pISSN 1229-1153 / eISSN 2465-9223 *J. Food Hyg. Saf.*
Vol. 34, No. 6, pp. 509~518 (2019)
https://doi.org/10.13103/JFHS.2019.34.6.509

Journal of Food Hygiene and Safety
Available online at http://www.foodhygiene.or.kr

Review

Immunosensors for Food Safety: Current Trends and Future Perspectives

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(Received December 6, 2019/Revised December 17, 2019/Accepted December 21, 2019)

ABSTRACT - To monitor the levels of antimicrobials, allergens, pathogens and other contaminants in foods meant for human consumption, it is imperative to have quick, accurate and low-cost tests. Advanced techniques (e.g. label-free biosensor assays) have been developed over the past 10–15 years to solve some of these problems. As biosensors, immunosensors can provide real-time measurements, a high degree of automation, and improved throughput and sensitivity. By comparison with conventional methods, immunosensors are less expensive, less sophisticated physicochemical instruments that require less time for analysis while also being more user-friendly. In this review, we discuss our current knowledge about immunosensors, their strengths and weaknesses, as well as the future of these biosensors in food safety.

Key words: Biosensors, Detectors, Food pathogens, Food contaminants, Nanoparticles

To ensure food safety, it is essential to assess the presence of both chemical contaminants and pathogenic bacteria. Though the conventional method of using selective media to isolate and count live microbial cells in foods are sensitive and inexpensive, they take longer times to give results since the method requires cells to multiply and form colonies. Also, the majority of chemical contaminants are commonly analyzed using separative techniques coupled to various detectors such as gas chromatography-flame ionization detector (GC-FID), gas chromatography-electron capture detector (GC-ECD), gas chromatography-mass spectrometry (GC-MS), high performance liquid chromatography ultra violet spectroscopy (HPLC UV), high performance liquid chromatography fluorescence detection (HPLC-FL) and high-performance liquid chromatography-mass spectrometry (HPLC-MS)[1)]. Many a time, food safety analysis is conducted on the food product but not the process of production and this makes it difficult to identify the source of contamination. However, this problem can be solved by analyzing the critical control points in the processing or the entire manufacturing processes. This will help in identifying the point of contamination. With the implementation of hazard analysis and critical control points (HACCP), the demand for fast, reliable and effective methods of biological and chemical contaminants has increased. Detection measures that will take few minutes or hours to give results are necessary for processors to take necessary steps when contamination is suspected at any point in time[2)]. The importance of biosensors lies on their high specificity and sensitivity over a broad spectrum of analytes even in complex mixtures with minimum treatment[3)]. Biosensors usually contain biological recognition components such as nucleic acids, microorganism, enzyme, proteins or antibodies with an appropriate transducer[4)]. Immunosensors typically contain two basic components connected in series, (1) a biologically sensitive element (receptor) and (2) a physicochemical transducer (a physical detection system). The receptor translates the biochemical information (i.e, amount of the analyte, etc) into electroactive specie, that is, an optical signal, chemical or mass change signal.

The transducer then accepts and translates the signal into an electrochemical, optical, calorimetric, mass change, magnetic or piezoelectric signal which is accepted by a detector. The detector transforms the signal into another signal that can be more easily measured, processed and

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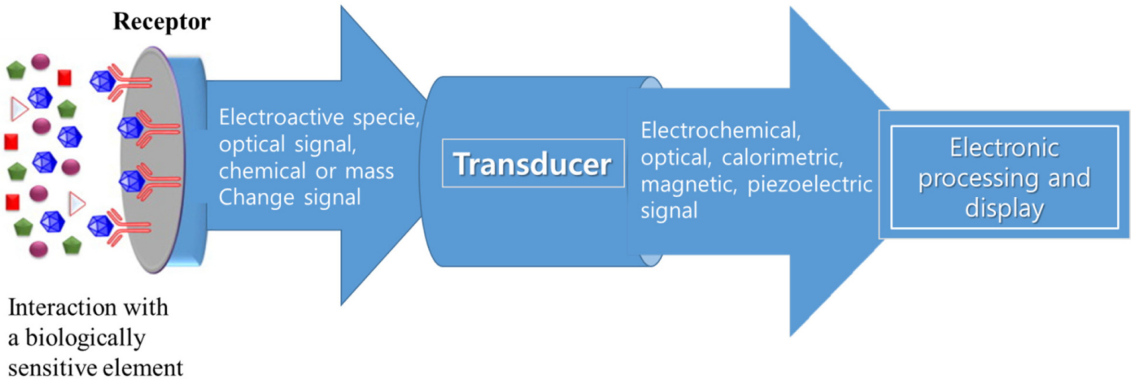

Fig. 1. Scheme of the basic integrated units of a biosensor.

quantified (Fig. 1).

Immunosensors may be classified as optical, electrochemical, acoustic wave or cantilever-based sensors depending on the mode of signal transduction[5].

Optical immunosensors

In optical immunosensors, the biological sensitive element is immobilized onto the surface of the transducer and responds to the interaction with the target analyte either by generating an optical signal, such as fluorescence, or by undergoing changes in optical properties, such as absorption, reflectance, emission, refractive index and optical path. The optical signals are collected by a photodetector and converted into electrical signals that are further electronically processed[6]. The main optical phenomena employed in optical immunosensors are summarized in Table 1. The optical transducers used respond to visible and ultraviolet radiation. Alternatively they may generate chemiluminescence or bioluminescence. Some transducers may be coated with enzymes for absorption of light, fluorescence and luminescence. The main advantage of optical transducers is their nondestructive operation style, their easy reading and their high sensitivity[7].

Table 1. Main optical phenomena employed in optical immunosensors.

Optical signal	Transducing technique
Absorbance	Light intensity measurement
Reflectance	Light intensity measurement
Fluorescence	Total internal reflection fluorescence
Refraction index	Interferometry Surface plasmon resonance (SPR) Total internal reflection
Optical path	Interferometry
Spectroscopy	Surface enhanced Raman scattering (SERS)

Currently, more sensitive optical immunosensors are being developed to detect very low amount of toxins and pathogens. Such new methods include the use of nanomaterials, optical waveguide based materials and others.

Nanomaterials in optical immunosensors

Nanoparticles (NP) such as gold nanoparticles (AuNPs), quantum dots (QDs), magnetic nanoparticles (MNPs), graphene and carbon nanotubes have specific optical, fluorescence and magnetic properties, and interactions between these properties give nanoparticles great potential for food analysis[8]. Their extremely high surface-to-volume ratios and exceptional nanoscale properties make nanoparticles very useful. Quantum dot (QDs) nanocrystals of inorganic semiconductors have emerged as promising alternative bioanalytical tools because of their unique optical properties including high quantum yield, photostability, narrow emission spectrum, and broad absorption[9]. The main application of QDs as sensors exploits the Forster resonance energy transfer effect (FRET) due to their narrow, size-tuned and symmetric emission spectra, which has made them excellent donors for FRET sensors[10]. These qualities greatly reduce the overlap between the emission spectra of donor and acceptor and avoid the cross-talk in such FRET pairs[11]. Meanwhile, QDs have broad excitation spectra as donors, and allow excitation at a single wavelength far removed (>100 nm) from their respective emissions, which enables QDs to be used in multiplex assays without the need for multiple excitation sources[12]. In addition, the high photobleaching threshold and good chemical stability of QDs greatly improve the detection sensitivities and detection limits[13]. Several studies have reported the benefits of using nanoparticles in their immunosensor design to improve performance[14]. For

instance, after measuring the concentrations of herbicides in grains using CdSe/ZnS QDs, Carrillo-Carrión et al. observed that the quantum dots strong reducing capacity when placed in organic media such as acetonitrile and ethanol[15]. Also, by using fluorescence and Raman spectroscopy, the QDs reduced diquat herbicides to their monocation radicals. These monocation radicals generated high fluorescence emission spectra which served as analytical signals for quantifying diquat herbicides in a short time. Several other studies have applied water-soluble bioconjugated QDs to detect food contaminants such as heavy metals, pesticides and toxins such as botulinum toxin, enterotoxins produced pathogens, and for the development of oligonucleotide-based microarrays has been studied extensively[16]. Other immunosensors have been fabricated using Gold Nanoparticles (GNP)-antibody conjugates to detect pathogens[17], pathogens[18], ochratoxin A, zearalenone, and aflatoxin B1[19]. Also, carbon nanotubes (CNTs) have also been explored for highly sensitive biosensing assays in recent years for detecting pesticides in cereals[20].

Wave fiber-optic immunosensors

Optical waveguide (such as fiber optic and planar waveguide) transmit light based on the principle of total internal reflect (TIR). The main components of fiber optic biosensors (Fig. 2) that influence sensitivity and detection limits include the light source, optical transmission medium, immobilized biological recognition element, optical probes (such as fluorescent markers) for transduction and the optical detection system[21]. Several researchers have applied wave fiber-optic biosensors in food safety studies. For instance, using biotin-avidin interactions, Valadez et al. immobilized anti-*Salmonella* polyclonal antibody on an optical fiber using Alexa Fluor 647-conjugated antibody (MAb 2F-11) as the reporter[22]. At the detection of *Salmonella,* an evanescent wave from a laser excited the reporter and the fluorescence was measured by a laser-spectrofluorometer. By this, they could use evanescent wave fiber optic biosensor for *Salmonella* detection in food samples. Recently, Tang et al. developed an optical fiber immunosensor to detect trace amounts of phthalate esters[23]. The sensor was developed by coating the surface of the optical fiber with an antigen so that the inhibition signal of phthalate esters to immune reaction between the fluorescent-labeled antibody and the coating antigen could be detected by an avalanche photodiode. The sensor has proven to have a good generation performance, superior stability and reproducibility. Plastic optical fiber immunosensors have also been developed for the detection of sulphur-reducing bacteria in water samples. The device detects up to 10^3 most probably number of bacteria per mL in about 30 minutes[24]. Generally, fibre optic immunosensors are not affected by electrical interference, may be reusable, are more versatile, and can be miniaturized. However, they are sensitive to ambient light interference and their biorecognition elements require special binding techniques. This reduces the effectiveness and speed of the device.

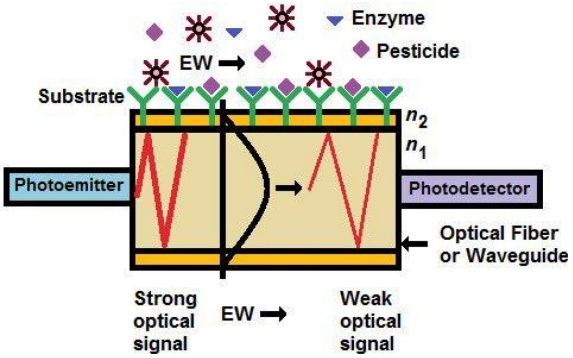

Fig. 2. Evanescent wave biosensor for pesticides based on optical fiber or waveguide[25].

Surface Plasmon Resonance (SPR) immunosensor

SPR is an optical technique which detects biomolecular interactions originating from electromagnetic waves resulting from fluctuations in the electron density at the boundary of two materials[26]. SPR operates on the principle that a thin layer of gold on a high refractive index glass surface can absorb laser light to produce electron waves (surface plasmons) on the gold surface. This occurs only at a specific angle and wavelength of incident light (Fig. 3). Also, it is highly dependent on the surface of the gold such that binding of a target analyte to a receptor on the gold surface yields a measurable signal. Surface plasmon

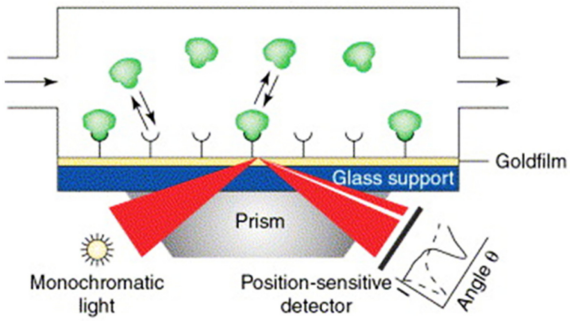

Fig. 3. Schematic diagram of the surface plasmon resonance. Monochromatic light is reflected on a gold surface. At a certain angle where the surface plasmons are excited, the reflected light is continuously measured. This angle is directly connected with the analyte bound to the surface[33].

resonance sensors operate using a sensor chip made of a glass plate supported by a plastic cassette with one side coated with a microscopic layer of gold. This side contacts the optical detection apparatus of the instrument. The opposite side is then contacted with a microfluidic flow system to create channels across which reagents can be passed in solution[27]. Light is reflected off the gold side of the chip at the angle of total internal reflection and detected inside the instrument. The angle of incident light is altered to correspond to the evanescent wave propagation rate with the rate of the surface plasmon plaritons propagation rate[28]. This induces the evanescent wave which penetrates the glass plate and the liquid flowing over the surface. The behavior of the light reflected off the gold side is dependent on the refractive index at the flow side of the chip surface. As analytes bind to the flow side of the chip, the refractive index is altered and the biological interactions can be measured. When biomolecules attach to the surface of the chip, the refractive index of the medium near the surface changes and the SPR angle is altered as a function of the change[29]. Recent developments exploit the high specificity and real-time measuring abilities that SPR offers. For instance, based on a sandwich assay, Liu et al. combined an antibody and functionalized Fe_3O_4 magnetic nanoparticles for rapid detection of *Salmonella enteritidis*[30]. Because SPR immunosensors are able to selectively detect chemical or biological molecules without the need for pretreatment of the samples, some recent studies have developed SPR immunosensors based on a sandwich direct method for detecting very low concentrations of antibiotics[31]. Similarly, Makaraviciute et al. developed a reusable SPR immunosensor by chemically cross-linking protein G and antibody complexes to improve its sensitivity for detecting human growth hormones in real samples[32]. This immunosensor will be very important in the food industry for detecting banned substances such as growth hormones in foods. Despite the advantages of optical immunosensors, they require bulky and power-intensive light sources, detectors and monochromators. Also, potential false signals may occur from complex colored samples. More so, since the sensitivity of optical methods follow the Beer–Lambert's law, a small sample volume and path length is required to achieve certain performances.

Electrochemical immunosensors

Electrochemical immunosensors are good alternatives for optical biosensors because they can be used even when the media is turbid, have comparable instrumental sensitivity and the device can be made portable[34]. Electrochemical biosensors are based on enzymatic catalysis of a reaction

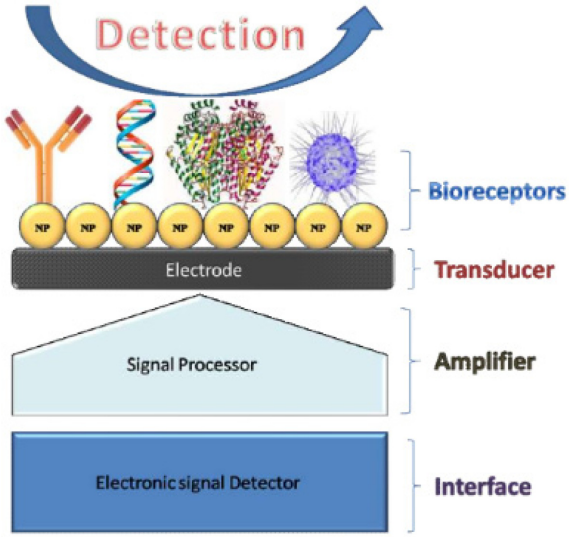

Fig. 4. Schematic presentation of electrochemical biosensor[37].

that produces or consumes electrons. The enzymes used are referred to as redox enzymes and the substrate usually contains three electrodes namely a reference electrode, a working electrode and a counter electrode[35]. The target analyte goes through a reaction at the active electrode surface and results either in electron transfer across the double layer to produce a current or contribute to the double layer potential to generate a voltage (Fig. 4). At any given potential, the current can be measured because the rate of flow of electrons becomes proportional to the concentration of the analyte. Alternatively, the potential difference can be measured at zero current[36].

There are several electrochemical techniques such as potentiometric, conductimetric and amperometric techniques which can be applied for analytical purposes.

Potentiometric Immunosensors

In potentiometric immunosensors, the signal from an antigen-antibody binding is measured as the potential difference at zero current between the working electrode and the reference electrode. The working electrode's potential depends on the concentration of the analyte in the gas or solution phase. The reference electrode usually provides a defined reference potential. Based on the blocking surface principle, Silva et al. recently developed a label-free potentiometric immunosensor using a paper-based sensing platform to detect *Salmonella* Typhimurium in fruit juice[38]. Some researchers have developed competitive immunosensors from gold nanoparticles and polyclonal aflatoxin B_1 for rapid detection of aflatoxin B1 in peanut[39], while others have used the developed similar immunosensors for detecting

pathogenic bacteria in foods[40] and heavy metals[41]. Also, potentiometric immunosensors can be used for estimating monophenolase activity in fruit juice[42], determining sucrose concentration in drinks[43] and measuring the concentration of isocitrate in fruit juices[44].

Conductimetric immunosensors

Conductimetric devices detect changes in conductivity between two electrodes. In conductimetric immunosensors, the binding of antigens to antibodies result in a change in resistivity which is measured. This immunosensor has several advantages. They do not require reference electrodes and they prevent Faraday processes on electrodes since they operate at low-amplitude alternating voltage. Also, they are not sensitive to light and they can be miniaturized[45]. This type of biosensor has been applied in detecting mycotoxins levels[46], glucose concentrations juices and nectars[47] and pathogens in foods[48].

Amperometric immunosensors

Amperometric biosensors operate by producing a current when a potential is applied between two electrodes (Fig. 5).

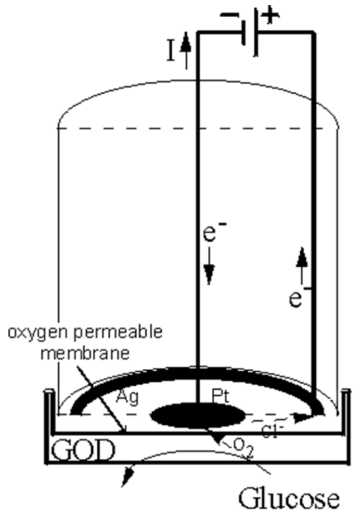

Fig. 5. Schematic diagram represents an amperometric biosensor. When a potential is applied between the platinum cathode and the silver anode, a current (I) is generated and carried between the electrodes by a saturated KCl solution. The electrode compartment is separated from glucose oxidase (GOD) by a plastic membrane which is only permeable to oxygen. The analyte solution is however separated from the GOD by another membrane which is permeable to the substrates and products. The biosensor is usually about a cm in diameter and yet can be reduced to a diameter of 0.25 mm by means of a Pt wire cathode within an anode made of silver needle plated with steel and utilizing dip-coated membranes (http://www1.lsbu.ac.uk/water/enztech/amperometric.html).

The working electrode is usually a noble metal such as gold, platinum or carbon, in the form of graphite, glassy carbon or pyrolytic graphite[49]. The commonest type of amperometric immunosensors can be considered as ELISA tests with electrochemical detection, where redox species generated by a redox enzyme (enzymatic label) are converted into a measurable current at a fixed or variable potential[50]. Classically, the sensor involves a three-electrode system, though this is often reduced in practice to two electrodes in many devices. By applying a given potential between the working and the reference electrode, the species of interest is either oxidized or reduced at the working electrode causing a transfer of electrons which results in a measurable current that is directly proportional to the concentration of the electroactive species at the electrode surface over a wide dynamic range[51]. Many amperometric biosensors have been developed for use in food. For instance, Shkotova et al. developed an amperometric biosensor based on the platinum SensLab electrode with immobilized lactate oxidase to determine the amount of lactate in must during wine fermentation[52]. The sensor showed a narrow dynamic range of 0.004–0.5 mM lactate concentration and higher sensitivity range (320 nA/mM. Multi-array amperometric biosensors have been used to detect and quantify several analytes in food. A typical instance is the biosensor developed by using platinum printed electrodes SensLab and immobilized enzymes (alcohol oxidase, glucose oxidase, and lactate oxidase) for analyzing ethanol, glucose, and lactate in wine. The developed amperometric biosensor demonstrated linear response within a concentration range of 0.3-20 mM for ethanol, 0.04-2.5 mM for glucose, and 0.008-1 mM for lactate. No decrease in ethanol and glucose biosensor activity was revealed during 2 months after fabrication. The developed biosensors showed high selectivity to the substrate and were successfully applied to the analysis of complex mixtures such as wine and must[53].

Acoustic wave immunosensors

Acoustic wave biosensors are detectors that operate by measuring the changes that occur in the physical properties of an acoustic wave as a response the molecules being measured[54]. The sensors are generally based on quartz-crystal resonators because quartz is abundant, cheap to manufacture and has good chemical stability. Most acoustic wave biosensors use piezoelectric transducers since piezoelectric materials have the ability to generate and transmit acoustic waves in response to a frequency[55].

Piezoelectrical immunosensors

Piezoelectric immunosensors are biosensors that combine

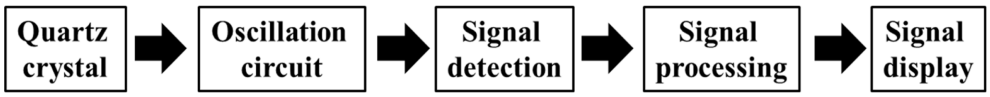

Fig. 6. Basic structure of a piezoelectrical immunosensor.

the high sensitivity of piezoelectric quartz crystal with the high specificity of antigen-antibody reaction[56]. The basic structure of a piezoelectrical immunosensor is shown in Fig. 6. Many piezoelectrical immunosensors have been designed for the detection of food toxins. For instance Pohanka et al. developed a gold coated quartz crystal microbalance based label-free biosensor which was very sensitive in detecting aflatoxin B1 in ground nut[57]. The researchers latter made their immunosensor reusable by using a sandwiched system consisting of secondary rabbit-immunoglobulin antibodies tagged with gold coated nanoparticles which cis capable of regenerating the bioelectrode[58]. Piezoelectrical immunosensors have also been developed for detecting of drugs[59] and different foodborne pathogens such as *Salmonella* sp.[60], *Campylobacter jejuni*[61], *Listeria monocytogenes*[62] and *E. coli* O157:H7[63]. Also, a piezoelectrical immunosensor that distinguishes *Salmonella* species from serogroups like *S. paratyphi*, *S. typhimurium* and *S. enteritidis* with a detection limit of 10^4 cells/ml even in the presence of 10^8 cells/ml of other non-pathogenic strains of Salmonella and *E. coli* has been developed[64]. Other piezoelectric immunosensors have been designed to detect chloramphenicol in chicken, milk, eggs and honey[65]. Ding et al. fabricated an reusable immune sensor for detecting 2,4-dichlorophenoxyacetic acid (2,4-D) with a detection limit of ~13.0 ng/mL[66]. Taken together, these quartz crystal microbalance sensors have excellent detection sensitivities and short detection times that are similar to SPR and electrochemical biosensors.

Cantilever-based immunosensors

Microcantilevers can act as physical, chemical or biological sensors. They act by detecting alterations in cantilever bending or vibrational frequencies. These sensors have a diving board that moves up and down at a regular interval. This movement changes when a given amount of analyte is adsorbed on its surface[67]. The bending-mode cantilever is the commonest operating mode of cantilever sensors used for biosensing in liquids. Surface-stress changes caused by changes in the medium surrounding the cantilever or on its surface cause expansion or contraction of the cantilever surface. As the target analyte binds to only one side of the cantilever, an asymmetric stress is generated in the cantilever structure which leads to bending of the cantilever[5]. Various research groups have shown the flexibility, sensitivity and low detection limits of cantilever-based sensors. Some examples include the biomolecular detection and recognition of cosmetic components[68], peptides, DNA[69], bacteria[70], poison agents[71] and heavy metals[72]. A nanocantilever made of silicon nitride capable of detecting a single piece of DNA of 1578 base pairs has been developed. To detect DNA, nanoscale gold dots were placed at the ends of the cantilevers and they acted as capture agents for double-stranded nucleic acids [73]. Recently, resonant cantilever gas sensors have been developed which detect volatile compounds. Although most mechanical resonant sensors poorly maintain high quality factor when placed in liquid, this new sensor possesses a liquid/gas separated detection system which makes it possible to detect volatile organic compounds in solution[74]. Although microcantilevers are sensitive, fast and can reliably detect small concentrations of analytes in air and liquids, they have some limitations. For instance single microcantilevers are prone to parasitic deflections resulting from changes in ambient temperature or chemical interaction between the cantilever and its environment especially when the cantilever is operated in a liquid[75].

Conclusion and future perspectives

To monitor the levels of pathogens and contaminants in food, it is imperative to have rapid, accurate and low-cost tests. For this reason, advanced techniques (e.g. label-free biosensor assays) have been developed over the past 10–15 years to solve some of these problems. These immunosensors have shown their ability to provide real-time measurements, a high degree of automation and sensitivity. To improve the sensitivity of immunosensors, many detection methods have been combined in single detectors. The involvement of nanomaterials in most current sensors is very common. Meanwhile, the main challenge with the use of nanomaterials is that, they their physical and chemical properties are composition-dependent and hence requiring careful optimization. Metallic nanoparticles (NPs), especially gold nanoparticles (AuNPs), together with carbon nanotubes (CNTs) are the most used materials[76]. Though the full potentials of nanoparticles are not explored, their application in biosensing opens new doors for the development of novel approaches for the detection of toxins and contaminants. In the near future, various portable

electronic devices used for daily activities such as keychain holders, smartphones and smart watches will be made sensitive to detect toxins, allergens and contaminants in food. In 2017, Chen et al. demonstrated how mesoporous core–shell palladium @ platinum nanoparticles could act as signal amplifiers in dual lateral flow immunoassay and how they could be integrated with smartphones to detect pathogenic bacteria[77]. Recently, also developed a smartphone-based Hg^{2+} biosensor which showed high sensitivity and specificity indicating how cost effective biosensors could be developed for use in homes and fields. Lu et al. have revised extensively on smartphones-based biosensors[78]. Other researchers have developed miniature systems consisting of disposable antigen extraction devices integrated with electronic keychain readers for rapid detection of gluten levels in food[79]. All these technologies have shown how electronic wearable devices as well as portable devices could be made into instruments for monitoring food safety. In the near future, such portable and reusable will be readily available, accessible and cheap for public use.

국문요약

사람이 섭취하는 식품 내의 항생제, 알레르기 유발 물질, 병원균 및 기타 오염물질의 수준을 모니터링하기 위해서는, 빠르고 정확하며 저렴한 비용으로 테스트 해야 한다. 이러한 문제 중 일부를 해결하기 위해 지난 10-15년 동안 진보된 기술(label-free biosensor assays)이 개발되어 왔다. 이 면역감지키트들은 실시간 측정이 가능하고, 높은 수준의 자동화를 제공하며, 향상된 처리율과 민감도를 가지고 있다. 또한, 기존의 방법과 비교하여 가격이 저렴하고, 덜 복잡하며, 분석 시간을 단축시켜주는 사용자 친화적 키트이다. 이 리뷰에서는 면역감지키트의 장단점, 그리고 미래의 식품안전검사에서의 사용성에 관한 것에 대해 논의해 볼 것이다.

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