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Surface plasmon resonance (SPR) biosensors for food allergen detection in food matrices

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ABSTRACT

Food allergies are recognized as a growing public health concern, with an estimated 3% of adults and 6-8% of children affected by food allergy disorders. Hence, food allergen detection, labeling, and management have become significant priorities within the food industry, and there is an urgent requirement for reliable, sensitive, and user-friendly technologies to trace food allergens in food products. In this critical review, we provide a comprehensive overview of the principles and applications of surface plasmon resonance (SPR) biosensors in the identification and quantification of food allergens (milk, egg, peanut, and seafood), including fiber-optic surface plasmon resonance (FOSPR), surface plasmon resonance imaging (SPRI), localized surface plasmon resonance (LSPR), and transmission surface plasmon resonance (TSPR). Moreover, the characteristics and fitness-for-purpose of each reviewed SPR biosensor is discussed, and the potential of newly developed SPR biosensors for multi-allergen real-time detection in a complex food system is highlighted. Such SPR biosensors are also required to facilitate the reliable, high-throughput, and real-time detection of food allergens by the food control industry and food safety control officials to easily monitor cross-contamination during food processing.

1. Introduction

Food allergies, immune-mediated adverse systemic immune responses, are now recognized as a global health issue with increasing prevalence in the field of food safety (Toral and Bryce, 2010). Food allergies can stimulate the immune system and induce a hypersensitivity mediated by immunoglobulin E (IgE), releasing allergic inflammatory transmitters and provoking severe acute hypersensitivity reactions, such as skin rash, urticaria, diarrhea, abdominal pain, and even anaphylactic shock, which is life-threatening (Sicherer and Suzanne, 2004). Recent studies indicate that a food allergy is estimated to affect approximately 3% of adults and 6-8% of children (Kumari et al., 2010). According to the FDA, there are 150 deaths each year from the serious allergic reaction known as anaphylaxis. Generally, more than 170 kinds of food and 923 allergens have been identified as causing allergic reactions. Among them, the “big eight” allergenic foods including milk, egg, peanut, soy, shellfish, fish, wheat, and tree nuts cause approximately 90% of all allergic reactions (Thompson et al., 2006). Nearly 1.9% of infants are sensitive to milk and dairy products (Warren et al., 2013) in the USA. The prevalence of a food allergy to wheat is 3.0–4.2% in Europe (Nwaru et al., 2014). A USA-based study demonstrated that $\leq 0.7\%$ and $\leq 3\%$ individuals are allergic to fish and shellfish, respectively (Levin et al., 2015). Approximately 1.5 million individuals are affected by peanut-induced anaphylaxis and 50 to 100 deaths occurred in the USA every year (Leung et al., 2003).

So far, no complete and effective treatment for food allergies exists, and the only effective instruction for susceptible customers is to avoid the ingestion of foods containing allergens. Many countries have promulgated food allergen labeling measures, requiring manufacturers to correctly identify allergen ingredients on labels to alert consumers not to eat certain food products. Currently, due to the development of food processing technologies, it has become a significant issue to identify the presence of allergens in food matrices. Therefore, the primary task of food allergy avoidance endeavors to develop a reliable, sensitive, and user-friendly technology for allergen detection in order to facilitate risk assessment and to manage and label allergenic ingredients in food

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products.

Over the past several decades, many effective techniques have been extensively applied to ensure the labeling and management of food allergens (Kirsch et al., 2009), such as enzyme-linked immune sorbent assay (ELISA), polymerase chain reaction (PCR), and liquid chromatography-mass spectrometry (LC-MS). The ELISA method has been widely used in the routine detection and screening of food allergens because of its high sensitivity and specificity. However, ELISA is prone to false positive and false negative results due to the influence of food processing methods, operations, and experimental reagents (Asensio et al., 2008). In addition, PCR technology is commonly used to monitor allergenic ingredients during food processing, with high specificity and a high degree of automation, since DNA is generally more stable than proteins in food processing. However, the application of PCR technology to food allergen detection is limited, since it is unsuitable for identifying target allergenic proteins with unidentified genes in food matrices (van Hengel, 2007). Furthermore, LC-MS has been developed for both online and offline quantification of food allergens based on target peptides (Bereszczak and Brancia, 2009), which is especially suitable for the determination of food allergens during food processing due to its indifference towards conformational protein epitopes. However, further studies are required on the application of LC-MS for food allergen detection, and the high cost of professional mass spectrometry equipment may limit its wide application in the food industry (Vogelstein B, 1999). Alternatively, biosensors are considered a powerful technology to rapidly analyze and track food allergens with high sensitivity and selectivity while allowing for site analysis (Pilolli et al., 2013), such as surface-enhanced Raman spectroscopy (SERS), amperometric biosensors, voltammetric biosensors, and quartz crystal microbalance (QCM) biosensors. However, these biosensors generally require expensive instruments and skilled operators. Hence, it is an urgent requirement to develop simple, accurate, sensitive, inexpensive, and easy-to-use methods to quantify allergens in food matrices.

Recently, surface plasmon resonance (SPR) biosensing has been developed for the determination of protein concentration because of its extreme sensitivity to species, including food allergens, toxic proteins, marker proteins, antibodies, and pharmaceutical proteins (Singh, 2016; Xia et al., 2010). SPR biosensors have been widely applied to the measurement of the kinetics and affinity of bimolecular binding in real-time and in a label-free fashion with low reagent consumption (Hyungsoon et al., 2009). In addition, the SPR biosensor serves as a powerful tool for the high-throughput analysis of food allergens in multichannel or array-imaging instrumental set-ups (Pilolli et al., 2013). In this review, we briefly introduce the basic composition and fitness-for-purpose of four types of SPR biosensors for food allergen detection (Table 1) including fiber-optic surface plasmon resonance (FOSPR), surface plasmon resonance imaging (SPRI), localized surface plasmon resonance (LSPR), and transmission surface plasmon resonance (TSPR). Scheme 1 provides schematic illustrations of the SPR biosensor-based quantitative platforms for food allergen detection. We also list in detail specific applications for the identification and quantification of food allergens in several food products, such as milk, egg, peanut, and seafood.

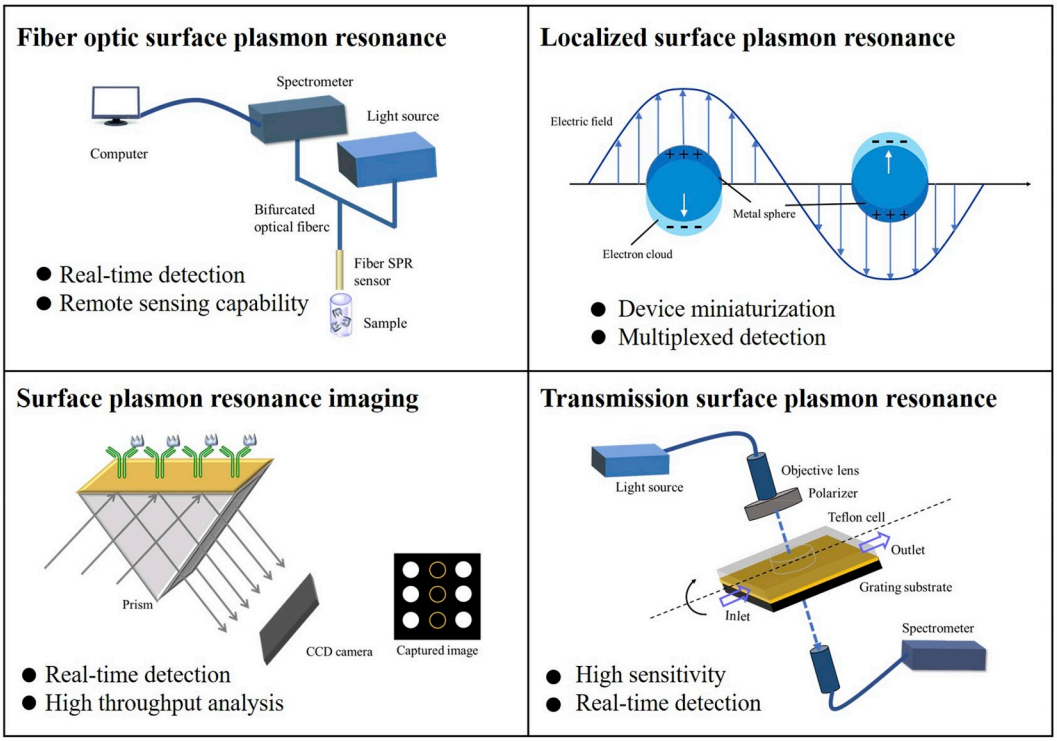
2. Methods for food allergen detection using SPR-based biosensors

Surface plasmon resonance (SPR) biosensors are based on a special mode of metal-dielectric waveguides, the surface plasmon, to measure the refractive index changes caused by the interaction of biomolecules with the surface of SPR biosensors (Šípová and Homola, 2013). The surface plasmons (SPs) are delocalized electron oscillations, which exist at the interface of a metal-dielectric medium. At room temperature, the free electron gas in metals can move freely in a positively charged nucleus lattice, so metals can be called a cold plasma. The physical process of surface plasmon excitation is called surface plasmon resonance (mainly excitation by attenuated total reflection (ATR) via evanescent waves). SPR is a highly sensitive optical sensing technology relying on the interactions of light with the free electrons in a semi-transparent noble metallic layer or chip and can realize the real-time monitoring of small changes in the effective refractive index of a metal-dielectric interface (Michel et al., 2017). A *p*-polarized incident light is illuminated from a denser optical medium (glass) into a thinner optical medium (gas or water), and total reflection occurs when the incident angle exceeds the critical value. Furthermore, the evanescent wave is generated when the incident light penetrates into a thinner medium, which has a depth of half the wavelength, and then gets back to a denser medium. Generally, surface plasmon waves form parallel to the metal surface when the free electrons in a thin metal film are excited by the incident light, resulting in the reflected light energy decreasing sharply because of the transfer of incident energy to the surface plasmon. The minimum value of the reflected light intensity happens at the angle corresponding to the incident angle, the SPR angle or θSPR, which changes at a typical depth of 200–300 nm when a single layer of molecules is formed on the metal surface in the vanishing field. Importantly, the SPR rotation offset is ultrasensitive to the refractive index or the mass density of a single layer near the metal surface; hence, the reaction between food allergens and their receptors can be monitored in real-time. Generally, SPR biosensors have been developed following a common approach: an optical biosensor, microfluidic chip, sampling system, and data acquisition/analysis software (Mariani and Minunni, 2014; Wang et al., 2013), including light source, optical system, sensing system and detection system. The optical system generates the incident light, the sensing system converts the signal to the change in resonance angle or wavelength, and the detection system measures the magnitude of the resonance angle or wavelength. According to the different types of media in which light is coupled to a gold film, four technologies exist for exciting SPRs including prism coupling, optical waveguide, grating coupling and fiber coupling, among which prism coupling and fiber coupling are the most used in SPR biosensors (Homola, 2003).

For example, Fig. 1 shows the principle of an SPR biosensor with a Kretschmann-type prism coupling to detect food allergens. Generally, the optical system consists of an excitation light source, a prism and a metal film cladded on the prism (approximately 50 nm) (Zhang et al., 2016). The evanescent wave passes through the metal film, and the SPR phenomenon occurs at the interface between the metal film and food allergens captured on the surface of the metal film. SPR biosensors are used for quantifying food allergens through monitoring the adsorption and dissociation of the binding of food allergens to their receptors in

Table 1
Four types of SPR biosensors for food allergen detection: basic composition and advantages.

Detection mode	Basic composition	Advantages
FOSPR	● Light source ● Sensing probes: sensitive layer, metal film and core. ● Sample cell ● Detector	●High stability ●High sensitivity ●Real-time detection ●Long-distance detection
SPRI	●Light source ●Kretschmann-type prism ●Metal film ●Sample cell ●Charge coupled device (CCD) imaging	●High sensitivity ●Device miniaturization ●Multiplexed detection
LSPR	●Light source ● Noble metal nanostructures ● Sample cell ● Detector	● Label-free detection ● Real-time detection ● High throughput analysis
TSPR	● Light source ● Grating substrate ● Sample cell ●Metal film ●Detector	●High sensitivity ●Real-time detection



Scheme 1. Schematic illustrations of SPR biosensor-based quantitative platforms for food allergen detection.

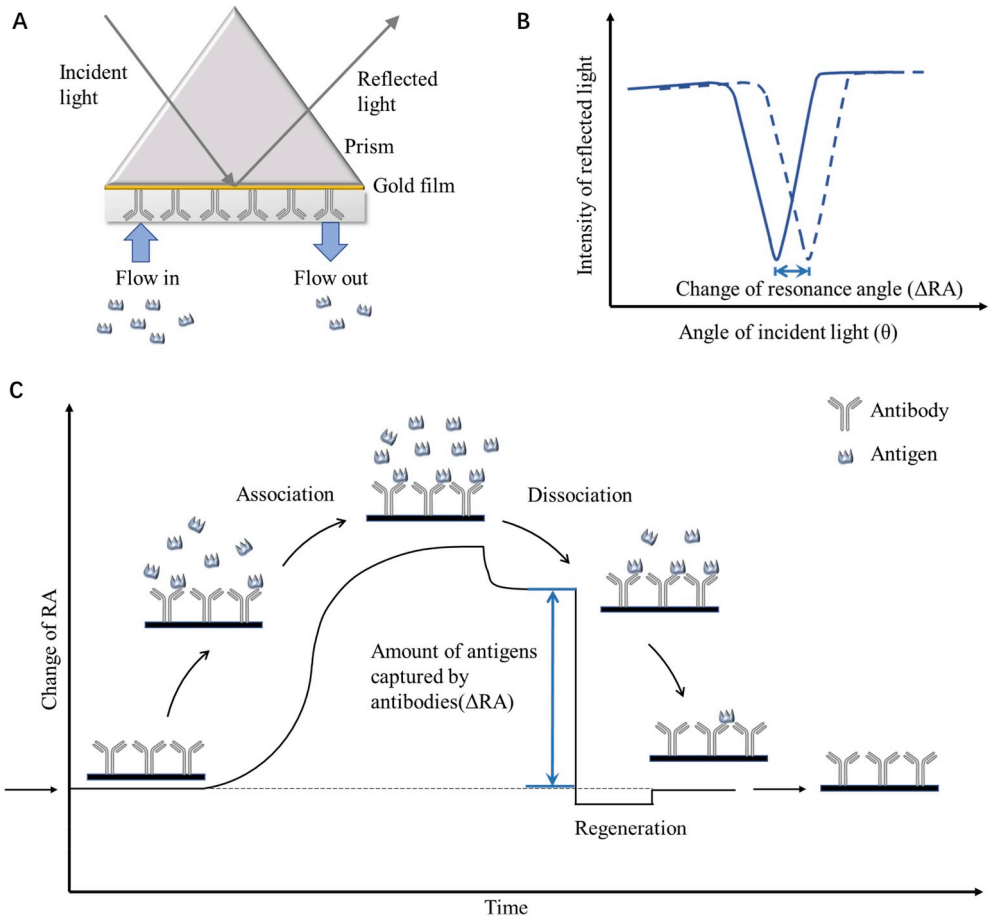


Fig. 1. The principle of an SPR biosensor for food allergen detection. (A) The structure of a Kretschmann-type prism coupling. (B) The change in the SPR resonance angle with a fixed incident wavelength. (C) The real-time SPR sensorgram of food allergens using antigen-antibody interactions.

real-time, recording the SPR signal value and analyzing the dissociation rate constant, Kd. Additionally, SPR biosensors can be regenerated by destroying the binding of the analyte to their receptor with a regeneration solution (a high-salt or acidic solution) (Wammes et al., 2015). The excitation of an SPR is determined by several parameters such as the incident angle, incident wavelength, metal film, prism refractive index and medium refractive index. According to different detection parameters, SPR biosensors can be divided into four types of methodologies to measure the SPR signal: angular modulation (Bévenot et al., 2001; SlavíK et al., 1998), wavelength modulation (Manuel et al., 1993), intensity modulation (Nelson et al., 1996) and phase modulation (Esteban et al., 2000; Kazuyoshi and Koji, 2002). The angular modulation SPR biosensor is utilized to measure the angle shift at resonance under a fixed incident wavelength. The wavelength modulation SPR biosensor is designed to monitor the wavelength shift at resonance under a fixed angle of incidence of the light source. The intensity modulation SPR biosensor is employed to detect the change in reflected light intensity to obtain the curve of refractive index-reflected light intensity at fixed incident wavelength and angle (Jirí, 2008). The phase modulation SPR biosensor is applied to detect the phase change in the reflected light and incident light and to obtain the curve of refractive index-phase difference at fixed incident wavelength and angle.

Among these methods, angular modulation and wavelength modulation are the most commonly employed for the development of SPR biosensors to quantify food allergens through the high affinity of food allergens to their corresponding biorecognitions.

2.1. Fiber-optic surface plasmon resonance (FOSPR)

Fiber-optic surface plasmon resonance (FOSPR) is an SPR-based multimode- and single-mode-optical fiber biosensor, and the SPR phenomenon is stimulated by total reflection at the interface between a core and cladding instead of total reflection at the prism surface (Jorgenson and Yee, 1993). Compared to the prism-based SPR biosensor, FOSPR, with its small size and flexible design, easily carries out the long-distance and real-time detection of food allergens. In addition, smartphone-based FOSPR devices have been developed for real-time detection with good accuracy consistent with that of commercial SPR instruments (Gms et al., 2018).

Several parameters have been introduced to affect the FOSPR sensing capability, such as the properties of the metal layer, the numerical aperture of the fiber, the fiber core diameter and the sensing length (Sharma et al., 2018). To excite FOSPR, three critical parameters should be considered. First, the core energy needs to be coupled to the fiber cladding, while the cladding energy mode can partially extend to the outer surface of the fiber. Second, the appropriate coating material should be selected, with the film thickness and uniformity being precisely controlled. Third, the polarization state of the fiber cladding mode needs to be precisely controlled so that the cladding mode, which satisfies the phase matching condition, can be coupled to the metal film of the fiber surface to form the SPR resonance wave.

Fig. 2A shows a schematic of fiber-optic SPR biosensor. FOSPR can be categorized as an on-line transmission type and an end-reflection type. The sensing probes of both types of FOSPR are generally composed of a sensing layer, metal film and core. Generally, the core of a sensing probe is coated with three layers, first a thin metal layer, then a buffer layer, and at last a sensing layer (food allergen samples). However, the on-line transmission type of the FOSPR biosensor probe is located in the middle of the fiber, while the end-reflection type of FOSPR biosensor probe is located at the end of the fiber. In the on-line transmission type of FOSPR biosensor, a high-reflectivity nanoscale metal film is deposited on the surface of the core to be used as a biosensor chip. A white light source is incident on the optical fiber, while the optical signal transmitted in the core interacts with the surface of the metal film. The on-line transmission type of FOSPR biosensor can be utilized for the identification and quantification of food allergens via the measurement of the change in the wavelength when a sample of different refractive index is in contact with the biosensor chip. Generally, a specific antibody is immobilized on the metal film of the biosensor chip to identify food allergens based on the antigen-antibody reaction. Muller et al. designed a sandwich-type FOSPR, by using this antibody-coated surface, αS1-casein in raw milk was detected with an LOD of 0.87 mg/ml (Muller-Renaud et al., 2005). The sensing probe of the end-reflection type of FOSPR biosensor is coated with a gold film on the end face, which is several hundred nanometers to reflect the light signal, and a metal film, tens or even hundreds of nanometers, is plated near the end face (approximately 5 mm). Due to the reflection of the light signal on the surface of the metal film, the optical signal passes through the SPR sensing portion twice, and two resonances occur (forward and reverse). The resonance spectrum signal is measured by the detecting terminal, which contributes to the reduction of the length of the fiber at the sensing portion by approximately 50% and omits the flow cell, and the SPR biosensor is applied to food allergen detection for remote testing occasions (Morton et al., 1995). Tran et al. introduced a novel sandwich-type FOSPR immunoassay between antibodies and Au NP-aptamer conjugates for the detection of peanut allergen (Ara h 1) in food matrices with an LOD of 75 nM (Tran et al., 2013).

2.2. Surface plasmon resonance imaging (SPRI)

Surface plasmon resonance imaging (SPRI), also called SPR microscopy, combines the SPR measurements with the spatial capabilities of imaging (Rothenhäusler and Knoll, 1988). SPRI has been widely applied in type I allergy diagnosis (Yanase et al., 2013), drug discovery (Ye, 2012), biomarker screening (Arghavan and Maryam, 2013), nucleic acid detection (D'Agata and Roberta, 2013), food safety (Piliarik et al., 2009a; Situ et al., 2010), and environmental monitoring (Mauriz et al., 2007) because of its good image resolution, image quality, and high sensitivity (Grigorenko et al., 1999; Hickel and Knoll, 1990). Especially, SPRI presents the ability to monitor allergenic protein affinity interactions in real-time without labeling, including DNA-binding protein, RNA aptamers/protein, antibody-antigen and carbohydrate/protein. Compared to classical SPR sensing, SPRI has the capacity to visualize the biochip surface in real-time and simultaneously monitor hundreds of molecular interactions in a single biochip with probe arrays (Scarano et al., 2010).

Currently, two types of prisms, the Otto-type prism and Kretchmann-type prism, are generally employed in SPR biosensors. However, the Otto-type prism is perceived as being difficult to fabricate and use, since its coupling structure is composed of a high-refractive-index metal film with a gap for the sample cell. The Kretchmann-type prism coupling biosensor directly fabricates the metal film at the bottom of the prism, and the sample cell is under the metal film. Due to its alignment simplicity and easily controlled parameters and variables, the Kretchmann configuration has become the standard technique for the prism-based excitation of SPR (Kretschmann and Kretschmann, 1972; Kretschmann and Raether, 1968). As shown in Fig. 2B, parallel *p*-polarized light passing through the prism, penetrates the metal film assembled with one or more food allergens and stimulates the SPR phenomenon when the incident angle is larger than the critical angle of total reflection. The SPR signal is related to the dielectric constants of the metal film and the food allergen array points loaded on the surface of the film. Hence, the intensity of the (total) reflected light received from the other side of the prism is different depending on the kind of food allergen. Through charge-coupled device (CCD) imaging, the reflected light image of the sample points and the whole biochip can be displayed in real-time for dynamic or static analysis. Currently, smartphones and certain apps are designed as SPRI attachments to enable consumer-friendly allergen detection (Gms et al., 2018). Guner et al. demonstrated a SPRI-smartphone platform (Fig. 3A) for high-throughput analyzing mouse IgG antibodies using metal coating of commercial Blu-ray discs immobilized layer of rabbit anti-mouse (RAM)

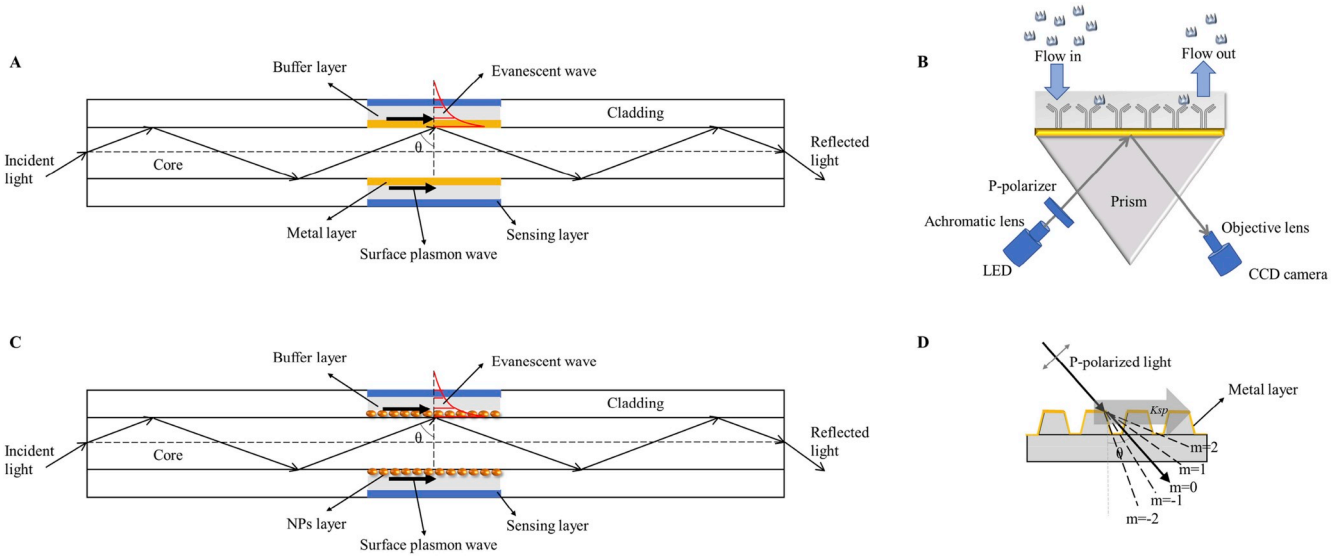


Fig. 2. Schematic diagrams of four types of SPR biosensors. (A) The fiber-optic surface plasmon resonance (FOSPR) biosensor. (B) The structure of a surface plasmon resonance imaging (SPRI) biosensor. (C) The localized surface plasmon resonance (LSPR)-based fiber-optic biosensor. (D) The conventional configuration of the transmission surface plasmon resonance (TSPR) biosensor.

IgG antibody with nanomolar level limit of detection (Guner et al., 2017).

SPRI technology has been considered a powerful tool for rapidly quantifying multiplex allergens in a food matrix through spatial modifications to the biochip surface, such as microarrays (Mohammed et al., 2001; Mullett et al., 2000). Joshi et al. constructed a SPRI microarray (Fig. 3B) with peptide and β-xylosyl glycoside (BXG) epitopes peanut allergen Ara h 2 to detect allergen-specific immunoglobulin E (IgE) antibodies in blood using magnetic beads loaded with polyclonal anti-IgE antibodies (Joshi et al., 2014). However, SPRI suffers from a lower sensitivity than that of SPR. To enhance the sensitivity of SPRI, several approaches have been employed to amplify the signal, including improving instrumental structure, improving probe modification, and incorporating various chemical and biological amplification principles.

2.3. Localized surface plasmon resonance (LSPR)

Localized surface plasmon resonance (LSPR) is an optical phenomenon caused by the interaction between the incident light and conductive nanoparticles (NPs) that are smaller than the incident wavelength (Petryayeva and Krull, 2011). When the frequency of incident light is consistent with the frequency of the free electron oscillations in the nanoparticles, then the interaction leads to the collective oscillation of surface electrons. In particular, there are several factors influencing the resonant frequency, including the composition, size, geometry, dielectric environment and particle-particle separation distance of NPs. The noble metals Ag and Au are the most commonly used materials for NP production. The specific binding between food allergens and the corresponding antibodies on the surface of a metal can be expressed as a change in color since the energy levels of d-d transitions show LSPR in the visible range of the spectrum (Stéphanie et al., 2007). The parameters can be manipulated to conveniently change the LSPR wavelength among the visible, near-infrared, and infrared regions, so LSPR biosensors are also available for specific applications requiring specific wavelengths (Cao et al., 2014). LSPR instruments are generally composed of three main sections: a light source (white light or laser), the sample cell and a detector. Fig. 2C presents a schematic diagram of the LSPR-based fiber-optic biosensor. The essential difference between LSPR and SPR is that LSPR uses noble metal nanostructures for ionic resonance, while SPR uses planar noble metals. Hence, each individual metal nanoparticle of a nanoparticle array in LSPR spectroscopy can also serve as an independent LSPR biosensor (Mcfarland and Duyne, 2003; Nusz et al., 2008). Single-nanoparticle-based LSPR biosensors demonstrate the advantages of a higher sensitivity, lower detection

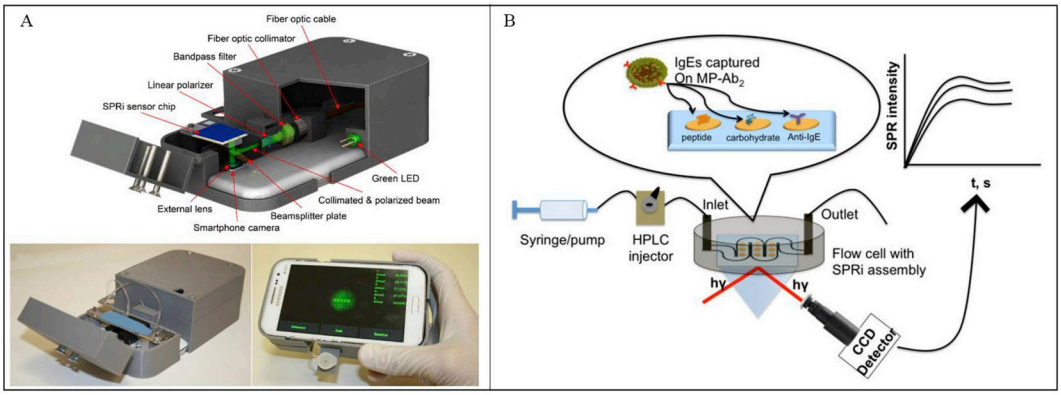


Fig. 3. (A) SPRI platform integrated with a smartphone for real-time and on-site monitoring of multiple sensing spots (Guner et al., 2017). (B) SPRI microarray configured to detect IgE binding to Ara h2 peptide, BXG, and anti-IgE using antibody-loaded magnetic particles (MP-Ab2) for capture and signal amplification (Joshi et al., 2014).

limit and reduced sample requirement (Anker et al., 2008; Willets and Duyne, 2007). In addition, as the LSPR absorption band changes with the size and shape of metal nanoparticles, different metallic nanoparticles can be applied to the construction of multiplexed LSPR biosensors.

So far, due to its small footprint, LSPR has been widely employed as a low-cost and effective method for point-of-care (POC) applications (Niu et al., 2015). A variety of biomolecular interactions, such as antigen-antibody, receptor-ligand, hormone-receptor, streptavidin-biotin, protein-protein, and protein-DNA have been widely applied in SPR and LSPR biosensors (Mernagh et al., 1998), even the immobilized protein can be detected by monitoring conformational changes (Sota et al., 1998). A biological and chemical sensing platform based on LSPR for food allergen detection usually depends on one or more of the following mechanisms: (1) resonant Rayleigh scattering, (2) charge-transfer interactions at the surface of the NP, (3) NP aggregation, and (4) changes in the local refractive index (Petryayeva and Krull, 2011). Hiep et al. proposed a label-free LSPR biosensor employing gold substrate modified with a silica nanoparticle layer to detect casein in milk (Hiep et al., 2007). Additionally, the coupling of LSPR biosensors to other identification techniques, including fluorescence, plasmon resonance energy transfer (PRET) and surface-enhanced Raman scattering (SERS), has increasingly emerged as a potential tool for the detection of unknown molecules. For example, Adegoke et al. demonstrated a semiconductor quantum dot (Qdot) nanocrystals in a molecular beacon (MB) biosensor (Fig. 4) employing LSPR signals to mediate the fluorescence signal for RNA detection (Adegoke et al., 2017).

2.4. Transmission surface plasmon resonance (TSPR)

SPR-enhanced light transmission through metallic nanohole arrays was first observed in 1998 (Ebbesen et al., 1998) and was called transmission surface plasmon resonance (TSPR). TSPR is an unusual extraordinary optical transmission that is more transparent at specific wavelengths than expected by classical theory. We can observe the extraordinary optical transmission phenomenon from the plasmonic nanostructures of nanohole arrays, diffractive nanostructures and nanosolid arrays (Lertvachirapaiboon et al., 2017b). The shift in TSPR response was observed upon changing the dielectric environment at the surface of a metallic film. According to several studies, the structures and number of holes are the main factors affecting the TSPR intensity. It is found that the TSPR intensity is stronger when the TSPR intensity is rectangular rather than round. They also found that the amplitude of transmission peak increased when the number of linear chains of holes was increased. Moreover, as an important structure in the development of TSPR substrates, several structures have been developed for nanosolid arrays, such as aluminum, double-layer gold slit array, multi-pitched diffraction grating structure, and other complex structures (Lertvachirapaiboon et al., 2017b). As shown in Fig. 2D, with the extraordinary transmission of parallel *p*-polarized light through the metal layer, a strong electric field is generated and is ultrasensitive to the local dielectric properties of the nanostructure arrays.

However, the fabrication processes for TSPR measurements are expensive, and a detector is still needed for the recording of TSPR signals. Although there are some limitations to TSPR, this technique is still highly useful in several applications, including real-time monitoring the growth of bacteria (Kee et al., 2013), the protein binding interactions (Malic et al., 2013) and the plasma drug concentration (Giulia et al., 2015). Compared with conventional SPR techniques, TSPR spectroscopy exhibits many advantages: (1) the TSPR optical signal is not impacted by optical noise originating from reflected light, (2) the transmitted light is enhanced, and (3) the signal-to-noise ratio is improved. In addition, the extraordinary transmission signals produced by TSPR substrates are strong and provide a substantially higher sensitivity to changes in the local dielectric condition. Furthermore, the TSPR biosensor is suitable to be further developed and modified into biosensors and active plasmonic devices for several applications because of its high selectivity, as well as its simple and flexible setup procedures. These biosensors based on TSPR can provide real-time data for binding processes (Lertvachirapaiboon et al., 2017b). For example, imaging technologies can be developed to combine with TSPR to provide high-resolution images, and mobile devices, for instance, smartphone cameras can also be applied. The TSPR imaging technique combined with imaging technologies and microfluidic technologies is expected to lead to a biosensor for practical applications. Lertvachirapaiboon et al. constructed a microfluidic transmission surface plasmon resonance (MTSPR) biosensor (Fig. 5A) by assembling a gold-coated grating substrate with a microchanne for glucose detection (Lertvachirapaiboon et al., 2017a). The detection limit of MTSPR for glucose was 2.31 mM. Furthermore, LSPR is also employed to enhance the signal from TSPR substrates by exciting the electric field further at the surfaces of metal gratings (Baba et al., 2013; Lertvachirapaiboon et al., 2014). Giulia et al. introduced a portable, palm-sized transmission-localized surface plasmon resonance (T-LSPR) setup (Fig. 5B and C) for real-time label-free detection of tobramycin in buffer, measuring concentrations down to 0.5 μM. In this study, the T-LSPR setup is comprised of off-the-shelf components and coupled with tobramycin aptamer-functionalized gold nanoislands (NIs) deposited on a glass slide covered with fluorine-

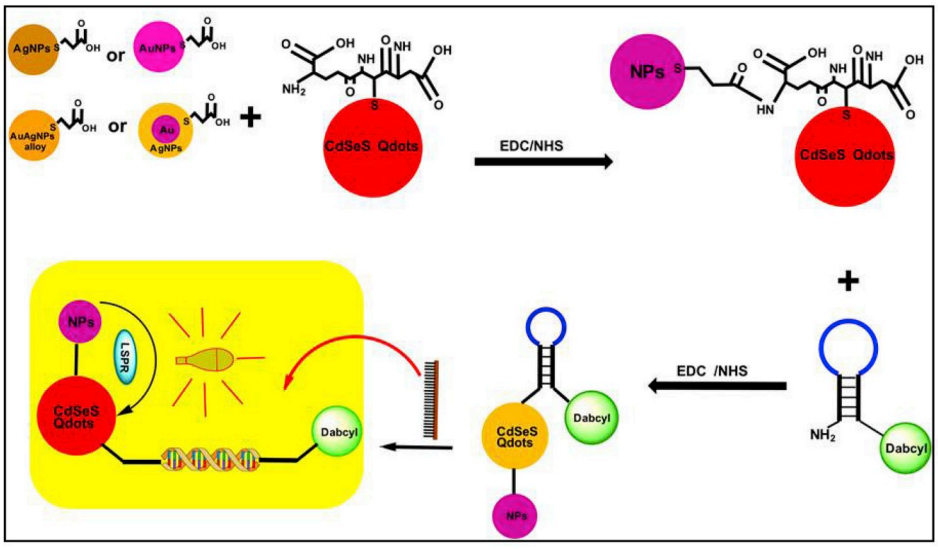


Fig. 4. The conjugation of the plasmonic NPs to GSH-CdSeS Qdots (Qdot646) to form the plasmonic NP-Qdot nanohybrids, then the plasmonic NP-Qdots are conjugated to the MB to form the plasmonic NP-Qdot-MB biosensor probe, finally, based on hybridization of the RNA with the DNA loop sequence of the MB, the ZIKV is detected by the LSPR-mediated fluorescence signal (Adegoke et al., 2017).

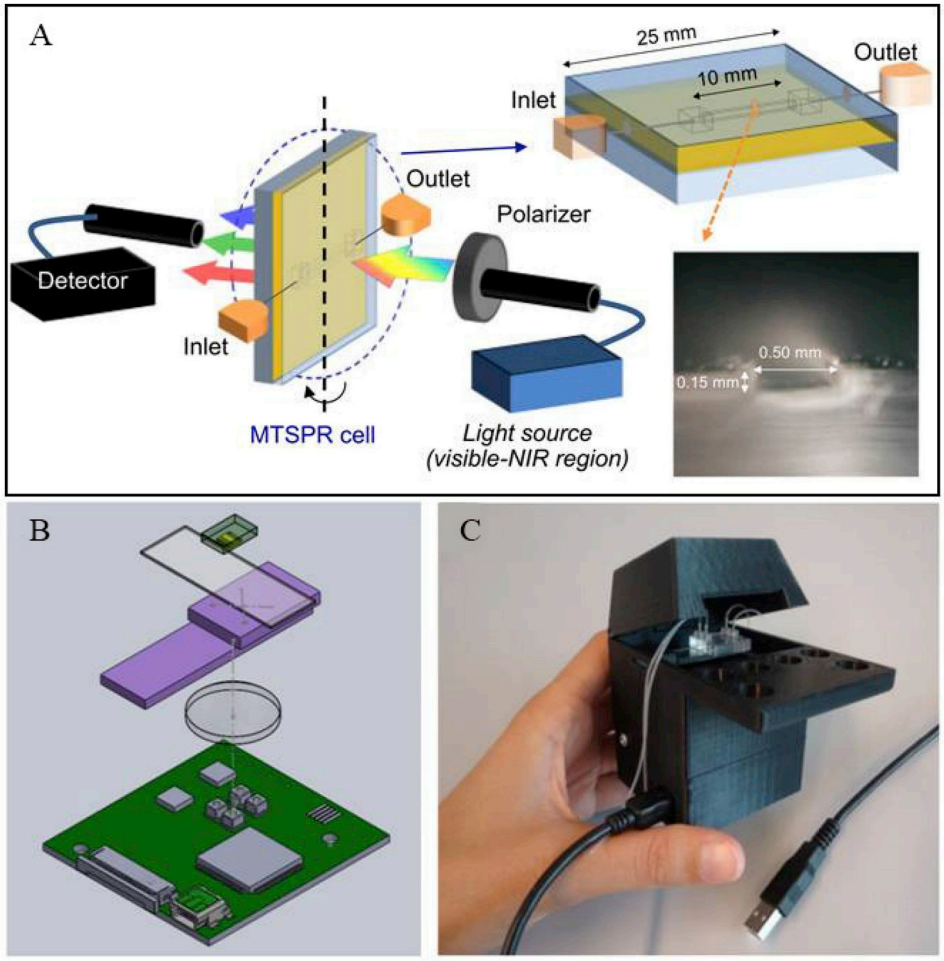


Fig. 5. (A) (Color online) Experimental setup of MTSPR measurement. Photographic image showing cross section of microchannel with the dimension of $0.50 \times 0.15\,mm^2$ (Lertvachirapaiboon et al., 2017c). (B) Digital rendering of the components of the T-LSPR setup. (C) Picture of the complete setup (Giulia et al., 2015). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

doped tin oxide (FTO), which acts as a biosensor (Giulia et al., 2015). These platforms represent a high possibility of further developing effective point-of-care devices and multiplex systems for food allergens concentration monitoring.

3. Sensitivity enhancement of SPR biosensors for food allergen detection

SPR biosensors offer a rapid, label-free, real-time, high selectivity and sensitivity method for capturing and qualifying food allergens in food matrices. However, conventional SPR biosensors have the disadvantage of low sensitivity for the detection of food allergens at low concentrations (less than 1 pM). To enhance the SPR sensitivity and measure food allergens at low concentrations for ultrasensitive detection, several approaches have been developed for SPR biosensors, including employing nanoparticles as external labels, multilayer thin-film structures and nanostructures over the gold film.

3.1. Gold thin film on a chip

Multilayer thin films added onto an SPR chip certainly affect the sensitivity of the SPR biosensor. A high-reflectivity metal film is commonly deposited on the glass or quartz substrate of an SPR biosensor through vacuum evaporation, cathode sputtering, electron beam evaporation or magnetron sputtering (Toyama et al., 2002). For food allergen detection, gold nanoparticles (Au NPs) are widely used to construct chips for SPR signal enhancement and to improve sensitivity because of their excellent chemical stability in air and solution (T A et al., 2000). TSPR spectroscopy with ultrathin evaporated Au-island films has been developed using biotin-avidin interactions for chemical and biological sensing, separating specific and nonspecific binding (Michal et al., 2004). Based on a gold film, the SPR signal is amplified by a factor of 3 through the increase in surface area and the remarkable enhancement in resonance coupling between the molecular absorption band in the analyte and the nanoparticle plasmon band (Jolanda et al., 2013) (Zhao et al., 2008). Hong et al. (Hong and Hall, 2012) investigated two main factors that enhance the signal, the LSPR-SPR coupling effect and the AuNP size/mass-material related properties, showing that the latter is the major factor in signal enhancement. Accordingly, the sensitivity of SPR biosensors depends quite a lot on the thickness of the gold film affecting the resonance depth. The resonance depth is negatively correlated with the thickness of the gold film within a certain range, that is, the smallest AuNPs have the maximum reflection coefficient. Consistent with studies, a gold film thickness of 50 ± 5 nm presents a strong protein binding signal in SPR biosensors.

Currently, the ultrasensitive detection of food allergens by specific interactions between food allergens and their respective biorecognition ligands (antibodies or aptamers) deposited on a gold film surface is a well-known mechanism widely applied in most SPR biosensors (Fig. 6). Generally, antibodies can be immobilized on the gold film by physical adsorption through electrostatic forces, covalent coupling by self-assembled monolayers, oriented immobilization by antibody binding

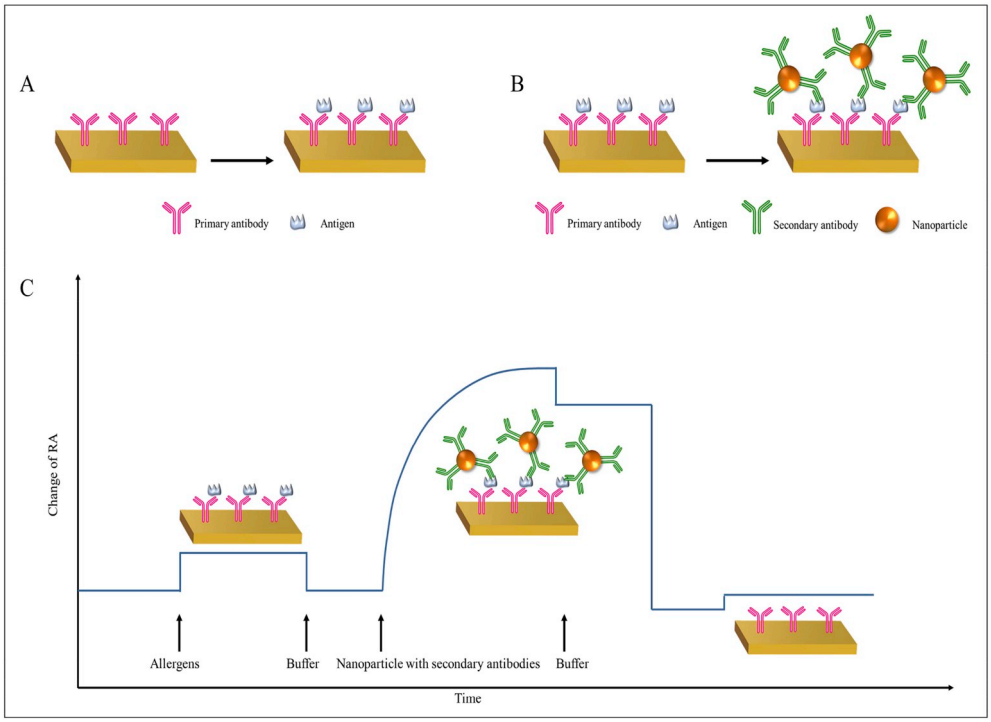


Fig. 6. Schematic diagram of antibody-based SPR biosensors to quantify food allergens. (A) Direct SPR immunoassay. (B) Sandwich SPR immunoassay. (C) The real-time SPR sensorgram of food allergens using an SPR immunoassay.

proteins, or by biotin-avidin specific adsorption (Mauriz et al., 2016). The most covalent attachment chemistries with gold are based on self-assembled monolayers (SAMs) with a functional group(s), such as a free amine or carboxyl group. Amine-reactive surfaces, thiol-reactive surfaces, and affinity immobilization are commonly applied for bonding biorecognition ligands toan SAM of alkanethiols on gold films.

Tomassetti et al. reported a label-free immunosensor based on SPR for lactoferrin determination in cow and goat milk samples, which utilized direct-type sensing with anti-lactoferrin antibodies covalently functionalized on a gold biosensor disk with the limits of detection (LODs) being 2.8×10^{-7} M and 5.0×10^{-8} M (Tomassetti et al., 2013). Pollet et al. presented a direct-type method based on a gold-coated fiber-optic SPR biosensor for fast and accurate peanut allergen (Ara h 1) detection with an LOD of 9 μg/ml by covalently binding anti-Ara h 1 antibodies (Pollet, J et al., 2011). Compared to typical ELISA methods, the SPR biosensor techniques have a remarkable ability to in situ detect food allergens in complex food systems in real-time without labeling antibodies (Piliarik et al., 2009b).

Aptamers are single-stranded DNA or RNA oligonucleotides that achieve a high specificity for a certain target allergen, and they have a higher stability and better reproducibility than antibodies in many assays as well as the ease of labeling with functional groups (Mckeague and Derosa, 2012). The labeled aptamers can be easily attached to the surface of a gold film for the amplified detection of food allergens without any negative influence on their recognition activity in SPR biosensors (Juan et al., 2015; Lin et al., 2016). Mihai et al. (2015) immobilized aptamers on an SPR surface through the neutravidin-biotin affinity for the determination of an egg allergen (lysozyme) with an LOD of 2.4 nM in spiked red and white wines, demonstrating a high sensitivity and good accuracy by using Au NP-aptamer conjugates.

Compared to gold, silver has a shorter excitation wavelength and a sharper spectrum drop because silver responds largely to analytes (Zhiqiang et al., 2015). Unfortunately, silver is prone to multilayering, and SPR chips alternately deposited with pure gold and silver films have also been reported. To improve the detection efficiency of SPR techniques, a microfluidic chip can be used as a reaction device in SPR biosensors. Microfluidic chips are composed of single-layer chips or multilayer chips. They have the advantages of a high throughput, high speed, low sample consumption, small size, one-time use and easy automation. David et al. developed a multilayer composed of a noble metal and ferromagnetic metal (Au/Co/Au) to combine the magneto-optical activity with the SPR biosensor, significantly improving the quadruple sensing performance of traditional SPR biosensors (David et al., 2011).

3.2. Nanostructure labels

Compared with bulk layers, nanostructured materials can significantly improve the interaction between the analyte molecules and the entities of the sensing surface because of their higher surface-to-volume ratio (or the aspect ratio). In addition, due to their small size, unique physical properties and strong plasmon response, nanostructured materials can be applied with SPR biosensors to quantify food allergens. Gold nanoparticles (AuNPs) and magnetic nanoparticles have recently been investigated as SPR signal-amplifying labels for the antibodies and aptamers of food allergens in the sandwich-type immunoassay and the indirect-type immunoassay (He and Hwang, 2016; Qinghui et al., 2012). Tran et al. (Tran, D. T. et al., 2013) designed a novel sandwich immunoassay between aptamers and antibodies based on FOSPR (Fig. 7) for the detection of peanut allergen (Ara h 1) in food matrices by employing Au NP-aptamer conjugates. In this work, the streptavidin-immobilized SAM on a gold-coated FO-probe is functionalized with biotinylated aptamers. In this assay, the anti-Ara h 1 antibodies are bound to AuNP-protein A conjugate, which is a bacterial protein with a high affinity towards the FC portion of antibodies.

Pollet et al. investigated an improved FOSPR detection for peanut allergen Ara h 1 using a gold-coated fiber and magnetite nanoparticles to immobilize antibodies in a secondary antibody sandwich assay (Pollet, J. et al., 2011). The LOD is 0.09 μg/ml, suggesting that the application of magnetite nanoparticles as a secondary immuno-tag can provide enhanced optical signals of 35-times greater than those of the conventional gold-film-based SPR detection. Saylan et al. developed an

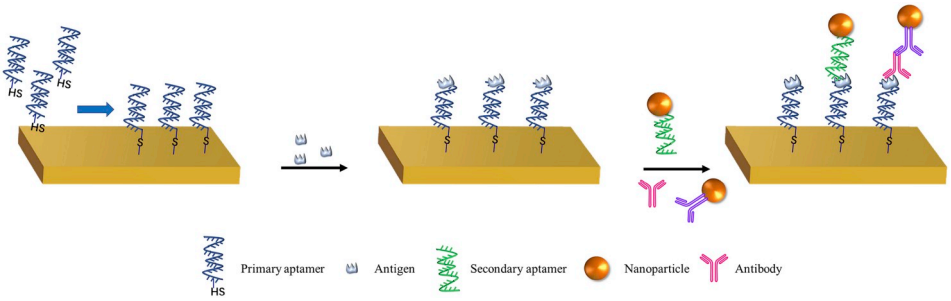


Fig. 7. Schematic diagram of an aptamer-based SPR biosensor for food allergens.

SPR sensor to detect egg allergen lysozyme with hydrophobic poly (N-methacryloyl-(L)-phenylalanine) (PMAPA) nanoparticles to modified gold surface, showing a low LOD of 0.66 nM (Saylan et al., 2017). Kaushik et al. designed Molybdenum disulfide (MoS_2) nanosheets to modify gold fiber for label-free detection of bovine serum albumin (BSA) with high sensitivity. The LOD of 0.29 μg/ml was improved as compared to the FOSPR biosensor without MoS_2 overlayer (LOD was 0.45 μg/ml) (Kaushik et al., 2019). Therefore, even if a label-free SPR biosensor may be more convenient for the real-time detection of food allergens, a hefty label can significantly increase the sensitivity of SPR biosensor-based detection.

4. Application of SPR biosensors the detection of different food allergens

Due to the high sensitivity, low cost, and easy fabrication, SPR techniques provide real-time methods to monitor the presence of allergenic ingredients in food matrices during the whole of processing. On the basis of four types of SPR biosensors, several food allergens, including those for cow's milk, peanuts, eggs and seafood, can be detected using antibodies and aptamers with high affinities (Table 3). Interestingly, two formats of antibody-based SPR biosensor platforms are chosen as typical approaches: the direct SPR immunoassay and sandwich SPR immunoassay. Furthermore, the selected aptamers are employed for the development of aptasensors based on an SPR biosensor to quantify food allergens in food matrix samples.

4.1. Milk allergens

Milk and dairy products are one of the main allergens in food and cause allergic reactions in 7.5% of children and less than 1% of adults (Bock et al., 2007). Among 25 different proteins, four proteins are identified as the major allergens in milk, including casein, α-lactalbumin, β-lactoglobulin, bovine serum protein and γ-globulin (Coscia et al., 2012; Monaci et al., 2006). α-Lactalbumin is a calcium-binding milk protein with a molecular weight of 14.4 kDa (Jean-Michel, 2002). β-Lactoglobulin, the most abundant protein with a molecular weight of 18 kDa in milk whey, is responsible for 60% of milk allergies (Natale et al., 2004). In particular, casein includes four kinds of proteins, αs1-casein, αs2-casein, β-casein and κ-casein, which account for 32%, 10%, 28%, and 10%, respectively. So far, several protein-based approaches have been widely used for the quantitative detection of the main milk allergens in common food substrates, such as the immunoassay lateral flow-based assay (LFA), ELISA, LC-MS and biosensors (Table 2). Song et al. constructed a competitive LFA method using fluorescent microspheres as labels for rapid quantitation of casein in milk with an LOD

Table 2
Examples of food allergens using other methods.

Sample	Allergens	Detection method	Limit of detection (LOD)	References
Milk	β-lactoglobulin	sandwich-ELISA	15.625 ng/ml	-
	casein	Fluorescent microspheres lateral flow assay	100 ng/ml	Song et al. (2017)
	Casein whey protein	UHPLC–MS/MS	0.5 mg/kg 5 mg/kg	Planque et al. (2016)
	β-lactoglobulin	Amperometric magnetoimmunosensor	0.8 ng/ml	Montiel et al. (2015a)
	β-lactoglobulin	Voltammetric biosensor	20 pg/ml	Eissa and Zourob (2017)
	Casein	Integrated Magneto-Chemical Sensor	0.17 mg/kg	Lin et al. (2017)
Egg	Ovalbumin	ELISA	0.31–2.5 ppm	Diaz-Amigo (2010)
	Lysozyme	Screen Printed Carbon Electrodes (SPCEs)	25 nM	Ocaña et al. (2015)
	Lysozyme	Competitive aptamer-based assay	10 nM	Mishra et al. (2016)
	Lysozyme	Surface Enhanced Raman Spectroscopy	0.5 mg/ml	Boushell et al. (2016)
	Ovalbumin	Screen-printed platinum electrodes	5 nM	Čadková et al. (2015)
	Ovalbumin	Integrated Magneto-Chemical Sensor	0.003 mg/kg	Lin et al. (2017)
Peanut	Ara h 1	Sandwich ELISA	0.34 ng/ml	Peng et al. (2013)
	Ara h 2	Sandwich ELISA	1 ng/ml	Peng et al. (2015)
	Ara h 1	microfluidic ELISA based Optical Sensor	15.2 ng/ml	Weng et al. (2016)
	Ara h 3	$MRM^{(3)}$-based LC-MS multi-method	1 μg/g	Korte and Brockmeyer (2016)
	Ara h 1	Microfluidic nano-biosensor	56 ng/ml	Weng and Neethirajan (2016)
	Ara h 6	Voltammetric biosensor	0.27 ng/ml	(Alves et al., 2015; Weng and Neethirajan, 2016)
	Ara h 2	Amperometric magnetoimmunosensor	26 pg/ml	Montiel et al. (2016)
	Ara h 1	Amperometric magnetoimmunosensor	6.3 ng/ml	Montiel et al. (2015b)
	Ara h 1	Integrated Magneto-Chemical Sensor	0.007 mg/kg	Lin et al. (2017)
	Ara h 1	Surface Enhanced Raman Spectroscopy	0.14 mg/ml	Gezer et al. (2016)
	Tropomyosin	Sandwich ELISA	0.09 ng/ml 0.64 ng/ml	Zhang et al. (2014)
	Tropomyosin	Aptamer-based fluorescent assay	0.5 ng/ml	Zhang et al. (2017)
	Tropomyosin	Fluorescent magnetic bead-based mast cell biosensor	0.03 μg/ml	Jiang et al. (2015)
	Parvalbumin	Fluorescent magnetic bead-based mast cell biosensor	0.16 ng/mL	Jiang et al. (2015)

Table 3
Examples of food allergens using different SPR biosensor platforms.

SPR biosensor	Sample	Capturing ligand	Format	Labels	Limit of detection (LOD)	References
FOSPR	Milk	Antibody	Sandwich	None	0.87 mg/ml	Muller-Renaud et al. (2005)
FOSPR	Peanut	Aptamer	Sandwich	Gold nanoparticles	75 nM	(Tran et al., 2013)
FOSPR	Peanut	Antibody	Sandwich	Superparamagnetic nanoparticles	0.21 μg/ml	Pollet, J. et al. (2011)
			Direct		0.09 μg/ml	
SPRI	Peanut	Antibody	Direct	Magnetic beads	0.5–1 pg/ml	Joshi et al. (2014)
LSPR	Milk	Antibody	Direct	gold-capped nanoparticle substrate gold-silica layer	10 ng/ml	Hiep et al. (2007)
SPR	Milk	NanoMIPs	Direct	None	127 ± 97.6 ng/ml	Ashley et al. (2018b)
SPR	Milk	Antibody	Direct	None	0.164 μg/ml	Ashley et al. (2018a)
SPR	Milk	Antibody	Direct	None	0–1000 ng/ml	Billakanti et al. (2010)
SPR	Milk	Antibody	Direct	None	2.8×10^{-7} M	Tomassetti et al. (2013)
					5.0×10^{-8} M	
SPR	Milk	Antibody	Direct	None	57.8 ng/ml	Ashley et al. (2017)
SPR	Egg	Antibody	Direct	None	0.03–0.2 μg/ml	Pilolli et al. (2015)
SPR	Egg	Antibody	Direct	None	0.2 μg/ml	Pilolli and Monaci (2016)
SPR	Egg	Aptamer	Direct	None	0.035 μg/ml	Nylander et al. (1983)
SPR	Egg	Antibody	Direct	PMAPA nanoparticles	0.66 nM	Saylan et al. (2017)
SPR	Milk	Antibody	Sandwich	None	5.54 ng/ml	Wu et al. (2016)
SPR	Peanut	Antibody	Sandwich	None	0.77 ng/ml	Wu et al. (2016)
SPR	Peanut	Antibody	Direct	None	0.7 μg/ml	Mohammed et al. (2001)
SPR	fish	Antibody	Direct	None	0.11 mg/kg	Lu et al. (2015)
					0.39 mg/kg	
SPR	shellfish	Antibody	Direct	None	1.0 μg/ml	Zhou et al. (2019)

being 100 ng/ml (Song et al., 2017). Planque et al. used ultra-high performance liquid chromatography coupled to tandem mass spectrometry for simultaneous detection of food allergens from milk, egg, soybean, and peanut allergens in different foodstuffs (Planque et al., 2016). Amperometric magnetoimmunosensor (Montiel et al., 2015a) and voltammetric biosensor (Eissa and Zourob, 2017) were developed for the determination of β-lactoglobulin using antibodies and aptamer to capture β-lactoglobulin with the LOD of 0.8 ng/ml and 20 pg/ml, respectively.

Currently, real-time labeled SPR biosensor technology is becoming a widely attractive approach to the detection of milk proteins, including plant protein adulterants, IgG, folate binding protein, lactoferrin, insulin-like growth factor, and casein (Sampson, 2000). A novel sandwich-type optical SPR biosensor was designed for α_{S1}-casein detection in milk (Muller-Renaud et al., 2005). In this work, the peptide segments corresponding to the N and C terminals of αs1-casein were selected as immunogens to obtain specific antibodies with a high affinity towards specific protein sites. More than 150 kinds of determinations can be achieved using this antibody-coated surface in raw milk with an LOD of 0.87 mg/ml. However, this method can only be applied to quantify the complete quantity of α_{s1}-casein and cannot quantify the degradation of α_{s1}-casein in milk products. Hiep et al. proposed a label-free immunosensor based on LSPR to detect casein without the effects of α-lactalbumin and β-lactoglobulin in milk. In this work, the gold film on a glass slide substrate is first modified with a silica nanoparticle layer to amplify the SPR signal (Hiep et al., 2007). The LOD of 10 ng/ml is 6 orders of magnitude lower than that of an optical SPR without amplification by AuNPs. Ashley et al. synthesized molecularly imprinted polymer nanoparticles (nanoMIPs) with a high affinity for bovine α-casein and designed a nanoMIP-based SPR biosensor (Fig. 8) to monitor α-casein in wash samples from cleaning-in-place systems (CIP), with the LOD being 127 ± 97.6 ng/ml (Ashley et al., 2018b). They also introduced a sensitive labeled SPR biosensor for detecting the milk allergen β-Lactoglobulin with an LOD of 0.164 μg/ml, which can be applied directly to the final rinse samples of CIP systems of food manufacturers (Ashley et al., 2018a). Kaushik et al. reported a FOSPR biosensor with Molybdenum disulfide (MoS_2) modified gold fiber for label-free detection of bovine serum albumin (BSA). In this novel approach, The sensitivity of the MoS_2 modified sensing probe with the LOD of 0.29 μg/ml was improved as compared with the FOSPR biosensor without MoS2 overlayer (LOD was 0.45 μg/ml) (Kaushik et al., 2019).

Additionally, SPR biosensors allow for the capture of multi-allergens in a single food sample for high-throughput multiplex analysis. Jagan et al. described an SPR-based technique that can simultaneously quantify five kinds of whey proteins in both raw and processed milk samples (including alpha, beta, bovine serum albumin, lactoferrin and immunoglobulin G) (Billakanti et al., 2010). Tomassetti et al. proposed a new method to detect lactoferrin using an SPR biosensor with batch and flow modes and a gold film signal amplification technique (Tomassetti et al., 2013). The LOD is as low as 10^{-8} M in flow mode and 10^{-7} M in batch mode. SPR biosensors present a remarkable accuracy for milk allergen detection such that the response value to interfering substances will not exceed 5%, while traditional immunoassays are prone to false positive results due to the interference of lactalbumin and lactoglobulin.

4.2. Egg allergens

Egg, as the second major cause of food allergy in children (Yoshinori and Marie, 2008), causing allergies in between 1.6% and 3.2% of individuals, accounting for 38.3% of food allergies and 25.8% of anaphylactic shock (Shoji, 2010). An egg allergy can cause symptoms in the skin (urticaria, edema, rash, and dermatitis), gastrointestinal tract (oral allergic syndrome, vomiting, abdominal pain, and diarrhea) and respiratory system (asthma) (Perry et al., 2004; Sampson, 2003).

Egg white has four main allergenic proteins, including ovarian mucin (11%), ovalbumin (54%), Ovotransferrin (12%) and lysozyme (3.4%). Ovomucoid (OVM, Gal d 1), a glycoprotein, 28 kDa, consists of 186 amino acid residues, contains three functional domains with independent homologous structures and contains 20-25% glycosyl components. Ovalbumin (OVA, Gal d 2), a monomer water-soluble protein, 45 kDa, consists of 385 amino acid residues. OVA is the only allergenic protein containing a free sulfhydryl group, which has the potential to change the molecular structure through heating, pH and cross-linking with a modifier during food processing (Diez et al., 1964). Ovotransferrin (OVT, Gal d 3), 77 kDa, is a mono saccharified polypeptide composed of 686 amino acid residues. Lysozyme (Lys, Gal d 4) is a kind of alkaline protein with a molecular weight of 14.3 kDa, consisting of 129 amino acid residues in a single polypeptide (Shoji, 2010). In food products, lysozyme is a natural food additive and immunoglobulin growth promoting factor. α-Livetin (Gal d 5), 66.8 kDa, is composed of 589 amino acid residues, which is considered an important factor in the pathogenesis of bird egg syndrome and has a potential glycosylation

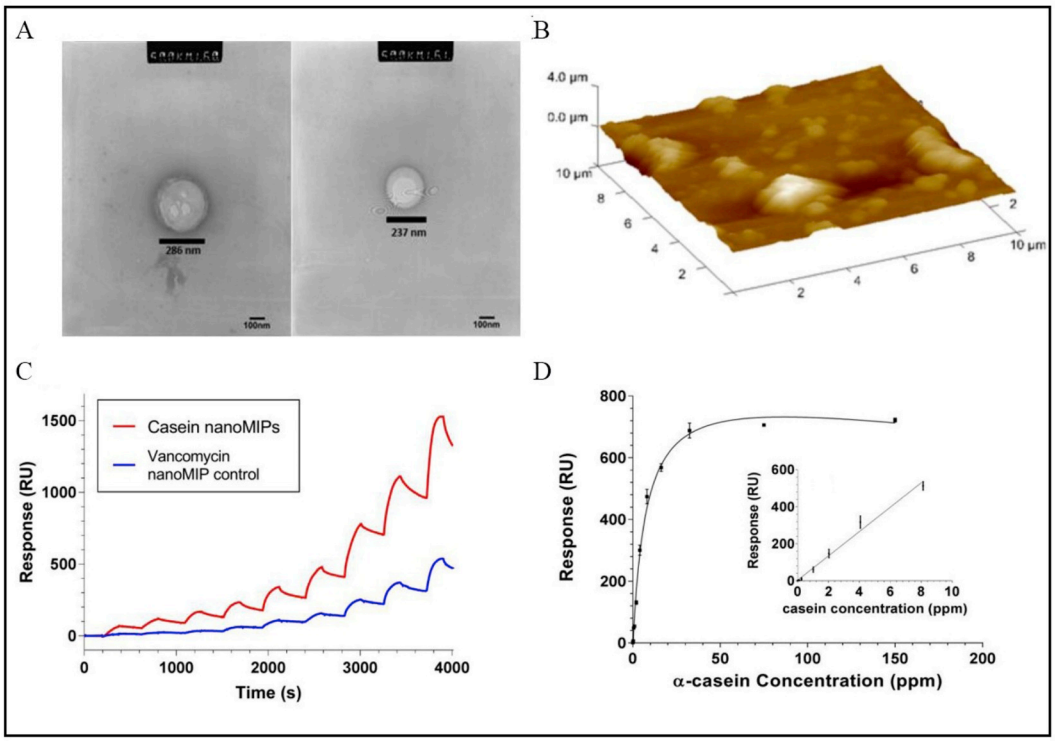


Fig. 8. (A) TEM image of α-casein nanoMIPs taken on a Phillips CM20. (B) AFM covalently attached nanoMIPs. (C) Typical sensorgram for a nanoMIP based biosensor synthesized from the bead-based method. (D) Non-linear (R^2 = 0.9934) and linear calibration (R^2 = 0.9779) plot for the α-casein nanoMIP based biosensor (n = 3) (Ashley et al., 2018b).

site in its structural domain (Quirce et al., 2010; Toorenenbergen et al., 1994). Yolk glycoprotein 42 (Gal d 6) has a molecular weight of 31.4 kDa and three glycosylation sites, which are stable to heat but unstable to pepsin (Shoji, 2010). Vitelline high-phosphatin, 35 kDa, has approximately 50% serine residues and contains 3-10% phosphorus and 6% carbohydrate (Clark, 1985; Taborsky, 1982).

Although many ELISA kits have been applied to the detection of egg allergens, the ability of ELISA to detect egg allergens in processed foods is limited because the conformational epitopes of allergens are easily changed during egg processing. In addition, different types of biosensors were widely employed for the determination of egg allergens (Table 2). For example, screen-printed platinum electrodes (Čadková et al., 2015) and integrated magneto-chemical sensor (Lin et al., 2017) were established for monitoring the serious egg allergen ovalbumin with the LOD of 5 nM and 0.003 mg/kg, respectively. Screen printed carbon electrodes (SPCEs) (Ocaña et al., 2015), competitive aptamer-based assay (Mishra et al., 2016), and SERS (Boushell et al., 2016) were reported for the immunoassay of Lysozyme with the LOD of 25 nM, 10 nM and 0.5 mg/ml, respectively. A novel and label-free SPR biosensor was developed for the sensitive and rapid detection of OVA in wine, using an anti-OVA antibody covalently immobilized on a dextran-coated biosensor chip for signal amplification (Pilolli et al., 2015). This assay has an LOD of 0.03–0.2 µg/ml. Pilolli et al. also applied LC-MS methods to the detection of egg allergens, demonstrating that SPR-based biosensors can effectively and accurately quantify egg allergens. Mihai et al. (2015) introduced a novel platform based on an SPR biosensor using aptamers on chip surface through the neutravidin-biotin affinity for the determination of an egg allergen (lysozyme) with an LOD of 2.4 nM in spiked red and white wines (Fig. 9). A novel method to perform in situ protein coupling with small molecules on an SPR sensing surface uses a small -molecule-protein coupled system modeled by progesterone (P4) and ovalbumin (OVA). This method is suitable for the coupling of small molecules and proteins and the coupling of short peptides and proteins (Wang et al., 2017). Therefore, it is easy to screen protein conjugates with different molecules to obtain the best detection.

4.3. Peanut allergens

As a common allergen food, the peanut accounts for 1-20% of food allergies, and the incidence in children is relatively high (Grundy et al., 2002). An important risk with the peanut allergy lies in peanut allergens hidden in food products during three stages: raw-food materials, the contamination of materials in food transportation, and the cross-contamination at stages of food processing (Wichers et al., 2004). Among the 13 allergens identified in peanuts (Emmett et al., 2015; Warner, 2010), Ara h 1 and Ara h 2 are responsible for more than 90% allergic patients (Knol et al., 2003; Koppelman et al., 2015). Ara h 1 is a soluble protein with an average molecular weight of 63.5 kDa (Burks et al., 1992), accounting for approximately 12–16% of all kinds of peanut proteins (Koppelman et al., 2015). In its natural state, Ara h 1 mainly exists in the form of monomers and trimers (Faber et al., 2016), which form by linking three monomers through hydrophobic interactions. Most epitopes are more or less hidden in natural protein trimer complexes, which can protect monomers from degradation, resulting in enhanced allergenicity (Maleki et al., 2000). Ara h 2 belongs to blue bean protein, accounting for 5.9–9.3% (Koppelman et al., 2015) of the all proteins in peanuts. Ara h 2 contains two genetic variants, Ara h 2.01 and Ara h 2.02, which have molecular weights of 16.7 and 18 kDa, respectively. Ara h 2 is very stable and resistant to enzymatic hydrolysis due to its disulfide bonds. Nowadays, several analytical methods were established for the detection of peanut allergens, including ELISA, LC-MS, voltammetric biosensor, amperometric magnetoimmunosensor, Integrated magneto-chemical sensor and SERs (Table 2). For instance, sandwich ELISA was reported for detecting the major peanut allergen, Ara h 1 (Peng et al., 2013) and Ara h 2 (Peng et al., 2015) using monoclonal antibodies (mAb). The LOD were 0.34 ng/ml and 1 ng/ml for Ara h 1 and Ara h 2, respectively. In addition, amperometric magnetoimmunosensor (Montiel et al., 2015b), Integrated magneto-

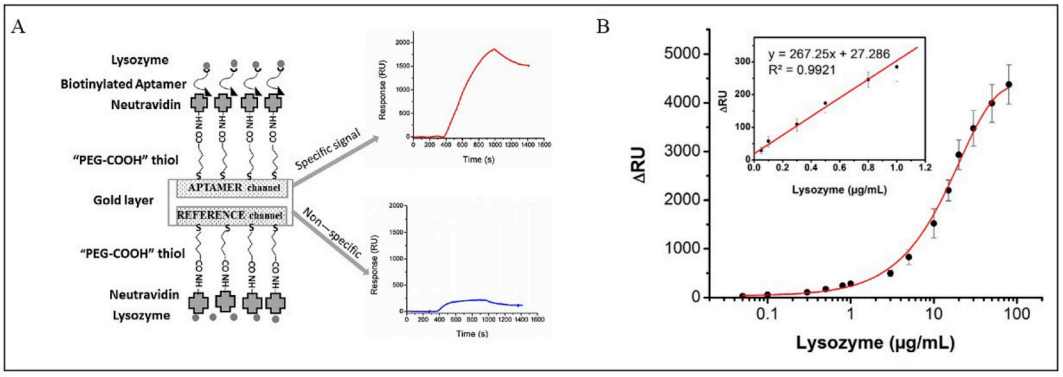


Fig. 9. (A) Design of the aptasensor for lysozyme detection in wines. (B) Calibration curve for lysozyme obtained with the aptasensor in the concentration range 0.05–80 g/ml (Mihai et al., 2015).

chemical sensor (Lin et al., 2017) and SERS (Gezer et al., 2016) were developed for highly sensitive immunoassays of Ara h 1 with the LOD being 6.3 ng/ml, 0.007 mg/kg, and 0.14 mg/ml, respectively.

Wu et al. developed a double antibody sandwich immunoassay using the SPR method to quantify β-Lactoglobulin and Ara h 1 (Wu et al., 2016). Affinity-purified monoclonal antibodies (mAb) were immobilized on the biosensor chip, and β-Lactoglobulin and Ara h 1 binding to the antibody surface was monitored through the change in resonance angle. This method exhibits an LOD of 5.54 ng/ml. Tran et al. designed an SPR aptasensor for the quantitative detection of Ara h 1 in both buffer and food matrices (Fig. 10); the approach coupled FOSPR and a gold-coated FO-probe to enhance the specificity for Ara h 1 (Tran, Dinh T. et al., 2013). Pollet et al. compared three approaches based on FOSPR for the quantification of Ara h 1 in chocolate candy bars: a label-free direct assay, a sandwich assay with a secondary antibody and a sandwich assay with magnetite nanoparticles (Pollet, J. et al., 2011). The LOD of the SPR bioassay for Ara h 1 was improved by two orders of magnitude from 9 to 0.09 μg/ml, demonstrating that functionalized nanobeads can remarkably improve the sensitivity of FOSPR biosensors. Joshi et al. constructed a SPRI microarray with peptide and β-xylosyl glycoside (BXG) epitopes from major peanut allergen Ara h 2 to detect IgE antibodies in sera (Joshi et al., 2014). In this study, magnetic beads loaded with polyclonal anti-IgE antibodies were employed to pre-capture IgE to develop the sensitivity with an LOD at 0.5 pg/ml with dilute serum in 45 min.

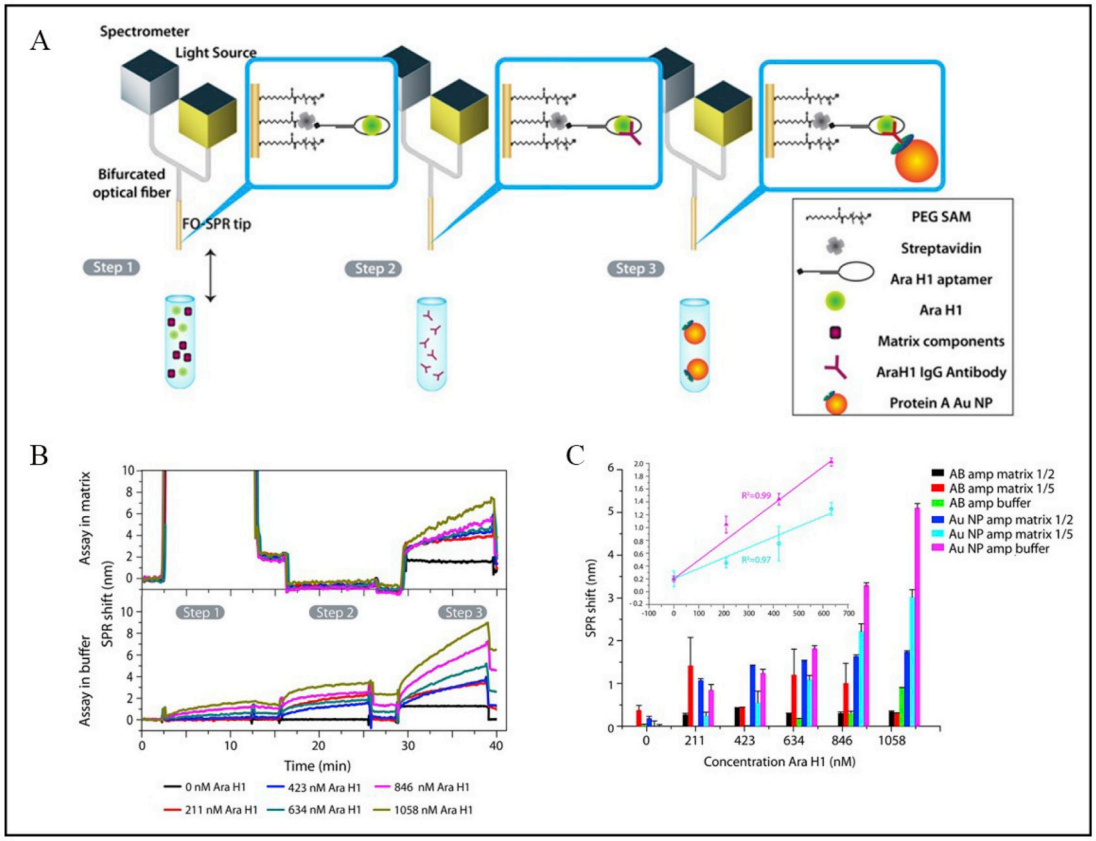


Fig. 10. (A) Schematic representation of multi-step protocol for Ara h 1 protein detection in food matrix samples. (B) Detection of FOSPR aptasensor of Ara h 1 protein at various concentrations using the multi-step protocol in TGK buffer and candy bar matrix. (C) Quantification of SPR signal shifts and calibration curves obtained with FOSPR aptasensor (Tran et al., 2013).

4.4. Seafood allergens

Recently, the consumption of seafood has been continuously increasing because of its rich nutrients and savory flavor. Seafood can be divided into two important groupings, fish and shellfish, and both are in the "big eight" categories of food allergens (Lopata et al., 2010). A seafood allergy is typically life-long affecting ≤5 of children and ≤2% of adults for both fish and shellfish (Gray et al., 2015). Food anaphylaxis to fish and shellfish happen frequently in daily life, including vomiting, diarrhea, and generalized pruritus; sometimes further reported signs/symptoms include pruritus and hives, wheezing and chest tightness, and angioedema, including fatal anaphylaxis (Arthur Helbling et al., 1999). The route of exposure includes ingestion, contact, or even inhalational exposures. Especially, the major route of sensitization to fish is the ingestion via cooking or processing. Among the number of allergenic proteins in fish, parvalbumin (PV) is considered the major allergen present in large amounts in the white muscles of lower vertebrates, and 95% of fish allergy patients are sensitive to PV (Kuehn et al., 2010). PV was initially identified and named Gad c 1 in cod as an IgE-reactive allergen (Elsayed and Bennich, 1975; Lim et al., 2008). PV, 10-13 kDa, is a stable acidic EF-hand Ca^{2+}-binding protein, resistant to heat, chemical denaturation, and proteolytic enzymes (Griesmeier et al., 2010). There are two isoform linages of PV, the α- and β-linages, of which β-linages are the main allergenic and are present in almost all bony fish (Sharp, Michael F and Lopata, Andreas L, 2014). PVs in different kinds of fish have highly conserver structures, and cross-reactivity exists (Sharp, M. F. and Lopata, A. L., 2014).

A number of allergens have been recently identified in shellfish such as tropomyosin, sarcoplasmic calcium-binding protein (Kazuo et al., 2008), myosin light chain (Rosalía et al., 2008) and arginine kinase (Aispuro-Hernandez et al., 2008). The major allergen in shellfish is tropomyosin (TM), a 38-41 kDa heat-stable IgE-binding allergen. TM is an essential protein in muscle contraction and even cross-reacts with insect-derived ones (Shafique et al., 2012). Even different kinds of shellfish species also have a high homology sequence and similar structures, and 75% of individuals allergic to TM are sensitive to other shellfish species (Tsabouri et al., 2012).

Currently, the two most commonly used methods for detecting TM are fluorescent technologies and ELISA (Table 2), including sandwich ELISA (Zhang et al., 2014), aptamer-based fluorescent assay (Zhang et al., 2017), fluorescent magnetic bead-based mast cell biosensor (Jiang et al., 2015), and so forth, of which the LOD are 0.09 ng/ml, 0.64 ng/ml and 0.5 ng/ml, respectively. A label-free SPR measuring system was reported for identifying PV within 5 min in processed food products, according to the allergen-mAb binding interaction on a carboxymethyl dextran (CMD) surface (Lu et al., 2015). A simple and label-free SPR sensor with gold patterned biochips (Fig. 11) was proposed for detection and quantification of TM in shellfish, with the LOD being 1.0 μg/ml (Zhou et al., 2019).

5. Conclusions and outlooks

Food allergy is regarded as a significant public health concern in the field of food safety, and therefore, accurate, sensitive and efficient methods for the identification and quantification of food allergens are considered an important priority in the food industry. Recently, the popularity of using SPR biosensors has greatly improved food allergen detection in real-time and label-free fashions with less reagent consumption. In this review, we provide an overview of the current research status and introduce prospective SPR biosensors employed for the analysis of food allergens in food matrices. Currently, three types of SPR biosensors are broadly applied for identifying, capturing, and quantifying target food allergens for different situations and demands, such as FOSPR, SPRI, and LSPR. In general, FOSPR is suitable for the long-distance and real-time detection of food allergens due to its small size and flexible design. The SPRI biosensor is capable of simultaneously monitoring hundreds of food allergens with probe arrays. The LSPR biosensor can be designed as a multiplexed biosensor for the real-time detection of food allergens in one or more food samples. However, tridiitional SPR technologies suffer from several performance limitations: (1) it is difficult to simultaneously analyze multiple allergens in food samples; (2) SPR equipments are too big and expensive thus cannot be applied for consumer-friendly detection of food allergen. With the development of materials and technologies, the SPRI biosensor can be coupled to LSPR and TSPR to provide an accurate, rapid, low-cost, and highly sensitive method to monitor hundreds of food allergens in one or more food matrices. Smartphones and certain apps can be integrated into SPRI and TSPR technique to develop mobile devices and POC devices for on-site and consumer-friendly detection of food allergen. LSPR biosensors can be coupled to other identification techniques, including fluorescence, PRET and SERS, for practical biosensor applications in food analysis. LSPR also can be employed to enhance the signal from TSPR substrates by exciting the electric field further at the surfaces of metal gratings. The TSPR technique combined with imaging technologies and microfluidic technologies can be developed as a biosensor for practical applications. Therefore, as a flexible, ultrasensitive and highly specific method, SPR biosensors have great potential for the future and can serve as a great advantage for food manufacturers, food processors, and food safety control departments.

CRediT authorship contribution statement

Jinru Zhou: Writing - review & editing. **Qinqin Qi:** Writing - original draft. **Chong Wang:** Writing - review & editing. **Yifan Qian:** Investigation. **Guangming Liu:** Supervision. **Yanbo Wang:** Conceptualization. **Linglin Fu:** Conceptualization.

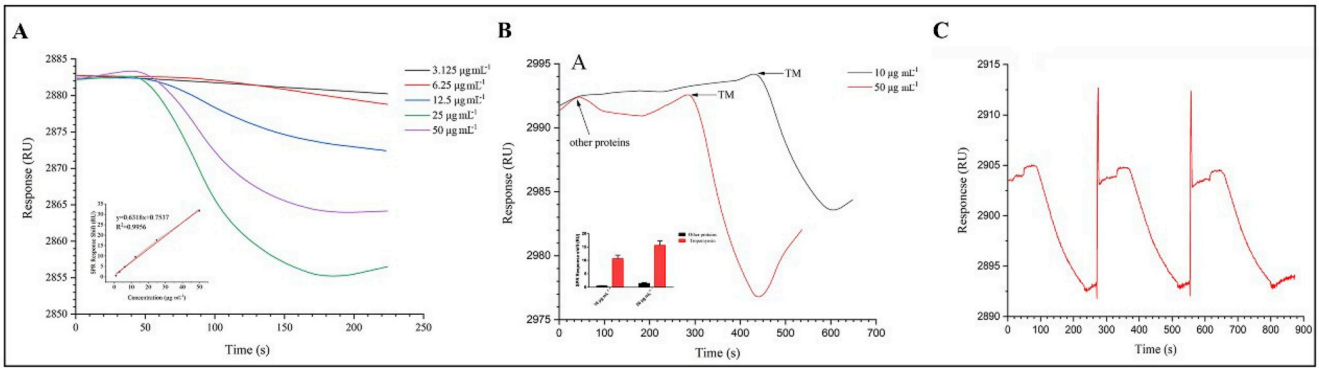


Fig. 11. (A) SPR sensorgram of tropomyosin standards at different concentrations and standard curve. (B) Relative responses of the other nonallergenic proteins in shellfish towards the sensor surface. (C) SPR sensorgram of tropomyosin standards under continuous injection.

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