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REVIEW ARTICLE

Biosensors- types and application in food processing industry

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ABSTRACT

The hazard identification and characterization are important steps in the microbial food safety risk assessment methodology. There have been various molecular techniques for the identification of microorganisms like Fluorescence microscopy, PCR and hybridization. The rRNA detection is suitable for detecting metabolically active bacterial populations. Genetic fingerprinting is applicable to only bacterial pure cultures. Therefore, new detection and real time methods are required for better assessment of the food products. The aim is to increase the detection specificity, reduction in the time of analysis, application on a large scale and decrease the resource requirement as in the molecular methods. There is a need for the development of automated techniques that will allow thorough and high output analysis of large number of samples. This will greatly facilitate the industrial microbial studies at all levels. The real time monitoring of the food samples using biosensors is a promising field and being explored for their utility for various food categories. This review explores types of biosensors, their working principles and their application in food fermentation and detection of hazards like allergens, antibiotics, heavy metals. It also highlights the advantages and the scope of further improvement in the existing technology.

Keywords: Analyte, biosensors, detection, monitoring, risk assessment

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INTRODUCTION

Food borne diseases are a major area of concern worldwide. Though various methodologies have been developed to minimize the incidences of food borne pathogens by ensuring good farm practices, good hygienic practices and food regulations, there is still a need to maintain a check of microorganisms in the later stages (Scott, 2003). According to the WHO statistics of 2016, around 1.4 million deaths are caused by diarrheal diseases annually. The reasons of these deaths are ascribed to consumption of spoiled food and water (WHO, 2018). In the developing countries, a high percentage of the annual budget is spent on food borne diseases. Therefore, food safety is an area to be evaluated in the developing countries in order to overcome the economic stress (Von et al., 2000).

A food borne disease occurs when an individual consumes food contaminated with either pathogenic microorganisms or microbial toxins. So, the microorganism or the toxin which has the potential to cause a disease is referred to as 'hazard'. The hazard identification and characterization are an important step in the microbial food safety risk assessment methodology. There

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have been various molecular techniques for the identification of microorganisms like Fluorescence microscopy, PCR and hybridization. Studies on microbial ecology are often based on ribosomal RNA or ribosomal DNA sequences. The rRNA detection is suitable for detecting metabolically active bacterial populations and on the other hand, genetic fingerprinting is a method applicable to only pure bacterial cultures.

New detection and real time methods are required for better assessment of the food products. The main aim of these methods is to increase the detection specificity, reduction in the time of analysis, application on a large scale and decrease the resource requirement as in the molecular methods. Development of automated techniques greatly facilitates the industrial microbial studies as these techniques allow high throughput analysis of large number of samples (Maukonen et al., 2003). Therefore, the emphasis of the ongoing research is to build biosensors for the analysis and monitoring of food samples in the real time situations. A biosensor is a device that recognizes a biological element using a transducer and produces electrical signals which can be measured. Biomolecules such as enzymes, antibodies, receptors, organelles and microorganisms or tissues can be used as the biological element in the sensors.

Clark and Lyons (1962) first described biosensors, by immobilizing glucose oxidase (GOD) on an amperometric oxygen electrode surface semi permeable dialysis membrane so as to quantify glucose concentration in a pattern without delay. They defined how "to make electrochemical sensors (pH, polarographic, potentiometric or conductometric) more sensible" with the aid of adding "enzyme transducers as membrane enclosed sandwiches" (Sassolas et al., 2003); (Nambiar, 2011). Biosensors are a substitute for analytical research methods that are technologically complex and require high-priced equipment and significant time consumption Biosensors provide a number of advantages including- high sensitivity and accuracy of measurements- which means biosensors are able to detect substances in the order of a very few grams; selectivity; determination of substances does not require preliminary preparation of an analytical sample; the ability of continuous monitoring; speed and ease of measurement; safety in use and low cost (Inshyna et al., 2020). There are various types of biosensors based upon BOD, bioluminescence, voltage measurement, color production, etc. Broadly, these sensors can be classified into electrical and optical sensors. Such types of biosensors have been discussed further including their advantages, disadvantages and their application in the food industry.

Biosensors mainly work on the principle of signal transduction. These components (as described in Fig 1) include:

i. a bio-recognition element, which detects the sample or the analyte as the case maybe,
ii. a bio-transducer which after detecting the sample tries to identify the sample for further analysis, and
iii. An electronic system which comprises of a display, processor and a signal amplifier for processing and displaying the results after the analysis.

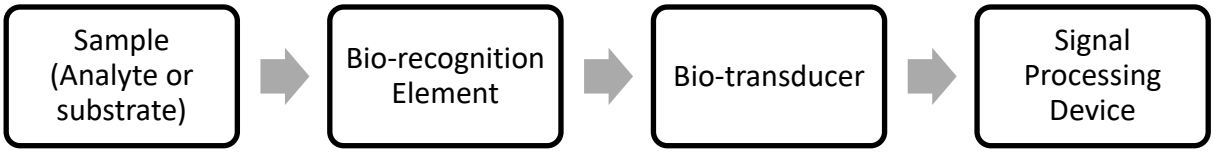

Fig. 1: Working of a biosensor

TYPES OF BIOSENSORS

Biosensors are classified according to their biological element or their transduction element. Biological elements can be the enzymes, antibodies, micro-organisms, biological tissue, and organelles. The change in the physicochemical alternate is the

basis of transduction which creates the sensing. Different types of biosensors are available based on transducer element. The mass based are called piezoelectric biosensors, potentiometric or amperometric are the electrochemical biosensors and optical kinds of biosensors also known as fiber optics (Malhotra et al., 2017).

Amperometric Biosensors

These electrochemical biosensor converts biochemical signals into electrical signals (Reshetilov et al., 2010). The current generated by oxidation or reduction reactions at the electrode surface is detected. This current produced is then related to the analyte present (Zhang et al., 2011). Chaubey et al., 2002 have stated that it is not necessary that the analyte can always generate suitable electrochemical reaction. In some cases, a suitable label has to be added to get quantitative results and then operated at fixed potentials to the reference electrode. The most common type of this sensor is based upon the Biological Oxygen Demand measurement (BOD). It lacks selectivity but possess good sensitivity and stability (Liu and Mattiasson, 2002; Sliwinska et al., 2014). They are used to monitor the freshness of milk stored at room temperature (Winquist et al., 1998), and also for examination of the ageing of wine, in the detection of heavy metal ions for environmental control. Other uses include monitoring cell respiration for surfactants such as organic pollutants using surfactant-degrading bacteria (Taranova, 2002). They are also used for measurement and identification of alcohols, cholesterol, urea, amino acids, and glucose (Goriushkina et al., 2009).

Impedimetric Biosensors

These types of biosensors detect the change in the impedance at a constant frequency or a frequency spectrum using an impedance spectroscopy (Escuder-Gilabert and Peris, 2010). They contain ion-sensitive silicon field-based sensors which increase the resolving power of the transducer by increasing its sensitivity. Usually, small proteins and peptides are determined on the basis of net charge on them using biologically modified impediment biosensors. One example of such a biosensor is based upon the change in impedance due to the production of charged metabolites by the growth of microorganisms or due to the adhesion of bacteria on electrodes. There are two ways of measuring these metabolic activities. The direct method detects the changes in metabolism using electrodes directly immersed in the medium (Felice et al., 1999). The indirect method detects the CO_2 produced by microorganisms which react with potassium hydroxide solution which results in the formation of carbonates which cause a decrease in conductivity (Owens et al., 1989). Pros of this are higher sensitivity, low cost and are simpler method (Brown, 1975). The major advantage of impedance technology is that it measures only live bacteria as only they can undergo metabolism and contribute to production of change in conductivity. They are used to estimate the microbial biomass, metabolism and physiological state of bacteria (Harris, 1985).

Potentiometric Biosensors

A reference electrode is used for measuring the potential in these types of biosensors (Bundschuh et al., 2018; Pisoschi, 2016). This biosensor consists of an ion-selective or a gas-sensing electrode which is coated with an immobilized microbe layer. A potential is generated when the microbe consumes the analyte which accumulates or depletes the ions. The difference between a working electrode and a reference electrode is measured by a transducer and the signal generated corresponds to the concentration of the analyte (Tran, 1993). However, this method requires a very stable reference electrode, which may be a limitation of these biosensors. Benefits include low cost, easier production on large scale, selectivity, wide detection range and high similarity with molecular recognition mechanisms. The potential generated may be varied by fluctuation in temperature and adsorption of solution components on electrodes which can vary the results (Ciosek et al., 2007).

They are mostly used in pH based sensors for e.g. using a modified glass pH electrode, and genetically engineered *E. coli*, expression of organophosphorus hydrolase inside cells and on external surface of cells can be detected. An oxygen electrode

with immobilized *Saccharomyces ellipsoideus* was also used to produce a potentiometric microbial biosensor for the determination of ethanol (Rotariu et al., 2004). Potentiometric sensors can also be used to monitor cheese fermentation, to evaluate the wine composition, to monitor alteration during beer brewing or to identify the botanical origin of honey (Esbensen et al., 2004, Rudnitskaya et al., 2009, Tan et al., 2001, Dias et al., 2008).

Microbial fuel cell type biosensors

Microbial fuel cells (MFCs) operate by converting the chemical energy in organic compounds to electricity by microbial catabolic reactions (Choi and Chae, 2012). A two chambered MFC is composed of two electrodes separated by a proton exchange membrane (PEM) (Du et al., 2007). This is connected to an external electric circuit. The bacteria in the anode oxidize organic compounds and release electrons, protons and carbon dioxide. These entities then travel towards cathode via PEM aided by external circuit and reacts with oxygen to form water. This flow also generates electricity. The current generated corresponds to the metabolic activity of the electro active bio film at the anode surface. If other parameters such as pH, temperature and conductivity are kept constant, fluctuations in the current can be correlated to some specific disturbance (Su, 2011). One such MFC is explained in Fig 2.

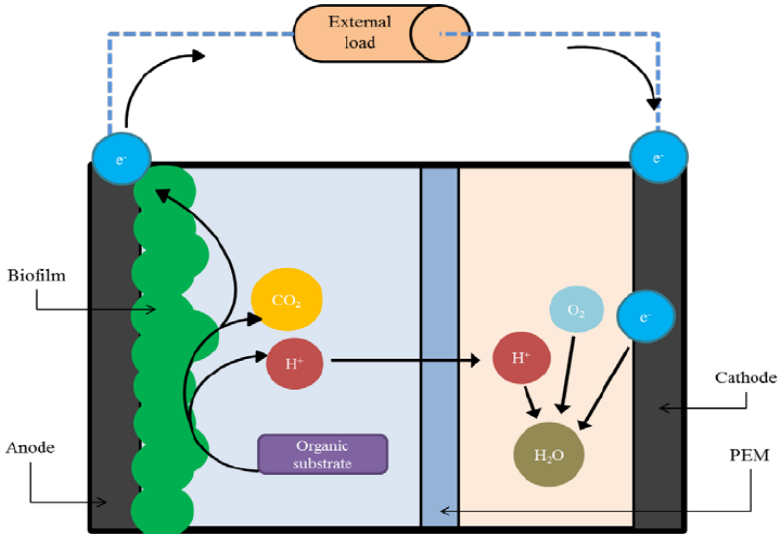

Fig. 2: Principle of operation of a two-chambered microbial fuel cell (not to scale) (Chouler and Lorenzo, 2015)

MFCs can be used as BOD biosensors, as the current density generated is linearly related to the BOD concentration (Peixoto et al., 2011). In 1977, Karube et al. described a BOD based MFC biosensor which used hydrogen produced by *Clostridium butyricum* immobilized on the electrode. BOD analysis would take up to days using conventional methods but the microbial sensors have a relatively fast response. A MFC-type of BOD biosensor has a high replicability, better stability and a wide linear range. Pollutants in wastewater inhibit the metabolic activity of electrochemically active bacteria, thus reduce the electron transfer and produces weak current (Vogrinic et al., 2015). A single chambered air cathode MFC, using real domestic wastewater for the detection of Cu (II) has also been reported (Shen et al., 2013). Another category of an MFC biosensor is a silicon-based MFC which is used as a toxicity biosensor that minimizes the time and the cost of evaluation (Davila et al., 2011). MFC biosensors are relatively less stable because of the toxicity of mediators (Chang et al., 2004).

Bioluminescence biosensors

Luminescence Fiber Optic Biosensor can be classified into two parts. The first being chemiluminescence and the other being bioluminescence. In fiber optic biosensors, chemiluminescence has been studied (Aboul et al., 2000). The property of living

organisms to produce light for signaling, mating, prey attracting, food hunting or self-protection is termed as bioluminescence (Belkin, 2003). Bioluminescence produced by organisms can be used to estimate the occurrence of a biological reaction. A bioluminescent microbial biosensor measures the change in density of bioluminescence produced by microorganisms which is in proportion to the concentration of analyte present.

The whole-cell biosensor consisting of genetically engineered *E. coli* cells produces luminescence in respond to the toxins. These cells carry a promoter-reporter gene fusion like that of recA::lucCDBAE fusion. The amount and type of toxin determine the intensity of illumination (Belkin, 2003). The promoter is toxin specific. Hence, several bacterial strains have been developed with different promoters for specific toxin (Elad et al., 2008). The luminescence is detected by a photodiode. The bacteria can be immobilized in a disposable PDMS biochip to maintain living cells and micro channels for the injection of samples. These sensors can also be used to check bioavailability of certain nutrients in aquatic environment. One such sensor was developed to estimate the bioavailability of phosphorus to *Cyanobacteria*. The reporter strain contains the gene which codes the reporter protein luciferase under the control of an inducible alkaline phosphatase promoter. This promoter is induced under phosphorous limitation and aids in phosphorus detection (Majeed et al., 2011)

Fluorescence biosensors

They are based upon the principle that the fluorescence produced is directly proportional to the concentration of the analytes at a low level (D'Souza, 2001). There are three types of Fluorescence Biosensing: direct, indirect and Fluorescence Energy Transfer (FRET). Direct fluorescence biosensing senses a specific molecule before and after a reaction has taken place, indirect fluorescence biosensing senses by adding a dye to transducer a specific molecule optically as used in the Green Fluorescent protein (GFP). Due to the benefits of stability and sensitivity, green fluorescent protein is most ordinarily utilized in fabrication of fluorescent microbial biosensors. It is a sensitive method and can detect the analyte in its low concentration (Pickup et al., 2005). The use of green fluorescent protein (GFP) has enabled investigators to analyse the location, structure and molecular dynamics within living cells. The GFP-based sensor is used to assess the heterogeneity of iron bioavailability on plants (Joyner, 2000). A microfluidic chip with yeast integrated was developed based upon the following mechanism for the recognition of toxic compounds (Garcia et al., 2009). Fluorescence energy transfer (FRET) is used to produce a distinctive fluorescence signal. A particular wavelength of light is used to excite a fluorophore which emits light of a particular wavelength. When two fluorophores are paired, excitation of one of them will intensify the fluorescence of the complementary (Garcia et al., 2009). These kinds of sensors are used in measuring water availability in a microbial habitat (Axtell, 2002). With the advancement in DNA recombinant technologies, fluorescence biosensors will become more popular.

Conductometric Biosensors

The property of many enzyme mediated reactions, to cause, a total ion concentration to change is the basis for conductometric biosensors. This further causes a net change in the conductivity of the reaction solution. Conductometric sensors are of 3 types which are generally also used in electronic noses. These are:

i. Conductive Polymer (CP) sensors - These are low cost and show accelerated reaction; on the other hand, vulnerability to humidity is a major problem with these sensors. They are used in electronic noses to recognize wine fermentation stages (Pinheiro, 2002); to monitor Atlantic salmon all along its storage at various temperatures for its decomposition (Olafsdottir et al., 2005) and to spot spoiled vacuum-packed beef (Blixt and Borch, 1999).

ii. Metal Oxide Semiconductors (MOS) - They are also less expensive, stable, user friendly, and greatly precise (Dimerski, 2011) but require a high temperature to operate (Oh et al., 2008). In electronic noses, they are applied to monitor red wine spoilage (Cynkar et al., 2007) and the dehydration of tomatoes (Pani et al., 2008); to ensure quality control in

Atlantic salmon; (Haugen et al., 2006) to determine the freshness of meat (Gorska-Horczyczak et al., 2016); to segregate fruits on the basis of their ripeness (Hines et al., 1999) and to detect aflatoxins in corn (Campagnoli et al., 2009).

iii. Metal Oxide Semiconductor Field-Effect Transistors (MOSFET) - These sensors are quite cheap and more portable; but unfortunately, they show a low sensitivity to carbon dioxide, ammonia and drifting baseline (Sujatha et al., 2012).

Another significant drawback of conductometric sensors is its fragility to various unspecific constituents formed during biochemical reactions, so to minimize errors; measurements are carried usually with help of a pair of sensors (Korpan et al.,1994). Despite the non-specificity of the detection of conductance of solution, conductance measurements are unbelievably sensitive (Turner et al., 1987). Ethanol determination in beverages was done using yeast-based conductometric biosensor and the results showed good correlation with the gas chromatography data. A sensor based on conductometric transducer and *Chlorella vulgaris* cells has been established for activity determination of intracellular alkaline phosphatase activity in the presence of cadmium ions. Algae were immobilized inside bovine serum albumin membranes cross-linked with glutaraldehye vapors (Chouteau et al., 2004).

Calorimetric Biosensors

The warmth capacity is the functioning standard of the calorimetric or thermal biosensors. These assess the alteration in the temperature of the solution which contains the analyte after the action of enzyme and decodes it in relationship of the concentration of the analyte concentration in the solution (Thakur and Ragavan, 2013). Since, most of the enzyme catalyzed reactions generate heat i.e. are exothermic in nature, the determination of the analyte is carried out by measuring the amount heat generated by the reaction. Calorimetric microbial biosensors determine the concentration of the target analytes by making use of the changes in the color of the unusual compound. A great selection of calorimetric sensors is available. They come with advantages such as low cost, simple technique and high selectivity. The thermal biosensors best returns comprise the prospect of uninterrupted measurements, elevated long-standing steadiness, not affected by electrical or ocular obstructions, no interfering act of the reaction products, towering reproducibility and swift responses (Reshetilov, 2005). On the other hand, the limitations include requirement of pretreatment of some samples and the likelihood of the system contamination due to continuous quantification of the unprocessed samples (Ramanathan et al., 1999). For recognition of methyl parathion, as shown in Fig 3, a calorimetric microbial biosensor, based on immobilization of *Flavobacterium* sp. in glass fiber filter and with an exposure limit of 0.3μM and a linear range from 4 - 80μM, was made (Kumar, 2006).

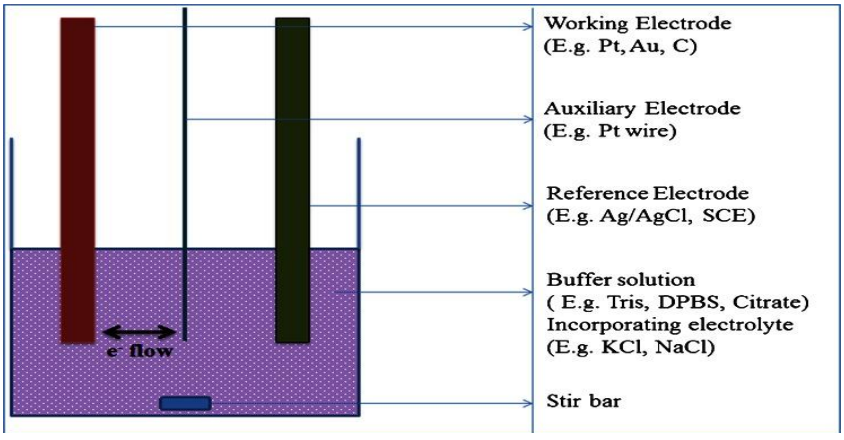

Fig. 3: Calorimetric biosensors (Kumar, 2006)

Piezoelectric Sensors

The functioning of piezoelectric sensors is evolved around a piezoelectric phenomenon (Sliwinska et al., 2014). The piezoelectric transducers facilitate binding of the analyte/any substance in order to produce a detectable signal such as the change in resonance frequency (Bizet et al., 1999). The major advantages of piezoelectric sensors are towering sensitivity, real-time quantification, tiny size, toughness, less expenditure and the concept of identifying analytes on the basis of the universal transformation in mass (Sun et al., 2008). Some limitations, though, are still required to overcome which include lack of specificity and sensitivity along with undue interference. A classical example of uses of a piezoelectric sensor is a quartz crystal microbalance (QMB) (Nagle et al., 1998). It is modified to the liquid medium that allows a straight reaction signal to describe the binding event between sensitive layers, fixed over the surface transducer, along with analyte to be sensed (Bizet et al., 1999). Piezoelectric sensors are frequently used in electronic noses (eg., to establish the optimal time for harvesting apples (Saevels et al., 2003) and to assess the value of tomatoes in electronic tongues (Sinesio et al., 2000).

Optical biosensors

The main principle of these biosensors is the measurement of light which is either absorbed or emitted during a biochemical reaction (Damborský et al., 2016), which is detected by optical fibers on the basis of light scattering fluorescence or absorption (Long et al., 2013). A change in refractive index between two media which have different densities causes changes absorbance or fluorescence which is detected by the sensing element (Pospíšilová et al., 2015). They are advanced as compared to nonelectrical biosensors since they allow detection of numerous analytes using different examining wavelengths (Dey and Goswami, 2011). Measurements using optic probes are preferred because of their capability to transmit signals that consider the changes in polarity, time, wavelength, wave propagation, distribution of the spectrum, or intensity of the light (Peltomaa et al., 2018).

Enzymatic biosensors

These sensors contain biological material such as an enzyme, which identifies and then reacts with the target molecule and produces a chemical signal. This signal is converted into a physical signal by a transducer and sent for processing to an amplifier. Upon application of electrochemically active potential, the simplest type of enzymatic biosensors is capable of reversible reduction or oxidation on the electrode (Bernards et al., 2008). Enzymatic sensors are further classified into inhibitor and substrate sensors. Inhibitor sensors confirm the reducing activity of the enzyme or substances, while substrate biosensors show the activity of selected substrates and its enzymatic reactions (Campanella et al., 2000).

Immunosensors

These are generally used to detect the immunochemical reaction that takes place between antigens and antibodies (Piro and Reisberg, 2017). Hence, they are used for detection of the presence of antibodies and are also used as a diagnostic marker for toxic substances. They determine the antigens in both biological liquids as well as in their natural environment (Balahura et al., 2019). Any molecule which has high selectivity and specificity against specific antibodies can be detected using immunosensors (Wen et al., 2017).

DNA Sensors

Nucleic acids, mostly DNA are the major element of DNA sensors. DNA probes or DNA primers are the sensing materials which indicate the specificity of the entire DNA structure. These probes or primers are produced by amplification of DNA by Polymerase Chain Reaction (Homs, 2002). Suitable modification is done to these in order to enhance their stability or to assist in the insertion of probes in the biosensors. These types of biosensors help in showing the non-macromolecular and

protein compounds which relate with specific DNA fragments (Diculescu et al., 2005). They can be classified as nucleic acid-based, enzymatic, whole cell-based, antibody-based, or aptamer-based biosensors on the basis of the biorecognition unit used (Rasheed and Sandhyarani, 2017).

APPLICATIONS OF BIOSENSORS

Since its development in 1960s, the biosensor technology has found its application in diverse fields ranging from food and water monitoring, quantification of metabolites and in disease detection (Fig. 4). During the last few years, vast advancement has occurred worldwide in development of biosensors using different recognition and detection elements (Grieshaber et al., 2008**;** Jianguo Shi et al., 2017). The biosensors have been used reliably for precise analyses of several components including pollutants, microbial load, quantification of various metabolites, toxins and many other substances like metals in environment (Rasheed et al., 2017**;** Mishra et al., 2018, Neethirajan et al., 2018). The simple glucose monitoring device is the most commonly used biosensor in our everyday life. Evaluation of quality of fish as well as shell fish in terms of its freshness, ageing of meat as well as quality control of fruits during their storage commonly employed biosensor based analytical devices (Prodromidis and Karayannis, 2002). Microbial biosensors are increasingly used because of being highly sensitive, economical, quick response and being portable (Arora et al., 2011). Since microorganisms provide significant advantages including low cost, long lifetime, use over a wide range of pH and temperature, these have been widely used as the biosensing element in the construction of biosensors.

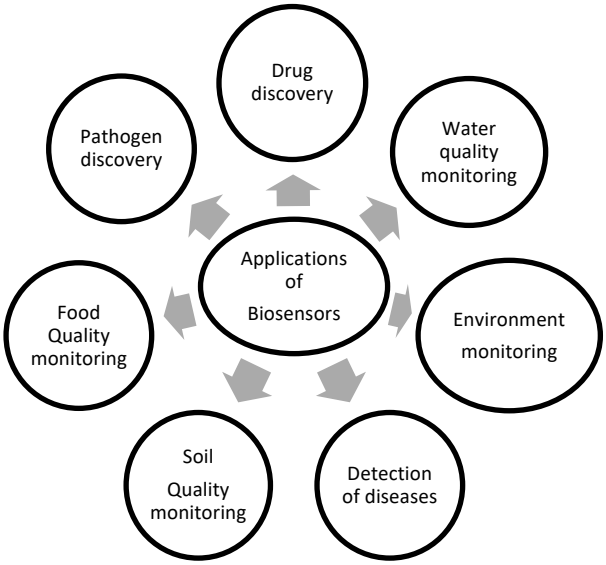

Fig. 4: Applications of biosensors

FOOD AND FERMENTATION

Fermentation of food is a common way of its preservation, production of new varieties and augmentation in its nutritive values (Barthelmebs, 2010). Production of different fermented foodstuffs and drinks require a carefully performed fermentation operation system, thus emphasizing a requirement for the sensitive, accurate and affordable methods for quality control of these products and controlling the fermentation process (Kim, 2009; Mello, 2002). Moreover, there exists a strong need for rapid and inexpensive detection of different components of foods and beverages along with the food borne and water borne pathogens, toxins and pesticide residues with high specificity. Safety of food and environment has been a major concern of food

technologists and health scientists in recent years. In this respect, biosensing technology provides a new rapid and efficient analytical approach for monitoring food quality and safety in food and bioprocessing industries (Thakur and Ragavan, 2013).

Inherent features of immunosensors such as specificity, sensitivity, speed, ease and on-site analysis can be used for various applications. Enzyme and microbial based biosensors (biosensors employing enzymes and microorganisms as recognition element) are commonly employed in dairy and beverage industry (Xiu-Ling et al*.,* 2008). Much research attention has been paid on development of biosensors for ethanol because of its important in food fermentation process as a main or by-product and for its toxicity. For estimation of ethanol, a reagent-less alcohol dehydrogenase-based biosensors and microbial biosensors based on immobilized cells of *Candida tropicalis* or *Saccharomyces ellipsoideus* were developed (Hikuma, 1995; Akyilmaz, 2005; Rotariu, 2004). Moreover, a wider linear range of 0.050 -7.5 mmol/L and a detection limit of 0.035 mmol/L was obtained by using a ethanol biosensor containing *Methylobacterium organophilium* immobilized on eggshell membrane and an oxygen electrode (Wen, 2012). A calorimetric sensor was developed using the copper nano-cluster with peroxidase like activity for detection of xanthine as reported by Yan et al., 2017 and a multicolor sensor was also developed by using gold nanorods (GNRs) for the detection of hypoxanthine as reported by Chen *et al*. (2017). Biosensor based systems for bacteria inactivation are emerging which can detect and kill/inactivate pathogens. An electrochemical sensor based on 3D zinc oxide nano rod was developed which can detect and result in 50% inactivation of bacteria (Yang, 2018). In a study conducted by Pundir et al. (2018), biosensors for detection of free amino acids in vivo were reported to be simple, fast and highly sensitive as compared to other methods for amino acid detection that were complicated and time consuming. Further, these biosensors measured amino acid in beverages, fruit juice, sera and urine and were reused two hundred times over a period of 7 to 120 days (Pundir et al., 2018). A potentiometric biosensor for the identification of beta-lactam in milk was also reported (Ferrini, 2008).

Mycotoxins are secondary metabolites, which pose serious threat to food safety. Methods known till date for detection of these metabolites are time consuming and require extensive preparation steps besides consuming hazardous chemical reagents. To overcome these drawbacks, sensitive, fast, low cost and portable biosensors are being developed using nano-particles for the detection of mycotoxins in food matrices (Santos, 2019). In the recent studies electro-chemical biosensors based on carbon nano-material are also being developed for the detection of food pathogens (Muniandy, 2019).

DETERMINATION OF CARBOHYDRATES

Carbohydrates are important and diverse biomolecules involved in a wide range of physiological/biological processes like growth and development of organisms, cell differentiation, protein trafficking, cell communication and signal transduction (Jelinek R and Kolusheva, 2004; Chevolot, 2009). Number of microbial biosensors e.g. using *S. cerevisiae*, *E. coli* K12 mutants and *Gluconobacter oxydans* has been devised for monitoring carbohydrates in natural samples (Tkac et al., 2000; Held, 2002; Reshetilov, 2010). A microbial sensor based on *Pseudomonas fluorescens* and oxygen electrode was used for glucose determination (Karube, 1979). The biosensor was fabricated for detection of sucrose and lactose using glucose oxidase attached to microbial cell surface by concanavalin A or polyethyleneimine (D'souza, 1989). An approach was developed to protect immobilized glucose oxidase from low pH deactivation (pH –3) by a cellulose acetate membrane modified with Tween-80, thus extending range of glucose detection in fresh fruits including citrus fruits (Maines, 1996); Katrlik et al. (1999) constructed a multi microbial biosensor for simultaneous determination of malate and lactate. Carbohydrates are present within the cell, on cell surface and in extracellular matrix. Any abnormality in the glycosylation pattern can be used as target analytes for detection of various diseases like Alzheimer's disease and cancers (Zhao et al., 2008). The biosensors using carbohydrates as an important building block or recognition molecules have been devised for diagnosis of pathogenic bacteria and cancer biomarkers (Nilsson and Mandenius 1994, Devillers et al*.,* 2017). Concanavalin A adhered to graphene quantum dots GQD – Fe_3O_4 nano-sensing probe provide the way for detecting cancer cells over expressing glycoproteins (Chowdhury et al., 2018). High selectivity and

ultra-sensitivity was reported in detecting the most reliable biomarker - carbohydrate antigen 15–3 (CA15-3) for breast cancer using aptamer based biosensors and impedimetric immunosensor (Zhao et al., 2020; Zhang , 2019). Research is continuously being done in the field of biomedicines for development of biosensors with better sensitivity and reproducibility.

ANTIBIOTICS

Excessive use of antibiotics as human and veterinary medicine or as a growth factor has resulted in their ubiquitous presence in food and spill over into soil and water. This poses a concern over the consumer health and emergence of resistant microbial strains (Chiesa, 2017). Traditional methods like HPLC, mass spectrometry, ELISA used to detect these antibiotics are costly, complicated and time consuming. Thus the alternative rapid, accurate but inexpensive, real time detection procedures are much needed for presence of antibiotics in food and environment. Several microbial biosensors based on genetically engineered *E. coli* expressing organo phosphorus hydrolase and wild-type organo phosphorus degrading *Flavobacterium sp.* have been devised (Mulchandani, 1998). Kumar et al (2008) developed a potentiometric biosensor for selective and rapid detection of cephalosporin group of antibiotics by modifying pH electrode by permeabilized *Pseudomonas aeruginosa*. Recently, a novel electrochemical biosensor has been devised by Mohammad- Razdari (2019) using reduced grapheme oxide (RGO) and gold nanoparticles for detection of sulfadimethyl oxide as low as 3.7x10-16 M in meat samples. Remarkable sensitivity and selectivity has been reported in detection of multiplex antibiotics like ampicillin, kanamycin using multifunctional aptasensor based on an ss DNA fragment to control aggregation of gold nanoparticles and by Fluorescence Resonance Energy Transfer (FRET) strategy (Youn, 2019; Wu et al., 2020). Fluorescent-labelled apatmers developed by Liu et al. (2020) exhibited ultra-sensitivity in detection of even trace amount of chloramphenicol and kanamycins in food samples. The whole cell sensing system utilizing genetically engineered *E. coli* cells with β –galactosidase as reporter signal on paper strips provided the visual online system for detecting tetracycline in the environment (Ma et al., 2020). Recent researches suggest that biosensors based on electrochemical, mass sensitive or optical signal transducing mechanisms provide promising detection technology for antibiotic in environment and food (Majdinasab, 2020).

ENVIRONMENTAL MONITORING

Use of hazardous material in industry, agriculture, and construction and in IT industry has resulted in their accumulation in terrestrial and aquatic environment. Heavy metals are quite commonly used in a number of industries viz. electronics, mining and metal finishing (Wang et al., 2013). The build-up of these metal ions in living organisms due to their non-bio-degradability results in a number of diseases (Gammoudi et al., 2010). The best way to detect them is by utilizing genetically engineered bacteria, which generate quantifiable signals on interaction with biomolecules (Yong, 2009). The fact that alkaline phosphate enzymes present in the cell wall of *Chlorella* cells become inactive in presence of mercury was explored by Singh et al. (2012) to estimate mercury using immobilized *Chlorella sp*. to fabricate a biosensor. Amperometric microbial biosensors and aerobic microorganisms that degrade organic compounds have been widely used in aquatic systems to quantify Biochemical oxygen demand (Liang, 2011; Chee, 2013). The microbial biosensors based on Recombinant *E. coli* having the packed lux CDABE cassette was used for monitoring pollutant in water system (Horsburgh, 2002; Bechor, 2002). The toxicity of phenolic compounds released from the paper and pulp and pharma industries was estimated in wastewater treatment plants (Philp et al., 2003). Turemis et al., (2018) fabricated the biosensor based on symbiotic interaction of *Paramecium-Chlorella* for real time evaluation of biotoxicity in marine environment. The presence of the Digital micro fluidic diluter based biosensor using whole cell microalgae-*Platymonas subcordiformis* - as bio reporter provided the sensitive system for detection of various pollutants in marine environment (Han, 2019). The colorimetric biosensors and enzyme-based biosensor systems represent another promising low cost and highly sensitive arena alternatives for monitoring environmental toxic pollutants (Liu, 2020; Sarkar, 2019).

BIOSENSORS FOR FOOD ALLERGEN DETECTION

In general the food is safe to consume, but globally 2-4% adult and 6-8% of the children suffer with allergy from food substances (Planque et al., 2017). To name a few, the common food allergens are eggs, milk, peanut, soy, fish, shellfish, mustard, gluten, sesame and nuts that are responsible for ~ 90% of all the food allergies. The unintended consumption of even a very small quantity of these allergens may lead to life-threatening situations. Therefore, as per EU regulation, it become mandatory to mention the ingredient suspected to cause allergy on the food labels. Efficient laboratory detection methods are needed to avoid accidental exposure to undeclared or hidden allergens and to manage cross contamination during food processing. The classical methodologies including immunological and DNA based assays and mass spectrometry is being replaced by more sensitive, cheap and eco-friendly bio sensing detection strategies (Alves et al., 2016). Wang et al (2011) reported simultaneous detection of eight food allergens i.e. soybeans, wheat, peanuts, cashews, shrimp, fish, red meat, and chicken by using the silicon based optical biosensor chips with .001 precisions. The peanut allergens (Archin - Ara h1) was detected in chocolate candy bars by Pollet et al. (2011) using surface Plasmon resonance (SPR)-immune-based biosensor. Electrochemical affinity based biosensors employing antibodies or aptamers were also designed for fast detection of the food allergens (Vasilescu, 2016). The electrochemical biosensor utilizing co-immobilized galactosidase and glucose oxidase enzymes was developed for lactose quantification (Marrakchi et al., 2008). Recently an impedimetric aptasensor was developed for detecting gliadin-a fraction of gluten, which came out with a limit of detection (LOD) of 5ppm, much lower than as maximum allowed limit 20ppm in gluten free products (White, 2018). An aptamer biosensor fabricated on Graphene oxide (GO) as a platform provided a sensitive method for monitoring Tropomyosin (TM)- major shrimp allergen to LOD as low as 2 nM (Chinnappan et al., 2020). These current advancements in biosensor technology provide a hope for development of low cost and easy to use real time detection method for accurate detection and proper management of allergenic constituents in food.

CONCLUSION

The term “biosensor” refers to a powerful and innovative analytical device involving a biological sensing element. Different types of biosensors are available depending on their biological or transducing elements, each having its own merits and demerits. The main features of biosensors are their stability, cost, and reproducibility. Many of them even allow rapid and on the site detection of analytes. Biosensors have a wide range of applications, such as determination of carbohydrates in food, detection of antibiotics, heavy metals and other contaminants in environment, monitoring of food allergens, and many more, which have been discussed in the present review. Since past many decades a lot of work is going on for developing this technology, there are still a lot of applications, which need to be explored further. Although biosensors offer a lot of advantages, one of the major disadvantages that need to be overcome is the problem of heat sterilization. Because of the denaturation of biological material, which is present, heat sterilization of biosensors is not possible. Further research is needed to improvise the technology with respect to decrease in background signals and increase in sensitivity and specificity and also availability of tailor –on- demand sensors. Also, research needs to be carried out to reduce the cost of biosensors along with increase in their stability and prevention of their denaturation during heat sterilization.

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