Advances on the biosensor based on nanotechnology

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Abstract: Biosensor is a detection instrument which is sensitive to biological substances and convert the signal of biological activity expression into electrical signal in order to determine the characteristic of samples. Besides, the development of nanoparticles greatly promoted the development and progress of biosensors. Biosensors are promising to be widely used in many fields such as food, pharmacy, chemical industry, clinical examination, biomedicine, environmental monitoring, they have gradually become a research focus on recent years hence. This paper presents a review of worldwide researches, particularly summarized and discussed in composition materials, classification, and application areas of biosensors as well. It is expected that this review can provide some help and references for further research on biosensors.

1. Introduction

Nanotechnology is based on manipulating individual atoms, molecules. In 1990 Don Eigler and Erhard Schweizer used the tip of an STM to deposit individual xenon atoms in patterns of their corporate logo IBM on a nickel-metal surface successfully, and that triumph marked the beginning of nanotechnology.[1] As nanotechnology developed, the National Nanotechnology Initiative made a more precise clarification of nanotechnology as the manipulation of matters which is sized from 1 to 100 nanometers at least one dimension. As the definition only depends on their size, nanotechnology is a comprehensive subject that includes many fields like biomedicine, organic chemistry, quantum mechanics, etc.

Biomedical is the application of biotechnology in the pharmaceutical industry, using the components of an organism and its cell, molecular, etc., combining with engineering to carry out research and manufacture products, including artificial materials, products, devices, and systems used for disease prevention, treatment, human function, etc. Due to the extremely small size, nano materials often perform many unique characteristics, as so, the cohesion of nanotechnology with biomedicine is quite promising. Nanotechnology can be applied in many aspects of biomedicine and can often show good effects.

Biosensors can be enhanced by taking the advantage of nanotechnology. For instance, some molecules are recognized as biomarkers that could show a significant change in some diseases’ development progress especially in cancer, they are of great significance for diagnosis. The biosensor is the instrument that is sensitive to those biomarkers and can convert their current state into electrical signals for detection.[2]

In drug delivery, nano materials like lipid nanoparticles, polymeric micelles, dendrimers, and nanogels, etc. are working as carriers to enhance drug effect. Depends on what we use, the nanomaterials can help drug delivery to be controlled, protect the drug from enzyme degradation, improve the effectiveness and safety, and prolong the drug’s effect in the target tissues, etc.[3]
With the unusual characteristics like faster electron/ion transport, negative refractivity and novel quantum mechanical properties, enhanced reactivity, catalytic activity and plasticity, and the properties of pronounced changes in thermal and optical, nano-biosensors may be faster and cheaper than existing diagnostic tools including enzyme-linked immunosorbent assays (ELISA), glucose test strips, mass spectrometry, and chromatography. [4] Salahandish et al. [5] developed a nanocomposite for detecting ascorbic acid biomolecules as breast cancer biomarkers to diagnosis the disease rapidly and sensitively. Besides, a rapid nano-gold test is currently developed to screen out COVID-19 positive cases, with high accuracy, efficiency, and cost performance. [6]

Implantable and wearable nano-biosensor is also the concern of current researchers. [7] Saminathan et al. [8] used a fluorescent DNA nanodevice called Voltair to report the absolute membrane potential of different organelles in live cells.

2. Nanomaterials of biosensors

2.1. Metal nanomaterials
Gold nanoparticles (AuNPs) are gold particles with a diameter of 1 to 100 nm, and they take on different shapes such as octahedral, spherical, etc. According to their different physical and chemical properties, different forms of AuNPs will be used in various fields. The production methods of nanoparticles can be divided into two main categories: the bottom-up and top-down methods, representing building up the nanoparticles from molecules or atoms and break the bulk material into nanoparticles. The synthesis method can also be divided into three aspects: physical and chemical biology. Different forms of AuNPs should be synthesized in different ways. The physical method includes two approaches for the synthesis of metallic NPs-evaporation-condensation and laser ablation. Without using chemical reagents, nanoparticles made by laser ablation is pure and uncontaminated.[9] AuNPs have a large active surface area and high stability which help the progress of biochemical reactions. High conductivity and strong surface plasmon absorption rationalized their application in the modification of biosensors. Nakhjavani et al. [10] developed a reliable and user-friendly electrochemical immunosensor for detecting breast cancer by sensitively sensing carcinoembryonic antigen (CEA). They increased the conductivity of the detecting area and the loading capacity of the biotinylated monoclonal antibody by using gold nanoparticles, meanwhile, they enhanced the electrochemical signal by using silver nanoparticles. Nodoushan et al. [11] developed an electrochemical aptasensor to detect staphylococcal enterotoxin B (SEB) which is one of the triggers of food poisoning. The sensitivity of the aptasensor was enhanced due to the innovative combination of reduced graphene oxide (rGO) and gold nano-urchins (AuNUs) on the working electrode.

Similar to AuNPs, platinum nanoparticles (PtNPs) are small particles of platinum with a diameter of 1 to 100 nm, they are present in various forms as well. Also, they are usually in the form of colloidal platinum, which is a suspension of platinum nanoparticles in a fluid. The Pt-based electrocatalyst is often used in glucose sensors for its high stability and ease to get. PDMS-based microfluidics with platinum black micro-electrode arrays are developed by R. Perrier etc. [12] in 2018 for analysis of islets non-invasively to monitor the type 1 diabetes patient condition and knowing their demand for insulin. Xuan etc. [13] developed a fabrication process that can solve the problem that wearable biosensors need materials with both high stretchability, high flexibility, and low resistance. The platinum and gold nanoparticles that they use on the 3D porous LIG improved electrochemical performance which results in enhancing the sensitivity.

Palladium Nanoparticles (PdNPs), black spherical high surface area metal particles, the diameter of PdNPs are normally 20 - 100 nanometers. PdNPs are available in ultra-high purity, high purity, and coated and dispersed forms. This precious metal has extraordinary catalytic and electronic features powerful mechanical, and electroanalytical properties. PdNPs are often synthesized as nanoenzymes to improve the performance of biosensors. Tan etc. [14] innovatively used PtPd nanocubes@MoS2 nanoenzymes in a label-free electrochemical immunosensor for detection of Hepatitis B surface antigen. (Figure 1). PtPdnanocubes@MoS2 shows higher peroxidase-like activity than separated MoS2 and PtPd
nanocubes, and results in a better sensitivity and a wider linear range. Zahed etc. [15] enhanced graphene oxide/Au/horseradish peroxidase with PtPd bimetallic nanodendrites/nanoflower-like clusters in and introduced it in an electrochemical nucleic acid sensor for detecting highly up-regulated in liver cancer to improve the catalytic efficiency and sensitivity. What is worthy to notice is that various nanoparticles are often combined to use due to their different features.

2.2. Carbon-based nanomaterials
Carbon-based nanomaterials are a kind of suitable material for biosensors as well, for they have remarkable electrical and thermal conductivity, exceptional tensile strength, high stability, and ease to be functionalized. [16, 17] In practical applications, carbon-based nanomaterials are often combined with or loaded with other biochemical substances such as metal nanomaterials and antibodies to realize and strengthen the function of biosensors. Their flexibility also makes them have an excellent application prospect in wearable biosensors.[16]

Graphene is a solitary graphite layer, comprising of a hexagonally arranged, sp2 bonded, a stable two-dimensional allotrope of carbon with plenty of unique properties. Graphene and its derivatives show high thermal conductivity, tunable optical property, high planar surface, and superior elasticity. Meanwhile, it has a remarkable strength that is about 100 times stronger than steel of the same thickness.[18] For all those great properties, graphene is widely discussed as a kind of biosensor material.
Weng etc. [19] applied a quantum dots aptamer functionalized graphene oxide as probes into a microfluidic system nano-biosensor. The biosensor is developed to detect Ara h 1, which is one of the major allergens appearing in peanuts, in about 10min with high accuracy and cost-effectiveness. Afsahi etc. [20] innovatively applied graphene in Zika biosensor. Linked monoclonal antibodies to graphene ensure a cost-effective real-time, quantitative determination of native Zika viral antigens. Meanwhile, the high sensitivity reduces the detection concentration to 450 pM.

Carbon nanotubes (CNTs) are tubes comprising of a hexagonal arrangement of hybridized carbon atoms which diameter is ranging from 1nm to 100nm. Carbon nanotubes have a tensile strength of 63 gigapascals and a specific strength of up to 48000 kN·m·kg⁻¹. Meanwhile, the extremely large aspect ratio and outstanding flexibility also can help improve the performance of biosensors. Chen etc. [21] designed an abundant active CNTs-Pan nanohybrid that has a unique flower-like structure with the large surface area. Then they developed a redox nanoprobe and nanocarrier based on it to generate and amplify the electrochemical signal. Applying the nanoprobe and nanocarrier, the amperometric DNA biosensor can detect specifically and sensitively. Fixing tungsten phosphide embedded nitrogen-doped carbon nanotubes to the electrode surface. Zhou [22] ensured the electrode with remarkable electrical conductivity and catalytic performance. Using this electrode, they developed a straightforward and practical analytical device for detecting an anticancer medication in whole blood.

3. Classification of biosensors

3.1. Electrochemical biosensor

Biosensor must contain transduction elements and biorecognition elements in direct spatial contact according to the International Union of Pure and Applied Chemistry (IUPAC). The data analyzer is also necessary to deal with data. Electrochemical biosensors are biosensors which mainly manufactured based on the electrochemical principle, their advantages like portability, low-cost, fast processing, high sensitivity, and selectivity make them powerful analytical tools. They can be divided into several categories: amperometric, impedimetric, potentiometric, and voltammetric. [23]

The function of transduction elements in electrochemical biosensors is to convert indicators such as heat, charge, and flow into electrical signals such as voltage, resistance and capacitance which are easy to be analyzed. The main component of the electrochemical transduction element is commonly two or three working electrodes: a chemically stable working electrode, and the electrodes are often made from conducting and semiconducting materials using various manufacturing processes including nanotechnology. The combination of nanomaterials and electrochemical biosensors improves the selectivity and sensitivity of electrochemical biosensors. Different materials and fabrication methods can affect various properties of electrodes, such as sensitivity, selectivity, detection range, and cost, etc., appropriate choices should be made from the demand.

The amperometric biosensor functions by detecting the current generated in the biological redox reaction at a constant potential. Due to the advantages such as high sensitivity, rapid and inexpensive, it is widely used. Carbon nanomaterials have been widely used in amperometric biosensors recently.[24]

Impedimetric biosensors are developed based on the electrochemical impedance spectroscopy (EIS) technique. When the materials are simulated by a small amplitude sinusoidal AC excitation, their electrochemical properties like resistive and capacitive properties will change. By determining and analyzing those electrochemical properties, we can learn about the tested object.[24] Since the biologically mediated redox reaction can be easily approached by the analyte solution while being close to the electrode surface, impedimetric biosensors have gained popularity.

Potentiometric biosensors learn the concentration of some components of the analyte solution by measuring the potential difference between the working electrode and the reference electrode at zero current. The device contains an electrochemical cell with two reference electrodes. Seema Jakhar developed a novel potentiometric urea biosensor with commercial urease nanoparticles in 2018. Applied in the measurement of potentiometric determination of urea, the biosensor displayed a low LOD, a wide working range, and high sensitivity with the capability of long-term storage.[25]
Cyclic voltammetry is the basis of voltammetric biosensors, it analyzes the analyte by measuring the resulting current under changing potential. We can use it to get the information about the redox potential and electrochemical rates of the analyte. In 2014, Mohamadi etc. [26] used a CNTs paste electrode changed with salmon sperm ds DNA to develop a label-free voltammetric biosensor for rapid determination of uric acid, which is already being applied in the examination of UA in human serum and urine samples.

3.2. Optical biosensor
Optical biosensors learn about the samples based on the changes in light absorption or light reflection, refraction, scattering, etc., of specific indicators on the sensor surface initiated by samples for testing. Recently, great development and progress have been made in the study of optical biosensors, especially in the study of fluorescent and bioluminescent cell-based sensors, there are some relevant reports and reviews hence.[27] Wang etc. [28] developed an optical biosensor using the characteristic that Mg-Al-CO3 layered double hydroxides can trigger luminol CL in weak acid solutions.

Surface plasmon resonance (SPR) biosensor is a popular optical biosensor, which has a polarized light source. The surface of its sensing chip is plated with a layer of gold, and the gold layer is connected with the microfluidic flow systems. The biosensor is capable to detect the interacts between biologic molecules in real-time once the gold layer is combined with the target objects. Therefore, SPR biosensors are widely used in medical diagnosis, food safety, as well as environmental monitoring. Jiajun Song etc. [29] integrated a PEC active gate electrode in an OECT to develop a transistor which they called organic photo-electrochemical transistor (OPECT). They used the OPECT as a DNA sensor and the objective DNA is marked with AuNPs and marked on the gate electrode. The novel DNA sensor turned out to show higher sensitivity and selectivity than the PEC-based sensor.

4. Application of biosensors

4.1. Medical diagnostic detection

4.1.1. Biosensors for the detection of glucose
The range of human blood glucose concentration is normally 3.9-6.0 mmol/L, and the method of human blood glucose detection has been one of the main topics in biosensor development. Blood glucose testing tools are in high demand as well due to a large number of patients with diabetes. To figure out the matter that the blood glucose concentration is hard to be detected in hypoglycem, nanoparticle biosensors offer a good solution. Park etc. [30] developed a novel amperometric glucose biosensor with glucose oxidase co-immobilized with the PNT on an AuNP-modified electrode. This biosensor can detect the human blood glucose concentration under the normal range (0.5-2.4 mmol/L) for the amplified effect of AuNPs.

4.1.2. Biosensors for the detection of cancer cells
Cancer seriously endangers human life health, while detection of targeted cancer cells can help the disease to be early diagnosed and be early treated, and that is an effective way to stop cancer development. Generally speaking, biosensors indirectly analyze the cell state and quantity based on the determination of current and impedance changes caused by the attachment of cancer cells to the sensor interface. The empirical values obtained from testing patients with known cancer status are necessary for new detection since the electrical changes could be influenced by numerous factors. Sasya Madhurantakam etc. [31] developed a nano-interfaced amperometric biosensor for detecting glucose utilization by cancer cells. They employed a hybrid nano-interface comprising a mix of CNTs and graphene to favor direct electron transfer and improve the surface zone of the working electrode. The amperometric biosensor can effectively measure the expansion of cancer cells. Zhang etc. [32] developed an impedimetric biosensor with bovine serum albumin-incorporated Ag submicron for better biocompatibility, low cytotoxicity, and great electro-conductivity. Based on specific recognition by 3-
aminophenyl boronic acid (APBA), the impedimetric biosensor can effectively and rapidly detect renal cell carcinoma.

4.1.3. **Biosensors for the detection of virus**
With the provincial and even worldwide flare-ups of infectious diseases such as SARS, MERS, and COVID-19 brought out great attention to epidemic viruses, scientific researchers are eager to find a rapid, accurate and convenient way to detect viruses. Rapid detection of the existence of viruses from contaminated food and water, patient samples, and surfaces of common articles is a prerequisite for effective resistance against viral outbreaks epidemics and bioterrorism, while nanoparticle biosensors provide a proper way for rapid detection as a key technology. Suk Fun Chin etc. [33] developed a disposable electrochemical immunosensor strip using a screen-printed carbon electrode modified with prepared carbon nanoparticles. It shows good performance in terms of LOD, detection time and detection effectiveness in detecting Japanese encephalitis virus, and is a more economical alternative to existing detection modalities. Hong etc. [34] used a composition of nanostructured gold electrode conjugated with concanavalin A in an electrochemical biosensor for the Norovirus detection. This electrochemical biosensor can detect Norovirus effectively with a shorter assay time and a good detection limit.

4.2. **Environmental detection**

4.2.1. **Biosensors for air pollution detection**
In recent years, with the matter of air pollution is getting more serious, biosensors are gradually being applied to the detection of air pollution. Air pollution can be caused by multiple pollution gases, and formaldehyde, as an ingredient in building paint, household decoration materials, become the main pollution gas of indoor air pollution. Excessive formaldehyde can cause great harm to human respiratory and digestive systems, especially to the respiratory system, formaldehyde is placed in the list of carcinogens published by WHO as well, and biosensors can achieve rapid detection of formaldehyde. Li etc. [35] developed a sensitive, selective gas sensor based on the 3D NiO nanowalls they composed. The biosensor shows a phenomenal exhibition with low LOD for formaldehyde (8 ppb).

4.2.2. **Biosensors for water quality monitoring**
The quality of water is closely related to people’s lives, and thus water quality monitoring becomes quite necessary. Water quality monitoring can be categorized into two parts: inorganic toxics detection and organic matter detection. Inorganic toxins detection includes detection for suspended substances, nonmetal toxicants (e.g., cyanide, arsenic), and metal toxic ions (e.g., mercury, chromium, copper, nickel), large-scale use of batteries, combined with the non-standard battery recovery, aggravates the pollution caused by inorganic toxicants. Organic matter detection includes detection for biochemical oxygen demand (BOD), pesticides, and microbial metabolites. Biosensors can achieve sensitive, simple and rapid detection, which can bring great convenience to field detection of water quality. Lin etc. [36] developed an electrochemical biosensor based on functionalized polypyrrole nanotube arrays modified with a tripeptide. This biosensor exhibits high sensitivity and selectivity to Cu (2+) in the range of 0.0064-1.92 mg/L. Microcystin is a hepatotoxin created by cyanobacteria, turns into a genuine threat to water security, while Shi etc. [37] developed a biosensor for microcystin detection based on AuNPs induced graphene oxide fluorescence quenching. The limit of detection was 0.5 and 0.3 μg/L for microcystin-LR and microcystin-RR respectively, which are both fulfill the norm of WHO.

4.3. **Food safety detection**
The food safety problems seriously affect human health, and highly efficient detection of toxic substances in food can provide powerful technical support for food safety. The application of biosensors would make food safety detection simpler and more reliable. For instance, clenbuterol, which may be added to fresh pork, may cause diseases like arrhythmia after long-term exposure or consumption. Thus, it is important to detect clenbuterol efficiently. Bai etc. [38] developed an ultrasensitive amperometric
biosensor based on AgNPs-decorated graphene oxide nanosheets. It exhibited reliability of clenbuterol detection in the scope of 0.01-10 ng/ml, with the LOD as low as 6.8 pg/mL. In addition, Escherichia coli (E. coli) is also a topic of wide concern in food safety. E. coli is a kind of bacteria that widely exists in natural environment and may cause diarrhea and food poisoning when food contaminated by E. coli. In order to solve the problem of E. coli detection, Wang etc. [39] created surface plasmon resonance (SPR) biosensors based on the spectroscopy of grating-coupled long-range surface plasmons (LRSPs) joined with magnetic nanoparticle (MNP) assay. It shows great sensitivity to E. coli with a low LOD of 50 CFU/mL.

5. Conclusion
The paper presents a review of the recent achievements of biosensors based on nanomaterials is summarized in detail. Respectively discussing nanomaterials (metal nanomaterials and carbon nanomaterials), classification of biosensors (electrochemical biosensors and optical biosensors), and application of biosensors (medical diagnostic detection, environmental detection, food safety detection), this review may provide a good reference for the development and utilization of biosensors, yet there is still insufficiency in the investigation of the mechanism. Besides, the applied range of biosensors is limited at present, and it is necessary to apply biosensors to more life scenes such as real-time detection of food safety in canteen and quality of fruits and vegetables in the future to benefit human beings.

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