REVIEW

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Biosensors: An effective toxicity biomonitoring tool

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The expanding necessities of growing population are met with broad utilization of synthetic chemicals resulting in environmental contamination and serious health issues in humans. These pesticides enter in food chain by permeation into soil, water, food commodities, plants, animals and most significantly in humans. Environmental toxicity is the main cause for severe diseases in humans. Thus, biomonitoring of these hazardous substances is extremely significant. Conventional chromatographic strategies used for pesticide recognition have been laboratory based, costlier, display longer response times and possess stumpy sensitivity. This urged the need for smart sensors that can intelligently detect the perilous substances from the environment as well as human blood in real time. Inalienable highlights of biosensor technology emerge as a center of attraction for toxin detection. Depending upon choice of transducers and bioreceptors, numerous biosensors for *in vitro* and *ex vivo* detection of pollutants have been discussed in the present study. This paper also compares the performance of various biosensors on different parameters. Electrochemical biosensors are cheapest among all and most of the research work has been concentrated on these devices. Biosensor design with low cost instrumentation is prime need of the current scenario.

Keywords: Pesticides, biosensors, toxicity, toxicity biomarkers, detection.

1. Pesticide toxicity and human health

Agriculture is the major constituent of Indian economy and serves dietary needs of billions of people[1]. However, growing pressure to fulfill food necessities of increasing population, crisscross strategic developments and practice implementation, lack of technical skills among farmers and their use in transport segments promoted intemperate use of synthetic chemicals leading to environmental contamination and human health issues[2–5]. A survey on pesticide consumption in India over years (2000-2013), reported that among 29 states, 70% of pesticide usage was contributed by Uttar Pradesh, Andhra Pradesh, Punjab, Haryana and Maharashtra[6]. Favorable climate conditions and availability of plentiful sources support the high intensity of pesticide use in Malwa region of Punjab[7]. Thus, their comprehensive and prolonged use would be an incredible risk to ecological balance in near future[8]. Bioaccumulation and biomagnification are two critical mechanisms linked to different elements in food chain. A magnificent example of biomagnification involved reproductive failures and eggshell thinning of organisms such as bald eagles, osprey, peregrine falcons when exposed to DDT, an organochlorine insecticide in 1972 in USA[9].

Due to adoption of rural practices[10] these pesticides filter into the soil and kill essential soil microorganisms. Their decimation reduces the soil fertility to great extent[11]. These residues can enter the ground water by leaching through soil, air drift, modern release, accidental spillage etc. Best example was immune system damage of fishes and several amphibians[12,13] due to presence of Atrazine in sea water. Even drinking water was found tainted with 39 pesticide deposits in US and Canada[14].

Presence of pesticide residues in food products are due

to direct application to food source, food chain, storage and transportation[15,16]. Fruits and vegetables that were commonly consumed in Kuwait[17] and China[18] contained pesticide deposits exceeding their MRLs (maximum residue levels). These toxic substances generally accumulate in animal tissues through plants consumed by them. Direct application of pesticides for crop protection against pests, results in contaminated feed or fodder[19]. Due to contaminated feed and fodder given to animals like sheep, goat[20], lamb, cow, buffalo, pesticide residues has been found in dairy products, meat, eggs[21–23]. Finally, pesticides reach the human population by eating meat of animals, dairy products etc.[24] therefore, creating exposure to higher toxification[25] and detrimental impacts[26].

In totality, abusive pesticide consumption has contaminated almost all the constituents of food chain. Higher the place of an organism in food chain, higher the level of accumulation of toxins in it.

The root cause of deleterious human health problems are contributed by toxic nature of organophosphates[27] and carbamates[28]. The World Health Organization (WHO) estimated that around 220,000 deaths happen every year due to pesticide poisoning among total 3,000,000 pesticide cases reported[29]. Exposure of pesticides to newborn children and youngsters is at high risk due to their immature immune systems in contrast to adults[30,31]. Pesticide exposure can be acute or chronic. Acute poisoning[32] prompts migraine, diarrhea, skin problems while chronic poisoning leads to cancer[33], depression[34], improper thyroid functioning[35], premature hair graying[36] etc. A multicenter case study among an Indian woman belonging to states of Haryana and Punjab assessed that breast cancer risk was lower in lactoovo vegetarians when compared with non-vegetarians and lacto vegetarians expressing close relationship between dietary patterns and breast cancer risk[37]. Researchers have also revealed that oxidative stress[38] and ground water contamination are the major causes of health issues in cancer prone area of Punjab.

2. Biosensors: An effective biomonitoring tool for toxin detection

Conventional spectrophotometric[39] and chromatographic methods[40,41] used to check toxicity in humans includes laboratory testing[42], huge dependence on skilled personnel[43], complex pretreatment sample procedures[44,45], results variation due to time gap between collection and analysis of sample[46], fear of lab testing[47] and lab to lab results fluctuation[48]. Presence of destructive chemicals and their noxious impacts on human health[49] emphasized upon development of better biomonitoring techniques that can estimate pesticide toxicity in real time. Professor Clark, known as father of biosensor, built an effective biomonitoring tool for blood glucose measurement in 1962[50]. Thereafter, a variety of biosensors have been developed to work in various areas such as environmental monitoring, medical use, pathogen identification, pesticide detection, food safety etc.[51–53]. Biosensor is a blend of bioreceptor and transducer[54], where bioreceptor senses the target element and produces some physiochemical changes; while transducer makes an interpretation of this acknowledgement and transform it into electrical signal. This technology ensures uninterrupted and real time monitoring of pollutants. Biosensor development relies upon immobilization procedures that bind bioreceptor with transducer[55]. To design low cost devices, lot of endeavors have been put to integrate bioelectronics with nanoelectronics[56] and utilize artificial bioreceptors[57]. Examples of biosensors are blood glucose monitoring[58], environmental for pesticide detection[59], DNA and pregnancy test biosensor[60].

2.1. Electronic transducers

Transducer plays a dynamic role in converting biorecognition event into an electronic signal, which can further be processed with signal conditioners to get value in readable form. The choice of transducer to be used in biosensor depends on the reaction result generated by the analyte upon interaction with biorecognition element and type of signal released by the bioreceptor. Transducer can be classified into electrochemical, optical and piezoelectric (Fig. 1) mode of action. Different types of transducers are explained underneath:

2.1.1. Electrochemical

This is most widely used transducer due to simple instrumentation and portable detection unit[61]. It relies upon the chemical interaction between bioreceptor and target molecule that modifies the electrolytic properties of solution. They can

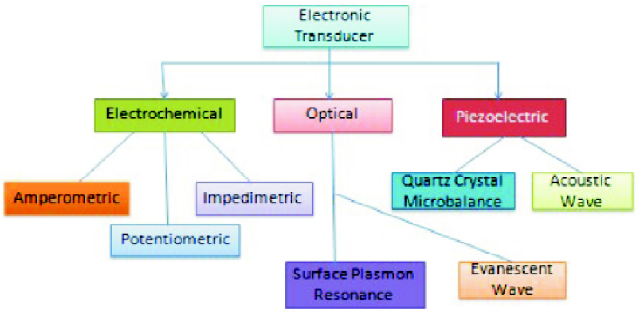

Fig. 1. Classification of electronic transducers based on different reactions and type of transducer response. Electronic transducers broadly divided into three groups – Electrochemical, Optical and Piezoelectric transducers. Each group is further classified according to the type of signal produced in response to analyte detection.

be amperometric[62], potentiometric or impedimetric based on measurable property used for analyte detection. Enzymes are the predominant biorecognition elements in electrochemical detection because of high specificity and characteristic biocatalytic action[63]. Electrochemical biosensors can provide both direct and indirect detection of neurotoxic substances[64].

Amperometric: An electrochemical biosensor that measure change in enzyme activity with and without inhibitor by estimating the current produced, when substrates are catalyzed by their enzymes[65]. Amperometric biosensor was developed for dichlorvos recognition based on immobilization of acetylcholine esterase (AChE) on screen printed carbon electrodes modified with dialdehydes and polyethyleneimine. Non-covalent immobilization of AChE on PEI modified electrodes provides lower detection limit up to 0.1 nM[66].

Numerous mono enzymatic or bienzymatic amperometric biosensors had been developed for detection of neurotoxic compounds[67]. Performance of mono-enzymatic and bi-enzymatic systems with *p*-aminophenyl acetate and phenyl acetate as substrates was compared for detection of organophosphates. Results demonstrated that phenyl acetate could be used as an alternate substrate to *p*-aminophenyl acetate or acetylthiocholine[68]. Generally, electronic potential required for oxidation or reduction of an electroactive species is high in amperometric biosensors. To lower such potential either redox mediators such as prussian blue[69], 7,7,8,8-tetracyanoquinodimethane, phthalocyanine[70], cobalt hexacyanoferrate etc. or nanomaterials such as multi-walled carbon nanotubes (MWCNT)[71], gold nanorods[72], nanowires[73] etc. can be used. To achieve broad linear range and lower detection limits for malathion detection, electrochemical (AChE) biosensor based on transition metal carbides nanosheets have been developed[74]. A low-cost biomimetic biosensor with polyacrylamide polyhydroxamicalkanoate (PHA) polymer as an alternative to AChE, was immobilized on modified electrodes. Detection limits estimated for pesticides paraoxon ethyl, fenitrothion and chlorpyrifos were 0.36, 0.61 and 0.83 μmol L^{-1} respectively[75].

Potentiometric: This technique involves measurement of change of potential caused by ions present in solution due to hydrolysis of natural substrates catalyzed by enzymes[76]. Electrodes can be ion[77], gas selective and pH sensitive. A dual amperometric/potentiometric biosensor with AChE and OPH (organophosphorus hydrolase) enzymes immobilized on screen printed electrodes was designed to achieve detection limits in micro molar range and response time of lesser than a minute in organophosphate recognition[78].

Impedimetric: These biosensors utilize interdigited microelectrodes to measure change in resistance due to chemical processes occurring in the solution[79]. A novel impedimetric biosensor using sol gel technique to immobilize molecularly imprinted polymers on the transducer surface was developed for detection of methidathion[80].

2.1.2. Piezoelectric

These biosensors offer simple construction, label free detection, optimum frequency response and minimal phase shift[81]. Jacques and Pierre Curie invented the piezoelectric effect[82] which can now be exhibited by gigantic number of biomolecules, natural and synthetic materials[83]. Quartz crystal is commonly used for piezoelectric biosensor construction[84]. A highly sensitive piezoelectric biosensor composed of macromolecular polymer and carbon nanotubes with silver coated crystal surface was presented for detection of pesticides in freshly picked radishes[85]. Immobilization procedures plays a dynamic role in piezoelectric biosensor development and influence its characteristic parameters[86,87]. To achieve ultra-sensitive detection on single chip, an integrated label free biosensor combining mass sensing capabilities with electrochemical measurements was developed[88]. A highly sensitive piezoelectric immunosensor was designed to detect the antibody of Nu-Tu-19 cancer cells in serum samples for early cancer detection based on antibody antigen interactions[89]. Another piezoelectric quartz crystal mi-

crobalance (QCM) biosensor based on correlation theory was developed to measure the resonant frequency at minimum impedance by sending series of multi-sinusoidal signals[90].

2.1.3. Optical

An optical biosensor is an analytical device that can detect desired range of target analytes using optical elements such as light source, optical transducer, sensing element, transmission medium and a detector system[91]. Focal points of optical technology involve high selectivity, multi analyte detection, immunity against electromagnetic interferences and minimally invasive for *in vivo* estimations[92]. Optical biosensors follow principles of light[93] i.e. evanescent wave[94], surface plasmon resonance[95], chemiluminescence, bioluminescence and so on. A label free optical immunosensor based on binding inhibition test, where immobilized hapten protein conjugate (CN4C-BSA) competes with free chlorpyrifos for binding to specific antibody was developed to detect chlorpyrifos at nanogram per litre levels in real water samples[96].

A bi-enzymatic optical biosensor was proposed for detection of seven organophosphates available in oxo, thio and mixed forms. Required fluorescence changes were provided by novel class of nanomaterials i.e. (CdSe/ZnS) quantum dots. There is a close relationship between fluorescence quenching of quantum dots, enzyme inhibition and pesticide toxicity[97]. Another biosensor using same optical principles to measure the photoluminescence changes produced by graphene quantum dots was presented for organophosphates detection[98].

In short, transducers are an integral component of biosensor. The phenomenon used for producing interactions on the surface decides the type of response generated at transducer output.

2.2. Biological components

Bioreceptor is an indistinguishable part of biosensor that helps to identify and then detect the target analyte. The main function of biological component is to ensure high specificity towards desired target analyte. Generally, it is accomplished by selective binding of analyte at molecular level. The selective binding in turn triggers a reaction such as enzyme catalysed reactions which are transduced in some signal form. There are numerous biological components categorized into naturally and synthetically made constructs. Naturally occurring components such as antibodies, enzymes utilize biologically evolved interactions to attain analyte specificity. Synthetic components are engineered to imitate physiological interactions. Hence, biosensors can have various bioreceptor elements such as enzymes, antibodies, whole cells etc. there are different classes of biological elements and based on their recognition structures, these elements are employed in several applications.

2.2.1. Direct detection of toxic chemicals

Rapid toxicity testing and analysis is essential in present scenario of environmental quality deterioration. Global industrialization has caused distribution of pollutants such as heavy metals, organic compounds and toxins in natural environment. These pollutants pose human health risks and ecological imbalance. Pollution remediation is directly linked to monitoring of toxic chemicals present in ecosystem. Hence, detection of toxicity in natural environment is extremely important. The perilous substances present in the environment can be directly estimated by study of different biological elements. Some of these biological elements mentioned below, serve as recognition compounds coupled with biosensors.

Enzymes: Enzymes are most widely utilized bio-recognition elements that work in lock and key mechanism with substrates[99]. Detection of commonly used pesticides can be best realized by measuring the inhibition of the activity of certain enzymes such as acetylcholinesterase (AChE), acid phosphatase (AP), urease (Ure), organophosphorus hydrolase (OPH) etc.[100]. Immobilization process must ensure mechanical stability to the enzyme[101]. Enzymatic biosensors can measure the analyte's concentration through catalytic and inhibition means. For catalytic biosensors[102], target analyte acts as substrate for enzyme and reaction product is measured. For example, organophosphorus hydrolase (OPH) enzyme hydrolyzes organophosphate compounds to produce two protons that can be detected electrochemically[103]. While for inhibition based, target analyte acts as inhibitor for enzyme and decrease of enzyme activity is estimated to determine target analyte concentration[104].

Antibodies: These are glycoproteins produced by the immune system against foreign attack by antigens such as viruses, bacteria etc.[105]. Crucial steps involved in antibody production include hapten design, choice of carrier protein, hapten carrier conjugate method and UV spectrometry[106]. A general protocol for generating polyclonal[107] or monoclonal antibodies[108] involves injecting immunogen combined with

adjuvant into animals at multiple sites. Blood of vaccinated animals are collected and serum can be separated. For monoclonal antibody production, spleen cells are fused with myeloma cell line[109]. Highly expensive, lower reproducibility and lack of availability of highly specific antibodies are the major issues associated with their use.

Whole cell microorganisms: A group of microorganisms such as yeast[110], bacteria (*Bacillus subtilis*), macroalgae[111], *Aspergillus niger* etc. are immobilized on transducer surface to generate signal[112]. The use of whole cells as a bioreceptor ensures longer life time and high stability when compared with enzymes[113]. An amperometric biosensor was proposed for detection of organophosphates based on immobilization of organophosphorus hydrolase (OPH) and microorganisms on transducer surface. OPH first hydrolyzes organophosphates to produce *p*-nitrophenol, followed by bacterial degradation, resulting in formation of compound that can be electrochemically detected[114].

Aptamers: These are oligonucleotide or peptide molecules that follow SELEX (systematic evolution of ligands by exponential enrichment)[115] criteria to bind several targets i.e. proteins, pathogens[116], pesticides[117] and nerve agents. Due to excellent biocompatibility, stability, shelf life and dynamic range[118], they are used for detection of neurodegenerative diseases such as Parkinson's and Alzheimer's disease[119].

Molecularly imprinted polymers: These are artificial biorecognition elements having excellent stability, reproducibility and stability against wide range of target analytes[120]. Molecular imprinting involves the interaction of template molecules with the monomers followed by template removal that generates the molecular polymer complementary to the template in size, shape, and location of functional groups[121,122]. An electrochemical sensor was developed for electro polymerization of polypyrrole on screen printed electrodes for detection of 2,4-dichlorophenoxy acetic acid in the presence of 2.4 D template molecules[123].

2.2.2. Toxicity biomarkers (Indirect detection)

Biological monitoring of these pesticides has become imperative due to their deleterious impacts on human beings[124]. This process involves measurement of substance called biomarker in body fluids to monitor chemical exposure and health issues[125,126]. Survey studies conducted in Hyderabad and Mirpurkhas districts of Pakistan, reported that the pesticide residues in blood samples of agro professionals were more alarming as compared to non-agro professionals[127]. Besides this, toxicity evaluation of pesticides among the group of children due to environmental and occupational exposure to adults[128] was performed and found that environmental exposure to children was more severe.

Four different approaches used for biomonitoring of toxicants exposure involves measurement of enzyme activity[129], recognition and detection of phosphorylated protein adduct[130], metabolites measurement in urine and determination of unbound organophosphates. Ellman assay[131], radioisotope assay and delta pH method of Michael are some of the assays used for enzyme activity measurement. Measurement of AChE activity as biomarker for detection of exposure to organophosphates using anti-AChE antibody followed by their electrochemical detection on the SPE surface modified with multiwalled carbon nanotubes gold nanocomposites[132] has been studied.

The measurement of phosphorylated protein adduct provides more accurate information regarding the type of pesticide exposure. An electrochemical QCM immunoassay based on selective properties of transition metal oxides zirconia (ZrO_2) and HRP labelled anti-AChE antibody was developed to capture and recognize phosphorylated adducts in plasma samples[133]. Ultrasensitive detection of phosphorylated AChE adducts could be achieved by use of zirconia nanoparticles (ZrO_2 NPs) and quantum dots (ZnS@CdS, QDs) labelled anti-AChE antibody in electrochemical immunosensor[134]. Mass spectrometry techniques such as liquid chromatography coupled with MS (LC-MS), matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF)[135] etc. has also been utilized for identification of phosphorylated protein adducts. An electrochemical measurement of AChE activity for detection of low dose organophosphates, through pralidoxime reactivation of inhibited enzyme has been performed. This method acts as a dual biomarker or detection of enzyme inhibition and phosphorylated protein adducts using Fe_3O_4-Au nanocomposites[136].

Examples of toxicity biomarkers

AChE (3.1.1.7) and BChE (3.1.1.8): An enzyme acetylcholinesterase is available in plasma, RBC's membranes in brain while BChE can be found in blood plasma, liver and pancreas. Enzymatic activities of cholinesterases are contributed by presence of three sites such as β anionic, aromatic gorge and active site[137,138]. The enzymes AChE and

BChE differ by their preferences over different substrates. Trp-279 is an essential amino acid present in the β anionic site of AChE while missing in BChE, which accounts for different inhibition sensitivities for variety of organophosphates. RBC AChE has 33-day half-life; while BChE has 11-day half-life, hence RBC AChE inhibition could be detected even after longer time of OP exposure[139–141].

Acyl peptide hydrolase (3.4.19.1)

This enzyme is serine esterase/protease present in membranes of RBC, brain and liver that eliminate N-acetylated amino acids from peptides. Since it is present in RBC (i.e. half-life 33 days) hence inhibition can be detected even after longer periods of organophosphate exposure. As a toxicity biomarker[142], it can be used to detect chlorpyrifos and metabolites of TCP (Tri ortho cresyl phosphate) which are powerful contaminants used in jet engines[143].

Neuropathy target esterase (EC 3.1.1.5): The enzyme also called Patatin is available in brain, spinal line, liver and kidney. This was first identified in 1930, when ginger extracts tainted with metabolites of 3,5,6-trichloro-2-pyridinol (TCP) were taken by individuals of the United States, caused delayed neurotoxic impacts (organophosphate induced delayed syndrome symptoms (OPIND))[144] to thousands of lives. This compound is also used in jet engines, so there is constant exposure of these compounds to pilot and passengers travelling in a plane[145].

In brief, direct and indirect detection of noxious chemicals can be possible by the study of different biological components as bioreceptors or toxicity biomarkers.

2.3. Comparison of cost of building instrument and recurring cost

Total cost of instrument is contributed by non-recurring and recurring costs. Non-recurring cost consists of expenses one time occurred for development of biosensor and recurring includes the expenses that occur repeatedly for each task performed. Limitations associated with conventional devices, impel the need to develop cheap, handheld and user-friendly devices. Thus, biosensor development is becoming one of the thrust areas of research in present scenario. Numerous electrochemical, optical and piezoelectric biosensors are available in market. Among all, electrochemical is relatively simple, least expensive and can produce electrical signals by interaction between sensor electrodes and target analyte[146]. Low-cost handheld blood glucose monitoring device[147] is an excellent example of electrochemical biosensor. Costly instrumentation, longer response time and limited availability of optical accessories make optical biosensor less popular[148]. While piezoelectric biosensors, suffer from calibration difficulties, higher sensitivity towards environmental conditions restricts their use.

Conclusions

Pesticides have been massively implicated in proliferation of modern agriculture. These synthetic chemicals due to their lethal nature and long persistence in the environment enter the various constituents of food chain and impose detrimental impacts on human health. Thus, biomonitoring of these neurotoxic compounds is matter of concern. The impediments in existing methods have forced the need for development of effective biomonitoring tools that would pave the way for real time estimation. Biosensors emerge as attractive solution for biomonitoring of noxious substances. Real difficulties in development of commercial biosensor for toxin detection are lower sensitivity, stability and reproducibility of transducer surfaces.

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