

New advances of nanozymes for the diagnosis and treatment of digestive system diseases (Review)

DAIHAN XIE^{1*}, LIXIN XIE^{1*}, CHAO FANG^{1*}, ZHEFEI DU¹, ZHENYU CAO¹, CHUNXIA SU¹ and YU HUO²

¹Department of Comprehensive Oncology Center, Shanghai Pulmonary Hospital, Tongji University Medical School Cancer Institute, School of Medicine, Tongji University, Shanghai 200433, P.R. China; ²Faculty of Chinese Medicine Science, Guangxi University of Chinese Medicine, Nanning, Guangxi 530222, P.R. China

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Abstract. Despite the significant progress that has been made in the diagnosis and treatment of digestive system diseases, these conditions continue to pose a serious public health concern worldwide. There is an ongoing need for strategies that are precise, efficient and minimally invasive. Nanozymes, engineered nanomaterials that exhibit catalytic functions, have attracted considerable interest in this context. However, clinical application of nanozymes remains limited primarily due to their diversity, targetability, biocompatibility and early-stage clinical translation. The present review presented a comprehensive analysis of nanozymes in digestive system diseases. The main enzyme-like activities of nanozymes are summarized to guide further material selection and characteristic exploration. Preclinical applications are highlighted with mechanisms and theranostic effects discussed alongside their potential limitations. Emerging combination therapies, including photodynamic therapy, sonodynamic therapy and biotherapy, are reviewed. Finally, the current challenges of nanozymes and possible future developments are discussed.

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1. Introduction

Digestive system diseases are a substantial burden on contemporary society, contributing to over one-third of all reported cases (1). These conditions arise from complex mechanisms, including mucosal damage, genetic susceptibility, inflammatory response, immune dysregulation, gut microbiota dysbiosis and motility or secretory dysfunction in organs (Fig. 1) (2-5). Notable examples include gastric ulcers, liver damage, pancreatitis, inflammatory bowel disease (IBD) and tumors (1).

Diagnosing and treating digestive system diseases remain challenging. Some diagnostic methods lack the sensitivity needed for early detection (6). Although invasive procedures such as endoscopy and biopsy are valuable, they can be distressing for patients (7,8). Current treatments may suffer from poor efficacy and notable side effects (9-11). There is a pressing demand for more precise, efficient and less invasive diagnostic techniques, as well as novel therapeutic strategies tailored to the complexity of digestive system diseases.

In recent years, the biomedical community has increasingly turned its attention to nanomaterials, owing to their unique properties. Nanomaterial-based imaging and biosensing have enabled precise diagnosis (12-16). Furthermore, nano-drug delivery systems allow targeted delivery to specific tissues, effectively overcoming the limitations of conventional therapies (17,18). The concept of 'nanozyme' was originally introduced by Pasquato and Scrimin in 2004 (19). It now specifically refers to nanomaterials that emulate the catalytic behavior of natural enzymes (20). These synthetic enzyme mimics have been employed across a wide range of disciplines (21-23). Compared with natural enzymes, nanozymes have several advantages, including lower production costs, adjustable catalytic activity and greater structural stability (24-26). Although research on nanozymes for

Correspondence to: Professor Yu Huo, Faculty of Chinese Medicine Science, Guangxi University of Chinese Medicine, 13 Wuhe Avenue, Nanning, Guangxi 530222, P.R. China
E-mail: huoyu_10@163.com

Professor Chunxia Su, Department of Comprehensive Oncology Center, Shanghai Pulmonary Hospital, Tongji University Medical School Cancer Institute, School of Medicine, Tongji University, 507 Zhengmin Road, Shanghai 200433, P.R. China
E-mail: susu_mail@126.com

*Contributed equally

Abbreviations: CAT, catalase; GPx, glutathione peroxidase; NIR, near-infrared; ROS, reactive oxygen species; SOD, superoxide dismutase; PDT, photodynamic therapy; POD, peroxidase; PTT, photothermal therapy; RNS, reactive nitrogen species; SDT, sonodynamic therapy

Key words: cancer, diagnosis, digestive system disease, nanozyme, treatment

digestive system diseases is still at a relatively early stage, the growing number of studies highlights the emerging promise in this field.

Given the limited reviews on nanozymes in digestive system diseases, the aim of the present review was to provide a comprehensive analysis of their applications in diagnosis and treatment (Fig. 2). It also explores the unique advantages of nanozymes. Additionally, the current review explores the prospects and challenges of nanozymes in this field and offers insights into their potential value.

2. Enzyme-like activities of nanozymes in digestive system diseases

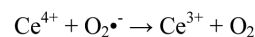
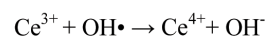
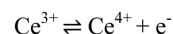
In 2014, Lin *et al* (27) proposed a structural-based classification system for nanozymes: Metal-based, metal oxide-based, carbon-based nanomaterials and other nanomaterials. As more nanozymes have emerged, researchers have shifted to classifying nanozymes by the types of enzymatic reactions they catalyze. The new classifications (24,26) are: i) Oxidoreductase-like family which includes oxidases, peroxidases (PODs), superoxide dismutases (SODs) and catalases (CATs) among others (Fig. 3); ii) hydrolase-like family which includes nucleases, proteases, phosphatases and esterases. This revised classification enhances our understanding of the potential applications of nanozymes in digestive system diseases. In the present review, an overview of the catalytic activities of nanozymes is provided.

Oxidase-like activity. In 2004, Comotti *et al* (28) reported that gold nanoparticles without a supporting matrix catalyze the oxidation of glucose to gluconate under mild conditions. However, their practical applicability was limited by their short lifespan. The catalytic mechanism involved the formation of electron-rich gold species through interactions between hydrated glucose anions and gold surface atoms, which subsequently activated molecular oxygen via nucleophilic attack. It has been proposed that intermediates such as Au^+-O_2^- or $\text{Au}^{2+}-\text{O}_2^{2-}$ function as electron transfer mediators (29). Clinically significant substrates include glucose, uric acid and ascorbic acid, which are used in the biosensing applications of nanozymes (30-32). A notable example involves the functionalization of MoO_3 nanoparticles with dopamine as a surface ligand and triphenylphosphonium as a mitochondrial localization agent. This design enabled the selective catalytic oxidation of sulfite to sulfate within the mitochondrial environment. The positive cooperative behavior of modified MoO_3 nanoparticles was confirmed by the Km and Hill coefficient, demonstrating activity comparable to goat and human sulfite oxidases (33). Some oxidase-like nanozymes generate H_2O_2 during reactions, which can enable H_2O_2 -mediated cascade reactions (34-36). These nanozymes hold promise for diagnosing and treating digestive system diseases.

POD-like activity. Natural PODs use heme as a cofactor to catalyze substrate oxidation using H_2O_2 as an electron acceptor. Gao *et al* (37) first reported that Fe_3O_4 nanoparticles exhibited POD-like activity, following a ping-pong mechanism. Since then, a wide range of nanomaterials including metals, metal oxides, metal-organic frameworks

and carbon-based systems have been investigated as POD mimetics (38-41). Most POD-like nanozymes decompose H_2O_2 into hydroxyl radicals ($\bullet\text{OH}$), which subsequently oxidize substrates such as 3,3',5,5'-tetramethylbenzidine, terephthalic acid and Trinder's reagents (42-44). Certain nanozymes exploit elevated H_2O_2 concentrations in tumor microenvironments to generate $\bullet\text{OH}$ species, initiating oxidative damage selectively in malignant tissues (45,46). V_2O_5 nanowires, studied by Vernekar *et al* (47), have been shown to exhibit GPx-like behavior, effectively neutralizing reactive oxygen species (ROS) while maintaining cellular redox homeostasis. Understanding these catalytic mechanisms will help identify suitable applications for POD-like nanozymes.

SOD-like activity. Superoxide can cause harmful oxidative stress in excess (48,49). SOD plays a key physiological role by converting superoxide radicals into oxygen and hydrogen H_2O_2 , a process further detoxified by CAT (50,51). Multivalent metal ions such as $\text{Fe}^{2+}/\text{Fe}^{3+}$, $\text{Mn}^{2+}/\text{Mn}^{3+}$ and $\text{Ce}^{3+}/\text{Ce}^{4+}$ are essential for this reaction (52-55). Nanoscale CeO_2 , with increased surface area and oxygen vacancies, exhibits SOD-like activity. These structural features, along with lattice defects, enable CeO_2 nanoparticles to regenerate, reducing the need for repeated administration compared to antioxidants such as vitamin C (56). The equations below describe this free radical scavenging mechanism, while a more comprehensive one was proposed by Celardo *et al* (57). Notably, the surface $\text{Ce}^{3+}/\text{Ce}^{4+}$ ratio is a determinant of catalytic performance, with higher Ce^{3+} content being associated with enhanced SOD-like function (58).



Fullerenes are recognized for their antioxidant and neuro-protective capabilities, but their water insolubility poses a challenge (59). Ali *et al* (60) addressed this with a tris-malonic acid derivative of fullerene C60 (C3), which scavenges superoxide radicals at a rate of $2 \times 10^6 \text{ mol}^{-1} \text{ s}^{-1}$. Semiempirical quantum-mechanical calculations indicated that the region around malonic acid groups on C3 had the least electron distribution, attracting superoxide anions. Two $\text{O}_2^{\bullet-}$ radicals were successively combined and dismutated in the presence of protons. The SOD-like activity of C3 is associated with the number and spatial arrangement of surface-exposed carboxyl groups on their surface (61). In addition to fullerenes, metals and their compounds such as Pt, Mn and Cu have also been found to exhibit SOD-like activity (62-64).

CAT-like activity. CAT, a natural enzyme localized primarily within cellular peroxisomes, facilitates the rapid breakdown of H_2O_2 into water and molecular oxygen. Kajita *et al* (65) synthesized gold and platinum bimetallic nanoparticles as potential CAT mimics. In recent years, numerous nanozymes that emulate CAT activity have been developed and reported (66-68). These nanozymes can mitigate oxidative stress-induced inflammation by decomposing H_2O_2 and, at the same time, help alleviate hypoxia within tumor tissues, thereby supporting cancer therapy (69).

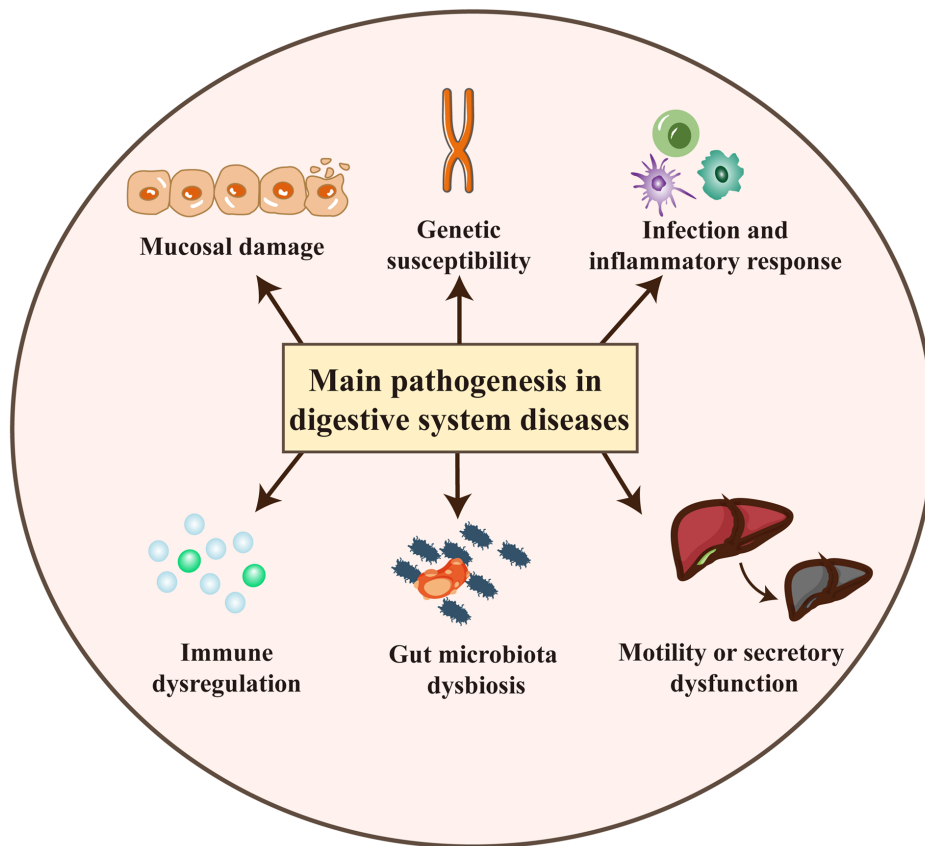


Figure 1. Main pathogenesis in digestive system diseases.

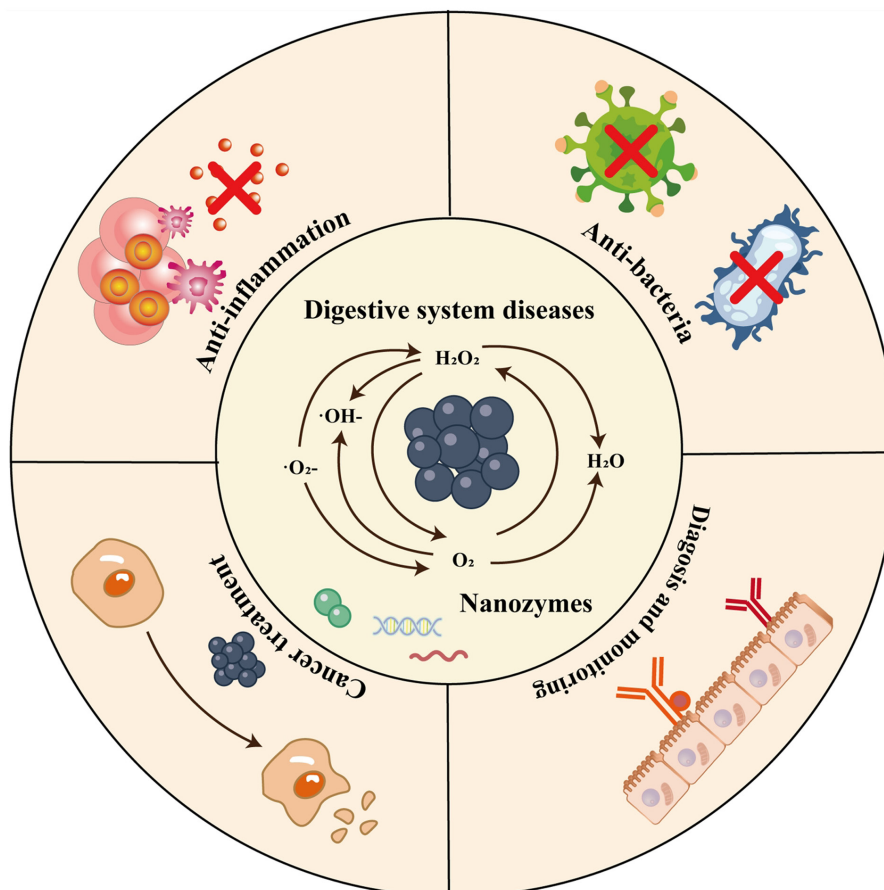


Figure 2. Representative application of nanozymes in digestive system diseases.

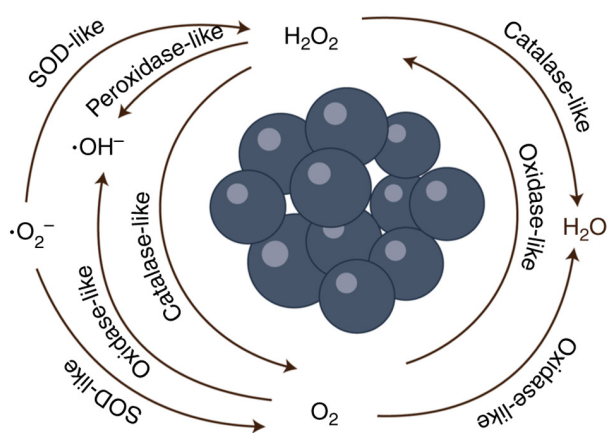


Figure 3. Oxidoreductase-like activity of nanozymes. SOD, superoxide dismutase.

Despite extensive investigation, the mechanistic underpinnings of CAT-like nanozyme catalysis remain incompletely understood. The decomposition of H_2O_2 by these nanozymes can occur via homolytic or heterolytic catalysis. In heterolytic catalysis, the nanozymes preferentially cleave the H-O bond in H_2O_2 , while in homolytic catalysis, the O-O bond is more readily broken (70).

Other enzyme-like activities. Redox reactions are only part of the enzymatic spectrum in biology. Exploring enzyme-like activities beyond redox enzymes expands the range of reactions nanozymes can regulate. Nanoparticles with hydrolytic, esterase and photolyase activities have been reported, suggesting the potential for nanozymes to catalyze a broader range of reactions in the future (71-73).

3. Application of nanozymes in digestive system diseases

The digestive system facilitates ingestion, breakdown, absorption, transportation and production of digestive enzymes and secretions, while interacting with intestinal microbiota (74-76). Its unique pH variations support efficient catalytic activity of nanozymes. The significant surface area and microstructures of the stomach and intestines enhance contact with nanozymes (77). Due to prolonged exposure, the digestive system is biocompatible, reducing immune reactions to nanozymes, making it ideal for their application (78).

Esophageal cancer. The prognosis for esophageal cancer is generally unfavorable. In cases without metastasis, the 5-year survival rate range is 20-35% (79). Radiation therapy, which damages DNA in tumor cells to control tumor growth and metastasis, faces challenges such as inadequate X-ray energy deposition, tumor microenvironment hypoxia, upregulated antioxidant systems and DNA repair proteins in tumor cells (80-83). Developing radiosensitizers and optimizing treatment strategies are essential to improve radiation therapy efficacy. Combinations of therapies are currently used for resistant tumors but often fall short at a fundamental level (84).

Zhou *et al* (85) developed a nanoparticle of multifunctional covalent organic framework named triiodide-modified covalent organic framework with ferrocene (Fc), which contains

iodine atoms and Fc functional groups. Iodine facilitated localized radiation dose deposition and promoted the generation of ROS, while Fc exhibited enzyme-like activities, leading to lipid peroxidation and iron deposition, reversing radiation resistance and disrupting redox homeostasis. Fc was identified as a potential radiosensitizer for resistant tumors (Fig. 4). To tackle radiation resistance stemming from the enhanced expression of antioxidant systems and DNA repair proteins within cancer cells, Zhou *et al* (86) designed a radio-sensitization strategy using high-Z elements, incorporating a GDY- CeO_2 nanoparticle enzyme and microRNA-181a. This combination exhibited CAT-mimicking capabilities. It relieved tumor hypoxia, augmented radiation-induced DNA damage and functioned as a radiosensitizer. This was achieved through targeting RAD17 and modulating the Chk2 pathway. Additionally, there has been significant interest in intelligent phototherapy nanotherapeutic systems. Liu *et al* (87) introduced a BSA- MnO_2 /IR820@carboxylated carbon nanocages nanoparticle loaded with efficient photosensitizers, demonstrating CAT-like activity and enabling near-infrared (NIR) imaging for photothermal therapy (PTT) and photodynamic therapy (PDT) implementation.

In recent years, nanozymes have shown great promise in the diagnosis of esophageal cancer. For instance, POD-mimicking nanozymes have been successfully employed in immunohistochemical staining to enhance the visualization of esophageal tumors, offering faster and more robust color development than natural enzymes (88). Moreover, the integration of targeting ligands has allowed for enhanced recognition of early esophageal lesions (89). In addition, a carbon nanocage-based nanozyme system activated by endogenous H_2O_2 has been developed to generate oxygen within the tumor microenvironment, enabling magnetic resonance imaging (MRI) and fluorescence bimodal imaging (87).

However, there are potential drawbacks in treating esophageal cancer with nanozymes. Current development of nanozymes involves complex synthesis and functionalization, incorporating multiple substances, which increases costs and limits scalability. The distinct mucosal structure and function in esophageal tissue are able to influence the adsorption, dispersion and bioactivity of nanozymes. Additionally, the rapid transport of food through esophageal peristalsis reduces the time that orally administered drugs remain in the esophagus, influencing drug release and absorption (90). Further investigation is required to ascertain the effectiveness of nanozymes in specifically targeting the deeply located lesions within esophageal cancer. It is also necessary to define their role in preventing both local recurrence and distant metastasis.

Gastric diseases. Gastric diseases, including gastritis, ulcers and cancer, have a high global incidence (91). A major pathological factor is *Helicobacter pylori*, a microaerophilic, spiral-shaped bacterium (92,93). Standard quadruple therapy faces limitations due to the acidic environment of the stomach and effect on symbiotic bacteria (94). Nanozyme offers a novel approach to address these challenges.

Zhang *et al* (95) synthesized a pH-responsive graphitic oxidase-like nanozyme (PtCo@G@CPB), which is made to selectively target and combat *H. pylori* without disrupting intestinal microbiota. The oxidase-like activity of PtCo@G

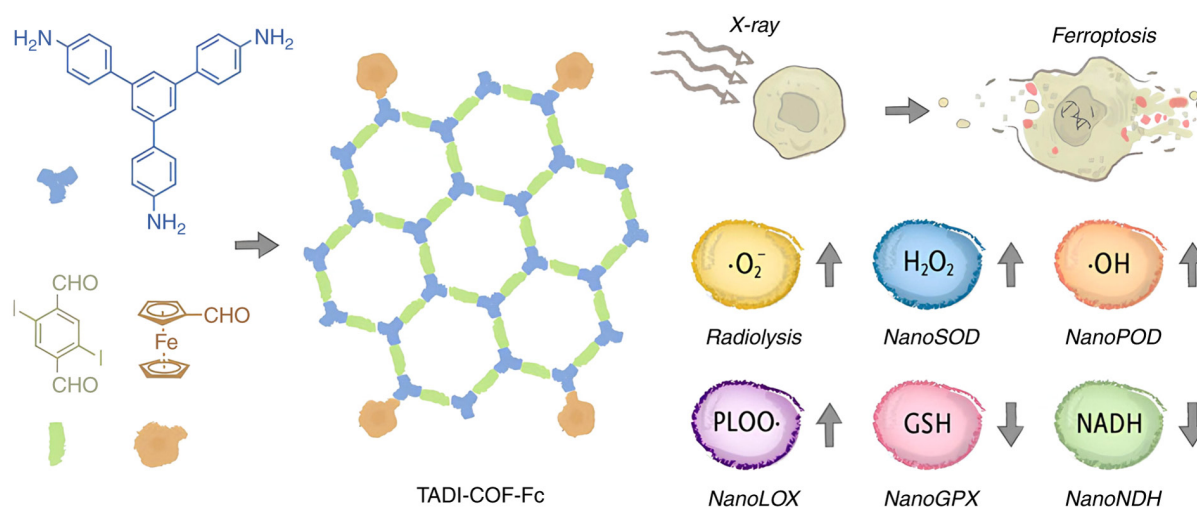


Figure 4. Illustration of the synthesis process for TADI-COF-Fc and the application of COF-based multi-nanozymes as radiosensitizers. Reprinted with permission from ACS Nano, copyright 2023. GPx, glutathione peroxidase; TADI-COF-Fc, iodine- and ferrocene-loaded covalent organic framework nanozyme; COF, covalent organic framework.

was stably activated under gastric acid conditions (pH 0.9-1.5), producing superoxide radicals from H_2O_2 . These radicals attacked the bacterial membrane, causing cell death. The enzyme activity was inhibited under the neutral conditions of the intestine, minimizing toxicity to normal tissues and commensal bacteria. Although *in vivo* short-term toxicity studies (lasting 6 days) indicated low toxicity levels, there is a dearth of comprehensive investigations regarding the long-term retention toxicity associated with heavy metals (96). Yan *et al* (97) developed a stable, pH-sensitive, persistent luminescence (PL) nanozyme (MSPLNP-Au-CB). It allows for autofluorescence-free long-term and real-time imaging *in vivo* and is aimed at targeted eradication of *H. pylori*. The PL nanozyme platform facilitated bioimaging as well as the treatment of bacterial infections under challenging circumstances.

Nanozymes also have extensive applications in the diagnosis and treatment for gastric cancer, achieving highly efficient tumor treatment by integrating PTT, PDT and nanozyme oxidation (98). Zhang *et al* (99) introduced a nanocomposite material, gold-doped mesoporous carbon spheres (OMCAPs@rBSA-FA@IR780), which exhibited POD-like activity from internally-doped gold nanoparticles that generated ROS, leading to oxidative damage and apoptosis in gastric tumor cells. Additionally, internal incorporation of NIR dye IR780 enabled PTT under 808 nm laser irradiation. A novel DNA-templated Ag@Pd alloy nanocluster (DNA-Ag@Pd NC) was developed with excellent stability *in vitro* and *in vivo*. It exhibited an impressively photothermal conversion efficiency reaching 59.32% and enhanced POD-like activity, enabling highly efficient photothermal-enhanced nanocatalytic therapy for gastric cancer, guided by high-contrast NIR-II photoacoustic (PA) imaging (100).

Recent advances have demonstrated the potential of nanozyme-based platforms in the early diagnosis of gastric diseases. Various strategies have been employed to enhance sensitivity and specificity, including MoS_2 -based nanozymes combined with hybridization chain reactions for microRNA detection and chiral POD-like nanozymes for enantiomer identification in gastric cancer (101,102). Additionally,

dual-functional systems integrating nanozymes with catalytic hairpin assembly or plasmonic surface-enhanced Raman scattering have been applied for the ultrasensitive detection of gastric precancerous lesions and D-amino acid biomarkers in saliva (103,104). These innovations highlight the versatility of nanozymes in molecular sensing and their emerging role in non-invasive and precise gastric cancer diagnostics.

As previously mentioned, the highly acidic environment and unique microbial community in stomach present challenges for nanozyme treatments. Current research focuses on short-term toxicity, lacking comprehensive long-term assessments. It is unclear whether exposure to normal tissues outside the affected area causes irritation, disrupts digestive function, or affects nutrient absorption. Some nanozymes are activated under acidic conditions, but prolonged exposure to low pH levels may cause structural denaturation or deactivation, affecting treatment efficacy. While certain nanozymes selectively eradicate *H. pylori*, more in-depth research is required to comprehend their long-term impact on the microbial community.

Liver diseases. Acute liver injury (ALI) represents a serious condition marked by necrosis of liver cells and impairment of liver function, caused by drug exposure, viral infection and alcohol abuse (105-107). N-acetylcysteine is a common therapeutic drug but has a narrow therapeutic window (108). Nanozymes show potential in ALI diagnosis and treatment. Zhou *et al* (109) designed the ultrasmall gold nanoparticles-tannic acid hybrid nanozyme, SAuPTB, that activated the Nrf2 pathway, offering anti-inflammatory and antioxidant effects. Similarly, Prussian blue nanozymes have shown protective effects on anthracene-induced ALI (110). Xia *et al* (111) demonstrated that reducing ruthenium nanoparticles to 2.0 nm markedly enhanced antioxidant activity and upregulated regulatory T cells. PA imaging is coming as a potent means for imaging intracellular ROS. A ROS-sensitive nanozyme-enhanced PA nanoprobe catalyzes oxygen micro-bubble production in the presence of ROS, amplifying the PA signal and reversing the hypoxic microenvironment

for simultaneous treatment (112). In alcoholic liver injury, current approaches focus on supportive care rather than directly metabolizing excess alcohol (113). Geng *et al* (114) proposed an alcohol detoxification strategy using an alcohol dehydrogenase/CAT/aldehyde dehydrogenase-cascaded nano-reactor (AA@mMOF) for targeted detoxification and ALI management.

Liver fibrosis, which results from chronic liver injury, has the potential to progress to cirrhosis and hepatocellular carcinoma. This process entails the generation of ROS, the activation of hepatic stellate cells (HSCs) and the overproduction of extracellular matrix (115-118). Effective anti-fibrotic methods are limited, with transplantation as the last resort. Addressing excessive ROS generation, Zhang *et al* (119) showed that MoS₂ nanozyme mimicked cellular enzymes and cleared ROS for liver fibrosis treatment. Lu *et al* (120) developed a sequential delivery strategy using a star-shaped nanozyme (Au NS@CAR-HA) loaded with carvedilol to clear ROS, inhibit autophagy and target HSCs for fibrosis treatment.

Nanozymes have garnered attention in liver cancer. While ferrotherapy shows promise, it faces limitations in catalytic efficiency (121,122). Jiang *et al* (123) reported the first hybrid semiconducting polymer nanozyme (HSN). It has augmented catalytic activity when under light irradiation, which combined NIR-II PA imaging with photothermal ferrotherapy to enhance the Fenton reaction, promoting cell apoptosis and ferroptosis. Anticancer mechanism of nanozymes lies mainly in the ROS generation triggered by changes in the metal element oxidation state. Meanwhile, some studies have found that metals with unchanged oxidation states can be explored and developed for catalytic activity. A CaF₂ nanozyme was designed with ultrasound enhanced POD-mimicking activity, inducing mitochondrial dysfunction through calcium-pumping channel regulation, achieving effective antitumor effects in an H22 liver cancer model (124). Metals such as Os, commonly used in battery technologies, have shown potential in cancer treatment. Os-Te nanorods (OsTeNRs) exhibited excellent photothermal conversion and photocatalytic activities (125).

Apart from its therapeutic applications, nanozymes can also be used for the diagnosis of liver diseases. Various nanozyme platforms have been developed to detect key pathological features associated with hepatic disorders, such as elevated ROS, abnormal enzyme activity and specific biomarkers (112,126). For example, POD- and oxidase-mimicking nanozymes have been used for colorimetric and fluorescent detection of alanine aminotransferase and aspartate aminotransferase, which are essential indicators of liver injury (127). Furthermore, nanozymes integrated with imaging modalities such as MRI, PA imaging and chemiluminescence imaging have enabled non-invasive and real-time monitoring of liver fibrosis, hepatitis and hepatocellular carcinoma (128,129). These advances highlight the potential of nanozyme-based diagnostic platforms to improve the accuracy, efficiency and accessibility of liver disease diagnostics.

The liver, essential for metabolism, detoxification and immunity, lacks comprehensive research on nanozyme degradation, clearance and potential functional effects. The immunogenicity of nanozymes and their compatibility with the immune system in liver are also unclear (130). The complex microenvironment in liver, with its pH variations,

redox potential, nutrient concentrations and metabolic byproducts, poses challenges for nanozymes due to inadequate organ-specific targeting, leading to uneven distribution and potential toxicity. Liver diseases involve diverse processes like inflammation and fibrosis. Current research often focuses on specific treatment aspects, highlighting the need for multifunctional nanozymes capable of addressing multiple pathological pathways simultaneously.

Pancreatic diseases. The pancreas is essential for digestion and hormone regulation. Acute pancreatitis (AP) causes severe abdominal pain due to the activation of pancreatic enzymes, leading to tissue damage and systemic inflammation (131-136). Oxidative stress plays a crucial role in AP progression (137,138). Nanozymes, which mimic antioxidant enzymes, present a promising approach for AP treatment (26).

In AP, the triggering of the NF- κ B signaling pathway results in the upregulation of inflammatory cytokines such as IL-1, IL-6 and TNF- α (133,139,140). Xie *et al* (141) reported that Prussian blue nanoclearance agents (PBzymes) effectively neutralize ROS, converting them into harmless H₂O and O₂ (Fig. 5). PBzymes demonstrate significant removal efficiency of $\bullet$ OH and $\bullet$ OOH (59.1 and 41.9% at 30 μ g/ml, respectively), exhibiting intrinsic antioxidant and anti-inflammatory properties through the inhibition of the TLR/NF- κ B signaling pathway. Severe AP (SAP) affects 20-30% of patients, leading to multi-organ damage and high mortality (131). Ferroptosis and oxidative stress are key factors in SAP pathogenesis (142-144). Ca/Fe-based nanozymes have been shown to reduce SAP-related biomarkers and inflammation, increasing GPx4 and FTH1, key factors in ferroptosis and intracellular iron regulation (145). To address potential biocompatibility concerns, Xie *et al* (146) introduced MoSe₂-PVP nanoparticles with high biocompatibility, ROS/RNS clearance, biodegradability and pancreatic accumulation properties.

Pancreatic cancer (PC) poses a severe threat, with a low 5-year survival rate of 8% (147). The low-oxygen tumor micro-environment promotes treatment resistance and malignant progression (148). A wide array of therapeutic strategies, like PTT, PDT, chemo-dynamic therapy and sonodynamic therapy (SDT), have been explored to combat PC. NIR lasers in phototherapy boost the catalytic activity of nanozymes and augment therapeutic effectiveness (113,149). Li *et al* (150) developed a dual-enzyme-mimicking nanozyme (PtFe@Fe₃O₄) with NIR enhancement, showing electron transfer between PtFe nanorods and Fe₃O₄ nanoparticles to boost catalytic activity. NIR laser-triggered POD and CAT-like activity achieved notable 99.8% inhibition of deeply located PC. Kang *et al* (148) presented a ruthenium-tellurium hollow nanorod for combined PDT and PTT in PC treatment, demonstrating excellent performance under UV-vis-NIR laser irradiation. Chen *et al* (151) developed a synergistic treatment platform utilizing ZIF-90 nanoparticles nucleating on platinum nanoparticles. This platform enhanced chemotherapy and SDT by relieving hypoxia, increasing chemotherapy sensitivity boosting ROS and singlet oxygen production under US irradiation, achieving a synergistic strategy between chemotherapy and SDT.

At present, the application of nanozymes in the diagnosis of pancreatic diseases is still limited. Zhang *et al* (152) developed

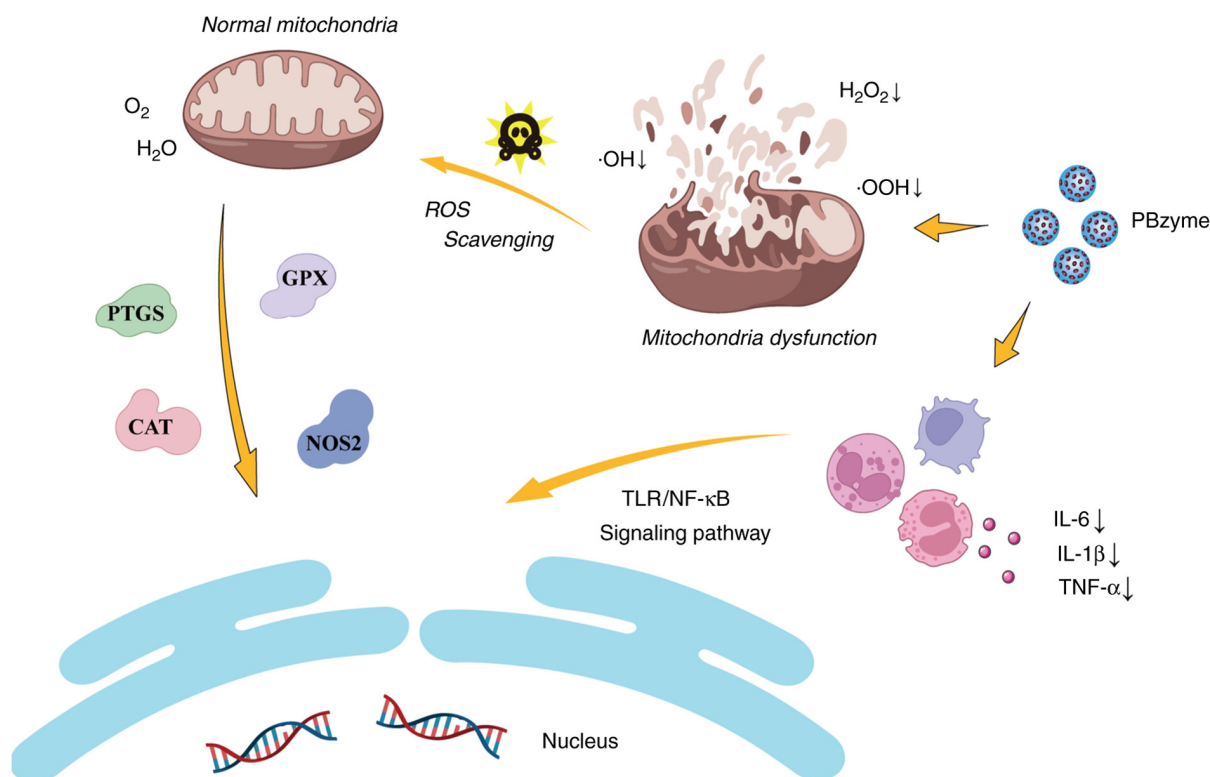


Figure 5. *In vitro* evaluation of ROS scavenging capacity of PBzyme. Adapted with permission from Theranostics, copyright 2021. ROS, reactive oxygen species; PBzyme, Prussian blue nanoclearance agents; GPx, glutathione peroxidase; CAT, catalase; PTGS, prostaglandin-endoperoxide synthase; NOS2, nitric oxide synthase 2.

gemcitabine-loaded carbonaceous nanozymes with POD-like and glutathione POD-like activities, thereby enabling MRI-guided imaging and enhancing diagnostic precision by responding to the tumor microenvironment.

The pancreas, essential for secreting digestive enzymes and hormones like insulin, presents unique challenges for nanozyme therapies. Current treatments may interfere with normal digestive and hormonal functions. PC often involves a hypoxic tumor microenvironment, where traditional nanozymes may be less effective, highlighting the need for design improvements to function in low oxygen conditions.

IBD. IBD, characterized by inflammation, oxidative stress, immune dysregulation and intestinal microbial imbalance, poses complex therapeutic challenges due to the intricate interplay of these factors (153,154). Excessive ROS accumulation in IBD lesions exacerbates the condition by directly damaging intestinal epithelial cells and altering intestinal microbiota composition (155,156). Nanozyme-based strategies targeting ROS have garnered attention as potential treatments for IBD.

Monitoring IBD activity is crucial for treatment evaluation and surgical timing (157). Cerium oxide (CeO_2) nanoparticles have emerged as promising CT contrast agents for gastrointestinal tract imaging. Cao *et al* (158) developed dextran-coated CeO_2 nanoparticles (D- CeO_2) for IBD surveillance. D- CeO_2 exhibited slightly higher CT values compared with iohexol at equivalent concentrations *in vitro*. In murine colitis models, D- CeO_2 enabled extended imaging windows and preferential accumulation at inflamed sites, outperforming iohexol in lesion targeting. Similarly, inulin-coated CeO_2 nanoparticles

(CeO_2 @IN nanoparticles) demonstrated excellent *in vivo* imaging performance, markedly extending the imaging duration by up to 12 h (159). Notably, due to their intrinsic SOD- and CAT-like activities, these nanozymes are capable of scavenging ROS, thereby also contributing to the mitigation of colitis-related tissue damage. In another approach, a BaSO_4 -based imaging platform, BaSO_4 @PDA@ CeO_2 /DSP, was developed to enhance adhesion to inflamed regions. The inherent gastrointestinal stability of BaSO_4 , combined with its functional modifications, offers a promising strategy for IBD diagnosis (160). Deng *et al* (161) introduced a multimodal imaging probe, metal-polyphenol network (MPN@ CeO_x), in which the exposed MPN serves as an MRI contrast agent, enabling MRI-guided diagnosis and potentially facilitating image-guided therapy for colitis. Another innovative approach involves a ROS-targeting nano-sensor, PPNC, designed to release platinum nanoclusters (PtNCs) at inflammation sites. After penetrating the intestinal barrier, PtNCs could be traced in urine through their enzyme-mimicking activity, facilitating non-invasive monitoring (Fig. 6) (162). However, concerns remain regarding nephrotoxicity of platinum derivatives, especially in geriatric populations, highlighting the need for patient-specific approaches despite the non-invasive advantage (163). Additionally, carbon dots (C-dots), owing to their favorable fluorescence properties and stability under inflammation-mimicking conditions have shown promise as imaging agents (164). However, limited differences in biodistribution between healthy and inflamed mice in major organs and the colon suggest that further optimization is required to harness their potential for inflammation-specific imaging.

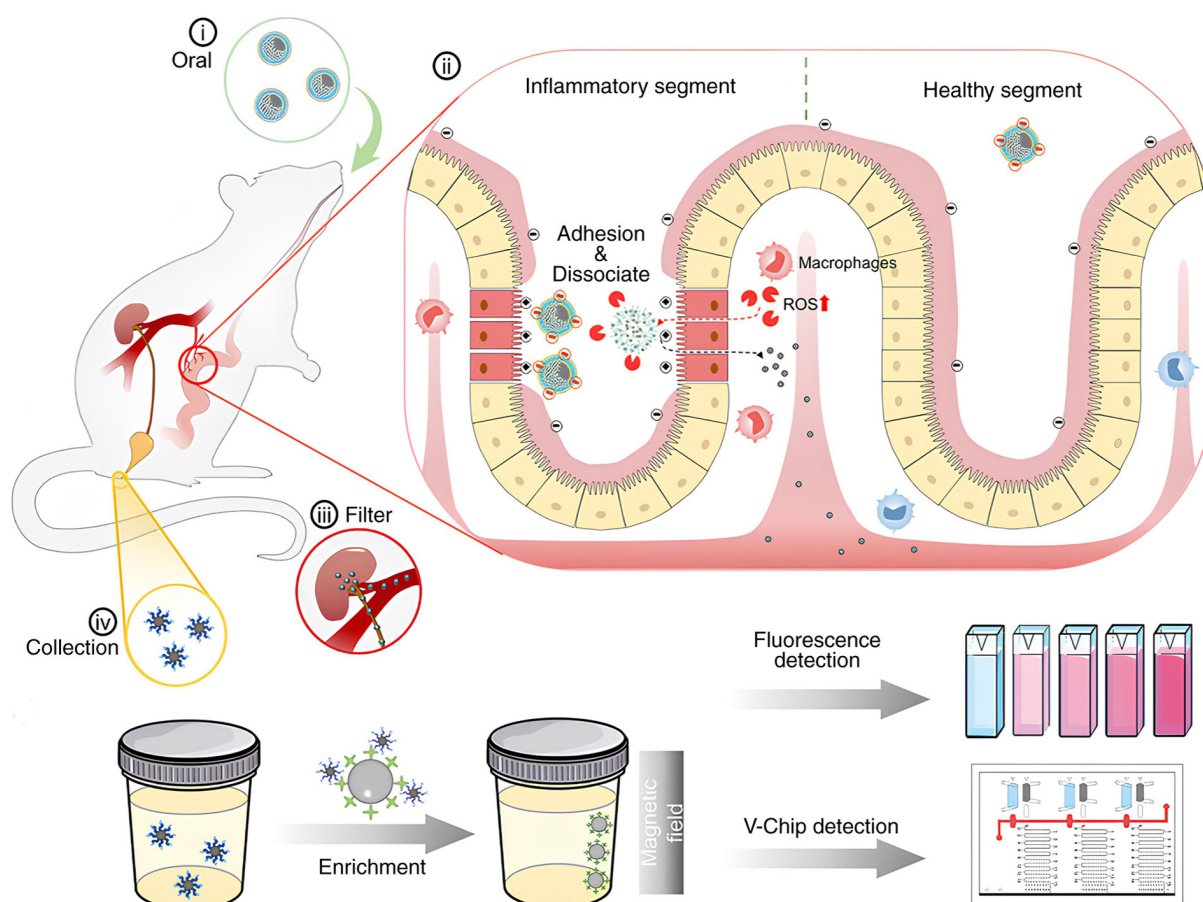


Figure 6. Schematic illustration depicting the detection mechanism of biotin-PtNC. Reprinted with permission from ACS Nano, copyright 2022. PtNC, platinum nanoclusters; ROS, reactive oxygen species.

Nanozymes have been strategically designed for direct therapy in IBD, functioning to neutralize ROS and mitigate inflammation. Zhao *et al* (165) introduced an innovative approach with CeO_2 @montmorillonite (MMT), which combines ROS-scavenging CeO_2 nanoparticles with MMT. The system not only maintains catalytic efficiency, but also minimizes potential intestinal toxicity, exhibiting superior therapeutic outcomes in a mouse model by alleviating symptoms and suppressing inflammatory markers. To tackle the issue of optimizing multiple enzymatic functions within a nanozyme, researchers employed a valence-engineering strategy, using spinel oxide ZnMn_2O_4 as a model. This led to the construction of LiMn_2O_4 , which excelled in various activity assays, including SOD, CAT and GPx further validating its performance in preclinical settings (166). Other nanozyme formulations, such as Pt@PCN222-Mn , Ni_3S_4 and MeNPs , have also been successfully tested in preclinical models for IBD treatment (167-169).

Nanozymes demonstrate synergistic effects in combination therapies, emphasizing the need for well-designed drug delivery systems. One approach involves decorating the anti-inflammatory agent curcumin (CCM) with a Prussian blue analog (CoFe PBA), resulting in a core-shell structure (CCM-CoFe PBA). Under acidic conditions, the interaction between CCM and CoFe PBA weakens due to the disruption of the coordination bond between Fe^{3+} in CoFe PBA and the keto-type structure. This feature facilitates targeted

drug delivery in mildly acidic inflammatory environments, although it may reduce efficacy in the acidic gastric environment. In a DSS-induced colitis mouse model, CCM-CoFe PBA treatment alleviated symptoms, polarized macrophages toward the M2 phenotype and improved the histological structure of the colonic mucosa (170). Cao *et al* (171) developed a single-atom nanozyme modified with *Bifidobacterium longum* (BL) to create a therapeutic system (BL@B-SA₅₀). This hybrid system exhibits both SOD- and CAT-like activities, effectively neutralizing ROS and shielding anaerobic probiotic bacteria from oxidative stress in inflamed intestinal environments. In murine colitis models, treatment with BL@B-SA₅₀ resulted in decreased levels of ROS and pro-inflammatory mediators (IL-6, IFN- γ , MPO), along with a notable elevation of the anti-inflammatory cytokine IL-10. Oral administration of this formulation in a canine model of ulcerative colitis facilitated mucosal repair in the colon, suggesting its translational therapeutic promise. Furthermore, C-dots synthesized from glutathione and biotin through a solvothermal reaction have demonstrated dual functionalities, mitigating colonic inflammation and enabling non-invasive imaging within the gastrointestinal tract (164).

Beyond ROS, RNS also play a role in mediating biomolecular damage in inflamed tissues (172). PEG-coated rhodium nanodots (Rh-PEG NDs) have shown effective scavenging capabilities against both ROS and RNS. In a murine colitis model, Rh-PEG NDs reduced tissue damage, inflammatory

cytokine levels and CD45⁺ cell counts and demonstrated excellent blood compatibility with a hemolysis rate <0.5% (173). Ultrathin trimetallic nanosheets (TMNSs; Ru₃₈Pd₃₄Ni₂₈) feature Ru-O and Ni-O bonds that efficiently clear ROS and RNS, with enhanced activity due to atomic vacancies on the surface. In a DSS-induced colitis model, mice treated with TMNSs showed weight recovery, improved colon length and reduced ROS and inflammatory factors (174).

Nanozymes have shown extensive application in preclinical models for IBD treatment. Enhancing nanozyme efficacy within the intestinal microenvironment remains crucial, necessitating the development of nanozyme therapeutics tailored to different IBD biological subtypes (175,176). Evidence suggests that Fe may worsen ulcerative colitis, while Se and Zn might help prevent its development and the roles of Cu and Mn in ulcerative colitis remain unclear (177,178). Additionally, microplastics and endocrine disruptors from nanozyme synthesis could negatively impact IBD patients (178). A metal-free melanin nanozyme has been proposed to avoid the risks associated with heavy metals (169). Improving synthesis processes and reducing impurities through separation steps are needed to address reagent residue issues.

The high manufacturing and storage costs of precious metal-containing nanozymes limit their clinical use (179,180). Probiotics and algae have ideal living conditions (181,182). While they can treat IBD *in vivo*, preserving probiotic- and algae-based nanozyme systems for large-scale production remains challenging. Gene editing technology might enhance their survival under adverse conditions.

The NF- κ B and JAK-STAT pathways are key targets in IBD treatment with nanozymes (183,184). Novel mechanisms, such as inhibiting T-cell differentiation and disrupting neutrophil extracellular traps, have been proposed to alleviate IBD symptoms (185,186). Enhancing nanozyme selectivity for inflammatory loci is crucial. Current strategies, such as absorption by charge or pH in the lesion sites, do not fully align with precision medicine. Ma *et al* (187) developed a macrophage membrane-coated nanozyme system with CRISPR/Cas9 to reduce CD98 expression. Future research should focus on precisely targeting disease sites with nanozyme systems.

Colon cancer. Colon cancer, a prevalent malignancy in the digestive system, involves a multistep and multigenic disorder (188). There is a strong link between IBD and the onset of colon cancer (189). Nanozymes target colon cancer by mitigating the hypoxic microenvironment, inducing ROS overload and initiating immunotherapy.

PTT employs NIR light in junction with photothermal agents to induce localized hyperthermia, effectively eliminating tumor cells (190). Zhu *et al* (191) introduced a multifunctional system [Ru@CeO₂-ruthenium complex (RBT)/resveratrol (Res)-DPEG] that integrates PTT with chemotherapy. The yolk-shell structured nanozyme demonstrated excellent catalytic efficiency and photothermal conversion capability. Additionally, it was co-loaded with RBT and Res. The dual-layer PEG-coating extended circulation time by reducing plasma protein adsorption. In both subcutaneous and orthotopic colon cancer models, Ru@CeO₂-RBT/Res-DPEG + NIR exhibited strong antitumor effects and reduced HIF-1 α levels in tumor tissues. Another tumor microenvironment-responsive

platform, the POD nanocrystals (CatCry-AgNP-DOX), which does not fall within the category of nanozymes, may present a novel approach for future drug delivery (192).

PDT selectively targets tumors with minimal invasiveness (193). Hao *et al* (194) developed a ROS-sensitive nanoplatfrom [camptothecin (CPT)-TK-HPPH/Pt nanoparticle], which integrates CPT with the photosensitizer HPPH. Pt nanoparticle-generated oxygen-facilitated HPPH consumption <660 nm laser irradiation, cleaving the thioketal bond to release CPT simultaneously (Fig. 7). *In vivo* experiments showed a marked tumor volume reduction and pronounced tumor necrosis in the CPT-TK-HPPH/Pt nanoparticle + laser group. However, the effectiveness of PDT is limited by the penetration depth of laser light. Duo *et al* (195) addressed this by inserting an optical fiber into the peritoneal cavity of mice for PDT treatment with orthotopic tumors, showing promising results. SDT offers high tissue penetration and non-invasiveness (196). A cascading nano-reactor [CCP@hollow polydopamine (HP)@M] was designed, incorporating the sonosensitizer Ce₆ and autophagy inhibitor chloroquine. The HP with metal-organic framework core demonstrated drug-loading capability and SOD-like activity. Additionally, platinum nanoparticles were doped onto the carrier HP, endowing the system with CAT- and POD-like activities to alleviate tumor hypoxia while amplifying ROS generation. In HCT-116 xenograft models, the combined approach of ROS elevation and autophagy inhibition, together with SDT, resulted in suppression of tumor. RNA-sequencing analysis showed downregulation of cancer, autophagy, apoptosis, ferroptosis pathways and HIF-1 α , aligning with the expected nano-reactor mechanism (197).

In recent years, growing evidence has highlighted the role of tumor-resident microbiota in tumor development and therapeutic resistance, opening new avenues for microbial-targeted strategies (198). Researchers developed a protein-supported copper single-atom nanozyme (BSA-Cu SAN) facilitating the conversion of H₂O₂ into highly reactive hydroxyl radicals ($\bullet$ OH). This oxidative stress was directed at *Fusobacterium nucleatum* within tumors, impairing its viability. In HCT-116 xenograft mouse models, BSA-Cu SAN administered intravenously or intratumorally effectively inhibited tumor growth. Of note, 48 h after intravenous injection, no notable drug accumulation was observed, reducing tissue damage from prolonged heavy metal retention (199). Another noteworthy therapeutic approach involves utilizing pH-dependent POD-like nanozymes that, upon sensing the tumor microenvironment, generate a small amount of ROS around the engineered probiotic BL999. This prompted the probiotic to produce acidic metabolites, feedback enhancing the POD-like nanozyme activity, ultimately generating a substantial amount of ROS to counteract tumor tissues (200).

Nanozyme-based diagnostic platforms facilitate the precision of cancer diagnosis. One feasible approach involves the use of multifunctional CeO₂ nanoparticles for the detection of T-cell immunoglobulin and mucin domain 1, a membrane glycoprotein associated with tumor angiogenesis. Compared with conventional diagnostic platforms, this method provides a moderate enhancement in sensitivity, a significant expansion of the linear detection range and a reduction in background current, thereby contributing to more accurate diagnosis and

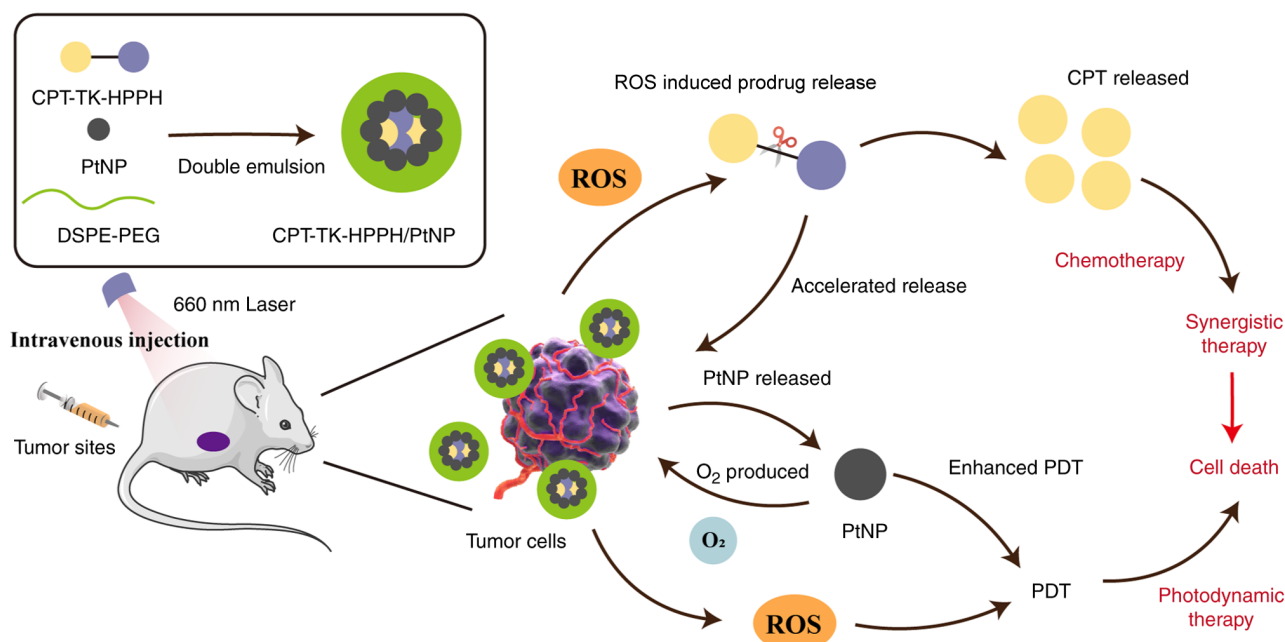


Figure 7. Conceptual depiction of a colon cancer therapy strategy utilizing CPT-TK-HPPH/Pt NP activated by 660 nm laser light. Adapted with permission from Advanced Science, copyright 2020. CPT-TK-HPPH, camptothecin-thioketal bond-2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide; Pt NP, platinum nanozyme; CPT, camptothecin; ROS, reactive oxygen species; DSPE, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine; PEG, polyethylene glycol; PDT, photodynamic therapy.

prognostic stratification in patients (201). Another diagnostic platform enables direct detection of circulating cancer stem cells from blood and fecal samples (202). Additionally, nanozymes have been employed in the detection of global DNA methylation in colorectal cancer cells using mesoporous iron oxide. Compared with traditional procedures, this method offers lower cost and higher detection sensitivity, making it a promising platform for rapid clinical screening (203).

Nanozymes, while promising, have shown relatively low efficiency compared with surgical treatments in eliminating tumors. As aforementioned, current strategies combine nanozyme with traditional treatments to enhance efficacy and minimize damage. Developing combinatory protocols that exploit complementary mechanisms is crucial for advancing cancer treatment.

The biological behavior of colon cancer varies, necessitating more specific approaches (204,205). Nanozyme systems need to target specific biomarkers and pathways unique to colon cancer, informed by molecular and genetic profiles, to improve effectiveness and reduce off-target effects.

Current research focuses on alleviating tumor hypoxia by enhancing oxygen supply (206-208). Exploring unconventional mechanisms, such as ferroptosis and amino acid depletion, has opened up promising strategies, particularly by disrupting metabolic processes and survival signaling in tumors (209,210).

Other digestive system diseases. Nanozymes have been used in the functionalization of stem cells for treating digestive diseases (211,212). Additionally, they have been applied in RNA interference technology for antiviral therapy (213). However, additional research is essential to determine the full extent of their applicability across various digestive system diseases.

4. Conclusions, challenges and perspectives

The present review highlighted the latest advances of nanozymes in preclinical models of major digestive system diseases, encompassing diagnostics, monitoring and, most importantly, therapeutic applications. A detailed overview of nanozyme applications in diseases affecting the esophagus, stomach, liver, pancreas and colon was provided. Primary enzyme-like activities were also discussed. Despite significant progress, the application in digestive system diseases is still in its early stages. In the current review, the challenges and potential prospects were outlined.

At present, nanozymes continue to encounter several critical shortcomings and unresolved challenges in both research and clinical applications. One of the primary issues is the lack of sufficient targeting specificity. A number of nanozymes exhibit poor tissue or cellular selectivity and are readily sequestered by non-target organs, such as the liver and spleen. In the gastrointestinal tract, their catalytic activity can be compromised by physiological barriers including mucus layers, gastric acid and digestive enzymes. Furthermore, concerns regarding the biocompatibility and potential toxicity of nanozymes, particularly those based on metal oxides, persist. Long-term accumulation or high-dose administration of such materials may induce cytotoxic effects or elicit inflammatory responses. Compared with natural enzymes, nanozymes often display suboptimal catalytic efficiency under physiologically relevant conditions, especially in environments with fluctuating pH or redox states. In addition, the *in vivo* biodistribution, metabolism and excretion of nanozymes are difficult to monitor, complicating dose optimization and therapeutic outcome evaluation. Immunological responses and clearance mechanisms triggered by nanozymes have not yet

been fully elucidated, raising concerns about the potential for immune tolerance or immune-related toxicity with prolonged administration.

To address these limitations, future research should focus on several key directions. First, surface modification strategies such as conjugation with antibodies, peptides, or oligonucleotides can enhance the targeting specificity of nanozymes. The development of stimuli-responsive nanozymes that are activated by pathological microenvironments such as acidic pH and high ROS levels may further improve site-specific efficacy. Second, the use of biocompatible and biodegradable materials to encapsulate or functionalize nanozymes can reduce exposure of the metal core and mitigate toxicity. Third, optimization of nanozyme morphology, particle size and surface catalytic sites, or the construction of synergistic systems with natural enzymes, may help improve catalytic performance. Last, designing nanozymes with strong mucosal adhesion and protective, pH-responsive coatings or integrating them with probiotics and microbiota-targeted therapies may enhance their stability and therapeutic effect within the gastrointestinal tract.

In conclusion, nanozymes hold tremendous potential as a next-generation tool for the diagnosis and treatment of digestive system diseases. However, their successful clinical application will rely on interdisciplinary efforts to overcome current limitations in biology, chemistry and related fields. Continued innovation in material design, targeting strategies and *in vivo* evaluation methodologies will be key to unlocking the full potential of nanozymes. In the future, nanozymes are expected to transition from promising preclinical agents to clinically viable therapeutic modalities.

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Authors' contributions

Conceptualization was by YH and CS. Investigation was by DX, LX and CF. DX and LX were responsible for writing and original draft preparation. DX, LX, CF, ZD, ZC and YH were responsible for writing, reviewing and editing. Visualization

was by DX and LX. Supervision was by YH and CS. Project administration was by YH and CS. CS made a significant contribution to the manuscript revision. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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