Electrochemical detection of methyl-paraoxon based on bifunctional cerium oxide nanozyme with catalytic activity and signal amplification effect

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1. Introduction

Organophosphorus pesticides (OPs), as one of the most widely used pesticides in the world, have had an irreplaceable position in recent decades and the foreseeable future \cite{1–3}. However, the widespread use of OPs has caused various degrees of contamination in Chinese medicine, food chain and the whole eco-system \cite{4–9}. Due to their history of prevalent use, severe health effects, including neurotoxicity, embryotoxicity, genotoxicity, cytotoxicity and immunotoxicity as well as long-term effects, have been reported previously \cite{10–13}. Among the commonly used OPs, oxo-form OPs and their active metabolites have shown the acute toxicity on the central nervous system as well as oncogenic and teratogenic risks via phosphorylation of serine residue in the catalytic site of acetylcholinesterase \cite{14,15}. Methyl-paraoxon (MP) is the most typical oxo-from OP which has attracted more research attention recently, not only because of its serious neurotoxicity and respiratory toxicity, but also for its common application as a nerve agent simulant to investigate structure properties of chemical warfare agents \cite{16–18}. Consequently, to develop new and sensitive methods for MP is pivotal for health protection and public safety.

Nowadays, many analytical instrument-based methods have been established for MP detection, such as gas chromatography, liquid chromatography, and these apparatuses coupled with mass spectrometry \cite{19,20}. These instrument-based methods can produce high accuracy results, but suffer from the drawbacks of long analysis time, requirement for skilled manpower, and the required instruments are large and expensive. Therefore, they cannot be
widely used for on-site testing. To solve this problem, rapid detection methods were designed and constructed for on-site analysis of MP as emerging technologies. Various on-site analysis methods based on the inhibition of bioenzymes activity, like acetylcholinesterase, have been applied for the rapid detection of MP [21,22]. Due to high specificity, sensitivity, simplicity, and efficiency, the enzyme-based sensing technique has become the mainstream of rapid detection. In recent years, inorganic nanomaterials have been developed for MP detection to improve the potential instability of biological enzyme and applicability of rapid detection methods [23]. Extensive nanomaterials including carbon dots, transition metal and polymer were introduced to establish various rapid detection methods for MP detection [24–27]. Nanozyme is also one kind of nanomaterials with mimic activity of biological enzyme. Due to their excellent stability, high catalytic and simple preparation, nanzymes have been widely used for the establishment of rapid detection methods [28–32]. Among these nanozymes based methods, electrochemical detection has received growing attention in recent years due to its advantages of short analysis time, high sensitivity, low cost, small sample required and easy operation [33].

To date, most of the electrochemical methods for pesticide detection have been developed based on the inhibitory mechanism of natural biological enzyme [34–37] which can be affected by many types of pollution, such as heavy metals and biological toxins. It makes the direct determination of MP lack selectivity, and even leads to false positive results. Some other researchers focused on the development and application of novel nanomaterials in electrochemical assays with signal amplification effect [38–41]. The materials formed by specific chemical reactions, like in situ generated nanozyme-initiated cascade reaction [41], can effectively complete signal amplification and obtain excellent detection results. Inspired by the utilization of nanozyme with bifunctional properties which can eliminate the shortcomings of biological enzymes and amplify the detection signal in electrochemical detection, we developed a new electrochemical technique based on the cerium oxide (CeO2) as nanozyme for pesticide detection in this study (Scheme 1). On the one hand, CeO2 exhibits the organophosphorus hydrolase mimicking activity, which can catalyze the decomposition of MP to generate para-nitrophenol (p-NP). On the other hand, the electrochemical signal of p-NP was amplified after the nanozyme coating on the surface of electrode. As far as what is known, there has been no report on the application of bifunctional nanozyme in the pesticide detection so far.

2. Experimental

2.1. Chemicals and reagents

Hydrogen peroxide (H2O2; 30%), ammonia solution (NH4OH; 30%), cerium chloride (CeCl3·6H2O; 99.95%), sodium hydroxide (NaOH; 96%), Nafion 117 solution (5%), hydrochloric acid solution (HCl, 6 mol/L) and ethanol (99.7%) were all purchased from Shanghai Aladdin Biochemical Technology Co., Ltd. (Shanghai, China). Phosphate buffer solution (PBS) was prepared from phosphate buffered salt powder supplied by NanJing SenBeiJia Biotechnology Co., Ltd. (Nanjing, China). Methyl-paraoxon (HPLC; 99.8%) and Tris base (≥99.8%) were obtained from Sigma Aldrich (St. Louis, MO, USA).

2.2. Instruments

Electrochemical analysis was performed using Princeton PAR-STAT electrochemical workstation (AMETEK, Oak Ridge, TN, USA). A conventional three-electrode system was used in all electrochemical measurements, and all electrodes were obtained from Shanghai Chenhua Instrument Co., Ltd (Shanghai, China). The system consists of a 3 mm diameter glassy carbon electrode (GCE, CHI 104), a saturated calomel electrode (CHI 111) as a reference electrode, and a platinum wire counter electrode (CHI115). The transmission electron microscopy (TEM) images were obtained from transmission electron microscopy (Talos F200x, FEI, Waltham, MA, USA) operated at 200 kV. The crystalline features of CeO2 nanozyme were characterized by X-ray diffraction (XRD) patterns on Bruker D8 Advance X-ray diffractometer (Smartlab, Rigaku Co., Tokyo, Japan) with Cu Kα irradiation (λ=0.15406 nm, 40 kV, 40 mA). UV–vis absorption spectra were recorded on DR 6000 UV–vis spectrophotometer (HACH, Loveland, CO, USA).

2.3. Synthesis and preparation of CeO2 nanozyme

The 7.5 mL of ammonium hydroxide and 2.5 mL of hydrogen peroxide (30%) were added to a solution of CeCl3 (1.0 g) in 75 mL of deionized water with vigorous stirring. The resulting mixture was stirred at 100 °C for 1 h. Light yellow dispersion could be observed when the temperature reached 100 °C. After the chemical reaction was completed, the reactants were centrifuged and washed several times with deionized water and ethanol. The obtained yellow powder was dried at 60 °C under vacuum for 12 h. Before the experiment, the powder was dispersed in deionized water and used as electrochemical sensing material.

![Scheme 1. Schematic illustration of the electrochemical method for methyl-paraoxon detection by using bifunctional CeO2 nanozyme.](image-url)
times with deionized water until the pH of supernatant became neutral. Finally, the solvent is removed by freeze drying for 20 h to yield the yellow nanoparticles.

2.4. Fabrication of the GCE

CeO₂ suspensions were used to modify the electrode surface by drop-casting. The GCE was polished on the felt with nano-alumina powders and thoroughly cleaned until a specular gloss was obtained. After this, further cleaning was achieved using ethanol and distilled water in ultrasonic bath to remove any traces of impurities. To form suspension, 4 mg of CeO₂ nanozyme was added to 700 μL of ethanol and 300 μL of 0.5% Nafion solution and sonicated for 30 min. The 12 μL of the resulting suspension was added dropwise to the surface of the GCE. In this way, CeO₂ nanozyme-modified GCE was prepared for further experiments.

2.5. Electrochemical detection of MP

The sample preparation procedure was carried out prior to pesticide detection according to our previous study with some modifications [42]. First, MP stock solution was diluted with 10 mM Tris solution. The above 2 mL of solution was taken and coexisted with PBS (pH 7.4) and 20 mg of CeO₂ nanozyme in centrifuged tube. After incubation in water bath at 75 °C for 1 h, the reactants were centrifuged at 15,000 rpm for 2 min. One milliliter of the obtained supernatant was diluted with 5 mL of PBS solution, and the pH was adjusted to 6 with HCl solution (1.5 mmol/L). Finally, the mixture was diluted with PBS (pH=6) to a final volume of 15 mL, obtaining the final electrochemical detection solution. All working solutions herein-after were referred to as this one. Nitrogen blowing was carried out to exclude the influence of dissolved oxygen in the electrochemical signal.

Cyclic voltammetry (CV), electrochemical impedance spectroscopy (EIS) and differential pulse voltammetry (DPV) were the electrochemical techniques used to explore the performance of modified electrode. CV measurement was performed by potential cycling, scanning from −1.0 V to 1.0 V (vs. Ag/AgCl) at a scan rate of 50 mV/s. EIS measurement was performed as follows: the applied DC voltage at 0.25 V (vs. Ag/AgCl) with amplitude of 5 mV, and the frequency range from 0.1 Hz to 100 kHz. DPV experiments with potential from 0.0 V to 1.0 V were conducted under the following conditions of scan rate at 50 mV/s: accumulation potential at 0.4 V with accumulation time of 20 s, and modulation potential at 0.12 V.

2.6. Real sample analysis

All herb samples were purchased from a pharmacy in Macau, China. Herbal extracts were strictly prepared in accordance with the requirements of the Pharmacopoeia of the People’s Republic of China (2015 Edition) [43]. In brief, 1.5 g of accurately weighed sample with MP at different concentrations was mixed with 10 mL of water in a 50 mL centrifuge tube under ultrasonic treatment for 20 min. Subsequently, 15 mL of acetonitrile and 4 g of anhydrous magnesium sulfate were added successively and shaken vigorously. After centrifugation at 4,000 rpm for 1 min, 10 mL of collected supernatant was evaporated to dryness under a stream of nitrogen and re-dissolved with working solution. The solution was centrifuged and diluted to the final volume of 15 mL after the addition of CeO₂ nanozyme. The MP concentration in sample solution was detected by DPV with CeO₂ nanozyme-modified GCE.

3. Results and discussion

3.1. Characterization of CeO₂ nanozyme

The XRD pattern of CeO₂ is demonstrated in Fig. 1 within the 20 range between 20° and 90°. The characteristic diffraction peaks could be indexed to the (1 1 1), (2 0 0), and (3 1 1) crystal planes (JCPDS Card No. 00-004-0593). No diffraction peaks of impurities appeared, indicating high purity of the CeO₂ synthesized in this work. The physical properties and apparent structure of CeO₂ nanozyme were further investigated through TEM. As shown in Fig. 2A, good crystallinity of CeO₂ with clear lattice fringes was obtained. The lattice fringes with an interplane spacing of 0.30 nm matched with (1 1 1) plane of CeO₂ (Fig. 2A inset). The synthesized CeO₂ was uniform in size and the estimated average diameter was between 3 and 4 nm (Fig. 2B). The small and uniform particle size provides a larger specific surface area and more active sites, leading to superior enhanced performance in electrochemical detection.

3.2. Electrochemical behavior of CeO₂ nanozyme-modified GCE

The electrochemical behavior of bare GCE and CeO₂ nanozyme-modified GCE was investigated by CV. After MP was catalyzed by CeO₂ nanozyme, apparent voltammetric peaks appeared for bare GCE and the modified GCE at scan rate of 50 mV/s scanning from −1.0 V to 1.0 V (Fig. 3A). The result is consistent with the reported voltammetric peak of p-NP [44,45], indicating the prepared CeO₂ nanozyme has successfully transformed MP into p-NP. It was further verified by UV–vis experiment, which is consistent with the previous literatures [31] (Fig. 51). This phenomenon is mainly due to the coexistence of Ce(III) and Ce(IV) on the spherical CeO₂ nanozymes synthesized in this study. It is reported that surface Ce³⁺ sites could play an important role in the dephosphorylation reaction considering the biomimetic functionality of the binuclear Ce(III)–Ce(IV) complex [46]. As Ce³⁺ is usually associated with the formation of oxygen vacancy [47], spherical CeO₂ nanozymes have the highest surface density of oxygen vacancies in their various particle shapes, thus exhibiting the best dephosphorylation activity [48]. Comparing the DPV response differences between the catalyzed MP and the original MP (Fig. 3B), an additional anodic peak appeared, indicating this method successfully converted undetectable components into detectable molecules directly. Moreover, the reaction parameters were optimized for the completed decomposition of MP (Fig. 82). Finally, 20 mg CeO₂ was selected to react with MP for 1 h at 75 °C in further experiments. According to the previous electrochemical studies for the detection of MP or other pesticides with similar structure, the electrochemical response of nitro group is commonly used for sensing [49]. The characteristic cathodic peak of nitro group could be observed ranging from −0.06 to −1.0 V due to the different working solutions, which is ascribed to the transfer of four electrons and four protons accompanied with reduction of nitro-group to hydroxyl-amine group. In general, there are many constituents containing

![Fig. 2.](image-url) (A) TEM image (inset: the lattice fringes with an interplane spacing of 0.30 nm) and (B) particle size distribution of the CeO₂.
The nitro group existing in real samples, especially herbal plants, which would be the interferences for pesticide detection by using electrochemical method. In this study, we selected the obtained anodic peak of phenolic hydroxyl group at 0.75 V for MP detection. As shown in Scheme 2, phenolic hydroxyl group connected with phosphorus atom in the original MP molecular at first. After the reaction of CeO2 nanozyme and MP being completed under water bath condition, the phenolic hydroxyl group could be obtained. Comparing the electrochemical signal (0.75 V) differences of sample solutions before and after treatment by CeO2 nanozyme, MP could be detected in the real samples more clearly and sensitively.

EIS was used to characterize the detection efficiency of the modified electrode. Fig. 4 shows the EIS result of bare GCE and CeO2 nanozyme-modified GCE in PBS buffer (pH=6) containing 10 μmol/L catalyzed MP. As shown in inset of Fig. 4, an equivalent circuit model clearly demonstrates the EIS data, where the R1, R2, W1, and CPE represent ohmic resistance, charge transfer resistance, Warburg impedance, and constant phase element, respectively. A slight increase in R1 indicates that CeO2 nanozymes covered on the GCE surface are good conductive materials. Meanwhile, the decrease of R2 means that the electron transfer process in CeO2/GCE is faster than that in the GCE [50]. Our results are coincident with those of the preliminary study, which also reveal the excellent electrochemical properties of CeO2 [51]. As is known, CeO2 has become one of the most active oxide catalysts in the rare earth oxide series, and its characteristic properties might put down to the unique crystal structure, high oxygen storage capacity, and strong oxidation-reduction performance [52,53].

Next, the effect of scan rate ranging from 10 to 200 mV/s was investigated on the electrochemical oxidation of the catalyzed MP on the modified electrode (Fig. 5). The increase in anodic peak current corresponds with the increased scanning speed and shows a linear relationship with correlation coefficient (R2) of 0.9954 (Fig. 5B). The similar result has been reported previously, which indicates the oxidation of p-NP is a typical adsorption controlled electrochemical process [49].

### 3.3. Optimization of the detection conditions

Some experimental conditions in this study were carefully explored to further enhance the electrochemical signal response, such as accumulation potential, accumulation time, and pH of the working solution.

As we mentioned above, the electrochemical oxidation of p-NP is an adsorption-controlled process. The parameters affecting adsorption process will greatly influence the sensitivity of the method. As shown in Fig. 5A, the peak current increased with the enhancement of accumulation potential, indicating p-NP was absorbed on the surface of modified electrode continuously. However, peak current began to decrease as the potential increased to 0.4 V. The peak current reached the maximum value when the accumulation potential was 0.4 V. However, the peak current began to decrease as the potential continued to increase, which might be due to the adsorption of more impurities on the electrode surface [50]. Accumulation time also affects the adsorption of p-NP on the electrode surface. With the extension of accumulation time from 5 s
to 100 s, the peak current increased accordingly (Fig. S4). Considering that this method is for rapid detection, we selected 20 s as the optimal accumulation time. The acidic and alkaline condition of working solution will greatly affect the ionization of the analytes and electron transfer [54]. Thus, pH ranging from 4 to 8 was optimized in this work. The phenolic hydroxyl group of p-NP was hardly ionized under acidic condition, then the peak current was very low (Fig. S5). The peak current on the electrode surface was the highest when pH = 6, indicating that p-NP could be absorbed and oxidized on the electrode surface in the near-neutral environment. This might be due to the pKa of the phenol group, and similar results have previously been obtained [55].

3.4. Electrochemical detection of MP by CeO2 nanozyme-modified GCE

Then, the applicability of this nanozyme-assisted electrochemical method was investigated under the optimal conditions. Fig. 6 shows the DPV curves of CeO2 nanozyme-modified GCE at different concentrations of MP. As shown in Fig. 6A, the anodic peak current increased with increased MP concentration. What’s more, the oxidation peak current increased linearly with MP concentration in the ranges of 0.1–10 µmol/L and from 0.1 to 10 µmol/L (inset), with correlation coefficients (R^2) higher than 0.99 for both two analytical curves (n=3, Fig. 6B). The calculated detection limit was 0.06 µmol/L (S/N=3). This electrochemical method for the detection of MP was
compared with other methods in Table 1 [56–59], and also compared with the previously developed electrochemical method for MP detection in Table 2 [32,37,40,60,61]. This method exhibited the remarkable performance thanks to the good electrochemical properties of CeO$_2$ nanozyme and superior sensitivity of DPV method.

### 3.5. Anti-interference experiment

In order to further explore anti-interference capability of this method for practical application, the interference study was performed in the presence of 10 $\mu$M MP and potential interferences like Cu$^{2+}$, Cl$^-$, SO$_4^{2-}$, Na$^+$, and K$^+$, respectively. DPV measurements were performed in triplicates for each sample. The selected inorganic ions demonstrated negligible disturbances on the MP detection by using this electrochemical method (Fig. 7A). Furthermore, other organophosphorus pesticides containing similar structure, such as malathion, chlorfenvinphos, ethyl-paraoxon, and fensulfothion, were selected for testing the anti-interference ability. It is found in Fig. 7B that most of those pesticides (10 $\mu$M) exhibited comparable responses with MP only at the same concentration except chlorfenvinphos. The carbon-carbon double bond connected with chlorines is the characteristic group of chlorfenvinphos, and the strong electron-withdrawing atom chlorine may promote the electron transfer from phenolic hydroxyl and then enhance the electrochemical signal in this work [62].

### 3.6. Real sample analysis

To verify the applicability of the developed method for MP detection, MP at different levels (0.1, 0.5, and 3.0 $\mu$mol/L) was tested in three herb samples, Coix lacryma-jobi, Adenophora stricta and Semen nelumbinis. It is evident from Table 3 that the detected values are consistent with the spiked concentrations. The recovery was presented with mean ± standard deviation ($n=3$). The recoveries of MP in three samples ranged from 80.91% ± 4.86% to 116.84% ± 1.42%. According to the recoveries for pesticide analysis (70%–120%, RSD < 20%) recommended by European Commission [63], the analytical performances in all three herb samples were acceptable and also confirmed that the present work is a promising technique for MP detection in real samples even with complex matrix.

### 4. Conclusion

In this work, an electrochemical method involving CeO$_2$ nanozyme was used for MP detection. Different from other nanozymes or nanomaterials used in previous electrochemical studies, CeO$_2$ nanozyme in this study plays significant roles in both substrate catalysis and signal amplification. UV–vis result revealed its catalytic activity for the conversion from MP to p-NP. Voltammetric studies indicated the signal amplification function of CeO$_2$ nanozyme-modified GCE towards MP detection due to its improved

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**Table 2** Comparison of different electrochemical detection methods for pesticide detection.

| Analyte                  | Electrode                                      | Linear range (μmol/L) | Limit of detection (μmol/L) | Real sample                      | Refs.   |
|--------------------------|------------------------------------------------|-----------------------|-----------------------------|----------------------------------|---------|
| Methyl-paraoxon, methyl-parathion and ethyl-paraoxon | TiO$_2$@dopamine@serine/histamine/glutamic acid modified electrode | 0.5–100              | 0.20                        | Vegetable (Lactuca sativa L.)    | [32]    |
| Paraoxon                 | Layer-by-layer assembled multi-enzyme/carbon nanotube biosensor | 0.5–40               | 0.50                        | Apple                            | [37]    |
| Carbaryl                 | Gold nanoparticles and graphene oxide modified screen-printed carbon electrode | 10–80                | 10                          | Cucumber and rice               | [40]    |
| Carbofuran               | Acetylcholinesterase immobilized screen-printed electrodes | 1.0–50000            | 0.50                        | Milk                             | [60]    |
| Chlorpyrifos             | Molecularly imprinted polymers and graphene modified glassy carbon electrode | 0.5–15               | 0.10                        | Rice                             | [61]    |
| Methyl-paraoxon          | CeO$_2$ nanozyme-modified glassy carbon electrode | 0.1–100              | 0.06                        | Herbal plant                    | This work |

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**Fig. 7.** The electrochemical response of MP coexists with (A) different inorganic ions or (B) other pesticide. MA: malathion; CF: chlorfenvinphos; EP: ethyl-paraoxon; FS: fensulfothion.
electrochemical properties. Under the optimized conditions, the present method offers high stability, wide response range and lower LOD. The desirable recoveries in different herbal samples show the potential of CeO₂ for practical applications. In summary, all the experimental results we have collected suggest that this CeO₂ nanozyme-modified electrochemical method is an attractive candidate for MP analysis with simplicity, rapidity, and sensitivity. Nevertheless, we believe there is still room for the present method to improve. To elaborate further, CeO₂ nanozyme in this work was used at two steps independently: sample preparation and detection procedure. The small amount of CeO₂ loaded on the electrode cannot guarantee the catalytic reaction completely, while the increased CeO₂ decreased the electronic conductivity and affected the signal enhancement effect. In the future, it might be possible to develop the electrochemical method with dual functions of catalysis and detection by supporting CeO₂ on porous materials or three-dimensional materials with a large surface area.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

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Table 3

| Sample              | Spiked (µmol/L) | Detected (µmol/L) | Recovery | Mean ± SD (%) | RSD (%, n = 3) |
|---------------------|----------------|------------------|----------|---------------|---------------|
| Semen menlunis     | 0.10            | 0.097            | 97.11 ± 3.22 | 3.31          |               |
|                     | 0.50            | 0.511            | 102.25 ± 6.30 | 6.16          |               |
|                     | 3.00            | 2.786            | 92.87 ± 3.18 | 3.43          |               |
| Coix lacryma-jobi  | 0.10            | 0.105            | 105.13 ± 4.19 | 3.98          |               |
|                     | 0.50            | 0.446            | 89.25 ± 2.21 | 5.48          |               |
|                     | 3.00            | 3.337            | 111.23 ± 7.64 | 6.87          |               |
| Adenophora stricta | 0.10            | 0.117            | 116.84 ± 1.42 | 7.21          |               |
|                     | 0.50            | 0.469            | 93.72 ± 9.21 | 9.82          |               |
|                     | 3.00            | 2.427            | 80.91 ± 4.86 | 6.00          |               |

* Standard deviation of three determinations.
