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Development & Applications of Nanobiosensors for Biomedical Diagnosis

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Abstract : Nanotechnology plays an important role in the development of biosensors. The application of nanotechnology in life sciences, nanobiotechnology, is already having an impact on diagnostics and drug delivery. Now, researchers are starting to use nanotechnology in the field of drug discovery.
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. Nanostructures in biosensing have 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 : Nanotecnology, Nanobiosensors, Medical Diagnosis, Nanomaterial.

Introduction:

Biosensors are currently used in the areas of target identification, validation, assay development, lead optimization and absorption, distribution, metabolism, excretion and toxicity (ADME-Tox).

A novel nanobiosensor (based on magnetic nanoparticles) has been developed for rapid screens of telomerase activity in biological samples.[1]

Nanobiosensor is any device built on the nanoscale has ultra- sensitiveability to detect single particles or even ultra-low concentrations of a substance,or in another word "A chemical or physical sensor constructed using nanoscale components, usually microscopic or submicroscopic in size" [2, 3]. Theunique physicochemical properties of NMs holds promise to meet sensitivity, accuracy and the reliability of nanobiosensers especially in the medical application to monitoring and diagnose disease in early stage. It is composed of a recognition elements and a signal transducer.[4,5] Common examples of recognition elements include antibodies, enzymes, receptors, nucleic acids, aptamers (are oligonucleic acid or peptide molecules), and other synthetic molecules.[2] Recent development in nanobiosensors can be easily applied for biochemical analysis and clinical diagnostics especially in medical diagnostics integrate nanoparticles encompass desirable properties for sensitivity and specificity of binding peptide or nucleic acid chemistry for enhancing sensitivity in the detection .[7]There are three most commonly known methods to obtain materials innanoscale ,which are top-down lithography, bottom-up assembly, and molecular self-assembly. [8, 9, 10]There are two different types of biosensors: biocatalytic and bioaffinity-based biosensors. The biocatalytic biosensor uses mainly enzymes as the biological compound, catalyzing a signaling biochemical reaction. The bioaffinity based

biosensor, designed to monitor the binding event itself, uses specific binding proteins, lectins, receptors, nucleic acids, membranes, whole cells, antibodies or antibody-related substances for bimolecular recognition[11,12,13].

Classification of biological recognizers:

Based on kinds of immobilized biomo-lecules as bio-receptor, biosensors can be divided into several classes including enzymatic biosensors, immunosensors, DNA biosensors, aptasensors,microbial biosensors.

Enzyme

Principally, enzymatic biosensors are based on immobilized specific enzyme which converts 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 [16-20].

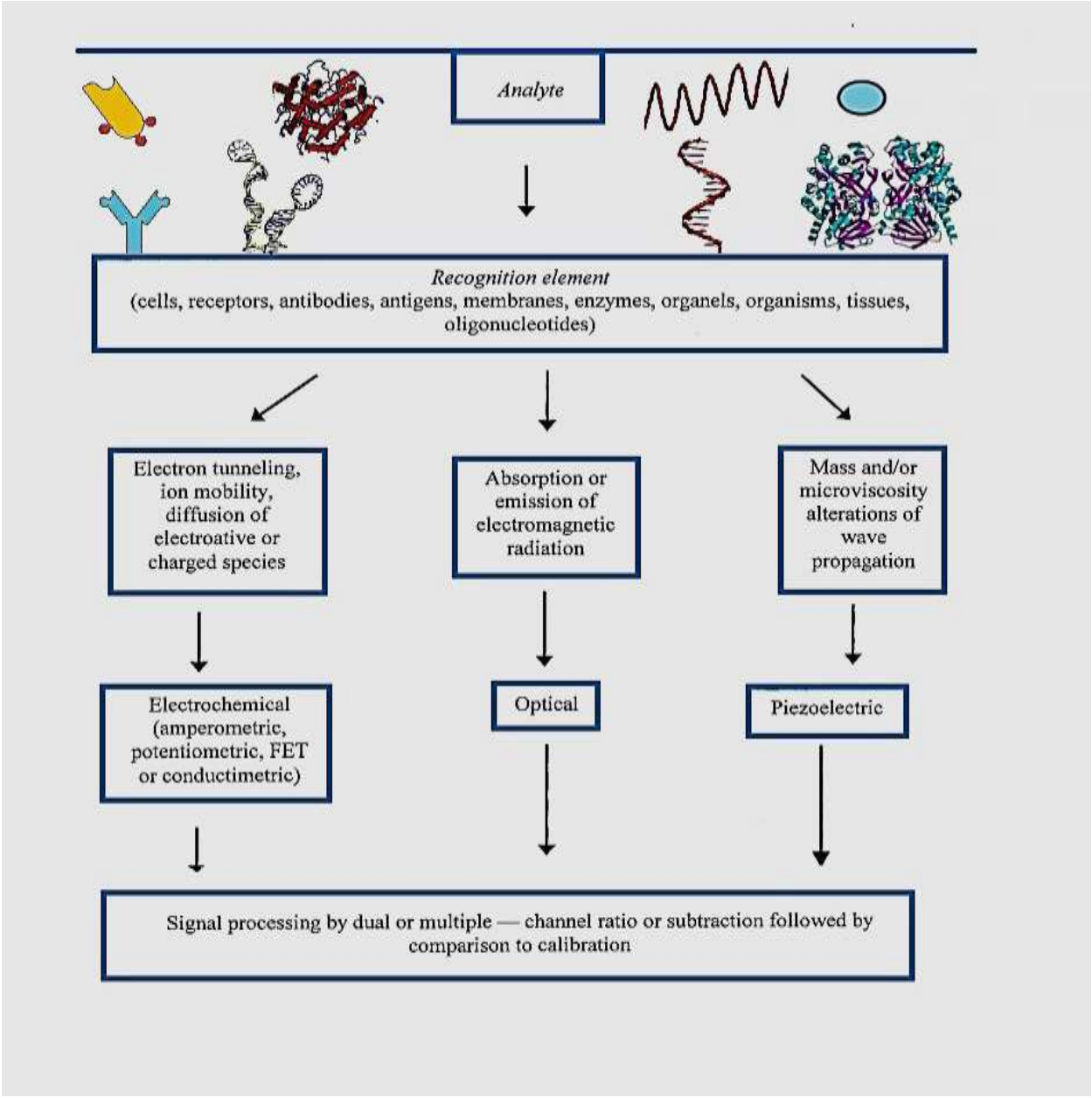

Figure 1:Elements of biosensors

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]

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 [28, 29].

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 [30, 31]. 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 [32, 33].

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’ [34]. 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 [35]. 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) [36, 37]. 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 [38, 39]. 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 [40-45].

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 [46-48]. These nanobiosensors offer rapid, accurate and sensitive detection of target analyte in fields as diverse as medicine, environmental monitoring, defense, food processing and safety [49-51]. 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 (52). 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 [53]. 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 [54, 55].

Biosensing Techniques

Biosensors can be classified either by the type of biological signaling mechanism they utilize or bythe type of signal transduction they employ. Transduction can be accomplished via a great variety of methods. Most forms of transduction can be categorized in one of three main classes. Mass detection methods. However, new types of transducers are constantly being developed for use in biosensors.

Electrochemical Biosensors

The first scientifically proposed as well as successfully commercialized biosensors were those based on electrochemical sensors .or multiple analytes [56, 57, 58]. At present, there are many proposed and already commercialized devices based on the electrochemical principle including those forpathogens and toxins [59]. This stems from a number of attributes of electrochemistry including the high sensitivity of electrochemical transducers, their compatibility with modern miniaturization/micro fabrication technologies, minimal power requirements, economical cost, and independence of sample turbidity and color [60, 61].

Potentiometric

Potentiometry, one of the oldest instrumental methods, has well-established position as the analytical techniques for biomedical needs. These types of bio-sensors 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 [62-64].

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 [64].

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 [65, 66].

Conductometric

Reactions in solution produce changes in the electrical resistance between two parallel electrodes [67]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 [68].

Optical Biosensors

Optical sensing for the detection of analytes is the most commonly used method in Nucleic Acid based Biosensors (NABs). Optical biosensor is based on optical transduction of a signal and comprises ultraviolet, visible and infrared spectrophotometry in transmission or reflectance modes. Lambert- Beer principle easily correlates the relationship between incident light intensity and the transmitted radiation. Optical phenomenon like absorption, refractive indices, fluorescence, phosphorescence, and chemiluminescence are exploited to monitor the biological recognition in biosensors.

Optical biosensors are based on fiber optics which converts the emission signal to a detectable fluorescent signal. DNA probe and target hybridization event was detected by fluorescence marker ethidium bromide. Total internal reflection in the optical fiber was measured which is proportional to the total amount of intercalated ethidium bromide [69].

Fluorescent biosensors

Principally fluorescence occurs when an orbital electron of a molecule, atom or nanostructure relaxes to its ground state by emitting a photon of light after being excited to a higher quantum state by some type of energy. [70]

In past forty years Organic fluorophre have been broadly studied. Recently inorganic nanocrystals quantum dots (QDs) emerged a novel fluorescent labels in biosensing and imaging. Quantum dots (QDs) tend to be brighter than organic dyes because of the effects of extinction coefficients that are an order of magnitude larger than those oforganic dyes therefore substituting the conventional organic fluorophores. The biggest advantage of QDs resides in their long periods of time brightness (minutes to hours) allowing the acquisition of crisp images over extended periods of time.[71-73]

Surface Plasmon resonance (SPR)

Fundamentals of SPR sensors is A Surface Plasmon excited by a light wave propagates along the metal film, and its evanescent field probes the medium (sample) in contact with the metal film. A change in the refractive index of the dielectric gives rise to a change in the propagation constant of the surface Plasmon, which through the coupling condition alters the characteristics of the light wave coupled to the surface Plasmon (e.g.,coupling angle, coupling wavelength, intensity, phase). The SPR peak position is related to the refractive index of the surrounding medium. It is extremely attractive sensor because of its simplicity and low cost. [74, 75]Nanoparticle-based SPR biosensors lead to create large electromagnetic field around NPs. It is one of attractive colorimetric biosensors because of its simplicity and low cost, the signal originate when the shifting occurred in the peak position results in visually colorimetric response.[76,79]

Figure (2): Principles of surface Plasmon resonance (SPR) (Cooper, 2002).

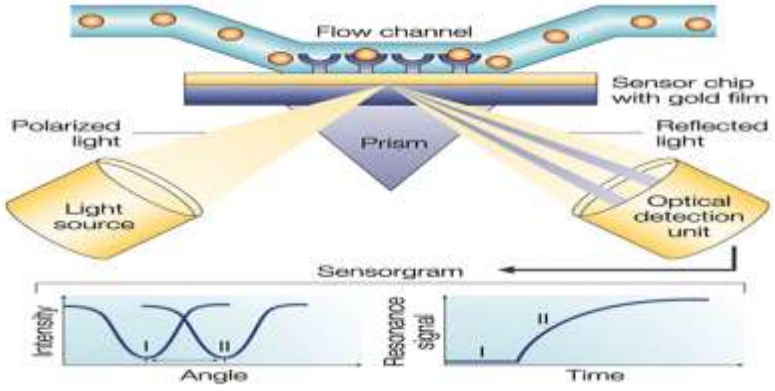

Figure 2: Principles of surface Plasmon resonance [80]

Piezoelectric biosensors:

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 [81, 82].Novel piezoelectric transducer based biosensor emerged when simultaneously detection and genotyping of 16 strains of the human papilloma virus was done by designing and immobilizing a degenerate probe (based on conserved genomic region) and two specific probes (based on less-conserved regions) [83, 84].

Nonmaterial's

The use of nanoscale materials for electrochemical biosensing has seen explosive growth over last decade. In recent years, nonmaterials such as gold nanoparticles, and carbon nanotubes have been used to increase selectivity and accuracy of biosensors.

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, chemi-cal stability and mechanical strength [85]. 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 [86].

Graphene:

Graphene is a novel one-atom-thick, two-dimensional graphitic carbon system with extraordinary electronic, thermal, and mechanical properties.[87,88] Despite its short history, graphene has been broadly studied because of its unique optical and electrical properties, and it has attracted considerable attention in variousapplication fields.[89] Recently, graphene has been successfully used in many bioassay and biomedical applications, such asDNA analysis,[90–92] enzyme activity analysis,[93] protein assays,[94]and drug delivery.[95–97] In particular, graphene oxide (GO), which is a water-soluble derivative of graphene, has attracted increasing interest in biological applications because of its unique characteristics, including good water dispersibility, facile surface modification and high mechanical strength.[98, 99,100] reported a platform to assay helicase unwinding activity based on the preferential binding of graphene oxide (GO)to ssDNA over dsDNA (Fig. 2a). After the helicase is added tothe mixture of dsDNA and GO, the fluorescence of dyes that were conjugated to ssDNA can be quenched owing to the high quenching efficiency of GO. [101,102]

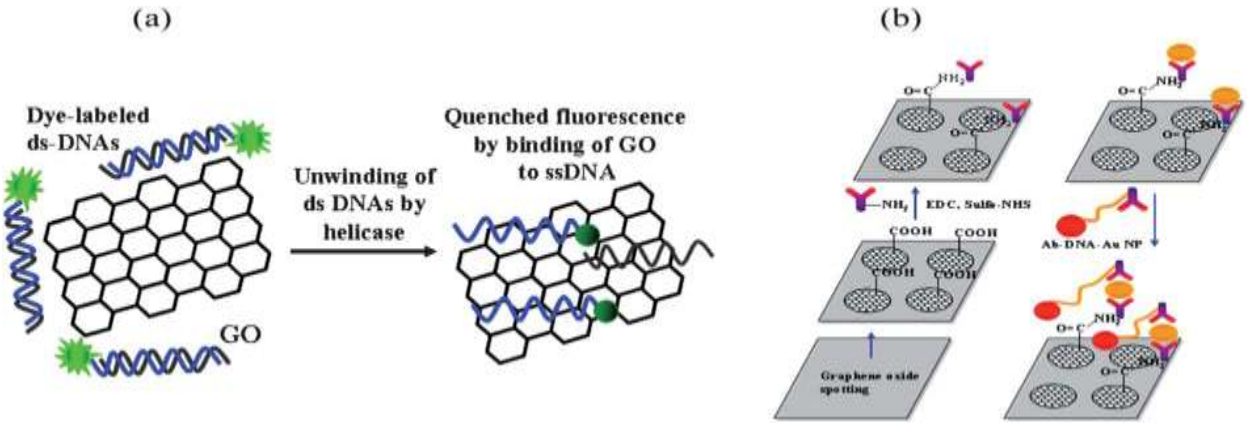

Figure 3: GO-based biosensor for the helicase unwinding activity assay (a) and rotavirus detection (b).

Gold

Gold nanoparticles (GNPs) and nanorods are the most extensively studied nonmaterial's 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[103, 104]. 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 [105, 106]. Recently, studies on nanobiosensors based on the immobilization of DNA or RNA on gold nanoparticles for cancer detection have been reported [107].

Silver

Among noble-metal nonmaterial's, 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 [108, 109]. 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 [110, 111].

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 [112]. 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 [113, 114].

Application of nanobiosensors

There is a big demand for fast, reliable and low-cost systems for the detection, monitoring and diagnosis of biological molecules and diseases in medicine [115,116].

1. Glucose Detection in Vivo:

One of the main clinical applications of biosensors is to develop point-of-care glucose concentration measuring devices for patients suffering from diabetes [117]. The most common enzymes used for glucose detection are glucose oxidase and glucose dehydrogenase [118]. Glucose biosensors generally make use of electrochemical transducers in their designs as they provide appropriate specificity and reproducibility and can easily be manufactured in large volumes at low costs [118]. These traditional amperometric-based biosensors have undergone recent miniaturization to enable subcutaneous implantation. In the minimed medtronic continuous glucose monitoring system (CGMS), a needle-type amperometric enzyme electrode is coupled to a portable data logger [119]. The sensor is based on the aforementioned sensing technology and the data recorded from the logger can be downloaded to a portable computer after 3 days of sensing [120].

2. Bacterial Urinary Tract Infections:

Bacterial infection in the urinary tract is the second most common organ system infection in the human body [121]. Microbial culture techniques are currently employed to identify urinary tract pathogens. These methods, however, are cumbersome and are accompanied by a 2-day lag period between the collection of the specimen and the identification of the pathogen [122]. As such, the development of tools to effectively decrease this lag period and increase diagnosis accuracy and efficiency is very appealing from an improved health care and reduced cost standpoint. Electrochemical DNA biosensors have been documented in the literature to detect and identify pathogens [123, 124]. In these designs, a layer of oligonucleotide probes functions as the sensory receptor and the sensory input is detected through the use of an electrochemical transducer. There are two basic modes to detect DNA with this configuration. The first method requires target immobilization followed by detection with a labeled probe [125]. In the second method, known as ''sandwich'' hybridization, the DNA target initially binds to a surface oligonucleotide through hybridization. This is followed by hybridization to a marker probe for signal transduction [125].

3. Immunoassay (detection of Ab-Ag reaction)

It is well well-known that the peak extinction wavelength of the localized surface plasmon resonance (LSPR) spectrum is reliant upon the size, shape and interparticle spacing of the nanoparticles as well as its own dielectric properties and those of its local environment including substrate, solvent and adsorbates.[126,127] The high sensitivity of the LSPR spectrum of non spherical nanoparticles to adsorbate induced changes in the local dielectric constant (viz., refractive index) are now being used to develop a different class of nanoscale

chemosensors and nanobiosensors. This sensor detects changes in the refractive index induced by molecules near the surface of noble metal thin films. [128,129]

4. As a Tool for Analysis in Food Products

Biosensor-based analysis is becoming increasingly important in the food industry where it has several applications;

- Vitamins analysis: The SPR biosensor monitors interactionsof a specific binding protein with the vitamin immobilized on a CM5 sensor chip.
- Antibiotics detection: Recently the presence of prohibited. Antibiotics was detected in honey. Biosensors analyze the presence of antibiotics reliably, effectively and in a short time.
- Detection of food spoilage: Amperometric biosensor using immobilized enzyme diamine oxidase (DAO) has been developed for the rapid monitoring of the histamine levels in tiger prawn (Penaeus monodon), similarly a potentiometric biosensor could analyse isocitrate using a 2 CO3 -selective electrode and enzyme– immobilization in flow injection analysis (FIA).
- Detection of microbial contamination: Immunobiosensors based on the surface immobilization of monoclone antibodies onto indium tin oxide (ITO) electrodes could detect Escherichia coli O157:H7. [130]

5. Application in cancer

Telomerase is a specialized reverse transcriptase, which is composed of an essential catalytic subunit and an RNA component [130,131] that, together with telomere-associated proteins, maintains telomere length and function. [132,133]In normal cells, a critical telomere length is eventually reached, thereby inducing cellular senescence and finally leading to apoptosis. Elevated levels of telomerase activity are found in the majority of malignancies and are believed to play a critical role in tumor genesis. [134-135]Telomere dysfunction also results in genetic instability with complex cellular and molecular responses involving the retinoblastoma gene/p53 gene checkpoints and apoptosis pathways. [136-138, 139]

6. As Tool for Effective Detection of DNA and Protein

Reported the first nanowire field effect transistor based biosensor which achieves simple and ultra-sensitive electronic DNA methylation detection and avoids complicated bisulfite treatment and PCR amplification. Similarly, using protein-ligand (antigen) interaction properties, protein-nanoparticles based biosensors can realize the ultra-sensitive detection of special protein molecules. The use of these DNA and protein detecting biosensors might play a vital role in detection of plant pathogens; certain abnormalities in plants linked to mineral deficiency, biomarkers, and discriminate one plant species from another etc. [140]

7. As Diagnostic Tool for Soil Quality and Disease:

Assessment Nano sensors may be used to diagnose soil disease (caused by infecting soil micro-organisms, such as viruses, bacteria, and fungi) via the quantitative measurement of differential oxygen consumption in the respiration (relative activity) of “good microbes” and “bad microbes” in the soil. The measurement proceeds through the following steps: two sensors impregnated with “good microbes” and “bad microbes” respectively, are immersed in a suspension of soil sample in buffer solution and the oxygen consumption data by two microbes were detected. By comparing two data, we can easily decide which microbe favors the soil. So, it is to be emphasized that the biosensor offers an innovative technique of diagnosing soil condition based on semi-quantitative approach [141].

Future Prospective:

Future Perspectives Clearly, there is an opportunity for nanotechnology to have a profound impact on energy, the economy and the environment, by improving the screening processes. A novel nanobiosensor based on magnetic nanoparticles can be utilized for rapid screens of telomerase activity in biological samples. In detection and monitoring of diabetes, traditional methods are often tedious and lack sensitivity. To avoid this problem, the nanorobot sensor can be used since it generates proteomic-based information to detect biochemical changes associated with hyperglycemia. This will also enable more rapid and effective treatment of diabetes. The detection of microbial pathogens and their toxins in patients is now possible by nanobiosensors.

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