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## RESEARCH ARTICLE

# RESEARCH PROGRESS IN GLUTATHIONE DETECTION TECHNOLOGIES

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### ABSTRACT

Glutathione is an important antioxidant and redox regulator in biological systems, playing a critical role in cellular metabolism, oxidative stress defense, and various physiological and pathological processes related to diseases. Accurate detection of glutathione is of significant importance for research in life sciences and health. This paper systematically reviews the physiological functions of glutathione, the characteristics of commonly used traditional detection technologies, and provides an overview of the basic principles and current developments of photoelectrochemical sensors. It focuses on summarizing the recent advancements in glutathione photoelectrochemical sensors, emphasizing innovations in nanofunctional materials, interface engineering, and sensing mechanisms. Finally, the existing challenges in this field and future development directions are discussed, aiming to provide references for the construction of high-performance glutathione sensing platforms.

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## INTRODUCTION

Glutathione (GSH), a tripeptide composed of  $\gamma$ -L-glutamyl-L-cysteine-glycine, is widely present in living organisms and plays a crucial role in various physiological processes in both humans and animals [1-2]. As a significant endogenous antioxidant, GSH exerts its protective effects by utilizing its sulfhydryl group (-SH) to scavenge reactive oxygen species (ROS) and free radicals, thereby safeguarding biological cells from oxidative damage. Moreover, GSH is vital for maintaining intracellular redox homeostasis, regulating protein bioactivity, and participating in cellular signal transduction and metabolic regulation. Clinical studies indicate that the concentration levels of GSH in serum, cells, and tissues can serve as physiological and pathological reference indicators for various diseases, including Parkinson's disease, Alzheimer's disease, diabetes, and liver injury [3]. Therefore, the efficient, rapid, and accurate measurement of GSH holds significant clinical relevance for the early screening of certain major diseases.

### TRADITIONAL DETECTION METHODS

#### High-Performance Liquid Chromatography

The most notable advantages of high-performance liquid chromatography (HPLC) are its high resolution and specificity. GSH in biological samples typically coexists with various other thiol compounds (such as cysteine and homocysteine) and matrix components. HPLC, particularly when coupled with ultraviolet, fluorescence, or mass spectrometry detectors, can effectively separate

these similar compounds in both time and space by optimizing the chromatographic column and mobile phase, allowing for the accurate quantification of GSH and GSSG. For instance, using a fluorescence detector combined with pre-column derivatization reagents, can significantly enhance the sensitivity and selectivity of detection, enabling the method to detect GSH at pico-molar concentrations or even lower, making it particularly suitable for the precise analysis of trace GSH in complex biological samples (such as blood, tissue homogenates, and plant extracts). The classic pre-column derivatization-fluorescence detection method, based on the work of Reed et al. [4], employs o-phthalaldehyde for derivatization and utilizes a combined step of N-ethylmaleimide masking and dithiothreitol reduction to specifically differentiate and quantify oxidized and reduced forms of glutathione. By incorporating phosphoric acid precipitation of proteins and EDTA chelation of metal ions in the pretreatment, this method achieves stable and highly sensitive detection of GSH at the pico-molar level in cellular extracts, providing a core method for determining the GSH/GSSG ratio and assessing the cellular redox state. Modern analysis tends to favor ultra-high-performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS). As described by Guan et al., this method eliminates the need for derivatization, effectively separating the highly polar GSH through hydrophilic interaction chromatography, and allows for direct quantification using electrospray ionization-tandem mass spectrometry in a multiple reaction monitoring mode with high selectivity [5]. This approach demonstrates excellent resistance to matrix interference, offers simple pretreatment, and is suitable for rapid, high-throughput analysis of complex food matrices such as yeast and fruits and vegetables, while also being extensible to the simultaneous determination of related metabolites.

The primary disadvantages of HPLC are its complexity and low efficiency. The HPLC measurement process is intricate, often involving complicated sample pretreatment steps such as protein precipitation, centrifugation, filtration, and critically, the derivatization reaction. These steps are not only time-consuming but also require skilled operators to ensure consistent derivatization efficiency, increasing the risk of oxidation or degradation of samples during pretreatment. Additionally, HPLC systems are expensive, with high operational costs (such as the consumption of high-purity mobile phases and chromatographic columns), and the analysis time is relatively long, potentially taking from tens of minutes to an hour from sample preparation to results. This makes it challenging to achieve high-throughput rapid screening or bedside clinical detection [6].

### Colorimetric Sensors

Colorimetric sensors have garnered significant attention in the field of GSH detection due to their simplicity of operation and visualizable results. The core principle involves the use of nanomaterials with enzyme-like activity to catalyze the color development of substrates, while GSH quantitatively inhibits this reaction. Significant progress has been made in related research. For example, ZIF-90-MnO<sub>2</sub> nanosheet composites can catalyze the color development of TMB under weakly acidic conditions, with GSH reducing MnO<sub>2</sub> to inhibit the reaction, allowing for a detection range of 1.25 to 30 μM and a LOD of 0.30 μM [10]. The Au-MnO<sub>2</sub> multi-nanocatalyst system enhances selectivity through the inner filter effect, reducing the LOD to 5 nM [7]. A CoFeCe triatomic hydroxide sensor combines colorimetric and photothermal dual modes, enabling portable detection via a smartphone, with an LOD of 0.092 μM [8]. However, this technology still faces three major challenges: first, insufficient selectivity, as structural analogs of GSH (such as cysteine) easily interfere; second, complex sample matrices (such as serum) can quench signals or generate background noise [11]; and third, the instability of colorimetric products and narrow linear ranges (typically in the micromolar range) make it difficult to cover the physiological concentration span [8].

### Fluorescent Sensors

Fluorescent sensors are widely applied in GSH detection due to their high sensitivity, real-time response, and spatial resolution. Their design is typically based on fluorescence resonance energy transfer (FRET) or molecular recognition mechanisms. For instance, Liu et al. constructed a weak-light photodetector based on upconversion nanoparticles (UCNPs), utilizing MnO<sub>2</sub> nanosheets to quench the luminescence of UCNPs, while GSH-reduced MnO<sub>2</sub>, restoring the fluorescence signal with a LOD of 41 nM. This sensor exhibits low background noise and is suitable for complex biological systems. Additionally, Wu et al. developed a molecularly imprinted core-shell fluorescent probe, where AuNPs quench the fluorescence of rhodamine B. GSH competes for binding to AuNPs, restoring fluorescence, while the molecularly imprinted layer provides specific cavities, significantly enhancing interference resistance, with an LOD of 0.18 μM. Such sensors have demonstrated good performance in serum, showcasing the practicality of molecular imprinting technology [9]. The performance of fluorescent sensors depends on the stability and selectivity of the probes. For example, Huang et al. utilized Au@BSA NCs-Cu<sup>2+</sup> to enhance chemiluminescence, where GSH quenched the luminescence signal, with a linear range of 0.50–6.00 mM and an LOD of 0.29 mM. Although the sensitivity is somewhat lower, the chemiluminescent method does not require an excitation light source, simplifying the equipment. A limitation of fluorescent sensors is their susceptibility to photobleaching; future developments could focus on ratio-type or upconversion probes to enhance reliability [10].

### Overview of Photoelectrochemical Sensors

Photoelectrochemical (PEC) sensors are analytical techniques that combine light excitation with electrochemical detection. The

fundamental working principle involves irradiating a photoactive material (such as semiconductor nanoparticles) fixed on the surface of an electrode with light of a specific wavelength. When the energy of the photons is equal to or greater than the bandgap energy of the material, electrons in the valence band are excited to the conduction band, generating electron-hole pairs [11]. These photogenerated charge carriers subsequently undergo separation and migration under the influence of an external electric field or an intrinsic energy level difference, resulting in a measurable photocurrent signal in the external circuit. In the presence of target analytes, specific interactions occur between the analytes and the photoactive material (for example, acting as electron donors or acceptors, or through quenching effects). This interaction alters the efficiency of electron-hole pair separation or recombination, ultimately leading to an enhancement (“signal-on” type) or a reduction (“signal-off” type) of the photocurrent signal, enabling quantitative detection of the target species (as illustrated in Figure 1) [12].

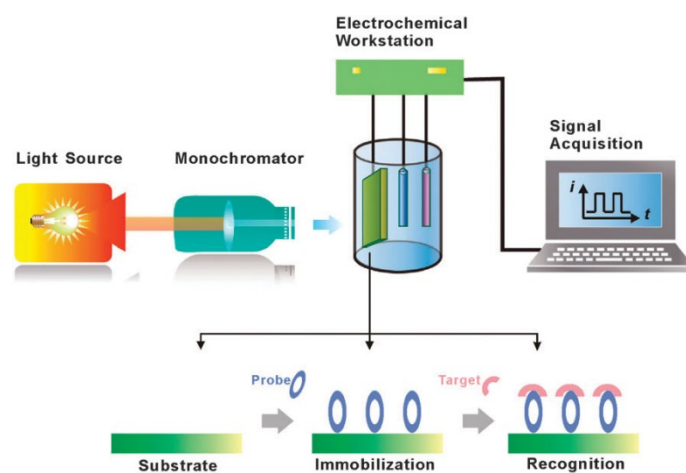


Figure 1. Working mechanism illustration of a photoelectrochemical sensor

The core advantage of PEC sensors lies in their unique separation of "energy input (light) and signal output (electricity)." This mode allows them to inherit the high sensitivity characteristic of optical methods while also benefiting from the low background noise typical of electrochemical techniques. Since the excitation light and the detected electrical signal are in different forms, they do not interfere with each other, significantly enhancing the signal-to-noise ratio and detection sensitivity. Moreover, PEC sensors are typically characterized by their simple instrumentation and ease of miniaturization. PEC sensors can be categorized based on the target analytes they detect, including small molecules, proteins, nucleic acids, and more. The core performance metrics for evaluating these sensors primarily include sensitivity (often measured by the LOD), linear detection range, selectivity (interference resistance), stability (light stability and repeatability), as well as recovery rates and relative standard deviation in actual samples (such as serum and urine) [13].

### Research Progress on Photoelectrochemical Sensors for GSH Detection

Xue et al. developed a PEC sensor based on carbon dots (CDs) hybrid nanocomposites (CDs/AgNPs, CDs/GO, and CDs@MS) for the detection of GSH [14]. In the presence of GSH, the CDs, acting as photoactive materials, undergo catalytic oxidation, resulting in an enhanced photocurrent signal. The morphology and composite structure of the nanomaterials were characterized using atomic force microscopy (AFM) and high-resolution transmission electron microscopy (HRTEM) (as shown in Figure 2). The sensor exhibited a linear response range of 0.02–4.0 μM for GSH at +500 mV, with a sensitivity of 57.6 nA μM<sup>-1</sup> and a LOD of 6.2 nM. In human serum and cardiomyocyte samples, the sensor demonstrated high recovery rates (92.2%–97.7%) and good selectivity against interfering substances such as cysteine and ascorbic acid. The CDs-based hybrid nanocomposites effectively integrated the advantages of PEC

technology with the catalytic properties of CDs, providing a high-performance platform for GSH detection. The CDs@MS composite material, with its porous structure, exhibited optimal sensitivity and stability. This sensor holds significant potential for biomedical detection, particularly in complex samples such as serum and cell lysates.

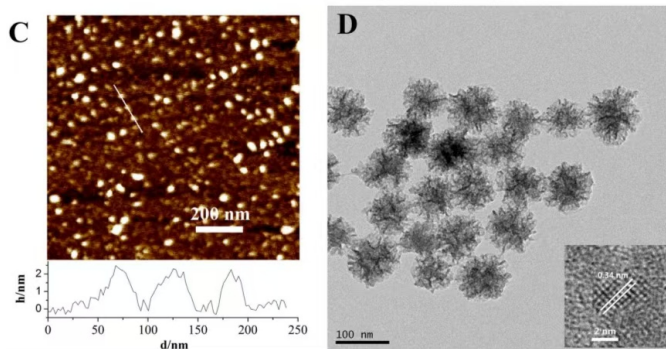


Figure 2. Characterization of CD hybrid nanocomposites

Chen et al. developed a dual-mode (colorimetric/PEC) sensing platform based on the decomposition of a copper-organic framework (CuHPT) for reliable detection of GSH [15]. A hollow CoS/In-CdS type-II heterojunction was synthesized using a ZIF-67 template as the photoactive material. Upon the presence of GSH, CuHPT decomposition produces catechol ligands and  $\text{Cu}^+$ , where  $\text{Cu}^+$  catalyzes the generation of hydroxyl radicals ( $\cdot\text{OH}$ ) from hydrogen peroxide through a Fenton-like reaction for colorimetric detection (based on the oxidation of TMB). Simultaneously,  $\text{Cu}^+$  undergoes ion exchange with CdS to form  $\text{Cu}_2\text{S}$ , disrupting the heterojunction structure and reducing the photocurrent for PEC detection.

The linear range for the colorimetric mode was found to be 0.05–1.20 mM with a LOD of 18  $\mu\text{M}$ , while the PEC mode exhibited a linear range of 0.5–800  $\mu\text{M}$  with an LOD of 0.11  $\mu\text{M}$ . The sensor demonstrated high recovery rates (93.8%–101.6%) and good interference resistance in human serum samples. This dual-mode sensor utilizes a unique mechanism whereby GSH triggers the decomposition of CuHPT, enabling complementary validation and thereby enhancing detection reliability (as shown in Figure 3). The CoS/In-CdS heterojunction effectively promotes charge separation, enhancing the photocurrent response. This platform holds significant promise for applications in clinical detection.

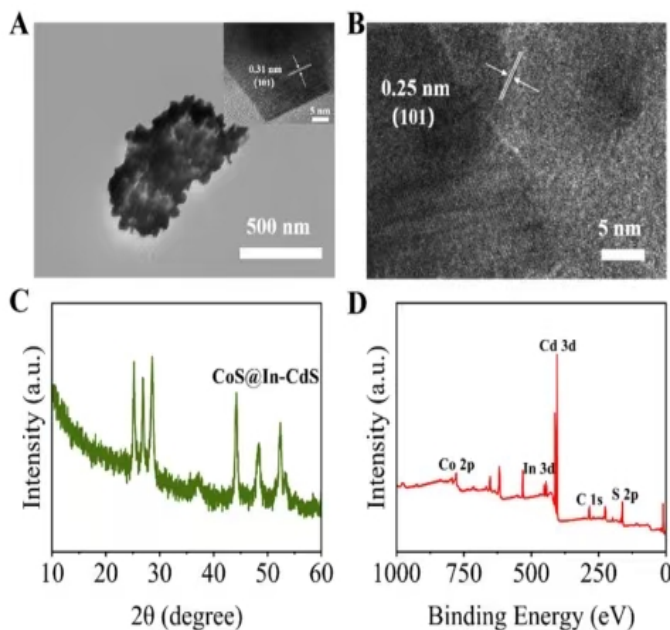


Figure 3. Comprehensive material characterization of hollow CoS/In-CdS II-Type heterojunctions: TEM, XRD, and XPS Analysis

Huang et al. synthesized a novel  $\text{Ti}_3\text{C}_2\text{T}_x/\text{AgI}$  heterojunction material (HM) to construct a cathodic photoelectrochemical (PEC) sensor for the detection of GSH [24]. The  $\text{Ti}_3\text{C}_2\text{T}_x$  MXene served as a support for AgI, forming the heterojunction via electrostatic self-assembly, and its metallic conductivity facilitated the separation and transport of photogenerated charge carriers. The band structure and charge transfer mechanism of the heterojunction were verified through VASP calculations (as shown in Figure 4) [16]. As a reducing agent, GSH consumes dissolved oxygen or reactive oxygen species, inhibiting electron transfer and resulting in a decrease in photocurrent. The sensor exhibited a linear response over the range of 1 nM to 10  $\mu\text{M}$ , with a LOD of 0.31 nM and high selectivity against interference from substances such as hydrogen peroxide and ascorbic acid. The  $\text{Ti}_3\text{C}_2\text{T}_x/\text{AgI}$  HM optimized the charge transfer pathway by constructing an internal electric field, significantly enhancing the PEC performance. The cathodic detection mode reduced background noise, providing a new approach for the design of enzyme-free PEC platforms.

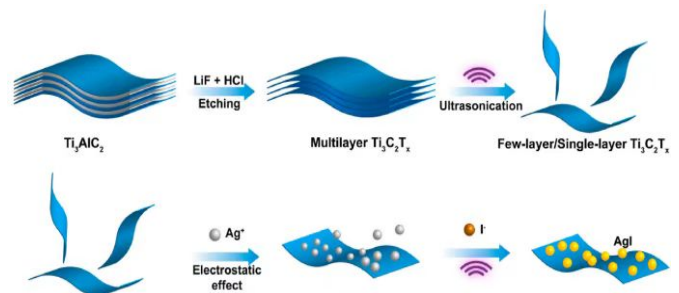


Figure 4. Band structure and charge transfer mechanism of heterojunctions

## Conclusions

In summary, GSH serves as a crucial antioxidant and redox-regulating molecule within the body, playing an irreplaceable role in maintaining cellular homeostasis, combating oxidative stress, and participating in various physiological and pathological processes. Although traditional detection methods are widely used, they still face limitations in terms of sensitivity, selectivity, portability, and real-time monitoring. PEC sensors, with their rapid response, high sensitivity, simple instrumentation, and ease of miniaturization, have emerged as a significant development direction for the efficient detection of GSH. In recent years, substantial progress has been made in the detection performance and application scenarios of GSH sensors, driven by innovations in the design of novel functional nanomaterials, construction of interface engineering, and advancements in sensing mechanisms. Looking ahead, the further development of high-selectivity recognition strategies, multi-signal cooperative enhancement systems, and wearable integrated devices holds great promise for achieving precise, in situ, and dynamic detection of GSH in complex biological systems. This progress is expected to provide more reliable technical support for the early diagnosis of related diseases and the study of physiological mechanisms.

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