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Study on the detection of anthrax by ICP-MS based on gold nanoparticle labeling

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Abstract.
BACKGROUND: In recent years, inductively coupled plasma mass spectrometry (ICP-MS) has been widely used in the field of molecular biology because of its unique advantages. Anthrax is a widespread and long-standing infectious disease, which affects and restricts people's work and life seriously.
OBJECTIVE: The study goal is to develop a new method for the detection of anthrax.
METHODS: A rapid, sensitive and accurate method for the detection of anthrax characteristic DNA was proposed by combing gold nanoparticles (AuNPs) and inductively coupled plasma mass spectrometry.
RESULTS: The linear range of this method is 100–2500 pmol/L and the limit of detection of 16.61 pmol/L.
CONCLUSION: The proposed method has numerous advantages, including simplicity of operation, high sensitivity, and specificity, which provides a new idea for the detection of anthrax. Importantly, this methodology has good potential for the detection of other biological substances such as bacteria and viruses by changing the modification sequence on the nanoparticle probe.

Keywords: ICP-MS, AuNPs, label, anthrax

1. Introduction

Anthrax is an infectious disease caused by *Bacillus Anthracis*. It poses a severe public health and safety threat due to its low infectivity, high lethality, ease of production, and transmission. Anthrax infections occur every year, and human cases are often zoonotic. At the same time, *Bacillus Anthracis* belongs to class A bioterrorism agents, because of their potential to rapidly cause severe disease and death, and may be weaponized [1]. Therefore, accurate and rapid detection of *Bacillus Anthracis* is essential to ensure public health safety. Currently, there are three main types of methods for detecting anthrax, including the earliest bacteriological test [2], which takes too long; the most commonly used serological test [3,4], but other bacteria can easily cross-react; and the rapid development of molecular biological test in recent years [5,6], typical molecular biological detection methods include PCR technology and DNA molecular hybridization technology.

Inductively coupled plasma mass spectrometry (ICP-MS) is an element analysis technology with high sensitivity, strong anti-interference, and multi-component analysis ability [7,8]. Metal nanoparticles have been widely used in the detection of biological samples by ICP-MS due to their unique advantages.

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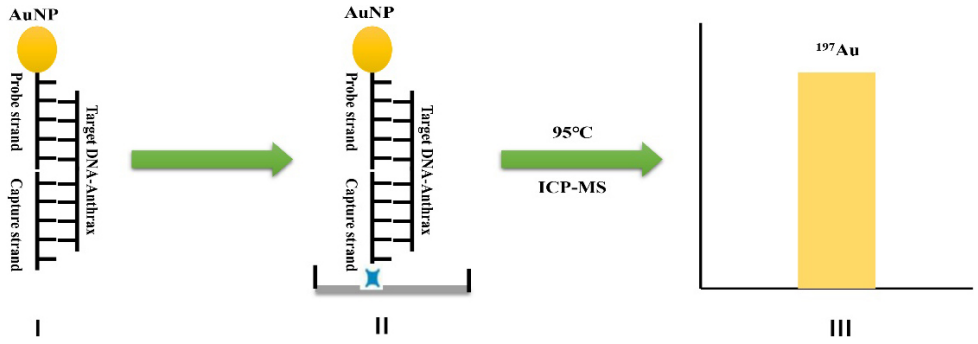

Fig. 1. Schematic diagram of detecting characteristic DNA fragment of anthrax by ICP-MS based on the amplification of gold nanoparticle: (I) hybridization; (II) incubation; (III) detection.

For example, Zhang Xinrong's team detected and distinguished three clinical diseases (HIV, HAV, and HBV) [9] and six intestinal related bacteria [10], Hu Bin's team successively detected circulating tumor cells (HepG2) [11], and target DNA in human serum samples [12] has also been applied to the detection of the novel coronavirus disease (SARS-CoV-2) [13,14]. In particular, Au nanoparticles with a diameter of 10 nm contain about 30, 000 Au atoms [15]. Therefore, the use of gold nanoparticle probes can significantly amplify the signal, making the detection more sensitive and lowering the detection limit. At the same time, ICP-MS is particularly suitable for the detection and analysis of anthrax due to its simpler process for detecting biological samples, its more concise and clear results, and its ability to provide quantitative information while identifying species. However, the application of this technique to anthrax detection has not been studied and reported.

In this study, a complex was generated based on the principle of DNA molecular hybridization using AuNP-labeled report probes, biotin-labeled capture probes, and nucleic acid fragments characteristic of anthrax. The resulting complex was fixed on a plate using a biotin-streptavidin system and the excess reactants were removed after washing. The complex was then pressed on a plate and finally, the ^{197}Au signal was detected by ICP-MS. Thus, the detection and analysis of anthrax have been achieved. A method for specific detection and analysis of anthrax by elemental labeling probes combined with ICP-MS and DNA molecular hybridization was developed. The main principle is illustrated in Fig. 1.

2. Experimental section

2.1. Apparatus and reagents

A PQMS Elite ICP-MS (Analytik Jena AG, Jena, Germany) was used for the detection of ^{197}Au, the operating conditions are listed in Table 1. An Agilent Cary-5000 UV-Vis-NIR spectrophotometer (Agilent Technologies, Palo Alto, USA) was used for the absorption spectra record. A 1–14K refrigerated centrifuge (SIGMA, Germany) was used for centrifugal separation. The Electro-Thermostatic Water Bath (Subo Instruments Co., Ltd., Shaoxing, China) was used for controlling the reaction temperature.

All oligonucleotides used in this study were synthesized and HPLC-purified by Sangon Biotech Co., Ltd. (Shanghai, China), their sequences and modifications are listed in Table 2. BA-rpoB, YPE-pla, ORF-1ab target probes were the characteristic sequences of *Bacillus Anthracis*, *Yersinia Pestis*, and SARS-CoV-2, with a length of 24–30 bases. BA-rpoB 1–2 were mismatched oligonucleotides. BA-rpoB probe was a 3'end modified sulfhydryl (-SH) labeled probe, which could be used to label DNA probes by

Table 1
Instrument parameters for ICP-MS

Operating parameter	
RF power (kW)	1.35
Plasma flow (L/min)	9.0
Auxiliary flow (L/min)	1.65
NebuLizer gas flow (L/min)	1.10
Dwell time (ms)	60
Rinse time (s)	10
Sampling depth (mm)	5.0

Table 2
The DNA sequence used in hybridization reaction

Names	Sequences (5'-3')
BA-rpoB-target	GTA CGC CAA TCG ATA TCA TGT TAA ACC
BA-rpoB-probe	TAT CGA TTA GCG TAC-$(A)_{10}$-$(CH_2)_6$-SH
BA-rpoB-capture	biotin-$(A)_{10}$-GGT TTA ACA TGA
BA-rpoB-1	GTA CG**T** CAA TCG ATA TCA TGT TAA ACC
BA-rpoB-2	GTA C**AT** CAA TCG ATA TCA TGT TAA ACC
YPE-pla-targe	ACT ACG ACT GGA TGA ATG AAA ATC
ORF-1ab-target	TGG TAA TGC AAC AGA AGT GCC TGC CAA TTC

combining sulfhydryl with AuNPs. BA-rpoB capture was a capture probe of 5'end modified biotin, which could capture hybridization products by combining with 96 well microplates coated with streptavidin.

20 nm gold nanoparticles (AuNPs, 0.05 mg/mL) were purchased from Zhongkeleiming Technology Co., Ltd. (Beijing, China). Tris (2-carboxyethyl) phosphine (TCEP, pH 6.8, 0.5 mol/L) was purchased from Phygene Biotechnology Co., Ltd. (Fuzhou, China). Streptavidin-coated 96 well microplates were purchased from Beaver Biomedical Engineering Co., Ltd. (Suzhou, China). Ethylenediaminetetraacetic acid (EDTA, pH 8.00, 5 mol/L,) and tris (hydroxymethyl) aminomethane (Tris-HCl, pH 7.4, 1 mol/L) were purchased from Sangon Biotech Co., Ltd. (Shanghai, China).

A series of buffers used in this work are as follows:

PBS buffer: 137 mmol/L NaCl, 2.7 mmol/L KCl, 8 mmol/L Na_2HPO_4 and 1.5 mmol/L KH_2PO_4 in DECP water (pH 7.4);
Hybridization buffer: 1 mol/L NaCl, 10 mmol/L EDTA and 1 mmol/L Tris-HCl in DECP water (pH 7.4);
TE buffer: 1 mmol/L EDTA and 10 mmol/L Tris-HCl in DECP water (pH 8.0).

Other conventional reagents were taken from the laboratory, and all reagents used were at least of analytical reagent grade. Ultrapure water (16.7 Ω/cm) was supplied by Smart-Q15MT water-purification system (Hetai, Shanghai, China) throughout this work.

2.2. Preparation and characterization of AuNPs-modified DNA

The method of the AuNPs-modified recognition probe was referred to the relevant literature and modified appropriately [16,17], as follows.

The company offers DNA fragments attached to the wall of a tube in the shape of a very light dry film. Each tube was equipped with 1 OD and each tube had an identification probe of 3.76 nmol. First centrifuge the centrifuge tube (4000 r/min, 60 s), and then add 37.6 μL of TE buffer solution, then blow and mix the liquid with a pipette gun, and finally 100 μmol/L solutions, stored at -20°C.

Before modification, the thiolated nucleic acid fragment needs to be reduced to break the S-S bond. 6 μL of 20 mmol/L TECP solution was added to 6 μL of BA-rpoB-probe solution,and the mixture was mixed and reacted at 3°C for 1 hour. After that, the mixture was added to 400 μL of 0.05 mg/mL gold nanoparticle solution and incubated overnight at room temperature. 12 μL of 1% Tween 20 was added and mixed well. Then, 2 mol/L NaCl solution was added four times, with an interval of more than one hour each time, and the concentration of NaCl in the final mixture solution was 0.3 mol/L. The mixture was then stored at room temperature overnight. The obtained gold nanoparticle-labeled probe solution was centrifuged at 10,000 r/min for 15 min, the supernatant was removed, and 400 μL of PBST washing solution (PBS buffer with 0.05% Tween20) was added. Repeat the centrifugation wash ste 4 times to further remove the excess probe. Finally, the nanoparticle probes were dissolved in 400 μL of PBS buffer and stored at 4°C away from light.

The UV-vis absorption spectrum analysis was performed on the nanoparticle solution before and after labeling. According to the red shift of the maximum absorption peak of the solution caused by the increase of the radius of the gold nanoparticle modification, it could be judged whether the nanoparticle and the identification probe were successfully connected [12].

2.3. DNA hybridization reaction

First, 10 μL target single-stranded DNA solution (BA-rpoB-target), 100 nmol/L capture DNA probe (BA-rpoB-capture), and 20 μl hybridization buffer solution were mixed in a centrifuge tube. Hybridization was carried out for 20 min at room temperature. Then, the prepared BA-rpoB-probe modified with AuNPs was added to the centrifuge tube and placed for 20 min at room temperature. The hybridization products were then transferred to streptavidin-coated microplates and the reaction was incubated at 3°C. The incubation solution was discarded and washed three times with PBST wash buffer and twice with deionized water. After washing, 250 μL of deionized water was added to each wel, and pyrolysis was performed in a water bath at 95°C for 20 minutes. After the pyrolysis was completed, the pyrolysis solution was removed and transferred to a 2 mL centrifuge tube, and the volume was fixed to 2 mL with deionized water before being tested.

2.4. ICP-MS testing

Before measuring the sample by ICP-MS, first, make sure that the instrument was in normal working condition. Use the tuning solution provided by Jena Instruments, Germany (containing 1 ppb of Be, Mg, Co, Ba, Pb, Ce, In, Bi) for mass spectrometry tuning, mainly to observe whether the signal sizes of ^{9}Be, ^{115}In, and ^{208}Pb reach the optimal range, and then carry out resolution calibration and mass calibration, both of which could be calibrated normally to ensure that the instrument was in normal working condition. When measuring the sample, the value of m/z = 197 was measured by scanning. Since the detected gold signal intensity had a positive correlation with the content of characteristic DNA fragments of anthrax, the detection and analysis of anthrax could be realized.

3. Results and discussion

3.1. ICP-MS detection of gold nanoparticle solution

The designed process for the detection of characteristic DNA fragments of anthrax is shown in Fig. 1. In order to verify the feasibility of DNA quantitative detection by ICP-MS based on gold nanoparticle

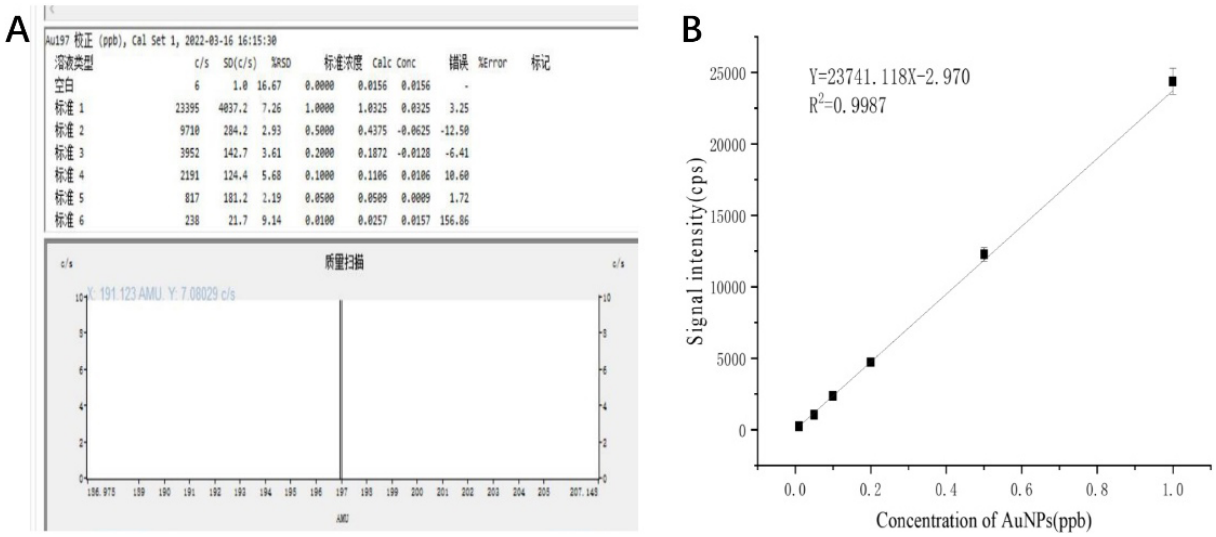

Fig. 2. (A) Results of single ICP-MS measurement of AuNPs solutions with different concentrations; (B) Quantitative relationship between the concentration of AuNPs and the signal intensity of gold detected by ICP-MS.

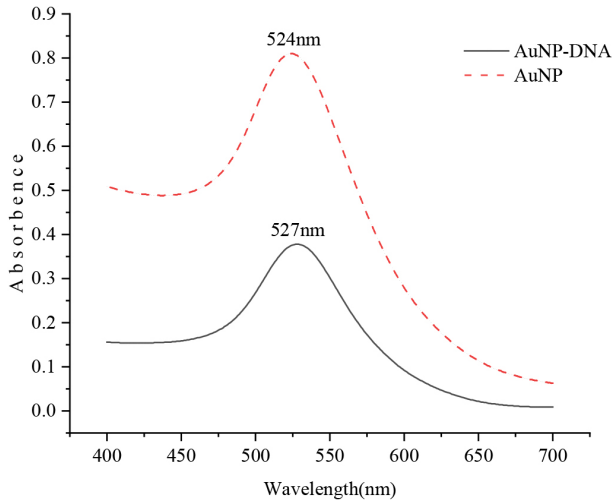

Fig. 3. UV-vis spectra before and after AuNP modified recognition probe.

probes, the gold nanoparticle solutions with different solubility were detected by ICP-MS first. 2 mL of gold nanoparticle solution with concentrations of 1.0 ppb, 0.5 ppb, 0.2 ppb, 0.1 ppb, 0.05 ppb, and 0.01 ppb were prepared for machine detection. Figure 2A shows the results of a single ICP-MS measurement on a solution of AuNPs solutions at different concentrations. The ICP-MS instrument will read each sample three times, and we also repeated the experiment three times for each set of samples. As can be seen, linear fitting was performed on the experimental data, as shown in Fig. 2B, the concentration of AuNPs was linearly correlated with the signal intensity of ICP-MS within the range of 0.01 ppb to 1 ppb, $Y = 23741.118X\text{-}2.970$, $R2 = 0.9987$. When the solution solubility of gold nanoparticles was 0.1 ppb, the corresponding RSD (relative standard deviation) was 1.95%. The detection limit (LOD = blank mean + 3SD, $n = 7$) for this method was 0.0002 ppb. These results indicate that ICP-MS can be used for the

quantitative analysis of gold nanoparticle solution, and provides a basis for the quantitative analysis of DNA.

3.2. Characterization and analysis of labeled probe DNA

The AuNPs solution before and after the reaction was scanned by UV-visible spectrophotometer with a wavelength range of 400–700 nm, as shown in Fig. 3. The highest absorption peak of the AuNPs solution was at 524 nm, and the highest absorption peak of the nanometer particle solution combined with the identification probe was at 527 nm. The absorbance value ranged from 0.810 to 0.378, indicating that the nanoparticles were successfully labeled with the recognition probe. At the same time, it was found that the nanoparticles would accumulate and sink in DNA-free gold nanoparticles solution when the precipitate was dissolved in PBS buffer by centrifugation, and the color of the solution would also change significantly. Nanoparticles modified with DNA, however, do not converge and sink, and the color of the solution is basically unchanged. This phenomenon also suggests that the nanoparticles have modified DNA successfully.

3.3. Optimization of experimental conditions

The effect of many key parameters affecting the performance of the method was investigated, including the amount of biotin-labeled probe and AuNPs-labeled probe, the reaction time of hybridization product and microplate, dwell time of ICP-MS [12,13,18,19]. The amount of target probe was investigated as 1 nmol/L.

3.3.1. Selection of ICP-MS dwell time

Firstly, the influence of the residence time of ICP-MS in 20–100 ms on the signal intensity detection of gold nanoparticles was studied. Here we directly used 0.5 ppb gold nanoparticle solution to select the best detection conditions by changing the dwell time of the instrument. As can be seen from Fig. 4A, strong signals can be detected within the dwell time of 20–100 ms, reaching the maximum at 60 ms, and the RSD at 60 ms and 80 ms are relatively small. Therefore, the dwell time of ICP-MS was chosen to be 60 ms in the subsequent experiments.

3.3.2. Selection of reaction time between hybrid products and microplates

We selected the effect of reaction time between the hybridization product and microplate in 10–50 min time on the final detected gold signal intensity. As can be seen from Fig. 4B, the signal intensity increases sharply and then almost stays the same within the reaction time of 10–30 min. In order to control the reaction time of the whole reaction, the reaction time between the hybrid product and the microplate was chosen to be 30 min in the subsequent experiments.

3.3.3. Selection of biotin-labeled probe amount

We selected the effect of the biotin-labeled probe in a volume of 2–30 μL on the intensity of the fial detected gold signal. As can be seen from Fig. 4C, the detected signal is the highest, and the RSD is low when the amount of biotin probe is 10 μL. The signal increased sharply when the amount of probe was from 2 μL to 5 μL. The signal gradually decreased when the amount of probe was higher than 20 μL. The analysis reason may be that when the hybrid complex solution containingan excessive biotin-labeled probe was transferred to the microplate, the excessive biotin-labeled probe would have a competitive reaction with the hybrid product that had been combined with the biotin-labeled probe, resulting in fewer opportunities for the hybrid product to combine with the microplate, thus reducing the amount of hybrid product captured, and ultimately leading to the inaccuracy of the detection results. Therefore, the amount of biotin-labeled probe was chosen to be 10 μL in the subsequent experiments.

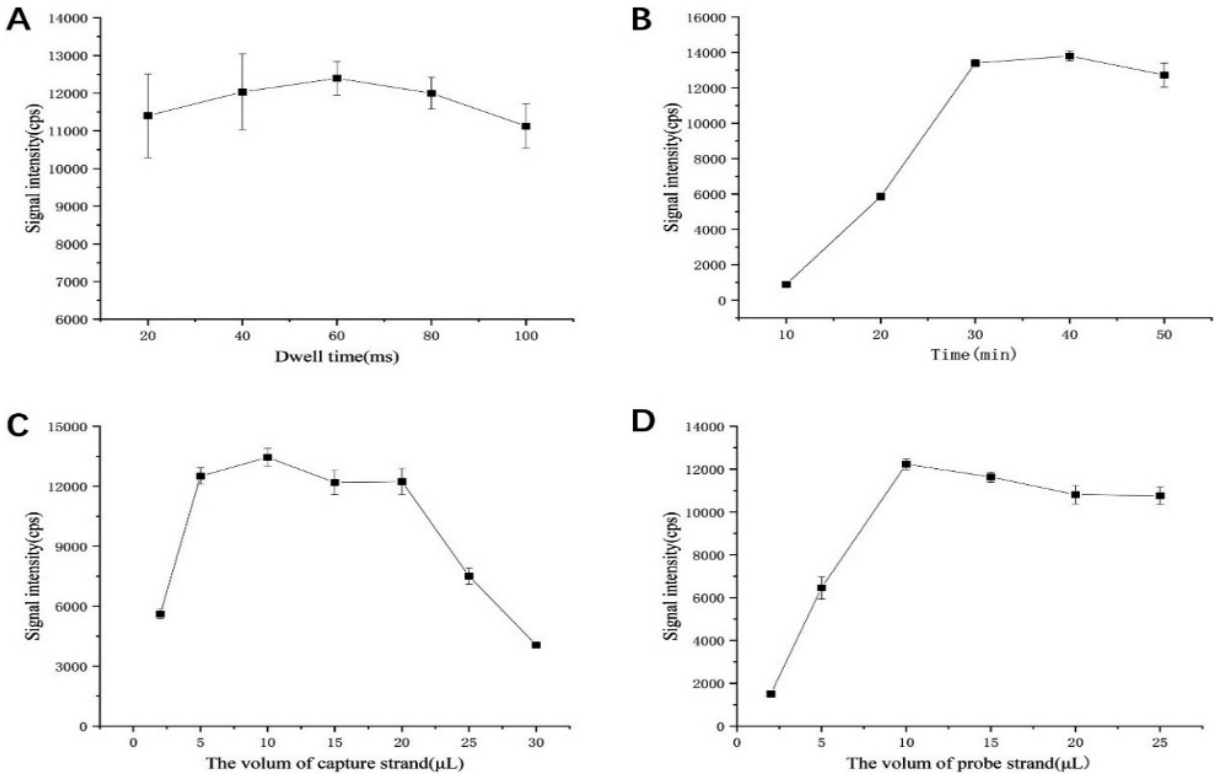

Fig. 4. The optimization of experimental conditions: (A) influence of instrument dwell time; (B) influence of the reaction time between hybrid product and microplate; (C) influence of biotin-labeled probe amount; (B) influence of gold nanoparticle-labeled probe amount.

3.3.4. Selection of AuNPs-labeled probe amount

We selected the effect of AuNPs-labeled probes in a volume of 2–25 μL on the final detected gold signal intensity. As can be seen from Fig. 4D, the signal intensity reaches the maximum at the AuNPs-labeled probe volume of 10 μL. There was almost no change in the intensity when the intensity was larger than 10 μL. Also, in order to save experimental coss, we chose the amount of AuNPs-labeled probe as 10 μL in the subsequent experiments.

3.4. Sensitivity and specificity

Under optimized experimental conditions, anthrax target DNA was detected at concentrations ranging from 0 to 10000 pmol/L and repeated the experiment three times for each group of samples. The obtained experimental data are processed and linearly fitted, as can be seen from Fig. 5A, the gold element signal detected by ICP-MS increased linearly (Y = 13.032X-401.666, R2 = 0.9973), as the concentration of anthrax target DNA increased from 100 pmol/L to 2500 pmol/L. The corresponding RSD (relative standard deviation) was 1.20% at the DNA concentration of 1000 pmol/L. The detection limit of this method (LOD = 3 × SD/K, $n = 7$, SD is the standard deviation of a blank sample, K is the slope of the standard curve) was 16.61 pmol/L.

To investigate the specificity of this method for anthrax target DNA detection, different target DNA solutions were analyzed. We tested anthrax (BA-rpob-target), plague (YPE-pla-target), and coronavirus

Table 3
Investigation on spiked recovery of complex samples

Sample	Added (nmol/L)	Theoretical (nmol/L)	Found (nmol/L)	Recovery (nmol/L)
1	0.50	0.75	0.71	84.0
2	1.00	1.00	1.07	114.0
3	2.00	1.50	1.47	97.0

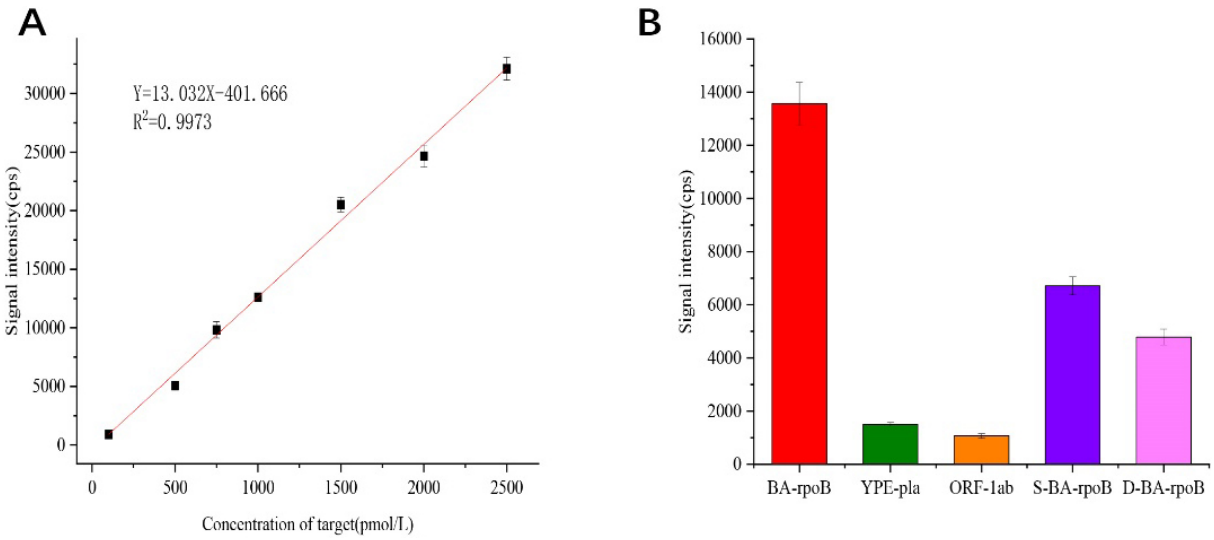

Fig. 5. (A) Qμantitative relationship between anthrax target DNA concentration and gold signal intensity; (B) ResuLts diagram of ICP-MS detection of different target DNA based on AuNPs.

(ORF-1ab-target) target DNA, and DNA with single and double base mismatch with anthrax target sequence (S-BA-rpoB, D-BA-rpoB) solutions at concentrations of 1 nmol/L, and repeated the experiment three times for each set of samples. As can be seen from Fig. 5B, the signal intensity of the perfectly matched anthrax target DNA is significantly different from that of the other four target DNA. It shows that this method has better specificity.

3.5. Recovery in complex samples

The detection of anthrax samples commonly requires the extraction of genomic DNA from the organism, and then pyrolysis to make the DNA in a single-strand-free state in practical applications, so there will be a large amount of irrelevant DNA in the sample at this time. Therefore, we added plague (YPE-pla) and novel coronavirus (ORF-1ab) target DNA into the samples to simulate the detection environment in practical application. They had similar DNA strand lengths but entirely different sequences from the targets to be tested. The concentrations of anthrax, plague, and COVID-19 in the above samples were all 1 nmol/L, and the hybridization reaction was carried out and then tested according to the previous experimental procedure. The results showed that anthrax target DNA could be detected. In addition, we also carried out the spiked recovery experiment, and the standard dosage was 10 μL anthrax target DNA solution with different concentrations. The results are shown in Table 3. The recovery rates of three complex samples with different concentrations were all between 84%–114%, therefore this method as an excellent recovery rate. The above experimental results indicate that the ICP-MS method based

Abbreviation:

Acronyms	Full Name in English	Acronyms	Full Name in English
ICP-MS	Inductively Coupled Plasma Mass Spectrometry	SARS-CoV-2	Novel Coronavirus
DNA	Deoxyribonucleic Acid	HPLC	High Performance Liquid Chromatography
AuNP	Gold Nanoparticle	TCEP	Tris (2-carboxyethyl) phosphine
HIV	Human Immunodeficiency Virus	EDTA	Ethylene Diamine Tetraacetic Acid
HAV	Hepatitis A Virus	DECP	Diethyl Pyrocarbonate
HBV	Hepatitis B Virus	RSD	Relative Standard Deviation
HepG2	Human Hepatoellular Carcinomas	LOD	Limit of Detection

on AuNPs-labelled for anthrax detection can detect and quantitatively analyze the target DNA in more complex samples.

4. Conclusion

By combining the signal amplification effect of ICP-MS and AuNPs with powerful elemental analysis ability, we constructed a highly sensitive method for anthrax-characteristic DNA detection. The whole detection process is simple, fast, and specific. The sample volume consumed is only 10 μL. In addition, the method has strong anti-interference. It provides a new idea for the detection of anthrax, and can also be extended to the analysis and detection of other biological substances such as bacteria and viruses.

Conflict of interest

None to report.

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