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Metal Oxide Nanocomposites-Based Electrochemical Biosensing Studies

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1. Introduction

The world's continuously growing population is facing challenges like energy crisis, environmental sustainability, global public health problems, etc. Among them, the resolution of public health issue is having the prime importance so that the people live happily as well as enjoy each moment of their life. However, the diseases like diabetes mellitus, HIV, cancer, Alzheimer's disease, stroke and other neurological diseases have no permanent cure yet. New life-threatening diseases and viruses like covid-19, Zika, Ebola, SARS, MERS and H1N1 etc. are affecting human beings leads into loss of life. The potential that life is saving and cost saving are achievable through early diagnosis, proper medical treatment and accessible health monitoring systems. Particularly, biosensing protocols in connection to early diagnosis as well as health monitoring have placed a significant importance in biomedical sector. In the current context where population and bio-testing capacity has remarkable gap, the effect of prompt and specific detection of target molecules is also important from the point of view of biosensor field[1]. Hence, the development of biomedical sensors having the features such as ease to handle, cost effective, short time span for analysis, multi-analyte sensing, sophisticated digital display, etc.is the need of hour. For example, glucometer is well-known example of biosensor device; glucometer measures the sugar content present in blood sample. Similarly, the various sensors such as glucowatch, tooth enamel biosensor, colorimetric sweat biosensor, etc. are existing in the market having wide application in biosensing for the analysis of the different biomolecules.

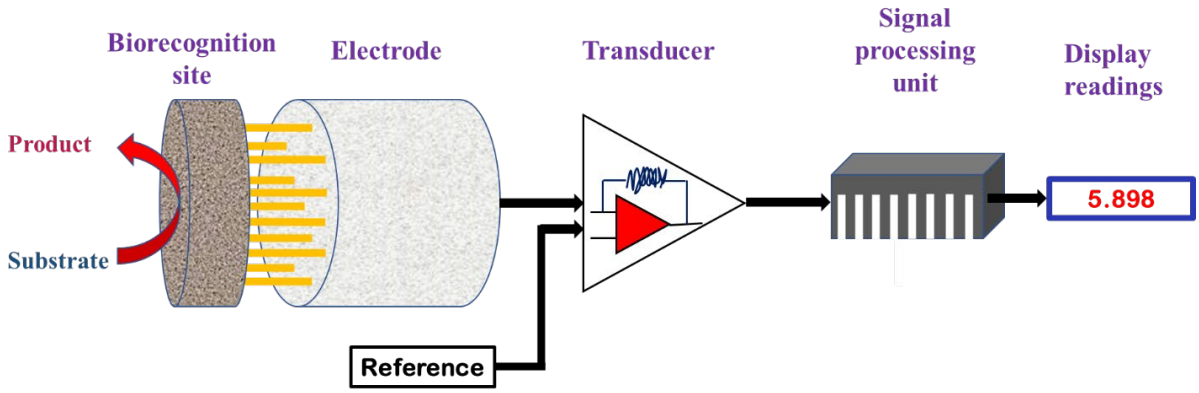

Fig.11.1 General Schematic of electrochemical biosensor

In addition to these, the nanomaterial's-based biosensor has gained much attention among the scientists[2]. This lead opportunities regarding to new materials for achieving specific

functionality and selectivity. Therefore, it is imperative to start with the basics of biosensors so the readers can understand the present aspects in depth. A biosensor is analytical devices thatsense an analyte (biomolecule usually) via interaction with a recognition element (receptor – biological and non-biological); which process through transducer system so as to get the electrical signals in relation to the analyte concentrations. Therefore, the analyte, receptor, transducer, output signal are the basic components of the biosensing device**(figure 11.1).**

Numerous approaches including optical, thermal, electrochemical and physical biosensor platforms have been explored in the field of biosensor technology[3]. Compared with other detection methods, an electrochemical approach offers a much less expensive, more facile and highly sensitive detection method, which enables the monitoring of the different analytes, fast response–recovery times and very low detection limits. Also, electrochemical detection is not affected by sample components such as chromophores, fluorophores, and particles that often interfere with spectrophotometric detection[4]. Based on the receptor, the electrochemical sensor has two types; one is enzymatic-based and other is non-enzymatic-based one. Especially, enzyme-based biosensors are of most interest from last many years, since sufficient research has been going-on but still there are various constraints in these biosensors[5][6]. The various constrains are instability, short shelf life, high cost of enzymes, difficult immobilization technique and critical operating procedure, etc. Therefore, considerable attentions have been focused to overcome these limitations and hence investigators trying continuously for the excellent electrochemical biosensors. Non-enzymatic sensor is the one of the sensing devices; which has a potential to overcome the limitations of enzymatic sensors. With the introduction of nanoscale materials, researchers are highly focusing on the development of novel nanomaterials as electrode material in non-enzymatic sensing substrates. This is because of their advantages such as improved catalytic reaction, more efficient electron transfer[7], increased surface area, good biocompatibility and fine control over electrode microenvironment, etc.[2]. Nanostructured materials viz. metals, metal oxides, conducting polymers (CPs), carbon nanostructures (CNs) have opened new ways to improve the efficiency of non-enzymatic electrochemical biosensors[8]. Among the various nanostructured platforms, metal oxides nanostructures possess overriding advantages such as high stability[9], ease synthesis, easily engineered for desired size, shape, and porosity, no swelling variations, easy incorporation into hydrophobic and hydrophilic systems and ease functionalization, etc. that make them a promising tool for biomedical applications[10].Various metals and their oxides including gold (Au), copper (Cu), cupric oxide (Cu_2O), copper oxide (CuO), cobalt oxide (CoO), manganese dioxide (MnO_2), nickel (Ni), nickel oxide (NiO),

palladium (Pd), platinum (Pt), tin oxide (SnO_2), titanium dioxide (TiO_2), etc. have shown attractive properties such as tunable structural-electrical properties, efficient biocompatibility, non-toxicity, and catalytic ability, which is beneficial in non-enzymatic biosensing determination[11]. These nanostructured materials display fast electron transfer rates and easy adsorption properties results in enhanced biosensing activity. To modulate desired properties of bare metal oxides, the functional nanocomposites of metal oxide with various materials such as conducting polymers, carbon nanostructures, noble metal nanoparticles, metal organic frameworks (MOF) are also promising materials for efficient non-enzymatic biosensing applications.

Therefore, this chapter focuses on recent advances in nanomaterial's based electrochemical sensors for biosensing applications. The chapter also provides the reader with a clear and concise view of new advances modification strategies for electrochemical signal amplification, and novel electrochemical approaches used in the miniaturization and integration of the sensors.

2. Present scenario of biosensor market

The global biosensors market was valued at $17,500.0 million in 2018, and is expected to reach $38,600.2 million by 2026, registering a CAGR of 10.4% from 2019 to 2026 **(Fig. 11.2).** New communicable, non-communicable diseases and increasing number of diabetes as well as cardiovascular patients demands the advanced and reliable biosensors.

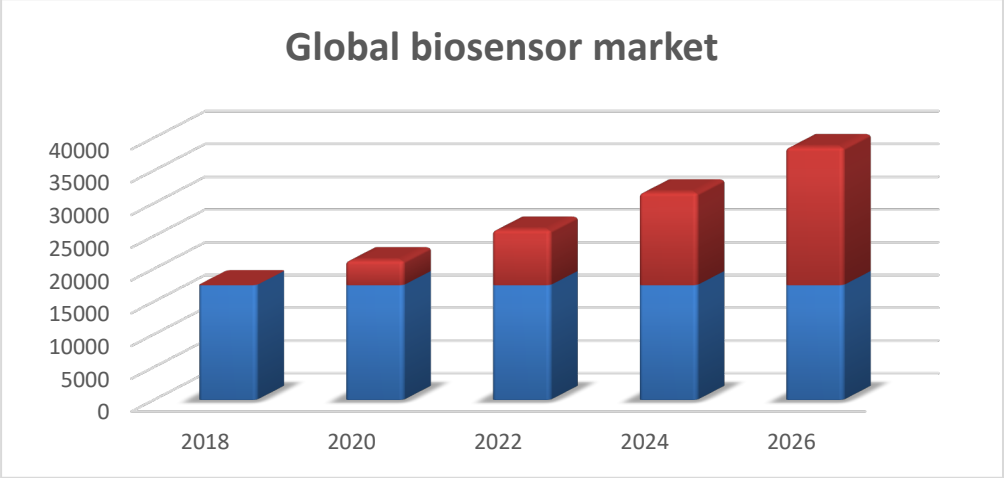

Fig.11.2. Global Biosensor market in million

Increasing applications of biosensors in healthcare sector, industries, research and point of care testing (POCT) drives the growth of global electrochemical biosensor market. However, factors such as strict regulatory requirements, reimbursement

policies issues in healthcare system are further hampering the market. Along with healthcare, applications of biosensors are increasing in various industries such as food, environment, drug discovery, and security, etc. Biosensors are also used for detection and identification of diseases in crops and for measuring the level of pesticides, herbicides, and heavy metals in soil and ground water. Similarly, increasing presence of toxins, chemicals, and pathogens in food is a major concern.

Biosensors are used to ensure quality and safety of products and detection of microbial pathogens and toxins in food, and are cost-efficient. Increasing number of harmful pollutants in the environment has also created a need for analytical and monitoring devices. Biosensors are also used in bio-defence for detection of harmful chemical and biological warfare agents, forensic identification for crime detection. Therefore, increasing applications of biosensors would boost the growth of the market.

4. Non-enzymatic electrochemical biosensors:

The non-enzymatic electrochemical sensors proved as an inexpensive and effective analytical method for quantitative detection of various biomolecules. After the discovery of amperometric glucose sensor by Clark, many developments are done in biosensor field. Clark's amperometric glucose sensor was categorized in 1st generation biosensor, where glucose is oxidized to gluconic acid in presence of oxygen and glucose oxidase immobilized on platinum electrode. As the instrumentation of Clarks, sensor is very complex and inconvenient because of free oxygen involvement, which restricts the application area of 1st generation biosensors. To solve problem related to use of free oxygen, 2nd generation biosensors have been introduced, where redox mediators used instead of direct oxygen. Commonly used mediators like ferrocene derivatives[12] possess essential aspects such as low molecular weight, insoluble nature, etc. These aspects of mediators provide a reversible or quasireversible process, effective diffusion throughout system, a suitably lowering redox potential to avoid oxidation of interfering species, a high stability and resistance to forming side compounds, and a low toxicity. Althoughmediators have fascinating properties, however problems may arise due to small and diffusive nature of mediator molecules resulting the difficulties to maintain concentration of mediator near electrode surface[13]. The constraints of 2nd generation biosensors are to be resolved with designing of 3rd generation biosensors. The 3rd generation biosensors are mediator free and based on direct electron transfer from enzyme to electrode. Although 3rd generation biosensors have many advantages and are successfully commercialized, few aspects again restrict 3rd generation biosensor applications. Along with stability and cost-effectiveness,

a major barrier lies in electron transfer between biological element and transducer system as only few proteins show direct electron transfer with electrode.

Therefore, the limitations of 3rd generation biosensor are the real motivations to construct the label-free (non-enzymatic) biosensors. These label-free biosensors potentially detect many biomolecules without using any biorecognition element and hence these form 4th generation biosensors. The need of fragile enzymes is eliminated by non-enzymatic approach. Non-enzy0000000matic biosensors can be defined as "Electrochemical sensors contain non-biologically active elements, improving the sensitivity and selectivity of the sensors in analyte detection". Non-enzymatic sensors generally detect chemical or biological species through their redox activity. However, metal oxide (MO) based electrochemical sensors are perfect for the electro analysis of biomolecules by virtue of their simplicity, inexpensive, quick response, and good portability. Hence, enzyme-free electrochemical sensors have been widely used for determining the presence of hydrogen peroxide, glucose, dopamine, uric acid, etc.[14]**(figure 11.3)**

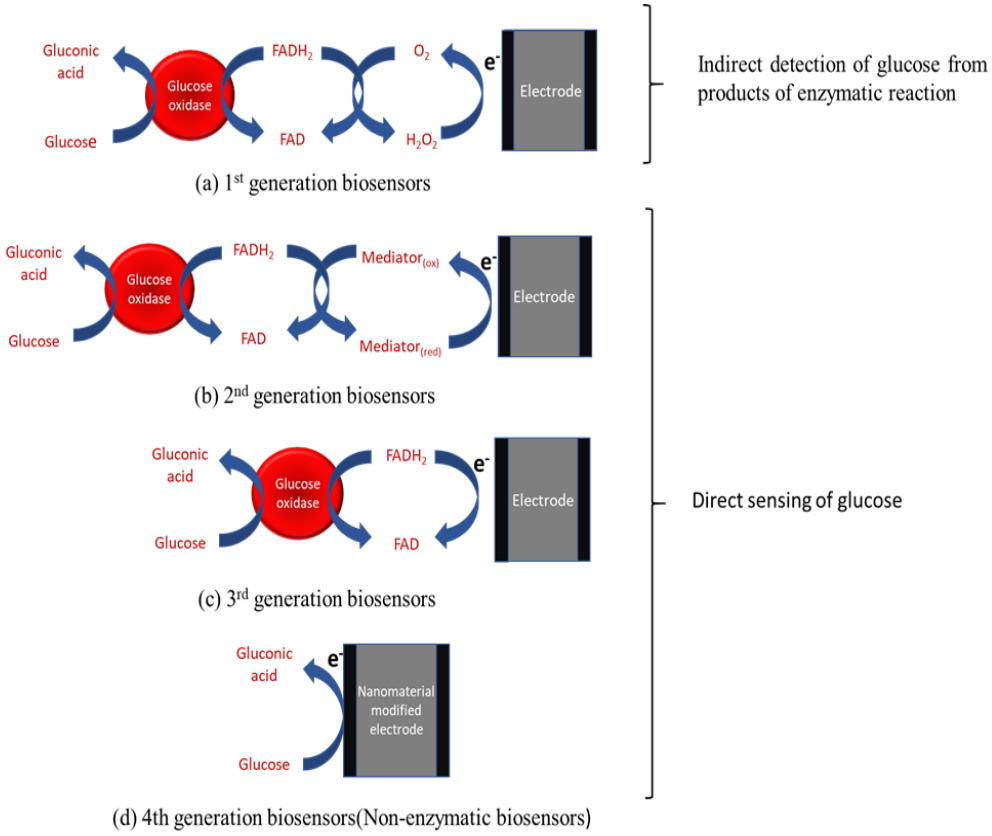

Fig.11.3. Evolution of electrochemical biosensors, (a) 1st generation biosensor (b) 2nd generation biosensor (c) 3rd generation biosensor (d) 4th generation biosensor

However, the analytical performance of enzyme-free electrodes has some drawbacks like, slow electrode kinetics and high over-potential, etc. Moreover, the poor measurement

stability caused by surface poisoning from the intermediate products adsorbed or the effect of co-existing electro-active species is still a serious problem in the application of these electrodes. Therefore, current efforts have mainly focused on discovering new materials with high electro-catalytic activity and good stability in order to construct enzyme-free sensors.

5. Functional nanocomposites in electrochemical biosensor

Nanocomposite is a multi-phase solid material where at least one of the combining phases/components having dimensions of less than 100 nanometres (nm). Functional nanocomposites are the nanocomposites where same host materials (usually nanocomposites) used for the different applications through their functionalization's or modification's. The functional nanocomposites have the promising properties through the additional surface modification; which are to be modified via chemical and physical routes. Bare materials possess some limitations which impede their usage in the applications. For instance, the electrical as well as ionic conductivity of bare metal oxide is poor which limits their applications in electronicsand electrochemical devices. Additionally, most of the bare metal oxide exhibits a wide band gap, due to which these are only responsive to ultraviolet light and cannot absorb visible light. Thus, additional surface modification is highly indispensable to improve the different physical and chemical properties. Further functionalization is also able to enhance their sensitivity as a diagnostic tool and imbue metal oxides with additional capabilities such as drug delivery and biomolecule sensing. Ascribed to the large surface to volume ratio and tuneable electronic band structure of planar MOs, functionalization of MOs with various approaches is relatively straightforward, such as surface modification via chemical bonding and physical adsorption and inducing oxygen vacancies and doping[15][16].

Along with surface functionalization, the morphology as well as covalent/non-covalent interactions of MOs with others is also playing dominant role in alteration of the properties of MOs. The creation of covalent bonds or coordinate bonds with atoms on the surface of 2D MOs occurs when organic molecules modify the surface via a chemical mechanism. Such a strong chemical bond is necessary to firmly anchor functional groups on MO surfaces as well as to modify properties of MOs that are not easily altered by the physiological environment. Polymers or smaller organic molecules are typical organic moieties covalently or non-covalently bonded to MOs for biosensing and therapeutic purposes[17]. The physisorption of desired biomolecules or target analyte onto the relatively broad basal surface of the MOs, allowing for maximum loading as well as interaction with the surrounding environment. Typically, physical adsorption is non-covalent and achieved via hydrophobic interactions, electrostatic attraction and van der Waals forces. The large surface area of metal oxides

provides large amounts of anchoring sites for guest agents, hence metal oxides nanocomposites can strongly adsorb diverse guest agent, which make metal oxides excellent for transducer systems[18].

The electronic functionalities and catalytic properties of MOs are strongly influenced by defects, doping,[19] and the cation oxidation state. Therefore, introducing oxygen vacancies and doping in MOs are important modification strategies for surface functionalization of 2D MOs to modify the electronic band structure and to adjust the Fermi level. For example, the existence of various oxygen vacancies endows molybdenum oxides with diverse interesting characteristics. Typically, fully stoichiometric MoO_3 is regarded as catalytically inert, while sub-stoichiometric MoO_3 introduces a large number of active sites due to the increment of oxygen vacancies. Furthermore, molybdenum oxides with different oxygen vacancies typically exhibit controllable band gaps of 2.8–3.6 eV. The change of stoichiometry of MOs can be achieved chemically orelectro-chemically, by removing oxygen via. chemical reduction reactions with proper reductants[20].**(Figure.11.4)**

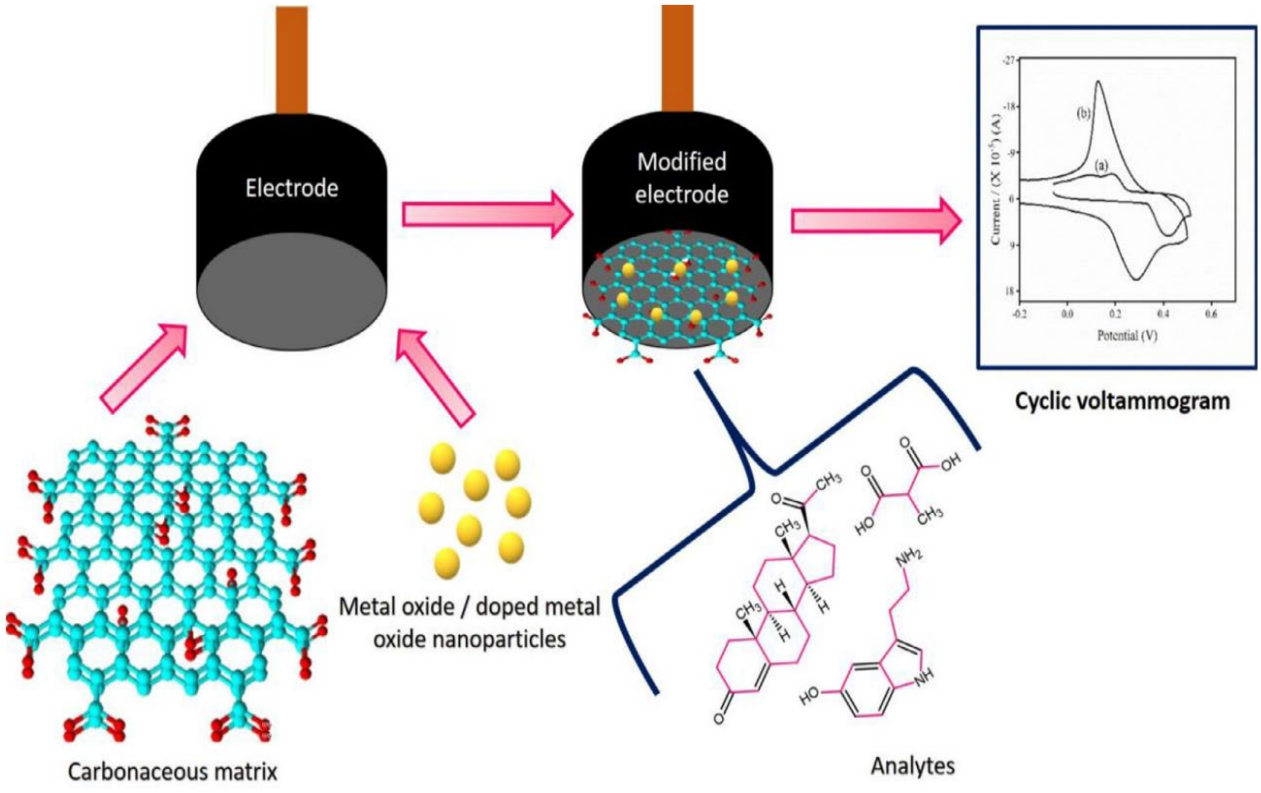

Fig.11.4Schematic representation of the role of metal oxide nanoparticles in electrochemical determination of analyte

As per the literature, the functional nanocomposites are broadly classified into the following types; which are used in non-enzymatic electrochemical biosensing:**(Table No.11.1)**

Table No. 11.1

Materials	Analyte	LOD	Linear Range	References
Metals				
Palladium	Glucose	10 μM	0.05–10 mM	[21]
	H_2O_2	0.01 μM	0.05 – 160 μM	[22]
	Ascorbic acid	4.9×10^{-8} M	1×10^{-3} – 1.5×10^{-2} M	[23]
	Dopamine	5.6×10^{-8} M	1×10^{-3} – 1.5×10^{-2} M	
	Uric acid	4.7×10^{-8} M	1×10^{-3} – 1.5×10^{-2} M	
Copper	Glucose	1.39 μM	0.02–2.3 mM	[24]
	Acetylcholine	39 μM	0.12–2.68	[25]
	Creatinine	0.0746 μM	6-378 μM	[26]
Platinum	Glutamate	83 μM	0.5–8.0 mM	[25]
	H_2O_2	1.2 μM	1.0–8.0 mM	[27]
	Ascorbic acid	0.43 μM	10–1800 μM	[28]
	Dopamine	0.07 μM	0.5–211.5 μM	
	Uric acid	0.63 μM	9.5–1187 μM	
	L- Glutamate	0.1 μM	0.004–0.9 mM	[29]
Nickel	Glucose	4.1 μM	0.2–9 mM	[14]
	Ascorbic acid	0.5 μM	1.0×10^{-5} M – 1.8×10^{-3} M	[30]
Pd–Au bimetallic cluster	Glucose	50 μM	0.1–30 mM	[21]
AuPd@GR	H_2O_2	1 μM	5 μM–11.5 mM	[31]
Silver	Glucose	0.79 μM	50 –0.1 μM	[32]
	H_2O_2	0.15 μM	0.02-20 mM	[33]
Molybdenum	Dopamine	1.26 nM	0.01 – 1609 μM	[34]
Iron	H_2O_2	0.53 μM	0.001−5 mM	[33]
Metal Oxides				
Copper Oxide	Glucose	11 μM	50 μM – 1 mM	[32]
	Dopamine	0.18 μM	0.3–1.4 μM	[35]
	Uric acid	0.08 μM	0.4–400.0 μM	[36]
	H_2O_2	0.04 μM	0.2–2000 μM	[37]
Zinc Oxide	Glucose	0.1 μM.	0.25–110 mM	[38]
	Dopamine	0.039 nM	0.12 nM-152 μM	[39]
	Uric acid	5.72 nM	6.25 – 625 nM	[40]
	Epinephrine	0.0093 μM	0.02 – 216 μM	[41]
	Norepinephrine	0.2 μM	0.5–30 μM	[42]
	Levadopa	0.08 μM	0.6 – 100.0 μM	[43]
	Urea	0.011 mg dL^{-1}	0.1 –250 mg dL^{-1}	[44]
	Serotonin	0.66 μM	7.5–300 μM	[45]
Iron Oxide	Glucose	234 μM	1–16 mM	[20]
	Dopamine	0.035 μM	0.3–210 μM	[46]
	Xanthine	0.092 μM	0.5–177 μM	[47]
	Uric acid	0.106 μM	0.5–265	

	H_2O_2	1.0 μM	5.0–4495.0 μM	[48]
Titanium Dioxide	Glucose	8 μM	0.03–14 mM	[49]
	Dopamine	0.03 μM	0.049-30 μM	[50]
	H_2O_2	0.7 μM	10 – 200 μM	[51]
	NADH	0.2 μM	10 –240 μM	
	Uric acid	70 nM	0.1–500 μM	[52]
	Guanine	50 nM	0.1–40 μM	
	Hemoglobin	0.3 μM	1–1170 μM	[53]
	L-Cyteine	250 μM	500–6000 μM	[54]
	Ascorbic acid	1.13 μM	2.5 to 100.0 μM	[55]
Nickel Oxide	Cholesterol	0.13 μM	2–40 μM	[56]
	Glucose	0.16 μM	1–110 μM	[49]
	H_2O_2	0.2 μM	3–700 μM	[57]
	Acetylcholine	26.7 μM	0.25–5.88 mM	[25]
	Dopamine	1.038 μM	2–100 μM	[58]
Cobalt Oxide	H_2O_2	0.015 μM	0.05–400 μM 450–1250 μM	[59]
	Glucose	0.04 μM 0.14 μM	5 – 60 μM 0.2 –3.0 mM	[60]
	Urea	5.0 μM	0.06–0.30 mM	[61]
	Lactic Acid	0.006 mM	0.05–3 mM	[52]
	L-glutamic acid	10.0 pM	1 nM –0.1 M	[62]
	Uric acid	60.0 pM	0.1 nM – 0.1 M	
Manganese Dioxide	Urea	14.693 μM	5–100 μM	[63]
	Glucose	1.8 μM	5μM–2 mM	[64]
	Dopamine	0.027 μM	0.1 μM–0.08 mM 0.08-041 mM	[65]
	H_2O_2	0.55 μM	40 –10230 μM	[66]

5.1. Metallic nanoparticles-based composites

Nanoparticles of various metals such as palladium, copper, platinum, nickel, gold, silver, etc. are comprehensively used in electrode preparation for detection of analytes like Glucose, Ascorbic acid (AA), Uric acid (UA), Dopamine (DA), Creatinine, hydrogen peroxide(H_2O_2), etc. A novel electrochemical sensor was fabricated by Demirkan et al. using palladium nanoparticles supported on polypyrrole/reduced graphene oxide (rGO/Pd@PPy NPs) composites. These composites were deposited onto glassy carbon electrode (GCE) for the simultaneous detection of AA, DA and UA. rGO/Pd@PPy nanocomposites-based electrodes were highly selective and sensitive towards the specific analytes. This is attributed to their

higher conductivity as well as superior catalytic activity in the reactions between analyte and composite materials for the detection of specific analytes with higher current as well as oxidation peak intensities[23]. Similarly, palladium nanoparticles decorated on the surface of magnetic graphene oxide functionalized with amine-terminated poly(amidoamine) dendrimer (GO-Fe_3O_4-PAMAM-Pd) was utilized for non-enzymatic electrochemical determination of H_2O_2 by Baghayeri et al.[22] Under optimum conditions, the designed sensor showed good electrochemical performance toward H_2O_2 reduction, offering extended linearity of 0.05 to 160 μM and a low detection limit of 0.01 μM. Raveendran et al. fabricated a disposable copper modified non-enzymatic sensor for creatinine. The estimation of creatinine was based on the formation of soluble copper-creatinine complex with linear range of 6-378 μM.[26].

Platinum nanoparticles are favourable candidates due to their surface electrical effect, and catalytic properties used widely in electrochemical biosensors. Zhang et al. prepared Pt NSs/C60/GCE electrode exhibited three well-resolved voltammetric peaks in the differential pulse voltammetry (DPV) measurements, allowing a simultaneous detection of these biomolecules. The limits of detection (LOD) (S/N = 3) are down to 0.43μM, 0.07μM and 0.63μM for AA, DA and UA, respectively. Bian et al. prepared Pt/polypyrrole (PPy) hybrid hollow microspheres by wet chemical method for determination hydrogen peroxide. The composite showed the linear range in between 1.0 to 8.0 mM with a relatively low detection limit of 1.2 μM as well as high sensitivity of 80.4mA$M^{-1}cm^{-2}$[21].

Another metal nanoparticles popularly used in electrochemical biosensor is gold. Nanosized gold nanoparticles exhibits extraordinary catalytic and biosensing, properties due to large surface-to-volume ratio and the interface-dominated properties, can decrease overpotentials of many analytically important electrochemical reactions. Shen et al. synthesized bimetallic Pd–Au cluster through direct chemical reduction method for non-enzymatic sensing of glucose. The glucose contents detected by the electrode were in good agreement with those from the hospital when the electrode was employed to detect glucose in blood samples[21].

The amperometric sensor developed with enzyme-free silver nanoparticles-based electrodes for the glucose detection. The excellent electrocatalytic activity toward non-enzymatic glucose sensors was reported through the excellent sensitivity (2.7664 mA mM^{-1} cm^{-2}), a wide linear range of detection (50–0.1mM), LOD (0.79mM) and rapid response time[68]. Guan et al. studied electrochemical performance of Ag/NCNFs-based sensor Ag/NCNFs-based sensor reported superior reproducibility and excellent stability and used for H_2O_2 detection in milk samples[69].

5.2 Metal oxide nanomaterial's-based composites

Metal oxides have gained practical as well as theoretical importance in the biological science, environmental science and analytical chemistry. This is due to their extraordinary properties such as low cost, ease to synthesize, high surface area-to-volume ratio, high chemical stability inphysiological environment and electrochemical activity. The metal oxides are widely used in electrochemical biosensors for non-enzymatic detection of biological species like proteins, sugars etc. due to their very well-known catalytic properties. Literature studies revealed that the various nanoparticles like gold nanoparticles (AuNPs)[70] and Fe_3O_4[71] showed enzyme like activity in biosensing studies. Non-enzymatic detection comes into light. Similarly, nanoparticles of Pt, Pd, NiO, CuO etc. with types of morphologies and dimensions are used for the development of the fourth generation of electrochemical biosensors. Therefore, numerous researchers have been focused on the various aspects of electrochemical biosensors so as to make extremely interesting technology in the field of biomedical applications. The modification of the working electrode using metal oxide nanoparticles conjugated with carbon matrix like graphene, graphene oxide, reduced graphene oxide, carbon nanotubes (CNTs), multiwalled carbon nanotubes (MWCNTs), conducting polymers, biopolymers, silanes, antibodies, etc. are conferred in detail. In addition, doping of transition metal oxide nanoparticles with various elements like nitrogen, noble metals and enzymes are also considered for modifying the properties of bare metal oxides.

Reddy et al. synthesized CuO nanoparticles of various morphologies by co-precipitation method, and used to prepare modified carbon paste electrode for electrochemical determination of DA. Due to properties like surface area of the electrode, the heterogeneous rate constant (k_s) and the lower detection limit (5.5×10^{-8} M), this sensor showed good results in electrochemical sensing of DA[35]. The copper/cuprous oxide (Cu/Cu_2O) nanocomposites were electrodeposited on a fluorine doped tin oxide (FTO) glass substrate for sensitive determination of H_2O_2 by Han et al. The sensor exhibited a wide linear range of 0.2–2000 μM for the determination of H_2O_2 with a detection limit of 0.04 μM[37]. Hassan et al. synthesized CuO-rGR/M3OIDTFB/CPE electrode for simultaneous detection of cholesterol (CL), AA, UA. The sensor displayed linear response in the concentration ranges 0.04–300.0 μM, 0.04–240.0 μM and 0.4–400.0 μM for CL, AA and UA with the detection limits 9.0 nM, 9.0 nM and 0.08 μM, respectively [36].

Imran et al. developed a non-enzymatic biosensor for glucose detection using graphitic carbon nitride (g-C_3N_4) modified with platinum and zinc oxide. The electrochemical glucose

sensing at the ZnO-Pt-gC_3N_4 occurred at low applied potential of +0.20 V (vs. Ag/AgCl) with high sensitivity 3.34 μA/mM/cm^2 and fast response (5s) time. This sensor exhibited a wide linear range 0.25–110 mM with lower limit of detection of 0.1 mM. The ZnO existence with Pt providing more hydroxyl ions and also promoting the electrocatalysis in neutral physiological buffer solution[38]. Song et al. studied DA-imprinted chitosan (CS) film/ZnO nanoparticles (NPs)@carbon (C)/three-dimensional kenaf stem-derived macroporous carbon (3D-KSC). This is a fast, efficient and sensitive method for detecting DA. The sensor has the detection limit of 0.039 nM, and the sensitivity of 757 μA mM^{-1} cm^{-2}[39]. Nickel (Ni^{2+}) ion doped zinc oxide-multi-wall carbon nanotubes (NZC) composites were used as electrode materials with glassy carbon electrodes (GCEs) for electrochemical detection of UA by Mullani et al. The limit of detection (LOD) and limit of quantification (LOQ) for the NZC 0.1/GCE were reported to 5.72 nM and 19.00 nM (S/N = 3) respectively, which is the lowest compared to the literature values reported so far for enzymatic and non-enzymatic detection techniques[40]. Zhu et al. synthesized epinephrine sensor based on the hierarchical flower-like zinc oxide nanosheets (flower-like ZnO) embedded into three-dimensional ferrocene-functionalized graphene framework. The flower-like ZnO/3D graphene@Fc exhibited excellent sensing performance for epinephrine with a wide linear range of 0.02 to 216 μM, a low detection limit of 0.0093 μM, high anti-interference and good cyclic stability. The sensor has a linear range of 0.192 to 527 μM and a detection limit of 0.1 μM for oxidized derivative of epinephrine[41]. Mullani et al. conducted efficient 5-HT sensing studies using the (ZnO $NRs)_{1-x}$ $(CNs)_x$ nanocomposites. The sensor has wide linear response range (7.5–300 μM); lower limit of detection (0.66 μM), excellent limit of quantification (2.19 μM) and good reproducibility[45].

One-step electrode position method of Polypyrrole-Chitosan-Iron oxide (Ppy-CS-Fe_3O_4) nanocomposite films developed by Abdul Amir Al-Mokaram for the fabrication of advanced composite coatings for biosensors applications. The fabricated electrode Ppy-CS-Fe_3O_4 NP/ITO showed a fast amperometric response with good selectivity to detect glucose non-enzymatically with improved linearity (1–16 mM) and the detection limit of (234 μM) at a signal-to-noise ratio (S/N = 3.0) [20]. Nitrogen and sulphur dual doped graphene supported Fe_2O_3 (NSG-Fe_2O_3) have been prepared by hydrothermal methods and subsequently utilized for the electrochemical determination of DA in presence of AA by Yasmin et al. The NSG–Fe_2O_3 has shown sensitivity (29.1 μA mM^{-1}), long linear detection range (0.3–210 μM) and detection limit (0.035 μM)[46]. Ganesan et al. synthesize a nitrogen-doped carbon quantum

dots (N-CQD) decorated iron oxide (N-CQD@Fe_2O_3) for simultaneous electrochemical determination of structurally similar analyte of anticancer drug 5-fluorouracil (5-FU) and inflammatory agents UA and xanthine (XA). The modified electrode, N-CQD@Fe_2O_3/MWCNT/GCE, showed excellent sensitivity for the detection of UA, XA, and 5-FU with the detection limit of 0.106, 0.092, and 0.019 μM[47].

Gao et al. prepared a electroactive $Ni(OH)_2$ and protective TiO_2 composite film on NiTi alloy($Ni(OH)_2$/TiO_2/ NiTi) for glucose sensing. The sensor has sensitivity of 192 A μM^{-1} cm^{-2}, short response time of less than 1 second, and detection limit of 8 μM[49]. Biswas et al. synthesized a titanium dioxide nanoparticle (NPs) by a sol-gel method. NPs were used to modify a graphite paste electrode for simultaneous determination of UA and guanine. The sensor has linear range of 0.1–500 μM and 0.1–40 μM for UA and GU, respectively and detection limit is 70 nM for UA and 50 nM for GU[52].

Nickel oxide is promising candidate for enzyme-free electrochemical detection of biomolecules, due to the existence of the redox couple of $Ni(OH)_2$/NiOOH formed on the electrode surface in alkaline medium. Mu et al. developed a fast and sensitive sensor for glucose determination based on NiO modified carbon paste electrode. The sensor has sensitivity of 43.9 nA/mM and detection limit of the electrode was found to be 0.16 μM[72]. Lata et al. immobilized cytochrome-c onto nickel oxide nanoparticles/carboxylated multiwalled carbon nanotubes/polyaniline modified gold electrode for H_2O_2 detection. The sensor has linear range of 3–700 mM and detection limit of 0.2 M with high sensitivity of 3.3 mA mM^{-1} cm^{-2}[57]. Sattarahmady et al. synthesized Lichen-like nickel oxide nanostructure and then applied to modify a carbon paste electrode for the fabrication of the electrocatalytic oxidation of acetylcholine (ACh). A sensitive and time-saving hydrodynamic amperometry method was developed for the determination of ACh. ACh was determined with a sensitivity of 392.4 mA M^{-1} cm^{-2} and a limit of detection of 26.7 μM[73]. Roychoudhury et al. developed a DA biosensor using nickel oxide nanoparticles (NPs). The electrochemical response studies of the fabricated electrode showed improved sensitivity (0.0602 mA/mM) for dopamine detection in wide linear detection range (2–100 mM) with fast response time of 45 s due to the presence of stable and highly catalytic NiO NPs that facilitates fast electron transport from bio-recognition element to the underlying ITO substrate[58].

Sakthivel et prepared polyhedrons structured cobalt oxide (Co_3O_4 PHs) and three-dimensional graphene oxide encapsulated cobalt oxide polyhedrons (3D GO–Co_3O_4 PHs) by hydrothermal route for determination of H_2O_2. The sensor has wide working range (0.05–400

μM and 450–1250 μM) and low detection limit (15 nM)[59]. Mondal et al. prepared a selective and sensitive non-enzymatic electrochemical glucose sensor by using cobalt oxide nanoflowers (NF). The developed amperometric glucose sensor exhibited excellent anti-interfering property and two wide linear ranges of 5 to 60 μM and 0.2 to 3.0 mM, with high sensitivities of 693.02 $mAmM^{-1}cm^{-2}$ and 228.03 $\mu AmM^{-1}cm^{-2}$ and detection limits (LOD) as low as 0.04 μM and 0.14 μM, respectively[60]. Nguyen et al. synthesized a $NiCo_2O_4$ bimetallic electro-catalyst on three-dimensional graphene (3D graphene) for the non-enzymatic detection of urea. The $NiCo_2O_4$/3D graphene/ITO sensor showed high sensitivity of 166 μA mM^{-1} cm^{-2}, detection limit of 5.0 μM and linear range of 0.06–0.30 mM[61].

7. Challenges and Future perspectives

The use of nanocomposite in electrochemical biosensor accompanied by various challenges, like stability of materials used at physiological conditions, good performance of biosensing device at different temperatures, must tolerate high ionic strength buffers, etc. In addition, the other desired properties such as less use of toxic materials and preparation cost of material should also be considered. The interaction between analyte and material plays major role in the outcome of biosensor, and many researchers not studied the interaction between analyte and material very well. There has been tremendous work was done yet, many publications lack the information regarding about operation conditions as well as experimental demonstrations. Although the electrochemical biosensors have been shown to be suitable for high-performance analysis in diverse field applications, the matrix interference influencing the bio molecular interaction from real samples (blood, food, etc.) still remains the most critical issues that need to be solved for improving the analytical performances.

The various constraints in the present state of art of biosensors have been resolved with the following research endeavours:

- Synthesize the functional nanomaterials for real-world applications of biosensors.
- Development of Multianalyte sensor for analysis of different biomolecules with single device effectively and selectively remains a challenge.
- Non-specific binding in non-enzymatic electrochemical biosensor is due to high surface to volume ratio of metal oxide. The high surface area of metal oxide nanomaterial's causes surface fouling. The materials with antifouling properties are the future of

biosensor materials. Polymers and polymer nano brushes show excellent antifouling properties.

- Selectivity is the issue in application of non-enzymatic based electrochemical biosensor. New strategies like Molecular imprinted polymers, Enzyme mimicking materials like MOFs, etc. can be used to improve selectivity.
- The application in physiological condition and reliability of results is important factor. Hence In concern with this stability study of material at various parameters like pH, temperature and interactions with other moieties is necessary for implementation of Biosensor.

Conclusions

Inherent sensitivity, simplicity, speed, and cost benefits continue to be strong driving forces for the development of electrochemical based biosensors. Metal oxides are considered as versatile materials that can be successfully integrated in biosensor technology. Based on features such as chemical stability, environmentally benign, non-toxic, electrocatalytic activity with or without light irradiation, and high surface area-to-volume ratio, these materials are highly competitive in the biosensors market. This chapter has outlined the basics of biosensors with their different types followed by the details about the metal oxide-based composites used in non-enzymatic electrochemical biosensors. The overall performance of biosensor depends upon the various parameters such as, properties of materials used, evaluation procedure or protocol designed, chemistry between materials-analyte during the biosensing process, etc. Several functional metal oxide-based nanocomposites have provided an innovative solid substrate for a highly sensitive on-site analysis via signal amplification in electrochemical biosensors. In this connection, the various types of functional nanomaterials (carbon nanotubes, graphene, metallic, silica nanoparticles, nanowire, indium tin oxide, and organic polymers), have been included in this book chapter. For the functionalization, the electrode surfaces can be coated with various organic groups (silanes, thiols and conducting polymers) for effective connectivity or interactions with analytes for efficient responses.

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