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Review

Recent developments and applications of surface plasmon resonance biosensors for the detection of mycotoxins in foodstuffs

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ABSTRACT

Over the past 10 years, great efforts on the development of methods for rapid mycotoxin detection in foodstuffs have been made. As one of the relatively new analytical techniques, surface plasmon resonance (SPR) has been proven particularly advantageous for rapid, label-free, sensitive analyte detection. Using SPR, qualitative and quantitative analysis can be performed in real-time. Mycotoxins are a group of small, toxic products formed as secondary metabolites by a few fungal species. They can contaminate foodstuffs on a large scale and consequently threaten human health through food chain. Thus, rapid, sensitive, and selective determination of mycotoxin is of great significance for the food safety. This contribution addresses the basic principle of SPR, the existing detection methods, and the progress on mycotoxin detection using SPR biosensor.

Contents

1. Introduction

Mycotoxins are small (MW < 700 Da), toxic chemical products formed as secondary metabolites by a few fungi that can contaminate a variety of foodstuffs like cereals, nuts, coffee, oil seeds, beans, and fruits. Contamination usually occurs pre- or post-harvest (e.g. deoxynivalenol and T-2 toxin produced by *Fusarium* pre-harvest, and ochratoxins (*Aspergillus* and *Penicillium*) and aflatoxins (*Aspergillus*) produced post-harvest). Mycotoxins pose a potential threat to human and animal health through food chain because of their teratogenicity, mutagenicity, and carcinogenicity.

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Generally, crops stored for some time become a potential target for mould growth and mycotoxin production. Contamination is found both in temperate and tropical regions around the world, depending on the species of fungi. Mycotoxins are often genotypically specific, but can be produced by one or more fungal species, and sometimes one species can generate more than one kind of mycotoxins. When specific conditions are changed (e.g. moisture, oxygen, and temperature), the capacity of producing toxin for the same strain will be varied. Mycotoxins existing in nature are more than 200 kinds and the harm of them has been reported previously. According to the research of Food and Agriculture Organisation (FAO), mycotoxins contaminate about 25% of agricultural products around the world each year, which causes billions of dollars losses.

Surface plasmon resonance (SPR) is a modern analysis technique based on the changes in the refractive index of material on the metal surface. In 1982, Liedberg first realised the biosensing potential of a prism SPR sensor with an immunoglobulin G (IgG) antibody adsorbed overlayer on the gold-sensing film, which allowed selective binding detection of IgG (Liedberg, Nylander, & Lundstrom, 1983). Originally, the SPR technique was applied in the analysis of gases, liquids, and solids. In recent years, SPR technique has an increasing application in biochemistry (Green et al., 2000; Homola, Yee, & Gauglitz, 1999), clinical diagnosis (Kanoh et al., 2006), food analysis (Spadavecchia, Manera, Quaranta, Siciliano, & Rella, 2005), environmental monitoring (Inamori et al., 2005), and so on. The popularisation of SPR is due to its properties of label-free, real-time detection, and high sensitivity. SPR can not only be used in analyte detection, but also provide rich information on the specificity, affinity, and kinetics of biomolecular interactions. In the last 10 years, much attention has focused on the detection of low-molecular-weight analyses in food and environmental fields using SPR biosensor. In present review, we address the basic principle of SPR, the existing detection methods, and the progress on mycotoxin detection using SPR biosensor.

2. SPR principle

SPR is a physical optics phenomenon based on the change in the refractive index on the metal surface. Several reviews have described the basic principle and operation of SPR (Hodnik & Anderluh, 2009; Shankaran, Gobi, & Miura, 2007). When a plane polarised light shines directly through the prism to the metal/solution dielectric interface over a wide range of incident angles, the evanescent wave will be generated under total internal reflection condition (Fig. 1). At a selected incident light wavelength or angle, the evanescent waves can resonate with surface plasmons (SP) produced by free electrons on the metal film of the sensor surface, and the energy of incident light will be absorbed by SP, which results in a narrow dip in the spectrum of reflected light. The angle at which the drop is maximum (minimum of reflectivity) is denoted as the "SPR angle". This "SPR angle" is extremely sensitive to the refractive index of the sample contacting with the metal surface, so that it is also highly influenced by the species and amount of biomolecules immobilised on the gold layer. Furthermore, the kinetics information of the interaction between molecules can also be obtained (Huang, Tu, Zhu, Du, & Zhang, 2009).

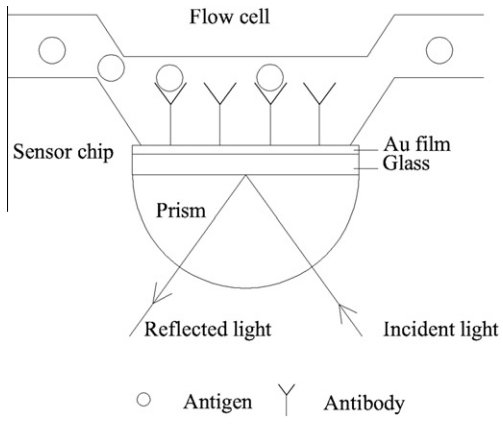

Fig. 1. Schematic view of the basic principle of surface plasmon resonance biosensor.

3. Detection methods for mycotoxins by SPR

SPR assays can be classified by the choice of the detection method depending on the characteristic of the analyte, analytical sample, and sensitivity of the SPR instrument. Direct detection is only useful for the detection of large molecules with molecular weight >10 kDa. However, mycotoxins are small chemical compounds that have inadequate mass to cause a measurable change in the refractive index. Therefore, sandwich assay and competitive inhibition assay are developed to detect small molecules. In addition, Au nanoparticles (Au NPs) are also used for enhancing SPR signal.

3.1. Sandwich assay

The sandwich mode (Cui, Yang, Sha, & Yang, 2003; Jang et al., 2009), which is often used to improve sensitivity and specificity, consists of two recognition steps. At the first recognition step, as Fig. 2 shows, the antibodies are initially immobilised on the SPR chip surface (Fig. 2A). The analytes bind with antibodies preimmobilised on the SPR chip surface (Fig. 2B). Then secondary antibodies are injected onto the sensor chip to interact with the previously captured analytes for signal enhancement (Fig. 2C).This is the second recognition step. It is essential that analytes bind with the first and secondary antibodies simultaneously during the sandwich assay process. As the number of molecule layers increases on the SPR sensor surface, the refractive index on the metal surface increases. Thus, SPR response signal is enhanced.

3.2. Competitive inhibition assay

As mycotoxins are generally low molecular-weight compounds, competitive inhibition mode is mainly used for detection of mycotoxin in SPR assays, in which antibodies act as a biological recognition element (McGrath, Baxter, Ferguson, Haughey, & Bjurling, 2005; Petz, 2009). In these work, conjugate between mycotoxin and protein (e.g. bovine serum albumin (BSA) and ovalbumin (OVA)), or mycotoxin derivative was preimmobilised onto the chip surface (Fig. 3A). Once the mixture of sample and a known concentration mycotoxin-specific antibody was injected onto the sensor chip (Fig. 3B), competition between the preimmobilised mycotoxin and free mycotoxin in the sample toward the mycotoxin-specific antibody will take place (Fig. 3C). If there is no mycotoxin in the sample, the antibodies will bind to the mycotoxin anchored on the sensor chip, leading to a larger value in SPR response units (RU). On the other hand, the competitive reaction between mycotoxin in the sample and the anchored mycotoxin will lead to a lower RU value. With the increase in the concentration of mycotoxin in the sample, the extent of inhibition will be higher, thus, a much lower SPR RU value will be obtained. Therefore, the amount of antibodies that bind to the chip surface is inversely proportional to the concentration of mycotoxin in the sample. Thus far, the competitive inhibition assay has attracted much attention due to its high sensitivity on detection of small molecules.

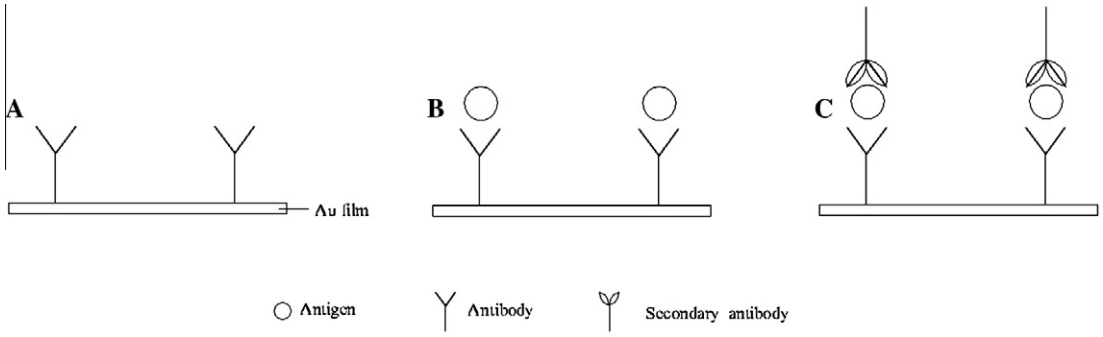

Fig. 2. Schematic view of sandwich assay.

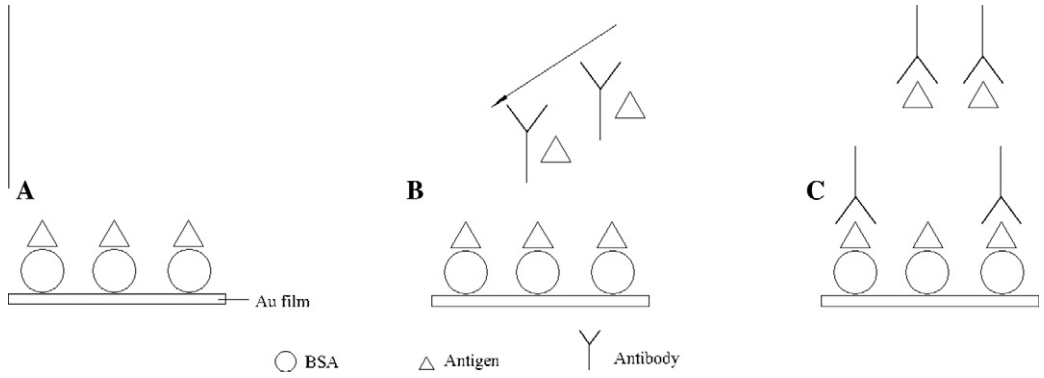

Fig. 3. Schematic view of inhibition assay.

In 2009, Yuan et al. used a competitive inhibition assay for detection of ochratoxin A (OTA) in cereals and beverages (Yuan, Deng, Lauren, Aguilar, & Wu, 2009). Mouse anti-OTA monoclonal antibodies were injected onto the chip surface where the OTA–OVA conjugate had been preimmobilised via a polyethylene glycol (PEG) linker. With the PEG linker, an optimal concentration of antibodies could be achieved. The mixed solutions of OTA with different concentrations and the antibodies with optimal concentration were flowed over the OTA–PEG–OVA surface. The limit of detection (LOD) of OTA in the sample was as low as 1.5 ng/mL.

3.3. Au NPs

Significant work has been reported in order to expand the applied range, simplify operating procedures and primarily improve sensitivity of SPR. Besides the methods mentioned above, Au NPs have attracted much attention in improving sensitivity of SPR for detecting small molecules.

It has been proved that, the electronic coupling interaction between the localised surface plasmon of Au NPs and the surface plasmon wave associated with the SPR Au films can significantly enhance the SPR response signal, and the enhancement depends largely on the particle sizes (Lyon, Pena, & Natan, 1999). Moreover, there are several advantages of Au NPs: (a) the capability of binding with various biomolecules; (b) safety for human; (c) the bio-function of molecule labelled by Au NPs barely change; (d) small amounts of Au NPs are needed in the test. Thus, Au NPs have been successfully applied as a biological marker for highly sensitive SPR detection of proteins, DNA, and drug molecules on a large scale.

Generally, there are two approaches to enhancing the sensitivity of the SPR biosensor by using Au NPs. One is that Au NPs is used as label by the antibody or antigen conjugating to enhance the signal of SPR response (Lyon, Musick, & Natan, 1998). The other is that Au NPs is used as active component by adsorbed onto the self-assembled monolayer (SAM) of thiol or dithiol formed on the SPR substrate. The adsorbed Au NPs collectively or selectively alters the SPR features of the substrate/SAM system, thereby enhancing the detection sensitivity of the SPR biosensor (Hutter, Fendler, & Roy, 2001).

When SPR biosensor is used to detect mycotoxins in foodstuffs, Au NPs also play an important role for increasing the refractive index of sensor surface. In the detection of OTA mentioned above (Yuan et al., 2009), the LOD of OTA in the sample was as low as 1.5 ng/mL. By using Au NPs (40 nm) as label of antibody for signal amplification, the LOD of OTA could be dramatically improved to 0.042 ng/mL, which is nearly 35× than that not using Au NPs.

4. Application of SPR on detecting mycotoxins

4.1. Aflatoxins

Aflatoxins are a group of highly toxic substances that are produced by fungi *Aspergillus flavus* and *Aspergillus parasiticus*, which can be found in many kinds of food and food materials, such as peanut, corn, cottonseed and milk. Naturally occurring aflatoxins include B_1, B_2, M_1, G_1, and G_2, and among all mycotoxins, aflatoxin B_1 (AFB_1) is the most toxic and carcinogenic. Its toxicity is 100× than that of potassium cyanide (KCN). Once aflatoxins are produced, it is difficult to destroy them during pasteurisation or other thermal treatments. Aflatoxins are sparingly soluble in water, but soluble in oil and some organic solvent. There have been some reports about the detection of aflatoxins by SPR biosensor.

In 2000, Daly et al. used commercial SPR sensor Biacore 1000 to detect AFB_1 based on competitive inhibition immunoassay (Daly et al., 2000). In that work, AFB_1 was conjugated to BSA and immobilised on dextran gel surface using amine coupling chemistry method.

The mixture of the AFB_1 and AFB_1 polyclonal antibody was injected into the SPR sensor chip. The limit of quantification of the assay was 3 ng/mL, and the assay had a linear range of 3.0–98.0 ng/mL with good reproducibility. The regeneration of the chip surface is important for the SPR biosensor since cyclic use of a same sensor platform in serial determination of various analytical samples would make the sensor system more cost effective and less time-consuming. In this assay, an organic solution consisting of ethanolamine and acetonitrile (pH 12.0) was used as eluent, which has been proved to benefit the chip surface regeneration.

Problems have been encountered when antibodies are immobilised onto a chip surface, directly or indirectly. The coupling chemical reagent will affect the binding capacity of antibody when the antibodies are directly immobilised onto the SPR chip surface. When antibodies are indirectly immobilised onto the SPR chip surface through either protein A or species-specific antibodies, it will be likely to result in incomplete binding between the captured antibody and the protein conjugate. To solve these problems, Dunne, Daly, Baxter, Haughey, and Kennedy (2005) focused on the development of SPR assays with specific single-chain fragment variable (scFv) for the detection of AFB_1. The gene encoding an AFB_1-scFv was isolated from a pre-immunised phage display library and used to express a monomeric and dimeric scFv, specific for AFB_1, in *Escherichia coli*. A CM5 chip was used to immobilise an AFB_1 derivative for the development of inhibition assays to detect AFB_1, incorporating the monomeric and dimeric scFvs that had been proved to have a high level of specificity for AFB_1 in cross-reactivity. Finally, the inhibition assays had a detection range of AFB_1 between 390 and 12,000 pg/mL for the monomeric scFv and between 190 and 24,000 pg/mL for the dimeric scFv.

Van der Gaag et al. analysed multiple mycotoxins, including AFB_1, zearalenone, deoxynivalenol (DON), and fumonisin B_1, by a miniature SPR device which has four serial connected flow cells (Van der Gaag et al., 2003). In this inhibition assay, four mycotoxins could be determined simultaneously in a sample with an appropriate cocktail of anti-mycotoxin antibodies. The LOD are 0.2 ng/g for AFB_1, 0.01 ng/g for zearalenone, 50 ng/g for fumonisin B_1, and 0.5 ng/g for DON.

4.2. Ochratoxins

Ochratoxins, including ochratoxin A, B, C, and D, are produced by several *Aspergillus* and *Penicillium* genera, which widely contaminate coffee beans and crops. For their properties of teratogenicity, immunotoxicity, and carcinogenicity, ochratoxins present a serious threat to human and animal health. It is well known that ochratoxin A (OTA) is a considerable toxic substance, and the OTA has been classified in group 2B as a possible human carcinogen by the International Agency of Research on Cancer (IARC) (Monographs on the evaluation of carcinogenic risk to humans (vol. 1), Lyon, IARC, 1993).

In 2004, Yu & Lai employed a polypyrrole (PPy) film on a miniaturised SPR device for the detection of OTA (Yu & Lai, 2004). It is well known that PPy film, which is relatively easy to be prepared by the electro-oxidation and is stable, can absorb different biomolecules. In their experiment, PPy film doped with chloride (PPy-Cl) was electrochemically polymerised on SPR chip surface. By monitoring the SPR angle, the thickness of each PPy-Cl film could be controlled in situ from 2 to 5 nm. The PPy films were found to exhibit good binding capability with OTA in 10% methanol solution, and when they are used for the OTA detection based on an increase in SPR angle, the linear range extended from 0.1 to 10 μg/ml. Fu demonstrated an SPR immumoassay for detection OTA based on nanogold hollow balls (GHB) with dendritic surface (Fu, 2007). A thionine thin film was initially electropolymerised onto the SPR chip surface, and then anti-OTA monoclonal antibody (anti-OTA) was immobilised onto the surface by GHB conjugation. The interaction of OTA and anti-OTA caused an increase in the resonant angle. The change of resonance angle is proportional to the concentration of OTA, and the LOD of OTA was 0.01 ng/mL. In 2009, Yuan et al. detected OTA in cereals and beverages (Yuan et al., 2009). Two different mixed self-assembled monolayers were compared through the effect of antibodies binding to OTA preimmobilised on SPR chip surface. One is the conjugate of OTA with BSA, and the other self-assembled monolayer is OTA–OVA conjugate with a polyethylene glycol (PEG) linker. The latter showed better binding capacity toward antibody than the former. A competitive inhibition immunoassay was carried out using the OTA–PEG–OVA surface. In addition, gold nanoparticles (40 nm) were applied on the OTA–PEG–OVA surface for signal enhancement. The LOD can be significantly improved to 0.042 ng/mL for OTA, though OTA concentration of as low as 1.5 ng/mL could be directly detected on this surface. The surface exhibited high stability with over 600 binding/regeneration cycles.

4.3. Fumonisins

Fumonisins, including fumonisin B_1 (FB_1) and fumonisin B_2, are produced mainly by *Fusarium moniliforme*, which is a common contaminant of corn in many parts of the world. FB_1 has been shown to give rise to a wide range of adverse biological effects, such as fatal leukoencephalomalacia in horses, pulmonary oedema in pigs and nephrotoxicity and liver cancer in rats.

In 1998, Mullett et al. utilised a SPR immunosensor to detect FB_1 in spiked samples (Mullett, Lai, & Yeung, 1998). This is the first time to detect mycotoxin by SPR. They immobilised polyclonal antibodies produced against FB_1 onto a thin gold film, which was coupled to a prism in the Kretschmann configuration. When a sample containing FB_1 was injected into the sensor chip, the intensity of the reflected light changed. At a specific angle, the shifts of the intensity of reflected light were proportional to the FB_1 concentration. After optimisation of the antibodies overlayer, a LOD of 50 ng/mL was obtained for the direct assay in 10 min. During the multiple mycotoxin analysis (Van der Gaag et al., 2003), FB_1 had a LOD of 50 ng/g by an inhibitive immunoassay based on SPR.

4.4. Trichothecenes

The trichothecenes produced by various fungal genera are a major group of mycotoxins, and are found in agricultural crops such as cereals, oilseeds, fruit, and vegetables. What cause most concern for human health is type A [T-2 toxin and HT-2 toxin] and type B [deoxynivalenol (DON) and nivalenol (NIV)] (Meneely, Ricci, Van Egmond, & Elliott, 2011). They are responsible for a wide range of disorder in animals, including feed refusal, weight loss, and vomiting, and have been found to inhibit synthesis of protein, DNA, and RNA, and to have immunosuppressive and cytotoxic effects. They have stable chemical properties, and DON is soluble in both water and organic solvents, but the other three can only be dissolved in organic solvents. No significant fluorescence was found under ultraviolet. They are relatively heat stable, and difficult to be destroyed during the cooking process.

4.4.1. Deoxynivalenol (DON) and nivalenol (NIV)

DON, also called vomintoxin, belongs to a group of mycotoxin, and it is produced by *Fusarium graminearumh* and *Fusarium culmorun*. DON is relatively less toxic, and is likely to occur in agricultural products.

SPR-based immunoassay was presented by Tüdös et al. for the selective and quantitative determination of DON in naturally contaminated matrices, where three different monoclonal mouse anti-DON antibodies were compared (Tüdös, Van den Bos, & Stigter,

2003). In the assay, the conjugate of DON and the protein casein was preimmobilised on the sensor chip surface. Then the mixture of the sample and monoclonal DON antibodies were flowed over the chip surface. It was found that the optimal working range was between 2.5 and 30 ng/mL in the tested solution. Guanidine chloride solution was used for regeneration, and the sensor surface could be reused more than 500× without significant loss of activity. At the same time, the cross-reactivity of the three antibodies in the SPR assay was tested with other trichothecene mycotoxins (3-acetyldeoxynivalenol, 15-acetyl-deoxynivalenol, nivalenol, HT2-toxin, and T2-toxin), where no significant SPR signal was observed. For naturally contaminated wheat samples, the DON detection results of the SPR-based assay were in agreement with that of liquid chromatography/tandem mass spectrometry measurements. During the multiple mycotoxin analysis (Van der Gaag et al., 2003), DON had a LOD of 0.5 ng/g by an inhibitive immunoassay based on SPR.

A competitive inhibition immunoassay based on SPR biosensor was developed to detect NIV and DON in wheat (Kadota et al., 2010). In the SPR assay, the DON–BSA conjugate was immobilised onto the CM5 chip surface using a standard amine coupling procedure, and a 1 M ethanolamine–HCl solution (pH 8.5) was employed to block redundant active groups of the chip surface. Seven mycotoxins, NIV, DON, DON-3-Glc, DOM-1, fusarenone-X, 3-acetyldeoxynivalenol, and 15-acetyldeoxynivalenol, were used in the cross-reactivity assay to check specificity of the monoclonal antibody. Calibration curves for each toxin were obtained. Half maximal inhibitory concentration (IC50) values were calculated from the resonance unit value at the midpoint of the calibration curves. The IC50 values of the SPR assay were 28.8 and 14.9 ng/mL for NIV and DON, respectively, and SPR analysis results were correlated with those obtained using a conventional liquid chromatography (LC)/mass spectrum (MS)/MS method for wheat co-contaminated with NIV and DON.

4.4.2. T-2 and HT-2 toxin

T-2 toxin that is produced mainly by *Fusarium sporotrichioides* and *Fusarium poae*, is one of the most dangerous naturally occurring food contaminants. Meneely et al. demonstrated a SPR screening assay for the combined detection of T-2 and HT-2 toxins using a sensor chip coated with an HT-2 toxin derivative and a monoclonal antibody (Meneely, Sulyok, Baumgartner, Krska, & Elliott, 2010). The antibody raised against HT-2 exhibited high cross-reactivity with T-2 toxin, and no cross-reaction was observed with other commonly occurring trichothecenes. A simple extraction procedure using 40% methanol was applied to baby food, breakfast cereal, and wheat samples prior to biosensor analysis. Then calibrants/samples were transferred to the "wells" of the microtitre plate and mixed with antibody solution and injected immediately over the surface of the sensor chip. A calibration curve of serial dilution of HT-2 toxin standard solution ranged from 0 to 80 ng/mL. The LOD of HT-2 toxin for each matrix was determined as 25, 25, and 26 μg/kg for baby food, breakfast cereal and wheat, respectively.

4.5. Zearalenone

Zearalenone, 6-(10-hydroxy-6-oxo-trans-1-undecenyl)-β-resorcyclic acid lactone, also called F-2 toxin, is produced by several species of the genus *Fusarium*, mainly *F. graminearum* and *F. culmorun*. Zearalenone has been found in some cereal crops, such as rice, wheat, and sorghum, and is known to act as an endocrine disruptor. This oestrogenic activity leads to the dysfunction of the reproductive system in humans and animals, which has the potential to cause substantial economic impacts. Tolerance levels have been established in many countries for grains and range from 30 to 1000 μg/kg (Food and Agriculture Organisation of the United Nations (FAO). Worldwide regulations for mycotoxins in food and feeds in 2003 FAO food and nutrition paper, 2004).

In 2009, Chol et al. used a SPR biosensor to investigate the feasibility of employing the molecular imprinting polymer technique for detecting zearalenone (Chol, Chang, Lee, Kim, & Chun, 2009). The molecularly imprinted polypyrrole (MIPPy) film was produced by electropolymerisation of pyrrole onto the bare Au chip in the presence of a template zearalenone molecule. Therefore shifts in resonance angle of the SPR sensor resulted from the rebinding of zearalenone to the MIPPy film. The MIPPy-SPR sensor showed a linear response in the range of 0.3–3000 ng/mL for zearalenone detection. The LOD and average recovery of blank corn matrix spiked with 30 ng/g zearalenone were 0.3 ng/g and 89%, respectively. The results suggest that a molecularly imprinted polypyrrole-based SPR sensor is a promising alternative method for the detection of zearalenone. During the multiple mycotoxin analysis (Van der Gaag et al., 2003), zearalenone had a LOD of 0.01 ng/g by an inhibitive immunoassay based on SPR.

5. Conclusion

In this review, the basic concepts and promising features of SPR, together with the identification and quantification of mycotoxin by various assay formats, such as sandwich assay, competitive inhibition assay, and Au NPs-based assay, have been highlighted. From the examples described above, it is evident that SPR, as a specific, sensitive, rapid, and versatile means, could be successfully utilised for the detection of mycotoxin in foodstuff and so far, enormous progress has been made on the determination of various artificial and real mycotoxin samples. Undoubtedly, with the growing interest in SPR and the further advances of other areas, such as material sciences, engineering, microelectronics, molecular biology, SPR will hold great promise for a variety of applications.

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