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REVIEW ARTICLE

BIOSENSORS: TYPES, APPLICATIONS, AND FUTURE ADVANTAGES

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ABSTRACT

With the developing technology and increasing population, nanotechnology has started to be used in all areas of life. The use of biosensors, which have an important place in the field of nanotechnology, is increasing day by day. Biosensors can be defined as biological devices that help us interpret the analyte concentration in a sample by converting it into measurable signals. Advantageously, it has both speed and high precision. There are many types of biosensors used in many fields. These; enzymatic, nucleic acid, electrochemical and optical biosensors. All of them can have different components and uses. Biosensors are used especially in early diagnosis of diseases, environment and agriculture, pharmaceutical industry, defense industry and food industry. For example, biosensors are used in the treatment of oncological diseases using electrochemical impedance spectroscopy, in the determination of pesticides, which is one of the environmental pollutants, in the potentiometric analysis of glutamate, in the detection of chemical warfare agents and toxic substances. In addition, it is expected that the usage areas of biosensors will become widespread in the future, and they will be used more widely in the early diagnosis of diseases. At this point, the use of biosensors has increased worldwide and has attracted the attention of scientists. In this study, classification of biosensors, application areas, characterization, studies on biosensors, technologies developed and applied for the future are mentioned.

Keywords: *Biosensor, Biosensor Types, Biosensor Applications, Biosensor Characterization, Biosensor Advantages.*

1. INTRODUCTION

Nanotechnology plays an important role in the use of devices in the processing of materials with dimensions less than 10 nanometers [1]. The suffix nano in the word nanotechnology derives from the Greek word "dwarf" and combines with the word technology to form nanotechnology [2]. The word nanotechnology was first used by Japanese researcher Norio Taguchi in 1974, approximately 50 years ago [3]. After the 2000s, nanotechnology has shown rapid developments in the field of biosensors and the use of biosensors has become widespread at this point [4]. Sensors can be used in all areas of technology now and have features that can be used in many devices. For example, there are sensors in the use of many large or small devices such as computers, refrigerators, and television remotes [5]. Sensors are devices that help detect physical and electrical changes such as pressure, temperature, humidity, motion, and force used to detect the content in a sample [3,6]. In a sensor, features such as sensitivity, selectivity, high resolution, repeatability, and response time are sought [5,7]. Biosensors can detect even low concentrations of certain pathogens and chemicals of various shapes or sizes [8]. The importance of size and shape for the analyte to recognize the substrate is shown in Figure 1.

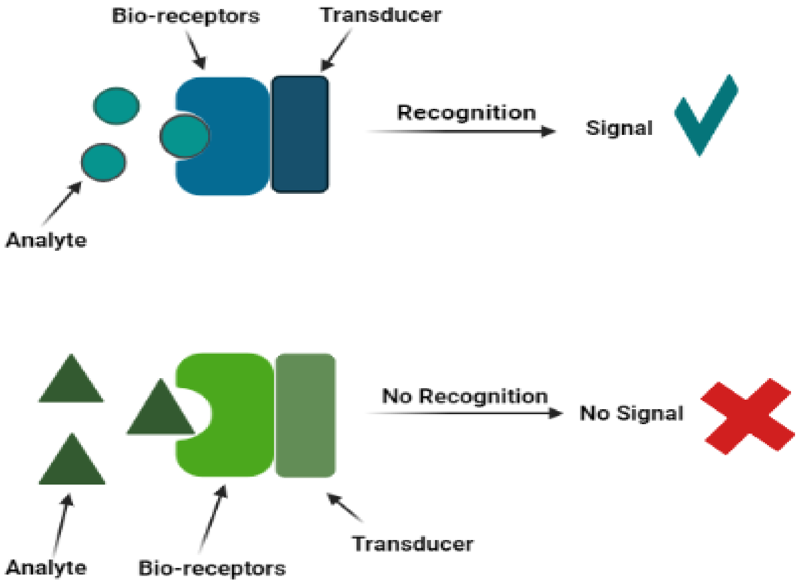

Figure 1. Importance of size and shape for the analyte to recognize the substrate [9].

The sensors consist of 3 main parts. These are defined as a receiver, converters, and reading systems [10,11]. In addition, a biosensor generally consists of the analyte, bioreceptor, transducer, electronics, and display parts [12], and biosensor components are shown in Figure 2. The analyte identifies the components as the detected substance, is detected by receptors, and converted into electrical signals [13]. A bioreceptor can be defined as a molecule or element that can detect the target substrate. Examples of these are DNA, RNA, enzymes, and antibodies [14,15]. Enzymes are one of the most widely used types of bioreceptors in the field of biosensors. They come first because they are natural proteins and can convert the substrate [16] molecule into a product without being consumed because of the reaction [11]. They are also highly selective, sensitive, and fast compared to other chemical reactions [17]. The transducer is very important for a biosensor. Devices that convert the detection or recognition event into a signal by establishing a connection in the presence of a chemical or a target [18,19]. Energy conversion is called signaling [12,20]. Transducers can be classified as optical, thermal, electronic, gravimetric, and electrochemical [15]. Electronic systems are intermediate devices that transform the signals produced by the converter into a larger signal and transfer it to the screen [21,22]. On the other hand, the screen is the digital medium provided for reading and interpreting digital, graphical, and tabular signals [12].

Figure 2. Components of a biosensor [23].

Some biosensor enhancements are being made for future work [24]. The first is to develop a sensitive biosensor [25]. A sensitive biosensor not only measures the analyte concentration; It also changes its configuration to improve its sensitivity, selectivity, and performance [26]. The second work is to develop a hybrid biosensor. The goal here is to develop a type of biosensor that combines engineering, and biological materials to create a more sensitive sensor [27]. The third is to develop in-body biosensors. The aim here is to develop nano electronic brain and body sensors that can be injected intravenously and implanted into the body to continuously monitor and record physiological variables [22,28].

In addition, nanomaterials have an important place in the creation of biosensors and in making them usable in application areas. These materials allow biosensors to work more efficiently. For example, in a study for the determination of ferritin, it was observed that using graphene as a nanomaterial maximized activity [29]. In addition, graphene appears to be used in different applications such as DNA damage detection [30]. At the same time, nanomaterials; are dopamine, ascorbic acid, uric acid, glucose, toxic substances, etc. It is seen that it is used extensively in biosensor applications by being used in many material determinations [31,32]. At this point, many studies and research are carried out today [33]. This review mentions many important issues such as biosensor types, working principles, application areas, characterization methods of biosensors, studies on biosensors, and future advantages.

2. TYPES OF BİOSENSORS

Today, because of developments in biological and nanoscience applications, biosensors are gaining more efficient performance features and developing by integrating innovations in many subjects. Biosensors are generally called bioanalytical devices, which are developed with the knowledge of various scientific fields such as physics, chemistry, biochemistry, biology, and engineering, using multidisciplinary methods, together with biological molecules, with the selectivity properties of systems and electronic technical process capabilities [34]. The diversity of biosensors enables them to be used and developed in many areas. At the same time, many analytes and receptors can be used in the creation of biosensors. For example, carbohydrates and nucleic acids are also used in different fields such as gene ring analyzes and cell surface characterizations. Biosensor classification takes place depending on the relationship that develops between transmission and measurement systems. For example, classified by bioreceptor domain (antibody/antigen interaction, nucleic acid interaction, cellular interaction, enzymatic interactions, biomimetic material interactions) or transducer type (electrochemical measurements, optical measurements, mass sensitivity measurements) [34]. Transducers are structures that measure the biological reactions elicited by the receptors and convert them into a physical signal. Detection of physical and chemical change is measured after the recognition of the analyte and transferred to digital signals. Transducer selection is made by considering biochemical reactions. Devices in the structure of biosensors (transducers) that convert one form of energy into another form of energy, electrochemical (with voltammetry, amperometry, capacitive, potentiometric, conductive, impedance ones), optical (chemical luminescence, surface plasmon resonance, absorption, fluorescence, biological luminescence, optical fiber) ones) exhibit piezoelectric (surface sound wave, quartz crystal microbalance) magnetic and calorimetric properties [35]. Biosensors are classified under two main headings according to their working principles, physical transducers, and biocomponents.

2.1. Classification of Biosensors by Biocomponent

Among the various designs of biosensors, biocomponents such as nucleic acids, enzymes, antibodies, microorganisms, tissue, and organelles are used [36]. At the same time, the transducing elements are divided into three groups. These are electrochemical biosensors, optical and mass-based, respectively. The classes mentioned are explained below. [37–39].The classification of biosensors is shown in Figure 3.

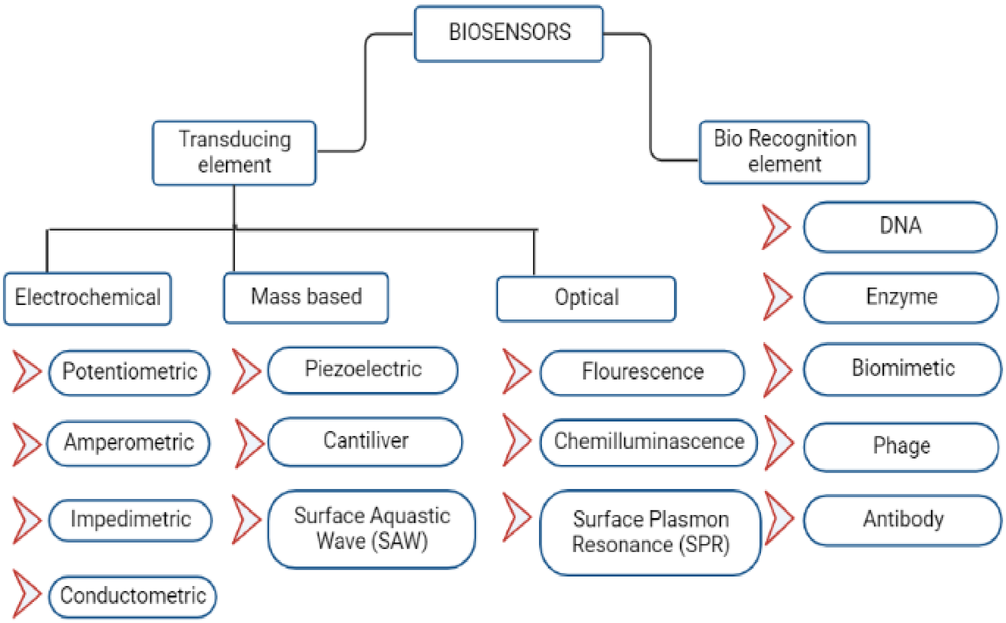

Figure 3. Classification of biosensors [40].

2.2. Enzyme Biosensors

Enzyme biosensors are one of the main sensors in which enzymes are used as biocomponents ed by comparing them with each other [41][42][43]. Enzymes are generally protein biomolecules with catalytic functions. During the catalytic reaction, by forming an enzyme-substrate complex, the product formed because of the reaction provides signals that can be indirectly measured by the biosensor [44]. Many enzyme-based biosensors use oxidoreductases as enzymes [45]. After the invention of the enzyme electrode, enzyme-based biosensors have attracted increasing attention due to a variety of potential applications [43]. The concept of an enzyme-based biosensor is generally based on placing the enzyme near the sensor surface. In enzymatic-based biosensors, the concentration of the substrate is determined by the enzymatic reactions on the sensor surface. It occurs through two reaction processes, enzymatic conversion in the substrate and diffusion in the enzyme layer of the product [45]. According to these two reactions, enzyme-based biosensors; It is an important technique used in the quantitative and qualitative analysis of various target analytes in the environment, biomedicine, food quality control, agriculture, and pharmaceutical industries. In addition, there are 4 types of enzyme-based biosensors used commercially and practically. These; are lactate (intensive care, food, biotechnology, sports medicine), glucose (food science, diagnosis, and treatment of diabetes, food science, biotechnology) glutamate/glutamine (food, biotechnology), and urea (clinical applications) [46,47]. Since enzymes show stability in properties such as temperature, pH, and ionic strength, their use in biosensors is limited. Therefore, while designing enzyme-based biosensors, it is tried to provide a suitable environment for enzymes to continue their activities. Enzyme-based biosensors generally consist of three components: biological recognition element, transducer, and signal processing signals. When these components are connected; the enzyme functions as recognition and is immobilized in the matrix on the transducer surface to maintain enzyme activity. The presence of certain analytes is determined by measuring factors such as detection principle, proton concentration (H^+), gas release or uptake (CO_2, NH_3, etc.), and light emission. The transducer then converts these changes into relevant measurable signals (electrical, thermal, or optical signals) that are used to identify the presence of relevant analytes.

2.3. Microbial Biosensors

They are biosensors in which microorganisms are used as biocomponents in biosensor design. Microorganisms as biological sensors have extensive advantages in chemical substance detection. Also, enzymes that are most used in the production of biosensors are structures with high sensitivity. Purification processes for enzymes are costly, tedious, and time-consuming. Microorganisms offer an ideal alternative to these problems [48]. In addition, the use of microorganisms also has disadvantages. Since the cell membrane structure creates a diffusion barrier, suitable biosensors cannot be prepared for molecules and macromolecules that cannot pass through the membrane[49]. Compared to enzyme sensors, the response time of microbial biosensors and the time to return to the basic signal point after use are quite long. Contamination and decreased activity during immobilization are among the most important problems.

2.4. Nucleic Acid Biosensors

In the use of biosensors, they are biosensors in which nucleic acids are used as biocomponents. Research on the use of various nucleic acids as a recognition surface area in biosensors designed for quantitative and qualitative analysis of DNA in this type of biosensor has become the focus of attention [50], [51], [52]. Biosensors with nucleic acid recognition surfaces can be used for various purposes such as revealing the interaction mechanism of the analyte (drugs, carcinogens, etc.) interacting with this surface, quantifying the studied substance, and monitoring hybridization events in some regions of the DNA base sequence [53].

2.5. Immunosensors

They are biosensors in which antibodies are used as a biocomponent in biosensor design. Glycoproteins produced by the immune system are called antibodies. This biosensor is prepared based on antibody-antigen interaction [54]. It is important to be able to directly examine antibody-antigen interactions. There are various immunosensor to study this interaction. One of them is impedimetric immunosensors [55]. Apart from this, immobilized antigens in different formats of electrochemical immunosensors are important in the effective use of antibodies [56].

2.6. Lactate Biosensors

Lactate is an essential key metabolite in the anaerobic metabolism pathway. Since the energy demand of the tissues is not sufficient with aerobic respiration, an increase in lactate concentration in anaerobic metabolism occurs [45], [57]. Lactic acid has mirror images, and they are divided into two L (+) and D (-). In mammalian metabolism, L (+) lactate is an intermediate, and D (-) lactate is generally produced by microorganisms, algae, and plants; but its use by humans is limited. Some microorganisms, for example, lactic acid bacteria form in both mirror images as a racemic mixture [58], [65]. It is widely used in electrochemical biosensors due to its low cost, excellent sensitivity, ease of use, and high selectivity, which are the most important factors in the determination of lactic acid. Among the enzyme-based lactate biosensors, the most widely used biosensors are lactate oxidase (LOD) and lactate dehydrogenase (LDH) based biosensors, due to the ease of enzymatic reactions and design. [59][60] [61].

3. CLASSIFICATION OF BIOSENSORS BY CONVERSION MEANS

Biosensors can be divided into three groups as conversion tools. These; It is an electrochemical biosensor, mass-based biosensors, and optical biosensors. In general, general information about electrochemical biosensors is given later in this review. In addition, the thermal biosensor, which is the subtitle of the electrochemical biosensor, and the piezoelectricity, which is one of the mass-based biosensors, are explained [62].

3.1. Electrochemical Biosensors

Electrochemical biosensors find a wide range of applications in terms of being portable, highly sensitive, simple, short-response, selective, inexpensive, and specific. Elements widely used in the design of electrochemical biosensors; electrodes made of silver, gold, carbon, or platinum [63]. Electrochemical biosensors are obtained because of the conversion of chemical change into electrical signals in proportion to its concentration [64]. As seen in Figure 4, in the electrochemical biosensor, the biological component recognizes the analyte, resulting in a binding event that produces an electrical signal that is monitored by a transducer proportional to its analytical concentration. Some of these sensor devices have reached the commercial stage and are frequently used in clinical, industrial, environmental, and agricultural applications [65]. Electrochemical biosensors play an important role in the transition of diagnostic devices to the present day. These various electrical devices are highly suitable for connecting to compact analyzers to provide diagnostic information simply, quickly, and cost-effectively. The remarkable properties of electrochemical devices show great promise for increasing the monitoring efficiency in cancer diagnosis and treatment [66].

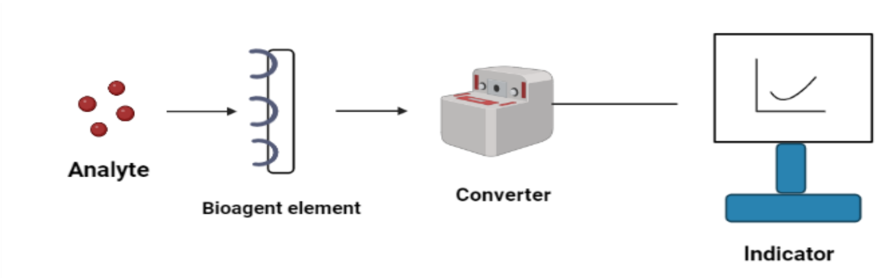

Figure 4. The general structure of electrochemical biosensors [67].

It can be defined as the current released by the electrochemical oxidation or reduction of an electroactive species. The resulting current is directly related to the concentration of electroactive species or the rate of mass production or consumption within the adjacent biocatalytic layer [68]. Potentiometry is generally based on measuring the potential difference between the working electrode and the reference electrode. The analyte concentration is one of the factors affecting the obtained potential difference. Among the transducer recognition elements can be an ion-selective electrode (ISE), an electrochemical sensor based on thin films, or selective membranes [69]. The most used potentiometric devices are pH electrodes, as well as (F, CN^-, Ca^{+2}, K^+, Na^+, NH^{4+}) or gas (CO_2, NH_3) selective electrodes [70]. Conductometric biosensors are used to determine the air humidity and the concentration of certain gases. The advantages of conductometric biosensors are that they do not use reference electrodes during analysis, operate at low voltage, and are insensitive to light. Conductometric biosensors have less application area than other sensors [71].

3.2. Optical Biosensors

It has been developed by taking advantage of the absorption of light, refraction of light, the reflection of light, scattering of light, or brightness of light as a transducer type. In optical biosensor studies, the reference electrode is not used [72].Today, optical biosensors, which are powerful detection and analysis devices in optical biosensors, have wide application areas in biomedical research, national security, environmental monitoring, medical products, and war. They can perform multiple and remote sensing in a single device. In addition, they are not affected by electromagnetic interference [73]. Among the advantages of optical biosensors, are signal or magnetic interference to be more resistant, fast, and high information content. Optical transducers: can detect changes such as light scattering, refractive index, absorbance, chemiluminescence, and fluorescence/phosphorescence [74]. In general, detection protocols can be divided into two, these are fluorescent-based and label-free detection. In fluorescence-based detection, both the target molecule and the bio-identifying molecular dyes are labeled with a fluorescent label. In label-free detection, target molecules are not affected in any way, and besides, they cannot be changed, they are determined only in their natural forms. This type of determination is not only easy and inexpensive but also facilitates the quantitative and kinetic measurement of molecular interactions [73],[74]. As an optical technique, surface plasmon resonance (SPR) is the technique used in the field of chemical sensing. SRP, which can be applied for biomolecular interaction analysis, is a phenomenon that occurs during the optical illumination of the metal surface [75].

3.3. Piezoelectric Biosensors

As a piezoelectric effect mechanism, it means that it generates a voltage because of a stretched surface. As a result of the change in the voltage sent to the surface of a piezoelectric material, oscillation or mechanical stress occurs and this change is proportional to the mass. There are many application areas in the design of analytical sensors 75]. Biosensors with piezoelectric transducers are also used to measure changes in viscosity, mass, or density on the sensor surface [76]. The piezoelectric crystal, which is used to take advantage of the piezoelectric effect, is coated with high-selectivity compounds with biological materials with enzymes or antibodies [77]. Piezoelectric transducers are used practically in immune applications, and in the fields of immune identification. Among the advantages of using this type of converter are it has tag-free identification, real-time tracking, and ease of use. However, the lack of sensitivity and specific features need to be eliminated. Also, piezoelectric biosensors have calibration and format problems [78][79].

3.4. Thermal Biosensors

Thermometric measurements are concerned with the measurement of heat absorbed during a biochemical reaction. Thermal biosensors take advantage of the fundamental properties of biological reactions such as heat absorption and heat release [58]. Thermal biosensors have been developed by combining a biomaterial, also called a calorimetric biosensor, with a physical transducer such as a thermometer. The use of thermal-based calorimetric biosensors is used to measure various conditions such as clinical monitoring, anhydrous environment measurements, and enzyme activity measurements by following the temperature changes [80]. In addition, thermal transducers have also been used in the determination of antibody-antigen interactions, and this technique is called the Thermometric Elisa Test. However, expensive instrumentation is among the disadvantages of this technique .

4. APPLICATION AREAS OF BIOSENSORS

The first biosensor is L.C. It was used by Clark in 1950 to measure the amount of glucose in the blood [81]. Today, studies on biosensors continue to gain importance considering the results obtained in recent years [59]. Because the working discipline of biosensors has a wide range. In general, the amount of glucose is used for the detection of drugs, viruses, diseases, etc. Its use continues to be widespread in many application areas [60]. In addition to these, it also operates in areas such as medicine, food, pharmacy, quality control, industry, animal husbandry, environmental pollution, waste control, and military applications [61]. In addition to these, the possible application areas of biosensors are as follows. Bacterial and viral diagnosis, Process control, Industrial wastewater control, Toxic gas analysis in mines and enterprises, Biomedical, Field agriculture, Vineyard-garden agriculture, Veterinary, etc. Although 25 biosensors have been used commercially so far, biosensors have been prepared for many more different substances. Although this number is not clear, it is known as more than 180 [82]. From these applications, biosensors have been used by utilizing silver nanoparticles in bacterial viral diagnosis [83]Figure 5 shows the application areas of biosensors.

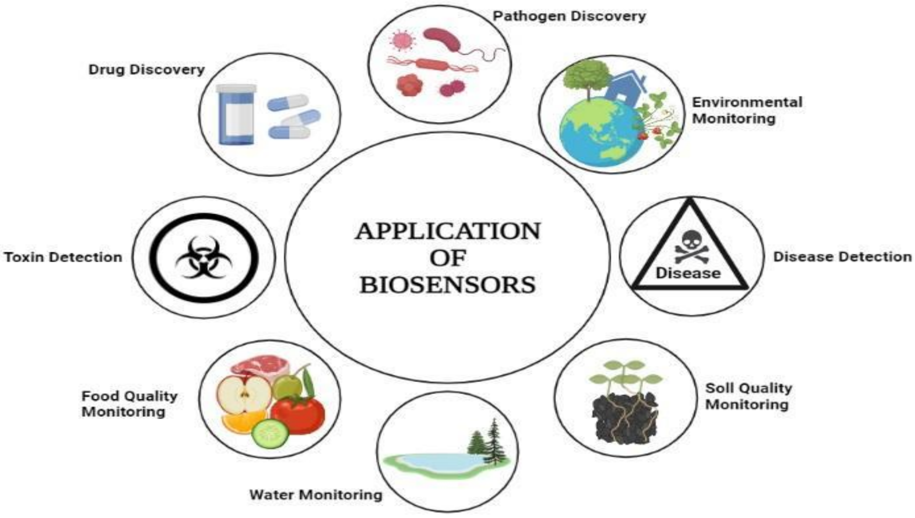

Figure 5. Application Areas of Biosensors [84].

4.1. Use of Biosensors in Medicine

Biosensors with high reaction specificity characteristics are suitable for use in the medical field [85]. Biosensors are most used in the medical field as an application. For example, in blood, it is used in many biological determinations. The glucose oxidase biosensor is known as the first produced and most used commercial biosensor in this field. The glucose oxidase biosensor is manufactured for diabetics and its use is becoming widespread as it is possible and easy to use at home [61]. In addition, it is noteworthy that biological products such as urea and sugar in the body are monitored, and microbial agents are detected and used in the monitoring of cancers [59]. The determination of the increased PSA level in prostate cancer, which is common in men, is an example of the use of biosensors in this area [86]. Another type of biosensor that is most often used is the enzyme sensor.

Because high sensitivity in measurements, ease of installation, and application, are the excess of commercially suitable transducer types. [69], [72]. Microbial sensors are not used in biosensors in the medical field. Because these sensors work with biological fluids, these liquids, on the other hand, form the environment that allows microorganisms to reproduce [85]. There are also diagnostic areas that are of vital importance. These; in the measurement of toxic gas and atmospheric gas, the diagnosis of infectious diseases spreading in a certain area, the detection of dangerous substances and high-dose drugs in the body, in determining the density of continuously used drugs in the blood, it is used in intensive care units and to determine the instantaneous drug density in the blood before critical surgeries [61]. In the medical field, when it comes to drugs, biocompatibility is the sought-after and most important parameter [82,87].

4.2. Use in the Field of Agriculture and Environmental Protection

Biosensors are also used in the diagnosis of pesticides, bad odors, artificial fertilizers, and plant-animal diseases in the field of agriculture. It is known that it is also used to understand the level of heavy metals and pesticides in soil and groundwater, and to determine the occurrence of soil diseases that cannot be resolved Another use is the rapid detection of plant diseases, especially bacteria and viruses, and used in agriculture and dairy technology. It is a reliable and fast option for the determination of lactose in milk [86]. Especially in cities, its use in the control of environmental pollution and quality monitoring, and its use in the control of microorganisms and toxins is observed. At the same time, it is used in the measurement of organic impurities in water in[85]. Chemical analyzes and eco-toxicological tests are usually used to clean nature that has been polluted for various reasons. However, these tests take a long time due to some steps. At this point, by applying biosensors, chemical information is obtained without processing the sample completely, and the process is accelerated and shortened [88].

4.3. Use in the Field of Food

Biosensors are used in determining food quality, determining basic nutritional components in foods, determining parameters such as aroma and freshness in the detection of mutagens, allergens, and mycotoxins, residue analysis of agricultural drugs, and determining the level of additives in food, etc. it shows usage in many fields [86]. It is also used to determine the physical properties of foods, the chemical components found in foods, and the amount of harmful microorganisms [89].

4.4. Use in the Defense Industry

Biological weapons are the weapons that cause the greatest danger of mass destruction. In biological attacks, it is very important to determine the danger in advance and develop methods to deal with possible problems. The use of biosensors is the most preferred method at this point. The reason for the preference is that biosensors provide fast, reliable, and accurate results [85]. Biological weapons are a way that can be used against the state, as they can create a wide fuss and trouble for terrorists [88]. According to studies conducted in previous years, calculating the cost of damage that will occur in a biological attack on the United States is an example of the use of biosensors in this area [86]. Due to the recent increase in bioterrorism and the spread of diseases, biosensors have been used to identify infectious agents. These agents are various bacteria, viruses, fungi, protein poisons, etc. since it causes the reproduction of structures, biosensors come into play in their detection [88].

4.5. Its Use in the Medical Field and Drug Research

In studies aimed at monitoring chemical substances, it is necessary not only to detect carcinogenic and toxic substances but also to bioassays that can determine the bioavailability of these substances.

Biosensors meet this requirement [88]. There is more than one type of biosensor usage in drug determination. Electrochemical and optical biosensors are some of them. Optical biosensors take advantage of the selectivity arising from drug-protein and antigen-antibody interactions. In this way, it is used in complex drug analysis and in the determination of physiological parameters [88,89].

4.6. Why is Nanotechnology Used in Biosensors?

Nanotechnology, since it works with smaller-sized structures, it facilitates the provision of high precision. At the same time, the processing capabilities of biosensors increase when small particles are transferred. In this way, it shortens the analysis time of small molecules with complex structures. If the value obtained is high when the surface area is proportional to the volume, its selectivity increases. The energy required in the studies is low and there is no diffusion problem. In this way, the long life of the biosensors is ensured. It ensures the conclusion of the study without damaging the cells in the studies [90].

4.7. Biosensors and Biochip

In addition to the application areas of biosensors, biosensors and biochips have been developed in the field of nanomedicine and have been implemented to shorten the diagnostic time [69]. Recently, laboratories on the chip have been established and studies have been carried out on microsystems. With this improved technology, it is possible to examine all genomes on a chip whose interactions between many genes have been determined and these chips are described as miniaturized DNA biosensors [82]. Another example is glucose nano biosensors prepared with high sensitivity non-enzymatic using different metals. Another example is glucose nano biosensors prepared with high sensitivity non-enzymatically using different metals [91]

5. CHARACTERIZATION OF BIOSENSORS

Characterization methods serve the purpose of determining the behavior and characteristics of equipment [92]. After the immobilization values and working conditions of biosensors are adjusted, characterization studies are started because of various stages [93]. Characterization Work Steps: these can be listed as linear measurement range, repeatability, reproducibility electrochemical impedance characterization, and real sample trials [41].

5.1. Linear Measurement Range

After the working possibilities of the developed biosensor and the adjustment of the bioactive layer components, biosensors are prepared under minimum conditions [94]. A standard graph is obtained by determining the values of the various concentrations of the substance to be studied. The range in which linear increase is observed in graphic interpretation is determined as the measurement range [95].

5.2. Repeatability

In the optimum conditions revealed in the repeatability tests of the analysis results made with the biosensors created, new measurements are taken with the biosensor prepared in the concentration of many substances, for example, tributyltin. Repeatability is observed by calculating the variation coefficients and standard deviations of the values taken [94]. As a result of the measurements made, it is determined whether the standard deviation and variation coefficients calculated, and the biosensors are reusable [95]. The variation coefficient must be less than 5% to prove that the biosensor system is workable [58].

5.3. Reproducibility

Reproducibility trials are carried out to determine how different the results obtained during the preparation stages of biosensors are from each other. To determine the result of this, standard graphs are created by preparing a certain number of biosensors with the same composition under the same conditions. Linear determination ranges and R^2 values of these graphs are interpret[1]. The suffix nano in the word nanotec

5.4. Electrochemical Impedance Characterization (EIS)

This characterization method is carried out using EIS. This structure is a way to detect the surface sensitivities, and electrical resistance of systems, as well as differences in their quantity [93]. Recently, it has been frequently preferred both in the observation of specific interactions of biomolecules and in the preparation stages of biosensors and quantitative analysis. EIS is an important and very helpful tool in illuminating surface morphology with imaging techniques [96].

5.5. Real Sample Trials

Biosensor systems produced because of the studies carried out are applied to real examples. As a result of this application, it provides commentary on whether the manufacturability and analysis repeatability of the biosensor assembly exists and the use of its properties in later studies [41].

5.6. The Used Techniques in Characterization Most

In characterization, Transmission Electron Microscope (TEM) is used to determine the properties of materials. X-ray Photoelectron Spectroscopy (XPS), Atomic Force Microscope (AFM), Scanning Tunneling Microscope (STM), X-Ray Diffraction (XRD), Water Contact Angle, and Environmental Scanning Electron Microscope (ESEM) analyses are frequently preferred. It is important to study the physical and chemical properties of materials. During the research, surface chemical analysis and surface hydrophobicity of the modified paper obtained in studies such as surface morphology, ESEM, XPS, water contact opener, and Washburn test are used to analyze the intracellular behavior of channels [92].

5.7. ESEM

Environmental scanning electron microscopy is called ESEM. ESEM has many features. these; the ability to condense and vaporize liquids are properties associated with the condensation, evaporation, and transport of water in carbon nanotubes [97]. ESEM is also used to view insulating samples without the need for prior sample preparation [98]. ESEM is a versatile device and is used in detailed material characterization. It is a very preferred powerful device due to its high sensitivity, resolution, and focuses features [99]. The first use of ESEM was used in 1960 as a tool for device studies and the importance of semiconductor materials. Today, it is used in many areas of science and technology. With the production of X-ray detectors, ESEM is making great progress [100]. ESEM is also used for imaging insulating samples without the need for prior sample preparation [98]ESEM has many features. These; the ability to condense and evaporate liquids are properties associated with condensation, evaporation, and transport of water in carbon nanotubes.

5.8. TEM

TEM is a characterization device used together with different techniques. It makes micro-examinations and illuminates the crystal structure. Attention is paid to the fine size of the substances to be analyzed in TEM characterization. The desired ideal fineness is sized samples with less than 50 nm [56].

5.9. XPS

The XPS device has high sensitivity. Thanks to this feature, it helps us learn about the content and structure of the materials [101]. It is a method of surface analysis. At the same time, information is obtained about the oxidation step and molecular structure of the elements with this method. This information is associated with the stimulation of electrons on the surface by the X-ray method and the photoelectric event.

5.10. AFM

Thanks to the AFM, surface images are obtained directly without the need for preliminary preparation. At the same time, surface roughness gives parameters numerically. Its nanometer-sized surfaces allow displaying its structure in three dimensions and high resolution [82].

5.11. Water Contact Angle

The angle formed between solid and liquid surfaces is called the angle of contact. The magnitude of this angle is related to adhesion and cohesion forces. This angle increases if the cohesion force is greater than the adhesion force. Surfaces with a contact angle less than 90^{o} are known as hydrophilic, and those larger than 90^{o} are known as hydrophobic surfaces [85].

5.12. STM

STM is used to examine the surfaces of samples that need to be investigated in atomic dimensions. STMs have many advantages because they are low-cost and small in size. The disadvantage is that it works at a low speed [100].

5.13. XRD

This method is used in powder and large-scale samples other than thin films. It works on the principle that the X-ray beam sent on the sample shows scattering and breaking at different angles. The purpose of use of this characterization method is to illuminate the chemical composition, and atomic and molecular structure of the crystal [86].

6. STUDIES ON THE BIOSENSOR

Nowadays, biosensors; It has begun to be researched and applied in many fields such as medicine, animal husbandry, agriculture, quality control, and military applications [102,103]. For this reason, scientists turned to biosensors, tools that provide cheap, small, fast, and sensitive data.[103]. If we look specifically at the studies on these sensors today, virus detection can be made using biosensors [88]. Electrochemiluminescence essence-based biosensors, which are strong in biosensing, were used to detect viruses [89]. In addition, affinity sensors, immunosensors, and genome sensors are used. According to another study besides virus testing, cancer detection can now be done with biosensors [90]. According to the studies of X. Wei et al., optical biosensors are used to detect cancer. The reason for using optical biosensors here is that it facilitates the diagnosis of cancer-causing substances such as deoxyribonucleic acid (DNA) proteins and tumor cells. In addition, another biosensor used as a cancer biomarker is the surface plasmon resonance biosensor [92]. Surface plasmon resonance biosensors, on the other hand, are preferred because of their high selectivity, and safety and are included in research topics [93] As noted in every article or review, biosensors have many uses. At the same time, studies and research continue for the development of biosensors. At this point, it is foreseen that faster and more sensitive determination can be made in the future.

7. FUTURE ADVANTAGES OF BIOSENSORS

Biosensors are the general name for tools developed to study the dynamic changes of biomolecules and bio-functions. Today, its use has become widespread in many fields. However, biosensors are tools developed in many fields that will be used not only for today's studies but also in the future [104]. In the future, there will be many applications with the following advantages of biosensor technology. These advantages are illustrated in Figure 6.

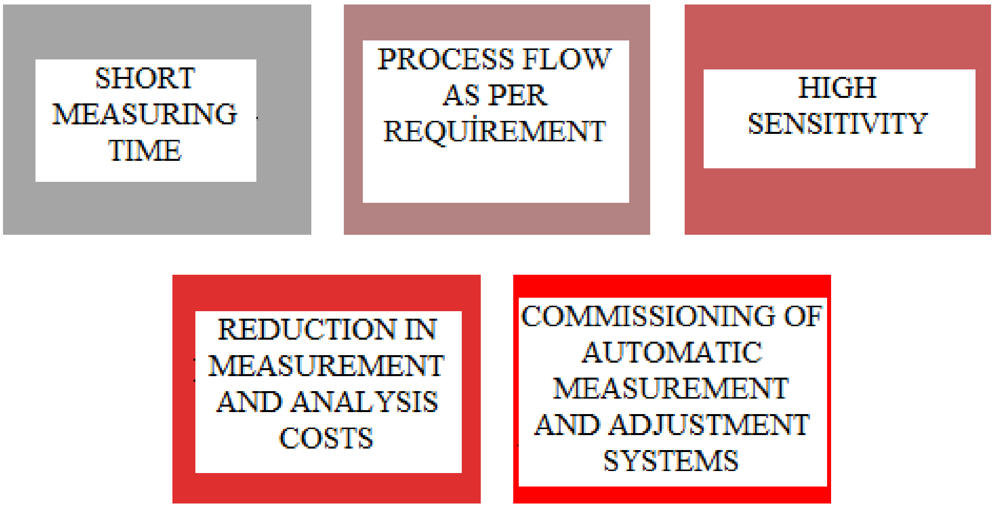

Figure 6. Biosensor usage advantages [101].

In addition, biosensors are promising biosensors because they give reliable results, provide practical and short-term results, are reusable, can be mass produced in a low-cost disposable way, give specific and reliable results, and do not require special experience during the use of these species. It clearly shows that there are sensors with the development of biochip technology, the application areas of biosensors will gain importance and increase their weight day by day [105]. Nanotechnology has also opened the horizons of biosensors and has given an advantage to various applications of biosensors in the future [101].

7.1. Future Advantages of Biosensors over Nanotechnology

The importance of nanotechnology will be understood more clearly as innovations and studies increase. Nanotechnology is revolutionary in many fields for the future. It is thought that biosensors, which are currently produced in the field of nanotechnology, will be developed, and will provide convenience and use in many areas in the future. Wall paints, germicidal filters, fungi, and bacteria-killing socks, and some of them in medicine can be given as examples [106]. At the same time, combining biosensors with nanotechnology will allow the development of faster and more sensitive methods in the future. We cannot have information about which viral or pathogenic microbial outbreaks await us in the future, but by improving the technologies we have, we can develop early methods of combating the problems that may occur in the future. For example, artificial intelligence and new detection methods, which can be used jointly with biosensors, provide convenience to prevent the uncontrolled spread of diseases and to keep them under control [107].

7.2. The Future Advantage of Biosensors in Healthcare

Biosensors are very common in medicine and have a very important place. The use of biosensors in the healthcare field is quite wide. For example, it detects glucose in blood and urine very quickly. It is used to monitor cholesterol levels and to evaluate muscle fatigue with acetylcholine electrodes. At the same time, it is thought that it will be of great benefit in elucidating structures such as antigen-antibody in the future [101]. Biosensors will facilitate detection in the early diagnosis and treatment of cancer in the future. Studies have been started for these applications, and the developed nano-devices are in the feasibility stage. Remote monitoring will be performed in patients without obvious signs of cancer. Thanks to this monitoring, the disease will be diagnosed at the earliest stage and intervention will be carried out [104]. Accordingly, in the future, biosensors in the form of chip applications can be used instead of expensive optical-based biosensors, offering point-of-care testing technology to cancer patients who hope for early diagnosis [105]. It is predicted that it will be soon to adjust and control the proportions of drugs in the body. Artificial pancreas studies are an example of this. It is the in vivo determination of low-concentration substances and short-lived hormones such as nitric oxide and superoxide [101]. In addition, the effects of drugs on the receptor, monitoring of bioprocesses at the nucleic acid level, and transmitter-receptor interaction are examples of important future studies of biosensors. Sequence recognition levels used in biosensor design will add new dimensions to known electrochemical levels and will play an important role in doctor-controlled analyzes in the future. Biosensors in which DNA is preferred as the recognition surface are called DNA biosensors [104]. The biosensors used today are larger and contain materials used only for in vitro diagnostics. Therefore, its sensitivity is low, and it is late to produce results. The emergence of bio-nanomaterials shows promise for the rapid detection of diseases and biomolecules due to their small size, large surface area, and intact stability. The amount of biocompatibility developed for these structures continues to increase day by day [108]. In the next 10 years, diagnostic devices that will be created with the development of biosensors will be put into use and the realization of thousands of measurements will become much faster and cheaper. The most widely used clinical diagnostic application will be the analysis of blood proteins, and the use of these devices is promising not only for the current period but also for the long term [110]. Nano diagnostics currently under development will help reduce test wait times soon [106]. In line with these considerations, it is expected that the urine results of people with infectious diseases come to the hospital, reach the doctors and a prescription is created quickly, thus reducing the cost of the process by shortening the patient's waiting time for results [108]. Considering the general characteristics of biosensors, project studies have been designed for convenience in the future. One of these works is the Japanese Nanorobot.

7.3. Japanese Nanorobot

The purpose of the development of this robot is to facilitate medical diagnosis and surgery. It is aimed for the robot to be in a size that can even fit inside a human hair and to be able to communicate with the special communication system to be created in this way. Today, project studies are carried out on nano-sized nanorobot technologies that will provide damaged organ repair by giving human blood. With the innovative developments in technology, robots that will assist doctors during surgery, as well as nurses and medical robots that will assist caregivers by taking over their duties, represent an example of the convenience that biosensors will create in the future. With the help of nanotubes moving with blood in the brain vessels, diagnosis and treatment can be done without problems, the blockages in the capillaries can be removed, and the paralysis caused by the lack of neural communication will be cured with artificial capillaries produced with nanotechnology [109]. Considering the extremely rapid development of biosensors, it is thought that the expected future will not be too distant [104].

7.4. Future Challenges of Biosensors

While biosensors have future advantages, they also have some challenges. For example, SPR biosensors have many advantages like other types of biosensors. However, working with smaller analytes other than large analytes is much more difficult. Because small analytes give small reactions. Therefore, SPR biosensors are disadvantaged for small analytes. This challenge will be overcome in the future if SPR biosensors are developed [110]. Another example is the contribution of microbial-based biosensors to many fields. However, there may be problems in terms of human values. The study by Ma et al. suggests that while microbial-based biosensors are an advantage for genetic modification, they may be a disadvantage for humans [111]. Better explanations on this subject are needed for further use of microbial-based biosensors in the future. According to another study, some features should be considered when using biosensors in production control. At this point, the sensors must be able to keep their activity constant and care must be taken as the activation of the sensor biomaterial is adversely affected at extreme temperatures [112]. In this context, biosensors can be difficult to use. In addition, biosensors in the ecology and food industry are not very well developed. At this point, there are deficiencies in the application areas. In the future, if these difficulties of biosensors are overcome, they will be preferred more in production control [112].

8. CONCLUSION

With the literature research carried out within the scope of the study, it has been seen that biosensors produce solutions to various problems according to their usage areas and this process progresses further as technology develops. In addition, biosensors provided the opportunity to work with different receptors by processing different samples. At the same time, it stands out in every field with its sensitivity, fast results, and detection of very small molecules. In addition, the use of enzymes and antibodies as receptors has become widespread. This is because they can convert the substrate into a product without being consumed by the reaction. It is seen that such biosensors have been developed more in the field of medicine, in line with research. At the same time, it is known that sensor studies for faster and earlier diagnosis of cancer diseases continue in the medical field. At this point, studies on the development of Nanodiagnostics, that is, early diagnosis tests, continue. In addition, the effects and usage areas of biosensors on transducer elements (electrochemical, gravimetric, optical, etc.) are changing by dividing them into different classes. For example, electrochemical biosensors are known for being inexpensive and responsive. They are mostly used in agriculture, environment, and industrial areas. Optical biosensors continue to evolve in medical products and biomedical research and come to the fore in SPR (surface plasmon resonance) studies. In addition, studies have shown that the selection of nanomaterials is very important for the acceptors and converter elements. In the literature; for sensor applications; nanomaterials; It has been seen that the sensor helps to obtain more selective, more sensitive, faster results and studies have been carried out for more cost-effective production. At this point, it is seen that especially carbon-based materials attract a lot of attention by researchers for sensor applications. For the characterization of these materials obtained for sensor application, ESEM, XPS, XRD etc. are often used. techniques are used. The most important feature of the environmental scanning electron microscope is its high sensitivity and its use for detailed material characterization. X-ray photoelectron spectroscopy is a very important characterization method in terms of obtaining information about material content and structure. The data obtained, it is expected that biosensors will come to the fore in the fields of medicine, food, agriculture, and environment and have a promising future in many fields. In addition, it is predicted that biosensors, which are easy to use in every field, will be an important factor in solving many problems in the future. At this point, it is thought that biosensor studies should be increased.

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