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Nanoparticle-based Biosensor: Emerging Application in Biology and Medicine

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Abstract: A biosensor can be defined as a receptor-transducer device with integrated processing power that can convert a biological reaction into an electrical signal. These analytes are frequently biological and may include DNA from viruses and bacteria, proteins produced by the immune system, antibodies and antigens, and living organisms infected or polluted. The effective signal collection of the bio-recognition event is one of the numerous difficulties in developing biosensors. These devices convert the analyte-biological element interaction to electrochemical, electro-chemiluminescent, magnetic, or optical signals. Among these nanomaterials, metal, especially gold nanoparticles, carbon nanostructures, including graphene and nanotubes, semiconductor quantum dots, and magnetic nanoparticles, are all being explored in great detail. These nanoparticles also play a key role in diagnosis and healthcare. This review focuses on the different nanomaterials that are vastly studied and their biosensing application.

Keywords: biosensors; electrochemical; electro-chemiluminescent; nanomaterials.

1. Introduction

A biosensor may be defined as a receptor-transducer device with integrated processing power that can convert a biological reaction into an electrical signal. Due to the vast range of biosensor applications, including drug delivery, environmental sensing, food and water quality control, health care, and illness detection, the development and design of biosensors have captured the attention of researchers and scientists in the last ten years [1].

A biosensor is a tool that combines an electronic component with a biological element, like an enzyme or an antibody, to produce a quantifiable signal. Information about a physiological process or the presence of different biological or chemical components in the environment is detected, recorded, and transmitted by the electronic component. They can measure and detect even very low quantities of certain diseases, harmful chemicals, and pH values [2].

The goal of incorporating nanomaterials or designing biosensor structures is to raise the level which would be necessary to stabilize biomaterials, which will increase sensitivity,

catalyze the reaction, enable reactions to occur at low potentials, and speed up the electron transfer from the active reaction center to the surface of the electrode [3]. By removing chemical intermediaries of electron transfer, the application of nanomaterials in the construction of biosensors can further simplify the devices, which is crucial for creating third-generation biosensors [4]. Due to their specific surface area and high free surface energy, nanoparticles play a significant role in the surface adsorption of biomolecules [5].

Comparing nanomaterial-based biosensors to the currently used large electrodes and sensors, the benefits of nanomaterial-based biosensors include quick response time, mobility, compact size, and high sensitivity. The fundamental technology behind small medicine is systems integration [6]. The classification of nanomaterial-based biosensor have been described in [figure1]

2. Different Nanomaterials and Their Bio-sensing Application

2.1. Metal nanoparticles.

Owing to the biocompatibility of the gold nanoparticles, their optical and electrical properties, and relatively simple manufacture and modification, they are the most commonly utilized noble metal nanoparticles for biosensor applications [7,8].

Optical behavior is present in the gold surfaces, where exposure to light of a certain wavelength results in resonant surface plasmons. The oscillating electrons cannot propagate through the surface as they would in the case of a conventional surface plasmon resonance setup when the particle size is substantially smaller than the incoming wavelength [9]. Using SPR transduction, Au nanoparticles tend to show their benefits in bioanalysis. The detection of the analyte can be recorded in several ways, such as alterations to the angle, intensity, or phase of the reflected light, and is often predicated on a change in the dielectric constant of the propagating surface plasmons' surroundings of gold films [10].

The potential of gold nanoparticles to create a strong transduction platform enabling the detection of a single molecule has also been demonstrated, utilizing isolated Au nanoparticles that are sixty nanometers in size, coupled with refractive index detection of the localized surface plasmon resonance and ELISA. Through the biotin-streptavidin linkage, the enzyme horseradish peroxidase has been immobilized successfully on these Au nanoparticles [11]. Additionally, a variety of electroactive biological species, as well as electrodes, can transfer electrons through the use of Au nanoparticles. When the biosensor unit catalyzes the analyte's oxidation-reduction reaction, this concept is primarily used for redox enzyme bio-sensing. In traditional electrochemical enzyme biosensor configurations, the electrode oxidizes or reduces the generated species to produce the electrochemical signal [12].

In addition to being used in developing nanocomposite-based biosensors, silver nanoparticles are more cost-effective than AuNPs. An amperometric nanocomposite biosensor based on TiO_2 nanotube arrays led to the enhancement of AgNP and demonstrated an acceptable response for glucose detection [5].

2.2. Quantum dots.

The semiconducting nanocrystals known as quantum dots, which are luminous and can be utilized for bioanalysis, are another well-known type of nanomaterial. Based on cadmium chalcogenides, colloidal QDs have received the greatest research [13]. The Förster Resonance

Energy Transfer, also known as FRET, which is used to describe the fluorescence quenching of QDs, is composed of non-energy transfer among an organic fluorophore quencher and the exiting QD, which is the donor [14,15].

Bioluminescence Resonance Energy Transfer is another application of non-radiative energy transfer that induces QD fluorescence [16]. Here, the energy is transferred to QDs by a protein label that emits light, which eliminates the need for an external light source for excitation. The most popular techniques for bio-sensing applications using the Quantum Dots as optical transducers include FRET and BRET, charge transfer quenching, and chemiluminescence resonance energy transfer [17,18].

2.3. Magnetic nanoparticles.

In biosensor devices, magnetic NPs are a viable replacement for fluorescent labels. Because there are fewer magnetic domains in nanoscale magnetic nanoparticles than in their bulk counterparts, these particles exhibit unusual magnetic behaviors, known as superparamagnetic behavior [19].

The ability to concentrate the analyte before the detection event is the key benefit of the magnetic nanoparticle method. Simple mixing of the receptor unit-modified magnetic NP with the analyte solution will cause them to bind selectively with the intended target. The nanoparticles aggregate and can be extracted from the solution after applying an external magnetic field [20,21].

In addition to optical and electrochemical detection methods combined with other frequently nanoscale labels, magnetic nanoparticles further provide a very sensitive transduction method in the field of diagnostic magnetic resonance. High-performance biosensors based on gigantic magnetoresistance, spin valves, or magnetic tunnel junctions might be created in this situation [22,23].

2.4. Carbon nanostructures.

Due to their advantageous characteristics, nanostructured carbons like carbon nanotubes and graphene are frequently utilized as electronic and electrochemical transducers in biosensor devices [24]. Nanowire shape, biocompatibility, and electrical characteristics come together in carbon nanotubes to create an exceptional material [25]. Since redox enzyme active sites can be approached, quick and effective electron transfers are made possible by the nanowire shape of CNTs. In several circumstances, the enzyme adsorbs to the nanocarbon, which causes the wiring to occur spontaneously [8].

Due to the unique electric properties of CNTs, the single-molecule limit of analysis and high sensitivities were achieved in field effect transistors, also known as FET biosensor setups, by altering the conductivity of the CNT channel or modulating the Schottky barrier following a bio-recognition event [26]. Most likely because of the poor photoluminescence quantum efficiency, additional spectroscopic properties of CNTs, such as NIR photoluminescence, as well as Raman scattering features needed for bio-sensing applications, are not documented [7].

Although CNT-based biosensors are unquestionably more advanced than graphene-based ones, curiosity in the case of this 2-D material in bioanalytical applications is steadily rising [27]. Materials based on graphene are typically found in electrochemical biosensors and field-effect transistor configurations. On the other hand, graphene serves primarily as an electrode material with an improved specific surface. In the case of optical as well as

colorimetric biosensor setups, graphene materials can potentially serve as the transduction element itself. In the cases of DNA, aptamer, immune sensor, or protein sensors, highly effective graphene-based FRET biosensors were created in conjunction with modified receptor units for organic dyes or quantum dots [8,28,29]. Different nanomaterials are currently used, which have been summarized on a categorical basis with their application in the field of medicine [Table 1].

Table 1. Summary of Different nanoparticles used in biology.

Category of Nanoparticle	Specific Type of NP	Application	Reference
Metal nanoparticles	Gold nanoparticles	Optical applications in biosensors, Surface plasmon resonance, Immunological applications including ELISA	[8]
	Silver nanoparticles	Glucose detection, Immunosensor	[5,30]
Quantum dots	Quantum dots	Förster Resonance Energy Transfer (FRET) biosensors, Bioluminescence Resonance Energy Transfer (BRET) biosensors	[13,14]
Carbon nanostructures	Graphene	Electrochemical biosensors, Immunosensor, Förster Resonance Energy Transfer (FRET) biosensors	[8,28]
	Carbon Nanotubes	Field Effect Transistor (FET) biosensor due to electric properties	[31]
Magnetic Nanoparticles	Magnetic Nanoparticles	Optical biosensor, Electrochemical biosensor, diagnostic magnetic resonance	[22,23]

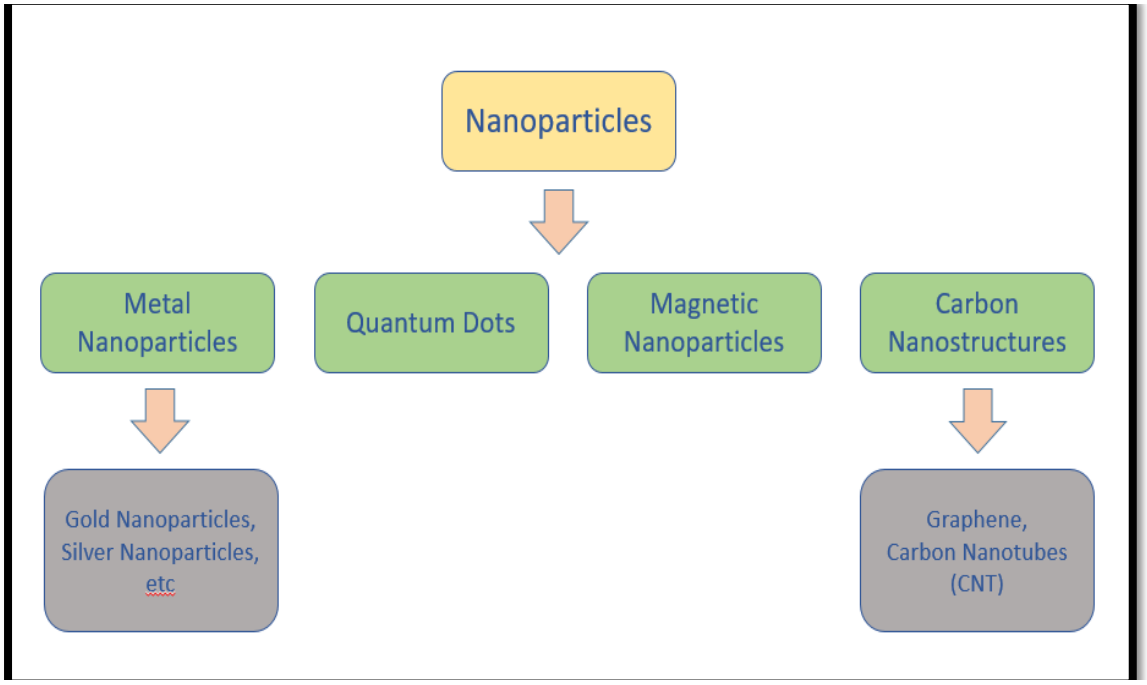

Figure **1.** Classification of Nanoparticles.

3. Nanomaterial for Healthcare Bio-sensing Application

The earliest enzymatic glucose sensing device, which Clark had proposed in the year 1962, dates back to the incorporation of the enzyme glucose oxidase into an oxygen

electrode [32]. There are two typical ways to combine an enzymatic reaction to electrochemical detection: first, mediator-based electron transfer, and second, direct electron transfer. In the first method, the mediator and analyte are both changed, and at some point, the electrons come into contact with the surface of the electrode [32,33].

Due to their use in diagnosing and treating diabetes, glucose biosensors are crucial. New electrochemical glucose nano biosensors have already been suggested employing various modifications to the electrodes and the nanostructures. Amperometric Nano biosensors have been developed using metallic nanoscale materials [34].

Due to its biocompatibility, reduced graphene oxide, also known as RGO, is a high-conductivity material particularly suited for enzyme-based biosensors [35]. RGO has been employed as a conductive substrate with a substantial surface area for the stability of nanometals. RGO sheets can clump despite their benefits, resulting in poor dispersion of the particles attached [36]. To combat this, some substances, such as polypyrrole, have been added to surfaces to improve their functioning and anchor gold nanoparticles for amperometric glucose sensing [37].

The APOE4 phenotype, a significant risk factor for Alzheimer's disease, was identified by employing an amperometric immune sensor created using fractal Au nanostructures as antibody carriers. Excellent sensitivity was achieved by using the Au nanostructure and the HRP enzyme to label the anti-APOE4 antibodies. In this case of sandwich-type immunoassay, hydroquinone, or HQ was added as an enzyme substrate that allowed the transfer of electrons and H_2O_2. The enzyme then carried out the catalysis of the oxidation of HQ to quinone and the changing of the reductive current, which was, in turn, proportional to the concentration of APOE4. It was recorded by chrono-amperometry [38].

Single-stranded DNA is employed in DNA biosensors as a probe because it has an affinity for a particular sequence of DNA of the target DNA molecule and is frequently used to identify genetic abnormalities caused by DNA mutation. Electrochemical DNA biosensors have been favored because they may be made smaller [39]. A drop in a redox indicator's voltammetry reduction current due to the DNA hybridization event allowed the sensor to detect dengue virus-related DNA. Due to the synergistic signal amplification impact of WS2 and AuNPs, satisfactory electrochemical behaviors were obtained, and complementary DNA was identified in Femto molar concentrations [40].

Due to their straightforward instrumentation and minimal time and cost demands, cyto-sensing systems are extensively integrated with electrochemical approaches [41]. Extremely sensitive electrochemical cyto-sensing can be achieved by using biofunctionalized nanoparticles and recognizer biomolecules, which can combine the specificity of the biomolecules and the signal amplification capabilities of nanoparticles [42]. A range of cyto-sensors, as well as biomaterial interfaces, have indeed been developed through the evolution of electrochemical cyto-sensors to immobilize cells and analyze the cell surface carbohydrates as well as glycoproteins, as variations in their expression may indicate various diseases, including cancer [43].

A wide range of target molecules can be efficiently identified by using Quantum Dots in a microfluidic platform. Several influenza viruses, including H1N1, H3N2, and H9N2, were recently identified and subtyped using such a sensor. Superparamagnetic beads immobilized with DNA served as capture probes, and streptavidin-coated quantum dots were immobilized with biotinylated, which DNA served as labels for fluorescence imaging. The nucleic acid on

the microfluidic chip was hybridized to operate the sensor in the presence of a controlled micro-magnetic field [44].

In a sandwich immunoassay, magnetic nanoparticle cores bearing gold shells functionalized using biotinylated *E. coli* Abs were used as *E. coli* capture probes, and chit-coated CdTeQds served as reporting probes. Before the fluorescence analysis, the bacteria had been isolated from the sensing solution by IMS. This method was used to detect lung cancer biomarkers utilizing multicolored Quantum Dots, with carboxyl functionalized micro-magnetic beads serving as immunological carriers [45].

Magnetic NPs have shown enormous promise for use in early-phase cancer sensing. As an illustration, magnetic NPs had been multiplexed with mAbs for sensing different biomarkers for ovarian cancer, Apo-lipoprotein A1, and 2-microglobulin. Then, the sandwiched particles were removed from the sensing medium using a magnetic force. Alongside this, a real-time comparison of the fluorescence variation to a standard concentration was made [46].

Nano motors, called molecular machines, are tiny devices that can propel themselves or be powered externally to move in a liquid. Modern and effective bio-sensing devices are being developed more quickly owing to molecular machinery functionalized with biomolecules. They may be coupled to biological molecules like antibodies, ODNs, or synthetic molecularly imprinted receptors [47].

It has been claimed that a simple method for creating a glutamate sensor involves employing a nanocomposite ink made of MWCNTs, PtNPs, silicone rubber, and ICP polystyrene sulfonate. On the nanocomposite, glutamate oxidase was finally immobilized. The rat spinal cord's glutamate release was also studied using the bio-sensing device. It demonstrated great promise in neurotrauma patients' implantable glutamate biosensors [48].

Numerous novel and enhanced sensing technologies have been developed owing to carbon nanotubes' special chemical and physical features. One of the most recent, intriguing, and ground-breaking applications of carbon nanotube-based biosensors is early cancer diagnosis *in vitro* systems. Carbon nanotubes' surface, specifically coated with antibodies, may be utilized to identify important proteins and viruses. The key discovery of this invention is that as the distance between Ab and the protein varies, the electrical conductivity of the nanotubes changes noticeably [49,50].

Cancer biomarkers can be detected early and non-invasively from blood samples using biosensors. Carcinoembryonic antigen biomarkers have been successfully found using surface plasmon resonance and electrochemical biosensors for the early identification of lung cancer. For the early diagnosis of cancer, epidermal growth factor receptors or EGFR biomarkers have been found using lab-on-a-chip and optical biosensors [51,52]. The clinical applications of nanoparticles have been extensively studied to detect various stages of cancer and are potent cancer biomarkers [Table 2].

Table 2. Clinical Application of Nanoparticles.

Type of Nanoparticle	Example of Clinical Application	Reference
Magnetic nanoparticles	Studied to enormous promise for use in cancer sensing	[53]
Carbon Nanotubes (CNT)	Detection of cancer biomarkers, EFGR biomarkers	[54]
	Identification of important proteins and viruses	[55]
Graphene (Reduced graphene oxide)	Particularly suited for enzyme-based biosensors	[56]
Quantum Dots	Detection of Influenza viruses	[57]
	Diagnosis of early stage Cancer	[58]

Type of Nanoparticle	Example of Clinical Application	Reference
Gold nanoparticles	Electrochemical aptasensor for the detection of breast cancer	[59]
	Enzymatic glucose bio-sensing	[60]
	Detection of pathogenic RNA viruses	[61]

4. Conclusion

Nanomaterials have grown in importance as part of bioanalytical equipment because of how much better they perform with respect to sensitivity as well as detection limits for single molecules. The unique features of such nano-objects can replace traditional transduction techniques. In addition, it is a well-accepted method to combine many nanomaterials, each with unique properties, to improve biosensor capabilities even more.

The development hasn't changed much, though. The electrochemical and optical sensors are by far the most successful in tissue engineering, while the thermometric and magnetic transductions have had no real-world application. This is even though many optical, electrochemical, magnetic, acoustic, thermometric, and piezoelectric sensors have already been described in the literature and are frequently on the market, demonstrating great sensitivity and sensibility. The downsizing and integration of biosensors in microfluidic systems present obstacles to their broad use in tissue engineering. Although it is still developing, continuous real-time analysis of analytes in tissue engineering has the potential to revolutionize the discipline.

A wide range of sensing platforms, including apta-sensors, immuno-sensors, enzymatic sensors, and many others, can be developed owing to nanomaterials' excellent affinity for biomolecules, which makes it possible to immobilize antibodies, enzymes, nucleic acids, enzymes, and several other clinically significant substances. Various innovative nanomaterials, from monomolecular nano-motors and considerably bigger nanocages, have been used in recent breakthroughs in bio-sensing platforms. In the near future, conventional, expensive sensing devices are predicted to be replaced by nanomaterial-based biosensors' quick, inexpensive, and simple operational methods.

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Conflicts of Interest

The authors declare no conflict of interest.

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