CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Available online at: http://www.iajps.com Review Article

A REVIEW ON BIOSENSORS: PRINCIPLE, WORKING, TYPE AND APPLICATION IN MEDICINE

Pranay V. Sharma[1]*, Vikrant P. Wankhade[2], Nirbhay A. Suryawanshi[3], Ayushi H. Mishra[4]
Vidyabharati College of Pharmacy, CK Naidu Road, Camp, Amravati

Abstract:
Research sciences and medical societies have recently shifted into using cost-effective biosensors to test food & water contaminants, control human biologic processes, assess precise health diagnosis, and more. Researchers and medical practitioners need safe and cheaper means of performing their research, ensuring public safety, and delivering customized health options to patients. One such solution can be easily carried out by using biosensors. In the new medical field, biomedical studies of diagnosis are of growing significance. Biosensors' applications are for screening infectious to early detection, chronic disease treatment, health management, and well-being surveillance. Improved biosensors technology qualities allow the ability to detect disease and track the body's response to care. Sensor technology is integral to numerous, low-cost, and improved-form factors feasible in modern medical devices. Biosensors have good potential, as it is easy, scalable and effective in manufacturing processes. This paper discusses biosensors and their significant benefits in the medical field. Distinctive capabilities of biosensors in healthcare services and for cardiovascular disease are provided and shown diagrammatically. The paper also discusses various diagnostic biosensors for cardiovascular diseases and provides novel aspects of biosensors for clinical and allied services. Thereby paper provides significant advancements in bio-sensors in the medical field. Finally, fourteen major applications of biosensors in the medical field are identified and discussed. Biosensors intelligent wearable properties now allow older people to control their health with lesser interference, and it directly exchanges their medical-related information with healthcare providers, thereby reducing hospital visits. Thus, biosensors have countless prospects for consumer and commercial uses in wellness, fitness, athletics, etc. Linked biomedical devices, apps, firmware, and sophisticated algorithms will do a lot, including allowing major new medical therapies and informing users about health reform, providing solutions and advice informed by real-time evidence[3].

Key Words: Biosensors, Transducer, Biosensor Application, Health Care

Corresponding author:
Pranay V. Sharma,
Vidyabharati College of Pharmacy,
CK Naidu Road, Camp, Amravati

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Please cite this article in press Pranay V. Sharma et al ***A Review On Biosensors: Principle, Working, Type And Application In Medicine.****,Indo Am. J. P. Sci, 2023; 10(01).*

INTRODUCTION:

Today a variety of digital biomedical devices are available in the market for measuring various aspects of human behaviour and performance. The quantity of worldwide connected wearable devices will increase from over 300 million in 2016 to over 1,000 million in 2022. The rapid advancement in technologies is fuelling the growth of telemedicine, e-Health and e-Hospitals. Electronic healthcare monitoring is gaining attention on both therapeutic and diagnostic sides due to the increasing healthcare workforce scarcity. Wireless pervasive monitoring is one of the key technologies emerged in the recent years in the fields of healthcare and biomedical applications. Updike and Hicks demonstrated the first biosensor in 1967. Biosensors have mainly two parts and they are a molecular recognition element (MRE) and a transducer. Animal or plant cells, receptors, organelles, antibodies, tissues, microbes and enzymes have been widely used as MREs. Artificial materials like MIPs (Molecularly imprinted polymers) and PNAs (Peptide Nucleic Acids) have also been used as MREs. MREs can be grouped into two categories namely affinity and catalytic bases. Catalytic base MREs includes plant or animal cells, microbes, organelles and enzymes. Whereas affinity base MREs includes MIPs, nucleic acids receptors and antibodies. The lifetime, thermal and chemical stability of biosensors can be enhanced by using engineered and purified enzymes and microbes. MIPs are of two types namely covalent bonding type and non-covalent bonding type. MIPs can be used to develop biomedical sensors such as beta-estradiol sensor, herbicide sensors and chloramphenicol sensors[2].

WHAT IS THE NEED OF BIOSENSORS?

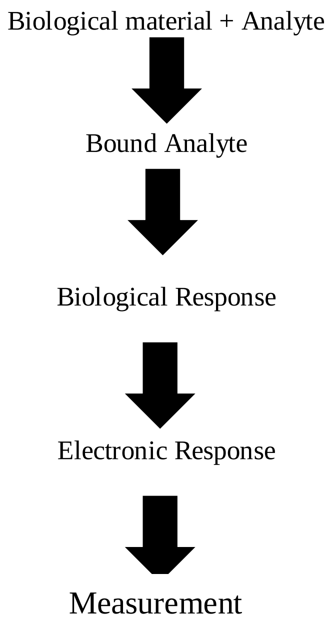
Sensitive and selective determination of various compounds of analytical and industrial relevance is one of the important and basic requirements of the present-day for the people working on it. Highly specialized instruments are being used for obtaining the desired information in the laboratories. Biosensors have the potential to measure constantly the presence/absence or concentration of specific organic or inorganic substances in desired specimens. Bio-devices yield information rapidly and at reasonable cost. In this context, the increasing rate of obesity and the alarming rise in the rate of diabetes in the contemporary world is driving the need for easy-to-use devices to monitor diabetic patients' glucose levels. The pharmaceutical research industry urgently requires new rapid assay biosensors to speed the progress in drug discovery. Some of the popular fields applying the use of biosensors in food industry to keep and check its quality and safety, to help distinguish between the natural and artificial; in the fermentation industry and in the saccharification process (The hydrolysis of polysaccharides to soluble sugars is called "saccharification".) to detect precise glucose concentrations; in metabolic engineering to enable in vivo monitoring of cellular metabolism [6].

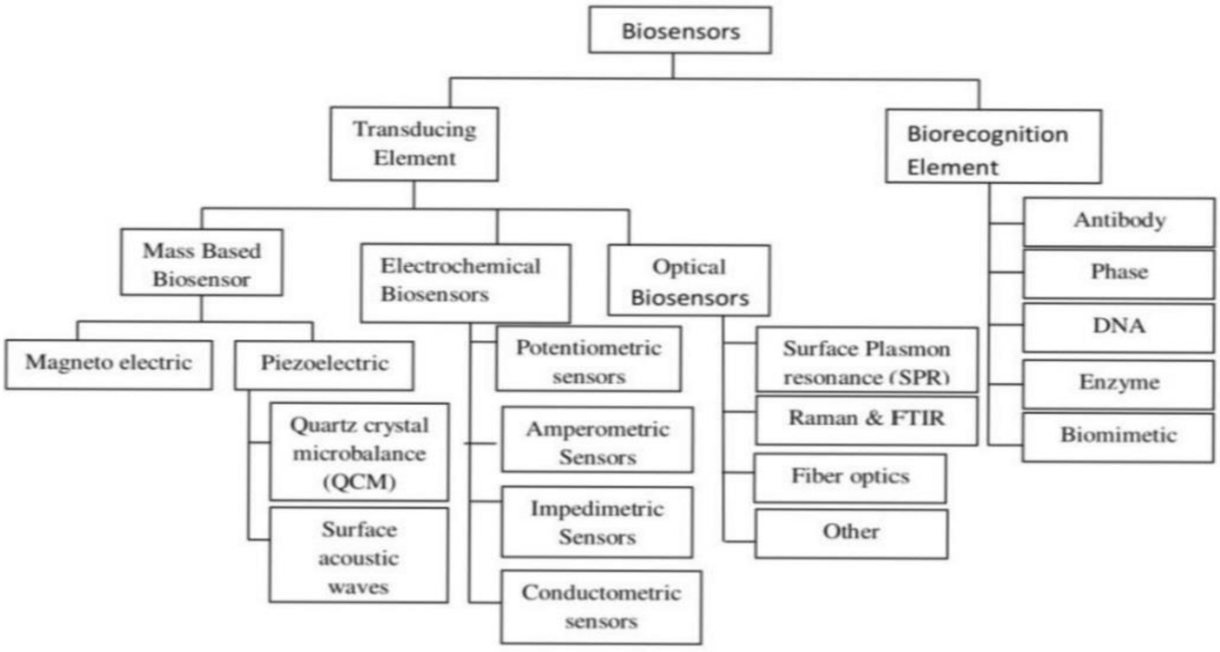
HISTORY OF BIOSENSORS:

The first biosensor was invented by Professor Leland C Clark Jnr. and he is known as the father of the biosensor concept. On 15 April 1956, at a meeting of the American Society for Artificial Organs during the annual meetings of the Federated Societies for Experimental Biology, the biosensor invented was named after him as "Clark electrode". In 1956, Clark published his definitive paper on the oxygen electrode. The concept was illustrated by an experiment in which glucose oxidase was entrapped at a Clark oxygen electrode using dialysis membrane (Turner, 1996). This biosensor was made from a thin layer of glucose oxidase (GOx) on an oxygen electrode [6].

PRINCIPLE OF BIOSENSORS:

Measurement The Principle Behind The biosensor involves firstly the immobilization of preferred biological substantial (commonly a particular enzyme) through traditional approach like non-covalent or covalent bonding, physical or membrane entrapment. This immobilization biologically material is in closely linked with transducer .The analyte attaches to biological element to form a bound analyte which in turn evokes the electronic signal that can be measured. In few cases, the analyte is transformed into a product which may be linked with the discharge of heat, gas (like oxygen) ,hydrogen ion or electron .The transducer can alter the product related variation in to electric signals which can be augmented as well as measured. The measurement flow for a biosensor illustrated in fig[3]





DIFFERENT BIOSENSORS:

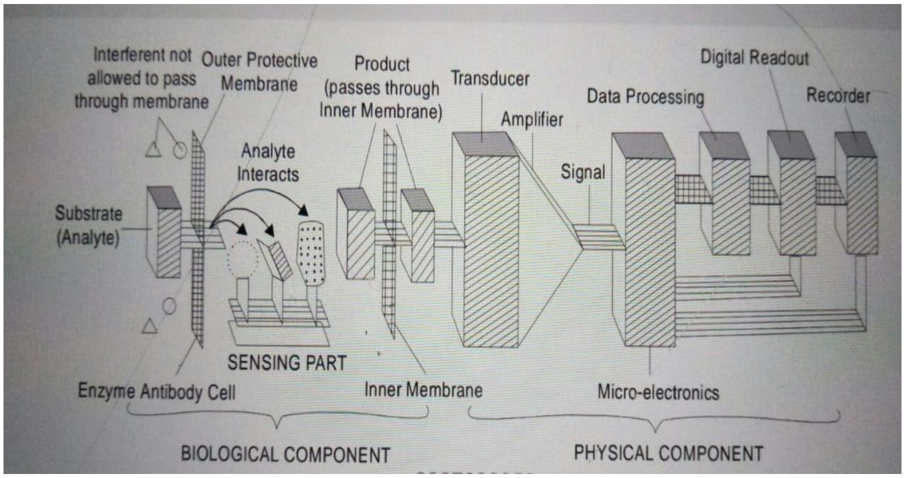
There are different biosensors which perform a variable role in the fields as provided. The following is a flowchart that represents different Classification of biosensors based on the transducer element & bio-recognition element[3].

Fig- Classification of biosensors based on transducer element & bio-recognition element[3]

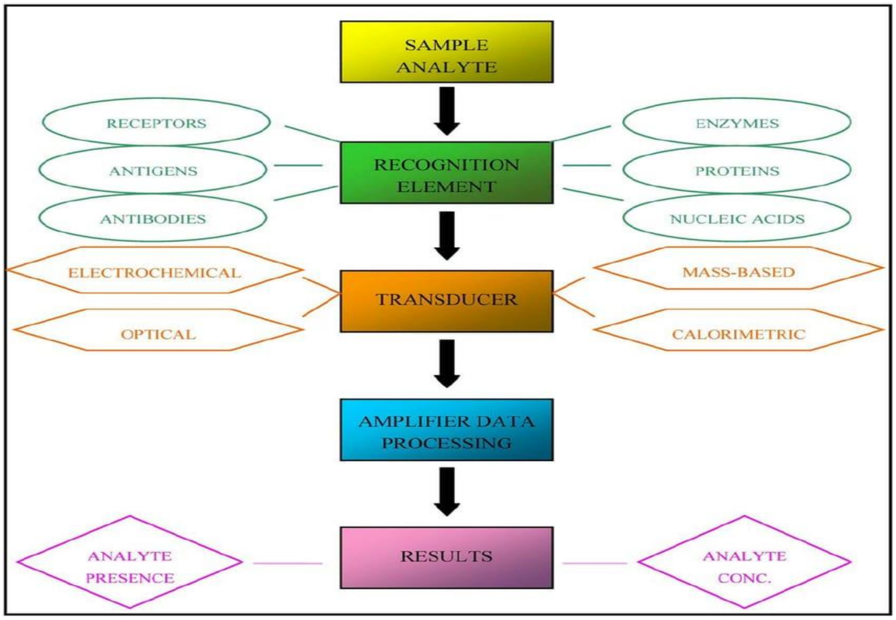
WORKING PRINCIPLE OF BIOSENSORS:

As indicated in the aforementioned sections, a biosensor comprises of a biological receptor coupled with a transducer and signal processing unit, and thus operate on the basis of signal transduction. The combination of these components is designed to convert the biological response into a corresponding electrical response and ultimately a measurable output.

In simpler terms, biosensors are responsible for the quantitative analysis of a molecule by relating its biological action into a measurable signal. Initially, the molecule of interest in the test sample binds or interacts specifically with the biological receptor, resulting in a physiological change. This further alters the physicochemical properties of the transducer that is in close proximity to the biological receptor. This further leads to a change in the optical or electronic properties of the transducer which is further converted into an electrical signal which is detectable. The signal generated by the transducer can either be a current or voltage, depending on the type of biological receptor. If the output from the transducer is in the form of a current, then this will be converted into an equivalent voltage. Also, the output voltage is usually very low and masked by a high frequency noise signal, which then requires further alterations, processing and amplification through various filters within the signal processing unit. [3].



Schematic Diagrammatic Sketch of biosensor depicting its vital components[3]



Basic Structure and Functioning of Biosensor[3]

BIOSENSORS WITH BIOLOGICAL EFFECT - BASED ANALYSIS

Biosensors techniques utilizing enzymes, natural receptors, bacteria or cells can be used to rapidly identify toxicity and other biological effects in water containing different chemicals known as bio-sensing. The determination of toxicity furnishes a merged picture of the overall impact on the environment. Research has been carried out where detection of arsenic is signalled as an easily detectable drop in pH and the chromogenic system. The endospores used can be stored and distributed in dried form without requiring freeze-drying or refrigeration. Whole organisms can also be used to measure the potential biological impact of a water or soil sample. Sensors for other areas of ecotoxicology, like genotoxicity and mutagenicity, has also been formulated, developed and described as "biosensors for environmental stresses". Genotoxicity is associated with different compounds, such as phenols, chlorophenols, PCBs and PAHs, and can constitute an early warning screening parameter for possible cancer-inducing pollution activity. Mammalian cells, which are more complex than bacteria, can give a more sensitive response when compared to bacteria. In the case of pharmaceuticals, their environmental presence triggered a proposal to include an environmental risk assessment in the registration procedure for medical products. An ecotoxicological test battery has been designed for that[3]

TYPES OF BIOSENSORS[3]:

The biosensors are of 5 types:
1. Calorimetric biosensors.
2. Potentiometric biosensors.
3. Acoustic wave biosensors.
4. Amperometric biosensors.
5. Optical biosensors.

There are various types of biosensors based on the sensor devices and some type of biological materials used. Electrochemical, amperometric, thermometric, optical, blood glucose, potentiometric, conduct metric, fiber optic lactate, optical for blood glucose, luminescent biosensors to discover urinary infections, piezoelectric, whole cell, and immune biosensors[3].

1) CALORIMETRIC BIOSENSORS:

The use of calorimetry in bioanalysis has many attractive features, which were recognized early in studies by conventional calorimeters. Since biological reactions usually are more or less exothermic, calorimetry offers a general detection principle insensitive to the optical properties of the sample. Enzymic reactions are associated with rather high enthalpy changes in the range of 20-100 kJ mol-1 and it is often possible to base measurements on only one enzymic step in contrast to other techniques where the detection is based on, for instance, the change in concentration of coloured reactants. Many enzymes catalysed reaction are exothermic generating heat which is used as a basis for measurement of rate of reaction and hence analyte concentration. The temperature changes are determined by thermistors e.g., cholesterol biosensors using cholesterol oxidize (heat output 53 KJmol-1)[3].

2) POTENTIOMETRIC BIOSENSORS:

By combining a bio-recognition element Potentiometric biosensors are developed essentially an enzyme with a transducer that senses the variation in protons or other ions amount, the recorded analytical signal being logarithmically correlated with the analyte concentration. It present Editorial deals with the presentation of several types of sensors based on different transducers and bio-recognition elements. Simplest transducer in the development of potentiometric biosensors is the glass pH electrode. Glucose oxidase immobilization achieved by using the cellophane, nylon or nitrocellulose membranes that are afterwards filed on the sensitive bulb of the pH electrode that senses the pH diminution, as a result of the bio-catalytical reaction occurring in the enzyme layer (glucose oxidation by glucose oxidase). This type of potentiometric enzyme sensors possesses a linear range of 10-4 to 5 × 10-2 M, allowing for glucose assay in fruit juices[6].

3) ACOUSTIC WAVE - BASED BIOSENSORS:

Acoustic Wave –Based Biosensors are based on detection of mechanical acoustic waves and integrated a biological component. These are mass sensitive detectors, which are operated based on an oscillating crystal that resonates at a fundamental frequency. After the crystals has been coated with biological reagents such as antibody and exposed to a particular antigen and quantifiable change occurs in the resonant frequency of the crystal, which is colligate to mass changes at the crystal surface. The huge majority of acoustic wave biosensors applies piezoelectric materials as the signal transducers. Piezoelectric material is idea for use in this application due to their ability to generate and transmit acoustic waves in a frequency dependent manner. The physical dimensions and properties of the piezoelectric material influenced the optimal resonant frequency for the transmission of the acoustic wave. Generally, most the commonly used piezoelectric materials include quartz ($SiO2$) and lithium niobate ($LiTao3$) which influenced the optimal resonant frequency for the transmission of the acoustic wave. Emerging science, driving new sensors to deliver the molecular information that underpins all this, includes the development of semi synthetic ligands that can deliver the exquisite sensitivity and specificity of biological systems without the inherent instability and redundancy associated with natural molecules. Currently aptamers, peptide arrays and molecularly imprinted polymers are particularly promising research directions in this respect. Chances of success are enhanced by the potential utility of some of these materials for novel therapeutic, antimicrobial and drug release strategies, since these complimentary areas will drive investment in these approaches [6].

4) AMPEROMETRIC BIOSENSORS:

In amperometric approach, the signal transduction process is accomplished by controlling the potential of the working electrode usually an inert metal at a fixed value relative to a reference electrode usually silver chloride and observing the current as a function of time. The applied potential serves as the driving force for the electron transfer reaction, and the current produced is a direct measure of the rate of electron transfer. Amperometric biosensors take advantage of the fact that certain molecules can be oxidized or reduced at the working electrode i.e., gold, carbon, platinum, etc. If the working electrode is driven to a positive potential an oxidation reaction occurs, and the current flow depends on the concentration of the electro active species diffusing to the surface of the working electrode. Similarly, if the working electrode is impelled to a negative potential, then a reduction reaction occurs. A third electrode called the counter or auxiliary electrode is often used to help measure the current flow. In most cases the bio-receptor molecule is immobilized on the working electrode, and as the analyte diffuses to the electrode surface the current generated reflects the retinae occurring between the bio-receptor molecule and analyte. The amperometric sensor for glucose is the most studied of all biosensors, noting that it employs an enzyme (glucose oxidase) to catalyse the conversion of glucose to gluconic acid. Similarly, the amperometric approach has become widely used for the detection of nucleic acid and antigens for disease identification/diagnosis. In fact, amperometric transduction is the most suitable and common electrochemical detection method in immunosensors. These biosensors are highly sensitive, rapid and inexpensive. In addition, they display a high degree of reproducibility, which removes the need for repeated calibration. A possible limitation with amperometric transduction is the interferences that arise from electro active compounds/ species, and this can sometimes generate a false current reading. However, these problems have been largely eliminated by the use of electrodes coated with various polymers[6].

5. OPTICAL BIOSENSORS:

Biosensors which signify the end product of a quickly growing field, which combines fundamental biological, chemical, and physical sciences with engineering and computer science to satisfy needs in a broad range of application areas. Therefore, the term ‘biosensor’ has different connotations depending on what field the user comes from. Causative agents of various infectious diseases are pathogenic microorganisms that are becoming increasingly serious worldwide. For the successful treatment of pathogenic infection, the fast and correct detection of multiple pathogenic microorganisms is of huge importance in all areas related to health and safety. In the middle of various sensor systems, optical biosensors permit easy-to-use, rapid, portable, multiplexed, and cost-effective diagnosis. Here, we review current trends and advances in pathogen-diagnostic optical biosensors[6].

MAJOR CHALLENGE IN FRONT OF BIOSENSORS

With all these diversified applications of biosensors, major challenges for biosensors are that out of hundred biosensors, only one is commercialized. Efforts of researchers can be seen in the form of advancements in the areas of biosensors. For commercialization, researcher’s main focus is on low-cost immobilization techniques. Research on these new immobilization materials is unstoppable as new materials are experimented daily in laboratories to get new best one. Secondly, to decrease and increase precision and accuracy to advertise biosensor in market, nanostructures like nanowires, nanorods and nanotubes are utilized in electrochemical biosensors. Carbon nanotubes (CNTs) is not only raised stability of immobilized biomolecules, rather, in addition, enhances sensitivity of biosensor. Besides, these CNTs can be used to fabricate electrodes which offer advantage of rise in electron transfer, reproducibility and stability of biosensor. To state the matter differently, CNTs can be used as amplifiers in biosensors. Apart from these Carbon nanotubes i.e., CNTs, other materials like porous silicon also are of great importance as substrate/support in biosensors. Now a day other flexible particles which are in focus are magnetic nanoparticles. Moreover, due to the fact of high sensitivity and specificity of nanostructures, they have been used to sense various analytes like hydrogen peroxide, glucose, cholesterol, DNA, inosine, bacteria, cancer etc. For further efficiency of biosensors, graphene entered into the field of biosensors due to its more surface area and electrical conductivity. Various graphene based electrochemical biosensors, to detect concentration of heavy ions in environment, have been develop [7].

LIST OF BIOSENSOR USED IN DRUG DELIVERY SYSTEM[6]:

Name	Biosensor	Uses
Chattarjee & Bandyopadhyay	Electrochemical Biosensor	Sensing application of corona virus
Arshad Et al	Medical Biosensor	Detection of dengue virus
Dolai & Tabib Azar	Potentiometric Medical Biosensor	Identify Zika Virus
Luo Et Al.	Optical Medical Biosensor	Detection of Hepatitis A & B
Name	Biosensor	Uses
Saylan & Denizli	Optical Medical Biosensor	Haemoglobin Detection
cimen et al.	Optical Medical Biosensor	Cardiac Troponin 1 determination
ozgur et al.	Optical Medical Biosensor	Cocaine detection
bakhshpour et al.	Piezo electric Biosensor	Detect human metastatic breast cancer

LIST OF BIOSENSOR BASED IN DRUG DELIVERY SYSTEM AVAILABLE IN MARKET & UNDER CLINICAL TRIALS[6]:

Accucheek Compact (Roche)
Sensocard Plus (BBI Healthcare)
Cholestrak (immbobilized enzyme)
Contour Blood Glucose Test Strip (Bayer Healthcare)
Cardio Cheak

APPLICATIONS OF BIOSENSORS[6]

1. Biosensors in Medical Diagnostics medium:

Medical Diagnostics represents has a huge well-established demanded market of biosensors. With increasing level of health problems, there increasing demand for inventing rapid and sensitive as well as modern methods of diagnostic devices[6].

2. Biosensors in Food and Agriculture level:

As we know that India is a growing Nation, and agriculture is the basic prime source of income. The increasing consumer demands for quality and safe food requires a lot of efforts for quality control by the industries[6].

3. Biosensors and Pathogen detection:

Different types of biosensors are being employed for detection of pathogenic microbes. It helps for the easy identification of the microbes present in body[6].

4. Environmental Monitoring:

Pollutants in the environment are great risks for the health of human beings. Several microbial biosensors are used for detection of organic and inorganic toxicities being extensively used in industry; heavy metal become a main toxicant in wastewater[6].

5. Biosensors for cardiac biomarkers detection:

Many biosensors have been developed to detect a wide range of cardiac marker to reduce the costs for healthcare[6].

6. Disease Diagnosis.

7. Cancer diagnosis:

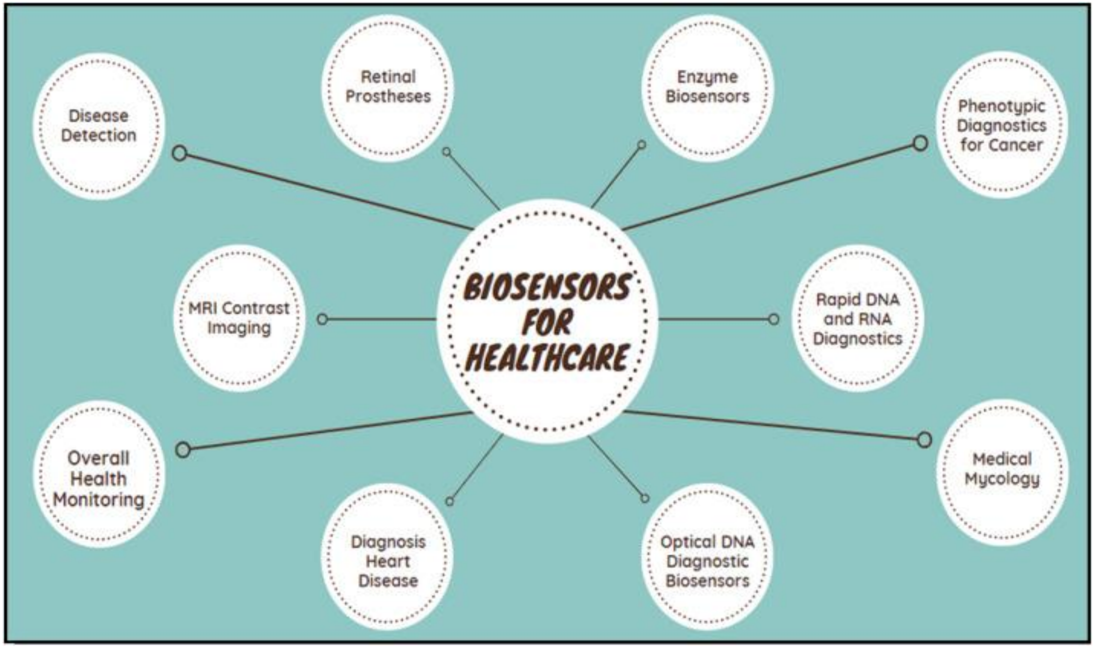
Tumour development is linked with gene and protein changes generally come about because of the mutations and these changes can be used as biomarkers for the diagnosis. Cancer biomarkers are possibly a standout amongst the most significant tools for early cancer detection. Biosensors have been developed with an end goal to improve the analysis and treatment of different cancers. Aptamers, ssDNA, dsDNA, antibodies and typical antigens (p53 antigen) can be utilized as the bio-component in these biosensors. Aptamer based on biosensors mutual with gold nanoparticles has been developed.[6].

a. Alzheimer disease.
b. Diabetes mellitus.
c. Cardiovascular maladies.
d. Tuberculosis.
e. Hepatitis.
f. Diarrhoea.

8. Biosensors: Industrial Biotechnology:

Biosensors and Food had borne Bacteria Monitoring. Milk Purification, the market trends showed about 10.4% growth in the development of biosensors for various applications, like in biopharma, food and beverages, biodefense, and environmental analysis.

Biosensor devices are ideal tools for environmental monitoring because they are sensitive, selective, easy, and rapid. Novel electrochemical biosensor was constructed for determination of cholesterol levels by Satvekar and co-authors. Bioenzymatic nanobiosensor was based on DNA-assembled Fe3O4Ag nanorod in silica matrix entrapping enzymes cholesterol oxidase and horseradish peroxidase onto surface of indium tin oxide electrode. Cholesterol levels were determined by cyclic voltammetry with limit of detection 5.0 mg/dl and linear range between 5.0 and 195 mg/dl[6].



Typical capabilities of biosensor in healthcare services[6]

FUTURE PROSPECTIVE AND CHALLENGES

Biosensors have extensive prospective applications in these different domains as screening and monitoring of both public as well as personal health, pathology, environmental monitoring e.g., the detection of pesticides, river water contaminants, etc., bioprocess, criminology, civil defence, and within the industry of food, water quality and beverage for safety. Biosensors are widely used in biomedical research, health care, pharmaceuticals research via spatially separated molecular probes immobilized on a solid surface to scrutinize or detect biomarker for diagnosis of various diseases. Fortunately, the development of biotechnology, nanotechnology and novel immobilization strategy in the past years the nanobiosensors are becoming more powerful in the field of medicine. The future prospects of whole cell-based biosensors may prove exciting. An early example of what this future might hold was demonstrated in a report on a portable whole cell-based optical biosensor named Luisens 2 developed to provide real-time online detection of pollutants [6].

CONCLUSION:

Biosensors have been miniaturized extensively in the recent years. Keeping in line with such developments, microbial cells with high enzyme behaviours may be needed. This is main and definitely when microbial cells are applied as replacements to enzyme-based sensors. Due to the low cost of microorganism, long lifetime and broad range of suitable PH and temperature; have been widely employed as the biosensing element in the construction of biosensors. So, the proper use of biosensors should be done in order to have a great benefit in future [6].

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