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Medical nanobiosensors: A tutorial review

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Abstract

A sensitive monitoring of biological analytes, such as biomolecules (protein, lipid, DNA and RNA), and biological cells (blood cell, virus and bacteria), is essential to assess and avoid risks for human health. Nanobiosensors, analytical devices that combine a biologically sensitive element with a nanostructured transducer, are being widely used for molecular detection of biomarkers associated with diagnosis of disease and detection of infectious organisms. Nanobiosensors show certain advantages over laboratory and many field methods due to their inherent specificity, simplicity and quick response. In this review, recent progress in the development of nanobiosensors in medicine is illuminated. In addition, this article reviews different kinds of bio-receptors and transducers employed in nanobiosensors. In the last section, overview of the development and application of various nanomaterials and nanostructures in biosensing has been provided. Considering all of these aspects, it can be stated that nanobiosensors offer the possibility of diagnostic tools with increased sensitivity, specificity, and reliability for medical applications.

Keywords: Medical diagnosis, Nanobiosensor, Nanomaterial, Nanomedicine

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Introduction

Nanotechnology has the potential to change the medical world in many positive ways.

This multidisciplinary field is the application of nanoscience, which is based on the manipulation, control, and integration of atoms and molecules to form materials, structures, components, devices, and systems at the nanoscale (a nanometer is one millionth of a millimeter).

Nanoscale materials exhibit remarkable properties, functionality, and phenomena due to the influence of small dimensions. Nanotechnology focuses on improving the existing methods by increasing efficiency of the processes and enhancing the reusability of nanomaterials, thus saving the cost of operation of the plant or processes (1-3).

The need to develop in disease diagnosis and treatment has led to the use of nanotechnology in medical applications, an emerging field known as nanomedicine. The use of nanotechnology in medicine presents unique prospects for development of global health.

This has given rise to promising new therapies and diagnosis for a variety of diseases, especially cancer (4).

Today's interest in nanomedicine keeps growing because of its varied advantages. Nanomaterials with various structures have been used in biomedical applications including molecules delivery (drugs, growth factors, DNA), tissue scaffolds, and implantable materials or nanodevices, such as biosensors (5).

Biosensors are the devices for detection of biological analytes which have wide applications, including biomarker detection for medical diagnostics, and pathogen and toxin detection in a specimen by binding analyte on the reactive surface (6, 7).

Biosensors usually contain two basic components. The first one is a biological element (such as enzyme, antibody, receptor or microorganisms) as molecular recognition system and the second one is a physico-chemical transducer (electrochemical, mass, optical and thermal).

The biosensor sensitivity depends on transducers properties and on the biorecognition element.

The mission of biosensor system are analyte recognition, signal transduction and readout (8, 9). Such devices hold great promise for the health care and pharmaceutical industries.

Fig 1 shows a schematic drawing of the biosensor set-up.Nanobiosensors can be defined as biosensors based on nanotechnology.

In the recent years many workers are beginning to combine nanotechnology with various biosensing techniques to develop analytical devices that utilize nanoscale detector components to identify minute biological elements with enhanced sensitivity (10, 11).

This strategy could be seen as the key to yielding devices, which exhibit rapid responses combined with high sensitivities.

The ultimate goal of nanobiosensors is to detect any biochemical and biophysical signal related to a specific disease at the level of a single molecule or cell (12, 13).

This review article looks at nanobiosensor as an emerging field in the medical by providing general efficient ways to detect biological analyte.

We discuss how nanomaterials can be used in nanobiosensors for the high sensitive measurement of metabolites.

Also, various classification of nanobiosensors based on bioreceptor and ansducer has been reviewed.

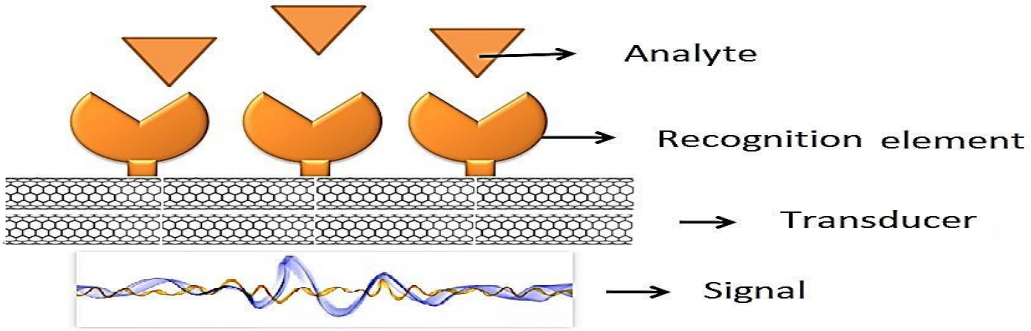

Figure 1. Schematic presentation of a biosensor.

Classification of biological recognizers

Based on kinds of immobilized biomolecules as bio-receptor, biosensors can be divided into several classes including enzymatic biosensors, immunosensors, DNA biosensors, aptasensors, microbial biosensors (Figure 2).

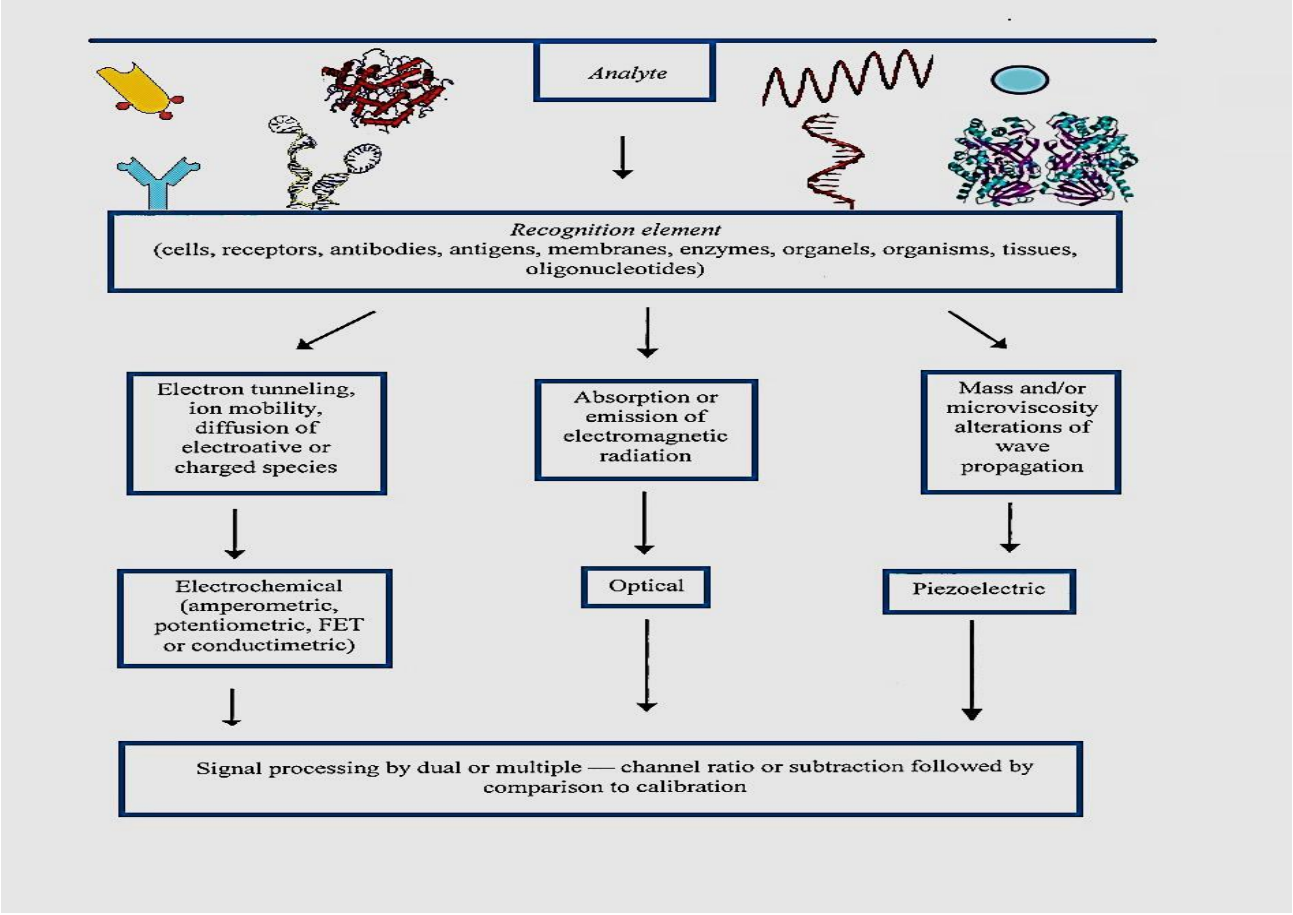

Figure 2. Elements of biosensors

Enzyme

Principally, enzymatic biosensors are based on immobilized specific enzyme which convert analyte into products measurable with a suitable transducer. Enzymatic biosensors measure the selective inhibition of the activity of enzymes by a specific target(14, 15). The performance of enzyme based biosensors largely depends on the heterogeneous electron transfer between the electrode and the protein redox center (16-18). Enzyme biosensors fall into various classes including those that is electrochemical. Also, the bienzymatic biosensor have been employed to detect analytes at nM levels (19, 20).

Antibody

Immunosensors, also known as antibody-based biosensors, use antibodies as the biological-recognition element and constitute another class of biosensors that have gained considerable interest in clinical analysis. Antibody arrays are suited to high-throughput methods for the functional characterization of disease at a molecular level (21, 22).

Antibodies are the most common bioreceptor and are highly specific in recognizing and although very promising. The high sensitivity of immunosensors enabled detection of microorganisms like E. coli, Salmonella, S. aureus, pesticides, herbicides etc, in hours or minutes. Appropriate Immunosensors reduce assay time and cost or increase the product safety (23, 24).

In addition, antibody-mediated targeting has been used to great effect for a variety of applications including single bacterial cell quantitation and cell-surface labeling. Tumor targeting anti-cancer therapeutics by conjugating tumor-specific antibodies is of great interest in nanomedicine (25-27). As an example, upon hybridisation between the antibody (bioreceptor) and the viral antigen, there is a measurable response in conductivity across the immunosensor surface, which is translated into a change in the resistance and/or double-layer capacitance following analyte capture (28).

Oligonucleotide (DNA/RNA)

As with other kinds of biosensors, high selectivity is critical for the achievement of DNA biosensors. DNA biosensors are defined as analytical devices incorporating a single-stranded oligonucleotide (probe) intimately associated with or integrated within a transducer or transducing micro-nanosystem, which may be optical, electrochemical, thermometric, piezo-electric, magnetic or micromechanical (29, 30).

DNA biosensor technologies are currently under deep investigation owing to their great promise for rapid and low-cost detection of specific DNA sequences in human, viral and bacterial nucleic acids (31, 32). The scientists developed many techniques such as surface plasmon resonance (SPR), etc., in DNA detection to attain higher sensitivity and selectivity, and many of them had been utilized in DNA biosensors. There are basically two purposes of using nanomaterials in DNA biosensors. The first one is using as substrates for DNA attachment and another one is signal amplifiers for hybridization (33, 34).

The development of DNA biosensors has recently attracted a lot of attentions in connection with research efforts directed at gene analysis, the detection of genetic disorders, tissue matching, and forensic applications (35). DNA biosensors can detect the presence of genes or mutant genes associated with inherited human diseases or infectious diseases. For instance, various strategies including DNA biosensor based electrochemical protocols have been used to detect genetic mutations (36-38). So, DNA based biosensors offer exciting opportunities for sequence-specific DNA detection. Also, there are many interesting applications of DNA biosensors in clinical diagnostics, forensic identification (39).

Recently, there has been great interest in using nano-materials for DNA biosensors. Because of their high surface-to volume ratios and excellent biological compatibilities, nano-materials could be used to increase the amount of DNA immobilization; additionally, DNA bound to nano-materials can maintain its biological activity (40). The nanomaterials used in DNA biosensors including nanoparticles, like gold, cadmium sulfide; nanowires like silicon, nanotubes like carbon nanotubes, etc.

Aptamer

Recently, aptamers have emerged as a class of nucleic acid recognition elements because of their high selectivity and affinity towards their targets. Aptamers are derived from the Latin word "aptus" which means 'to fit' (41) . They are attracting an increasing amount of interest in the development of sensors for proteins, DNAs, and small molecules. Aptamer technology enabled the enlargement of nucleic acid biosensors to virtually any type of analyte, because of the unique three-dimensional shape of single stranded nucleic acid molecules (42). They are nucleic acid ligands (single stranded DNA or RNA) that are chosen from random sequence libraries by an in vitro selection process called SELEX (Systematic Evolution of Ligands by Exponential enrichment) (43, 44).

Nucleic acid-based aptamers are being developed for a variety of diagnostic applications, including detection of a wide range of non-nucleic acid analytes. Aptamers are potentially useful biosensor reagents that can both substitute for antibodies and that can be adapted in novel ways to sensor platforms (45, 46). DNA aptamers have also been applied for the separation or capture of pathogens and small molecules. Numerous aptamers with high affinity and selectivity have been created against a variety of respective targets, such as small organics, peptides, proteins, and even whole cells (47-49). Aptamer biosensors have been immobilized on variouse transducers, introduced into micromachined chips on the electronic tongue sensor array, and used for the detection of proteins (50).

In addition, aptamers are easy to manipulate and synthesize, facilitating the application of aptamers in the development of sensors (51). However, a disadvantage of aptamers is that so far there are no standardized protocols available concerning the selection process, which is applicable without specific modifications of different targets. Anyway, aptamers offer advantages over antibodies that make them very promising in analytical and diagnostic applications in more unique ways (52).

Microorganisms and cells

A microbial biosensor is an analytical device which integrates microorganism(s) with a physical transducer to generate a measurable signal proportional to the concentration of analytes. A microbial or whole cell nanobiosensor consists of nanomaterials as transducer in conjunction with immobilized viable or non-viable microorganism/whole cells (53-55). These nanobiosensors offer rapid, accurate and sensitive detection of target analyte in fields as diverse as medicine, environmental monitoring, defense, food processing and safety (56-58).

However, microbial sensors are less sensitive to the inhibition for other compounds present in the sample. But they are more tolerant to the pH variations, temperature and generally have a longer lifetime (59). Among several sensing methods, electrochemical and optical techniques are most widely used in the development of microbial biosensors. To improve the selectivity of microbial biosensors undesired metabolic pathways and transport mechanisms might be blocked or inhibited whereas appropriate metabolic activities might be induced (60). On the other hand, immobilizing microorganisms on appropriate

nanomaterials as transducers plays an important role in the fabrication of microbial biosensors. Exemplarily, several microbial biosensors for glucose detection have been fabricated based on the oxygen consumption of the respiratory activity in the microbes (61, 62).

Sensing techniques

During these years, many techniques have been developed to increase the quality of nanobiosensors for detecting a range of biological agents. These sensing techniques can detect the interaction between bio-receptors and target compounds using different appropriate nanostructures.

The two principal components of biosensors are biological element and a transducer. Biological element interacts with an analyte to produce a detectable change. The other key component transducer converts the physico-chemical change in the biologically active material resulting from the interaction with the analyte into an analytical useful/measurable signal. According to the transducers, the biosensors can be classified as electrochemical, optical, and peizoelectric biosensors.

Electrochemical methods

Among several sensing techniques, electrochemical methods are of particular interest worldwide because of their remarkable advantages, such as high sensitivity, small dimensions, low-interference characteristics, low cost, and compatibility with microfabrication technology (16, 63, 64).

Electrochemical nanobiosensors hold great potential for determining various analytes in medical diagnoses, such as cancer diagnostics and detection of infectious organisms and some have been commercialized.

Generally, electrochemical biosensors are mainly based on the fact that during a biointeraction process, electrochemical species such as electrons are consumed or generated producing an physically readable electronic signal which can be recorded by applying different electrochemical detections. This produced electrical signal is related to the concentration of the analyte (65).

Depending upon the electrochemical property to be measured by a detector system, electrochemical biosensors can be divided into four sub-categories of potentiometric, amperometric, conductometric, and impedimetric biosensors (66-68).

Potentiometric

Potentiometry, one of the oldest instrumental methods, has well-established position as the analytical tachniques for biomedical needs. These types of biosensors are based on analytical information obtained by converting the biorecognition process into a potential signal and monitoring the potential of a system at a working electrode, with respect to an accurate reference electrode, under conditions of essentially zero current flow (69-71).

Amperometric

The amperometric biosensors are mostly utilized in medical devices since they are studied to a greater extent and offer many advantages including high sensitivity, low cost, and wide linear range. These class of biosensors measure the current produced for the electrochemical oxidation or reduction of an electroactive species. The amperometric biosensor is fast, more sensitive, precise and accurate than the potentiometric ones, so it is not necessary to wait until the thermodynamic equilibrium (72).

Impedimetric

However, impedance biosensors are less frequent compared to potentiometric and amperometric biosensors, but due to their all-electrical nature, they have significant potential for use as simple and portable sensors. Impedimetric biosensors measure the electrical impedance of a particular

biological system in order to give information about that system (73, 74).

Conductometric

In conductometric biosensors, conductivity changes in the solution after the specific binding of the target to the immobilized partner, can be detected. The principle of the detection is based on the fact that many biochemical reactions in solution produce changes in the electrical resistance between two parallel electrodes (75, 76).

Optical techniques

Optical biosensors are known to be powerful detection instruments and versatile tools which are highly sensitive to biomolecular targets, insensitive to electromagnetic interference, and present real time response to biomolecular interactions. Optical methods employed in nanobiosensors include surface plasmon resonance, localized surface plasmon resonance, fluorescence spectroscopy, interferometry, surface plasmon resonance, localized surface plasmon resonance, total internal reflectance, light rotation and polarization (77).

A quick survey of the literature points to the success of SPR based biosensors in fundamental biological studies, health science research, drug discovery, and clinical diagnosis. SPR biosensor, developed by Liedberg et al. (78) in 1983, can monitor a wide range of analyte surface binding interactions such as absorption of small molecules, proteins, antibody-antigen, DNA and RNA hybrid-dization.

Surface plasmon resonance (SPR) is an optical phenomenon in which the freq-uency of electromagnetic wave propagating at the metal-dielectric inter-face is resonant with the oscillation of the surface conduction electrons in metal (79, 80).

In localized surface plasmon resonance (LSPR), light interacts with metallic nanoparticles much smaller than the incident wavelength. This leads to a plasmon that oscillates locally around the nano-particle (typically gold, silver, and copper nanoparticles) with a frequency known as the LSPR (81, 82).

Moreover, in SPR, light is in contact with the surface of the metal film via a prism, while in LSPR plasmon is excited by direct illumination.

The main advantage of both SPR and LSPR methods is that they are label free sensing methods and do not require labeling of the target molecules with different types of reagents. However, most of the conventional SPR and LSPR biosensors require bulky and expensive optical equipment and data analysis instrument (83, 84).

Recently, microfabrication and thin-film techniques have been used to improve the sensitivity and also facilitate optical fibers fabrication. Optical fibers are ideal media that can be used to guide light for the excitation of the surface plasmon wave (85).

Piezoelectric methods

Piezoelectric biosensors have been widely used to detect viruses, bacteria, proteins, and nucleic acids, because they are extremely sensitive. These types of biosensors are based on the measurement of the change in resonant frequency of a piezoelectric quartz oscillator in response to changes in surface adsorbed mass. The surface of crystal is coated with a layer containing the biorecognition element designed to interact selectively with the target analyte.

Binding of the analyte on the sensing surface of crystals results in the mass change of the crystal which causes a measurable change in the resonance frequency (86, 87).

Nanomaterials

The use of nanoscale materials for electrochemical biosensing have seen explosive growth over last decade. In recent years, nanomaterials such as gold nanoparticles, and carbon nanotubes have

been used to increase selectivity and accuracy of biosensors.

The first sub-section (4.1) focuses on carbon nanostructures as a favorable transducer for biosensing. The different kinds of carbon based nanostructures in biosensing devices are discussed. The next sub-sections (4.2 and 4.3) focus on gold and silver nanoparticles for use in optical and electrochemical biosensors. In sub-section 4.4, we illustrate that semiconductors including ZnO, TiO_2, and QDs can be used efficiently as a transducer of the biosensor.

Carbon nanotube

The application of carbon nanotubes (CNTs) in nanobiosensors has become the subject of intense investigation since its discovery in 1991. Such considerable interest reflects the unique behavior of CNT, including their high electrical conductivity, excellent biocompatibility, chemical stability and mechanical strength (88).

CNT with the advantages of high surface area, fast heterogeneous electron transfer, and long-range electron transfer, has been widely used to develop nanobiosensors in the last decade. The first usage of CNT-modified electrode for biosensing was reported in 2003 by Wang and Musameh (89). Biomolecules (e.g., proteins and DNA) can also be electrostatically adsorbed onto the surface of CNTs and can be attached to functional groups on modified CNTs (88).

Graphene

Graphene because of the unique physical properties has attracted considerable attention from both the experimental and theoretical scientific communities in recent years. Most of graphene used in nanobiosensors are produced with the last method of graphene oxide (GO) reduction (90, 91). The optical properties of graphene and GO, a topic of fundamental interest, are largely unexplored and could facilitate biological and medical research such as biosensing, and imaging. Graphene from GO reduction, which is also called functionalized graphene sheets or chemically reduced graphene oxide, are advantageous for nanobiosensors and especially electrochemical base nanobiosensor applications (92, 93). Graphene is a perfect material for fabricating biosensors because it has an intrinsically high surface-to-volume ratio and high electron transfer ability. Graphene has shown excellent performance in direct electrochemistry of enzyme and electrochemical detection of small biomolecules such as NADH. In comparison with CNT, graphene has demonstrated superior performance in these applications (94).

Graphene is an excellent electrode material for electroanalysis and electrocatalysis, and there is still much room for the scientific research and application development of graphene-based theory, materials, and devices. In summary, different kinds of graphene-based materials, especially nanoparticle-decorated graphene nanocomposites, are appropriate for application in electrochemical and optical biosensors (90-94).

Gold

Gold nanoparticles (GNPs) and nanorods are the most extensively studied nanomaterials for use in biosensors and bioelectronics because of their unique properties, such as rapid and simple synthesis, large surface area, strong adsorption ability and facile conjugation to various biomolecules (95, 96). So far, majority of the studies have focused on application of GNPs in electrochemical and optical nanobiosensors. It has been demonstrated that colloidal gold, can help proteins to retain their biological activity upon adsorption and be used for the study of direct electron transfer of redox proteins. In aqueous solutions, gold nanostructures exhibit strong plasmon bands depending on their geometric shape and size (97, 98). Recently, studies on nanobiosensors based on the immobilization of DNA or RNA on gold

nanoparticles for cancer detection have been reported (99).

Silver

Among noble-metal nanomaterials, silver nanoparticles (AgNPs) are one of the most commonly used metal-nanoparticles, which have received considerable attention in biological detection. AgNPs can frequently be useful in electrochemical and SPR biosensors due to their attractive physicochemical properties including the surface plasmon resonance and large effective scattering cross section of individual silver nanoparticles (100, 101). Also, it has been demonstrated that hydrophobic Ag–Au composite nanoparticles show strong adsorption and good electrical conducting properties, and therefore can be used in biosensing (102, 103).

Semiconductors

Biosensors based on semiconductor nanoparticles have found wide application for detection of analytes. Semiconductor surface potential plays an important role in the performance and characteristics of semiconductor-based biosensors (104). The tunable fluorescence properties of semiconductor nanoparticles have been used for the photonic detection of biorecognition processes. They exhibit size-dependent tunable absorbance and fluorescence. The unique optical, photophysical, electronic and catalytic properties of semiconductor nanoparticles attracted substantial research efforts directed to the use of semiconductor nanoparticles as fluorescence labels for biorecognition processes (105, 106).

Especially, zinc oxide (ZnO) and titanium dioxide (TiO_2) nanoparticles are the most versatile semiconductor oxides with applications across a wide range from cosmetics to medical devices. Extensive efforts have been made to synthesize ZnO nanostructures, such as nanorods, nanosheet, nanobelts, nanoporous, nanodisks, nanoparticles, and radial nanowire array, for biosensors owing to its biocompatibility, low toxicity, high electron mobility, and easy fabrication (107).

Morphology is one of the important factors determining the properties of semiconductors nanostructures like ZnO NPs. On the other hand, ZnO is a biocompatible material with a high isoelectric point (IEP) of about 9.5, is beneficial for the adsorption of proteins or enzymes with low pI (e.g., glucose oxidase, GOx, pI = 4.2− 4.5) at physiological pH of 7.4 by electrostatic attraction. Moreover, ZnO nanostructures have unique advantages including the high specific surface area, nontoxicity, chemical stability, electrochemical activity, and high electron communication features. Therefore, they are promising for biosensor applications because of good biocompatibility, large surface area, good dispersing properties and fast electron transfer ability (108-110).

Many biosensors have been developed using quantum dots (QD), because of its intrinsic electronic and optical properties including their unique size-dependent tunable emission, resistance to photobleaching, high photochemical stability and high brightness (111).

QDs are colloidal nanocrystalline semiconductors having diameters between 1 nm and a few microns, which are composed of a combination of II–VI elements (CdS, CdSe, etc), or oxides, halides, tellurides and combinations of III–V elements, (InP and InAs). The disadvantage of QDs is their toxicity (112-114).

Conclusion

Future prospective and challenges

Biosensors are widely used in biomedical research, health care, pharmaceuticals research via spatially separated molecular probes immobilized on a solid surface to scrutinize or detect biomarker for diagnosis of various diseases. Fortunately, with the development of biotechnology, nanotechnology, and novel immobilization strategy in the past years, nanobiosensors

are becoming more powerful in the field of medicine.

To summarize, in this paper, we have discussed the fundamental differences of the different types of nanobiosensors including genosensors, immunosensors, enzymatic, and microbial biosensors based on different transduction approaches, such as electrochemistry, optic, and piezo-electric measurements. A high-level overview of different types of biosensors is also given. For instance, in electro-chemical section, various kinds of electrochemical biosensors have been described. Although it would be beneficial to have comparison of nanomaterials in nanobiosensors. Working principles, construc-tions, advantages, and applic-ations of nanomaterials in biosensors were presented. Recent advances in application of nanomaterials such as carbon (graphene, CNT), gold, silver, and semiconductors (QDs, TiO_2, ZnO) in nanobiosensors, were reviewed briefly.

Considering all of these aspects, it can be stated that nanobiosensors offer the possibility of diagnostic tools with incre-ased sensitivity, specificity, and reliability for in vivo and in vitro analytical applications.

However, nanobiosensors still need to achieve the confidence of potential users, especially considering that the comer-cialization of new devices is the aim of nanobiosensor technology development.

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