-acetylcysteine within real samples, e.g., urine, serum, and drugs.

Similarly, Taherkhani et al. designed a CPE chemically adjusted using multiwalled carbon nanotubes (MWCNTs) and FC which acted as a specific electrochemical sensor to simultaneously determine trace quantities of folic acid and cysteamine. The modified electrode exhibited extremely efficient electrocatalytic behavior for cysteamine anodic oxidation. The folic acid and cysteamine peak currents of DPV linearly increased with their concentration within the 0.7–200 μM cysteamine and 5.0–700 μM folic acid ranges at 0.3 μM and 2.0 μM detection limits for cysteamine and folic acid, respectively.

Raof et al. fabricated a chemically adjusted CPE with 1-[4-(ferrocenyl ethyl) phenyl]-1-ethanone (4-FEPEM) that was applied to examine l-cysteine electrocatalytic oxidation. At the optimal conditions of pH = 7, the l-cysteine oxidation at the electrode exterior took place at approximately 350 mV less positive potential compared to a bare CPE. Linear reliability on l-cysteine concentration was shown by the catalytic oxidation peaks. Linear analytical curves were acquired within the $9.0 \times 10^{-5}$–$4.9 \times 10^{-3}$ M and $2.0 \times 10^{-9}$–$2.8 \times 10^{-6}$ M ranges of l-cysteine with 0.9981 and 0.9982 correlation coefficients in CV and DPV approaches at $9.9 \times 10^{-6}$ M and $5 \times 10^{-6}$ M detection limits, correspondingly. This approach was also employed to selectively determine l-cysteine within patient blood plasma and several pharmaceutical arrangements via the standard addition approach.

Ahkgar et al. reported a CPE modified via incorporating CNT and FC and examined in pH 7.0 PBS via the CV method. This modified electrode demonstrated exceptional electrocatalytic impact on norepinephrine oxidation. In PBS (pH = 7), the oxidation current was linearly enhanced with NE concentration within the $0.47–500.0$ μM range at 0.21 μM detection limit (3σ) by DPV. This adjusted electrode was applied to detect norepinephrine in an abundance of tryptophan and acaminophen via the DPV approach.

Esfandiari Baghbamidi fabricated a CPE adjusted with CNT and FC. The electrochemical examination of the adjusted electrode and a study on its electrocatalytic oxidation efficiency for folic acid and benserazide uric acid was conducted. The oxidation of benserazide at the modified electrode’s surface took place at 285 mV lower potential compared to that of an unmodified CPE. A linear dynamic range was achieved by SWV within $8.0 \times 10^{-7}$ to $7.0 \times 10^{-4}$ M at $1.0 \times 10^{-7}$ M detection limit for benserazide.

Raof et al. implemented a modified CPE with 2,7-bis(ferrocenyl ethyl)fluoren-9-one (2,7-BFEOF) to examine ascorbic acid electrocatalytic oxidation within an aqueous mixture. At optimal conditions, i.e., pH = 7, ascorbic acid oxidation at the electrode exterior took place at 300 mV less positive potential compared to a bare CPE. Catalytic oxidation peak currents exhibited linear reliance on ascorbic acid concentration, while linear analytical curves were achieved within the $8.0 \times 10^{-5}$–$2.0 \times 10^{-3}$ M and $3.1 \times 10^{-3}$–$3.3 \times 10^{-3}$ M ranges of ascorbic acid with 0.9986 and 0.9976 correlation coefficients in CV and DPV approaches at $2.9 \times 10^{-5}$ M and $9.0 \times 10^{-6}$ M detection limits. This method was also assessed to determine ascorbic acid within pharmaceutical preparations.

CHA, DPV, and CV methods were applied to examine the electrochemical activity of ascorbic acid at chemically adjusted electrodes assembled via the incorporation of 7-bis(ferrocenyl ethyl) fluoren-9-one (2,7-BFEFO) into a carbon paste matrix proposed by Raao et al. At optimal conditions, pH = 7, this modified electrode exhibited highly electrocatalytic behavior concerning the oxidation of ascorbic acid. The overpotential for ascorbic acid oxidation was reduced by over 200 mV, and the relevant peak current was substantially raised. The FC/FC' redox couple plays the role of an adequate mediator to indirectly oxidize ascorbic acid by taking the advantages of the 7-bis(ferrocenyl ethyl) fluoren-9-one (2,7-BFEFO) in a carbon paste matrix. The modified electrode’s voltammetric reaction was linear versus ascorbic acid concentration within the $5 \times 10^{-5}$–$2.65 \times 10^{-3}$ M and $9 \times 10^{-6}$–$3.5 \times 10^{-3}$ M ranges with CV and DPV methods at 1.8 $\times 10^{-3}$ M and 4.2 $\times 10^{-6}$ M detection limits.

Molvlaee et al. fabricated a modified CPE using graphene (GR) and ethyl 2-(4-ferrocenyl-[1,2,3]triazol-1-yl) acetate (EFTA) which took the role of an electrocatalytic oxidation for levodopa. At optimal conditions, at pH = 7, levodopa
oxidation takes place at approximately 280 mV potential against Ag/AgCl via SWV that is less positive compared to a bare CPE. This reconstructed electrode is capable of resolving levodopa, tyrosine, and acetaminophen voltammetric peaks. Within the levodopa concentration range of 0.2–400.0 μM, the peak current was linear, while the analytical ranges were 1.0–150.0 μM for acetaminophen and 5.0–180.0 μM for tyrosine.11

Beitollahi et al. synthesized 2-chlorobenzoyl ferrocene (2CBF) and applied it to design an adjusted graphene oxide (GO) sheet paste electrode. At the modified electrode surface, the electro-oxidation of hydrochlorothiazide was examined. At optimal conditions, hydrochlorothiazide’s SWV peak current was linearly enhanced with hydrochlorothiazide concentration within the $5.0 \times 10^{-8}$ to $2.0 \times 10^{-4}$ M range at $2.0 \times 10^{-8}$ M detection limit for hydrochlorothiazide. This modified electrode displayed favorable distinction among the voltammetric peaks of folic acid and hydrochlorothiazide, making it adequate to detect hydrochlorothiazide with the existence of folic acid within real samples.12a

In a study conducted by Molaakbari et al. that fabricated a CPE adjusted with TiO$_2$ nanoparticles and ferrocenemonomocarboxylic acid (FM), it was utilized to create an original electrochemical sensor. The aim of modifying this electrode was to discover electrochemical activity to detect methyldopa with the existence of folic acid and glycine. In a PBS of pH = 7.0, the peak potentials were 325, 750, and 880 mV vs Ag/AgCl/KCl (3.0 M) for methyldopa, folic acid, and glycine. At optimal conditions, i.e., pH = 7, methyldopa oxidation took place at an approximate potential of 160 mV less positive compared to a bare CPE. The catalytic current reaction with methyldopa concentration exhibited linear correlation within the $5.0 \times 10^{-8} - 9.0 \times 10^{-4}$ M range at 90.0 nM detection limit for captopril. This modified electrode displayed favorable distinction among the voltammetric peaks of tryptophan and captopril, making it adequate to detect captopril with the existence of tryptophan in real samples.6e

Beitollahi et al. conducted more research where they fabricated a modified CPE with Ag–ZnO nanoplates and 2CBF to determine D-penicillamine with the existence of tryptophan. They recommended an EC$'$ method as presented in Figure 1 to depict D-penicillamine electrochemical oxidation at the exterior of the adjusted electrode. In this method, oxidation of D-penicillamine occurs at the catalytic, i.e., C, reaction via oxidized 2CBF created at the modified electrode surface by an electrochemical, i.e., E, response. At optimal conditions, i.e., pH = 7.0, D-penicillamine oxidation at the modified electrode surface takes place at approximately 165 mV less positive potential compared to that of an unmodified CPE. The suggested approach displayed an extensive linear dynamic range within the $0.03 - 250.0$ μM range at 0.015 μM detection limit, S/N = 3. The modified sensor was applied to determine tryptophan and D-penicillamine within real samples.6g

2CBF and ZnO–CuO nanoplates were synthesized by Beitollahi et al. and employed to design a modified CPE. The 6-mercaptopurine electro-oxidation at the adjusted electrode surface was investigated. At optimal conditions, the SWV peak of 6-mercaptopurine linearly increased with 6-mercaptopurine concentration within the $0.075 - 500.0$ μM range and 0.045 μM detection limit for 6-mercaptopurine. This modified electrode was applied to simultaneously determine folic acid and 6-mercaptopurine. Ultimately, this modified electrode was implemented to determine folic acid and mercaptopurine within biological and pharmaceutical samples.6h

In a study conducted by Beitollahi et al., a modified CPE with 2CBF and CNT was designed and implemented for isoproterenol electro-oxidation. At the optimal state, the SWV isoproterenol peak currents were linearly enhanced with isoproterenol concentration within the $2.5 \times 10^{-7} - 8.0 \times 10^{-5}$ M range.
Figure 2. Benzyloferrocene-modified multiwalled carbon nanotube paste electrode for the measurement of methionine concentration. Reused with permission from ref 14d.

10^{-5} M range at the 9.0 \times 10^{-8} M detection limit for isoproterenol.14a

Mahmoudi Moghaddam et al. proposed a modified CPE via incorporating graphene nanosheets and a 2,7-bis(ferrocenyl ethyl)fluoren-9-one (2,7-BF). The modified electrode demonstrated exceptional electrocatalytic impact on epinephrine oxidation. The relevant oxidation current linearly increased with epinephrine concentration within the 0.05–550.0 \mu M range at 27.0 nM detection limit (3\sigma) for epinephrine. This electrode was applied for the determination of epinephrine within an excess of folic acid and uric acid via SWV.14b

Akbari et al. used a Cu/TiO2 nanocomposite/IL/2-(ferrocenylethynyl)fluoren-9-one (2FF) modified CPE (Cu/TiO2-IL-2FF/CPE) to electrochemically determine levodopa. The acquired data indicated that the levodopa electro-oxidation at the exterior of the adjusted electrode was substantially facilitated, which was accredited to high Cu/TiO2 nanocomposite, IL, and 2FF electrical conductivity. Favorable electron-mediating activity was exhibited by the Cu/TiO2-IL-2FF/CPE which was followed by clearly segmented oxidation signals of tyrosine and levodopa. The DPV peak current displayed a linear correlation corresponding to levodopa concentrations within a 0.03–700.0 \mu M linear range at a 12.0 nM detection limit.14c

Mirrakhimi et al. fabricated a benzyloferrocene (BF) modified carbon nanotube paste electrode to determine two amino acids, ß-penicillamine and tryptophan, within an aqueous mixture at pH = 7.0. The outcomes showed that the electrode was effective in regard to electrocatalytic behavior to oxidize ß-penicillamine, causing an overpotential decrease of over 155 mV. By employing SWV, measuring tryptophan and ß-penicillamine in the form of a concoction may be conducted independently from one another with 250 mV potential difference. The suggested electrochemical sensor demonstrated a linear calibration plot within a 1.0 \times 10^{−6}−8.0 \times 10^{−4} M range at a 1.3 \times 10^{−7} M detection limit for ß-penicillamine.14d

Soltani et al. modified a CPE with CNT and benzyloferrocene to assemble an electrochemical sensor to detect glutathione. The reaction of the catalytic current with glutathione concentration displayed linear correlation within the 1.0 \times 10^{−7}−1.0 \times 10^{−4} M range at a 3.0 \times 10^{−8} M detection limit. This method was applied to determine glutathione within real samples.14e

Beitollahi et al. presented an approach to detect methyldopa with no phenylephrine and guaifenesin involvement. In this regard, a CPE was adjusted with GR and ethyl 2-(4-ferrocenyl[1,2,3]triazol-1-yl)acetate (EFTA). This modified electrode exhibited a 0.4–500.0 \mu M linear range at 0.08 \mu M detection limit. There were no changes regarding the modified electrode’s sensitivity concerning methyldopa with the existence of guaifenesin and phenylephrine, enabling independent or simultaneous calculation of the three moieties. By determining these substances within real samples, the effectiveness of the suggested electrode was assessed.14b

Movlaee et al. used GR and EFTA-adjusted CPE to determine droxidopa. Because of the beneficial properties of the modified electrode, there was a linear correlation among droxidopa concentration and the anodic peak current within the 2.0–400.0 \mu M range at 9.0 \times 10^{−8} M detection limit (S/N = 3) achieved by SWV. This method exhibited exceptional properties for droxidopa electrocatalytic oxidation with the existence of tyrosine and acetaminophen.10c

Ahmadipour et al. examined L-cysteine electro-oxidation via a BF-modified multiwalled carbon nanotube paste electrode. At optimal conditions of pH in CV, L-cysteine oxidation takes place at 215 mV potential less positive compared to a bare CPE. The catalytic oxidation peak currents relied on L-cysteine concentration, while a linear calibration curve was acquired within the 0.7–350.0 mM range via the SWV approach at 0.1 mM detection limit. This approach was applied to determine L-cysteine within real samples.10c

A carbon-paste electrode adjusted with 2,7-BF, and CNT was implemented for the purpose of sensitive voltammetric levodopa detection. The electrochemical reaction properties of this electrode regarding uric acid, folic acid, and levodopa were examined by Beitollahi et al. The outcomes indicated the electrode’s favorable catalytic behavior concerning levodopa electro-oxidation, leading to a reduction in the overpotential of over 320 mV. The electrode was utilized to determine levodopa within real samples. By using the SWV method, the linear calibration curve was acquired within the 0.1−700.0 \mu M range at 58.0 nM detection limit.14c

Levodopa electrochemical oxidation at the modified CPE surface with graphene nanosheets, 1,4-BBFT, and hydrophilic ionic liquid (n-hexyl-3-methylimidazolium hexafluoro phosphate) acting as a binding agent was examined by Tajik et al. Levodopa oxidation at the modified electrode surface took place at approximately 210 mV less positive potential compared to a bare CPE. The graph depicting peak current versus levodopa concentration was linear within the 5.0 \times 10^{−8}−8.0 \times 10^{−4} M concentration range at 15.0 nM detection limit for levodopa.40

Beitollahi et al. reported a modified multiwalled carbon nanotube paste electrode to measure methionine concentration as presented in Figure 2. At the optimal state, the SWV peak current of methionine was linearly enhanced with methionine concentration within the 1.0 \times 10^{−7}–2.0 \times 10^{−4} M range at 58.0 nM detection limit for methionine. This sensor was used to measure methionine concentration within human urine.14d

Beitollahi et al. examined hydrochlorothiazide electro-oxidation at the surface of a benzyloferrocene-adjusted multi-
walled carbon nanotube paste electrode. At optimal conditions, i.e., pH = 7, the SWV peak current of hydrochlorothiazide is linearly enhanced with hydrochlorothiazide concentration within the $6.0 \times 10^{-7} - 3.0 \times 10^{-6}$ M range at $9.0 \times 10^{-8}$ M detection limit for hydrochlorothiazide. The suggested sensor was used to determine hydrochlorothiazide in tablet samples and human urine.14e

Salmanipour et al. fabricated a 1-benzyl-4-ferrocenyl-1H-[1,2,3]-triazole (BFT) and CNT-modified glassy carbon electrode (GCE) to simultaneously determine folic acid and N-acetylcysteine. The oxidation peak separation for folic acid and N-acetylcysteine was approximately 280 mV. The N-acetylcysteine calibration curve was within the $0.1 - 600.0$ μM range at 62.0 nM detection limit ($S/N = 3$) for N-acetylcysteine. This method was applied to determine N-acetylcysteine within real samples.15a

Beitollahi et al. designed a selective and sensitive electrochemical CPE that was modified using EFTA and GR to simultaneously determine tryptophan, ascorbic acid, theophylline, and isoproterenol. By utilizing the electrodes in SWV and CV, the electrochemical response of isoproterenol was examined with outcomes indicating a substantially facilitated reaction that was shown by improved oxidation current and oxidation potential shift to a less positive potential in contrast to the unmodified CPE. Oxidation current had a direct correlation to isoproterenol concentration within the $0.1 - 600.0$ μM range at 0.034 μM ($S/N = 3$) detection limit regarding this analyte via SWV evaluation on the basis of the modified electrode.10d

3. FERROCENE AND FERROCENE DERIVATIVE MODIFIED ELECTRODES FOR ENVIRONMENT POLLUTANT AND PESTICIDE DETERMINATION

Quantifying pollutant compounds, namely, phenol, sulfite, hydrazine, and hydroxylamine, are vital for the industry. From the analytical methods utilized for environmental, pharmaceutical, and biological compound analysis, the electrochemical approaches are becoming prevalent in industrial processes.

Pesticides are widely used to avoid or limit damages stemming from weeds, pests, and illnesses and thus are beneficial for the agricultural field. Farmers use numerous pesticides to protect crops and for pre- and post-harvesting purposes. It is predicted that implementing pesticides entails approximately 30% of production of crops across the world. Pesticides are organic toxic mixtures that are used to eliminate a wide range of pests and can enter the food industry by different means, leading to health issues for animals and humans. Researchers verified that high exposure to pesticides may result in several illnesses. Prompt detection of pesticides is extremely important because of their toxicity and stability.

Karimi Maleh et al. presented a modified CPE with CNT and FC as a voltammetric sensor to determine sulfite as shown in Figure 3. The outcomes indicated that at optimal conditions, i.e., pH = 7, using the CV approach, sulfite oxidation takes place at 280 mV less positive potential compared to that of an unmodified CPE. At optimal conditions, a sulfite electrocatalytic oxidation peak current exhibited linear dynamic range within 0.1–120.0 μM at a 0.1 μM detection limit for sulfite. This approach was assessed as a selective means of voltametrically determining sulfite in various real samples, namely, weak liquor from the paper and wood industry, river water, boiler water, tap water, and industrial water.14d

Figure 3. Mechanism for oxidation of sulfite at the surface of a modified electrode with a carbon nanotube and ferrocene. Reused with permission from ref 5f.

Esfandiari Baghbamidi et al. designed a graphene paste electrode modified using a ferrocene derivative composite, 2,7-bis(ferrocenyl ethynyl) fluorene-9-one (2,7-BFE). Hydroxylamine electro-oxidation at the modified electrode surface was examined via CHA, SWV, and CV methods. At the optimal state, the SWV peak current of hydroxylamine was linearly enhanced with hydroxylamine concentration within the $2.0 \times 10^{-7} - 2.5 \times 10^{-4}$ M range at a $9.0 \times 10^{-8}$ M detection limit. This electrode was utilized to determine hydroxylamine in various water samples.16b

Beitollahi et al. examined the electrochemical activity of hydrazine at 1-benzyl-4-ferrocenyl-1H-[1,2,3]-triazole-triazole (BFT) and CNT-adjusted GCE. This electrode demonstrated exceptional electrocatalytic behavior for hydrazine oxidation and expedites the electron transfer rate. The electrocatalytic current is linearly enhanced with hydrazine concentration within the $0.5 - 700.0$ μM range at 33.0 nM detection limit for hydrazine. This method was used to determine hydrazine within water samples.15b

Elancheziyan et al. adjusted a nonenzymatic catechol sensor on the basis of FC immobilization on graphene oxide (GO). An adjusted GCE with GO was silanized using (3-aminopropyl)trimethoxysilane (APTMCS). Immobilization of ferrocencarboxaldehyde on GO by Schiff base formation is depicted in Figure 4. Examination of CV-modified electrode indicated two clarified redox peaks with +0.380 and +0.277 V anodic and peak potentials, respectively, associated with the FC/FC+ redox couple. The electrode modified with FC displays exceptional electrocatalytic behavior concerning catechol oxidation at a normal working voltage of +0.45 V (vs Ag/AgCl). The reaction was linear within the $3 - 112$ μM range of catechol concentration at 1.1 μM concentration and 1184.3 μA mM$^{-1}$ cm$^{-2}$ sensitivity. It was used to determine catechol in lake water samples and spiked tap water.16

Liu et al. covalently modified a glassy carbon substrate using a combined layer of 4-aminophenol and phenyl by appropriate electrografting of their arylidiazonium salts within acidic mixtures. SWNTs were vertically and covalently anchored on the electrode surface by forming amide bonds, resulting from the reaction among amines on the adjusted substrate and carboxylic groups on the ends of nanotubes. For the next stage, ferrocenedimethyamine (FDMA) was connected to the SWNT ends via amide bonding prior to attaching an epitope (endosulfan hapten) that was binded to an antibody, as depicted in Figure 5. Associating or disassociating the antibody with a sensing interface results in ferrocene electrochemistry modulation. The antibody complex electrodes were susceptible to spiked endosulfan samples, i.e., unbound target analyte within environment water prior to being examined via the SWV approach. For the purpose of detecting the endosulfan
across the 0.01−20 ppb via a disposition assay, the designed electrochemical immunosensor was implemented. The minimum detection limit for the immunosensor was 0.01 ppb endosulfan within 50 mM phosphate buffer and pH = 7.0.17

Figure 4. Schematic representation of the fabrication of a glassy carbon electrode modified with graphene oxide which then silanized with (3-aminopropyl) trimethoxysilane and ferrocenecarboxaldehyde. Reused with permission from ref 16.

Figure 5. Ferrocenedimethylamine and single-walled carbon nanotube modified sensing interface for the detection of endosulfana. Reused with permission from ref 17.
Jiao et al. fabricated a sensitive aptamer sensor to quantitatively detect chlorpyrifos. For the purpose improving aptasensor sensitivity, modification of mesoporous carbon (OMC) functionalized by chitosan (OMC−CS) and ferrocene hybrid chitosan (CS) dispersed multiwalled carbon nanotubes (FC@MWCNTs-CS) was conducted at the electrode exterior as depicted in Figure 6. More aptamer would be efficiently detected by FC@MWCNTs-CS while increasing electron transfer between potassium ferricyanide and the work electrode surface because of the electrical conductivity and biocompatibility. At the optimal state, the modified aptasensor displayed an extensive linear range within 1−105 ng mL\(^{-1}\) at 0.33 ng mL\(^{-1}\) (S/N = 3) detection limit for chlorpyrifos. The suggested chlorpyrifos aptasensor displayed favorable selectivity, stability, and reproducibility that enables ultrasensitive chlorpyrifos residue detection within fruits and vegetables.\(^{18}\)

Figure 6. Stepwise preparation of the glassy carbon electrode with mesoporous carbon functionalized by chitosan and ferrocene hybrid chitosan dispersed multiwalled carbon nanotubes for the detection of chlorpyrifos. Reused with permission from ref 18.

4. FERROCENE AND FERROCENE DERIVATIVE MODIFIED ELECTRODES FOR HEAVY METALS

The majority of metal ions is cancerous and causes detrimental health issues originating from the production of free radicals. Thus, rapid and precise detection of metal ions is a vital issue. From the various metal ions, chromium, mercury, lead, cadmium, and arsenic possess the highest toxicity. In order to detect metal ions, electrochemical sensors are designed. Developing such electrochemical sensors is a prominent area of research for future prompt and quantitative analysis entailing optimal sensitivity.\(^{19}\)

The ferrocene-appended chalcone (FAC) based voltammetric sensors were designed by Kamel et al. to selectively detect the Cu(II) ion. The CV approach of FAC displayed a changeable redox couple (Fe\(^{2+}/Fe\(^{3+}\)) when it was scanned within the 0.4 V to −0.2 V vs Ag/AgCl potential range. The CV method of FAC is subjected to electrochemical variances because of the creation of a FAC−Cu(II) composite when Cu(II) ions are added. Within the 5.0 × 10\(^{-5}\)−4.0 × 10\(^{-4}\) M concentration range at a 2.0 × 10\(^{-6}\) M detection limit, the voltammetric sensor exhibits favorable performance. The analytical benefits of the suggested sensors were approved further by predicting Cu(II) ions in several specimen matrices with exceptional outcomes.\(^{19}\)

Research conducted by Karthick et al. investigated nanomolar concentrations of Pb\(^{2+}\) using GO−FV composite electrochemical sensing which was amalgamated by a simple approach. On the basis of the CV curves, with FC loaded on GO, the GO−FC compound was selected to assess the lead sensing characteristics. Sensing examinations displayed a 0.168 μg/L detection limit and 250 μg/L significant sensitivity. The outcomes showed that GO−FC nanocomposites may be utilized for sensing lead within environmental specimens.\(^{20}\)

5. FERROCENE AND FERROCENE DERIVATIVE MODIFIED ELECTRODES FOR FOOD ANALYSIS

One of the areas of continuous focus is food safety. Pesticide residue will directly or indirectly be detrimental to human health when applied for the protection of crops. Thus, it is vital to promptly and precisely oversee pesticide residue in foods.

Rabti et al. proposed a compound including chitosan consisting of azidomethylferrocene which was covalently immobilized on RGO-reduced sheets and drop casted on polyester to create a screen-printed electrode to determine nitrite via CHA and CV. Nitrite reduction and oxidation can occur because of the electrode’s high electron transfer rate. At optimal conditions, with a 0.7 V versus Ag/AgCl potential at pH = 7 solution, within the 2.5−1450 μM concentration range at an ∼0.35 μM detection limit, the calibration plot was linear. This sensor was used to detect nitrite in spiked mineral water specimens with 95−101% restoration ranges.\(^{21}\)

Huang et al. conducted a study where an electro-active GO nanocomposite was initially assembled by covalent grafting (4-ferrocenylethylene) phenylamine (FC-NH\(_2\)) onto the GO exterior. The GO-FC-NH\(_2\)-incorporated hybridized nanocomposite coupled with HAuCl\(_4\) was concurrently electro-deposited on GCE to achieve RGO-FC-NH\(_2\)/AuNPs/GCE. Applying the catalysis impact of the nanomaterial and electron mediator coupling with a great active exterior and great amassment scope of rGO-FC-NH\(_2\)/AuNPs leads to the successful establishment of a synergetic signal enhancement platform to sensitively determine bisphenol A. By using this sensor, the bisphenol A oxidation peak currents linearly relied on bisphenol A concentration within the 0.005−10 μM range at 2 nM detection limit.\(^{22}\)

Wang and Anzai examined using DPV and CV on ferrocene boronic acid (FcBA), 1,1′-ferrocene diboronic acid (FcDBA), ferrocene carboxylic acid (FcCA), 1,1′-ferrocene dicarboxylic acid (FCDCA), ferrocenylmethanol (FCM), and ferrocenylethanol (FCE) on GCE with the existence of a hypochlorite ion. The ferrocene compounds’ redox current in DPV and CV was reduced, while hypochlorite ion concentration increased at a μM level. The substituent within the ferrocene compounds substantially impacted the electrochemical reaction to the hypochlorite ion. From all tested FC compounds, FCBa, FCDba, and boronic-acid-substituted compounds exhibited higher sensitivity toward the hypochlorite ion compared to alkylated FC derivatives and carboxylic acid due to higher C-bond reactivity in FCDba and FCBa to the hypochlorite ion. These ferrocene compounds may be implemented as redox markers to detect hypochlorite ions in water.\(^{23}\)

Kanyong et al. designed a screen-printed electrode that was modified using ionic liquid, 1-ethyl-3-methylimidazolium tetrafluoroborate ([EMIM][BF\(_4\)]), ferrocene carboxylic acid (FCA), and cellulose acetate (CA) to electrochemically sense hydrogen peroxide within commercially packed aseptic milk. The modified electrode was successful in the sensitive detection of hydrogen peroxide, while there were no interferences from electro-active species, namely, uric acid, glucose, dopamine, and ascorbic acid. The linear range to
Table 1. Some Analytical Performances of Electrochemical Determination by Modified Electrodes with Ferrocene and Ferrocene Derivatives

| electrode                        | modifier                  | electrochemical method | analytes         | linear range       | detection limit | ref |
|----------------------------------|---------------------------|------------------------|------------------|--------------------|-----------------|-----|
| CPE                              | 1,4-BBFT/IL               | SWV                    | isoproterenol    | 6.0 × 10^-3–7.0 × 10^-4 M | 12.0 nM         | (4a) |
| CPE                              | FC/CNT                    | DPV                    | methyldopa       | 0.1–500 μM         | 0.08 ± 0.002 μM | (5a) |
| CPE                              | 2CBF/Ag–ZnO nanoparticles | SWV                    | glutathione      | 5.0 × 10^-3–2.0 × 10^-4 M | 20.0 nM         | (6a) |
| CPE                              | FC/CNT                    | DPV                    | N-acetylcycteine | 1.0–400 μM         | 0.6 μM          | (5b) |
| CPE                              | 4-FEPFM                   | CV                     | l-cysteine       | 9.0 × 10^-3–4.9 × 10^-3 M | 9.9 × 10^-6 M   | (5c) |
| CPE                              | FC/MWCNT                  | DPV                    | cysteamine       | 0.7–200 μM         | 0.3 μM          | (7)  |
| CPE                              | 2,7-BF/BBFT/IL            | CV                     | folic acid       | 5.0–700 μM         | 2.0 μM          | (7)  |
| CPE                              | 2,7-BF/BBFT/IL            | CV                     | ascorbic acid    | 8.0 × 10^-3–2.0 × 10^-3 M | 2.9 × 10^-5 M   | (5d) |
| CPE                              | FC/CNT                    | DPV                    | norepinephrine   | 0.47–500 μM        | 0.21 μM         | (5e) |
| CPE                              | 2,7-BFE/BBFT/IL           | CV                     | ascorbic acid    | 5.0 × 10^-3–2.65 × 10^-3 M | 1.8 × 10^-5 M   | (8a) |
| CPE                              | ZnO–CuO nanoparticles     | SWV                    | 6-thioguanine     | 0.05–200 μM        | 25 ± 2 μM       | (9a) |
| CPE                              | FC/CNT                    | DPV                    | benserazide      | 8.0 × 10^-7–7.0 × 10^-4 M | 1.0 × 10^-7 M   | (6b) |
| CPE                              | EFTA/GR                   | SWV                    | levodopa         | 0.2 μM–0.4 μM      | 0.07 μM         |     |
| CPE                              | 2CBF/GO                   | SWV                    | acetylsalicylic acid | 5.0 × 10^-6–2.0 × 10^-4 M | 20.0 nM         | (6c) |
| CPE                              | FM/TiO2 nanoparticle      | DPV                    | methyldopa       | 2.0 × 10^-7–1.0 × 10^-4 M | 8.0 × 10^-8 M   | (11) |
| CPE                              | FCD/CNT                   | DPV                    | norepinephrine   | 0.03–500 μM        | 22.0 μM         | (12) |
| CPE                              | 2CBF/CNT                  | SWV                    | N-acetylcycteine | 5.0 × 10^-3–4.0 × 10^-4 M | 2.6 × 10^-5 M   | (6d) |
| CPE                              | 2CBF/CNT                  | SWV                    | ascorbic acid    | 1.0 × 10^-7–7.0 × 10^-3 M | 64.0 nM         | (6e) |
| CPE                              | 2CBF/Ag–ZnO nanoparticles | SWV                    | α-penicillamine  | 0.003–250 μM       | 0.015 μM        | (6f) |
| CPE                              | 2CBF/Ag–ZnO nanoparticles | SWV                    | 6-mercaptopurine | 0.075–500 μM       | 0.045 μM        | (6b) |
| CPE                              | 2CBF/CNT                  | SWV                    | isoproterenol    | 2.5 × 10^-7–8.0 × 10^-3 M | 9.0 × 10^-8 M   | (6i) |
| CPE                              | 2,7-BF/GR                 | SWV                    | epinephrine      | 0.05–550 μM        | 27.0 μM         | (8b) |
| CPE                              | Cu/TiO2-IL-2FF            | DPV                    | levodopa         | 0.03–700 μM        | 12.0 μM         | (13) |
| CPE                              | BF/GO/GR                  | SWV                    | α-penicillamine  | 1.0 × 10^-4–8.0 × 10^-4 M | 1.3 × 10^-7 M   | (14) |
| CPE                              | BF/GO                     | SWV                    | glutathione      | 1.0 × 10^-7–1.0 × 10^-4 M | 3.0 × 10^-8 M   | (14b) |
| CPE                              | EFTA/GR                   | SWV                    | methyldopa       | 0.4–500 μM         | 0.08 μM         | (10b) |
| CPE                              | BF/GO/GR                  | SWV                    | dioxidoxide      | 2.0–400 μM        | 9.0 × 10^-8 M   | (10c) |
| CPE                              | BF/MWCNT                  | SWV                    | l-cysteine       | 0.7–350 μM         | 0.1 μM          | (14a) |
| CPE                              | 2,7-BF/GR                 | SWV                    | levodopa         | 0.1–700 μM        | 58.0 μM         | (8c)  |
| CPE                              | 1,4-BBFT/IL/GR            | SWV                    | levodopa         | 5.0 × 10^-3–5.0 × 10^-4 M | 15.0 nM         | (4b) |
| CPE                              | BF/MWCNT                  | SWV                    | methionine       | 1.0 × 10^-7–2.0 × 10^-4 M | 58.0 nM         | (14d) |
| CPE                              | BF/MWCNT                  | SWV                    | hydrochlorothiozide | 6.0 × 10^-7–3.0 × 10^-4 M | 9.0 × 10^-8 M   | (14e) |
| GCE                              | BPT/FT                    | SWV                    | N-acetylcycteine | 0.1–600 μM         | 62.0 nM         | (15a) |
| CPE                              | EFTA/GR                   | SWV                    | isoproterenol    | 0.1–600 μM        | 0.034 μM        | (10d) |
| CPE                              | FC/CNT                    | DPV                    | sulfitre          | 0.1–120 μM        | 0.1 μM          | (5f)  |
| CPE                              | 2,7-BFE                   | SWV                    | hydroylamine      | 2.0 × 10^-7–2.5 × 10^-4 M | 9.0 × 10^-8 M   | (9b)  |
| GCE                              | BPT/CNT                   | SWV                    | hydrazine        | 0.5–700 μM        | 33.0 ± 2.0 nM   | (15b) |
| CPE                              | FC/APTSMS/GO              | DPV                    | catechol         | 3–112 μM          | 1.1 μM          | (16)  |
| CPE                              | FDMA/SWCNT                | SWV                    | endosulfan       | 0.01–20 ppb       | 0.01 ppb        | (17)  |
| CPE                              | FC@MWCNT-CS               | CV                     | chlorpyrifos     | 1–105 ng/mL       | 0.33 ng/mL      | (18)  |
| Pt                               | FAC                       | CV                     | Cu^2+           | 5.0 × 10^-5–4.0 × 10^-4 M | 2.0 × 10^-8 M   | (19)  |
| Pt                               | FV/GO                     | CV                     | Pb^2+           | 0.1–1000 μg/L     | 0.1 μg/L        | (20)  |
| SPE                              | azidomethylferrocene/RGO  | CV                     | nitrite          | 2.5–1450 μM       | 0.35 μM         | (21)  |
| GCE                              | RGO–FC-NH2/AuNPx           | DPV                    | bisphenol A      | 5.0 × 10^-5–1.0 × 10^-3 M | 2.0 × 10^-9 M   | (22)  |
| GCE                              | FCA                       | CV                     | hydrogen peroxide | 1.0 μM–1.2 mM        | 0.35 μM         | (24)  |
| GCE                              | FCA                       | CV                     | hydrogen peroxide | 10 μM–10 mM       | 2.07 μM         | (25)  |
determine hydrogen peroxide was within 1.0 μM–1.2 mM at 0.35 μM detection limit and 10.6 nA μA⁻¹ μM⁻¹ cm⁻² sensitivity. The resulting accuracy, i.e., n = 6, and recoveries were 0.53% and 97.8% when applied to analyze hydrogen peroxide residues within milk.²⁴

Mattousi et al. investigated a maperometric hydrogen peroxide sensor on the basis of redox-active polymer by physically entrapping FCA onto a cross-connected aminopoly-(ether sulfone) film (signified as FCAPS) in a single-stage procedure at the surface of GCE. This electrode displayed favorable redox activity originating from a ferrocene/ferrocenium redox couple. This sensing platform was most efficient at an optimum voltage of +0.6 V versus SCE and demonstrated electrocatalytic behavior in regard to the oxidation of hydrogen peroxide at a 2.07 μM (at S/N = 3) detection limit and 10 μM–10 mM wide linear range. This electrode was useful in detecting H₂O₂ within refined cow milk specimens with significant restorations.²⁵

6. ANALYTICAL PERFORMANCES OF ELECTROCHEMICAL SENSORS MODIFIED WITH FERROCENE AND FERROCENE DERIVATIVES

The electrochemical methods performances were dependent on ferrocene as well as ferrocene derivative modifiers formation. Numerous depictive examples are comprehensively reviewed below (Table 1).

7. CONCLUSIONS

This is a concise mini-review on current advancements in the field of modified sensor and biosensor design via the implementation of FC as a modifier. FC as a typical type of metalocenes aroused intensive attention owing to its unique electronic and chemical features. The mini-review discusses recent developments in applying FC for electrochemical sensing. The advantages of FC have enabled the creation of extensive electrochemical sensors and biosensors that demonstrate favorable analytical properties. The improved electrochemical response is coupled to resistance to surface fouling which entails high stability. These advancements imply that future interdisciplinary work may lead to new generations of sensors and biosensors based on FC for extensive uses. Meanwhile, there also remain challenges for the use of FC in the sensing such as material conductivity, structural stability and integrity, and further functionalization toward desirable features. Therefore, it is noteworthy that real biosensing prospects of FC will emerge in the future by obtaining more research efforts.

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Notes
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■ ABBREVIATION

FC, ferrocene
CV, cyclic voltammetry
CHA, chronomperometry
SWV, square wave voltammetry
EIS, electrochemical impedance spectroscopy
DPV, differential pulse voltammetry
ASV, anodic stripping voltammetry
CPE, carbon paste electrode
GCE, glassy carbon electrode
SPE, screen-printed electrode
PBS, phosphate buffer solution
1,4-BBFT, 1-(4-bromobenzyl)-4-ferrocyenyl-1H-[1,2,3]-triazole
IL, ionic liquid
CNT, carbon nanotube
GR, graphene
GO, graphene oxide
RGO, reduced graphene oxide
MWCNT, multiwalled carbon nanotube
SWNT, single-walled carbon nanotube
2CBF, 2-chlorobenzoyl ferrocene
4-FEPEM, 1-[(4-ferrocenyl ethynyl) phenyl]-1-ethanone
2,7-BFEM, 2,7-bis(ferrocenyl ethynyl)fluoren-9-one
2,7-BFEO, 2,7-bis(ferrocenyl ethynyl)fluoren-9-one
EFTA, Ethyl 2-(4-ferrocenyl-[1,2,3]-triazol-1-yl) acetate
FM, ferrocene monocarboxylic acid
FCD, ferrocene dicarboxylic acid
MWCNT, multiwalled carbon nanotube
SWNT, single-walled carbon nanotube
1,1-BPF, 1,1-bis(phenylacetyl) ferrocene
BF, benzoylferrocene
EFTA, ethyl 2-(4-ferrocenyl-[1,2,3]-triazol-1-yl)acetate
BFT, 1-benzyl-4-ferrocenyl-1H-[1,2,3]-triazole
FDMA, ferrocenedimethyamine
FAC, ferrocene-appended chalcone
Fc-F, ferrocene-phenylalanine

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FcBA, ferrocene boronic acid
FcDBA, 1,1′-ferrocene diboronic acid
FcCA, ferrocene carboxylic acid
FcDCA, 1,1′-ferrocene dicarboxylic acid
FcM, ferrocenylmethanol
FeE, ferrocenylethanol
[EMIM][BF4], 1-ethyl-3-methylimidazolium tetrafluoroborate
PANI/GR-FCA, polyaniline/graphene-ferrocenecarboxylic acid
HTBP, hydroxyl-terminated polybutadiene
MC, mesoporous carbon
CS, chitosan
CA, cellulose acetate
AChE, acetylcholinesterase

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