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Metal nanoparticles-based nanoplatforms for colorimetric sensing: A review

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Abstract: With the progress of analysis technology and nanotechnology, colorimetric detection has become one of the research hotspots in the field of analytical chemistry. Compared with traditional detection methods, the colorimetric method has many advantages, such as high sensitivity, good selectivity, convenience and fast, as well as low cost. In recent years, metal nanoparticles have been introduced into colorimetry, making the research and application of colorimetry develop rapidly. In this work, we summarize the usual colorimetric detection methods based on metal nanoparticles-based nanozymes and their applications in the last five years. We hope that this work will help readers understand the mechanism and practical application value of nanozyme-based colorimetric biosensors. Meanwhile, this work may give some hints and references for future colorimetric detection research to promote the application and development of nanozyme-based colorimetry in biomedical and environmental analysis.

Keywords: metallic nanoparticles, nanozyme, colorimetric, biosensing

1 Introduction

Colorimetry is a method to determine the content of metric components by comparing or measuring the color depth of the solution of colored substances. Compared with other detection methods, the colorimetric method is more intuitive. Some results can even be directly observed with the naked eye, and the target can be detected without the help of sophisticated instruments [1-3]. In recent years,

colorimetry has been developing rapidly and used widely. The colorimetry based on metal nanoparticles (NPs) has been a hot topic. These methods are applied to biosensors [4-6], medical diagnosis [7], environmental management [8], and many other aspects. The combination of nanomaterials and colorimetry gives new vitality to traditional colorimetry, which makes colorimetry have relatively low detection limit and high sensitivity, and the real accurate analysis is achieved. The introduction of metal NPs broadens the field of vision and leads the new research direction to develop colorimetry.

It has been found that Fe_3O_4 NPs have a catalytic activity similar to horseradish peroxidase in 2007 [9], which were called nanozymes. In subsequent studies, researchers found that some other metals or metal oxide NPs, such as Au, Ag, Pt, Cu, and others also have similar enzymatic catalytic activity [10-12]. The appearance of nanozymes has solved many academic problems and influences many research fields. With the deepening of research, scientists found that some metal nanomaterials after processing or modification can also show enzyme-like catalytic activity. For example, azacrown ether has been used to modify the surface of gold nanoparticles (AuNPs), and the catalytic function of enzymes could be simulated after chelation. Therefore, many experimental studies based on metal NPs had been carried out, and many materials with excellent nanozyme activity had been discovered [13,14]. The colorimetric methods, which are near related to nanozyme have been developed to prepare colorimetric materials with useful properties, which were utilized for the colorimetric detection of various analytes.

In the past five years, there have been a lot of reports on colorimetry, which are the latest achievements of colorimetry and the foundation for its further development. It is necessary to make a systematic summary of these findings. It not only enables us to have a deep understanding of colorimetric detection, but also gives us immense help and inspiration for our future work. In this work, the research progress of colorimetry based on metal NP-based nanozymes in recent five years is summarized. The colorimetry applications of different metal NPs are introduced

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and discussed. The development status of colorimetry is presented from many fields.

2 Colorimetric detection based on Au NPs

Au is one of the most commonly used metals in colorimetry. AuNPs have high absorption extinction coefficient and high sensitivity, which can be modified to obtain potential nanozymes with high catalytic activity [15,16].

AuNPs can be used to detect heavy metal ions. For example, Du *et al.* tested Hg^{2+} by using the mechanism that

prevented melamine from causing AuNPs aggregation in an aqueous solution [17]. The linear range was 50-250 nM and the detection limit was 50 nM. Liu *et al.* directly detected Hg^{2+} in solution with single AuNPs [18]. They used oligonucleotides to modify Hg^{2+} . Due to the hybridization of the oligonucleotide, AuNPs aggregated in the presence of Hg^{2+} , resulting in the color of solution change. The change of color was proportional to the concentration of Hg^{2+} , and the detection limit was 1.4 pM.

Kanamycin may be contained in milk. The glycosides on kanamycin are specific to AuNPs, so they can interact with each other, which induces the aggregation of kanamycin, as shown in Figure 1a [19,20]. These changes resulted in the properties of AuNPs changing intuitively,

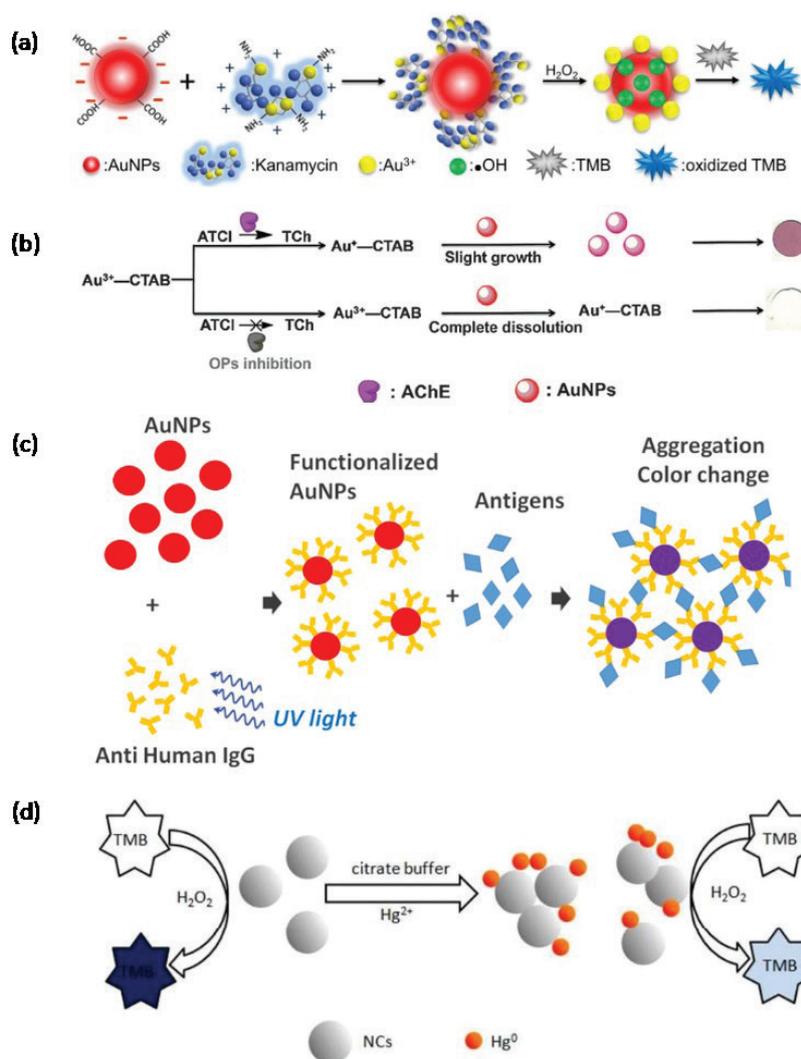


Figure 1: (a) Schematic diagram of AuNPs-based colorimetric detection of kanamycin. Reprinted image with permission from Ref. [20], Copyright 2016, Elsevier B.V. (b) Schematic diagram of OPs colorimetric analysis based on AuNPs dissolution. Reprinted image with permission from Ref. [22], Copyright 2016, Elsevier B.V. (c) AuNPs-based IgG detection scheme. Reprinted image with permission from Ref. [32], Copyright 2018, American Chemical Society. (d) The mechanism of Hg^{2+} detected by DNA-Ag/Pt NCs. Reprinted image with permission from Ref. [42], Copyright 2016, Royal Society of Chemistry.

so that kanamycin can be quantitatively detected by calculation. The detection line was 73.1 nM [19] and 288 nM [20], respectively.

Organophosphorus pesticide (OP) pollution has serious adverse effects on human health and the environment. They are not easily found in the soil, so detecting them needs high sensitivity and selectivity. AuNPs play an essential role in the detection of parathion. The combination of phosphorus with citric acid [21], Au³⁺-hexadecyl trimethyl ammonium bromide (Au-CTAB) [22], fatty acid [23], cysteine [24], single-stranded DNA [25], and other substances exhibited potential activity to inhibit the aggregation of AuNPs, resulting in the color of system unchanged. Therefore, AuNPs can be modified with the materials mentioned above to detect phosphate-containing materials, as shown in Figure 1b. The detection method using the modified AuNPs was simple and useful for detecting general pesticides and many organic pesticides.

The colorimetry based on AuNPs can be used to prepare a large number of highly selective biosensors for the detection of biomolecules such as proteins [26], sugars [27], lipids [28], and neurotransmitters [29,30]. For example, Huo et al. found that the adenosine triphosphate (ATP) aptamer complex has a strong protective effect against salt-induced aggregation of unmodified AuNPs [31]. Therefore, an adaptive ATP colorimetric sensor with high sensitivity and selectivity was developed using the unmodified AuNPs as a probe. In the range of 50-1000 nM, the logarithmic concentration of ATP had a good linear relationship with absorbance. Iarossi and co-workers proposed an AuNPs-based colorimetric immune sensor, which could detect human immunoglobulin G (IgG) in the human body [32], and the mechanism is shown in Figure 1c. The positive IgG reaction ranges from 50 to 500 ng/mL. Borghei et al. established a simple and sensitive colorimetric biosensor for detecting cancer cells based on the principle of adaptor receptor interaction [33]. The linear response for MCF-7 cells in a concentration range from 10 to 10⁵ cells was obtained with a detection limit of 10 cells. Almudena and co-workers also used AuNPs to detect nerve agent simulators with visual and intuitive results. It can be founded from the above applications that AuNPs have a wide range of applications for the fabrication of colorimetric biosensors, enabling efficient detection of nutrients, biotoxins and even cancerous cells in vivo [34].

AuNPs have been used as signal recorders for decades. However, due to the limitations of the inherent technology, how to improve the detection sensitivity of AuNPs substantively is still a considerable challenge [35,36]. Therefore, many methods have been explored to increase the sensitivity and activity of AuNPs. For example,

Gao et al. developed unique dual-function AuNPs to circumvent this limitation by coating conventional AuNPs with ultrathin platinum skin at ten atomic layers (Au@Pt NPs) [37]. The nuclear power source of Au@Pt NPs retained the initial plasma activity of the AuNPs and had ultra-high catalytic activity activated by the Pt shell. The visual detection limit of LFAs was about 2 ng/mL.

In recent years, the nanomaterials synthesized by using DNA as a template have been widely used. These materials have advantages, including simple synthesis, precise size control, and good biocompatibility [38-40]. More importantly, no additional functionalization of the DNA template material is required to construct the biosensor. Zheng et al. used DNA as a template to synthesize silver/platinum bimetal nanoclusters (DNA-Ag/Pt NCs), which effectively enhanced the catalytic activity of peroxides of NPs. The synthesized bimetal nanoclusters were applied for the detection of proteins, realizing more efficient detection [41]. In the range of 1-50 nM, there was a linear relationship between the absorption intensity and human thrombin concentration. The detection limit was 2.6 nM. Wu et al. further found that the peroxidase activity of DNA-Ag/Pt NCs could be selectively inhibited by Hg²⁺ as shown in Figure 1d. Based on this principle, a colorimetric detection method for Hg²⁺ was established. The detection limit was 5.0 nM and the linear range was 10-200 nM. This method not only had high selectivity, but also reduced the cost of detection [42]. Based on the same principle, they also used DNA-Ag/Pt NCs for the colorimetric detection of L-cysteine [43]. The detection limit was 2.0 nM, and the linear range was 5.0-500 nM. The high peroxidase-like activity of DNA-Ag/Pt NCs was not affected by DNA enzymes. Thus, it could be used to detect cancer markers such as DNA methyltransferase [44] and abnormally expressed MicroRNA-21 [45]. The detection limits were 0.05 U/mL [44] and 0.6 pm [45], respectively.

Wang and co-workers doped Fe₃O₄ NPs with AuNPs to synthesize Au@Fe₃O₄ hybrid NPs by one-step solvothermal method. The synergistic effects between Fe₃O₄ NPs and AuNPs effectively enhanced the peroxidase-like activity of Au@Fe₃O₄ NPs [46]. Based on these results, they developed a colorimetric sensor, which could detect ochratoxin A (OTA) with a detection limit as low as 30 pg/mL.

In 2017, Zhang et al. took advantage of the excellent self-assembly property and chemical elasticity of amyloid peptide to form AuNPs with self-assembled fiber hybrid structure. The AuNPs have excellent electrochemical and colorimetric sensing performance. Its linear response to H₂O₂ and Hg²⁺ ranged from 0.1-25.85 mM and 10-70 μM, respectively [47]. They also applied the same technology

to AuNCs to produce self-assembling nanofibers with motif design peptides. This change allowed AuNCs to achieve nearly 70-fold luminescence enhancement with a quantum yield of 21.3 [48].

Transverse flow analysis (LFAs) is based on biochemical interactions of antigen-antibody or probe DNA-target DNA hybridization. In the LFAs system, we often use various metal NPs, color latex particles, carbon NPs, quantum dots (QDs) and enzymes as markers to improve the sensitivity of detection methods [49]. LFAs has the advantages of low cost, simple operation, convenient use, quick field response, quick visual observation results and so on [50-52]. Alina *et al.* used AuNPs with different shapes to make immunochromatographic strips with different colored lines. This idea solved the problem that the same color of the detection and control areas of the LFAs test paper might lead to incorrect detection results. Using the T-2 toxin (T2T) as an example, an instrumental detection limit of 30 pg/mL and a working range 0.06-0.9 ng/mL were achieved in an analysis of water-organic corn extracts [53]. AgNPs have been also exploited in lateral flow assays for signal enhancement. Laura's team used both Au and Ag NPs to set up a multicolor multilayer transverse flow immunoassay (xLFIA). AgNPs and two kinds of AuNPs were combined as colorimetric probes to establish a visual detection method for allergen detection [54]. The xLFIA detected allergens as low as 0.1 mg/L and could easily identify allergens in commercial biscuits based on the color of the probes.

AuNPs have also been used for nucleic acids detection and biomarkers detection [55,56]. For example, Xun *et al.* proposed a simple and fast method for simultaneous detection of nucleic acids and proteins using AuNPs and horizontal flow device [57]. The method could simultaneously detect at least 0.5 nM of target DNA and 2 ng/mL IgG

within 15 min. This method had broad prospects in the field and real-time detection of disease-related circulating nucleic acids and protein biomarkers in biological fluids.

3 Colorimetric detection based on CuNPs

Similar to AuNPs, CuNPs are also important nanomaterials in colorimetry. Besides their catalytic activity, CuNPs can interact with many substances and affect the reactions in the system. According to these properties, CuNPs have an ample number of applications in the field of colorimetry [58-60].

Tang *et al.* used QDs with photocatalytic activity to detect Cu^{2+} , as shown in Figure 2a, and the detection limit was 5.3 nM [61]. Yin *et al.* used the principle that Cu^{2+} can catalyze the oxidation of 2,4-dinitrophenylcysteine (DNPC) in the presence of oxygen to detect it, and the maximum detection limit was 0.5 nM [62].

In the presence of pyrophosphate, the catalytic activity of CuNPs is greatly inhibited [63]. Therefore, the activity changes of CuNPs can be used to detect the presence of pyrophosphate or alkaline phosphatase (ALP). Liu and coworkers used pyrophosphate ion to adjust the chelating cooperation between Cu^{2+} and bovine serum albumin (BSA), which caused the change of the luminescence phenomenon, and the pyrophosphate could be detected based on this phenomenon [64]. The linear range of this detection method was 0.16-78.1 mM, and the detection limit was 0.083 mM. Pyrophosphoric acid can inhibit Cu^{2+} catalyzed oxidation of 2,2'-diazobin (3-ethylbenzothiazoline-6-sulfonic acid) ammonium salt by H_2O_2 . Pyrophosphatase can make pyrophosphate hydrolyze and resume its original

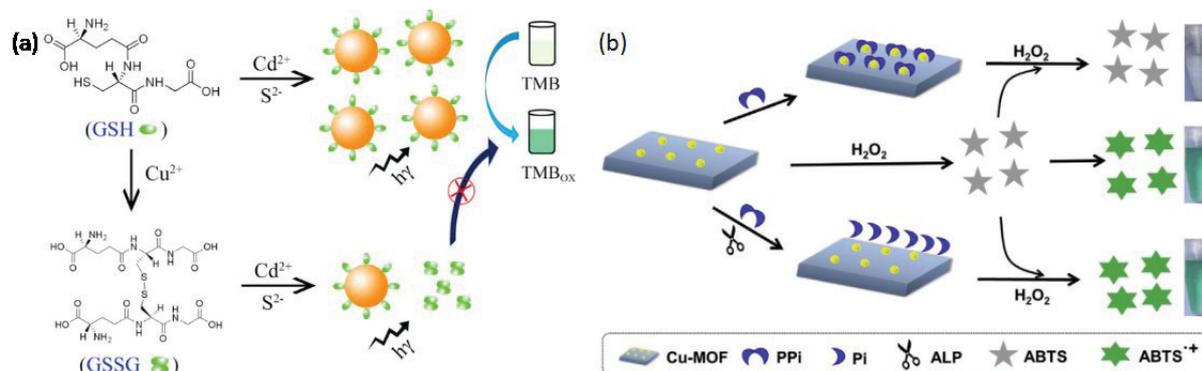


Figure 2: (a) Schematic diagram of alkaline phosphatase activity detection. Reprinted image with permission from Ref. [61], Copyright 2016, Elsevier B.V. (b) Pyrophosphate (PPI) colorimetric sensor based on BSA-AuNCs-Cu²⁺. Reprinted image with permission from Ref. [66], Copyright 2017, Elsevier B.V.

catalytic oxidation reaction, so as to detect the activity of pyrophosphatase. Based on this mechanism, Zhang and co-workers detected the pyrophosphatase activity [65]. The detection limit was as low as 0.027 U/mL. Wang et al. established a colorimetric detection method for alkaline phosphatase activity using Cu-MOFs as hydrogen peroxide analog and pyrophosphate as recognition elements (Figure 2b). Compared with previous method for quantitative analysis of ALP, this method was simple and intuitive, with high sensitivity and good sensing performance in serum samples [66]. The detection limit is 0.19 U/L.

4 Colorimetric detection based on FeNPs

As one of the earliest metal NPs with peroxidase activity, Fe_3O_4 NPs have long been used in colorimetric detection

[67-69]. In the subsequent studies, it was found that not only Fe_3O_4 NPs, but also FeNPs and its various oxides could simulate the activity of enzymes and serve as catalysts. After the experimental investigation, the researchers applied them to colorimetric detection. For example, Wang et al. proposed a colorimetric label-free detection method based on Fe-MIL-88A (a Fe-based MOF material) to simulate the activity of enzymes [70]. This method is used for colorimetric detection, which can detect H_2O_2 , glucose, and biomolecules. This adaptor sensing strategy could be universally applied to detect a series of environmental factors or biomolecules (Figure 3a). The limit of detection of 10 nM could be achieved with naked eyes.

Lu et al. reported a multifunctional biosensor platform for sensitive H_2O_2 and glucose colorimetric detection using an asymmetric hematite silica mixture of Janus- $\text{Fe}_2\text{O}_3/\text{SiO}_2$ NPs (JFSNs) (Figure 3b) [71]. The results showed that JFSNs had inherent peroxidase-like catalytic activity. JFSNs nanozyme can be used over a wider range of pH

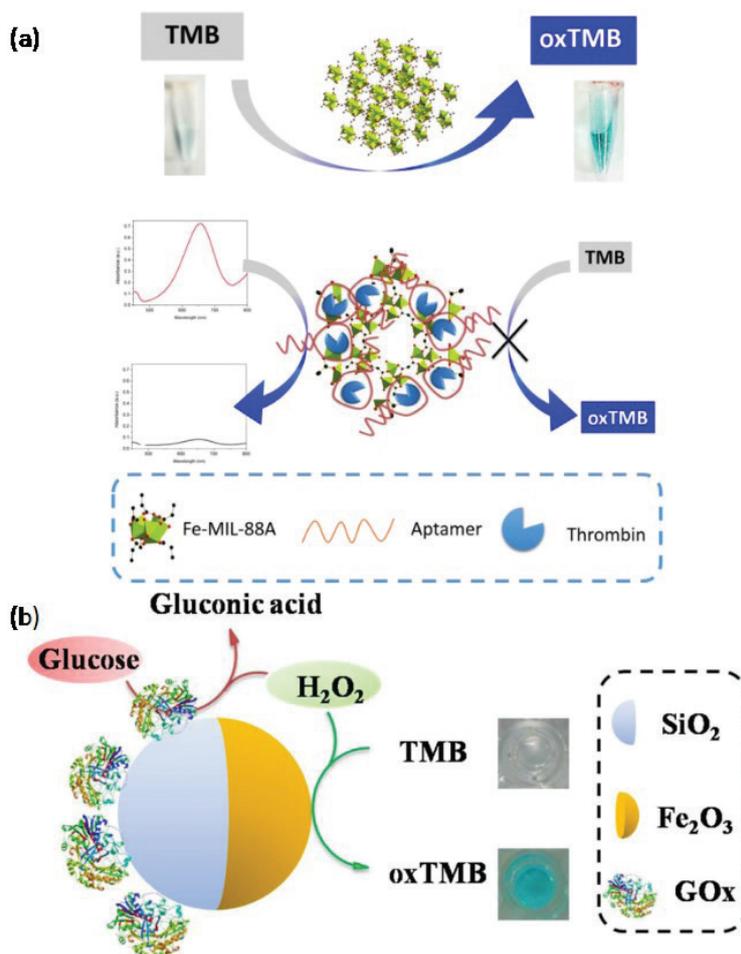


Figure 3: (a) Schematic diagram of Fe-MIL-88A's sensing mechanism for thrombin colorimetric detection. Reprinted image with permission from Ref. [70], Copyright 2016, Elsevier B.V. (b) Schematic diagram of biosensor using GOx-JFSNs to detect H_2O_2 and glucose. Reprinted image with permission from Ref. [71], Copyright 2015, American Chemical Society.

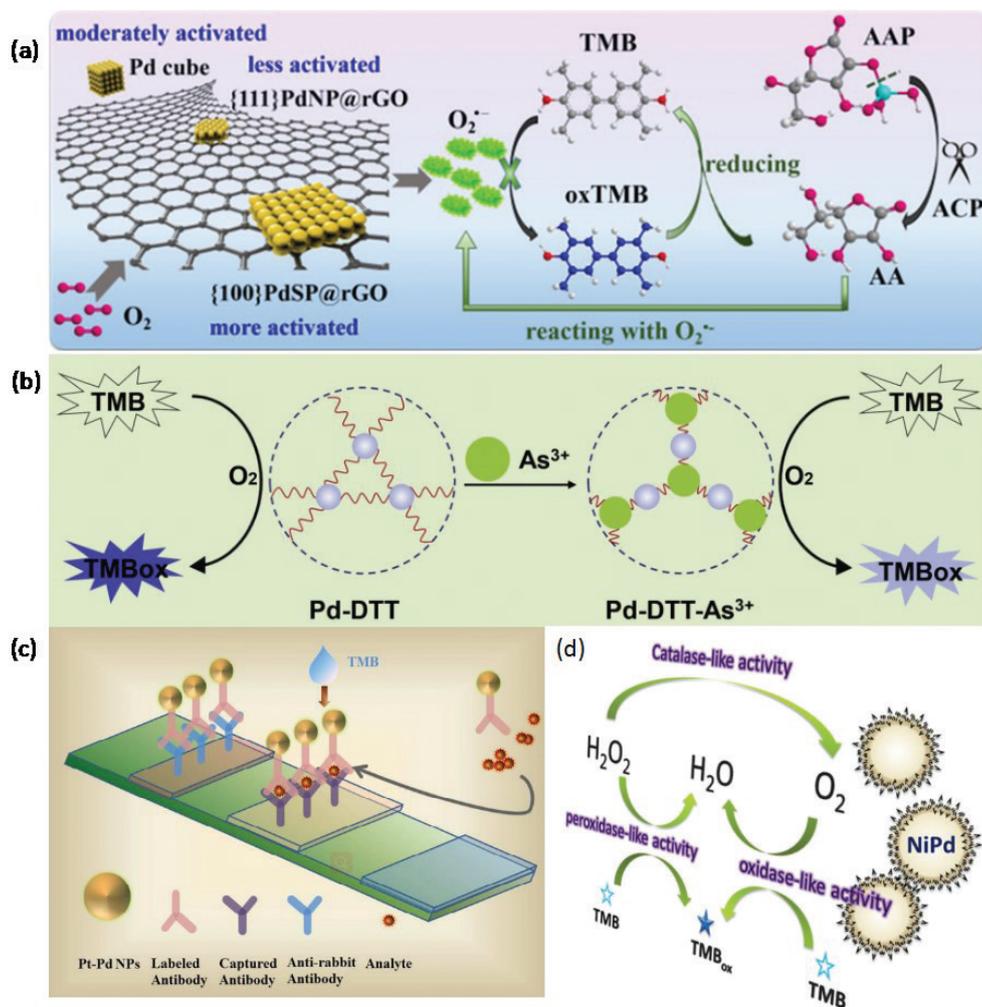


Figure 4: (a) Schematic diagram of oxidative activity of various Pd nanomaterials in the catalytic TMB oxidation. Reprinted image with permission from Ref. [73], Copyright 2019, American Chemical Society. (b) Schematic diagram of As^{3+} mechanism of Pd-DTT colorimetric analysis of simulated activity inhibition of polylactic acid induced oxidase. Reprinted image with permission from Ref. [77], Copyright 2019, Elsevier B.V. (c) Schematic diagram of Pt-Pd NPs immunochromatography bands for the detection of p53 protein. Reprinted image with permission from Ref. [79], Copyright 2016, American Chemical Society. (d) Schematic diagram of the activity of NiPd-HNPs trienzyme simulation. Reprinted image with permission from Ref. [80], Copyright 2016, Royal Society of Chemistry.

and temperature than the natural enzymes and are more stable over time. Due to its multi-component and synergistic multifunctional nanostructure, it is able to perform multiple tasks in a single nanosystem. The linear range was 1-100 μM , and the detection limit was 10.6 nM.

5 Colorimetric detection based on other metal NPs

Besides the above-introduced metal NPs, many other metal NPs are also commonly used for colorimetric detection. For example, Pt and Pd are also common metal nanozyme. Wei *et al.* used BSA as a nucleation template

to synthesize Pt-based peroxidase with an average diameter of 2.0 nm, and detected Hg^{2+} through peroxidase activity simulation of metal NPs. The realized Hg^{2+} detection limit was found to be 7.2 nM, with a linear response range of 0-120 nM [72]. Chen and co-workers reported that two-dimensional Pd nanoplates enclosed by {100}-facets [{100}PdNP@rGO] exhibit substantially enhanced intrinsic oxidase-like activities relative to the {111}-facets ones and Pd nanocubes in the catalytic 3,3',5,5'-tetramethylbenzidine (TMB) chromogenic reaction (Figure 4a) [73]. Taking ascorbic acid 2-phosphoric acid as substrate and converting to ascorbic acid in the presence of acid phosphatase (ACP), ACP can be efficiently detected without destroying H_2O_2 . The linear relationship was good within the range of 0.01-6.0 mU/mL, and the detection limit was

8.3 $\mu\text{U/mL}$. This method is superior to most of the reported methods and can be applied to the high precision determination of serum samples.

Pd nanocubes (PdNCs) showed peroxidase activity, which was inhibited in the presence of sulfur ions. Based on this principle, a colorimetric detection method for sulfur ions was established [74]. Similarly, PdNPs also has this catalytic activity and can be used to quantitatively detect cysteine and homocysteine [75]. After the modification with histidine (His), PdNPs exhibited significantly improved simulation activity due to their good physico-chemical properties, including small size and good hydrophilicity. Wenchi et al. proposed a new and efficient colorimetric method for Ag^+ detection based on histidine-mediated PdNPs with adjustable peroxide activity. They could be used to sensitively detect Ag^+ with a linear scope of 30-300 nM and detection limit of 4.7 nM [76]. Xu's group measured As^{3+} in the drinking water and river water (as shown in Figure 4b) based on the oxidative catalytic activity of Pd NPs (Pd-DTT) coated with dithiopropanol, which showed very high sensitivity [77]. The linear range was 33 ng/L–333.3 $\mu\text{g/L}$, and the detection limit was 35 ng/L.

Atrazine is an herbicide widely used. However, the Environmental Protection Agency (EPA) has issued a warning about Atrazine because of the reports of its potential harm to animals and humans. Therefore, it is very important to develop an effective method to detect herbicide residues. Pt-Pd bimetallic NPs (Pt-Pd NPs) can

bind directly to a primary antibody and detect Atrazine more efficiently and simply than ELISA that requiring a secondary antibody. The detection limit is 0.5 ng/mL [78]. Tao et al. reported an immunochromatographic detection band based on Pt-Pd NPs, and the detection process is shown in Figure 4c, which can intuitively and quantitatively detect p53 protein [79]. The method had a detection limit of 0.05 ng/mL with the linear range of 0.1-10 ng/mL. Compared with the traditional test strip based on color gold colloid, the sensitivity was improved by 2000 times.

Wang et al. proved that Ni-Pd hollow NPs (NiPd-HNPs) had oxidase-like, peroxidase-like, and catalase-like activities. Then, they developed a simple glucose biosensor with a wide linear range (0.005-0.5 mM) and a low detection limit (4.2 μM) using peroxidase as a simulation (Figure 4d) [80]. After continuous verification, it has been found that biological molecules such as ATP could be used to enhance the enzyme activity of metal NPs [81,82]. The colorimetric ability of materials can also be improved by wrapping metal particles into fiber morphology [83].

It should be noted Cd [84], Zr [85], Co [86], Pt [87], Zn [88], and other metal materials are rarely used in large quantities due to price or resource reasons, but they can also be used for colorimetric detection in some cases.

To get a more intuitive understanding of the different metal NPs and their colorimetric sensing applications, we present a table (Table 1).

Table 1: Comparison of the properties of different metal NPs and the application of colorimetric sensors

Metal nanoparticles	Characteristics	Colorimetric sensor applications
Au	AuNPs have excellent optical and electronic properties, high absorption extinction coefficient and sensitivity.	Detect heavy metal ions such as Hg^{2+} [17,18,42,47]; detect antibiotics in foods [19,20]; detect parathion [21-25]; detect biomolecules [26-34,41,43-45]; detect mycotoxins [46]; LFAs [53,54]; detect nucleic acids and biomarkers [55-57].
Cu	CuNPs have large specific surface area, high thermal, high electrical conductivity and catalytic activity. CuNPs are difficult to synthesize, and they are easy to aggregate and oxidize due to their great specific surface energy and reducibility.	Detect organics [61,62]; detect pyrophosphate or alkaline phosphatase (ALP) [64-66].
Fe	FeNPs have good activity and specific surface area. However, they have poor dispersion and stability and are easy to aggregate in water.	Detect H_2O_2 and biomolecules [67-70].
Pt	PtNPs have good catalytic activity, strong adsorption capacity, high biocompatibility and are easy to be modified.	Detect heavy metals [72] and H_2O_2 [87].
Pd	PdNPs are excellent hydrogen storage materials, fuel cell electrodes and heterogeneous catalysis materials.	Detect metals [77] and nonmetal ions [72]; detect acid phosphatase (ACP) [73]; detect biomolecules [75,79,80]; detect toxic substances [78].

6 Conclusions and outlooks

The introduction of metal nanomaterials in recent years has led to the rapid development of colorimetry and many new colorimetry methods have been reported. This review focuses on metal NPs and summarizes the most representative colorimetric studies in the past five years. The colorimetric properties based on Au, Cu, Fe, and other metal NPs and their oxides are described and discussed. The mechanisms and principles of many mature colorimetric detection methods are introduced. In addition, some typical applications involving environmental governance, biological research, clinical medicine and other aspects are listed, which fully demonstrate a mature field of colorimetry detection. A comparison of the above colorimetric methods and their applications shows that by developing colorimetric methods, we are trying to simplify complex problems to achieve simple operations and efficient detection.

Although the methods of colorimetric detection based on metal NPs are emerging in an endless way at the present stage, the researchers still need to think about how to improve the performance of metal nanomaterials on the existing technical level again, which is also the constant goal and problem in the research field. Researchers are working to improve the performance of existing metal nanomaterials, and have had some success [89-92]. Though we have found something through the research and experiment, it is still the power source to stimulate our continuous innovation to synthesize more sensitive and selective materials, or to maintain an efficient detection system under harsh conditions. The researchers have also been working hard to implement the existing colorimetric methods into convenient forms such as test strips and sensors. In addition, there are many new materials with outstanding performance, such as the perovskite materials or metal-doped composite materials. Perovskite is a ceramic oxide whose molecular formula is ABO_3 . The A is usually rare earth metal and the B is transition metal. Both A and B can be replaced by other metal ions of similar radius for forming a variety of compounds. Some studies have shown that perovskite oxide can be used for colorimetric detection by its enzyme-like activity [93]. However, up to now, the research on this aspect is still very few [94,95]. Whether they can show excellent performance in the field of colorimetry is waiting for us to discover and study.

In recent years, the design and synthesis of metal nanomaterials have developed rapidly, but it is necessary to develop more clean, diversified and efficient

nanomaterials to construct sensitive sensors. For example, how to design novel functional metal NPs and adjust the size and morphology for broadening the application field of metal nanomaterials; how to develop new preparation techniques and methods to achieve the research and development of low-cost and high-quality metal NPs. We suggest that these issues are the key to the development of metallic nanomaterials in the next few years.

It is hoped that our work can provide some hints and help for the future research of colorimetry, so as to promote the application of colorimetry in biomedical detection and environmental analysis. We also believe that with the continuous development of science and technology, colorimetric method can constantly bring forth new ideas and solve more difficult problems.

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Author contribution: Ning Xu: writing – original draft, writing – review and editing; Shuang Jin: writing – review and editing; Li Wang: resources, funding acquisition, supervision.

Conflict of interest: Authors state no conflict of interest.

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