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Biosensors Based Medical Devices For Disease Monitoring Therapy

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Abstract: *A Biosensor is a bio-analytical device which is used to collect physical, chemical or biological information and then convert that information into an electrical signal. Nowadays Biosensors are distributed over a considerable extent in biomedical diagnosis and a broad variety of other fields like monitoring of treatment and progression of disease, environment and agriculture monitoring, food safety, discovery of drug, biomedical & forensics research. The first biosensor was designed over a century ago in 1906, but it was clearly defined & established later in 1956. A broad range of techniques can be used for biosensor growth and their combination with high affinity biomolecules enable a variety of analysts to be sensitive & selective. Biosensors and their importance in medical science which includes human's early stage of detection of interleukin-10 causing heart diseases, fast discovery of human papilloma virus, etc. are various important aspects. Fluorescent biosensors also play a very important role in discovery of drug and in cancer. Biosensor applications are ubiquitous in the plant biology segment to discover out the missing links which is required in metabolic processes. Other applications are implicated in defense, clinical sector, marine applications and also biosensor illustrates the span of bimolecular sensing strategies with the growth of nanotechnology approaches that are now available.*

Keywords: Biosensors, Analytical, Molecular Diagnostics, Health, and Safety, Health Biomarker, Disease Diagnosis.

I. INTRODUCTION

Biosensors are an bio-analytical device that converts a physical, chemical or biological response into an electrical signal, whereas the word "biosensor" is frequently used to cover chemical sensor systems used to access material and other biological interest parameters even though they do not explicitly use a biological system."L.L Clark" American biochemist invented the first Biosensor in the year 1950."Cammaan" coined the term "biosensor" in 1977.Eventually, L.L Clark became the father of biosensors because he had a capability for demonstrating anamperometric enzyme electrode for glucose detection later in 1962.In 1969 Guilbault and Montalvo implemented a potentiometric biosensor in 1969 by the use of glass electrodes.The first commercial biosensors were developed by Yellow Spring Instruments (YSI) in 1975. [1]

It consist essentially of three key components, the biological sensing component and signal processing system that are connected to a detector or transducer component. An antibody, a nucleic acid, an enzyme, a cell or several others things could be the biological factor. A transducer is based on transduction methods such as electrochemical, optical, calorimetric or acoustic. Although, Biosensors in medicine is the most promising of all areas, provided that the detection, monitoring and treatment of various health conditions require new and improved devices with sensitivity, precision, reliability and biocompatibility**. [2]** In addition, real-time troubleshooting Biosensors must also be able to simultaneously detect several analytes, or stimulus, in biological fluids, both outside and inside the body to track and treat health problems.

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Various biosensing elements and devices have been built over the past several years. Biosensors are commonly used in various fields such as contaminants bio-monitoring, disease diagnostic, etc. Blood glucose biosensor is the most widely used biosensor for the regulation of blood glucose levels.

New advancements in recombinant DNA technology have contributed to the development of diagnostic biosensors based on DNA or oligonucleotides, which serve as a diagnostic tool in the clinical evaluation. Embedding nanoparticles into biosensors helps to boost parameters such as reliability, validity, lowered detection limit, time of residence, stability, sensitivity, etc**.** [3, 4]

Several trials of skin-integrated and implantable medical devices have been performed in research and development. Heart electrical signal, blood pressure, pulse rate, blood sugar level and respiration efficacy are the most frequently controlled vital signs in these devices.

All this advancement in the field of biosensors opened up new opportunities to improve the health, diagnostic systems and commodities of the patient.[5]

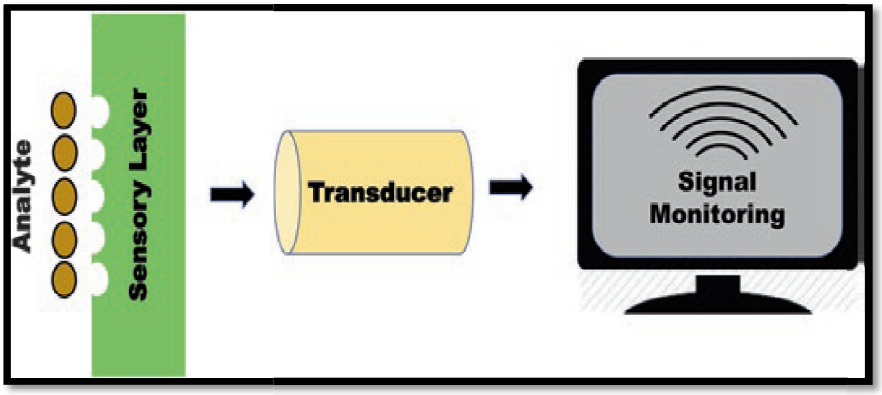

Figure 1: General component of Biosensor [5]

III. Characteristics Of A Good Biosensor [6, 7,8]

- It must give accurate, precise, reproducible results
- Must be free from electrical noise.
- It should be inexpensive, lightweight, compact, semi trained operators able to use it.
- The reaction must be independent of the physical parameters such as stirring, pH and temperature.

III. Biosensor Design and Operation

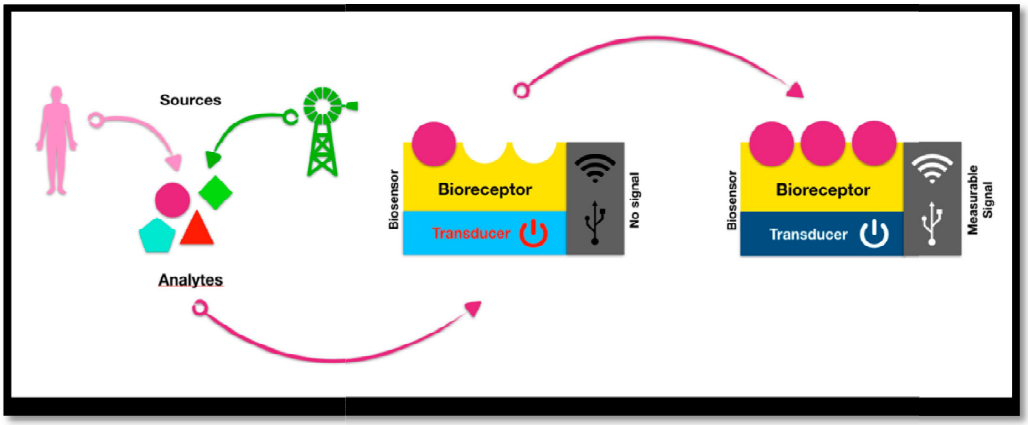

Figure 2: Standard Biosensor [8]

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It is an analytical device that further incorporates biological substances to recognise certain molecules as a signal for processing and recording by providing their presence and concentration. Biosensors typically contain three components: one is the recognition element, which is a membrane with different biological structures. The second is the transducer and the third is the electronic device that amplifies the signal and records the data presentation signal. The core part of any sensor is the recognition factor which responses one or more analyte between different substances. Biological structures such as live cells, nuclear acids, receptors, antibodies and enzymes are often used as identification factors .**[9]** When a reaction occurs between an analyte and the selective biological substrate, transducers transform variations into optical or electrical signal. This signal is further analyzed using a device that is electronic or sensitive to light. The biological entity is immobilized by membrane or physical entrapment, covalent binding, or non-covalent interactions. Analytes bind to biological material that induces an electronic response. These reactions may also be exogenous or release oxygen, hydrogen or electrons. The transducer amplifies the changes in the signal connected to the product. Signal processing involves decreasing the reference signal from a similar biological transducer and also smoothes the unwanted signal noise.[10]

IV. TYPES OF BIOSENSORS

4.1 Voltammetric Biosensors

Voltammetric biosensors determine current generated when the electro-active reactant or substance is reduced or oxidised. The electroactive species reduction or oxidation current in voltammetric biosensors is analyzed by generating the potential decrease. This refers to the reference electrode and the constant potential for working electrode, which measures the current directly proportional to the formation of a biocatalytic layer or the amount of electroactive species concentration.[11]

4.2 Biosensors Potentiometric

They normally measure biosensor electrode potential in response to a reference electrode. The potential drop carries the analytical signal among the two reference electrodes or between the reference electrode and the membrane separated analytical electrode. The Ion Selective Electrode (ISE) is the transducer used in potentiometric transducer.**[12]**

4.3 Biosensors Conductometric

These biosensors suggest improvements to the actions resulting from the biochemical reaction. These biosensors calculate the solution's electrical conductivity during a biochemical reaction. The sensing factor is an enzyme, which detects affine interactions less frequently.[13]

4.4 Biosensors Optical

It monitors the absorption or release of light during a biochemical reaction. In these biosensors, the optical fibres measure fluorescence or absorption from light diffusion. The biosensors assess affinity as well as catalytic reactions. The sensing component causes a change in absorption or fluorescence, which changes the refractive index between two densities media. They are beneficial to any biosensor because they enable multiple analysis detection using different wavelengths of monitoring. The adaptability of optical samples is due to their ability to transmit signals that are dependent on polarity, time, wavelength, wave propagation, spectrum distribution or light intensity changes. They entirely depend on the theory of the absorption of light dispersion, internal reflection, fluorescence, surface plasm resonance, or light spectroscopy.[14]

4.5 Calorimetric Biosensors

They work on a change in enthalpy during a reaction, also known as thermal biosensors. The biosensor components are incorporated into a physical transducer. It is used to measure change in optical density or colour of the test sample in order to detect a pathogen in water and food after a chemical reaction.[15]

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4.6 Enzymatic Biosensors

These sensors contain biological material with antibiotic activity. The simplest type of enzyme biosensors can be used. Reversible electrode reduction or oxidation when electrochemically active potential is used. Enzyme sensors have been classified further In inhibitors and sensors of the substratum. Sensors inhibitors also help to decide the enzyme or substances decreased activity, while substrate biosensors appear to determine selected substrates and their enzyme reactions.[16]

4.7 Immunosensors

They are used commonly to detect the immunochemical reaction between antigens and antibodies. They are therefore used to identify the presence of antibodies and to diagnose toxic substances. The antigens in both media (biological liquid and natural environment) are determined. They detect any compound with high selectivity and different antibodies.[17]

4.8 DNA Sensors

Nucleic acids, primarily DNA, are the key component of the DNA sensors. These sensing materials are fragments commonly referred to as DNA primers or DNA samples that represent the specificity of the whole structure of the DNA. These samples and primers are synthesized by PCR (polymerase chain reaction) amplification of DNA. They have been updated so that the stability is improved or samples can be introduced in bio-sensors. This type of biosensor assists in the identification of non-macromolecular compounds and protein interacting with unique DNA fragments. Based on the type of biorecognition unit, they are known as biosensors of nucleic acid, enzyme, entire cell, antibody or aptamers**.[18]**

V. BIOSENSORS IN MEDICINE

As a fast-growing sector, biosensors have found applications in many fields, including agriculture and food protection, environmental monitoring, biotechnology, genetic engineering, pharmacology, defense, homeland, since they can significantly improve a number of analysis challenges and problems. In agriculture biosensors are used to detect organophosphates and carbamates from pesticides, microbial bio-sensors to measures methane and ammonia and bacterial-based ammonia in certain situations, such as biosensors for enzymes.[19]

As far as the food industry is concerned, biosensors are used for the measurements of amino acids, carbohydrates, inorganic ions, alcohol, acids, etc. Despite all the above areas of application, the application of medicine and biomedical diagnostics is the most common and of incredible potential. This potential is driven by the requirement to solve the health issues like diabetes, cancer, chronic conditions such as heart disease, respiratory disorders, stroke, obesity, etc. Therefore, measurement of blood metabolites such as glucose, lactate and urea, and cancer biomarkers, are identified in healthcare; folic acid, biotin, pantothenic acid and vitamin B12**.**[20]

The first application of the biosensor to medicine was in 1962 when Leland C. Clark and Champ Lyons created an amperometric enzyme electrode (platinum) for the glucose sensor. These platinum electrogens found oxygen as a result of the change in enzymatic activity of enzyme glucose oxidase embedded in the membrane of the dialysis, depending on the surrounding oxygen concentration. Until now, glucose biosensors have been the most frequent and many other biosensors for medicine have been developed to improve them in the sensitivity, selectivity, and ability to multiplex.[21]

Biosensors must be extremely precise, reliable in the medical and biomedical fields and should exhibit high long-term stability with very low drift and resist the application of mechanic force such as pulsative blood flow. Moreover, implantable and wearable medical devices should also be small or otherwise incomplete or voluminous for the patient, especially if used in restricted volume areas such as blood vessels, lungs and brain. Biosensors should not impact the measuring environment or the well-being of the patient. While the technical advancements are more complicated, both implantable and wearable devices have in common the fact that they allow vital signals to be captured (e.g. heart rate, respiration rate, skin temperature) and hence the long-term health monitoring of the patient.[22]

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VI. BIOSENSOR BASED MEDICAL DEVICES FOR DISEASE MONITORING THERAPY

6.1 Biosensors for Diabetes

6.1.1 Glucose as Diabetes Marker

Approximately 2 - 3% of the world's population is diabetes, the leading cause of death, and its prevalence is increasing rapidly. Diabetes is a metabolism condition that leads to abnormally elevated blood sugar concentrations. Diabetic people have greater heart disease, stroke, high blood pressure, blindness, kidney failure, risk neurological problems, and other risks linked to their health without proper control of the levels of blood glucose.

Many of these complications can be greatly minimized through the preparation of patients, routine tests and stricter blood glucose control.[23] Optimal diabetes treatment requires the assessment and monitoring of blood glucose levels in patients. Under physiological circumstances, rapid plasma glucose concentration is in the 6.1–6.9 mmolL−1 range so the difference in blood glucose level may imply, in addition to other conditions, diabetes mellitus. As a result, the quantitative content of glucose is extremely significant because it is the key biomarker of diabetes. The American Diabetes Association suggests that insulin-related diabetics monitor blood glucose three or four times a day, while insulin-related type 2 diabetics monitor blood glucose once a day. Nevertheless, regular self-monitoring of glucose levels is difficult because of the time, pain and discomfort involved with effective measurement. Several glucose analysis methods have been published. Most of these approaches, however, require complicated procedures or are costly. A quick, responsive, reliable, micro-volume and low-cost approach for glucose analysis should, therefore, be produced, suitable for fast field testing and as an alternative to existing methods.[24]

6.1.2 Biosensors for Glucose Measuring

Invasive and non-invasive technologies can monitor glucose. The first recorded biosensor was glucose biosensor and a large number of different glucose biosensors have been developed, including implantable glucose-measuring sensors in blood and tissue. Glucose sensors are now commonly available as inexpensive, minimally invasive instruments measuring subcutaneous fat interstitial glucose levels. In vivo glucose sensor criteria include system miniaturization, long term reliability, oxygen dependence elimination, user comfort and biocompatibility.[25] The main requirement was long-term biocompatibility and the use of in vivo glucose monitors, both subcutaneous and intravascular, was limited to short periods of time. The diffusion of low-molecular - weight sample substances through the outer membrane of the sensor contributes to a loss of sensitivity. In order to solve the problem, glucose biosensors are combined with microdialysis or ultrafiltration technology. Currently available invasive glucose monitoring systems use electrochemical glucose oxidase-based and electrochemical methods into the interstitial fluid region, sensors are inserted. While sensors, like drift, calibration errors and delay in the interstitial sensor value behind the blood value are still in nature, most sensors are fairly exact.[26] The glucose biosensor is the most commonly used example of a biosensor based on an amperometric electrode imprinted on a screen. This form of biosensor has been commonly used worldwide for home glucose monitoring to perform a diagnosis on site.[27]

The ultimate aim of glucose monitoring is the noninvasive detection of the glucose and the key approaches to the production of glucose sensors are: infrared spectroscopy, excreted physiological fluid (tears, sweat, urine, saliva) monitoring, microcalorimetry, enzyme electrodes, optical sensors, ionophoresis and sonophoresis for each of which can be extracted. Nevertheless, Relative ease of use, speed and minimum risk of infrared spectroscopy infections are disrupted by low sensitivity, poor variety, often required calibration and miniaturization problems. Problems related to direct glucose analyses by excreted physiological fluid include a poor relation between excreted fluid and blood glucose levels. Exercise and diet that adjust the amount of glucose in the fluids often yield misleading results. The need to create an artificial pancreas drives ongoing biosensor research. However, before such an insulin modulating device can be accomplished, limitations of in vivo biosensors must be overcome. [28]

6.2 Biosensors for Cardiovascular Disease

6.2.1Cardiovascular Disease Biomarkers

Cardiovascular disorders are largely preventable but are the leading cause of human death worldwide. Hypercholesterolemia, meaning elevated cholesterol levels in the blood, is one of the key factors behind the rising

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occurrence of cardiovascular diseases and cardiac arrest. Therefore in clinical applications it is critical to estimate cholesterol levels in the blood. The early identification of patients with symptoms suggested by acute coronary syndrome is of great clinical importance. In this context, biomarkers are increasingly necessary to enhance. Medical history and electrocardiographic results since one or both may be deceptive**.[29]** Cardiac troponin is the only marker used frequently in this field today, since it is a myocardial tissue that is easily identified and useful in therapeutic decision making. The determination of other non-myocardial markers, such as myeloperoxidase, copeptin, factor 15 and Innovative, may also be beneficial. CRP, which represents various development aspects of Atherosclerosis or acute ischemia, a plasma protein known as the acute-phase protein, has a dramatic increase in its levels during the inflammation of the body. This increase is due to an increase in the plasma level of IL-6 that is mainly released by macrophages and adipocytes. CRP will increase with inflammation as much as 1000-fold. CRP was found to be the only inflammation marker that predicts the danger of a heart attack independently.[30]

6.2.2Biosensors in Cardiovascular Disease

Cholesterol detection biosensors form the majority of the papers published in the field of cardiovascular diseases. In the manufacture of a cholesterol bio-sensor for free cholesterol and total cholesterol estimation, the sensing elements are cholesterol oxidase (ChOx) and cholesterol esterase (ChEt) (Fig 3). Electrochemical transducers have been used to estimate cholesterol in the system effectively. A variety of optical transducers were used for cholesterol detection, specifically monitoring: luminescence, colour shift, fluorescence and others based on the number and accurate optical methods. Certain biomarkers of cardiovascular disease are also quantified. CRP measurement primarily relies on immunosensing technologies with optical, electrochemical and acoustic transducers, in combination with methods used to quantify simultaneous analytes, Streptavidin polystyrene microspheres on the electrode of the SPEs to improve cardiac troponin T's analytical reaction. Precise and fast quantification of cardiac muscle-specific blood biomarkers allows accurate diagnosis and treatment and patient prompt care. It is evident, in contemporary society, that rising cardiovascular disease and heart arrest is a sign of the need to have cholesterol and other biomarker bio-sensors. However, only a handful was released on the market successfully. One explanation is the implementation of important parameters such as stabilizing the enzyme, quality control and the design of instruments. Efforts to improve biosensors for cardiovascular diseases have the marketing of a few cholesterol biosensors has resulted. A better understanding of bioreagents and technological advancement in the field of microelectronics will probably speed up the marketing of even-needed cardiovascular diseases biosensor systems.[31]

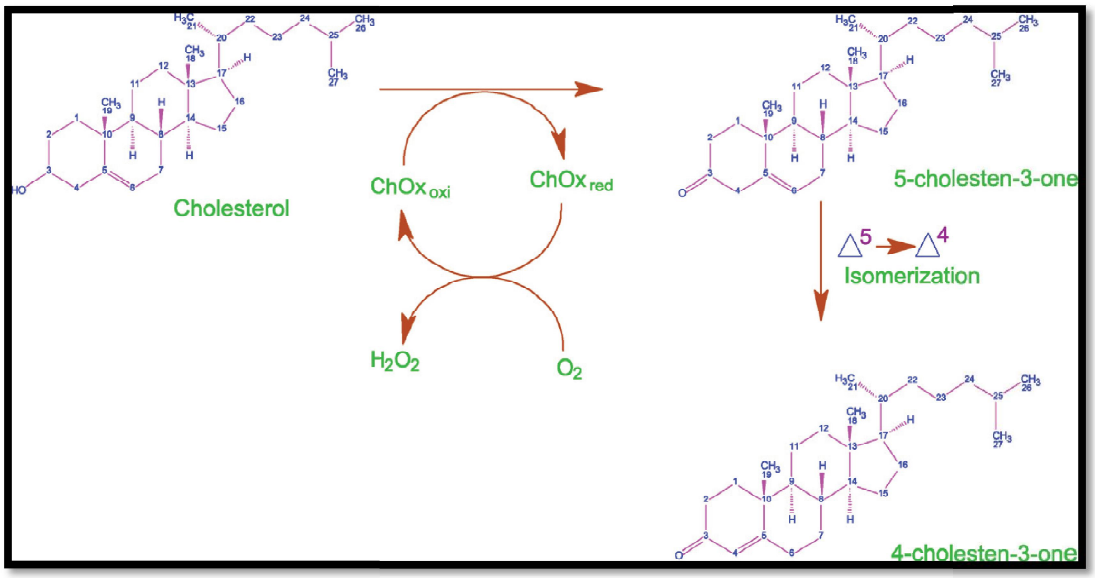

Figure 3: Pathway of cholesterol oxidase enzyme reaction [31]

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6.3 Biosensors for Cancer

6.3.1Cancer Biomarkers

In advanced industrialized countries cancer is the leading cause of death and the second most common cause in developing nations. The global increase of this disease is mainly due to the ageing and growth in the world population and the rising acceptance of cancer-causing behaviors, particularly smoking.**[32]** Breast cancer is the most widely diagnosed cancer and is the common cause of cancer death in women and lung cancer in men. Breast cancer is already a common cause of cancer death among women in economically developed nations, the most common cause of cancer killing was cervical cancer, following a decade earlier. Solid cancers are a world's leading cause of morbidity and mortality, primarily because of a failure to effectively diagnose and treat metastatic diseases at remote locations. A number of factors, both genetic and environmental, can cause cancer**. [33]** The production of cancer may involve chemical or physical factors including exposure to carcinogenic compounds, radiation, bacterial (e.g. stomach cancer), viral infections (e.g. cervical cancer) and toxins (aflatoxin, e.g. liver cancer). Since the causes of cancer are so complicated, clinical trials are often very challenging. Multifactorial (genetic and epigenetic) variations may cause disease and cancer cell formation. Nevertheless, no specific gene is uniformly modified during this phase, but a number of it which makes the correct diagnosis of diseases difficult. All the variations in tumours from different locations (organs) and in tumours from the same place may be so varying and overlap that a particular alteration or marker for diagnosing those cancers is difficult to choose. Perhaps by,a number of biomarkers for the diagnosis of diseases can theoretically be examined. These biomarkers or molecular signatures can either be generated by the tumour itself or the body in response to cancer. The study in biomarkers in body fluids , such as blood, urine and others, is one of the techniques used to diagnose the disease. Table 1. Multi-marker profiles, present and the level of concentration may be important for early disease diagnosis. These approaches should provide physicians with knowledge in order to make better clinical decisions and improve the patient survival rate. A number of biomarkers for various cancers have been identified. These involve DNA changes, RNA, proteins (enzymes and glycoproteins), hormones and associated molecules, immune system molecules, oncogenes and other altered molecules. Various biomarkers, including genes and proteins are currently being researched, but few of them would be relevant for routine cancer trials because of their sensitivity. Developing protein-based biomarkers for biosensors for cancer diagnosis is more desirable than genetic markers because of the availability of protein, recovery and economically efficient approach to developing healthcare facilities**.** [34]

Breast	ER,PR, HER2, CA15-3, CA125, CA27.29, CEA BRCA1, BRCA2, MUC-1, CEA, NY-BR-1, ING-1
Bladder	BAT, FDP, NMP22, HA-Hase, BLCA-4, CYFRA 21-1
Cervix	P53, Bcl-2, Brn-3a, MCM, SCC-Ag, TPA, CYFRA 21-1, VEGF, M-CSF
Colon	HNPCC, FAP, CEA, CA19-9, CA24-2, p53
Esophagus	SCC
Leukemia	Chromosomal aberrations
Liver	AFP, CEA
Lung	NY-ESO-1, CEA, CA19-9, SCC, CYFRA21-1, NSE
Melanoma	Tyrosinase, NY-ESO-1
Ovarian	CA125, AFP, hCG, p53, CEA
Pancreas	CA19-9, CEA, MIC-1
Prostate	PSA, PAP
Solid tumors	Circulating tumour cells in biological fluids, expression of targeted growth factor receptors
Stomach	CA72-4, CEA, CA19-9

Table 1: Cancer Biomarker

6.3.2 Biosensors in Cancer Disease

Current cancer screening methods are based primarily on cell morphology using staining and invasive microscopy techniques. Moreover, at the early onset of the disease, tumor elimination can neglect cancer cells. Biosensor-based

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detection for cancer clinical trials becomes realistic and beneficial as it is simpler, easier to use, less costly and technically less challenging than microarray or proteomic testing. **[35]**Nevertheless, important technological enhancement itself is needed, especially for protein-based products Biosensor. Multi-array sensors for cancer detection will be useful for multi-marker research. There are a variety of molecular detection molecules used for biomarker detection, which are the most commonly used antibodies. Recently, synthetic (artificial) molecular recognition elements such as nanomaterial, aptamers, phage show peptides, synthetic and synthetic proteins, as well as metal oxides have been produced as affinity materials and used to analyse analysis. In cancer diagnostics tests for cancer cells and biomarkers, antibodies (monoclonal and polyclonal) have been added. Polyclonal antibodies may be elevated of these molecules in sensors has been effective against any biomarker or cells and by incorporating high-performance techniques. However, the use of monoclonal antibodies leads to more accurate studies**.[36]** The disadvantages are that monoclonal antibodies are harder to implement and cost more than polyclonal antibodies. Consequently, the replacement of natural biomolecules with synthetic receptors or biomimics in recent years has become a promising field of study. The benefits of using these molecules are that they are rugged, more robust, cheaper to produce and easily adjusted to enable the sensor surface to immobilzse and also allow the addition of labels as detection manufacturer. These molecules can be synthesized in comparison with the antibody molecules after a collection from combinatory libraries with higher specificity and sensitivity.[37]

Bioaffinity-based electrochemical biosensors are commonly used to identify gene mutations in biomarkers and protein biomarkers for the study of cancer biomarkers. Anti-bodies-based electrochemical biosensors have high selectivity and sensitivity for early detection of cancer, including amperometric, potentiometric and impedimetric / conductivity instruments..Amperometric and potentiometric transducers have become the most widely used, but in recent decades a lot of attention has been provided to transducers on an impedance basis because they have been labelled as label-free sensors. However, much of the technology is already in the field of science. In addition to antibodies, electrochemical devices based on DNA hybridisation have been developed and used in the detection of cancer gene mutations. A single stranded DNA sequence is immobilised in this type of structure on the electrode surface where DNA hybridization occurs. ELISA-based surface tests are the most widely used cancer protein marker monitoring methods, such as CEA. The antibody (or antigen) is marked with a horseradish peroxidase (HRP), or alkaline phosphatase (AP), and both are then catalysed to create an electroactive species on an electrochemical transducer. Electrochemical sensing of unusual circulating tumour cells can provide clinicians with an independent method for simple and regular treatment of productive cancer to detect and track changes in cell counts during therapy. Several commonly produced platforms use the detection method with fluorescence labels. The instruments used for signal read-out, however, are typically costly and best suited for laboratory environments**.[38]** For instance, the Affymetrix gene chip can be used to diagnose cancer and to identify cancer genes. Additional biomarker diagnostics have also been used for other biosensor platforms such as grating couplers, resonant mirrors and surface plasmon based systems. These are known as free-label and real-time reaction detection systems. Different SPR-based biosensors for cancer marker detection based on the above listed optical systems have been created. Microcantilever-based sensors have progressively also been used to diagnose hepatocellular carcinoma in early stages. While the cancer biosensing production has been achieved, the point-of - care testing is not yet available. To achieve this aim, issues such as: production of reproducible biomarkers; progress in recognition ligands; creation of multi-channel biosensors; improvements in the preparation of samples; miniaturization and integration of device systems; production of more responsive transducers; integration of microfluids; advanced manufacturing techniques and costs reduction must be addressed.[39]

6.4 Skin Integrated Wearable Biosensors

Epidermal electronic system (EES) are skin integral extendable devices which are ultra - portable, soft , low modulus, delicate and skin-like sheets, and which can be embedded in the uneven epidermis deeply and physically through vanderwaals forces alone with no mechanical fixing hardware or adhesive tapes. The EES with using the similar mechanical properties of skin might act as a "secondary skin." Therefore, it adheres and laminates to the skin

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surface in a manner that is mechanically invisible and imperceptible to the patient, like a temporary tattoo transfer. They can also be conveniently applied at anywhere on the skin of the patient [40, 41, 42]. They are natural interface which can evolve and manage skin motions without mechanical restrictions, build stable, non-irritating skin / electrode contact and allow the intimate integration of different classes of sensors and electronics.

The use of such sensors is promising to preserve and improve the quality of life and thus overcomes conventional systems. These typical systems are known to have wires or cords, point-to-point electrodes or mechanical adhesive pads on the skin, Clamps or straps, primarily regulated by conductive gels or penetrated needles. Other than that, they are also inappropriately suited to functional applications outside of the clinical setting because their robust, scheduled and hard formats and components can lead to pain, irritation and inflammation, loss of sticking over time, a lack of mobility, and only one physiological signal monitoring.

Assuming that the skin constitutes the protective barrier between both the inner structures of the body and its surrounding, any device in contact with the skin requires the principles of design and manufacturing, in order to imitate its specific mechanophysiological effects and does not restrict or change its own natural movements or actions. Biocompatibility should be a must for this. Device to prevent body-foreign reaction. Various electronic devices were then recorded that were flexible and stretchable.

A few skin-integrated devices, whether by placing the electronics on a versatile surface or directly on to skin, have been developed over the past 10 years [43,44]. The first methodology is popular and many reports on the integration of electronics into stretchable elastomers by 2D can be found or 3D patterns. For example, by spray deposits directly on a poly(dimethyle siloxane) substrate, Bao and his group developed clear, stretchable and conducting one-walled carbon nanotubes (SWCNT) films[36]. A versatile pressure sensor with Chang and coworkers using Carbon nanotubes with a vertical alignment (VACNT) provided by a PDMS matrix that retained their structural flexibility after repeated compression [45]. PDMS is a suitable method for developed flexible, wearable skin substrates, which derive various sensors because of their chemical characteristics, biological compatibility, transparency and thermal stability, and in particular their adhesion and non-adhesive areas that are clearly visible in UV light and easily attachable on the surface of electronic materials.

6.5 Implantable Biosensors

The observation and monitoring procedure inside the human body is a fascinating and effective application of bio-sensors. These sensors are classified as implantable biosensors when partly or completely inserted into the human body in order to stay there on a non invasive basis for long periods of time. Implantable devices are yet another suitable option to continuous monitoring that decreases the person's pain and discomfort.

These embedded electronic devices would become a significant biomedical tool in the near future as they can provide a summary of the cascade of events within the body over a certain period of time, helping to track chronic diseases or improvement following treatment and/or surgery. They must be found in the body, heart, eyes, blood and brain . Implantable biosensors have many advantages over other tracking devices as they can directly track biological metabolites, nerve electric stimulation, electric signal detection, regeneration of body functions and drug distribution between others[46]. A perfect example is blood pressure control, a critical parameter in all organs of the Human body. A pressure change can lead to a deterioration or injury to the physiological function. Hypertension and infarction are common and severe health issues related to cardiac muscle activity or dysfunction. Implantable and miniaturized blood pressure biosensor experiments are being performed for continuous hypertension monitoring and the resultant treatment [47].

In order to develop a completely implantable bio-sensor, heterogeneous components, including electrodes for specified analysis / vital sensor detection, a circuit designed to manage measurements and data transmissions, and a power source, are required. The final method and Implantable bio-sensor dimensions should be biocompatible and well managed by the host to prevent toxicity and chronic inflammation.

One of the greatest challenges to the production of implantable devices therefore inhibits the difficulties of a match between the rigid, planar surfaces of semiconductor chips and the delicate, curvilinear tissue of biology systems. Due to

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their sharp borders, stiffness, shape, and scale, they appear to easily damage the surrounding tissue during insertion and exert chronic stress on the adjacent biological environment [48,49]. Thus, conventional sensors, partially or fully stiff, are more likely to be chosen and preserved, based on silicon wafer substrates.

These materials are identified as causing fibrous capsules to form around the system to reduce the output of the sensor in vivo, causing a sensor failure [50,51]. For medical applications, the substitution of silicon chips with biocompatible, soft and flexible substrates is therefore compulsory,

Like the substrates of biopolymer to mitigate that body-foreign problem and to suppress the encapsulation of fibrotic tissue [52,53]. Polymethylene naphthalate, polyethylene terephthalate and polyimide are commonly used substrates[54]. These polymer substrates are necessary if the mismatch between rough planar surfaces and soft curvilinear biological tissues of the wafers is to be overcome [55,56].

When the biosensor is inserted in the human body, it instantly induces biofo, and an adverse biological reaction to the foreign matter itself called FBR which is the principal cause of the device's loss of functionality as a consequence of tissue trauma / damage. and low sensor content biocompatibility. According to several review articles, the adverse reaction of the body may depend on various characteristics of the biosensor including shape , size, design, roughness, morphology and porosity, composition, material / device interface, sterilization, Implant, packaging and degradation time [57,58].

VII. Recently Developed Biosensors Along With Their Principles Of Working and Biosensors [59]

- **Analyte:** Ebola, dengue & yellow fever
  - **Biorecognition Element:** Antibody tagged that multicolored which is of siolver nanoparticles onto small strip of paper
  - **Sample:** Blood
  - **Technology:** Paper strip based multiplex disease diagnostics
  - **Advantages:** Detecting down to tens of ng/ml
- **Analyte:** Ebola virus glycoprotein
  - **Biorecognition Element:** Ferrous oxide magnetic nanoparticles (nanozyme)
  - **Sample:** Blood
  - **Technology:** Nanozyme strips
  - **Advantages:** Lower detection limit :1ng/ml
- **Analyte:** Urinary pathogens like E.coli and Enterococcus faecalis
  - **Biorecognition Element:** Glass-polymer hybrid chip forms a centrifugal microfluids platform that captures bacteria directly.
  - **Sample:** Urine sample
  - **Technology:** Microfluids and Raman microscopy
  - **Advantages:** Detection within 70 minutes
- **Analyte:** Candida infection
  - **Biorecognition Element:** Nanoparticles with supermagnetic properties which is coated with specific targeted binding agents
  - **Sample:** Blood
  - **Technology:** Miniaturized magnetic resonance that calculates water molecules reaction at the presence of magnetic fields
  - **Advantages:** 91.1% sensitivity,99.4% specificity, and 1CFU/ml(colony forming unit milliliter)
- **Analyte: Blood Glucose (noninvasive)**
  - **Biorecognition Element:** Nonengineered silica glass with the ions that fluoresce in infrared light when a low power laser light hits them
  - **Sample:** Skin touch to the glass (no finger prick needed

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- **Technology:** Low powered lasers which penetrates in the skin and it measures the length of the time and fluorescence remains and measures the blood glucose
- **Advantages:** Wearable, non invasive

VIII. Newer Generation Biosensors: Nanobiosensors

Nanobiosensors are techniques that monitor a biochemical as well as biological event using either electronic , optical or magnetic technology using a portable device. Current advancements in nanotechnology and innovative manufacturing technology in electronics collide to establish a new collection of biosensors called nanobiosensors and launch a new age of bionanotechnology for disease diagnosis.65

8.1 Quantum Dots

Optical biosensor sensitivity and specificity can be improved if combined with quantum dots (QDs). QDs are nanometer-scale semiconductor crystals with special effects of quantum containment. They have wide excitation and narrow bandwidth, negligible photobleaching, and ultrastability [60]. They perform on the theory of fluorescence transduction due to directly and indirectly analyte interaction with QD surface, either by photoluminescent activation or quenching. Surface alterations (carboxy-functionalized) of QDs has started developing multimodal probe-based biosensors that can be clearly connected to the target. p eptides, ligands, nucleic acids. These nanocrystals have a broad range of applications from pH and ion detection to quantification of organic derivatives and biomolecules (DNA , RNA, enzymes , proteins, amino acids, drugs). Applications are inhibited by their toxic effect and minimal reusability**[61].** Yet more progress is needed in methods of synthesis and conjugation to address the challenges.

8.2 Graphene Based Biosensors

Graphene is a layer of tightly arranged carbon molecules in the pattern of the honeycomb (hexagon shaped). Region and excellent electrical conductivity to serve as a conductor of electrons between protein or enzyme redox centres and electrode surface. Rapid transfer of electrons allows precise, selective detection of biomolecules. They are beneficial over carbon nanotubes in low cost, large specific surface area, excellent stability, and better electrocatalytic efficiency. They have less toxins, such as transition metals Fe , Ni, and so on, thus considered purer than carbon nanotubes, thus providing a better forum for studying carbon atom electrocatalytic behaviour and better understanding. Graphene is now a favoured alternative for producing different biosensor devices for its high compressive strength and other characteristics. Graphene-based electrodes are used to measure small molecules like H2O2, NADH, glucose, amino acids, and neurotransmitters. These electrodes implement oxidation-reduction on their structures. Grapheme electrodes are optimized (chemically reduced grapheme oxides or multilayer nanoflake film) to enhance the transfer rate of electron similar to other electrodes, contributing to high biosensing performance[62].

Graphene can sometimes be excellent for electrochemical biosensors. Graphene-based enzyme biosensor can be used in gene therapy to track metabolic processes continuously. Enzymes like glucose oxidase are covalently and Immobilized with chemical graphene. Graphene-based nanomaterials are often used to test biomolecules; for instance, graphene designed with gold nanoparticles / Nafion nanocomposite biosensors demonstrates a very fast reaction in monitoring glucose molecules and chemical contaminants such as heavy metal ions. High sensitivity and long-term stability are nonenzymatic biosensors. Graphene-based electrochemical DNA biosensor provides high sensitivity and selectivity to detect particular DNA sequence or mutated genes in a specific human disease.

Biosensors, such as 0D Gdots, are photoluminescent materials derived from graphene or carbon fibres. They also have the peculiar optical properties of atomic containment and a wide variety of excitation-emission spectra. Due to their higher photostability against photobleaching, greater biocompatibility and low toxicity, Gdots are superior to other imaging agents including cadmium Qdots. These features allow coupling of Gdots in electronic and electrochemical and photoluminescence sensors . Gdots' modular size enables ssDNA analysis, enzyme immobilization, and avian leukosis virus. Gdot-based electrochemiluminescence sensor often detects metal ions and amino acids. When adjusted with gold nanoparticles, Gdots' planar surface improves the detection limit to very minute levels[63].

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8.3 Carbon Nanotubes

Carbon nanotubes (CNTs) are cylindrical rolled-up graphene sheets. CNT-based biosensors are gaining importance for biomedical application due to their graphene-derived desirable chemical and physical properties. Because of the frequency of atomic bonds in carbon nanotubes, they can reach very high temperatures and serve as excellent electrical and thermal conductors. Coated antibodies or unique samples They can monitor antigens such as viruses, nucleic acid, enzymes and biomolecules. CNT-based biosensors work on the concept of electrical conductivity shift highly correlated with the distance between both the target analyte and the electrical metre-readable probe. CNTs can also be combined with electrochemical biosensors to improve enzyme electrodes, immunosensors, and biosensing of nucleic acid. Their incredible tensile strength and elastic actions make it easy to twist, pliable, and miniaturise. The only drawback is the synthesis of pure CNT without losing any of its properties. Apart from three obstacles to functionalization, pharmacology and CNT toxicity limit their widespread use in biomedicine. They have restricted aqueous medium solubility and their pharmacokinetics based on their non-cogent form, scale, chemical structure, and aggregation potential. This nanoparticles below 100 nm can easily avoid phagocytosis and inflammatory response, and can tolerate redistribution from their original site. CNTs have been extensively investigated for promising oligonucleotide and enzyme-based sensors. CNTs are special in the way benefits and disadvantages can be exploited for biomedical applications.

8.4 Lab-on-a-chip

A highly advanced device of immense diagnostic significance fits into a single chip needed to analyze one or more specifications like biomolecules, DNA, or RNA. The major requirement for lab-on-a-chip production is microfluidics and molecular biotechnology. These devices are manufactured with multiple microchannels implanted with antibodies, antigens, or oligonucleotides, allowing thousands of biochemical reactions from one drop of blood. Polydimethylsiloxane (PDMS), thermoplastic polymers, glass, silicon or paper-based technologies are typically used to make labon-a-chip. However, PDMS and paper-based lab-on-a-chip are even more frequently used due to their low cost and easy to use and manufacture.

The benefits of lab-on-a-chip are its relatively inexpensive, equivalent sensitivity to standard clinical diagnosis, rapid testing time, ease of use, ease of maintenance, low volume samples and real-time monitoring; it can also be used anywhere without any ambient impact.[64]

IX. Conclusion and Future Direction

Biosensors are sensors that detect target analytes in a sample mixture. These are consisted of bioreceptors and transducers responsible for monitoring a particular signal that is interpreted in a recognizable output signal. However, biosensors can be applied to different fields. Health monitoring is their most enticing programme. They can be used for effective treatment and monitoring equipment of high-mortality diseases such as cancer and cardiovascular diseases, greatly leading to reducing mortality rates and enhancing the patient's quality of life.

These devices require interaction between the various disciplines and are dependent on Distinctive characteristics including interaction of biomolecular analytes with recognition components, system manufacturing and design, on-chip electronics, sampling techniques, microfluidics, etc. The use of nanoparticles in biosensors offers a chance to create sensing technologies. Nanoparticles enhance biosensor electrical,optical, electrochemical and mechanical properties. None reports have been conducted on understanding the mechanism of activity among biomolecules and nanomaterials on nanofilms or electrode surfaces for new-generation biosensors. Nevertheless, nanoparticles-based biosensors offer promising prospects for process control, food analysis, environmental control and clinical evaluation in near future.

A specific diagnosis is necessary for effective care and treatment of patients undergoing from it. Diagnostic methods have to be easy, robust, and able to detect multiple biomarkers in biological fluids at low concentrations. Biosensors should meet these requirements.Future advancement in biosensor technology, including patterns of biomarkers, software and microfluidics, will make these devices wide opportunity for healthcare systems. The idea of using nanomaterials to build sensors for diagnosis of biomarkers would make these instruments extremely sensitive and more

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appropriate to early diagnosis point-of - care. Early detection will help improve patient survival, and effective production of biosensors for disease diagnosis and monitoring will require adequate support for transferring technologies from research to consumer goods**[65]**

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