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ORIGINAL PAPER

A gold/Fe_3O_4 nanocomposite for use in a surface plasmon resonance immunosensor for carbendazim

Qian Li[1] · Xiaowen Dou[1] · Xiangsheng Zhao[2] · Lei Zhang[1] · Jiaoyang Luo[1] · Xiaoyan Xing[1] · Meihua Yang[1]

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Abstract

A surface plasmon resonance (SPR) biosensor for the pesticide carbendazim is described that has enhanced performance due to the use of a Au/Fe_3O_4 nanocomposite as an amplifying label on the surface the carboxymethyldextran-coated gold layer of the sensor. The surface was further modified with monoclonal antibody to obtain a sensor for real-time detection of carbendazim. Binding of carbendazim results in a change in refractive index. SPR detection in the absence of Au/Fe_3O_4 nanocomposite and by UPLC-MS analysis demonstrated the improved performance to be due to the use of the Au/Fe_3O_4 nanocomposite. Response is linear in the 0.05 to 150 ng·mL^{-1} carbendazim concentration range, and the limit of detection is 0.44 ng·mL^{-1}. This is more than 1 order of magnitude lower than that of the conventional SPR assay. The recoveries from spiked medlar are between 102.4 and 115.0%. The selectivity was tested by using the pesticides benzimidazole, 2-mercaptobenzimidazole, 2-benzimidazole propionic acid, and 2-(2-aminoethyl) benzimidazole as potential interferents. Conceivably, this Au/Fe_3O_4 nanocomposite-based method has a large potential for the detection of other small analytes at trace concentrations.

Keywords Biosensor · Real-time detection · Nanoprobe · Enhancement · Fungicide

Introduction

Carbendazim (methyl 2-benzimidazole carbamate, MBC) is a broad-spectrum benzimidazole fungicide that has been applied in agriculture for protection against a variety of pathogens [1]. MBC is widely used on a variety of plants, vegetables, and fruits, such as turf grasses, cucumbers, and oranges [2]. MBC is persistent in the environment, and has been detected frequently in agriculture products [3]. The International Codex Alimentarius Commission (CAC) has set 46 maximum residue limits (MRLs) for MBC in cucumber, orange and other crops, ranging from 0.05 to 20 mg·kg^{-1} (dry pepper) according to the food category (CAC, 2013). Due to adverse effects on human health [4], MBC has been banned in the USA and most European Union countries [5, 6]. But MBC formulations are still allowed to be used in India, Brazil, and China. In 2016, Chinese Ministry of Agriculture has planned to carry out risk assessment of MBC in China (MOA, 2016) [7]. Therefore, there is an urgent important need to detect MBC effectively and specifically to ensure food safety.

A number of methods have been reported to detect MBC in agriculture products, including high-performance liquid chromatography [8], liquid chromatography-mass spectrometry [6], fluorescence spectrophotometry [9], molecularly imprinted polymer [10], and electrochemistry [2, 11]. However, these techniques have some disadvantages, such as requirements for expensive instrument, complex pretreatments needed, or time-consuming analytical steps involved. Most of the present methods cannot provide real-time results. Nowadays more screening and check scenarios need real-time quantify results on site. It is changeling and an urgent call to set up a real-time method for MBC determination, which can be applied to a broad range of food products.

The surface plasmon resonance (SPR) biosensors, technology was well developed in recent years for trace detection, which is promising to provide real-time dection results for

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✉ Meihua Yang
yangmeihua15@hotmail.com

[1] Key Laboratory of Bioactive Substances and Resources Utilization of Chinese Herbal Medicine, Ministry of Education, Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences and Peking Union Medical College, Haidian District, Beijing 100193, China

[2] Hainan Branch of the Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences and Peking Union Medical College, Haikou 570311, China

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pesticides including MBC. SPR is an important optical physical phenomenon based on the excitation of surface plasmons, where SPR sensors monitor changes in the refractive index of biomolecular interactions on metal surfaces [12, 13]. The SPR biosensor has a having a rapid response, allows direct real-time monitoring.It is less time consuming. Labelling steps are not needed [12]. Therefore, it was widely used in numerous analytical fields, medical diagnostics [14], environmental monitoring [15], and food quality and safety analyses [16]. However, the sensitivity of SPR to low molecular weight molecules (less than 8 kDa) was not satisfied, since these molecules only induce small signal responses at the sensor interface of metal film [17].

Nanomaterial-functioned SPR technologies were reported to enhance the signal responses at the interface. These nanomaterials were used as amplification tags, including Au nanoparticles (NPs), AgNPs, magnetic nanoparticles (MNPs), et al. [18–22]. MNPs have attracted increasing attentions due to their special features, due to their special features, including super paramagnetism, high specific surface areas, and low toxicity [20, 23]. AuNPs are also considered as practical material for biosensors due to its unique characteristics, including its exceptional optical features and facility of surface functionality [24, 25]. To date, more advanced methods combining the advantages of magnetic components with gold nanoshells have received much attention [25]. Considering gold-coated magnetic coreshell particles, they are highly attractive to enhance the SPR signal and to provide separation supports.

In this work, a MBC nanoprobe was established based on Au/Fe_3O_4 nanocomposite enhancement of SPR signals for the quantification of MBC in real samples using the indirect competition method. The Au/Fe_3O_4 nanocomposites were employed in biosensor to amplify the SPR response signal and to simplify the immunoassay procedures. The mixture of MBC and a certain concentration of Au/Fe_3O_4 conjugated with anti-MBC monoclonal antibody (MBC-mAb-Au/Fe_3O_4) was injected into the cell. MBC-bovine serum albumen (BSA) competed with MBC for binding to the MBC-mAb-Au/Fe_3O_4 conjugates. The selectivity was tested by using the pesticides benzimidazole, 2-mercaptobenzimidazole, 2-benzimidazole propionic acid, and 2-(2-aminoethyl) benzimidazole as potential interferents. Medlar samples were assessed using the traditional SPR method, enhanced SPR method, and ultra-performance liquid chromatography-mass spectrometry (UPLC-MS/MS) method. These results demonstrate the sensitive SPR method is a feasible tool for MBC detection in real samples. This Au/Fe_3O_4 nanocomposite-based separation and amplification strategy has great potential for detection of other small analytes at trace levels in a wide range of fields due to its high selectivity and sensitivity, which are achieved by altering the target analyte-capture agent labeled to the carboxyl-coated Au/Fe_3O_4 nanocomposites.

Materials and methods

Reagent and materials

The common reagents 3-mercaptopropionic acid (MPA), Bovine Serum Albumin (BSA), 1-ethyl-3-(3-dimethylamino-prophl) carbodiimide hydrochloride (EDC), n-hydroxysuccinimide (NHS), sodium dodecyl sulfate (SDS), 2-(N-morpholino)ethanesulfonic acid (MES), 11-mercaptoundecanoic acid (11-MUA, 95%), and the inorganic salts for preparation of phosphate-buffered saline (PBS) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Methanol was purchased from Merck. Hydrochloric acid (HCl) and sodium hydroxide (NaOH) were purchased from the Tianjin Chemical Reagent Factory. Chloroauric acid hydrate ($HAuCl_4$), ferric chloride ($FeCl_2$), ferrous chloride ($FeCl_3$), and tetramethylammonium hydroxide pentahydrate (TMAOH) were purchased from Beijing Chemicals Corporation (Beijing, China). All other chemicals and reagents were purchased from Aladdin.

Carbendazim conjugated to BSA (MBC-BSA; 1.0 mg·mL^{-1}) and carbendazim monoclonal antibody (MBC-mAb, 1.0 mg·mL^{-1}, $K_D = 2.75 \times 10^9$ mol·L^{-1}) were purchased from Wuxi Ditengmin Biological Technology Co., Ltd.

Standard solutions of MBC, benzimidazole, 2-(2-aminoethyl) benzimidazole, 2-benzimidazole propionic acid, and 2-mercaptobenzimidazole were purchased from Beijing Shiji'aoke Biological Technology Co., Ltd. The concentrations of the stock solutions are 1.0 mg·mL^{-1}.

All reagents were analytical grade and ultra-pure water was used in experiments. MBC-mAb was dissolved with 0.01 mol·L^{-1} PBS (pH 7.4). MBC-BSA was dissolved with 0.01 mol·L^{-1} acetate buffer (pH 4.5). MBC was dissolved with 0.01 mol·L^{-1} PBS containing 5% methanol. The blocking buffer was 1 mol·L^{-1} methanolamine (pH 8.5).

Apparatus

SPR measurements were performed on an SPR instrument (Beijing Inter-bio Tech CO) using the Kretschmann configuration. Changes in the angle of the reflected light indicate shifts in mass on the surface and were detected with a charge-coupled device. Thoroughly degassed 0.01 mol·L^{-1} PBS (pH 7.4) buffer was used as the system buffer and was applied at a constant speed of 10 μL·min^{-1}.

Modification of the sensor chip

The CM5 sensor chip has carboxymethylated dextran matrices on gold surfaces and was purchased from Inter-bio (Beijing, China). MBC-BSA was covalently immobilized onto the chip surface using the active ester method. The sensor chip was rinsed with 0.01 mol·L^{-1} PBS (pH 7.4) at a flow rate of 10 μL·min^{-1}. A solution of EDC (0.4 mol·L^{-1}) and NHS (0.1 mol·L^{-1}) in MES buffer (0.1 mol·L^{-1}, pH 6.0) was injected into the instrument to activate the carboxylic groups on the chip. After dissolving MBC-BSA in sodium acetate buffer (0.01 mol·L^{-1}, pH 4.5), the solution was covalently bound to the modified sensor surface. Any molecules attached through non-specific adsorption were washed away with 50 μL PBS. Finally, blocking solution was injected for 10 min to block unbound carboxyl sites.

Preparation of gold/Fe_3O_4 nanocomposites

The Fe_3O_4 nanoparticles and Au/Fe_3O_4 nanocomposites were synthesized using chemical coprecipitation methods as previously reported [26–28]. The Au/Fe_3O_4 nanocomposites were prepared as follows. First, neutral MPA and 0.012 g sodium citrate were dissolved in 50 mL deionized water. Under nitrogen gas protection, Fe_3O_4 nanoparticles (0.2 mL) were added quickly to the boiling solution. After 5 min, $HAuCl_4$ (0.012 mol·L^{-1}) was added to the boiling solution. The color of the solution changing to red indicated the Au shell had successfully formed on the Fe_3O_4 nanoparticle surfaces. The obtained solution was precipitated by magnetic separation to remove free Au nanoparticles. The resulting precipitate was washed with ultra-pure water and 5 mL of 1 mol·L^{-1} HCl was added to remove any uncoated Fe_3O_4. In this manner, the nanocomposites were washed, 25 mL of 0.05 mol·L^{-1} NaOH was added to the precipitate, and Au/Fe_3O_4 nanocomposite solution was again obtained. Transmission electronic microscopy (TEM) was used to characterize the nanocomposites.

Preparation of gold/Fe_3O_4 nanocomposites coupled with antibody

First, a solution of EDC (0.4 mol·L^{-1}) and NHS (0.1 mol·L^{-1}) in MES buffer (0.1 mol·L^{-1}, pH 6.0) used to activate the carboxyl groups of MPA on the Au/Fe_3O_4 nanocomposites for 30 min. The activated carboxyls react with the protein amino groups, while unactivated carboxyl binding to amino groups is unlikely at room temperature. Au/Fe_3O_4 colloid solution (1 mL) was precipitated using a magnetic separator and the precipitate was washed with PBS (pH 7.4) three times. MBC-mAb (1 mL) dissolved in PBS (pH 7.4) was added to the Au/Fe_3O_4 colloid solution. After 4 h, Au/Fe_3O_4 nanocomposites conjugated with MBC-mAb were obtained. The solution was then precipitated with a magnetic separator and the supernatant containing unreacted antibodies was removed. The precipitate was diluted with 1 mL PBS and stored at 4 °C.

Immunoassay

MBC was detected using an indirect competition assay with MBC-mAb-Au/Fe_3O_4 serving as an amplification material. At room temperature, MBC was dissolved in 0.01 mol·L^{-1} PBS containing 5% methanol. The same concentration of MBC-mAb-Au/Fe_3O_4 and different concentrations of MBC were mixed for 15 min at room temperature. These solutions were then injected into the flow cell of the SPR biosensor system. A schematic diagram of the experimental procedure is shown in Fig. 1.

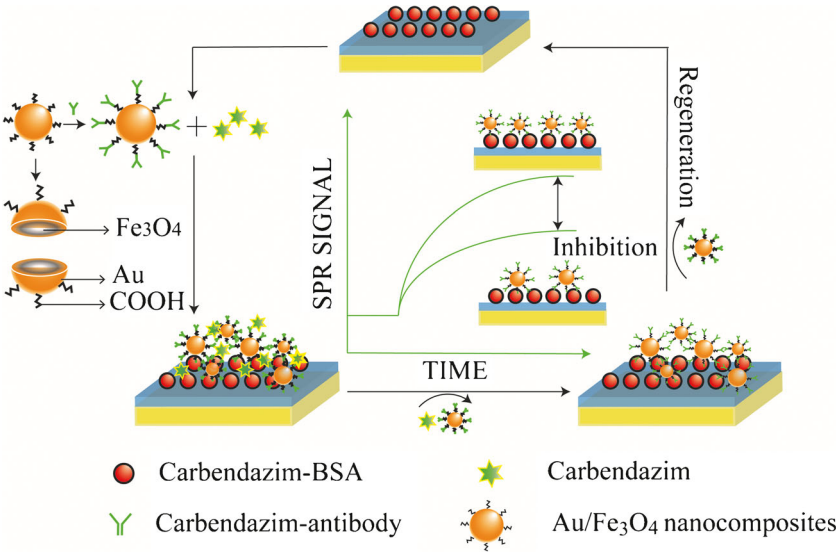

Fig. 1 Schematic diagram of the experimental procedure and the preparation of Au/Fe_3O_4 nanocomposites coupled with antibody

After a series of immunoassays were performed, the sensing membrane of the SPR biosensor was regenerated. MBC-mAb-Au/Fe_3O_4 was removed using a regeneration solution of 0.1 mol·L^{-1} HCl (1% SDS) at the end of each test cycle.

Preparation of real samples

Medlar samples were purchased from a supermarket and were tested to confirm they contained no MBC. The smashed medlar was extracted with 10 mL of 80% (*v*/v) methanol for 30 min using an automatic shaker. The crude extract was centrifuged at 8000 rpm for 10 min. The supernatant was then diluted with PBS. Finally, the residue was dissolved in 1 mL of 0.01 mol·L^{-1} PBS containing 5% methanol for analysis. For all experiments, samples were filtered before use.

Results and discussion

Preparation and characterization of functionalized nanoparticles

Fe_3O_4 nanoparticles were synthesized as seeding material using a previously reported chemical coprecipitation method. Au was deposited on the surface of the Fe_3O_4 nanoparticles in the presence of MPA to form Au/Fe_3O_4 nanocomposites. As previously reported, proper shell thickness is essential to obtaining a high enough magnetic-field intensity to influence the SPR response and stability of the MNPs [29]. Figure 2 shows TEM of MNPs and the Au/Fe_3O_4 nanocomposites. The average size of Au/Fe_3O_4 is about 50 nm and is larger than pure MNPs. Au/Fe_3O_4 has large aggregations due to the high

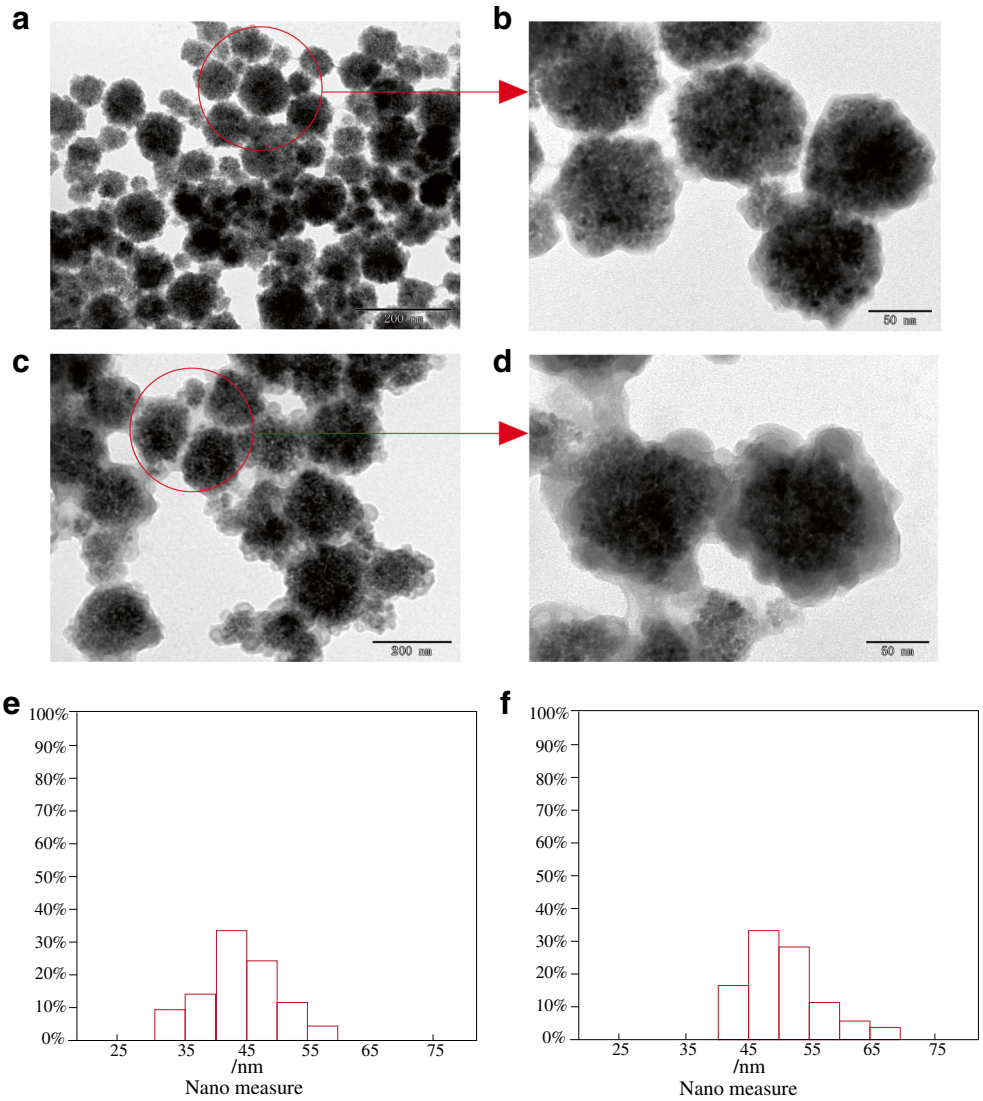

Fig. 2 TEM images of Fe_3O_4 nanoparticles (**a**, **b**) and Au/Fe_3O_4 nanocomposites (**c**, **d**). The particle size distributions of Fe_3O_4 nanoparticles (**e**) and Au/Fe_3O_4 nanocomposites (**f**). The scale bar of (**a**) and (**c**) was 200 nm and the scale bars of (**b**) and (**d**) were both 50 nm

surface energy of the nanoparticles. In addition, there is magnetic attraction between Fe_3O_4 nanoparticles. Because the high interfacial energy exists between Au and magnetic nanoparticles, the Au prefers to growing on the surface with the lowest interfacial energy instead of covering the MNPs completely [30]. Au/Fe_3O_4 nanocomposites immobilized on the SPR biosensor enhance the SPR curve through a shift in intensity, which increases the sensitivity of the SPR biosensor.

Determination of MBC

The MBC-BSA and MBC compound competed for MBC-mAb-Au/Fe_3O_4 and the amount of MBC-mAb-Au/Fe_3O_4 coupled to the MBC-BSA was monitored as a shift in the SPR signal. Consequently, the change in the SPR signal increased as the concentration of free MBC decreased and was used to quantify MBC.

After the MBC-BSA was immobilized on the chip surface using the optimal concentration, the MBC-mAb-Au/Fe_3O_4 and MBC solution was injected into the SPR cell at 10 μL·min^{-1} to detect MBC using the indirect competition method.

For further comparison of amplification by MBC-mAb-Au/Fe_3O_4, an indirect competition method was also constructed using an SPR sensor without Au/Fe_3O_4 nanocomposites. Equal volumes of MBC-mAb and nine different concentrations of MBC (150, 100, 75, 50, 10, 5, 2.5, 0.25, and 0.05 ng·mL^{-1}) were mixed for 15 min at room temperature. These solutions (150 μL) were flowed on the chip surface and measurements were obtained in a similar manner using the indirect competition method to monitor the shift of signal response. Figure 3 shows the SPR response signal gradually decreased as the MBC concentration increased and under the same conditions, the SPR signal based on MBC-mAb-Au/Fe_3O_4 exhibited a higher response. A linear relationship is obtained from nine MBC concentrations ranging from 0.05 to 150 ng·mL^{-1}. The regression equation is $y = 19.43 + 101.62/(1 + (x/5.71)1.96)$ ($R^2 = 0.996$) and the LOD is 2.81 ng·mL^{-1}. The enhanced SPR method constructed based on MBC-mAb-Au/Fe_3O_4 was also used to detect MBC. A linear relationship is observed from nine MBC concentrations ranging from 0.05 to 150 ng·mL^{-1}. The regression equation is $y = -3.89 + 248.23/(1 + (x/3.31)^{0.68})$ ($R^2 = 0.992$) and the LOD is 0.44 ng·mL^{-1}.

When comparing the experiments involving Au/Fe_3O_4 nanocomposites to the experiments in the absence of the nanocomposites, the signal amplification is clearly seen for a lower LOD and wider linear range in the presence of the nanocomposites. The biosensor using Au/Fe_3O_4 nanocomposites was more sensitive, where the enhancement observed is due to the larger mass and higher refractive index of the Au/Fe_3O_4 nanocomposites.

Regeneration

For repeated use, the MBC-mAb-Au/Fe_3O_4 bound to the MBC-BSA should be dissociated from the surface of chip without damaging the sensing layer. Therefore, regeneration conditions were optimized to increase the repeatability of sensor chips and the stability of the sensor response.

Figure 4 shows a comparison of the baseline shift and elution response after use of the four regeneration solutions

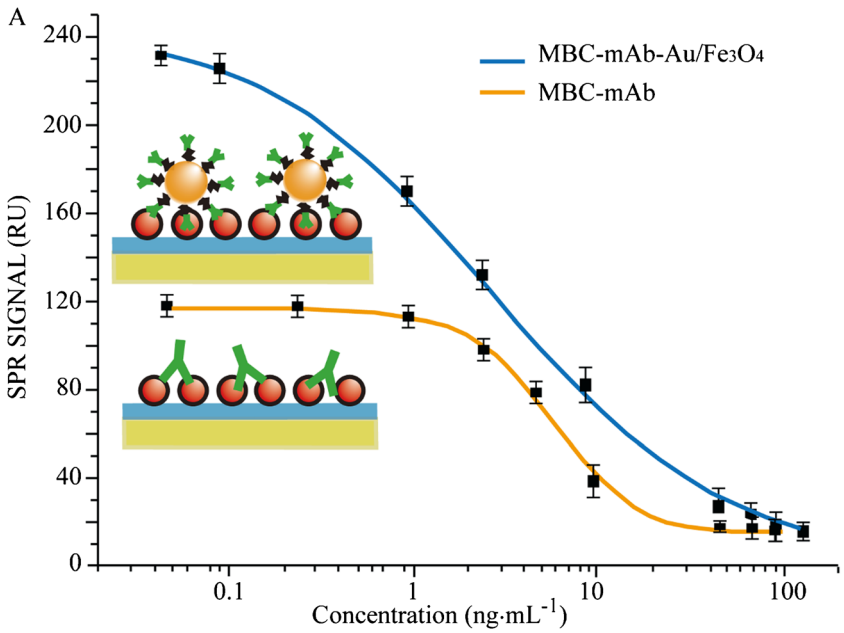

Fig. 3 The inhibition curve between the concentration of MBC and the shifts of resonant signal resulting from enhanced format with Au/Fe_3O_4 nanocomposites. Error bars represent the standard deviations for three replicates

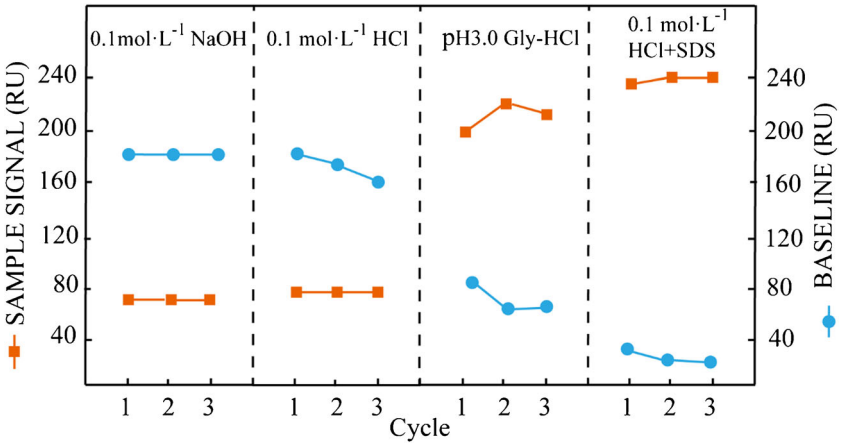

Fig. 4 Comparison of the baseline shift and sample response using the four regeneration solutions for MBC-mAb-Au/Fe_3O_4

0.1 mol·L^{-1} HCl, 0.1 mol·L^{-1} Gly-HCl (pH 3.0), 0.1 mol·L^{-1} NaOH, and 0.1 mol·L^{-1} HCl containing 1% SDS. When 0.1 mol·L^{-1} HCl containing 1% SDS was used, the baseline and sample responses were stable without obvious fluctuations. By contrast, the baseline gradually increased after reuse cycles when 0.1 mol·L^{-1} HCl and Gly-HCl (pH 3.0) were used, indicating MBC-mAb-Au/Fe_3O_4 was not completely eluted from the sensor chip. Moreover, when using 0.01 mol·L^{-1} NaOH, a marginal response signal was observed after each reuse cycle, demonstrating the NaOH solution damages the sensing film and reduces the service life of the biosensor chip. Hence, 0.1 mol·L^{-1} HCl containing 1% SDS solution was determined to be optimal for the elution of MBC-mAb-Au/Fe_3O_4.

Specificity

Being able to assess the specificity of the method to selectively detect target analytes is an important capability of an SPR immunosensor. The specificity of the immunosensor was investigated by a series of structural and functional analogues of MBC, including benzimidazole, 2-(2-aminoethyl) benzimidazole, 2-benzimidazole propionic acid, and 2-mercaptobenzimidazole. These fungicides were diluted in 0.01 mol·L^{-1} PBS containing 5% methanol to create solutions with concentrations of 4.0 and 25.0 ng·mL^{-1} and were tested using the same indirect competition assay as for MBC.

Therefore, MBC and four structural and functional analogues, benzimidazole, 2-mercaptobenzimidazole, 2-benzimidazole propionic acid, and 2-(2-aminoethyl) benzimidazole, were tested by the enhanced method. From the results shown in Fig. 5, it is observed the SPR signal is the highest when detecting MBC. These results illustrate this method has good specificity for MBC detection.

Real sample analysis

After easy pretreatment, the MBC-spiked medlar samples at final concentrations of 4.0, 10.0, and 25.0 ng·mL^{-1} were detected using the SPR sensor in the presence and absence of

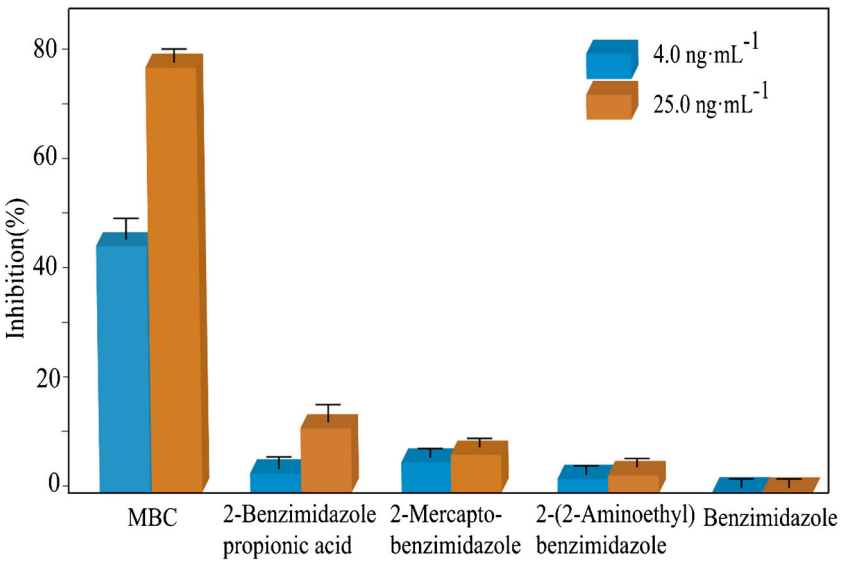

Fig. 5 Specificity analysis of Au/Fe_3O_4 enhanced SPR detection. Error bars represent the standard deviations for three replicates

Table 1 Recovery test results for medlar samples

Sample	Traditional SPR method			Enhanced SPR method			UPLC-MS/MS method		
Amount spiked ($ng{\cdot}mL^{-1}$)	Amount measured ($ng{\cdot}mL^{-1}$)	Recovery (%)	RSD (%)	Amount measured ($ng{\cdot}mL^{-1}$)	Recovery (%)	RSD (%)	Amount measured ($ng{\cdot}mL^{-1}$)	Recovery (%)	RSD (%)
1 4.0	4.7	117.5	10.2	4.6	115.0	9.2	3.8	95.0	5.2
2 10.0	11.3	113.0	9.4	10.6	106.0	7.8	9.7	97.0	6.4
3 25.0	26.8	107.2	7.5	25.6	102.4	7.4	24.6	99.2	4.8

Au/Fe_3O_4. For comparison, the samples were analyzed using a traditional SPR sensor, an enhanced SPR sensor, and the UPLC-MS/MS method.

The blank samples were analyzed by UPLC/MS to confirm MBC was undetectable. The detection results are shown in Table 1. The recovery results indicates this enhanced SPR approach have satisfactory accuracy for detecting MBC in medlar samples. The validation of MBC determinations in real samples was accomplished by chromatographic methods, which yielded results consistent with one another. The correlation with the UPLC-MS/MS method ensures its capability as a valuable analytical screening tool for the continuous monitoring of pesticides. Since the enhanced SPR method has universality in the recognition element, it can detect targets rapidly and with high specificity, allowing it to be easily applied in practice.

Conclusion

An indirect competition method using an enhanced SPR immunosensor combined with Au/Fe_3O_4 nanocomposites was established for MBC measurements with high sensitivity and accuracy. The Au/Fe_3O_4 nanocomposites were functioned as probes to selectively recognize and separate MBC, and as amplification targets to enhance the SPR signals. This approach made sample pretreatments simplified. Through specific identification between MBC-mAb-Au/Fe_3O_4 and MBC, the selectivity and sensitivity were improved for complex food matrixes. This method has several advantages, including having a short detection time and low LOD and being suitable for real-time monitoring. The study demonstrates that this method can detect various types of small molecules through alterations in the types of biomolecules immobilized on the chip surface and the corresponding antibody.

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Compliance with ethical standards The author(s) declare that they have no competing interests.

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