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An insight into the multifarious applications of biosensors and the way forward

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Abstract

A biosensor is a self-reliant integrated device that is proficient in providing specific quantitative or semi-quantitative analytical information. It has been using a biological recognition component that is in direct spatial contact with a transduction component. It is an appliance that consists of two main parts: a bioreceptor and a transducer. Bioreceptor is a biological component that recognizes the objective of an analyte and a transducer. A physicochemical detector component has also been employed that converts the recognition incident into a measurable signal. All the biological materials including enzymes, antibodies, nucleic acids, hormones, receptors, organelles, or whole cells can be used as sensors or detectors in a device. Biosensors can provide low-priced and highly capable devices for being used in other day-to-day applications. It has multifarious potential applications of various types such as monitoring of treatment, disease progression, drug discovery, food control, and environmental monitoring as well as it continues to play a crucial role across numerous fields including biomedical diagnosis. In this review, we give a general introduction to biosensors and their applications, including a brief historical overview.

Keywords: Biosensor, Bio-receptor, Transducer, Analyte, Detector.

Introduction

Biosensors are analytical devices for the investigation of bio-material samples to achieve an understanding of their bio-composition, layout, and principle by transforming a biological response into an electrical signal. The bio-recognition element (e.g. enzyme, antibody, nucleic acid, hormone, organelle, or whole cell) essentially a bioreceptor, is allowed to interact with a specific analyte (e.g. Glucose, urea, drug, pesticide) to get a measurable response.[1] Any biosensor consists of the following three basic components (a) a bioreceptor, which is a selective membrane involving various biological structures; (b) a transducer component (semi-conducting material/nanomaterial); and (c) an electronic system that includes a signal amplifier, processor & display.[2]

However, the production of biosensors, transducing devices, equipment, and immobilization techniques requires multidisciplinary research in chemistry, biology, and engineering. The materials used in biosensors are categorized into three groups based on their mechanism.

- Bioaffinity-based biosensors include antibodies and nucleic acids.
- A biocatalytic group comprising enzymes.
- Microbe-based containing microorganisms.[3]

Biosensor tools are applied in various fields and industries such as disease monitoring, drug discovery, detection of pollutants, disease-causing micro-organisms, and markers that measure disease in body fluids (blood, urine, saliva, sweat).[4]

History

The history of biosensors started in the year 1962 with the development of enzyme electrodes by the scientist Leland C. Clark (Father of biosensors). He represented how "to formulate electrochemical sensors (pH, Polarographic, Potentiometric or Conductimetric) more brilliant" by adding "enzyme transducers". The first example was exemplified by entangling the enzyme Glucose Oxidase in a dialysis membrane above an oxygen probe. The addition of glucose discovered a decrease in oxygen concentration. The first biosensor was delineated in the published paper inventing the term "enzyme electrode". Then consequently in 1967 Updike and Hicks use the same term "enzyme electrode" to explain a similar appliance where once more the enzyme glucose oxidase was immobilized in a polyacrylamide gel onto a surface of an oxygen electrode for the quick and quantitative ascertainment of glucose.[5]

Principle and components of the biosensor

The principle of biosensors depends on the mechanism of signal transduction and biorecognition of elements. In a device, all biological materials can be used as sensors or detectors. The desired biological material is usually in the form of an enzyme and the deactivated enzyme is located in propinquity to the transducer. The analyte (which is tested) is associated with the specific enzyme (bio-receptor) and produces a transformation in the biochemical property of the enzyme. It gives an electronic response during an electron enzymatic approach. The electron enzymatic method is the chemical method of transforming the enzymes into corresponding electrical signals with the help of a transducer. Now, the electrical signal is a direct demonstration of the biological material (i.e. analyte and enzyme) being measured from a transducer. The electrical signal is usually changed into a physical display for its suitable investigation and demonstration. Principle of biosensor diagrammatically shown in fig-1.[4, 6]

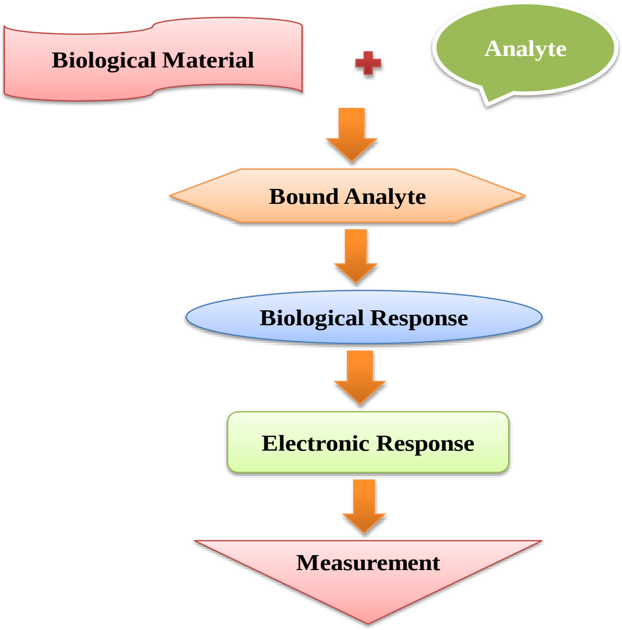

Fig-1 Principle of Biosensor

Biosensors are based on the principle of signal transduction. These components consist of a bio-recognition element, a transducer, and an electronic system composed of an amplifier, processor, and display. Fig. 1 depicts the overall principle of the biosensor.

Components of Biosensor

It consists of a bio-recognition site, transducer component, and electronic organism which contains a signal amplifier, processor, and display. It combines high selectivity of biological/ chemical substances with high precision of solid state devices. However, interfacing poses complicated troubles. The biological material can be a membrane, enzyme, antibody/antigen, receptor, protein, intact cells, tissue, or whole organ and the analyte must achieve the reaction site in the biological material.[7]

It consists of the following components.

Analyte: An analyte is a compound (e.g. Glucose, urea, drug, pesticide) whose concentration has to be measured. For example, glucose is an 'analyte' in a biosensor designed to identify glucose.

Bioreceptor: A molecule that particularly identifies the analyte is known as a bioreceptor. Some examples of receptors are enzymes, cells, deoxyribonucleic acid (DNA), and antibodies. The method of signal generation (in the form of light, heat, pH, charge or mass change, etc.) that results from the interaction of the bioreceptor with the analyte is termed bio-recognition.

Transducer: The transducer is a component that transforms one form of energy into another. The main role of the transducer in a biosensor is to convert the bio-recognition event into a computable signal. This process of energy translation is known as signalization. Most transducers create either optical or electrical signals that are generally proportional to the quantity of analyte–bioreceptor interactions.

Electronics: The main work of this part of a biosensor is to process the transduced signal and make it ready for display. It consists of intricate electronic circuitry that performs signal conditioning such as amplification and translation of signals into the digital form. The processed signals are then evaluated by the display unit of the biosensor.

Detector: It consists of a user elucidation system such as the liquid crystal display of a computer or a direct printer that produces numbers or curves comprehensible by the user. This component frequently consists of a mixture of hardware and software that creates results of the biosensor in a user-friendly way. At the endpoint, the output signal on the display can be numeric, graphic, tabular, or an image.[4, 8]

Components of biosensor diagrammatically shown in fig-2.[9]

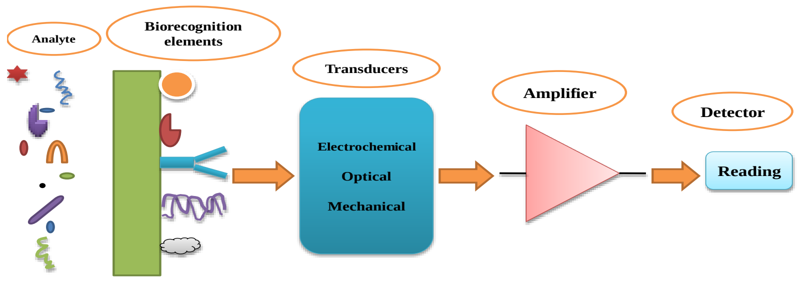

Fig-2 Schematic Diagram of Components of Biosensor

The important components of a biosensor are (1) a bioreceptor (e.g., enzymes, antibody, microorganism, or cells); (2) a transducer of the physicochemical signal, and (3) a signal processor to interpret the information that has been converted.

Classifications of Biosensors

Biosensors can be assembled according to their biological element or transduction element. Biological elements consist of enzymes, antibodies, micro-organisms, biological tissue, and organelles. The technique of transduction depends on the type of physicochemical change resulting from the sensing occurrence. Mainly biosensors based on transducer components are mass-based (piezoelectric, etc), electrochemical biosensors (Potentiometric, Amperometric, etc), and optical types of biosensors. Various types of biosensors are represented in fig-3 [9, 10].

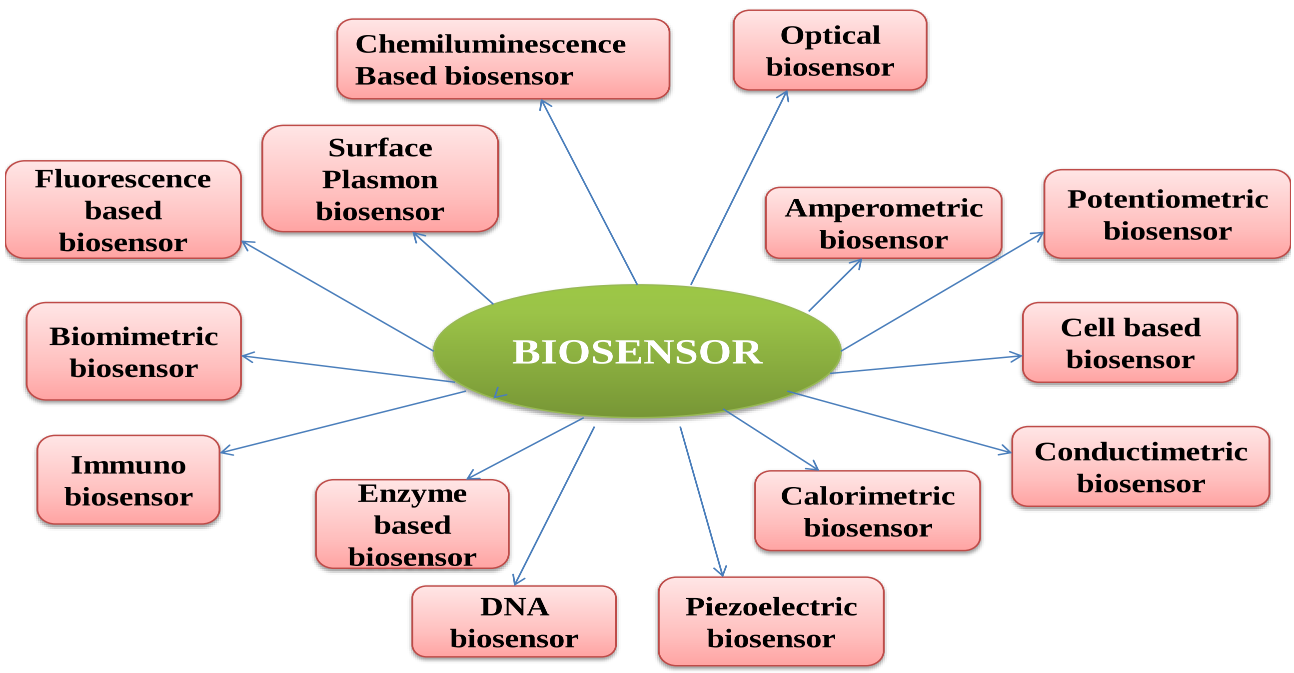

Fig -3 Classification of Biosensor

A schematic representation depicting the classification of biosensors finds application in different fields.

Optical biosensor

In this type of biosensor, the optical fibers permit recognition of analyte on the origin of absorption, fluorescence, or light distribution. At this point, both catalytic and affinity reactions can be measured.[9] These biosensors contain a light source and in addition, various optical segments to generate a light bar with particular qualities and to shortcut this light to a balancing operator, an adjusted detecting head alongside a photodetector.[10]

It mainly involves antibodies and enzymes like the transducing elements and these are classified into two types that are direct optical detection biosensors and labeled optical detection biosensors. Optical techniques like SPR (Surface Plasmon Resonance) and ellipsometry for the detection of bacterial pathogens are used by researchers.[11]

Amperometric biosensor

These types of biosensors measure either the current or potential resulting from a chemical reaction of electroactive materials on the transducer surface whereas an invariable potential or current, respectively, is applied. The change in current is linked to the concentration of the target species.[12]

Potentiometric biosensor

These types of biosensors have the potential to advance the detection of numerous biological compounds and assist in the timely diagnosis of various diseases and belong to the convenient analytical class of biosensors for monitoring biomarkers in the human body. They contain ion-sensitive membrane sensors which can be used to find out potassium, sodium, and chloride ions activity while being used as a biomarker to gauge human health. The Potentiometric-based ion-sensitive membrane systems can be joined with various techniques to make a sensitive device for the fast and early detection of cancer biomarkers and other critical biological compounds.[13]

Cell-based biosensor

The Cell-based sensor is the kind of biosensor, which consumes a living cell as the biospecific detecting element and depends on the ability of the living cell to identify the intracellular and extracellular microenvironment state, physiological parameter, and produces reaction during the collaboration between jolt and cell.[10]

Even though entire-cell-based biosensors are not as susceptible to environmental changes as molecular-based ones, cell-based sensing platforms are individually competent in providing functional information associated to sample toxicity or pharmacology by using the cell physiology appraisal, so becoming an important enabling resource for biological research and the pharmaceutical industry. Consequently, their applicative potentials become paramount in environmental and biomedical analysis and their developments are always in the spotlight.[14]

Conductimetric biosensor

This type of biosensors has vital advantages: they do not require the use of a reference electrode: they work at low-amplitude alternating voltage, therefore preventing Faraday processes on electrodes: they are insensible to light: and they can be miniaturized and integrated simply using a cheap thin-film standard technology.[15]

Calorimetric biosensor

These biosensors measure the change in temperature of the solution containing the analyte following enzyme action and interpret it in terms of the analyte concentration in the solution.

It is based on bioanalytical calorimetry rest upon the fact that most of the biological reactions are exothermic. Mainly the reactions are connected with high molar enthalpy changes (20-100KJ per mol) in a single enzymatic step. An enzyme immobilized electrode coupled to a calorimetric appliance forms a thermometric sensor. These are simple to use procedure-wise, insensible to the optical properties of the sample, and acquire high specificity.[7, 16]

Piezoelectric biosensor

These types of biosensors are considered mass-based biosensors and it is based upon the principle of affinity interaction recording. It serves as an assembly of analytical devices. [17]

These biosensors also generate an electrical signal when a mechanical force is applied. In this method, sensing molecules are attached to a piezoelectric surface a mass-to-frequency transducer in which interactions between the analyte and the sensing molecules set up mechanical vibrations that can be translated into an electrical signal proportional to the amount of the analyte. An example of a piezoelectric sensor is quartz crystal micro or nano balance.[9]

DNA biosensor

This class of biosensors is used for DNA discovery and is also known as bio-detectors. The purpose is to segregate and determine the potency of single DNA–DNA or antibody-antigen bonds, which in turn helps in detecting and characterizing single molecules of DNA or antigen. It has been shown as a great potential candidate for the next-generation biomedical detection device due to its strong chemical properties and customizable biosensing functions. DNA-based biosensor provides advantages as compared to conventional biosensors, such as wider detection targets, a more long-lasting lifetime, and minor fabrication costs. Furthermore, the inspired DNA structures can manage signal conduction near the biosensor surface, which could drastically improve the presentation of biosensors.[18, 1]

Enzyme based biosensor

An enzyme biosensor is a systematic device that combines an enzyme with a transducer in a sort to generate a signal proportional to the target analyte concentration. As compared to the cell-based biosensor, these are more specific sensors. It more rapidly responds due to shorter diffusion paths and they are pricey to produce due to the problem of isolating the enzyme. A Glucose biosensor is typically used biosensor. This type of biosensor always attracts the concentration of researchers due to its fabulous potential for upcoming bioanalysis, high sensitivity, and specificity.[7, 19]

Immuno biosensor

Immuno-nanosensor is a type of biosensor to identify the development of an immunocomplex using an antibody or antigen as a bioreceptor with the help of nanomaterials. Several proteins such as a superior prostate-specific antigen, platelet-derived growth factor, carbohydrate antigen, interferon-γ, carcinoembryonic antigen, antigenic target 6-kDa protein, human chorionic gonadotropin, urinary lactoferrin, etc., have been created to correlate with the incidence of different diseases. These proteins can be quantitatively analyzed by immuno-nanosensors. [20]

Biomimetric biosensor

Biomimetic sensors are novel technology with the major purpose to accumulate data and methods. These sensors propose is to diagnose the patients, such as those who suffer from diabetes or neurological diseases, and signify a window for information development related to the human body and wits.[21]

Fluorescence biosensor

Currently, one of the most ordinary approaches in the field of optical biosensors is to join the high sensitivity of fluorescence identification in a mixture with the high selectivity provided by the ligand-binding proteins. [22] Furthermore, Fluorescence-based biosensors have been explored for various applications such as medical diagnostics, drug delivery, drug discovery, environmental monitoring, and food safety. Maintenance of the basic principles in analysis, different working strategies can be planned for fluorescence biosensors to identify different analytes. Various parameters can be explored in fluorescence biosensors, for example, fluorescence anisotropy, decay time, energy transfer (radioactive or non-radioactive), quenching efficiency, fluorescence intensity, and quantum yield. [23]

Surface Plasmon biosensor

These instruments are able of characterizing binding reactions in real-time devoid of labeling necessities. The SPR (Surface Plasmon Resonance) technique is based on the optical measurement of refractive index changes linked with the binding of analyte molecules in a sample to identify molecules immobilized on the SPR sensor.[24] Consequently, SPR biosensors have the chief device for the study of interactions of several biological systems from proteins, oligonucleotides, oligosaccharides, and lipids to small molecules, phages, viral particles, and cells in life science and pharmaceutical research.[25, 26]

Chemiluminescence based biosensor

Luminescence is the emanation of light from an electronically energized compound returning to the ground state. The source of excitation energy serves as a basis for the classification of the various types of luminescence. Chemiluminescence occurs in the path of some chemical reactions when an electronically excited state is created. Bioluminescence is a particular case of Chemiluminescence occurring in some living organisms and involves a protein, normally an enzyme.[27, 28]

Applications of biosensor

A Biosensor is a diagnostic tool for the detection of an analyte that combines a biological element with a physio-chemical detector element. Consequently, the applications of biosensors are in an extensive variety. This comprises of drug discovery, pathogen detection, disease discovery, environmental monitoring, food quality monitoring, and various more as delineated in Fig-4. A review of the few elected representatives and instances of developed applications of biosensors are described below in fig-4.[29, 30, 31, 32, 33]

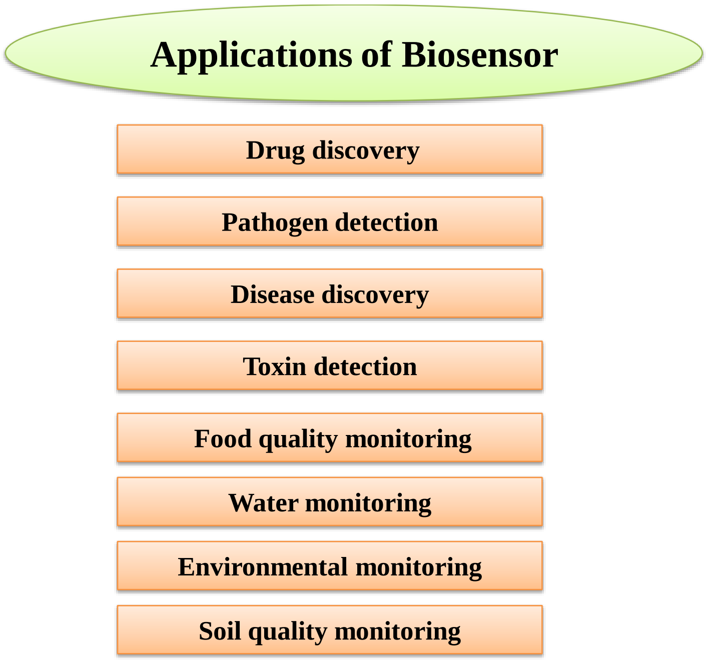

Fig-4 Various applications of Biosensor

Illustration of Major areas of applications for biosensors in fig-4

Drug discovery

Different biosensors based on the cells, enzymes, antibodies, synthetic membranes, and whole animal tissues can be engaged in drug development and could lead to new proficient screening systems in the future. The main purpose of biosensors is to detect drug compounds can be considered an essential element of medical progress and testing. Curiosity in biosensor research is determined by the increasing requirement for specific sensors to facilitate fast routine measurements in many fields of analysis. A quite high number of newly developed biosensors are capable of detecting several hundreds of analytes, for example- sugars, enzyme cofactors, and amino acids, which are important for biological systems.

Electrical devices such as electrodes, semiconductors, and optical components are frequently used as transducer elements of biosensors. Few of these have been miniaturized to obtain chip-based sensory systems. These approaches in particular may succeed in drug screening because they allow a high throughput of samples with practical experimental apparatus.[34]

Modern attempts and strategies are described and precious approaches are summarized in Table 1.

Table 1: Current examples of bioactive compounds detectable by optical, whole cell, and enzymatic biosensors.

Objective	Principle of sensor
Optical sensors	
-DNA-binding compounds	DNA, SPA[35]
-Thrombin inhibitors	Thrombin inhibitors, RIfS[36]
-Estrogens	Estrogen receptor, SPR[37]
-HIV protease inhibitors	HIV protease, SPR[38]
Electrodes based Enzymatic sensors	
-Cysteine sulfoxides	Potentiometry with alliinase[39]
-Antibiotics (penicillin)	Electrolyte-insulator-semiconductor, penicillinase H^+ISFET, penicillin acylase[40]
-Cyanogenic glycosides	Potentiometry with cyanides[41]
-Polyphenols	Amperometry with tyrosinase[42]
-Flavonols	Amperometry with polyphenol oxidase[43]
Animal tissues, membrane constituents, and Whole-cell systems.	
-Local anesthetics	Crayfish walking leg, electrode[44]
-Saponins	Endothelial cells, microphysiometer[45]
-G protein-coupled receptors	Confocal microscopy[46]
-Glycine receptor blocker	Neuron, micro-contact array[47]
-T lymphocyte activators	Intracellular fluorescence, the silicon support[48]
- Neurotransmitter antagonists	Rat brain interneurons, patch clamp detection[49]

Pathogen detection

Pathogens are transmittable agents that cause disease. They include molecular-scale infectious agents, such as viruses, prions, and microorganisms, such as fungi, protozoans, and bacteria. Airborne, waterborne, and foodborne pathogens penetrate the body during different modes of infection and are responsible for millions of deaths annually worldwide. Some of the mainly general pathogens comprise viruses, such as influenza virus, norovirus, and bacteria, such as *E. coli* and *S. aureus*. Pathogens vary in various regards, such as virulence, contagiousness, mode of transmission, and infectious dose. For instance, the world is presently facing a global pandemic related to the COVID-19 virus, for which virulence and infectious dose statistics are still rising. Methodologies for susceptible and quick detection of pathogens in intricate matrices, such as body fluids and aerosols, and on surfaces are critical to the healing of infectious diseases and controlling the growth of the disease.

The methodology used to recognize and enumerate pathogens can be broadly illustrious as immunoassays or DNA-based assays. The use of DNA-based assays, as opposed to immunoassays, depends on different factors, including the period of infection and the accessibility of antibodies and DNA sequence data, such as toxin-producing genes, and viral DNA, in addition to species and strain-selective genes. Immunoassays are omnipresent across medical diagnostics and food protection applications. Pathogens can be recognized during the presence of generated antibodies in an organism, which may be present both during and after infection. In such assays, both the biorecognition element and the target are antibodies. If antibodies are accessible for the pathogen (*e.g.,* anti-*E.coli*), one can also directly identify the pathogen using immunoassays.

Pathogen detection via electrochemical biosensor -An electrochemical sensor is an appliance that transforms chemical information into an analytically valuable signal, for instance, the concentration of a particular sample component or total compositional analysis. The electrochemical technique utilized is a distinctive facet of an electrochemical biosensor. Additionally to the electrochemical process, the sample handling approach and sensor signal readout system also give distinguishing aspects of a biosensor-based approach for pathogen detection.[50, 51]

Disease detection

In the medical field, biosensors can be used for the discovery and identification of tumors and the measurement of blood glucose concentration in diabetic patients. An extremely useful application of biosensors is the quantitative measurement of the cardiac marker in serum (undiluted), immune-sensor for detection of leukemias, and most latest is quick detection of cancer markers by incorporation of the biochip. The diamond micro-needle electrode is another innovation used for neuro-chemical discovery.

Techniques comprise immunoaffinity column assay, fluorometric, and enzyme-linked immunosorbent assay used for the detection of cardiovascular disease. These are difficult, time-consuming, and necessitate qualified employees. Biosensors recognized on electric measurement employ biochemical molecular identification for the preferred selectivity with a particular biomarker of curiosity.

Furthermore, the rapid spread of the new severe acute respiratory syndrome coronavirus disease, COVID-19, brought major societal challenges. Significantly, appropriate medical analysis procedures and clinical administration of the disease are developing needs, which must be anchored on novel investigative techniques and devices. New molecular analytical devices relying on nucleic acid augmentation testing have emerged worldwide and are the recent gold standard in COVID-19 identification. However, the necessity for widespread testing methodologies for quick, valuable testing in numerous epidemiological scenarios remains a vital step in the battle against the COVID-19 epidemic. Paper and cellulose-based biosensors can be predominantly related in the pandemic period, for renewability, secure environmental disposal, and the possibility of mass fabrication with sustainable methodologies. [52, 53, 54, 32]

Future aspects

The biosensor is a very essential and promising technique. In the future, these techniques will investigate the developing variety of choices to create precision drugs, instruments, and diagnostics. Biosensor chip technology could be inserted into the body to identify complex blood DNA mutations before any disease signs in the early stages of development. A Biosensor can also be used for constant tracking of implantable equipment. It can observe samples, such as salivary, exhaled condensate breath, minimally invasively in blood and interstitial fluid, using intelligent wristbands when they are fixed into wearable systems. The most important key to the enlargement of a successful biosensor involves a better combination of bio-sensing and bio-fabrication with synthetic biological approaches using either electrochemical or bio-electronic principles. Incessantly, research will be helpful to overcome all challenges with the use of biosensors in cancer. Furthermore, various biosensors used for different kinds of purposes like nanomaterial-based biosensors, optical biosensors, DNA-based biosensors, electrochemical biosensors, etc, show great attractive prospects, which will be mostly applied in food analysis, clinical diagnosis, process control, pathogen detection, drug discovery and environmental monitoring in the future, etc. [55, 56, 57]

Discussion and Conclusion

In this review paper, we have chiefly focused on various applications of biosensors in detail. First and foremost, we have studied the introduction and basic components of a biosensor and afterward reviewed different types of biosensors, their working, principles, and in brief applications of various biosensors are described. Mainly commercial biosensors developed to date are required to focus on clinical applications. An accurate investigation or diagnosis of a disease is necessary for a successful treatment and improvement of patients suffering from it. Diagnostics techniques must be easy, susceptible, and capable to identify numerous biomarkers that exist at low concentrations in biological fluids. Biosensors can accomplish these necessities.

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