

Manganese dioxide nanosheets: from preparation to biomedical applications

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Abstract: Advancements in nanotechnology and molecular biology have promoted the development of a diverse range of models to intervene in various disorders (from diagnosis to treatment and even theranostics). Manganese dioxide nanosheets (MnO₂ NSs), a typical two-dimensional (2D) transition metal oxide of nanomaterial that possesses unique structure and distinct properties have been employed in multiple disciplines in recent decades, especially in the field of biomedicine, including biocatalysis, fluorescence sensing, magnetic resonance imaging and cargo-loading functionality. A brief overview of the different synthetic methodologies for MnO₂ NSs and their state-of-the-art biomedical applications is presented below, as well as the challenges and future perspectives of MnO₂ NSs.

Keywords: MnO₂ nanosheets, synthetic methods, biocatalysis, fluorescence sensing, controlled drug delivery, stimuli-activated imaging

Introduction

Advances in nanotechnology and molecular biochemistry, the ability to decrypt and elaborate multiple artificial materials, the continuous search for new targets, and the disentangling of diverse signaling pathways of many medical disorders have had a conspicuous influence on modern medical practices.¹⁻⁴ Among the various nanomaterials designed for biomedical applications, two-dimensional (2D) materials, especially transition metal dichalcogenides (eg, MoS₂, WS₂, TiS₂, MoSe₂, and WSe₂)⁵ and transition metal oxides (TMOs, eg, MnO₂),⁶ have received a substantial amount of recent attention due to their distinct structure–property relationships in multiple fields, eg, optoelectronics, spintronics, catalysis, defect engineering, and energy-related applications.⁷⁻⁹ Among these materials, manganese oxides have attracted increasing attention because Mn is the twelfth most common element on the planet and the third most abundant transition element after iron and titanium.¹⁰ Manganese (II) ions function as cofactors in a number of enzymes with varying functionalities as well as being key components in the oxygen-evolving complexes of photosynthetic plants.¹¹ Additionally, manganese oxide (Mn-oxide) has a variety of structures (nanorods, nanobelts, nanosheets (NSs), nanowires, nanotubes, nanofibers and so on)¹² and compositions (MnO, Mn₅O₈, Mn₂O₃, MnO₂, and Mn₃O₄)¹³ which further broadens its applications in a diverse range of fields. Hoseinpour et al reviewed the structures, sizes and applications of Mn NPs prepared via different green synthetic methods in detail.¹⁴ Among the various nanostructures, NS is two-dimensional nanostructure with thickness ranging from 1 to 100 nm. A typical NS example is graphene, which is composed of a single layer of carbon atoms with hexagonal lattice.¹⁵ NS shares several

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similar common features, eg, ultralarge specific surface areas and high surface-to-volume ratios, allowing easy contact between reactant molecules and the active sites, thus providing enhanced catalytic activities¹⁶ as well as unique optical properties (described below) and excellent photothermal therapy (PTT), etc.¹⁷ MnO₂ nanosheets (MnO₂ NSs) are composed of MnO₆ octahedra that share edges, with manganese ions occupying the centers of the octahedra and being coordinated to the six nearest oxygen ions, while each oxygen ion is coordinated to the three nearest manganese ions.^{18,19} Similar to the structures of other 2D materials, MnO₂ NSs possess high specific surface areas and a thickness of nanometers to micrometers. Moreover, the redox reactions between MnO₂ and glutathione (GSH) in acidic environment have favored their applications in activatable fluorescent biosensors, controlled drug delivery and activatable T₁-MR imaging.^{20–22} As a class of novel and facilely synthesized 2D TMOs with good biocompatibility, MnO₂ NSs have received increased attention across a vast range of disciplines, especially biomedicine. In this review, we aim to provide an overview of the state-of-the-art syntheses, biomedical applications, toxicological assessments and challenges/opportunities in the research field of MnO₂ NSs. First, various synthetic strategies for the preparation of MnO₂ NSs are introduced. Then, we briefly discuss their main biomedical applications. Furthermore, the *in vitro* and *in vivo* toxicological evaluations are highlighted. Ultimately, we provide some personal perspectives on the future directions of this promising research field.

Synthesis of manganese dioxide nanosheets (MnO₂ NSs)

As a class of 2D nanomaterials, NSs are characterized by their nanometer thicknesses as well as lateral dimensions ranging from the submicrometers to micrometer scales. MnO₂ NSs with extremely large surface-area-to-mass ratios (SMRs) display a number of distinctive physicochemical properties compared with their bulk form. Hence, the synthesis of MnO₂ NSs is of great significance for a variety of novel biomedical applications. To date, several methods have been developed for the preparation of MnO₂ NSs. In general, these methods can be classified into two categories: top-down and bottom-up approaches, as is also true of other types of 2D nanomaterials.²³ In 2003, Omomo et al. first reported the formation and characterization of unilamellar 2D crystallites of MnO₂ as well as the swelling and exfoliation behavior of layered

manganese oxide, H_{0.13}MnO₂·H₂O, which was dissolved in tetrabutylammonium hydroxide solution.²⁴ This traditional top-down approach always utilizes ion-exchange and exfoliation of bulk MnO₂ templates to obtain MnO₂ NSs. However, this route entails a cost-demanding and time-consuming multistep high-temperature solid-state synthetic process. Moreover, one hurdle that the obtained NSs possess a wide thickness distribution, which is a challenge that must be overcome before their possible future application. In 2008, Kazuya Kai et al demonstrated a single-step bottom-up approach to directly synthesize MnO₂ NSs for the first time,²⁵ drawing from the synthetic methodology for producing Ti_{1-δ}O₂ monosheets with uniform shapes and sizes reported by Yoon and coworkers.²⁶ Since then, the bottom-up strategy, as a novel approach to synthesize MnO₂ NSs, has attracted the attention of most researchers in this field, owing to its significant advantages, such as an easier preparation and better controlled exfoliation and reaction steps. In this review, we focus on the bottom-up methods for obtaining MnO₂ NSs, and their sizes and morphologies when prepared by different approaches have been summarized in Table 1.

Manganese ion (Mn²⁺) based oxidative methodology

The preparation of multilayer MnO₂ NSs (ca. 10 nm in thickness) with bottom-up approaches has mainly been achieved by the oxidation of Mn²⁺ or the reduction of KMnO₄ with a self-sacrificing template (eg, graphene oxide nanosheets; GO NSs) or a chelating agent (eg, EDTA)²⁷ in the presence of reducing or oxidizing reagents. In 2007, Oaki and Imai proposed bottom-up approach to obtain MnO₂ NSs by the oxidation of manganese ions with dissolved oxygen in the solution.²⁷ EDTA was utilized as a chelating agent for the manganese ions (Mn²⁺) to hinder the rapid precipitation of Mn(OH)₂. However, their precipitate consisted of multiple layers with thicknesses of 10 nanometers or greater (ie, over 10 layers). Moreover, the time-consuming process (at least 3 days) was unavoidable. To address these issues, inspired by the single-step route reported by Yoon for the synthesis of titanate dioxide nanosheets (Ti_{1-δ}O₂ NSs), Kazuya Kai and coworkers attempted to prepare MnO₂ NSs with hydrogen peroxide (H₂O₂) as an oxidant in an alkaline medium and TMA cations for the exfoliation of layered H/MnO₂. However, unlike the method from Yoon, their reaction readily proceeded at ambient temperature instead of heating under reflux (Figure 1).²⁶

Table 1 Summarized sizes and morphologies of MnO₂ NSs synthesized by different approaches

Method	Reaction materials	Morphology	Lateral dimensions	Thickness	Reference
Top-Down	H _{0.13} MnO ₂ ·0.7H ₂ O + TBAOH	Nanosheet structure	<50 nm	0.91 ±0.07nm	24
Bottom-Up (reductive)	KMnO ₄ + MES	Nanosheet structure	141 nm	~1.5 nm	28
Bottom-Up (reductive)	KMnO ₄ + SDS	Single-layered nanosheet	~200 nm	0.77~0.95 nm	29
Bottom-Up (oxidative)	MnCl ₂ + EDTA + NaOH	Thin film of nanosheet	2~5 μm width	~10 nm	27
Bottom-Up (oxidative)	MnCl ₂ + TMAOH	Single-layered NS	<200 nm	Nearly 80% <1 nm	25
Bottom-Up (oxidative)	MnCl ₂ + H ₂ O ₂ + TMAOH	A two-dimensional sheet structure	~200 nm	~1.3 nm.	111
Bottom-Up (oxidative)	MnCl ₂ + (NH ₄) ₂ S ₂ O ₈ + TMA.OH	Flat morphology	2 μm	~4.07 nm	35
Bottom-Up (oxidative)	MnCl ₂ + H ₂ O ₂ + TMA.OH	A sheet-like structure	N/A	~1.5 nm	36
Bottom-Up (oxidative)	MnCl ₂ + H ₂ O ₂ + TMA.OH	Nanosheet structure	100~200 nm	N/A	69
Bottom-Up (oxidative)	MnCl ₂ + H ₂ O ₂ + TMA.OH	Polycrystalline sheet structure	141 nm	1.5 nm	150
Bottom-Up (oxidative)	MnCl ₂ + H ₂ O ₂ + TMA.OH	Single-layer sheet structure	200 nm	~1.5 nm	170

Abbreviations: TMA.OH, tetramethylammonium hydroxide; TBA.OH, tetrabutylammonium hydroxide; NS, nanosheet.

Potassium permanganate (PP, KMnO₄)-based reductive methodology

Compared to the top-down and the oxidative bottom-up methods, a reductive bottom-up method has been developed in recent years. With KMnO₄ as the Mn source, different reactive agents have been introduced to prepare MnO₂ NSs. For example, Liu et al first obtained MnO₂ NSs via the addition of an aqueous KMnO₄ solution into a 2-(N-morpholino)ethanesulfonic acid (MES) buffer at pH 6. Compared with other reducing reagents (eg, MnCl₂ and ethanol), the use of the MES buffer as the reducing agent showed the best results (Figure 2A).²⁸ Later, in 2015, Yin and coworkers developed a facile template-free, one-step and one-phase reductive strategy to synthesize single-layered MnO₂ NSs with sodium dodecylsulfate (SDS) as the reducing agent. In their system, SDS not only played the role of a precursor of dodecanol to reduce KMnO₄ but also was a structure-directing agent to promote the formation of the MnO₂ monosheets, which opened up the possibility of constructing other NS without the use of an exfoliation reagent (Figure 2B).²⁹ Indeed, this reductive method was more facile in both principle and practice because a variety of reductants could be selected. Furthermore, the synthetic process for the MnO₂ NSs was more controllable. Nonetheless, an inevitable drawback was that KMnO₄ tended to decompose in hydrothermal environments (*ca.* 95°C), which challenged researchers attempting to verify the exact mechanisms of the corresponding chemical reactions.^{30–34}

Biomedical applications of MnO₂ nanosheets (MnO₂ NSs)

Since the intriguing 2D structure and distinct physical/chemical properties were initially identified, MnO₂ NSs have received much attention and have exhibited favorable potential for application in a wide range of disciplines, such as physics,³⁷ chemistry,³⁸ material science³⁹ (especially energy-related applications, eg, solar cells,⁴⁰ supercapacitors,^{41–45} and lithium-ion batteries^{46,47}), optoelectronics,^{48,49} spintronics,¹⁸ biomedicine,⁴⁰ and so forth. Particularly, their broad use in biological sensing and catalysis, drug delivery and controlled release, PTT and chemo-dynamic therapy (CDT),²¹ molecular imaging and engineering, etc., has shown promising potential. Herein, we summarize a majority of the MnO₂ NS applications in recent years in the field of biomedicine (Figure 3).

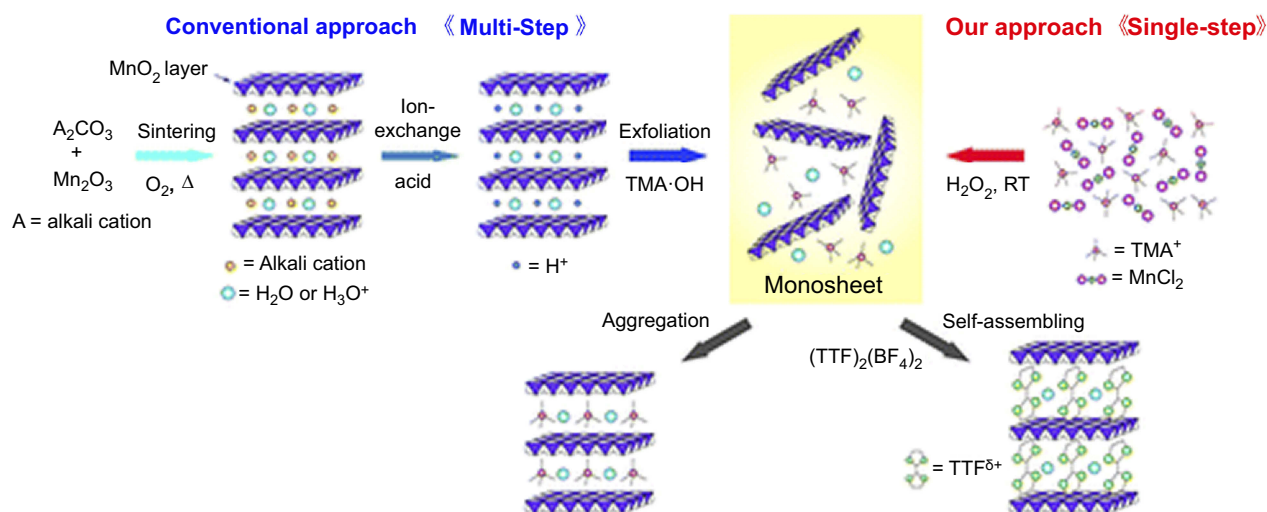


Figure 1 Schematic illustration of the single-step oxidative method with H_2O_2 at room temperature versus the conventional method.

Note: Reprinted with permission from Kai K, Yoshida Y, Kageyama H, et al. Room-temperature synthesis of manganese oxide monosheets. *J Am Chem Soc.* 2008;130(47):15938–15943.²⁵ Copyright (2008) American Chemical Society.

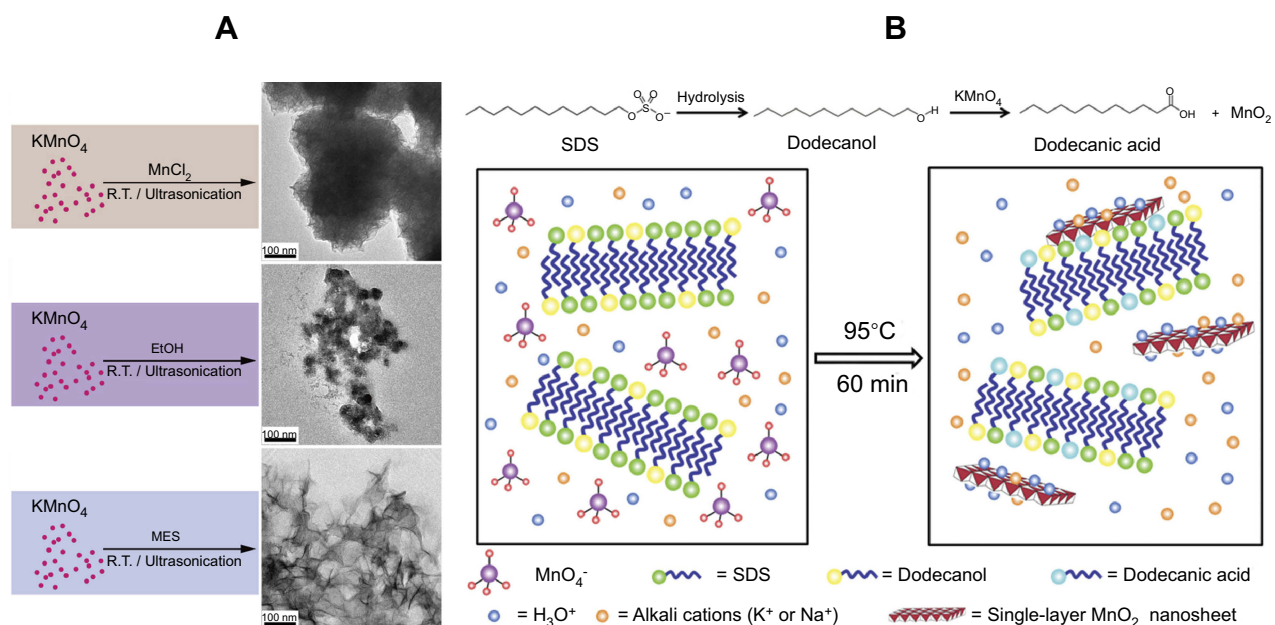


Figure 2 (A) Schematic illustration for the control experiments of reductants employed in the growth of MnO_2 nanomaterials at ambient temperature (left) and TEM characterization of the corresponding products (right). Reprinted with permission from Deng R, Xie X, Vendrell M, Chang Y, Liu X. Intracellular glutathione detection using MnO_2 -nanosheet-modified upconversion nanoparticles. *J Am Chem Soc.* 2011;133(50):20168–20171.²⁸ Copyright 2011 American Chemical Society. **(B)** Schematic illustration for MnO_2 NS formation based on the KMnO_4 and SDS reaction. Reprinted with permission from Liu Z, Xu K, Sun H, Yin S. One-step synthesis of single-layer MnO_2 nanosheets with multi-role sodium dodecyl sulfate for high-performance pseudocapacitors. *Small.* 2015;11(18):2182–2191.²⁹ Copyright © 2015, John Wiley and Sons.

As a nanozyme: biocatalysis based on MnO_2 NSs

In recent decades, nanotechnology and biochemistry have flourished, including artificial materials with multiple applications.^{7,50,51} Certain nanomaterials possess enzymatic-like profiles and substrate specificities, which are commonly called “Nanozymes”. Despite the substrate specificities of nanozymes rarely being as high as those of natural enzymes,

their multiple active sites favor more efficient and steady catalytic activity. Additionally, owing to their tunable structures, their related properties can be controlled and optimized.^{52,53} Furthermore, compared with natural enzymes, nanozymes are more compatible with specific environments, such as high temperatures, and low or high pH conditions.⁵⁴ These features give rise to their promising applications in a variety of fields.

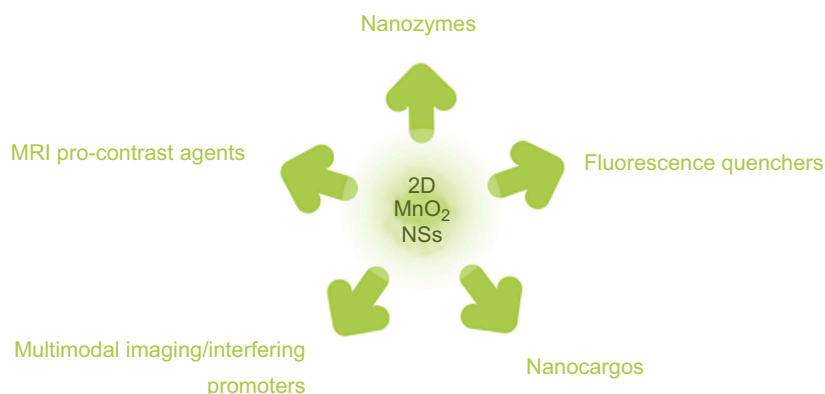


Figure 3 Schematic illustration of the diverse roles MnO₂ NSs have played in the field of biomedicine.

Nanozymes, mainly comprising carbon,^{55,56} metal,^{57,58} and metal oxide,^{59,60} mimic the functionality of natural enzymes, but have different structures. Amongst them, 2D nanomaterials,⁶¹ with ultralarge surface areas and flexible structures, enable their excellent catalytic activity and can be incorporated into the surrounding environment to improve substrate specificity. For instance, graphene oxide has been confirmed to possess intrinsic peroxidase-like activity in the presence of hydrogen peroxide (H₂O₂),^{62,63} so as to ultrathin graphitic carbon nitride (g-CN)^{64,65} and molybdenum disulfate nanosheets (MoS₂ NSs),⁶⁶ which are only pragmatic for use as *ex-vivo* or *in vitro* substrates. MnO₂ NSs, a typical 2D nanomaterial, also possess intrinsic oxidase-like activity. In 2012, Liu and Wang et al. employed 3,3',5,5'-tetramethylbenzidine (TMB) as a tracer to test this property.⁶⁷ The oxidation of the pale yellow-

colored substrate (TMB) to the blue-oxidized product (ox-TMB) indicated the catalytic activity of the MnO₂ NSs. Based on this, Liu and colleagues have developed a selective, rapid, and reliable colorimetric assay for the determination of GSH because GSH can further lead to a concentration-dependent reduction of ox-TMB and a proportional decrease in the absorption at ca. 650 nm (Figure 4A).⁶⁸ Notwithstanding their utilization as a group of nanozymes with oxidase activity, MnO₂ NSs can also act as indirect DNA partzymes to some extent. Recently, Zhao et al fabricated a MnO₂ NS-powered target/probe Janus protected DNA nanomachine to achieve RNA imaging. In this DNA machine, the MnO₂ NSs were utilized as both promoters for the cellular uptake of DNA and generators of Mn²⁺ as indispensable DNAzyme cofactors, ensuring the efficiency of catalytic cleavage (Figure 4B).⁶⁹

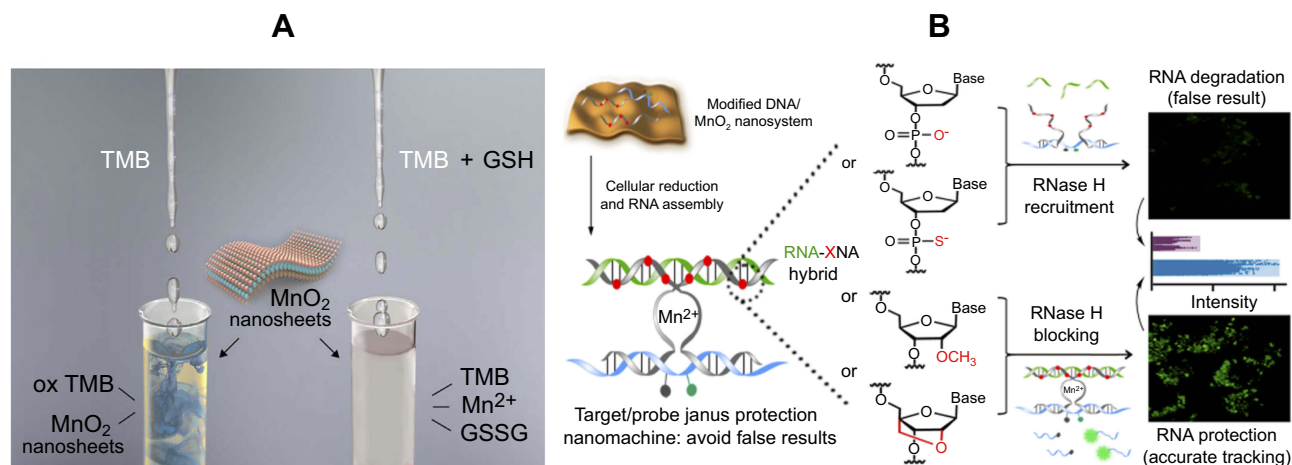


Figure 4 (A) Illustration of the MnO₂ NS-based colorimetric assay for GSH quantification, where the MnO₂ NSs acted as an oxidase-like nanozyme for the formation of ox-TMB and GSSG. Reprinted from *Biosensors and Bioelectronics*, 90, Liu J, Meng L, Fei Z, Dyson P, Jing X, Liu X. MnO nanosheets as an artificial enzyme to mimic oxidase for rapid and sensitive detection of glutathione, 69–74, Copyright (2017), with permission from Elsevier.⁶⁸ (B) Schematic design of the Janus protected DNA nanomachine, where miRNA-21 is employed as a model cellular RNA target (green sequence), the red X denotes DNA, PS (phosphorothioate)-DNA, 2'OMe (methylation)-DNA and LNA (locked nucleic acid) monomers, which are highlighted in the DNA partzymes (gray sequences). Reprinted with permission from Chen F, Bai M, Zhao Y, Cao K, Cao X, Zhao Y. MnO₂ nanosheet-powered protective janus DNA nanomachines supporting robust RNA imaging. *Anal Chem*. 2018;90(3):2271–2276.⁶⁹ Copyright 2018 American Chemical Society.

As a quencher: fluorescence sensing based on MnO₂ NSs

The use of 2D nanomaterials with light harvesting and/or electron-conducting capacities has emerged as a promising nanoplatform for biological and/or chemical sensing based on the fluorescence resonance energy transfer (FRET), photoinduced transfer mechanisms, etc.^{70,71} Fluorescence or Förster resonance energy transfer (FRET) is a mechanism delineating nonradiative energy transfer⁷² from a luminescent donor to an energy acceptor in proximity (ie, 1–10 nm) mediated by dipole-dipole coupling.^{73,74} Due to its high sensitivity and suitability for homogeneous detection, FRET has been universally utilized in a variety of fields, eg, microscope,⁷⁵ immunoassay,^{76,77} nucleic acid hybridization^{78–81} and macromolecule interactions.^{82,83} As a 2D nanomaterial as well as an ultrathin semiconductor, MnO₂ NSs exhibit a broad and intense absorption band at ca. 374 nm,²⁴ making them as an efficient broad-spectrum quencher, which is resulted from the d–d transitions of manganese ions in the ligand field of the edge-sharing MnO₆ octahedral crystal lattice.²⁴ The use of MnO₂ NSs as fluorescence quencher can mainly be ascribed to two aspects: their broad and intense absorption band at ca. 374 nm and the break-up of the NSs structure with the reduction of MnO₂ into Mn²⁺. Ji et al designed a multifunctional nanosystem, CaO₂/MnO₂@polydopamine-methylene blue (MB) nanosheets (CMP-MB), where the fluorescence of MB was suppressed by the MnO₂ NS. Once exposed to a tumor microenvironment, the MnO₂ NSs could decompose into Mn²⁺, which triggered the emission of MB fluorescence. Hence, switch-controlled tumor cell imaging was achieved.⁸⁴ Xia et al. found that the MnO₂ NS mediated quenching effect can be reversed via the reduction of MnO₂ into Mn²⁺ by ascorbic acid (AA), resulting in MnO₂ NS destruction. Based on this, they developed a carbon dot (CD)-MnO₂ nanocomposite for the determination of ALP with help from the hydrolysis of 2-phosphate (AAP) into AA. Utilizing the CD-MnO₂ nanocomposite as a sensing probe, a label-free fluorescent switching strategy for detecting ALP activity was realized with a limit of detection (LOD) of 0.4 U/L.⁸⁵ In 2015, with the reduction of MnO₂ into Mn²⁺ by GSH, Wang and coworkers employed fluorescent CDs and MnO₂ NSs as an energy donor-acceptor pair to construct a nanoplatform for GSH detection (Figure 5A).⁸⁶ In addition to employing MB and CDs as fluorescence donors, Yan et al fabricated a graphene quantum dot (GQD)-MnO₂ NS-based optical sensing platform for GSH detection (Figure 5B).⁸⁷

Chu and colleagues developed a MnO₂ NS-modified upconversion (UC) nanosystem for sensitive switchable fluorescence detection of H₂O₂ and glucose in blood. The enzymatic cleavage and unification of glucose by glucose oxidase (GOx) generated H₂O₂, which was then utilized to reduce MnO₂ to Mn²⁺, similarly to GSH (as depicted by the equation: MnO₂+H₂O₂+2H⁺=Mn²⁺+2H₂O+O₂) (Figure 5C).⁸⁸

In addition to sensing relatively more tractable and visible substances, such as GSH and H₂O₂, MnO₂ NSs can also be utilized for tracking RNAs even at very low levels. As is well-known, miRNAs can regulate gene expression by promoting the degradation or inhibition of the translation of target messenger RNAs (mRNAs) in epigenetics,^{89–91} thereby playing momentous roles in cell differentiation,^{92–95} proliferation,⁹⁶ tumorigenesis,^{97,98} metastasis,^{99,100} apoptosis,⁹⁸ autophagy^{101,102} and many other biochemical processes. Despite quantitative determination of various miRNAs being accomplished by traditional detection strategies, eg, PCR and northern blot, these previously developed methods possess unavoidable costs and are time-consuming as well as having sensitivity limiting shortcomings. Therefore, recent alternatives have incorporated a variety of signal amplification approaches such as nanomaterials,^{80,103–106} enzymes,¹⁰⁷ electrochemical¹⁰⁸ or electrochemiluminescent¹⁰⁹ transduction fashion to detect target miRNAs with both high selectivity and high sensitivity. In 2017, Xiang and colleagues reported a biodegradable MnO₂ NS-based hybridization chain reaction (HCR) strategy to determine miRNA expression even at exceedingly low levels in living cells.¹¹⁰ They designed two hairpins which were separately labeled with the organic dyes FAM (as a FRET donor) and Tamra (TMR, as a FRET acceptor) and loaded onto MnO₂ NSs. Thereafter, once entering living cells, the hairpins would be released because of the displacement responses as well as the degradation of the MnO₂ NSs by intracellular GSH. Then, miRNA-21 in living HeLa cells triggered the hairpins to convene into double-stranded polymers, resulting in prominent amplification of the FRET signal for the determination of trace levels of miRNA-21 in living cells (Figure 6).¹¹¹ It is anticipated that this inspiring work might open up new opportunities for monitoring multiple trace-level RNA species in living cells with greater accuracy, sensitivity and integrity.

Finally, the applications of various MnO₂ NS-based fluorescent biosensors for determining specific targets are

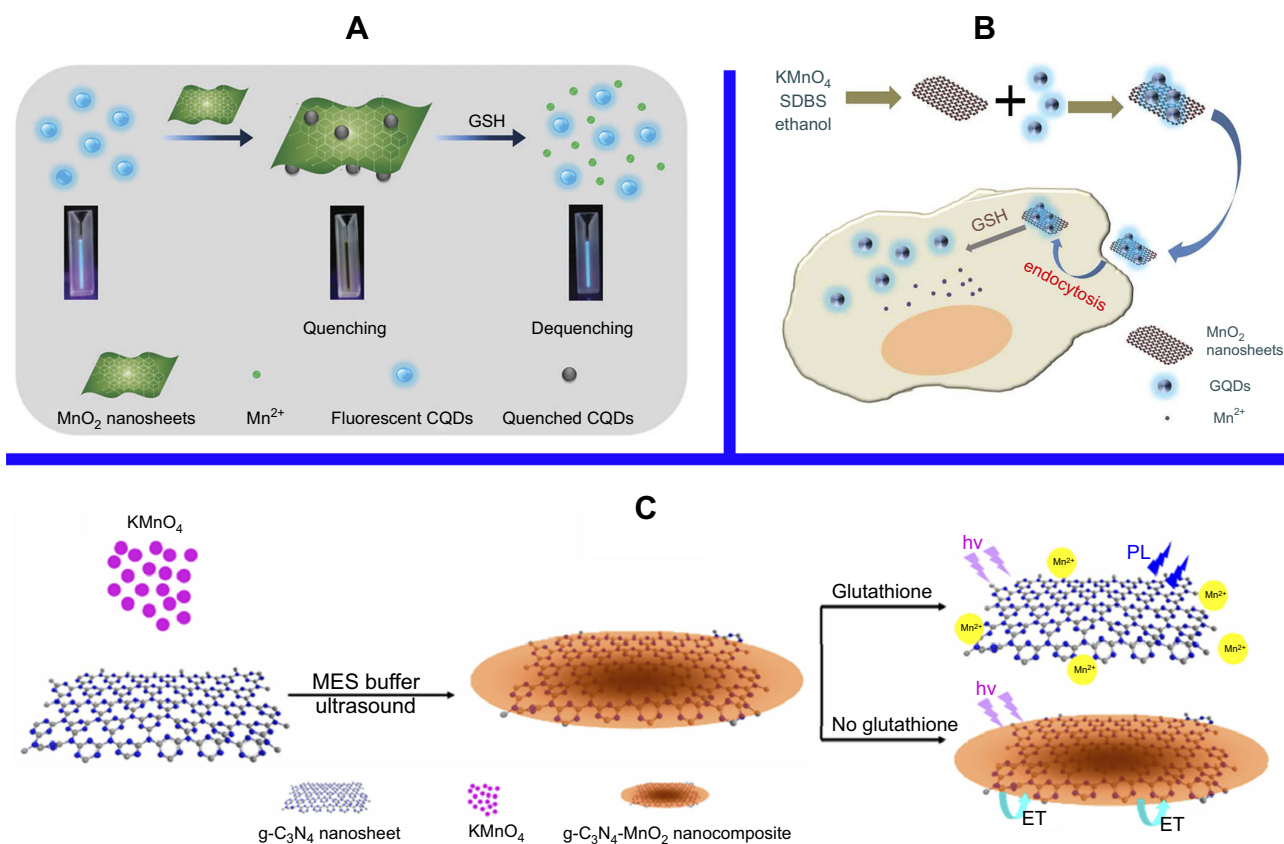


Figure 5 (A) Schematic illustration of the preparation of CDs-MnO₂ NSs and the principle of the FRET-based CD-MnO₂ NSs architecture for GSH sensing. Republished with permission of Royal Society of Chemistry, from A sensitive turn-on fluorescent probe for intracellular imaging of glutathione using single-layer MnO₂ nanosheet-quenched fluorescent carbon quantum dots, He D, Yang X, He X, et al, 51, 79, 2015; permission conveyed through Copyright Clearance Centre, Inc.¹⁷⁰ (B) Scheme for the preparation of MnO₂ NSs and the mechanism of a GQD-MnO₂ NS-based optical sensing nanoplatfor for monitoring GSH in MCF-7 cells. Reprinted with permission from Yan X, Song Y, Zhu C, et al. Graphene quantum dot-MnO₂ nanosheet based optical sensing platform: a sensitive fluorescence “Turn Off-On” nanosensor for glutathione detection and intracellular imaging. *ACS Appl Mater Interfaces*. 2016;8(34):21990–21996.⁸⁷ Copyright 2016 American Chemical Society. (C) Schematic illustration of a g-C₃N₄ NS-MnO₂ NS sandwich-like nanocomposite for GSH sensing. Reprinted with permission from Zhang X, Zheng C, Guo S, Li J, Yang H, Chen G. Turn-on fluorescence sensor for intracellular imaging of glutathione using g-C₃N₄ nanosheet-MnO₂ sandwich nanocomposite. *Anal Chem*. 2014;86(7):3426–3434.¹⁵¹ Copyright 2014 American Chemical Society.

listed in Table 2, and their different values for the limits of detection (LODs) as well as the linear concentration ranges of the corresponding targets are mentioned.

As a nanocarrier for controlled drug delivery: cargo-loading functionality based on MnO₂ NSs

As mentioned above, MnO₂ NSs, with extremely large SMRs, exhibit a wide range of distinctive physicochemical properties compared with their bulk composition. One of most typical biomedical applications of MnO₂ NS, is drug delivery due to their large SMRs. Moreover, distinct from conventional drug delivery systems (DDSs), MnO₂ NS-based nanoplatforams can function as controlled or on-demand DDSs. The controlled drug delivery systems (c-DDSs) for current medications have received increasing interest from numerous chemists and

clinical physicians owing to their low toxicities, broad therapeutic windows and ideal administrative efficacies compared with conventional DDSs.^{117–121} On-demand DDSs triggered by intrinsic physiological microenvironment changes (eg, pH,¹²² redox agents,^{123,124} enzymes,¹²⁵ and heat^{126,127}) and/or external artificially introduced stimuli^{128,129} (eg, light,¹³⁰ laser pulses,¹³¹ magnetic/electronic fields,¹³² and ultrasonication¹³³) can simultaneously diminish the side-effects of anticancer agents toward normal tissue to improve the therapeutic effects. Previous reports on DDSs have mainly focused on nanocomposites, such as magnetic composites and upconversion nanoparticles, and most of them have been magnetically functionalized mesoporous materials or hollow spherical particles with the drugs being released via changes in the pH or temperature.^{121,134–137} For the use of MnO₂ NSs as controlled drug delivery nanocarriers, two main

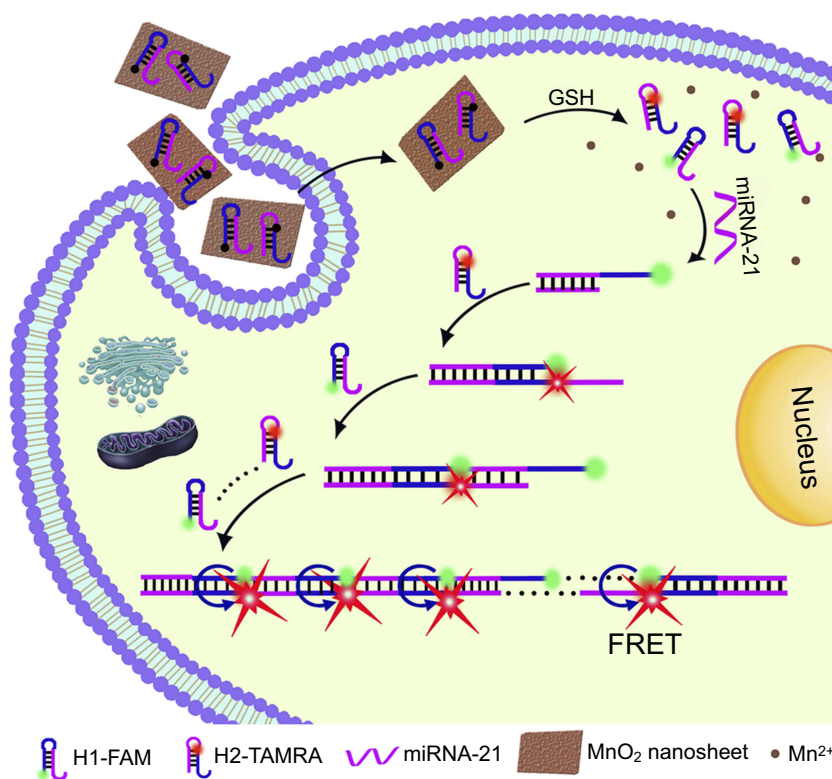


Figure 6 Schematic illustration of the MnO₂ NS-mediated intracellular-hybridized chain reaction (HCR) signal amplification system for efficiently detecting miRNA-21 in living HeLa cells. The MnO₂ NSs could deliver two types of hairpin DNA probes into the cytosol. Overexpressed glutathione (GSH) in HeLa cells and displacement reactions by other proteins or nucleic acids promoted the decomposition of the MnO₂ NSs to release free hairpins, which assembled into double-stranded (dsDNA) polymers upon binding to the target miRNA-21. Subsequently, enhanced FRET signals were produced to realize accurate and sensitive detection. Reprinted with permission from Li J, Li D, Yuan R, Xiang Y. Biodegradable MnO₂ nanosheet-mediated signal amplification in living cells enables sensitive detection of down-regulated intracellular MicroRNA. *ACS Appl Mater Interfaces*. 2017;9(7):5717–5724.¹¹¹ Copyright 2017 American Chemical Society.

properties are beneficial: a large specific surface area and a sensitive response to the tumor microenvironment. In 2013, Zhao et al proposed a novel and facile strategy for the fabrication of multifunctional nanocomposites with silica-coated Fe₂O₃ particle cores and NaYF₄:Yb, Er shells, on which MnO₂ NSs were further grown for delivery and release of a model drug, Congo red (CR). In this nanosystem, the MnO₂ NSs served not only as carriers for the loading and release of CR *in vitro* but also as efficient quenchers for the UC luminescence to monitor intracellular GSH concentration (Figure 7).¹³⁸ The drug was released upon reduction of MnO₂ to Mn²⁺ by GSH, while simultaneously increasing the UC luminescence. The fabricated nanocomposite is a promising platform due to its GSH-stimulated smart drug delivery and UC luminescence monitoring. Indeed, the nanocarrier functionality of MnO₂ NSs has rarely been applied individually and has always been combined with other pragmatic components, eg, fluorescence quenchers and magnetic resonance imaging (MRI) probes, which will be mentioned below.

As an MRI pro-contrast agent: stimuli-activated imaging based on MnO₂ NSs

MRI was originally known as nuclear magnetic resonance (NMR)¹³⁹ imaging and belongs to a configuration of NMR, albeit the “nuclear” employed in the acronym was omitted to avoid negative associations with the word. Certain atomic nuclei are capable of absorbing and releasing radiofrequency (RF) energy in the presence of an external magnetic field. Hydrogen atoms are typically applied to boost the detectable RF signals which can be received by antennas in proximity to the corresponding anatomy for examination. By altering the parameters of the pulse sequence, different degrees of contrast may be generated between tissues based on the relaxation properties of their hydrogen atoms.^{140,141} Compared with other imaging modalities, the main advantage of MRI is its superb spatial resolution whereas its major drawback is the limited sensitivity. As such, chemistry and materials science research has focused on searching for solutions capable of solving this challenging hurdle.¹⁴² The introduction of contrast

Table 2 Fluorescent biosensors based on MnO₂ NSs

Nanomaterials	Targets	Linear response concentration	Limit of detection (LOD)	Reference
CDs-MnO ₂ NS architecture	GSH	0.2–600 μM	22 nM	86
CDs-MnO ₂ nanocomposite	ALP	1–100 U/L	0.4 U/L	85
CQDs-MnO ₂ nanocomposite	GSH	0.01–200 μM	0.01 μM	170
GQDs-MnO ₂ nanoplatform	GSH	0.5–10 μM	150 nM	87
g-C ₃ N ₄ -MnO ₂ nanosandwich	GSH	200–500 μM	N/A	151
MnO ₂ NS-UCP nanosystem	GSH and H ₂ O ₂	0–250 and 250–400 μM	3.7 μM	88
MnO ₂ NS-UCP nanosystem	L-lactic acid	50–400 and 450–800 μM	10 μM	88
MnO ₂ NS-FAM +TMR hairpins	miRNA-21	100–250 nM	100 nM	111
MnO ₂ NS label-free platform	Mercury(II) (Hg ²⁺)	0–20 n M	0.8 nM	112
MnO ₂ NS label-free platform	Ochratoxin (OTA)	0.02–2 nM	0.02 ng/mL	113
MnO ₂ NS label-free platform	Cathepsin (Cat D)	1–100 ng/mL	N/A	113
MnO ₂ NS-7-hydroxycoumarin	Ascorbic acid	0.5–40 μM	0.09 μM	114
MnO ₂ NS-7-hydroxycoumarin	GSH	1–25 μM	300 nM	68
MnO ₂ NS & ligand-DNA FP	Silver ions (Ag ⁺)	30–240 nM	9.1 nM	115
Ru(BPY) ₃ @MnO ₂ nanoprobe	GSH	0–300 μM	420 nM	157
MSNs-G@MnO ₂ NSs	GSH	100 nM to 10 μM	34 nM	116
MnO ₂ NS-cascade logic circuit	GSH	20–2,000 nM	6.7 nM	152

Abbreviations: CD, carbon dot; GSH, glutathione; NS, nanosheet; GQD, graphene quantum dot.

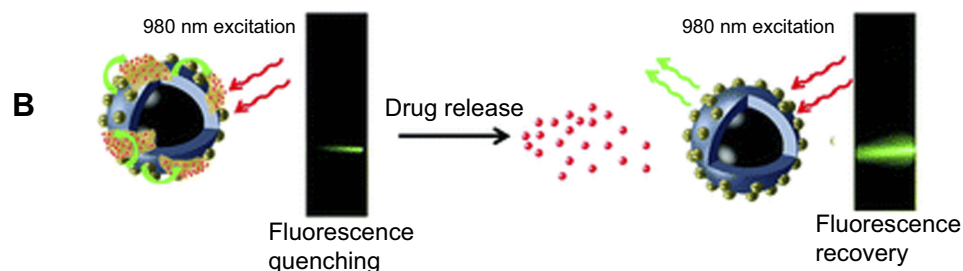
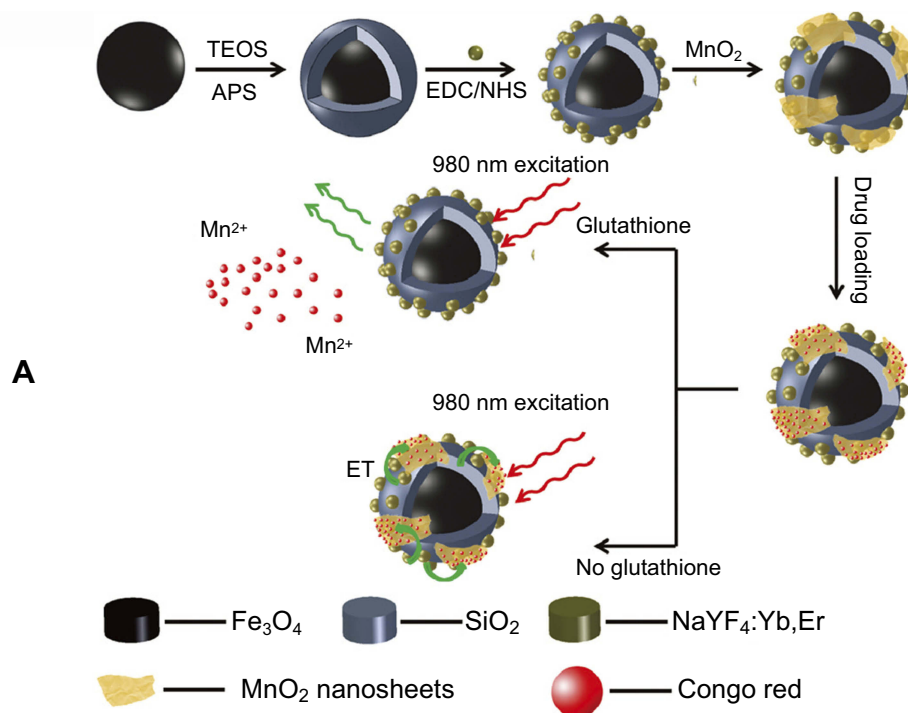


Figure 7 (A) Schematic illustration of the synthetic procedure for the preparation of the MSU/MnO₂-CR drug delivery system. (B) Images of the MSU/MnO₂-CR system before and after drug delivery under 980 nm excitation. Republished with permission of Royal Society of Chemistry, from Multifunctional MnO₂ nanosheet-modified Fe₃O₄@SiO₂/NaYF₄:yb,Er nanocomposites as novel drug carriers, Zhao P, Zhu Y, Yang X, et al, 43, 2, 2014; permission conveyed through Copyright Clearance Centre, Inc.¹³⁸

agents (CAs) has been the main solution. Paramagnetic complexes comprising metal ions with symmetric electronic ground states, eg, gadolinium (Gd³⁺)¹⁴³ and manganese (Mn²⁺),¹⁴⁴ have been successfully applied as MRI CAs since the late 1980s¹⁴⁵ in virtue of their outstanding capabilities to decrease the longitudinal relaxation time T₁ of water protons dipolarly interacting with the unpaired electrons of the metal ions. Manganese-based oxides have been demonstrated as alternative CAs for T₁-weighted MRI, with relatively improved biocompatibilities and cytotoxicities, to replace the clinically widespread gadolinium-based CAs, which have been warned by US Food and Drug Administration (FDA) due to the correlation between gadolinium and nephrogenic systemic fibrosis, kidney dysfunction, etc.^{146–149} The Mn

atoms in MnO₂ nanosheets are coordinated in an octahedral geometry to six oxygen atoms and shielded from aqueous environments, making no contribution to the longitudinal or transverse relaxation of the protons.¹⁵⁰ As Zhang and co-workers reported, the relaxation rate (r₁ value) of initial PEG-MnO₂ NSs was very low (0.007 mM⁻¹ s⁻¹), which was ascribed to the high valence (IV) of manganese and the shielded paramagnetic centers being inaccessible to water molecules.¹⁵¹ Upon disintegration and degradation, the released Mn²⁺ gives rise to a highly improved T₁-MRI performance because of the five unpaired 3d electrons and the enhanced accessibility of the paramagnetic centers to the surrounding water molecules. As illustrated by Zhang et al, the longitudinal relaxivity r₁ and transverse relaxivity r₂,

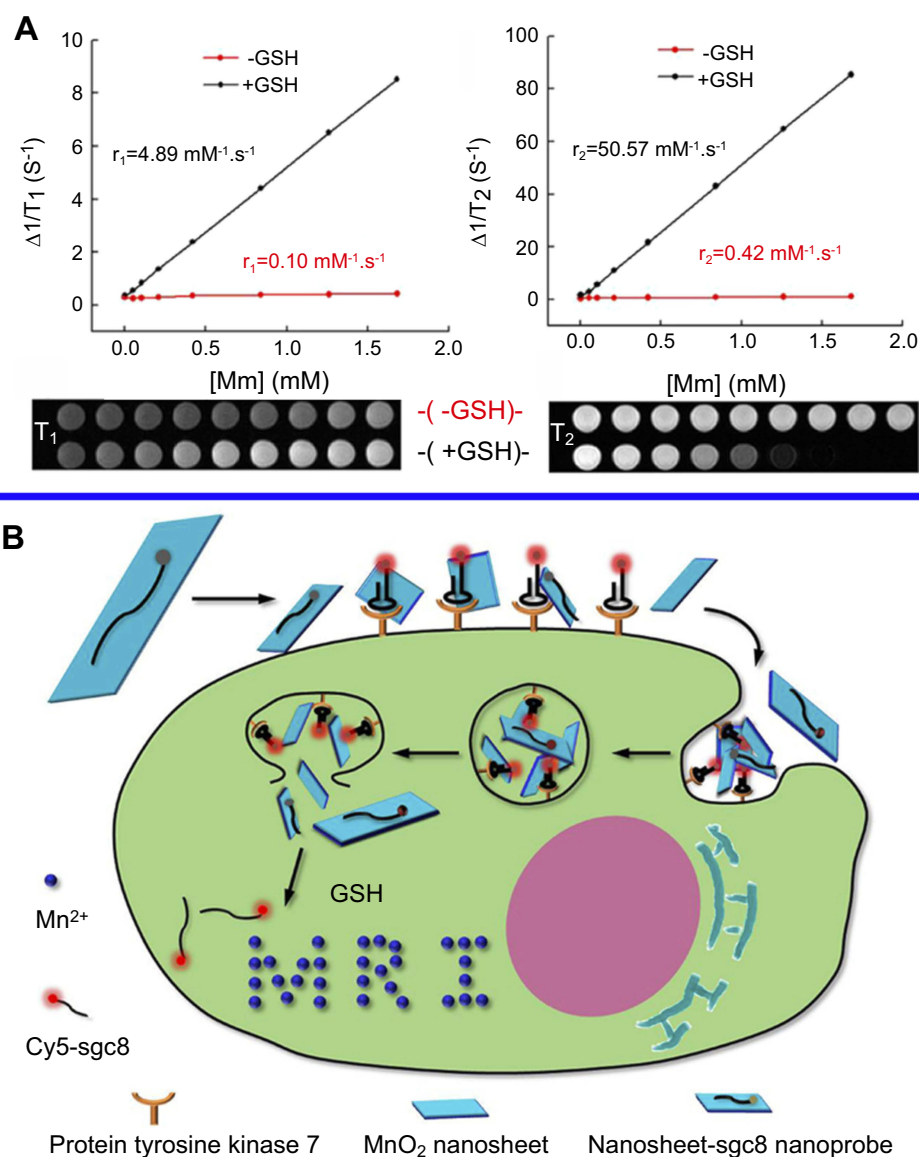


Figure 8 (A) Determination of the T_1 (left) and T_2 (right) relaxation rates of a MnO_2 nanosheet solution (red lines) and MnO_2 nanosheet solution treated with GSH (black lines). The related T_1 -weighted and T_2 -weighted MRI images were presented below. **(B)** Schematic illustration of the activation mechanism of the MnO_2 NS-aptamer nanoprobe for fluorescence/MRI bimodal tumor cell imaging. Reprinted with permission from Zhao Z, Fan H, Zhou G, et al. Activatable fluorescence/MRI bimodal platform for tumor cell imaging via MnO_2 nanosheet-aptamer nanoprobe. *J Am Chem Soc.* 2014;136(32):11220–11223.¹⁵⁰ Copyright 2014 American Chemical Society.

obtained by measuring the relaxation rate as a function of Mn concentration, exhibited a 48- (from 0.1 to $4.89 \text{ mM}^{-1} \text{ s}^{-1}$) and 120-fold (from 0.42 to $50.57 \text{ mM}^{-1} \text{ s}^{-1}$) enhancement, respectively, when the MnO_2 NSs were reduced to Mn^{2+} by GSH (Figure 8A).¹⁵⁰ The decomposition of MnO_2 NSs in the tumor microenvironment (GSH-activated^{152,153} or pH-dependent^{154,155}) to release Mn^{2+} can be utilized for tumor cell MR imaging. Wang and Shi's group in 2014, presented an intriguing achievement with their report on an intelligent theranostic platform based on highly disperse 2D MnO_2 NSs for concurrent ultrasensitive pH-responsive MRI and drug delivery/release.¹⁵⁶

In addition to MRI, MnO_2 NSs have shown promising potential for the fabrication of dual-activatable fluorescence/MRI bimodal platforms. In 2014, Tan and coworkers designed a redox-capable MnO_2 NS-aptamer nanoprobe for multimodal imaging of tumor cells (Figure 8B).¹⁵⁰ In this platform, the MnO_2 NSs played three roles as a DNA nanocarrier, fluorescence quencher and intracellular GSH-activated MRI CA. Upon encountering the target cells, the binding of the aptamer to the corresponding target weakened the absorption of the probe on the NSs and produced a fluorescence recovery as well as aptamer-mediated endocytosis. The intracellular GSH further reduced the MnO_2

NSs into a large amount of Mn^{2+} suitable for MRI. Using a similar principle, a MnO_2 NS-Ru(II) complex nanoarchitecture, $Ru(BYP)_3@MnO_2$ ($BYP = 2,2'$ -bipyridine) has also been developed for determining GSH in vitro and in vivo.¹⁵⁷

Despite the multimodal imaging applications of MnO_2 NSs in conjunction with their fluorescence and MR imaging, many exploits have been attempted to accomplish theranostic applications (ie, imaging and killing at the same time). Notably, the PEG- MnO_2 NSs reported by Wang and colleagues in 2014 promoted ultrasensitive pH-triggered concurrent diagnostic and therapeutic functionalities (designated as theranostics) for cancers, which provided a novel and facile platform for concurrent ultrasensitive pH-stimulated T_1 -weighted MRI and anti-tumor drug (doxorubicin, Dox) release (Figure 9).¹⁵⁶ The pH-triggered rapid decomposition of 2D MnO_2 NSs in a mildly acidic microenvironment could facilitate the controlled release of delivered anticancer agents and circumvent the multidrug resistance of cancer cells by bypassing the typical P-glycoprotein (P-gp)-induced efflux process with MnO_2 NSs due to their larger size than free Dox molecules.¹⁵⁸

MnO_2 NSs themselves can be used not only as nanocarriers for drug delivery, but also as therapy agents. Recently, Xiaoyuan Chen and colleagues at the National Institute of Health (NIH) reported that the construction of MnO_2 -based nanoagents can augment the efficiency of CDT (Figure 10).²¹ CDT utilizes iron-initiated Fenton chemistry to kill tumor cells via the conversion of endogenous H_2O_2 into hydroxyl radicals ($\cdot OH$), which have a high toxicity, inducing intracellular oxidative stress.^{159–162} To date, a number of iron-carrying nanoparticles have been employed as CDT agents to induce ferroptosis¹⁶³ in tumor cells via H_2O_2 -dependent Fenton-like reaction.^{164–167} As envisaged, the overproduction of GSH in tumor cells ought to be one of the most formidable hurdles for the CDT effect in that GSH serves as a scavenger of the highly reactive $\cdot OH$ generated by chemodynamic agents, thereby increasing the resistance of cancer cells to oxidative stress and diminishing the efficacy of CDT.^{168,169} Chen et al was the first time to report that MnO_2 , which possesses both Fenton-like Mn^{2+} delivery and GSH depletion capabilities, could play a role as a novel chemodynamic agent in order to improve the CDT of cancer via simultaneously disrupting the antioxidant system and loading an $\cdot OH$ generator into cells. Ultimately, they utilized MnO_2 NSs to successfully construct an activatable theranostic nanosystem for an MRI-monitored chemodynamic combination regimen.²¹

In conclusion, as an MRI CA, MnO_2 NSs can produce an activatable MRI signal upon the degradation of their structure in the tumor microenvironment, favoring the improvement of the signal-to-noise ratio and specificity. Additionally, benefitting from the high surface area, fluorescence quenching ability and CDT ability of MnO_2 NSs, MRI-based theranostic platforms and multimodal imaging nanoproboscopes can be easily fabricated with the help of MnO_2 NSs, which undoubtedly broadens the applications of MRI.

Taken together, MnO_2 NSs have displayed promising potential in multiple modalities for the diagnosis, treatment and theranostics of tumors in vitro and in vivo.

Toxicity evaluation of MnO_2 nanosheets (MnO_2 NSs)

With the widespread use of MnO_2 NSs in a range of biomedical applications, their toxicological assessment both in vitro and in vivo is extremely important. Nonetheless, there are still a limited number of toxicity studies on MnO_2 NSs especially in vivo. MTT assays and cell counting kit-8 (CCK-8) assays are two commonly employed methods to assess the toxicity of MnO_2 NSs in various cells. Herein, we present the main cytotoxicity testing results of various nanomaterials based on MnO_2 NSs. He et al developed a single-layer MnO_2 NS-quenched fluorescent carbon quantum dots, and their nanosystem exhibited no apparent cytotoxicity at the concentrations of 30 $\mu g/mL$ or less when exposed to HeLa human cervical carcinoma cells for 24 hrs.¹⁷⁰ Similarly Yan et al reported of GQD- MnO_2 NS based optical sensing nanoplat-form and confirmed that this nanomaterial had low toxicity even at a concentration of 40 $\mu g/mL$, toward MCF-7 breast adenocarcinoma cells.⁸⁷ Zhang et al have reported that their graphitic- C_3N_4 NS- MnO_2 sandwich-like nanocomposite displayed no apparent loss in cell viability even at a 50 $\mu g/mL$ exposure to HeLa cells.¹⁵¹ Recently, corresponding cytotoxicological assessments of MnO_2 NS-based nanosystems in HeLa and MCF-7 cells were carried out by the Xiang group,¹¹¹ Chen and coworkers⁶⁹ and Shi and colleagues.¹⁵⁷ They all reported excellent biocompatibilities and insignificant viability losses as listed in Table 3. It is also remarkable that the effort of Zhao et al to fabricate MnO_2 NS-aptamer nanoproboscopes early in 2014 verified that 79% of CCRF-CEM and Ramos human B lymphoma cells remained alive following by exposure to their nanoproboscopes at a concentration of 1 mM for 24 hrs.¹⁵⁰

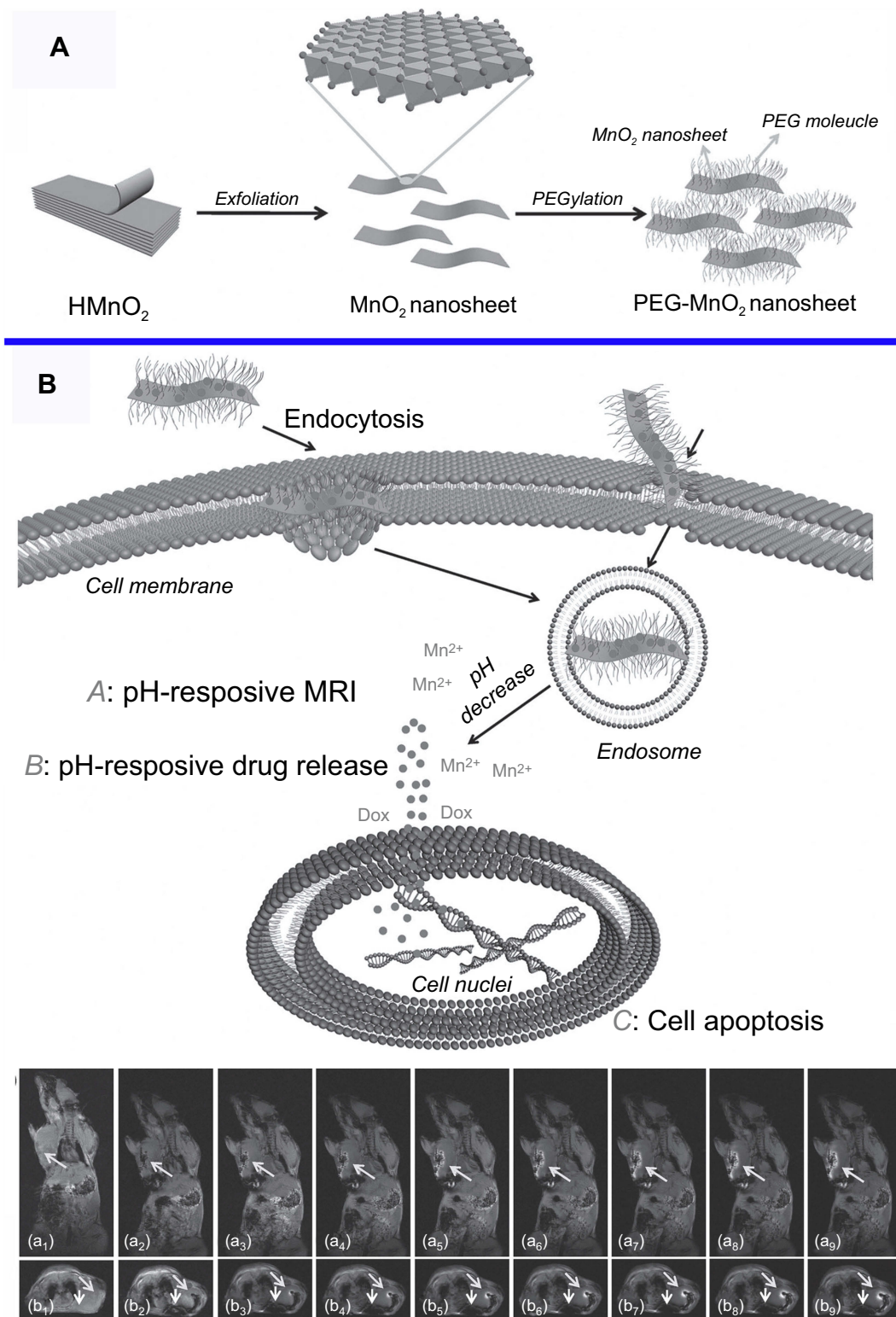


Figure 9 (A) Schematic illustration of the synthetic procedure for the PEG-MnO₂ NSs. (B) Theranostic functionality of the PEG-MnO₂ NSs for intracellular pH-responsive drug release and the axial and coronal T₁-MRI images of 4T1 tumor-bearing nude mice before (a₁, b₁) and after (a₂ – a₉ and b₂ – b₉) administration of the PEG-MnO₂ nanosheets within the tumor and normal subcutaneous tissue. PEG denotes ethylene glycol. Reproduced with permission from Chen Y, Ye D, Wu M, et al. Break-up of two-dimensional MnO₂ nanosheets promotes ultrasensitive pH-triggered theranostics of cancer. *Adv Mater Weinheim*. 2014;26(41):7019–7026. ¹⁵⁶ Copyright © 2014, John Wiley and Sons.

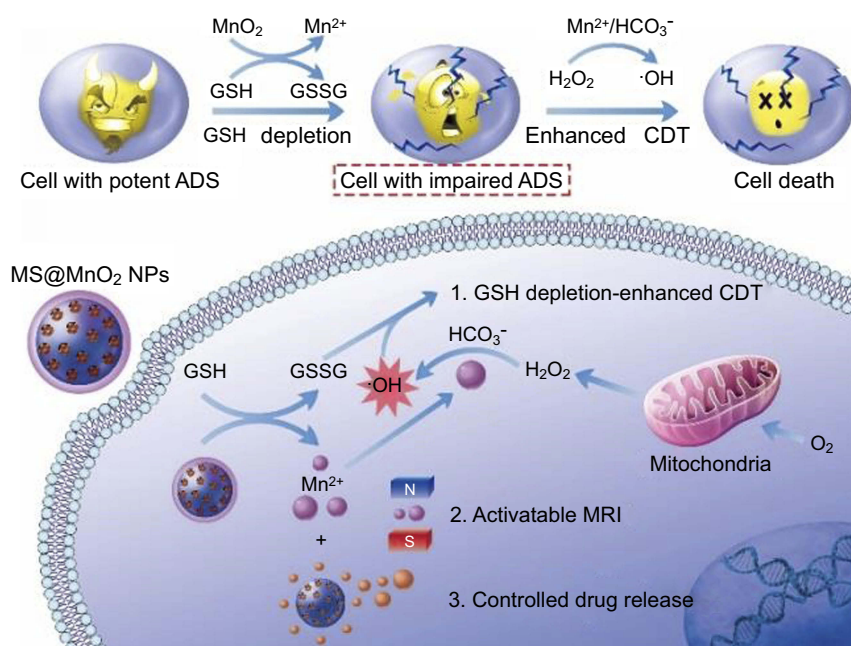


Figure 10 Schematic illustrations of the mechanism and application of mesoporous silicon (MS)@MnO₂ NPs for MRI-monitored chemo-chemodynamic combination therapy. Reproduced with permission from Lin L, Song J, Song L, et al. Simultaneous fenton-like ion delivery and glutathione depletion by MnO₂-based nanoagent to enhance chemodynamic therapy. *Angew Chem Int Ed Engl.* 2018;57(18):4902–4906.²¹ Copyright © 2018, John Wiley and Sons.

Conclusion and perspectives

Over the last few decades, research on the synthesis and biomedical applications of MnO₂ NSs has thrived and seen impressive advancements. In this review, first of all, we highlighted the state-of-the-art strategies that have been developed for the preparation of MnO₂ NSs by top-down or bottom-up methods. Notwithstanding, in contrast to other 2D nanomaterials, the top-down approach of MnO₂ NS synthesis is obviously costly and time-consuming. Moreover, it is fairly difficult to completely exfoliate the protonated compounds completely into single-layer NSs (monosheets), thus, previously obtained NSs have always had a wide thickness distribution in practice. The bottom-up strategies, comprising the oxidative and the reductive methods, have been widely utilized widespread. MnO₂ NSs can be facilely prepared via the reduction of KMnO₄ in the presence of an MES buffer at pH 6 or through the oxidation of MnCl₂ with oxidants, eg, H₂O₂ in the coexistence of TMA·OH as summarized above. Numerous reductants can be selected, and the synthetic process for MnO₂ NSs is tunable. Although many intriguing methods have been developed in this inspiring research field, it is still urgent to develop new facile and effective methods for the synthesis of high-quality MnO₂ NSs.

Then, we provided an overview of the main applications of MnO₂ NSs in biomedicine. MnO₂ NSs can play multiple roles as nanozymes, nanocargos, fluorescence quenchers and activatable MRI probes. Hitherto, almost all of the reported biomedical applications have been based on these four fundamental functionalities and their roles are not dichotomies towards each other. Numerous researchers have focused on integrating MnO₂ NSs into multiple modalities to explore increasingly novel uses in biomedicine.

Last but not the least, biosafety is one of the most concerning issues for the use of nanomaterials in biomedical employments before end-point clinical translation, despite the knowledge of the toxicity for MnO₂ NSs are still very preliminary and limited. Therefore, the toxicity of MnO₂ NSs should be systematically and comprehensively validated, especially in vivo. In addition, several intermediate metabolites accumulate in living organisms and cannot be easily degraded or detoxified, resulting in long-term toxicity issues, which should be further considered.

In the future, for MnO₂ NS-related research, the biosafety should be considered first. Thus, green synthetic approaches are preferred for obtaining MnO₂ NSs with controllable thicknesses, sizes and morphologies. The biomedical applications of MnO₂ NSs have experienced markedly rapid advancement over the last few

Table 3 Cytotoxicity results of various nanomaterials based on MnO₂ NSs

Nanomaterials	Cell lines	Response, maximum exposure concentration, and duration	Testing assays	Reference
CQDs-MnO ₂ NS	Hela	No apparent loss of cell viability, 30 µg/mL, 24 hrs	MTT	170
GQDs-MnO ₂ nanoprobe	MCF-7	Low cytotoxicity, 40 µg/mL, 24 hrs	MTT	87
g-C ₃ N ₄ -MnO ₂ nanosandwich	Hela	No apparent loss of cell viability, 50 µg/mL, 24 hrs	CCK-8	151
MnO ₂ NS-FAM + TMR hairpins	Hela	Insignificant viability loss, 86% alive, 60 µg/mL, 24 hrs	MTT	111
MnO ₂ NS-FAM + TMR hairpins	MCF-7 & HepG2	Low cytotoxicity, 90 µg/mL, 24 hrs	MTT	171
MnO ₂ NS-janus DNA machine	MCF-7	Good biocompatibility, 100 µg/mL, 24 hrs	MTT	69
MnO ₂ NS-apptamer nanoprobe	CCRF-CEM and Ramos	79% of cells remained alive, 1 mM, 24 hrs	MTS	150
Ru(BPY) ₃ @MnO ₂ nanoprobe	Hela	The viabilities remained higher than 87%, 160 µM, 24 hrs	MTT	157
MnO ₂ NS-"DD-A" binary probe	HepG2	Low cytotoxicity, 90 µg/mL, 24 hrs	MTT	172

Abbreviations: CCK-8, cell counting kit-8; NS, nanosheet; GQD, graphene quantum dot.

decades. However, the targets are relatively limited. Extra attention should be paid to integrating proper targeting aptamers/antigens/antibodies especially those that play important roles in cancer cell signaling pathways with MnO₂ NSs. This will help to improve both the performance of biosensors and the efficacy of cancer theranostics based on MnO₂ NSs. Furthermore, additional applications of MnO₂ NSs such as PTT and imaging-guided combination therapy, should be considered to broaden their biomedical applications. As envisaged optimistically, the MnO₂ NSs will provide promising opportunities for the realization of more advanced medical imaging. We also believe that this review may entice other scientists in multiple disciplines to join into this new but growing research field.

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Disclosure

The authors report no conflicts of interest in this work.

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