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# Cancer diagnosis using nanomaterials based electrochemical nanobiosensors

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ABSTRACT

Cancer is one of the most important causes of mortality in the world, which can be severely reduced by early detection to avoid future problems in the field of economics and mental health. Hence, electrochemical nanobiosensors as portable devices for rapid detection of cancer biomarkers, have found an important place in clinical medicine for diagnosis, managements or cancer screening. Although, these biosensors have been receiving attention in the recent years, their principles are unchanged. By progress in nanotechnology, a great potential has been giving to nanobiosensors. Applications of a wide variety of nanomaterials in developing electrochemical biosensors, led to the production of potential nanobiosensors. Due to the high electrical conductivity, and increased surface area relative to the volume along with more repeatability, the application of NPs in electrochemical biosensors has been developed. Therefore, in this review, we discussed the impact of nanomaterials on the accuracy of biosensors in early cancer detection such as lung, prostate, breast, and other cancers. However, the modification of electrode performance by nanomaterials is relatively complicated, which causes limitation for some nanomaterials to be used inbiosensor applications. Indeed, the construction of electrodes based on nanomaterial requires a simple, reliable and inexpensive route to increase the sensitivity and reproducibility. Thus, the aim of this study can be defined as determining the detection limit of electrochemical nanobiosensors as well as introducing the challenges of fabricating and designing electrochemical nanobiosensors based on nanomaterials and their evaluations in the future medical setting.

## 1. Introduction

According to WHO reports nearly 9 million people died in 2015 from variety of cancer cases (Forouzanfar et al., 2016). While death rates sharply increases, the risk of cancer mortality may reduce if the speed of cancerdetection improves. The most commonly used conventional tools for cancer detection are based on tissue sampling, imaging (such as magnetic resonance imaging, computed tomography, etc.), and so on. But today, the use of biosensors for cancer diagnosis has accelerated diagnostic activities (Hsieh et al., 2016). Biosensors are one of the important subdivisions of chemical sensors which convert a biological response into a detectable signal. The term 'biosensor' is often used to cover sensor devices to determine the concentration of a target substance through a biological process. Biosensors as diagnostic tools have found applications in drug detection, biomedical assessment, environmental monitoring, etc. (Peng et al., 2014; Touhami, 2014; Turner, 2013). However, biosensors have an inaccuracy in the early cancers detections due to the very low concentrations of cancer biomarkers in blood or tissue fluids. Therefore, interests in new approaches such as nanotechnology have been receiving great attentions to improve detection limits. The progress of electrochemical nanobiosensors is probably an encouraging problem solving approach related to sensitivity, velocity, and selectivity.. In this line, Sarkar et al. (2008) showed that magnetite NPs with horse radish peroxidase labeled secondary antibodies, increased the accuracy of diagnosis of free PSA with a LOD of < 0.1 ng/mL. Furthermore, Pan et al. (2017) showed that GO

*Abbreviation:* BRCA, Breast cancer susceptibility gene; CA, Carbohydrate antigen; CNT, Carbone nanotube; CEA, Carcinoembryonic; CTC, Circulating tumor cell; EC, Electrochemical; EGFR, Epidermal growth factor receptor; GCE, Glassy carbon electrode; Au, Gold; GO, Graphene oxide; HER-2 or HER-3, Human epidermal receptor-2 or -3; LOD, Limit of detection; MUC, Mucine protein; NPs, Nanoparticles; NSE, Neuron-specific enolase; PSA, Prostate-specific antigen; Ag, Silver; VEGF, Vascular endothelial growth factor

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containing ssDNA on Au electrodes along with poly-$_L$-lactide NPs (for signal amplification) for VEGF and PSA detection caused a significant increase in selectivity and sensitivity with a LOD of 0.5–100 ng/mL for VEGF and 1–100 ng/mL for PSA compared to conventional methods. Recently, with the development of electrodes based on AuNPs and $Bi_2Se_3$ NPs ($Bi_2Se_3$ @Au), the ability to detect cancer with a LOD of $10 \times 10^{-9}$ M and with a dynamic range of $0.1 \times 10^{-6}$ to $27.3 \times 10^{-6}$ M increased by tracking $H_2O_2$ generated from breast cancer cells (MCF-7 and MDA-MB-231) (Mohammadniaei et al., 2018). Therefore, the main problem of electrochemical biosensors is the lack of suitable electrodes with high sensitivity and unique recognition. However, the incorporation of NPs along with biomarkers greatly resolves the detection limits (Vigneshvar et al., 2016). Also, one of the important factors in biosensing is the signal transduction which should be optimized. An appropriate solution to increase the sensitivity is the use of nanomaterials with determined dimensions in biosensors (Malik et al., 2013). Thus, there has lately been a raised emphasis on applying nanotechnology to decrease the size of electrochemical biosensor and increase the selectivity of the biomolecules, the signal-to-noise ratio and the signal per effect by multiple receptors (Azimzadeh et al., 2015; Ding et al., 2013). Also, innovations in electrochemical nanobiosensors is focused on improving the detection limit, examination time, and portability along with greater accuracy (Ozsoz, 2012; Vigneshvar et al., 2016). For these reasons, electrochemical nanobiosensors are one of the most significant technics of medical analytics (de Planell-Saguer and Rodicio, 2013). Realizing the potential role of electrochemical nanobiosensor in diseases detection, this study has selectively reviewed the recent progress in cancers detection by electrochemical nanobiosensor. Despite the variety of nanomaterials used in electrodes, we have highlighted the use of carbon nanostructures, AuNPs, and metal oxides in electrochemical nanobiosensors. Further, the challenges of cancer diagnosis by electrochemical nanobiosensors were investigated.

## 2. Basic concepts of nanobiosensors

Generally, biosensors (Fig. 1) comprise of a bio-receptor as a sensing element and a signal transducer to transform a biological signal to physical signal. Conversion of a biological or chemical signal into a measurable signal can be done by a physicochemical transducer based on optical, electrical, mass or thermal techniques. A signal processor also is required to amplify the signal. A bio-receptor (such as enzymes, antibodies, DNA, and RNA) is linked to the target analyte, an jointing structure where a special biological changes occurred and increases the signal strength (Fracchiolla et al., 2013; Xie et al., 2017). A biosensor must be highly specific and independent of physical parameters such as temperature and pH, and it's better to be reusable (Erden and Kilic, 2013). Therefore, for fabrication of biosensors with such properties, multidisciplinary research are required in the fields of chemistry, biology, physics, engineering, etc. (Xie et al., 2017). In this regard, nanobiosensnors consist of a bio-element and a nanomaterials-based sensor-element (Fig. 1). The sensors and the bio-elements could be combined together in one of the five possible methods: Matrix semi-permeable membrane; physical adsorption; encapsulation; covalent bonding and cross-linking (Table 1) (Adamson and Gast, 1997; Malik et al., 2013). Altogether, the analytical devises used in the development of nanobiosensors comprise of two paths directly derived from the interface between the analyte and identifying factor, or indirectly, include the connection between mediators and reactions.

The main challenge in designing of sensors/biosensors is to decrease the LOD and enhance the signal to noise ratio. There are many helpful biomarkers for early diagnosis of some cancers with low concentrations. Therefore, the miniaturization of the device to have a portable system as chips or implantable devices is of great importance. By recent advances in nanotechnology, some remarkable developments have been achieved in the sensing concepts. This means that the nanosensors were generated using active nanoscale elements in the production of sensors (Chinen et al., 2015). Accordingly, nanobiosensor is one sensor that converts a biological signal to physical signal using nanomaterials. Nevertheless, the two main factors in nanobiosensors should be considered in comparison with nanosensors, which include: affinity along with specificity and shelf lives of biological agents (Touhami, 2014). One of the main challenge in designing nanobiosensor is the use of the nanomaterials-based receptor and the incorporation into transducers without reducing and changing their activity (Vigneshvar et al., 2016). In recent years, nanomaterials-based electrochemical biosensors are usually supplied by improving the surface of the metals (Au, Ag, and Cu NPs) and carbon (graphite, graphene, and nanotubes) electrodes using bio-materials (Fig. 2) (Ding et al., 2013; Guo, 2013; Wang et al., 2014a). Across the metallic NPs, AuNPs have more applications due to their constancy versus oxidation (Fogel et al., 2016) and lack of toxicity, whereas other materials like AgNPs are toxic for internally routes (Malik et al., 2013). Also, in addition to corrosion resistance, Au enhances the transfer of electrons directly between redox centres and bulk electrode materials, which allows electrochemical sensing without using mediators (Touhami, 2014). Au also has shown some features like enhanced Raman scattering and strong surface, fluorescence properties, anisotropic chemical reactivity, good biocompatibility, high electrical conductivity, and inertness. On the other hand, carbon structures are one of the most commonly used compounds in nanobiosensors on account of thier cheapness and abundance (Haynes, 2012). On the whole, electrodes prepared from carbon structures show an extraordinarily low background current, broad potential window, appropriate modification, high space for entrapment of different compounds, renewability, and low cost to incorporate different substances during preparation.

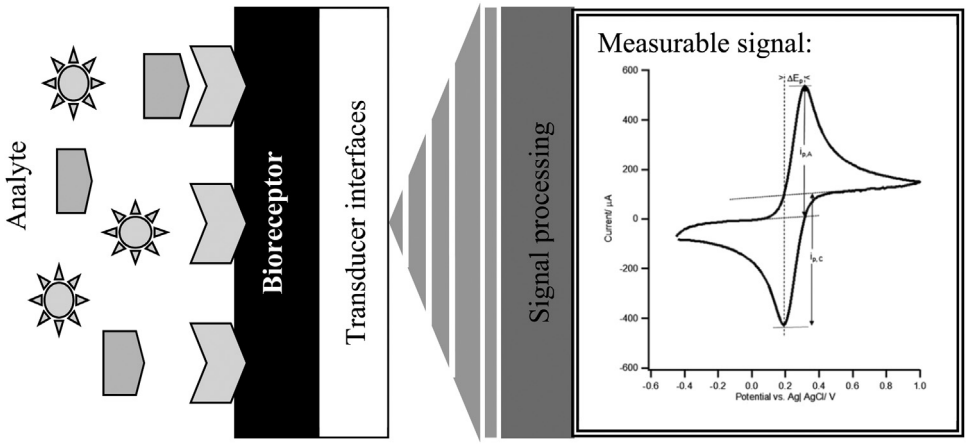


**Fig. 1.** A schematic representation of electrochemical nanobiosensor.

**Table 1**
Five methods for immobilization of nanomaterials and biomaterials in nanobiosensors.

| Immobilization method | Binding nature | Advantages | Disadvantages |
|---|---|---|---|
| Affinity | Affinity bonds between two affinity partners | Oriented immobilization, remarkable selectivity, simple. | High cost. |
| Physical Adsorption | Hydrophobic, van der waals or ionic interactions. | Simple, cheap, fast, little conformational change of the biomaterials, direct method, suitable for DNA, RNA. | Desorption by change of ionic or detergent, nonspecific adsorption, random orientation, poor reproducibility. |
| Covalent bonding | Chemical binding between functional groups of the biomaterials and support. | No biomaterials leakage, potential for biomaterials stabilization in long term. | Matrix and biomaterials are not regenerable, major loss of activity, slow, use of linker molecules, irreversible, problem of crowding effect. |
| Entrapment | Occlusion of a biomaterials within a polymeric network like agar, agarose and gelatine | Wide applicability | Cause barriers to the diffusion of substrate and retaredation of the reaction |
| Cross-linking | Molecules are cross-linked by a functional reactant such as glutaraldehyde | Biocatalyst stabilization, improved orientation, well controlled, high specificity, reversible. | Softness of biomaterials layers, higher biological demands, multilayer formation affecting the activities of diffusion, expensive, poor reproducibility, problem of crowding effect, slow, loss of activity, mass transfer limitations, cross-linked biocatalysts are less useful. |

Another major challenge in designing nanobiosensors is the ability to detect biological materials based on the type of nanobiosensor. Like chemical sensors, based on transduction of the signal, nanobiosensors are also classified into four types include optical, mass, thermal, and electrochemical detection (Fig. 3b) (Ozsoz, 2012). The validity of the approach depends on the biochemical materials to be detected (Table 2) (Barry and O'Riordan, 2016). Nevertheless, one of the most commonly diagnostic methods is the use of electrochemical nanobiosensors because of simplicity, low cost, portability, and speed of measurement compared to other biosensors (Hammond et al., 2016; Touhami, 2014; Vigneshvar et al., 2016). Meanwhile, among the electrochemical nanobiosensors like a potentiometric, amperometric, impedimetric, conductimetric and capacitative, potentiometric biosensors show the highest electrochemical application for qualitative and quantitative analysis (Table 3 and Fig. 3a).

## 3. Functional of nanomaterials in electrodes

Biomolecules can be improved with NPs/nanomaterials to provide specific targeting. These features result in incorporating nanomaterials in biosensors for any function and developing the application of nanomaterials in nanobiosensors (Table 4). Also, the incorporation of nanotechnology into the bio-electronic may expose novel feasibilities to miniaturize settings and to augment biological tools for detection. This synergy developed the accuracy and precision of the diagnosis due to an increase in the surface-to-volume ratio of nanomaterials which makes electrical sensors more sensitive to exterior influences (Doria et al., 2012; Zhang et al., 2014b). Generally, the nanomaterial integration can include improvements such as: immobilization support, signal generating probe, signal amplifier, enzyme mimics, and nano-hybrids/composite (Saha et al., 2011). Nanomaterials not only improve the immobilization of biomolecules at the electrode surface, but also prevent biological changes such as denaturation and loss of bioactivity (Chinen et al., 2015). However, the effects of nanomaterials on achieving high sensitivity and selectivity should be considered (Doria et al., 2012; Saha et al., 2011). In the previous methods, for generating an output signal in the electrochemical biosensor several approaches such as enzymes, electroactive molecules, redox complexes, metal ions, etc. were used. However, with the use of nanomaterial labels specially Au and oxide NPs (Hayat et al., 2014), in addition to increasing the sensitivity, increasing the signal/noise ratio was also obtained (Wang and Alocilja, 2015). The strategies that use NPs as labels include: (i)

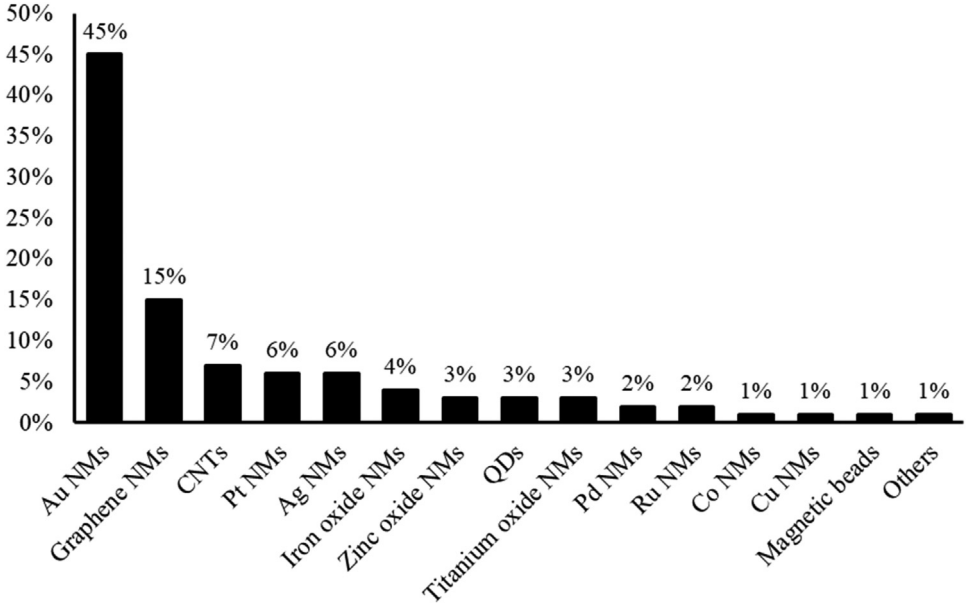


**Fig. 2.** The most commonly used nanomaterials in biosensors for cancer detection (Azimzadeh et al., 2015).

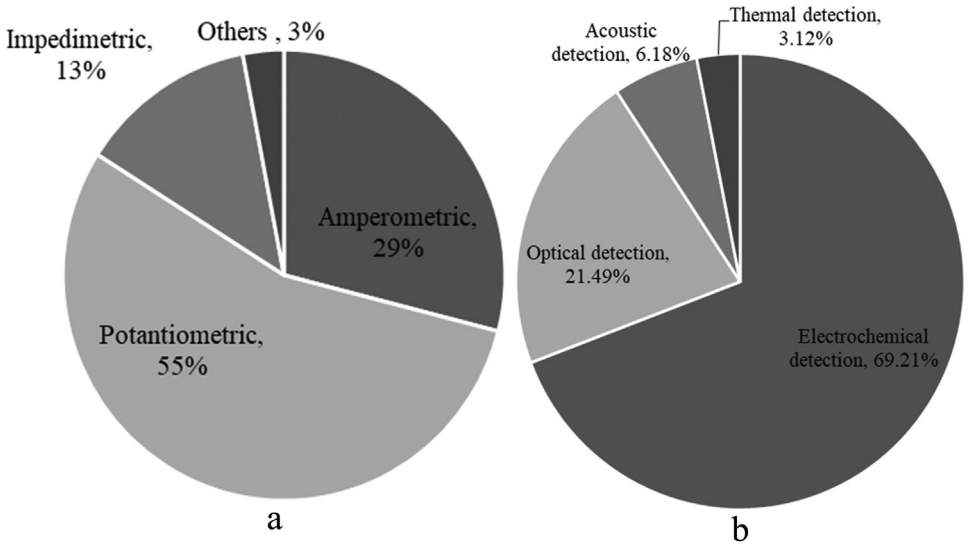


**Fig. 3.** The most common electrochemical methods (a), and techniques used for biosensing between 1998 and 2016 (b) (from Web of Science database).

**Table 2**
Correct selection of the bio-receptor and transducer.

| Transducer | Bio-receptors | | | | |
|---|---|---|---|---|---|
| | Enzymes | Immunoagents | Genetic compounds | Tissue | Microorganisms |
| Optical | + | + | + | + | + |
| Electrochemical | + | + | + | + | + |
| Thermal | + | + | – | – | – |
| Acoustic | + | + | – | – | – |

**Table 3**
A glance at comparison of electrochemical nanobiosensors (Hammond et al., 2016; Rackus et al., 2015).

| Approach | Most usage | Advantages/Disadvantages | Sensitivity |
|---|---|---|---|
| Potentiometric | Enzymatic activity | Advantages: Low cost, reproducibility, rapid measurements, reusable, and suitable for placement of enzymes.<br>Disadvantages: Sensitive to the environment and temperature. | Achieve up to pg/mL |
| Amperometric | Commercial activity such as diagnosis of blood glucose, nucleic acid, antigens, pesticides, food quality and so on. | Advantages: Low cost, reproducibility, rapid measurements, reusable, suitable for placement of enzymes, no need for calibration and more appropriate for mass production.<br>Disadvantages: Need redox elements to enhance the current production, time consuming, sensitive to the environment. | Achieve up from ng/mL to pg/mL |
| Impedimetric | Widely used to detect DNA hybridization, direct monitoring of antibody-antigen connected reactions, and enzyme reactions | Advantages: Enabled label-free recognition, ease of detection for genomics and proteomics, upper signal-to-noise ratio, cost-effective, short period of assessment.<br>Disadvantages: Sensitive to the environment, bulky devices required, require theoretical stimulation for data analysis. | Achieve up to μg/mL to pg/mL |
| Conductometric | Many enzyme reactions, many biological membrane receptors, clinical analysis, detect foodborne pathogens, drug detection and pollutant detection | Advantages: Inexpensive, reusable, insensitive to light, without any reference electrode, possibility of miniaturization, and reducing power consumption due to voltage reduction. | Achieve up to μg/mL to pg/mL |

**Table 4**
Nanomaterials performance in some of electrochemical biosensors.

| Nano materials | Function | nanobiosensor | Ref. |
|---|---|---|---|
| Nano Au/graphene | Improve electrical properties | Electrochemical myoglobin biosensor | (Li et al., 2013a) |
| AuNPs and polyaniline nanofibers | Immobilization support | Electrochemical immunosensor | (Zhang et al., 2014a) |
| Graphene nanoplatelet and titanate nanotube | Immobilization support | Electrochemical enzymatic biosensor | (Liu et al., 2014) |
| GO and AgNPs | Immobilization support | Electrochemical enzymatic biosensor | (Palanisamy et al., 2014) |
| Iron oxide and chitosan | Immobilization support | Electrochemical enzymatic biosensor | (Jeyapragasam and Saraswathi, 2014) |
| Magnetic beads | Signal generating probe | Electrochemical immunosensor | (Akter et al., 2014) |
| $MnO_2$ | Enzyme mimics | Hydrogen peroxide sensor | (Babu et al., 2014) |
| AgNPs and Platinum nanotubes | Signal amplification | Electrochemical DNA biosensor | (Song et al., 2014; Xu et al., 2014) |
| Ferroferric oxide NP | Signal amplification | Electrochemical immunosensor | (Wang et al., 2014b) |
| Cu@Ag NPs | Signal generating probe | Electrochemical immunosensor | (Gao et al., 2015) |

nanomaterials rising the loading of electroactive species; (ii) NPs acting as ultra-microelectrode for the electrolysis of substrates. Nowadays, nanomaterials play major role in enzyme mimetic research due to reactive groups of abundance on their surface and catalytic activity. In this regard, catalase, oxidase, and peroxidase activities have been confirmed for different kinds of nanomaterials (Panraksa et al., 2018; Sapountzi et al., 2017). These nanomaterial-based enzyme mimetics provide improved stability and a constant level of activity (Doria et al., 2012; Liu and Liu, 2017). Likewise, one of the significant advantages of enzymatic nanomaterials is their application as signal amplifying nanoprobes for electrochemical cytosensing. These types of nanobiosensors are capable of detecting low numbers of cancer cells in blood, such as CTCs. CTCs play crucial roles in the metastasis process and are valuable biomarkers for early cancer diagnosis. However, detecting CTCs has been a significant challenge because of their low abundance ($1-10$ CTCs per 1 billion blood cells). As a model, Zheng et al. (2014) and An et al. (2018) developed a cytosensive based on $Fe_3O_4$ NPs and AuNPs, respectively, that were able to detect breast cancer at a concentration of 5 cells/mL of blood.

Overall, as shown in Fig. 2 the most investigated nanomaterials are metal NPs such Au or magnetic nanomaterials and carbon nanostructures like nanotube and graphene. Besides, nanocomposites fabricated with different nanomaterials have diverse aspects such as an electronic structure along with selectivity and sensitivity. These linked assemblies can act as immobilization backing, signal amplifiers and electrochemical signal producing probe (Hayat et al., 2014; Pingarron et al., 2008). The greatest hybrid combinations include: metal-chitosan, metal-nanotube, NPs-silica, etc. Among the items mentioned, electron transfer in electrochemical nanobiosensors is considered as an important factor used to identify cancer markers (Choi et al., 2010). Also, various techniques have been established to manufacture AuNPs, including chemical procedures (chemical reduction, co-precipitation, hydrolysis, etc.) and physical procedures (vapor deposition, laser ablation, and so on). The final goal is to synthesize NPs with a good uniformity and optimum size, shape and surface attributes (Doria et al., 2012). AuNPs can be fixed on electrodes by active groups, such as -CN, $-NH_2$, or -SH, which AuNPs and could form covalent bonds (Pingarron et al., 2008). Moreover, electro-deposition of AuNPs through $HAuCl_4$ solution in constant potential is the simplest path to construct AuNP-modified electrodes.

Carbon nanomaterial's like CNTs, graphene, reduced GO, carbon nanosphere, etc. nowadays have gained much attention in the field of nanobiosensors, because of their specific physical and chemical features (Choi et al., 2010; Wang et al., 2014c). Since, carbon nano-structure are able to create diverse signal amplification routes in electrochemical nanobiosensors, their usage is recommended as electrode substances, carriers for signaling elements, demodulator and collectors, catalysts, and mediators (Balasubramanian and Burghard, 2006; Yáñez-Sedeño et al., 2017). Despite being toxic compared to AuNPs, due to large surfaces, lightweight, chemical stability, mechanical strength, and the compatibility of carbon nanostructures, they are potential candidates for medical settings. On the other hand, nanomaterials are suitable carriers for signal transduction due to the high capacity in mediating fast electron transfer (Adhikari et al., 2015; Balasubramanian and Burghard, 2006). So, electrochemical nanobiosensors are generally considered as GCE or metal electrode for analyte detection (Adhikari et al., 2015; Yáñez-Sedeño et al., 2017). Although, there are various methods for producing carbon-based nanobiosensors, electrochemical nanobiosensors are generally obtained by casting a solution (casting method) of carbon nanostructure such as nanotubes onto an electrode. This method, in addition to improving the electrical connection between active sensing and conducting substrate, and accelerating the transfer of electrons, causes the nanobiosensor to be free from impurities affected by surfactants or connectors (Yáñez-Sedeño et al., 2017). Chemical vapor deposition procedure is a common method for the direct growth of CNTs or a CNTs network, and chemical vapor deposition-grown CNTs have revealed the best performance; but dielectrophoresis is a simpler and more cost-effective technique , and does not require special materials and high temperature for the growth of CNTs (Balasubramanian and Burghard, 2006). CNTs are a cylindrical porous structure from carbon having one or more wall formed by the one-atom-thick sheet with the diameter of 0.5–50 nm which attain the length of micrometers. As well as, graphene sheets, which are hypothetically made in the form of two-dimensional crystals with a variety of chemical and physical flaws, are prepared by the chemical vapor method. Although, flaws can damage the two-dimensional electron conduction, the electron transfer in the electrochemistry of carbon nanomaterials occurs at the edge planes and flaws, that can be beneficial in electrochemistry (Ambrosi et al., 2011). After the construction of graphene sheets, the simplest manner to persuade extra sensing ability to graphene is via altering its physical-chemical structure by oxygenation, hydrogenation and fluorination (Guy et al., 2012). Inexpensive, easy processing, solubility and dispersibility, and the active edges existence causes GO to be considered as a favorite material in progress of electrochemical nanobiosensors. Similarly, carbon nanosphere (CNS) has considered as potential candidate in electrochemistry owing to their convenient structure, high surface to volume, great mass transport, and biocompatibility. So, a type of modified CNSs based on PdNPs decorated nitrogen-doped graphene quantum dots (NGQDs) incorporated into nitrogen-doped carbon (NC)-CNSs was developed. The structure of NGQD@NC@Pd CNS performed as dual signal-amplifying nanoprobes and a nanozyme in $H_2O_2$ released from living cancer cells. For *in vitro* cancer detection, the proposed biosensing system demonstrated its ability to distinguish a trace amount of $H_2O_2$ released from various living cancer cells, as well as estimating the therapeutic effect of chemotherapy and radiotherapy towards cancer (Xi et al., 2016).

In many cases AuNPs and carbon nanostructures due to their unique properties simultaneously are used for immobilizing biological molecules on the electrode surface to obtain high sensitivity, binding capacity, and rapid response along with more effective immobilization (Dong et al., 2015). For this purpose, carbon nanostructures are initially assembled onto the electrode surface, and then the AuNPs electrostatically are adsorbed on the carbon surface (Cui et al., 2008). For example, the recovered AuNPs with GO offered 2.3-fold higher electrocatalytic torrent in comparison with individual materials (Govindhan et al., 2015). Eventually, the AuNPs-modified on electrode would be adjusted for detecting analytes such as DNA, RNA, metal ions, small organic combinations, antibodies, and several bio-samples. For instance, nanocomposites of CNTs and AuNPs along with platinum and propyl gallate molecules, increase electron transfer and sensor sensitivity (detection limit as low as $2.51 \times 10^{-8}$ mol/L, and a wide linear range from $7 \times 10^{-8}$ to $1 \times 10^{-5}$ mol/L) (Cui et al., 2015). Also, AuNPs decorated graphene quantum dots (GQDs) was developed and modified activated carbon fiber (ACF) microelectrode. Microelectrode of AuNPs/GQDs/ACF was applied in electrochemical sensing systems for sensitive detection of $H_2O_2$ as a cancer biomarker in human breast cancer cells and tissues (Xu et al., 2018).

## 4. Cancer biomarkers

Cancer biomarkers are often protein substances that have a higher concentration in cancerous conditions than normal conditions. They are also commonly used as an index for cancer prognosis, diagnosis of various stages, and as an indicator of cancer severity. Transmission without damage of cancer biomarkers on diagnostic sensors which is related to the type of nanoparticle and transmission method can significantly improve their bioavailability and diagnostic value. The most important biomarkers for the diagnosis of cancer are including alpha-fetoprotein (AFP), cancer antigen 125 (CA125), cancer antigen 153 (CA15-3), cancer antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), breast cancer (BRCA), epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), interleukins (ILs),

mucin 1 (MUC 1), prostate-specific antigen (PSA), squamous cell carcinoma antigen (SCC-Ag), tumor necrosis factor alpha (TNF-α), and vascular endothelial growth factor (VEGF).

## 5. Nanomaterial-based biosensors in cancer detection

Biosensors can be used to diagnose a variety of factors such as cancers or neurological diseases, infections, poisoning, toxic agents, and even drugs. Earlier biosensors were widely used for detection of diseases and metabolic disorders from serum biomarkers like DNA, RNA, antigens/antibodies, enzymes, a fragment of protein, etc. Nowadays, a variety of studies have shown that the application of nanomaterials with biomarkers in diagnostic sensors increases the detection power. For instance, some studies illustrated that AuNPs functionalized with an biomarkers in nanobiosensors such as anti-CA15-3 (Ambrosi et al., 2010) and anti-BRCA1 (Wang et al., 2015) for breast cancer, CEA antigen (Feng et al., 2013) for lung or bladder cancers, anti-HPS70 (Jensen et al., 2011) for prostate and pancreatic cancers are extremely more accurate and faster than the enzyme-linked immunosorbent assay (ELISA) method, up to about 10–100 times (with a detection limit of 0.01–50 ng/mL). A biomarker is an indicator of a biological state, therefore, can be used as a marker for a detection of disease. Biomarkers can be applied in cellular processes to recognize alterations in the cellular processes of cancer cells. In order to develop an appropriate nanobiosensor to detect cancer, a specific biomarker or an array of biomarkers should be identified. Despite of a wide variety of cancers, this review focuses on some of the most common cancers in the world such as breast, prostate, lung, etc.

### 5.1. Electrochemical nanobiosensors for breast cancer detection

Generally, electrochemical nanobiosensors designed to detect breast cancer are mainly based on antibody or aptamers, immuno or gene, and peptide sensors (Table 5). In this regard, Elshafey et al. (2013) displayed that EGFR as a protein expressed in epithelial tumours such as breast cancers, can be detected by the AuNPs modified with anti-EGFR in the concentration of 1 pg/mL to 1 g/mL. Whereas, by using antibodies and aptamers simultaneously in electrochemical nanobiosensors, in the detection of EGFR by immobilizing of anti-EGFR onto AuNPs, the detection limit increased to 50 pg/mL with a linear amplitude of 1–40 ng/mL (Ilkhani et al., 2015). Moreover, by using AuNPs containing the hairpin oligonucleotide aptamer labeled with the thiol and biotin and horseradish peroxidase, as well as the MUC1 as a biomarker, Hu et al. (2014) improved the breast cancer diagnosis. In contrast to other aptasensors, this nanobiosensor showed valuable linear amplitude (8.8–353.3 nM) and a lower LOD of 2.2 nM. In another method, it was shown that carbon electrodes improved with CNTs along with breast cancer marker as MUC1 in impedimetric system also increased the detection capacity of biomarker panel for breast cancer diagnoses with a liner range of 0.1–2 U/mL and LOD of 0.02 U/mL without any additional amplification (Nawaz et al., 2016). Furthermore, Marques et al. (2014) and Sonuc and Sezginturk (2014) proposed an electrochemical nanobiosensor for the analysis HER-2 and HER-3 in human serum based on electrode modified with AuNPs and biomarkers that could show a detection range of 0.4–2.4 pg/mL and 0.1–100 ng/mL for serum samples, respectively. Also, Salimian et al. (2017) developed an unlabeled aptasensor for fast HER2 detection on AuNPs, which detected $10^{-12}$–$10^{-8}$ M of HER2 in a 1% serum with methylene blue and the ferricyanide redox indicator.

On the other hand, it has been shown that the application of magnetic nanocomposite containing an CEA along with Au-graphene nanolabeles in electrochemical immunosensor increased the detection power with a LOD of 1 pg/mL in real serum (Chen et al., 2012). Moreover, Li et al. (2013b) developed a label-free electrochemical nanobiosensor with graphene-improved electrode for recognition of CA15-3 with low recognition limits of 0.012 U/mL and a wide linear range of 0.1–20 U/mL. Likewise, Xu et al. (2015) developed a electrochemical immunosensor with an anti-CEA and horseradish peroxidase as a label on glassy carbone electrod to detect antibody with a range of 0.01–60 ng/mL and a LOD of 0.32 pg/mL that could detect antibodies in 20 min. The next report showed that by correction of non-enzymatic electrochemical immunosensor for CEA by nanocomposite of stannic oxide, GO and AuNPs, the detection limit was increased to 0.17 pg/mL with a linear amplitude of 0.5 pg/mL to 25 ng/mL (Han et al., 2016). In the following, Yang et al. (2017) described an unlabeled electrochemical immunosensor with AuNPs-decorated Prussian blue-poly(3,4-ethylenedioxythiophene) nanocomposite porous to detect CEA with a detection limit of 0.01 ng/mL in a concentration between 0.05 and 40 ng m/L, which could be exploited clinically due to the proper association with ELISA. In another study, Benvidi et al. (2015) reported that with the utilization of the BRCA1 gene immobilized into the Au electrodes by impedimetric system, the detection power increased with a linear range within $1.0 \times 10^{-19}$ to $1.0 \times 10^{-7}$ M and a detection limit of $4.6 \times 10^{-20}$ M. Analogously, another experiment exhibited that glassy-carbon based nanobiosensors along with AuNPs and BRCA1 related 19-mer DNA sequence, could detect cancer with a liner amplitude of 50 fM

**Table 5**
Electrochemical biosensors for detection of breast cancer by biomarker.

| Sensor platform | Target | Method[a] | Liner of range | LOD | Ref. |
|---|---|---|---|---|---|
| AuNPs-modified SPCE | miRNA-32,122 | SWV | 10 aM–1 μM | 5 aM | (Labib et al., 2013) |
| GCE/CP + $[Fe(CN)6]^{3-/4-}$ | Human mammaglobin-DNA | IMD | $1 \times 10^{-9}$-$2 \times 10^{-8}$ M | $5.0 \times 10^{-10}$ M | (Xu et al., 2013) |
| Au-SPE | miRNA-21 | DPV | 100 aM–100 pM | 100 aM | (Hong et al., 2013) |
| Multi wall CNT- AuNP | HER3 | EIS | 2–14 fg | 2 fg | (Asav and Sezgintürk, 2014) |
| GCE/graphene/DNA/AuNPs | BRCA1 | CV | 1 Fm − 1 nM | 5.89 fg | (Rasheed and Sandhyrani, 2014) |
| AuNPs-aptamer with SiO2@Multi wall CNT | MUC 1 | DPV | 1–100 nM | 1 pM | (Chen et al., 2015b) |
| ITO/Mesoporous zinc oxide nanofibers + Antibody | EGFR | IMD | 1 fM − 0.5 mM | 1.0 fM | (Jarczewska et al., 2015) |
| SPGE/RNA Aptamer + ferro/ ferricyanide solution | Osteopontin | DPV | 25 nM–200 nM | 3.7 nM | (Meirinho et al., 2016) |
| SPCE/AB onto MB + HRP | RTPK | AMP | 0.1–32.0 ng/mL | 26 pg/mL | (Eletxigerra et al., 2015) |
| Au electrode and miRNA | miRNA-21 | AMP | 0.5 fM–1 pM | 0.2 fM | (Xia et al., 2015) |
| Magnetic GCE and acridone | miRNA-21 | SWV | 20–100 aM | 6 aM | (Li et al., 2015) |
| GCE with AuNPs using PDDA | miRNA-21 | SWV | 100 aM–1 nM | 30 aM | (Miao et al., 2015) |
| Tungsten oxide-graphene with AuNPs | miRNA-21 | DPV | 0.1 fM − 100 pM | 0.05 fM | (Shuai et al., 2016) |
| GCE with AuNRs on GO | miRNA-155 | DPV | 2.0 fM − 8.0 pM | 0.6 fM | (Azimzadeh et al., 2016) |
| Au-SPE | miRNA-155 | SWV | 10 aM–1.0 nM | 5.7 aM | (Cardoso et al., 2016) |
| Multi GCE | miRNA-21 | EIS | 0.5–40 fM | 60 aM | (Zhang et al., 2016) |
| FET/GR/PtNP/scFv | HER3 | CHI | 300 fg–300 ng | 300 fg | (Rajesh et al., 2016) |
| GF-nTiO2 | ErbB2 | DPV | 1.0 fM–0.1 μM | n.a. | (Ali et al., 2016) |

[a] Method: AMP = amperometry, EIS = electron impedance spectroscopy, DPV = differential pulse voltammetry, SWV = square wave voltammetry and CHI = chemiresistor.

to 1.0 nM and a detection limit of 1.72 fM (Wang et al., 2015). Furthermore, Miao et al. (2016) using the iridium (III) complex as a peroxidase-like mimic to catalyze of $H_2O_2$ and probe miRNA-21 immobilized on AuNPs along with methylene blue label, detected breast cancer with a linear range of 5.0 fM to 1.0 pM and a detection limit of 1.6 fM. The development of electrochemical nanobiosensors with nanocomposite probes derived from polyethylene glycol and polyaniline nanofibers along with BRCA1 gene caused an increase in the accuracy of breast cancer detection with a linear range from 0.01 pM to 1 nM (Hui et al., 2017). Analogously, Wang et al. (2017b) by using poly (ethylene glycol) and ATP aptamer, improved the ability to diagnosis breast cancer by detecting an ATP level in biological sample with a detection limit down to 0.1 pM and the linear range of 0.1–1000 pM Also, nanocomposites designed on graphene electrodes composed of citrate, nickel NPs and BRCA 1 gene placed on zwitterionic peptides increased the detection accuracy of breast cancer with a LOD of 0.03 fM. This trial showed that zwitterionic peptides increases the accuracy and sensitivity of biosensors in complex biological conditions without biofouling (Cui et al., 2017; Wang et al., 2017a). Recently, Sun et al. (2018) produced an electrochemical nanobiosensor based on Au electrodes containing the sequence BCRA1 and methylene blue, which increased the ability to detect breast cancer at a concentration of 1 nM to 1.5 μM.

### 5.2. Electrochemical nanobiosensors for prostate cancer detection

Despite the wide variety of biomarkers for diagnosis of prostate cancer, the use of PSA biomarker in prostate cancer has been further considered (Table 6). Nowadays, electrochemical nanobiosensors developed for prostate cancer detection are generally based on aptamers and immunosensors. In this regard, Liu et al. (2012) developed an aptamer-based electrochemical nanobiosensor and graphite mesoporous NPs coated with AuNPs that increased the prostate cancer detection rate with a LOD down to 0.25 ng/mL. Meanwhile, another experiment using DNA aptammer and molecular imprinting for selective PSA immobilized on Au electrodes showed that the power of detecting prostate cancer increased three times more than common sensors with a LOD of 1 pg/mL and a linear amplitude of 100 pg/mL to 100 ng/mL (Jolly et al., 2016). In addition, Rahi et al. (2016) obtained a satisfactory detection from prostate cancer with a liner range of 0.12–200 ng/mL and a LOD of 0.05 ng/mL using PSA aptamer rich in guanine and methylene blue with AuNPs. Furthermore, Heydari-Bafrooei and Shamszadeh (2017) developed an PSA aptamer with nanocomposite of AuNPs, GO and carbon nanotube that could detect prostate cancer with a linear range of 0.005–100 ng/mL. While, fabricating the specific primer-AuNP-aptamer/PSA/anti-PSA sandwich increased the detection capacity of prostate cancer with a detection limit of 0.02 ± 0.001 fg/mL. Additionally, Pan et al. (2017) demonstrated that by using the sandwich structure of two biomarkers such as PSA aptamar and VEGF for prostate cancer, the detection, selectivity and sensitivity of the electrochemical aptasensor increase with liner amplitude of 0.05–100 ng/mL for VEGF and 1–100 ng/mL for PSA.

In addition to aptamers, the use of immunosensors is also commonly used in the diagnosis of cancer. For instance, Yang et al. (2010) planed an ultrasensitive electrochemical nanobiosensor employing graphene sheet for the immobilization of anti-PSA, presenting a wide range of linear response 0.002–10 ng/mL and low detection limit of 1 pg/mL. Also, by using Ag hybridized mesoporous silica NPs and anti-PSA, the detection limit was improved to 15 pg/mL with a linear amplitude of 0.05–50 ng/mL (Wang et al., 2013). Likewise, Ren et al. (2014) reported that using a PSA biosensing with methylene blue and mesoporous silica nanoprobe with anti-PSA could detect prostate cancer with a range of 0.002–100 ng/mL of PSA and a LOD of 1.3 pg/mL. Moreover, Chen et al. (2014) by using tetra DNA, containing the alkyne group at the end of the chain, were able to reduce the prostate's LOD from 500 to 1 pg/mL in the presence of AuNPs (5 nm) and the sandwich structure of the two biomarkers anti-PSA and HRP/signaling antibody. In the latter trial, the electrodes were produced with multi wall carbone nanotube/ionic liquid/chitosan/AuNPs-polyamidoamine dendrimer based on sandwich structure using anti-PSA and HRP which their LOD was 20 times lower than the previous sensors (Kavosi et al., 2014). Whereas, Kavosi et al. (2015) revealed that the PSA detection limit by a nanobiosensors with the anti-PSA along with the AuNPs was 0.5 pg/mL, which was about 70–100 times more susceptible than the ELISA technique (Fig. 4). At the same time, it has been shown that the use of three dimenssion graphene-based Au nanocomposites increases the detection limit of PSA to 0.59 ng/mL with a linear range of 0–10 ng/mL (Jang et al., 2015). Also, Çevik et al. (2016) descripted that the use of cysteamine Au electrode containing denderimers polyamidoamine and PSA antigen can increase the diagnostic power of prostate cancer in human serum with a detection limit of 1 pg/mL and a linear amplitude up to 100 ng/mL. Recently, Han et al. (2017) designed electrodes via printing procedure using GO with AgNPs to detect PSA with a range of 1.0–1000 ng/mL and a low detection limit of 0.01 ng/mL. However, it was shown that the use of redox hydrogel composed of aniline and vinyferrocene can reduce the PSA detection limit to 0.54 pg/mL with a linear range of 0.001–200 ng/mL (Li and Ma, 2017). In this experiment, the presence of PSA reduces the oxidation of ascorbic acid by ferrocene. Meanwhile, Li et al. (2017) with the development of an amino functionalized cuprousoxide@ceric dioxide nanocomposites in the presence of AuNPs containing of anti-PSA as electrochemical immunosensor, captured PSA at a concentration of 0.1 pg/mL to 100 ng/mL and with a LOD down to 0.03 pg/mL. At the same time, Jiao et al. (2017) by development of an electrochemical immunosensor with a sandwich structure from two Pt-Cu hierarchical trigonal bipyramid nanoframes and $Fe_3O_4$ NPs/rGO/polydopamine composite for PSA, could increase the detection limit of 0.03 pg/mL PSA with a linear range from 0.1 pg/mL to 5 ng/mL. In this regard, the use of hybrid nanocomposite of graphene nanoplatelets with diblock co-polymers and Au electrodes along with anti-PSA increased the ability to detect prostate cancer in human saliva with a detection limit of 40 fg/mL in the linear range of 0.1 pg/mL to 100 ng/mL (Khan et al., 2018).

**Table 6**
Summary of the best selected biosensor devices for detection of PSA.

| Sensor platform | Method[a] | Linearity range | LOD | Ref. |
|---|---|---|---|---|
| CNT/AuNP | CV | 0.01 to 0.5 ng/mL | 7 pg/mL | (Tian et al., 2012) |
| CNT/AuNP/Chitosan | ECL | 1 pg/mL to 50 ng/mL | 0.6 pg/mL | (Zhang et al., 2012) |
| AuNPs/glycoprofiling | EIS | 4 aM to 40 nM | 4 aM (0.13 fg/mL) | (Pihíková et al., 2016) |
| Si-nanowires/DNA aptamers | EIS | 33 aM to 330 fM | 23 aM (0.74 fg/mL) | (Tzouvadaki et al., 2016) |
| Thymine/ CuNPs | DPV | 0.05–500 fg/mL | 0.020 ± 0.001 fg/mL | (Zhu et al., 2016) |
| Au-rGO nanocomposite/MB | SWV | 1.0 fg/mL to 100 ng/mL | 0.11 fg/mL | (Tang et al., 2017) |
| Platinum NPs/BSA/Cu NCs | SWV | 0.5 pg/mL to 100 ng/mL | 146 fg/mL | (Zhao and Ma, 2017) |
| $Fe_3O_4$ NPs/GO sheets | CV.SWV | 61 fg/mL to 3.9 pg/mL | 15 fg/mL | (Sharafeldin et al., 2017) |

[a] Instrumental techniques: SWV = square wave voltammetry, EIS = electron impedance spectroscopy, ECL = electrochemical luminescence, DPV = differential pulse voltammetry, and CV = cyclic voltammetry.

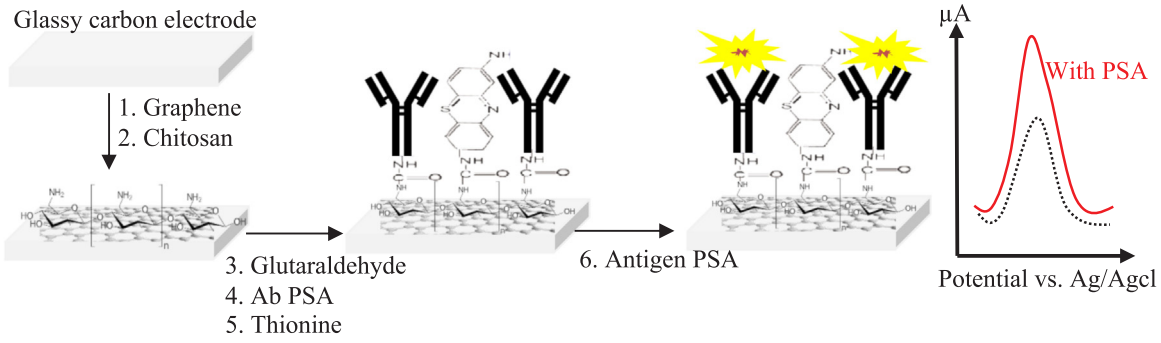


**Fig. 4.** Schematic of nanobiosensor fabrication process for PSA detection.

### 5.3. Electrochemical nanobiosensors for lung cancer detection

Because, lung cancer is the second most important cancer in men and women, this part of the paper focuses on the diagnosis of this cancer. Biomarker diversity is very high in lung cancer; however, a small number of biomarkers are used in nanobiosensors. In the regard, Chen et al. (2013) illustrated that electrodes based on graphene modified with AuNPs, chitosan along with anti-CEA and anti-AFP for lung and liver cancer have much higher susceptibilities with recognition limit of 0.1 ng/mL and 0.05 ng/mL, respectively. Similarly, Choudhary et al. (2014) developed a voltammetry electrochemical immunosensory based on two anti-MAGE A2 and anti-MAGE A11 biomarkers applying CNTs-chitosan composite, which increased the detection capacity of lung cancer at the linear range of 5 fg/mL to 50 ng/mL. Other study results also showed that the application of a nanocomposite consisting of carboxyl-functionalized GO and copper oxide nanowires in an electrochemical DNA sensor with a CYFRA21-1 biomarker, in addition to improving the test speed, increasing sensitivity of the sensor with a LOD of $1.18 \times 10^{-13}$ M in a concentration of $1.0 \times 10^{-12} - 1.0 \times 10^{-6}$ M of CYFRA21-1 (Chen et al., 2015a). At the same time, Liu et al. (2015) demonstrated an electrochemical genosensor based on lung cancer specific microRNAs and AuNPs blocked with mercaptoethanol that could increase the detection limit to 10 pM and linear range of 100 p.M. to 1 μM (Fig. 5) While, Mir et al. (2015) developed a aptamer-based amperometric nanobiosensor with a polymer nanocomposite formed through the self-assembly of 4-([2,2′:5′,2″-terthiophen]-3′-yl) benzoic acid (TTBA) on AuNPs and biomarker A549 that detects human non-small-cell lung cancer cells at a LOD of 1 cells/mL at a concentration of $15–1 \times 10^{6}$ cells/mL. Furthermore, using an electrochemical aptasensors based on carbon-Au mesoporous nanocomposites to detect the factor $VEGF_{165}$, it was possible to detect lung cancer with a detection limit of 1.0 pg/mL at a concentration of 10–300 pg/mL of $VEGF_{165}$ (Amouzadeh et al., 2015). Likewise, Shan and Ma (2016) with a comparison of electrochemical immunosensors based on 5 biomarker including the CEA, neuron specific enolase (NSE), CA125, cytokeratin 19 fragment antigen 21–1 (CYFRA21-1), squamous cell carcinoma antigen (SCCA), and one kind of a polyaniline-Au composite, showed that SCCA biomarker had a higher LOD of 30 pg/mL than other biomarkers 0.2 ng/mL, 0.9 ng/mL, 0.4 ng/mL, and 0.9 U/mL respectively.

In the following, Wang and Ma (2017) by applying an amperometric immunoassay with a glassy carbon electrode containing polyresorcinol, $HAuCl_4$ and $H_2PtCl_6$ nanocomposite, detected lung cancer with 7.8 pg/mL and a LOD in the linear response of 10 pg/mL–100 ng/mL of NSE concentration. The results, in addition to increasing the speed of the test, showing improved sensitivity in high-frequency diagnosis and repeatability compared to electrochemiluminescence immunoassay. Analogously, it was exhibited that AuNP/reduced GO nanocomposites on chitosan with NSE biomarker in the detection of electrochemical immunosensing, can detect lung cancer in the range of 0.1–2000 ng/mL of NSE with a detection limit of 0.05 ng/mL (Wei et al., 2017). Moreover, Chen et al. (2018) developed a electrochemical DNA sensor with a lung cancer susceptible CYFRA21-1 biomarker immobilized on 3D GF/AgNPs that increased the detection limit for cancer down to $1.0 \times 10^{-14}$ M with a concentration range of $1.0 \times 10^{-14}$ to $1.0 \times 10^{-7}$ M. The responses obtained from the experiment provided satisfactory results.

## 6. Microfluidic electrochemical in cancer detection

Microfluidic chips are commonly used for multi-purpose experiments in reactions, separations, detections, cell cultures, sorting, etc. In this line, Azahar et al. (2016) developed a label-free microfluidic immunosensor based on EGFR2 or ErbB2, and porous hierarchical graphene foam (GF) modified with titanium dioxide nanofibers ($nTiO_2$), which increased the capacity to detect breast cancer by pulse voltammetry and electrochemical impedance with sensitivities of 0.585 μA/μM/cm and 43.7 kΩ/μM/cm in a concentration range of $1 \times 10^{-15}$ (1.0 fM) – $0.1 \times 10^{-6}$ M (0.1 μM) and $1 \times 10^{-13}$ (0.1 pM) – $0.1 \times 10^{-6}$ M (0.1 μM), respectively (Fig. 6). Likewise, a disposable microfluidic electrochemical array device containing a biomarker estrogen receptor alphain and horseradish peroxidase with a very low cost and recovery between 94.7% and 108% along with eight carbon electrodes was produced, which provided an extraordinary LOD of 10.0 fg/mL for breast cancer in less than 2 h (Uliana et al., 2017). Meanwhile, Veselinovic et al. (2018) designed a microfluidic channel based on nanoporous Au for DNA detection, which increased the loading speed of the samples (25 times in comparison to conventional sensors), as well as allowed the diagnosis of multiple breast cancer biomarkers with a high detection limit. On the other hand, an electrochemical microfluidic device containing 8 ports with 256 sensors with the PSA biomarkers, prostate specific membrane antigen, interleukin-6, and platelet factor-4 immobilized onto Au disk was designed by Tang et al. (2016), which, in less than an hour, have a high capacity for detecting prostate cancer with a LOD of 0.05–2 pg/mL in the range of sub pg/mL to above ng/mL levels. It has also been shown that the application of microfluidic electrochemical immunosensors based on nanostructures containing PSA (Table 7), CD-14, ERG, GOLM-1, PEDF-1, IGF-1, VEGF-D and IGFBP-3 markers caused detection of prostate cancer simultaneously by all markers under 30 min with ultra-low detection limits in the sub fg/mL levels (Otieno et al., 2016).

## 7. Challenges of electrochemical nanobiosensors in cancer detection

Many progresses have been developed in diagnosis approaches by nanobiosensors, but clinical applications of nanobiosensors for cancer detections are poorly reported. Because, the medical diagnosis requires a sensitive, accurate, fast, and portable system, many of the prototypes of biosensors in the laboratories are not practically viable. However, due to fast results, economic efficiency, real-time monitoring, and self-care facilities the demand for a low-cost and disposable medical nanobiosensors increases. Since, nanobiosensors may simultaneously

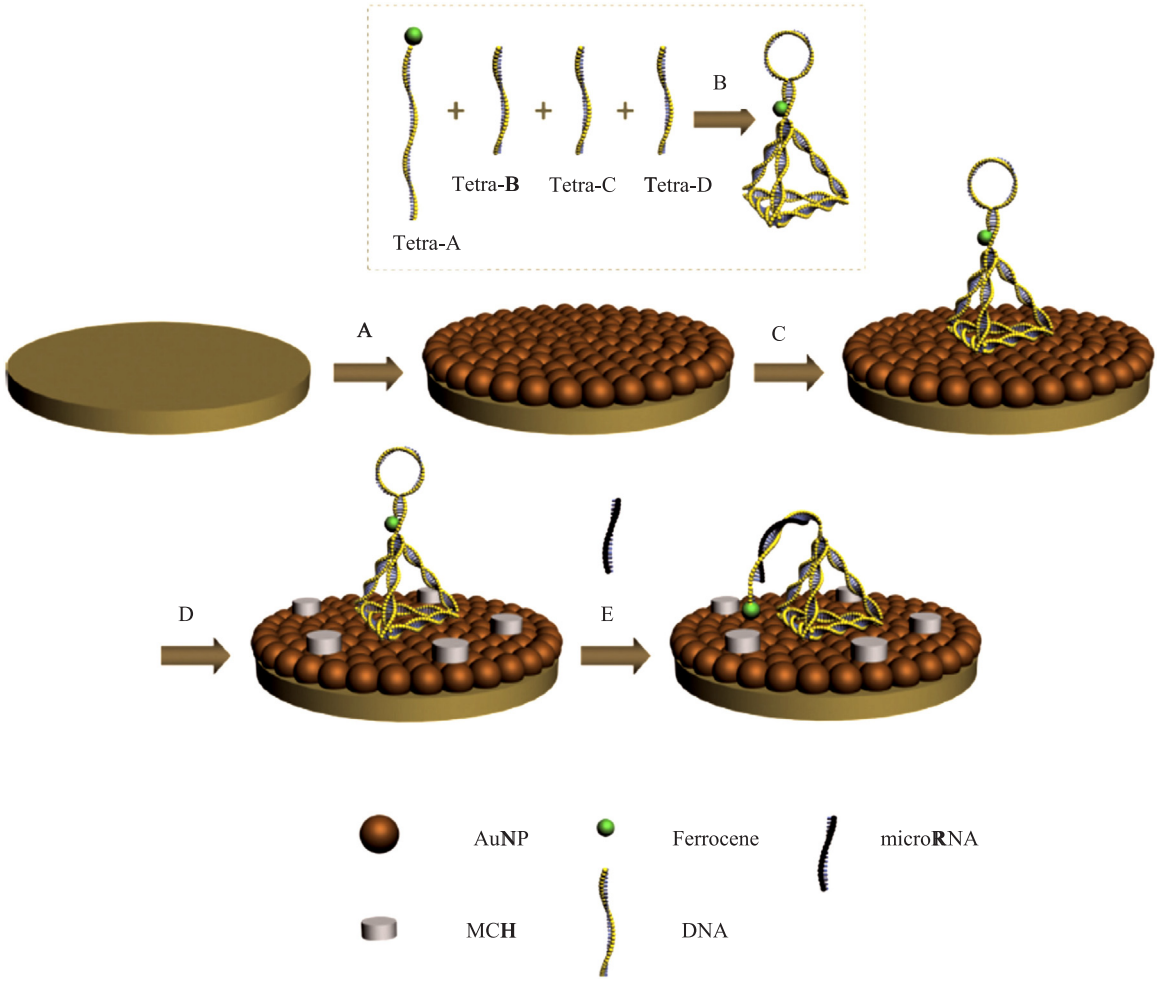


**Fig. 5.** Scheme of the proposed electrochemical genosensor to detect target microRNA in prostate cancer. (A) Au NPs were electrochemically deposited on a bare Au disk electrode. (B) Constructing 3D DNA probes with four oligonucleotides (Tetra-A, Tetra-B, Tetra-C and Tetra-D). (C) The 3D DNA probes were self-assembled on the electrode surface. (D) The Au NPs-coated Au electrode was blocked with MCH. (E) With the presence of microRNA, the stem-loop structure of the 3D DNA probe was opened and the ferrocene groups had access to the Au electrode surface after the hybridization with the target microRNA. Reprinted with permission from reference (Liu et al. 2015).

measure multiple parameters; this feature itself will save notable time over the sample processing as an important part of hospital activity. Nowadays, electrochemical biosensing based on nanomaterial is facing some serious challenges, such as:

1. Stability of nanobiosensors in single or reusable electrodes.
2. Cost-intensivness of electrochemical nanobiosensors in cancers detection.
3. Samples analysis and biocompatibility.
4. The complexities of constructing electrochemical nanobiosensors.
5. The lack of mechanism transparency of interaction between nanomaterials and biomolecules.
6. Processing, creating special features, jointing difficulties, accessibility of excellent quality nanomaterials, and the nature of these nano-scale combinations on the electrodes plane.

Therefore, the development of current nanobiosensors is focused on reducing the mentioned problems. Hence, a variety of procedures have been utilized to minimize the challenges in nano-biosensing. The most important solution presented is the integration of various mechanical, electrical, chemical, and biological systems by application of specific nanomaterials. If this process of order occurs, new diagnostic nanobiosensors can be expanded for highly sensitive cancer detection and treatment without serious adverse effects. For instance, AuNPs offer less reactivity to proteins, inhibiting the immune responses and reducing invasion due to the minimization of many in vivo electrochemical nanobiosensors (Khashayar et al., 2017). Accordingly, Guo (2013), Hutter and Maysinger (2013), and Peng et al. (2014) displayed that NPs-related techniques, in addition to reducing the limitation of the biosensors, may increase LOD and eliminated negative effects. Development of non-invasive electrochemical nanobiosensors as reliable tools for therapeutic, antimicrobial, drug delivery, and cancer detection in the complex condition can be recommended. In order to decrease the problems, the researchers, in addition to using specific NPs, applying the nanocomposites derived from two or more nanomaterial with other compounds for reducing defects.

## 8. Conclusion

This review highlighted the importance of applying specific biomarkers along with nanomaterial for developing electrochemical nanobiosensors in cancer detection. Also, we noted the inherent sensitivity, simplicity, rapidity, accuracy, and cost-effectivness of electrochemical nanobiosensors. The biomaterials based on nanomaterials, not only improve the electronic attributes, susceptibility, specificity, and increment rate of the signal, but also generate detectable signals for indirect detection of targets. However, despite significant advances in the production and application of nano-biosensors, still a

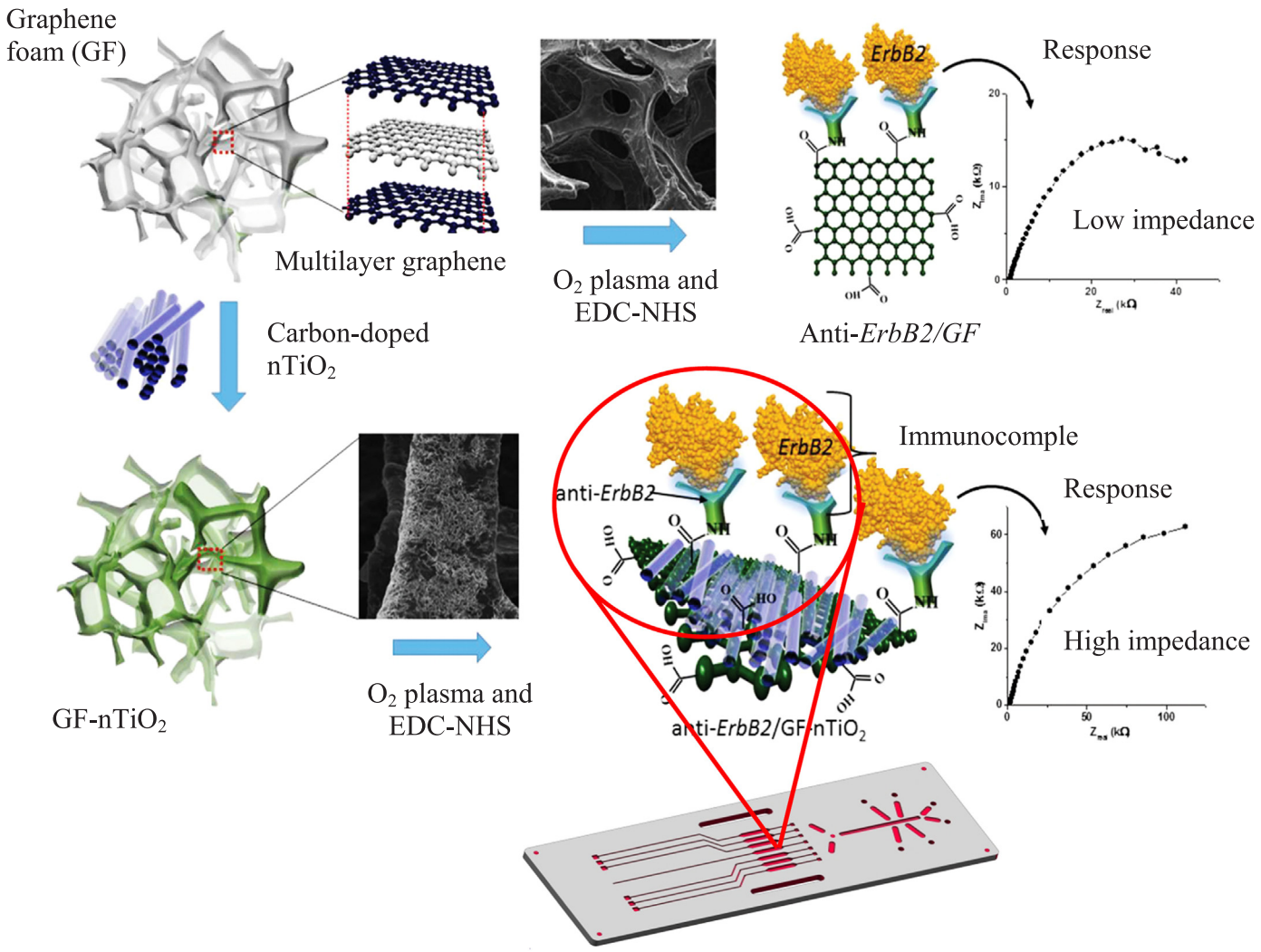


**Fig. 6.** Functionalization of anti-ErbB2 molecules on the surface of GF and GF–nTiO2 electrodes immobilized onto microfluidic channels using EDC–NHS chemistry followed by oxygen plasma treatment. Reprinted with permission from reference (Azahar et al. 2016).

**Table 7**
Summary of the best selected microfluidic devices for cancer detection.

| Sensor design | Target | method[a] | Linearity range | LOD | Ref. |
|---|---|---|---|---|---|
| Immunosensing chip using chromium and Au film deposition on glass wafer | CEA<br>CA 19-9 | DPV<br>DPV | 0.37–90 ng $mL^{-1}$<br>10.75–172 Um$L^{-1}$ | 0.37 ng $mL^{-1}$<br>10.75 Um$L^{-1}$ | (Xie et al., 2015) |
| Multiplex ligation-dependent probe amplification on printed circuit board | mRNA markers | CV, EIS | – | 25 pM | (Sánchez et al., 2016) |
| Paper based microfluidic electrochemical inmmunosensor | CEA | CV, DPV | 50 pg/mL – 500 ng $mL^{-1}$ | 10 pg $mL^{-1}$ | (Wang et al., 2016) |
| Electrochemical immunosensor chip using CMK-3/poly-acrylamide-*co*-methacrylate of dihydrolipoic acid and porous silica substrate | EGFR | CV | 0.01–50 ng $mL^{-1}$ | 3.03 pg/$mL^{-1}$ | (Regiart et al., 2017) |
| A multiplexed on chip using $Fe_3O_4$@graphene oxide | PSA | AMP | 1.25–1000 pg/mL | 1.25 pg/mL | (Sharafeldin et al., 2017) |

[a] Instrumental techniques: AMP = Amperometry, EIS = electron impedance spectroscopy, DPV = differential pulse voltammetry, and CV = cyclic voltammetry.

lot of important processing should be carried out to design ultra-sensitive sensors. The use of ultra-sensitive electrochemical nanobiosensors is probably one of the most promising solutions to some of the problems associated with, the accuracy, speed, and cost-effectiveness of cancer detection, which will provide a clear future for diagnosis and management of this disease.

## Conflicts of interest

The authors have none to declare.

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