1 **Quartz crystal microbalance sensor based on molecularly imprinted polymer**
2 **membrane and three-dimensional Au nanoparticles@mesoporous carbon**
3 **CMK-3 functional composite for ultrasensitive and specific determination of**
4 **citrinin**

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ABSTRACT

Citrinin (CIT) is difficult to measure since only trace levels are present in commercial food products. In this study, a novel three-dimensional (3D) molecularly imprinted quartz crystal microbalance (QCM) sensor for trace citrinin (CIT) detection was constructed by electro-polymerizing *o*-aminothiophenol (*o*-AT) in the presence of the dummy template 1-hydroxy-2-naphthoic acid (HNA) on an Au nanoparticles@mesoporous carbon CMK-3 (AuNPs@CMK-3) functional composite modified Au electrode (AuE) surface decorated by Au nanoparticles@mesoporous carbon CMK-3 (AuNPs@CMK-3) functional composite. Herein, AuNPs@CMK-3 functional composite acted as signal amplifier since the 3D structure and large specific surface area of the AuNPs@CMK-3 functional composite were beneficial to increase the amount of effective imprinted sites and subsequently improve the sensitivity of the sensor. The preparation process of the QCM sensor was characterized by scanning electron microscope (SEM), transmission electron microscope (TEM), cyclic voltammetry (CV) and electrochemical impedance spectroscopy (EIS). Under the optimal conditions, the proposed sensor showed a linear frequency shift to the concentration of target CIT ranging from 6.0×10^{-9} to 2.0×10^{-7} mol L⁻¹ with a low detection limit of 1.8×10^{-9} mol L⁻¹ (S/N = 3). The sensitive sensor exhibited excellent selective recognition, anti-interference capability, reproducibility and long-term stability, and was successfully applied to analyze trace CIT in cereal samples with satisfactory recoveries, suggesting the proposed sensor is promising for the detection of CIT at trace levels in foods.

36 **Keywords:** quartz crystal microbalance sensor; molecularly imprinted polymer;
37 citrinin; Au nanoparticles@mesoporous carbon CMK-3.

1. Introduction

Molecular imprinting technology (MIT) is an exciting technology which concerns the creation of specific recognition sites with memory of the template molecules in size, shape and functional groups [1]. Researchers have poured increasing attention towards molecular imprinted polymer (MIP) which is produced through MIT due to its excellent performance of high selectivity, chemical/mechanical tolerance, low cost, ease of synthesis and reproducibility [2]. In view of these advantages, MIP have been widely accepted and applied in various fields including chromatographic separation [3], solid-phase extraction (SPE) [4], immunoassays [5] and sensors [6]. Among these applications, the MIP based sensors have been widely reported in current years. Generally, MIP can be used as recognition element in the development of electrochemical sensors [7-10], surface plasmon resonance (SPR) sensors [11-13] and quartz crystal microbalance (QCM) sensors [14-17].

~~Quartz-crystal-microbalance (QCM)~~, as a kind of mass-sensitive detector at nanogram levels, has exerted a tremendous fascination on researchers for the development of sensitive sensors ~~due to its attractive performance because of a range of benefits~~ such as extreme sensitivity, cost effective and simple operation ~~[7]-[18]~~. And outstanding selectivity can be realized ~~from QCM sensor by using introduction of-MIP as recognition element-of-QCM-sensor~~. Consequently, MIP based QCM sensors have captured considerable attention in food safety, environmental analysis, biological and medical detection ~~[8-12]-[19-23]~~. As it is well known, the ~~The~~ integration of MIP and the transducer surface of the sensor ~~modified-layers-on-the~~

60 ~~sensor surface~~ has direct influence on the performance of ~~sensor during fabrication~~.

61 Among various modification methods, electropolymerization is a simple and effective
62 ~~method way~~ to prepare MIP membrane ~~directly~~ on the ~~transducer~~ surface of QCM
63 sensor since the thickness of ~~the~~ MIP membrane can be easily controlled through
64 varying the number of cyclic voltammetry (CV) scanning cycles. ~~Generally As it is~~
65 ~~well known~~, the sensitivity of the imprinted sensor depends on the amount of effective
66 imprinted sites which are modified on the surface of sensor. Therefore, to further
67 increase the amount of effective imprinted sites on the surface of sensors, functional
68 materials should be implemented to enlarge the specific surface area [13][24].

69 Ordered mesoporous carbon (OMC), a vital member of the ~~carbon-based material~~
70 ~~family of carbon-based material~~, has drawn significant interest ~~since it was reported in~~
71 ~~1999~~ due to its excellent performance such as high specific surface areas, excellent
72 thermal/mechanical stability, large pore volume and good electrical conductivity ~~since~~
73 ~~it was reported in 1999 [14][25]~~. As a kind of OMC, CMK-3 mesoporous carbon has
74 been demonstrated to be an attractive modified material ~~of on~~ the electrode due to its
75 excellent properties mentioned above [15-17][26-28]. Au nanoparticles (AuNPs), the
76 quintessential example of metal nanoparticles, have exhibited a series of attractive
77 properties such as high surface area, excellent biocompatibility, long-term stability
78 and good electrical conductivity [18][29]. Because of the above advantages and the
79 ability to form self-assembled monolayer (SAM) with functional monomer containing
80 thiol group, AuNPs were applied to MIP based sensors in order to enhance the
81 sensitivity of sensors [19-22][30-33]. The functional material ~~which~~ combined the

merits of CMK-3 and AuNPs ~~have~~ ~~has~~ been attempted to amplify the response signal of electrochemical sensor using its electrochemical property. However, few investigations have focused on the effect of ~~using Au nanoparticles@mesoporous carbon CMK-3 (AuNPs@CMK-3) functional composite to increase~~ ~~increasing~~ the effective MIP sites and thus ~~amplify~~ ~~amplifying~~ the signal of MIP based QCM sensor ~~with the help of Au nanoparticles@mesoporous carbon CMK-3 (AuNPs@CMK-3) functional composite.~~

Citrinin (CIT), a nephrotoxic mycotoxin with high toxicity, carcinogenicity, teratogenicity and mutagenicity, contaminates various commodities of plant origin, especially the cereals [23]–[34]. Several analytical methods have been successfully developed to assay CIT in complex samples such as high performance liquid chromatography (HPLC) [24]–[35], high performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) [25]–[36], enzyme-linked immunosorbent assay (ELISA) [26]–[37] and thin-layer chromatography (TLC) [27]–[38]. Nevertheless, every method was born with shortcomings, for example, HPLC and HPLC-MS/MS needed to consume a large amount of mobile phase, enzymes or antibodies used in ELISA were hard to obtain and inconvenient to store, the sensitivity of TLC was relatively low in general. ~~In addition, MIP based sensors for CIT analysis have been reported. In these literatures, the CIT imprinted voltammetric sensor and SPR sensor were developed and successfully applied for the sensitive and selective determination of CIT in food samples [39, 40].~~

In this study, a novel QCM sensor was fabricated for CIT determination using a

poly(*o*-aminothiophenol) (Po-AT)-MIP membrane as recognition element on Au electrode (AuE) surface modified with AuNPs@CMK-3 functional composite. To the best of our knowledge, this is the first attempt to ~~modified AuNPs@CMK-3 functional composite on the transducer surface to construct a MIP based QCM sensor. AuNPs@CMK-3 functional composite was used to increase the effective imprinted sites and thus amplify the frequency response signal, by increasing effective surface area on the electrode and enhancing effectiveness of the self-assembly process. assay CIT with MIP based QCM sensor with high sensitivity, selectivity, simplicity, reproducibility and stability.~~ The new technology is a strong complement for traditional methods of CIT determination. ~~Furthermore, AuNPs@CMK-3 functional composite with three dimensional (3D) structure was modified on the electrode surface as a function layer to enhance the sensitivity of the MIP based QCM sensor for the first time.~~ This research was aimed at overcoming some shortcomings of weak signal response, complicated fabrication process with MIP based sensor, and also offering a sensitive, selective, simple, reproducible and stable QCM method for CIT determination.

2. Experimental

2.1 Instruments and reagents

All electrochemical experiments were performed using a PARSTAT 2273 electrochemistry workstation (Princeton Applied Research, USA) coupled with a QCM (QCM-922, Princeton Applied Research, USA) equipped with a commercial 9

MHz AT-cut quartz crystal coated with AuE (area 0.196 cm²) on both sides (Seiko EG&G). ~~In the experiments, the The~~ quartz crystal was mounted into the Teflon holder (well-type, QA-CL3, Seiko EG&G) to ensure that only one side of the AuE was exposed to the solution. ~~All electrochemical experiments were performed with a conventional three-electrode system, consisting of a bare or modified quartz crystal AuE as the working electrode, a saturated calomel electrode as the reference electrode, and a platinum column electrode as the counter electrode. This was employed as the working electrode in a typical three-electrode system with a saturated calomel electrode and a platinum column electrode as the reference electrode and the counter electrode, respectively.~~ QCM was also used to record the frequency change of the quartz crystal AuE. Transmission electron microscopy (TEM, JEM-2010FEF, JEOL, Japan) was performed to visually show the morphological characteristics of the AuNPs@CMK-3. The surface morphologies of electrodes were characterized by scanning electron microscope (SEM, 1530VP, LEO, Germany). HPLC (LC-20AB, Shimadzu, Japan) was utilized to validate the results obtained from the proposed sensor for cereal samples detection. The pH of solution was measured on FE 20 Mettler-Toledo pH meter (Switzerland).

CMK-3 was obtained from XFNANO Materials Tech Co., Ltd. (Nanjing, China). CIT, 1-hydroxy-2-naphthoic acid (HNA), deoxynivalenol (DON), ochratoxin A (OTA), zearalenone (ZEN), aflatoxin B1 (AFB1), gold chloride (HAuCl₄) and trisodium citrate were purchased from Sigma-Aldrich (St. Louis, MO, USA). The chemical structures of CIT, HNA and structural analogs (DON, OTA, ZEN and AFB1) were

shown in Fig. S1 in the Supplement Material. Tetrabutylammonium perchlorate and *o*-aminothiophenol (*o*-AT) were supplied by Alfa Aesar (Tianjin, China). Potassium ferricyanide ($K_3[Fe(CN)_6]$), methanol and other chemicals used in the experiments were obtained from Tianjin No. 1 Chemical Reagent Factory (Tianjin, China) and were of at least analytical grade. Milli-Q purified water was used throughout the experiment.

2.2 Synthesis of AuNPs@CMK-3

The AuNPs (with diameter ~ 17 nm) were synthesized via reduction of $HAuCl_4$ by trisodium citrate according to a reported method [28]–[41]. The ~~and the~~ synthesis process of AuNPs was described in detail in the supplementary material.

Based on the literature procedure [29]–[42], AuNPs@CMK-3 was fabricated with the following procedure: 30 mg CMK-3 was added into 100 mL AuNPs solution and the mixture was further stirred for 4 h. The resulting AuNPs@CMK-3 was collected by centrifugation (9000 rpm, 20 min) and dried in vacuum.

2.3 Preparation of MIP/AuNPs@CMK-3/AuE

Prior to modification, the bare AuE of quartz crystal was ultrasonically washed with ethanol and then cleaned with freshly prepared “piranha” solution (30% H_2O_2 /concentrated $H_2SO_4 = 1:3$, v/v) for 5 min. After rinsing with ultra-pure water, acetone, and ethanol, the crystal was blown dry with a gentle flow of pure nitrogen gas and mounted into the well.

Schematic representation of the MIP/AuNPs@CMK-3/AuE fabrication process was shown in Fig.1.

Fig. 1

(A) Preparation of AuNPs@CMK-3/AuE: the as-prepared AuNPs@CMK-3 (2.5 mg) was dispersed in 5 mL N,N-dimethylformamide (DMF) in a glass tube with the help of ultrasonic treatment to form a homogeneous AuNPs@CMK-3 suspension (0.5 mg mL^{-1}). Then, the AuE was coated with 5 μL of the resulting AuNPs@CMK-3 suspension solution and allowed to dry at room temperature.

(B) *o*-AT and HNA self-assembly on the AuNPs@CMK-3/AuE: the pretreated AuNPs@CMK-3/AuE was immersed in an ethanol solution containing *o*-AT (20 mmol L^{-1}) overnight to allow for monomer self-assembling self-assembly to obtain *o*-AT-AuNPs@CMK-3/AuE. After being washed with ethanol and ultra-pure water, the *o*-AT-AuNPs@CMK-3/AuE was then immersed into a methanol solution of HNA (as dummy template, 10 mmol L^{-1}) in-methanol for 6 h. HNA molecules accordingly assembled onto the *o*-AT-AuNPs@CMK-3/AuE to complete the pre-assembly between HNA and *o*-AT through hydrogen bond interaction. Then the electrode was taken out, rinsed with ethanol, and dried with nitrogen at room temperature.

(C) Electropolymerization: after *o*-AT and HNA self-assembly, the AuNPs@CMK-3/AuE was immersed in a N_2 -deoxygenated methanol solution containing *o*-AT (20 mmol L^{-1}), HNA (10 mmol L^{-1}), tetrabutylammonium perchlorate (5 mmol L^{-1}) and HCl (10 mmol L^{-1}). The electropolymerization was performed by 20 CV sacannings between -0.2 V and $+1.2 \text{ V}$ (scan rate 50 mV s^{-1}).

(D) Template removal: the above electrode was washed three times (15 min each time) with a methanol/0.5 mol L⁻¹ HCl solution (9:1, v/v) to remove HNA molecule entrapped within the polymeric matrix. ~~to obtain MIP/AuNPs@CMK-3/AuE.~~ Then, the **resulting** MIP/AuNPs@CMK-3/AuE was rinsed with ultra-pure water and ethanol, and **then** dried under nitrogen for further use. **When HNA was washed off from the imprinted polymers, the imprinted caves for HNA were left for the selective adsorption of CIT.**

As a control, the non-imprinted polymer (NIP)/AuNPs@CMK-3/AuE was also fabricated and treated following the same procedure above but without adding HNA template in the self-assembly and electropolymerization process, and the MIP/AuE was constructed through the same process but missing the AuNPs@CMK-3 functional composite modification step.

2.4 Measurement experiments

The modified electrode was submerged in 20 mL ~~of~~ methanol solution with magnetic stirring. After a steady resonant frequency (f_0 , Hz) was recorded, a small aliquot of methanol with desired concentration of CIT was injected into the solution. The resulting frequency (f_i , Hz) was recorded until it became steady. The frequency shift Δf ($f_i - f_0$, Hz) **could be calculated, which is** associated with mass change caused by the specific recognition of CIT on the MIP membrane ~~was calculated.~~

2.5 Sample preparation

Detailed sample preparation was described in the supplementary material.

2.6 HPLC analysis

Traditional HPLC was employed to verify the results obtained from the MIP based QCM sensor developed for CIT detection. The HPLC system consisted of a LC-20AB pump and a RF-10AXL fluorescence detector (E_x , 331 nm; E_m , 500 nm; Shimadzu, Japan). All separations were performed on a C_{18} column (4.6 mm $\times$ 250 mm, 5 μ m; Agilent, USA) with acetonitrile/water (45:55, v/v, pH was adjusted to 2.5 with phosphoric acid) as the mobile phase at a flow rate of 1.0 mL min⁻¹ at 30 °C column temperature.

3. Results and discussion

3.1 Morphological characterization of the AuNPs@CMK-3

TEM was performed to visually show the morphological characteristics of ~~the~~ AuNPs@CMK-3. As shown in Fig. 2A and B, a large number of globular shaped AuNPs with an average diameter of 17 nm were uniformly distributed on the ordered mesoscopic matrix of ~~the~~CMK-3. ~~The 3D porous nature of CMK-3 is highly beneficial to provide a large specific surface area of the modified AuE.~~ Little AuNPs could be seen in the background of ~~the~~TEM images, suggesting that AuNPs were stably and firmly attached onto the CMK-3.

Fig. 2

3.2 Characterization of the modified electrodes

It is advisable to select dummy template when synthesizing MIP due to its high toxicity and expense. HNA, which is similar to CIT from the viewpoint of structure as shown in Fig. S1, was selected as the dummy template in this study. Before electropolymerization, AuNPs@CMK-3/AuE was immersed in an *o*-AT solution overnight. A SAM of *o*-AT molecules could be formed on the surface of the AuNPs@CMK-3/AuE through Au-S bonds between the thiol groups of the *o*-AT molecules and the AuNPs on the surface of AuNPs@CMK-3/AuE. by immersing the AuNPs@CMK-3/AuE into the *o*-AT solution overnight. After further immersing the *o*-AT-AuNPs@CMK-3/AuE into the HNA solution for several hours, HNA was assembled on the surface of the *o*-AT-AuNPs@CMK-3/AuE through hydrogen bonding between the carboxyl and hydroxyl of HNA and the amino groups of *o*-AT. The SAM of *o*-AT and HNA served as an initial polymerizable monolayer to drive the electropolymerization and increase the amount of imprinted sites on the AuNPs@CMK-3/AuE surface [21, 30] [32, 43]. Detailed experiments also reveal that if the self-assembly procedure was omitted from the preparation procedures of MIP/AuNPs@CMK-3/AuE, the frequency shift to CIT would decrease to about 15% under the same experimental condition. As a control, frequency shift to CIT obtained using MIP/AuNPs@CMK-3/AuE omitting the self-assembly procedure was about 15% lower than the modified electrode using self-assembly procedure.

As shown in Fig. S2, representative cyclic voltammograms were recorded during the electropolymerization process of *o*-AT membrane on the AuNPs@CMK-3/AuE

in the presence of HNA. The cyclic voltammograms behavior of *o*-AT showed that it underwent an entirely irreversible oxidation process. An apparent oxidation peak of *o*-AT was observed at a potential of + 0.64 V in the first positive potential scan and the current intensity became weaker under successive cyclic scans. The results indicated that *o*-AT was electrochemically oxidized at the anode and the successive formation of the *Pol*-AT membrane on the surface of ~~the~~-AuNPs@CMK-3/AuE suppressed the voltammetric response. Moreover, the cyclic voltammograms of the electropolymerization of *Pol*-AT membrane had no significant difference in the presence or absence of HNA, suggesting that HNA had no electroactivity in the chosen potential range and its structure was not electrochemically altered under the experimental conditions.

The surface morphologies of the modified electrodes displayed by SEM also confirmed *Pol*-AT membrane was electrodeposited onto the surface of the electrodes. Compared with MIP/AuE (Fig. 2D), MIP/AuNPs@CMK-3/AuE (Fig. 2C) showed a rougher surface due to the 3D porous support structure of AuNPs@CMK-3. Changes of the surface morphology on the electrode largely increased the specific surface area of the electrode, promoting the formation of thinner MIP membrane and more effective imprinted sites.

3.3 Electrochemical behavior of the sensor

CV is an effective and convenient method to investigate the electron transmission procedure of the surface-modified electrodes. In this work, various modified

electrodes were monitored in 1.0 mmol L⁻¹ K₃[Fe(CN)₆] solution containing 0.2 mol
 L⁻¹ KNO₃ by CV. As shown in Fig. 3A, the cyclic voltammogram of ~~the~~ bare AuE
 showed a couple of redox peaks (curve a). ~~When the electrode surface was covered~~
~~with the AuNPs@CMK-3 functional composite, After the AuNPs@CMK-3 functional~~
~~composite was coated on the surface of AuE,~~ the redox peak current in CV curve was
 significantly increased (curve b). ~~Hence, it is clear that AuNPs@CMK-3 functional~~
~~composite effectively increased the electrode active area and catalytic activity. This~~
 probably originated from three factors: firstly, AuNPs ~~played the role of a conducting~~
~~wire or electron-conducting tunnel, so it could~~ provided an effective electron
 conductive pathway and promoted electron-transfer reactions of the redox probe [34]
 [44]. Secondly, the greatly enhanced electrochemical behavior on
 AuNPs@CMK-3/AuE may be attributed to a large number of CMK-3 ~~made a~~
~~contribution to enhancing the electrochemical performance because of plenty of~~ edge
 plane defect sites at the surface of CMK-3 accessible for the electrolyte [32] [45].
 Thirdly, the synergistic effect of ~~the~~ AuNPs and CMK-3 also greatly accelerated the
 mass and electron transfer processes and expanded electrical activation area of the
 electrode surface. Compared with the AuNPs@CMK-3/AuE, almost no
 electrochemistry response could be observed with the NIP/AuNPs@CMK-3/AuE
 (curve c). ~~This is likely because the non-conducting NIP membrane covered the~~
~~surface of AuNPs@CMK-3/AuE inhibiting electron transfer. ,indicating that electron~~
~~transfer was hampered by the non-conducting NIP membrane covered on the surface~~
~~of AuNPs@CMK-3/AuE.~~ Whereas, after MIP membrane was coated on the

AuNPs@CMK-3/AuE (curve d), a CV response was restored with a pair of redox peaks after elution of the template. This result indicated, suggesting that the large number of imprinted cavities were produced in the MIP membrane after removal of template molecules. The probe $K_3[Fe(CN)_6]$ was able to diffuse through these cavities to the electrode surface to complete redox reaction. Additionally, the emergence of curve e were measured after could be attributed to the incubation of the MIP/AuNPs@CMK-3/AuE with a 1.0×10^{-7} mol L⁻¹ solution of CIT. This could be explained by the rebinding of CIT to the imprinted cavities, which blocking diffusion of the probe $K_3[Fe(CN)_6]$ to the electrode surface.

Electrochemical impedance spectroscopy (EIS) is an effective electrochemical technique for monitoring the interface properties of surface-modified electrodes. Generally, a typical EIS consists of a semicircle part lying on the Z'-axis followed by a straight line. The semicircle region at higher frequencies corresponds to the electron-transfer limited process, whereas the linear portion at lower frequencies may be ascribed to diffusion. Moreover, the semicircle diameter equals to the electron-transfer resistance (R_{et}), which depends on the dielectric and insulating features at the electrode/electrolyte interface, and shows the electron transfer kinetics of the redox probe [33, 34][46, 47]. As shown in Fig. 3B, the EIS of bare AuE (curve a) exhibited low R_{et} to the redox of the probe $K_3[Fe(CN)_6]$. After modification of AuNPs@CMK-3 on the surface of AuE, almost a straight line was observed in curve b. This could be attributed to the modification of AuNPs@CMK-3 accelerating electron transfer processes. Almost a straight line was displayed in curve b, which

indicated that the probe $K_3[Fe(CN)_6]$ underwent a very fast electron-transfer process when the AuE surface was modified with the AuNPs@CMK-3 functional composite. Curve c showed the EIS of the AuNPs@CMK-3/AuE after surface modification with NIP membrane. As expected, the semicircle diameter on curve c was clearly enlarged, indicating The diameter of the semicircle increased dramatically (curve c) after NIP membrane was electrodeposited onto the AuNPs@CMK-3/AuE surface, indicating that non-conducting NIP membrane blocked the penetration of the redox probe. Compared with curve c, a relatively smaller semicircle diameter was shown in curve d. This result might be assigned to the large number of specific recognition sites formed appeared on the AuNPs@CMK-3/AuE surface, which enhanced the diffusion rate of the redox probe through the MIP membrane and accelerated the electron-transfer process. An increment of R_{et} could be found (curve e) when immersing MIP/AuNPs@CMK-3/AuE to a 1.0×10^{-7} mol L^{-1} solution of CIT, which was attributed to since the rebinding of CIT into the imprinted cavities, inhibiting diffusion of the probe $K_3[Fe(CN)_6]$ to the electrode surface. These results were accordant with CV assays as described in details above. All these results indicated that the modification of AuNPs@CMK-3 functional composite could effectively accelerate electron transfer processes and expand electrical activation area and the MIP/AuNPs@CMK-3/AuE had been successfully fabricated.

Fig. 3

3.4 Optimization of conditions for MIP membrane preparation

The molar ratio of template molecule to functional monomer during electropolymerization determines the MIP membrane structure plays a crucial role in the membrane structure forming process of MIP which influences affects the amount of specific recognition sites available for selective rebinding of template [35][48]. To evaluate the imprinting effect of different template/monomer molar ratios, Experimental results of a series of MIP membranes (molar ratio of template molecule/functional monomer, 1:1, 1:2, 1:3, 1:4) modified AuNPs@CMK-3/AuEs were synthesized. As shown in Fig. S3A, the frequency shift to CIT reached the maximum with the template molecule/functional monomer molar ratio of 1:2. When the molar ratio of template molecule/functional monomer was lower or higher than 1:2, the frequency shift became decreased. Thus, suggesting that the optimal molar ratio of template molecule/functional monomer was maintained at 1:2 in the following experiments.

The thickness of MIP membrane is a another critical factor that influences the sensitivity of the sensor. In this research, the membrane thickness which could be controlled by adjusting the number of scanning cycle during the electropolymerization procedure. As shown in Fig. S3B, the frequency shift to CIT reached the maximum with 20 cycles, and then decreased with additional cycles. Thus, 20 cycles was considered as the optimized scanning cycle to produce a MIP membrane that achieved the largest frequency shift to CIT.

In addition, the amount of HCl in electropolymerization solution can influence affect the electrochemical activity of the monolayer o-AT and further influence affects

the performance of the MIP membrane prepared [11, 36, 37] [22, 49, 50]. ~~A series of electropolymerization solution added HCl from 6 mmol L⁻¹ to 14 mmol L⁻¹ and the electropolymerization solution without HCl addition were prepared. It was found that~~ Through evaluation of the frequency shift, the MIP membrane prepared using 10 mmol L⁻¹ HCl showed the largest frequency shift after CIT adsorption (Fig. S3C). Therefore, the optimal concentration of added HCl was chosen as 10 mmol L⁻¹.

3.5 Evaluation of binding performance

The binding affinity of CIT to the established sensor was evaluated by measuring the change in frequency response upon consecutive additions of CIT stock solution. With the ~~increase increment~~ of CIT concentration, more imprinted sites were rebound with CIT, and the frequency response reduced accordingly. The results in Fig. 4 (curve a) showed that the frequency shift was directly proportional to the concentration of CIT ranging from 6.0×10^{-9} mol L⁻¹ to 2.0×10^{-7} mol L⁻¹ with a detection limit of 1.8×10^{-9} mol L⁻¹ (S/N = 3) ~~using MIP/AuNPs@CMK-3/AuE as working electrode.~~ The linear regression equation was expressed as $-\Delta f \text{ (Hz)} = 615.55 C_{\text{CIT}} (\mu\text{mol L}^{-1}) + 23.55$ ($R^2 = 0.9950$). Compared with MIP/AuE ($-\Delta f \text{ (Hz)} = 279.60 C_{\text{CIT}} (\mu\text{mol L}^{-1}) + 24.44$, $R^2 = 0.9918$, linear range of 1.0×10^{-8} mol L⁻¹- 2.0×10^{-7} mol L⁻¹, Fig. 4, curve b), the frequency shift range and linear range obtained from MIP/AuNPs@CMK-3/AuE were broader. ~~This may be explained by an increase in the number of effective imprinted sites on the MIP membrane induced by modifying AuNPs@CMK-3 on the electrode surface. It was attributed to the presence of the~~

376 ~~AuNPs@CMK-3 functional composite.~~ When AuNPs@CMK-3 was introduced into
377 the MIP/AuNPs@CMK-3/AuE, the frequency shift range and linear range were
378 enlarged further than that of the MIP/AuE. It is inferred that by increasing effective
379 surface area ~~of~~ on the electrode and enhancing ~~the~~ effectiveness of the self-assembly
380 process, the AuNPs@CMK-3 functional composite can largely increase the ~~more~~
381 effective imprinted sites and thus amplify the frequency response signal. ~~were~~
382 ~~obtained on the MIP/AuNPs@CMK-3/AuE, and thus wider linear range and greater~~
383 ~~frequency shift to CIT was recorded.~~ Moreover, MIP/AuNPs@CMK-3/AuE required
384 less frequency response time (~14 min) compared with MIP/AuE (~16 min) when
385 measuring at the same concentration of CIT (2.0×10^{-7} mol L⁻¹). ~~The rapid response~~
386 ~~characteristic was attributed to ,since the modification of AuNPs@CMK-3 functional~~
387 ~~composite~~ enhanced diffusion of analyte ~~to~~ towards the MIP membrane ~~fabricated on~~
388 ~~the AuNPs@CMK-3 functional composite.~~ The frequency shift of the
389 MIP/AuNPs@CMK-3/AuE (curve c) was much lower than that of the
390 MIP/AuNPs@CMK-3/AuE and MIP/AuE, indicating that the
391 MIP/AuNPs@CMK-3/AuE had excellent specificity. To further affirm the superior
392 performance of the prepared sensor, the detection range and detection limit were
393 compared with other methods reported in the literatures. The detailed results were
394 shown in Table 1. The linear range of the prepared sensor was improved and a lower
395 detection limit was achieved, suggesting superior performance of prepared sensor as
396 expected.

Fig. 4

Table 1 Comparison of different methods for the determination of citrinin

Methods	Linear range	Detection limit	References
ELISA	20-640 ng mL ⁻¹ (8×10^{-8} - 2.56×10^{-6} mol L ⁻¹)	10 ng mL ⁻¹ (4×10^{-8} mol L ⁻¹)	[26] [37]
Reversed phase-HPLC-fluorescence detection	0.0107-0.537 µg mL ⁻¹ (4.28×10^{-8} - 2.15×10^{-6} mol L ⁻¹)	0.187 µg mL ⁻¹ (7.48×10^{-10} mol L ⁻¹)	[38] [51]
HPLC-MS/MS	5.81-100 µg kg ⁻¹ (4.65×10^{-8} - 8×10^{-7} mol L ⁻¹)	1.74 µg kg ⁻¹ (1.39×10^{-8} mol L ⁻¹)	[25] [36]
Electrochemistry sensor	7.988-99.4 µmol L ⁻¹		[39] [52]
MIP based disposable evanescent wave fiber optic sensor	0.5-2.5 µg mL ⁻¹ (2-10 mmol L ⁻¹)		[40] [53]
MIP based QCM sensor	6.0×10^{-9} - 2.0×10^{-7} mol L ⁻¹	1.8×10^{-9} mol L ⁻¹	This work

3.6 Selectivity and anti-interference capability experiment

Selective recognition capacity towards the template molecule was an important merit for MIP-based sensor. ~~It is of great significance to evaluate the selective recognition of the proposed sensor based on specific binding interactions between the imprinted sites and the analyte.~~ To investigate the selectivity of the proposed sensor,

frequency shifts towards CIT and its structural analogs on MIP/AuNPs@CMK-3/AuE and NIP/AuNPs@CMK-3/AuE were compared and the results were shown in Fig. 5A. For simplicity, the ~~The~~ imprinting factor (IF) was defined as $\Delta f_{\text{MIP}}/\Delta f_{\text{NIP}}$, where Δf_{MIP} and Δf_{NIP} were the frequency shift of the five analytes tested with MIP and NIP sensor at the same concentration of $2.0 \times 10^{-7} \text{ mol L}^{-1}$, respectively. As shown in Fig. 5A, the IFs for CIT, DON, OTA, ZEN and AFB1 were 3.19, 1.48, 1.78, 1.76 and 1.74, respectively. Obviously, the IF for CIT was higher than the IFs for these structural analogs, and there was almost no difference in the adsorption of these structural analogs using the MIP and NIP sensors. Moreover, the selectivity coefficient (SC) was also used to evaluate the selectivity of the proposed sensor, which was defined as $\alpha_{\text{CIT}}/\alpha_{\text{analyte}}$, where α is the slop of the calibration curves. As shown in Fig. 5A, the frequency shifts for the analytes DON, OTA, ZEN and AFB1 were much less significant than for the CIT with SC values of 4.40, 2.90, 3.07 and 3.90, respectively. The results of IF and SC showed that MIP/AuNPs@CMK-3/AuE had higher adsorption capacity for CIT in comparison to DON, OTA, ZEN and AFB1 due to selective cavities in the polymer structure. This could be attributed to the complementarity of the size, shape and position of recognition functional groups between CIT and the binding sites on MIP/AuNPs@CMK-3/AuE. On the other hand, the self-assembled o-AT and HNA monolayer on the surface of AuNPs@CMK-3 may also play a role to drive the selectivity during the electropolymerization process. The above results ~~of IF and SC~~ confirmed that the proposed sensor exhibited excellent selective recognition towards CIT.

Furthermore, anti-interference capability of the proposed sensor was also evaluated in this study. Four structural analogs which might coexist with CIT in cereals were chosen to test the anti-interference capability of the proposed sensor. The anti-interference capability of the proposed sensor ~~towards structural analogs which might coexist with CIT in cereals~~ was valued by frequency shift ratio ($\Delta f_m/\Delta f_o$) of CIT response in the presence of structural analogs including DON, OTA, ZEN and AFB1, respectively. Δf_m and Δf_o were frequency shift to CIT in the presence and absence of interference. As shown in Fig. 5B, compared with reference frequency shift ratio of CIT ($\Delta f_m/\Delta f_o = 1$), $\Delta f_m/\Delta f_o$ was only slightly varied from 103.5% to 119.3% in 10-fold excess of interfering substances over CIT. The above results indicated that the proposed sensor showed an excellent interference immunity capability, allowing the detection of CIT from structural analogs with little interference.

Fig. 5

3.7 Reproducibility and stability

Reproducibility and stability of the developed QCM sensor are important for successful CIT detection. Therefore, ~~the~~ reproducibility of the proposed sensor was evaluated by measuring the frequency shifts of five freshly prepared MIP/AuNPs@CMK-3/AuE at the same CIT concentration of 1.0×10^{-7} mol L⁻¹. And an acceptable relative standard deviation (RSD) of 5.7% was obtained. Besides, the RSD for five repeated measurements of a 1.0×10^{-7} mol L⁻¹ CIT using the same MIP/AuNPs@CMK-3/AuE (scilicet, used each time after elution procedure) was

estimated to be 4.3%. The above results revealed that the proposed sensor had favorable reproducibility. To evaluate the stability of the proposed sensor, the frequency shift of MIP/AuNPs@CMK-3/AuE towards 1.0×10^{-7} mol L⁻¹ CIT solution was measured and recorded weekly. The proposed sensor retained 94% of its original response after two weeks stored at room temperature, and still retained 86% of the original response after being stored for a month. These results revealed that the proposed sensor possessed remarkable long-term stability. The good reproducibility and stability of the developed QCM sensor are ~~attributed~~ attributed to the good stability of AuNPs@CMK-3 functional composite and rigid structure of the MIP membrane.

3.8 Practical sample analysis and HPLC validation

The practical performance of the proposed sensor was evaluated by spiking and recovery studies which analyzed trace CIT in rice, wheat and white rice vinegar. The statistical results were shown in Table 2, mean recoveries ranged from 85.8% to 94.5% with SDs (n = 3) from 4.4% to 6.5%, which was in accord with the results (mean recoveries, 83.8-90.4%; SDs, 4.2-7.9%) obtained from the traditional HPLC method. The above results confirmed that the developed imprinted sensor was reliable and effective for analyzing trace CIT in practical samples.

Table 2 Recoveries of CIT from spiked cereal samples determined by the proposed sensor and traditional HPLC.

Sample	Added (μg)	The proposed sensor			Traditional HPLC		
		Found	Recovery%	RSD%	Found	Recovery%	RSD%

	$\text{kg}^{-1}/\mu\text{g}$ L^{-1}	$(\mu\text{g}$ $\text{kg}^{-1}/\mu\text{g}$ $\text{L}^{-1})$	(mean $\pm$ SD) (n = 3)	(n = 3)	$(\mu\text{g}$ $\text{kg}^{-1}/\mu\text{g}$ $\text{L}^{-1})$	(mean $\pm$ SD) (n = 3)	(n = 3)
Rice	10.00	8.58	85.8 ± 5.2	6.1	8.64	86.4 ± 3.7	4.2
	50.00	43.83	87.6 ± 4.3	4.9	44.88	89.8 ± 6.4	7.1
	100.00	90.18	90.2 ± 4.3	4.8	90.36	90.4 ± 5.5	6.1
Wheat	10.00	9.06	90.6 ± 4.7	5.2	8.63	86.3 ± 3.8	4.4
	50.00	44.48	89.0 ± 4.5	5.1	41.91	83.8 ± 6.4	7.6
	100.00	90.51	90.5 ± 5.2	5.7	89.75	89.7 ± 6.3	7.0
white	10.00	9.28	92.8 ± 4.1	4.4	8.94	89.4 ± 4.4	4.9
rice	50.00	46.54	93.1 ± 6.0	6.5	45.11	90.2 ± 7.2	7.9
vinegar	100.00	94.52	94.5 ± 4.8	5.0	89.15	89.2 ± 5.9	6.6

4. Conclusion

In summary, a novel 3D MIP based QCM sensor for determination of trace CIT had been successfully constructed by electro-polymerizing MIP membrane onto AuNPs@CMK-3 functional composite decorated AuE surface for the first time. This research had combined the advantages of 3D structure and large specific surface area of AuNPs@CMK-3 functional composite, high specificity from MIP and high sensitivity from QCM. Under optimal conditions, the proposed QCM sensor using MIP/AuNPs@CMK-3/AuE as working electrode could selectively recognize trace CIT under the interference of structural analogs. Moreover, repeated measurements

470 and long-term storage could hardly affect the stability of the proposed sensor. In
471 addition, the proposed sensor was successfully applied for detecting trace CIT in
472 cereals with satisfactory recoveries, making it possible to detect trace CIT in foods.

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Figure captions:

Fig. 1 Schematic representation of the MIP/AuNPs@CMK-3/AuE fabrication process.

Fig. 2 TEM images of AuNPs@CMK-3 (A and B); SEM images of MIP/AuNPs@CMK-3/AuE (C) and MIP/AuE (D).

Fig. 3 Cyclic voltammograms (A) and nyquist plots (B) obtained from 1.0 mmol L^{-1} $\text{K}_3[\text{Fe}(\text{CN})_6]$ and 0.2 mol L^{-1} KNO_3 at bare AuE (a), AuNPs@CMK-3/AuE (b), NIP/AuNPs@CMK-3/AuE (c), MIP/AuNPs@CMK-3/AuE (d) and MIP/AuNPs@CMK-3/AuE after incubating with $1.0 \times 10^{-7} \text{ mol L}^{-1}$ CIT (e).

Fig. 4 The corresponding frequency shifts of MIP/AuNPs@CMK-3/AuE (a), MIP/AuE (b) and NIP/AuNPs@CMK-3/AuE (c) for different concentrations of CIT.

Fig. 5 (A) Frequency shift corresponding to the MIP/AuNPs@CMK-3/AuE and NIP/AuNPs@CMK-3/AuE for different concentrations of CIT, DON, OTA, ZEN and AFB1; (B) frequency shift ratio ($\Delta f_m/\Delta f_o$) of MIP/AuNPs@CMK-3/AuE to $1.0 \times 10^{-8} \text{ mol L}^{-1}$ CIT, and $1.0 \times 10^{-8} \text{ mol L}^{-1}$ CIT in the presence of $1.0 \times 10^{-7} \text{ mol L}^{-1}$ DON, OTA, ZEN and AFB1, respectively.

FIGURES

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

A

B

Author Biographies

Guozhen Fang received her Ph.D degree in Department of Analytical Chemistry in 2005 from Nankai University, Tianjin, China. Now she is serving as a professor in Tianjin University of Science and Technology. Her researches mainly focus on the molecular imprinting technique and instrumental analysis, also their relative application in the detection of food and environmental contaminants.

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Shuo Wang received his Ph.D. in 1999 from The University of Sydney, now he is serving as a specially appointed professor in Tianjin University of Science and Technology and responsible for Key Laboratory of Food Nutrition and Safety, Ministry of Education of China. He has long been engaged in the research fields of Food Safety and Food Science.