MINI-REVIEW

Nanomaterials for cascade promoted catalytic cancer therapy

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Abstract
Catalytic therapy utilizing special substances (e.g., hydrogen peroxide and glucose) in tumor sites has attracted wide interest to achieve tumor-specific therapy or improve the efficacy of other treatments. Benefiting from the selectivity and high activity of catalytic chemistry, efficient cancer therapy is available with negligible side effects. Numerous works, which are focused on further augmenting catalytic therapy with cascade strategies, have been reported with biocompatible nanomaterials composed of natural enzymes and/or nanozymes. Herein, we summarized catalytic reactions and nanomaterials in cascade strategy-involved cancer therapy. With rapid advances in chemistry and nanomaterials, developing more selective and efficient cascade catalytic strategies will continue to be promising and challenging for cancer therapy.

KEYWORDS
Cascade, catalytic therapy, cancer therapy, nanozyme, nanomaterials
1  |  INTRODUCTION

Cancer is a global health concern for humans and has motivated very large efforts in clinical treatment and therapeutic technology innovations. Extensive nanomaterials with light, thermal, and chemical responsiveness have been developed to improve the therapeutic effects of conventional chemotherapy or radiotherapy and emerging therapies, such as phototherapy and gas therapy.\textsuperscript{1–3} Meanwhile, bottlenecks of most conventional treatments occur, such as limited efficacy resulting from tumor hypoxic and acidic microenvironments, multidrug resistance, and inevitable side effects.\textsuperscript{4,5}

Catalytic therapy is an emerging strategy to address these problems, improving therapeutic efficacy and reducing side effects by transferring nontoxic or low-toxic endogenous substances into highly toxic molecules to kill tumor cells. The tumor microenvironment (TME) was identified to be quite different from normal tissue, involving higher acidity, overexpressed lactic acid (LA), and accumulation of hydrogen peroxide.\textsuperscript{6,7} These special chemicals and conditions can be utilized to initiate a series of catalytic reactions,\textsuperscript{8–11} such as the Fenton reaction and LA oxidization\textsuperscript{9,12} only inside tumor sites to enable tumor-specific therapy. Furthermore, the adverse conditions (hypoxic and acidic microenvironments) to conventional treatments can be reversed or normalized by catalytic reactions to improve therapy efficacy.\textsuperscript{13} A series of reviews have been published to propose advances in catalytic therapy, including catalytic chemical reactions,\textsuperscript{14} chemodynamic therapy (CDT),\textsuperscript{15,16} glucose oxidase (GOx)-based therapy,\textsuperscript{17,18} various nanozymes for catalytic therapy,\textsuperscript{19–21} and nanoplatform-based cascade engineering.\textsuperscript{22} These reviews have concluded catalytic chemistry utilizing specific molecules in tumor sites, such as hydrogen peroxide (H$_2$O$_2$) to produce toxic reactive oxygen species (ROS) and nitric oxide (NO), exhausting glucose to supply fuels such as H$_2$O$_2$ or oxygen for other therapies, and cascade strategies.

However, single catalytic therapy is insufficient to ensure therapeutic efficacy. For instance, endogenous H$_2$O$_2$ is insufficient and thus requires supplementation. This requirement can be fulfilled by catalytic reactions to provide additional H$_2$O$_2$ from glucose or LA oxidation. Such catalytic reactions could cause further cascades with other therapies, such as CDT, photodynamic therapy (PDT), sonodynamic therapy (SDT), and gas therapy, by providing H$_2$O$_2$. To augment the efficacy of catalytic therapy, many studies have developed cascades to provide more fuels, improve hypoxic tumor microenvironments, or synergize with other therapies.

Herein, we summarized nanomaterials and corresponding catalytic reactions for cascade-promoted catalytic cancer therapy. Nanomaterials utilized to immobilize enzymes or participate in cascades as nanozymes were discussed according to characteristics, such as chemical classifications, architectures, long circulation, or local retention. The rational integration of various components that take advantage of different nanomaterials was concluded. In summary, this review concentrated on nanomaterial selection and integration to achieve cascade-promoted catalysis with high selectivity and synergistic effects for cancer therapy.

2  |  NANOMATERIALS FOR CHEMICAL REACTIONS IN CATALYTIC CANCER THERAPY

In recent years, catalytic chemistry based on nontoxic but catalytically active substances has been applied to produce highly toxic species such as $\cdot$OH, NO, and HClO or supply fuels such as oxygen (O$_2$) or H$_2$O$_2$ for cancer therapy. As shown in Table 1, catalytic reactions and catalysts applied in cascade-promoted catalytic cancer therapy are summarized. The Fenton reaction with Fe-based catalysts is a hotspot which could produce $\cdot$OH to induce cancer cell death. Fenton-like catalytic reactions with other metal catalysts could also induce tumor cell apoptosis by the production of $\cdot$OH. Catalase and catalase-like catalytic reactions are the main methods to generate O$_2$ for O$_2$-dependent therapies. To provide more H$_2$O$_2$ for $\cdot$OH production and O$_2$ generation, glucose oxidation and LA oxidation are utilized and catalyzed by natural enzymes or nanozymes.

2.1  |  Nanomaterials for Fenton/ Fenton-like reaction

Hydroxyl radicals are special ROS with the strongest oxidizability and can cause oxidative damage to DNA, lipids, and proteins. Local production of $\cdot$OH with nanomaterials can induce efficient tumor treatments. Thus, Fenton reactions and peroxidase (POD) and superoxide dismutase (SOD)-mediated catalytic reactions were adopted to produce toxic $\cdot$OH to kill cancer cells. Inspired by the concepts of ferroptosis and CDT, Fe-based inorganic nanomaterials (including amorphous Fe(0) nanoparticles,\textsuperscript{12} iron oxides,\textsuperscript{23–27} [FeO(OH)$_n$],\textsuperscript{28} layered double hydroxide,\textsuperscript{11} M(Zn, Sn)Fe$_2$O$_4$,\textsuperscript{29,30} and ferrocene (Fc)\textsuperscript{31}) have been studied widely for cancer therapy. In terms of catalytic activity, Fe(II) shows high activity, which could cause efficient CDT, while Fe(III) and Fe(0) show poor activity, which requires reduction/redox to transfer into
Fe(II). The high catalytic activity of Fe(II) requires strict protection to avoid biooxidation during blood circulation and side effects on normal tissues. Amorphous Fe(0) nanoparticles (AFeNPs) were prepared with Pluronic F127 and polyvinylpyrrolidone (PVP) to ensure stability during blood circulation (Figure 1A). As shown in Figure 1B and 1C, AFeNPs present different catalytic activities and cell toxicities at various pH values, which could enable specific therapy of tumors. However, the catalytic efficiency of Fenton reactions require acid condition, typically pH below 4, is limited in TME. Thus, more nanomaterials were studied to enable high catalytic efficiency in TME. Compared with Fe-based catalysts, other metal catalysts (Mn$^{2+}$, Ti$^{3+}$, Cu$^{2+}$, and Mo$^{5+}$) show different catalytic activities, which are dependent on pH changes. For instance, compared with Fe(II), Cu$^{2+}$ ions show higher
2.2 Nanomaterials for oxygen generation

Oxygen generation in tumor sites/cells is an emerging issue that could improve hypoxic conditions in tumors to enhance the efficacy of cancer radiotherapy, photodynamic therapy, or chemotherapy. Even though exogenous oxygen has been delivered to tumor sites with perfluorocarbons (PFCs) and hemoglobin, premature leakage of O₂ is a concern that may cause failure of therapy.⁴⁰,⁴¹ Catalase is a remarkable enzyme that can convert intratumoral H₂O₂ into water and O₂ and has been used widely to improve cancer therapy efficacy.⁴²–⁴⁴ Additionally, many catalase-mimicking nanozymes, including MnO₂,⁴⁵,⁴⁶ PtFe@Fe₃O₄,⁴⁷ and Pd,⁴⁸ have been developed for highly efficient tumor catalytic therapy.

2.3 Nanomaterials for H₂O₂ production

The production of H₂O₂ with catalytic nanomaterials is an emerging strategy in cancer therapy. GOx is a natural oxidase that can efficiently catalyze glucose oxidation into gluconic acid and H₂O₂.⁴⁹ Based on the catalytic chemistry of GOx, various strategies have been developed for cancer therapy: (1) starvation therapy inhibits tumor growth by obstructing the supply of glucose; (2) O₂ consumption exacerbates hypoxia to enhance hypoxia-activated therapy; (3) the acidity of TME would be augmented by...
the generation of gluconic acid, which is helpful for Fe–Fenton reactions and pH-responsive drug release; and (4) most importantly, the generation of H$_2$O$_2$ is a key part of cascade-promoted catalytic cancer therapy. Furthermore, ultrasmall gold nanoparticles present GOx-mimicking catalytic activity, which can be utilized to design nanomaterials for cancer therapy.\textsuperscript{50,51} Compared with glucose, LA is an alternative source of H$_2$O$_2$, which is a specific metabolite in tumor sites and critical for tumor survival and progression. Catalysis of LA oxidation can deplete LA with LOx to modulate the TME and produce H$_2$O$_2$ precisely in tumor sites.

\section*{2.4 Nanomaterials for other catalytic reactions}

Recently, more nanomaterials for catalytic therapy have raised considerable attention. For instance, nanomaterials immobilized chloroperoxidase (CPO) or amino acid oxidase (AAO) were developed to achieve cascade-promoted catalysis for cancer therapy. Specifically, the natural singlet oxygen ($^1$O$_2$)-generating strategy of neutrophil lysosomes is thought to involve $^1$O$_2$ produced by a biocatalytic system of myeloperoxidase (MPO), hydrogen peroxide (H$_2$O$_2$), and halide ions. CPO is a robust POD that shows similar catalytic property and higher resistance to oxidative inactivation in comparison with MPO.\textsuperscript{52} Consequently, CPO could be utilized to catalyze oxidation of halides with H$_2$O$_2$ to hypochlorous acid (HOCl), and then produce $^1$O$_2$ by the subsequent decoposition of HOCl for inducing tumor cell apoptosis.

\section*{3 Nanomaterial-immobilized natural enzymes for catalytic cascades}

The application of natural enzymes such as GOx and catalase for cancer therapy has been developed in past decades. Recently, these enzymes were adopted in cascade strategies to produce H$_2$O$_2$ or improve the hypoxic TME for catalytic therapy. The catalytic specificity and high efficiency are two remarkable characteristics of natural enzymes, which enable its potential in catalytic therapy. On the contrary, the poor stability and cellular permeability of natural enzymes are two significant limitations in practical application, which requires rational design of nanomaterials for effective delivery. Physical encapsulation, covalent linking, and mineralization are three main routines to achieve nanomaterial-immobilized natural enzymes (Table 2) for catalytic cascade-promoted cancer therapy.

\subsection*{3.1 GOx-involved cascade enhancing cancer therapy}

In previous studies, GOx, which exhausts glucose and O$_2$ and produces gluconic acid and H$_2$O$_2$, has been widely utilized to provide fuels for CDT or gas therapy. Mesoporous materials are excellent carriers for GOx because their mesostructures can enable high loading capacity and highly dispersed catalytic active sites. As shown in Figure 1D, Huo et al.\textsuperscript{27} achieved selective tumor modalities by sequential catalysis with GOx and ultrasmall Fe$_3$O$_4$ nanoparticles. In this work, dendritic mesoporous silica nanoparticles (DMSNs) were chosen as nanocarriers and catalyst supports due to their mesoporous structure. Similarly, Yao et al.\textsuperscript{53} delivered GOx with ferrocene covalently linked DMSNs with a hyaluronic acid coating, which is designed to attenuate the possible damage to normal tissues during transportation.

In addition, albumin is another carrier to deliver GOx and other catalysts because of its biocompatibility and physiological stability. A nanoreactor involving GOx and Fe$^{3+}$–tannic acid (TA) metal–polyphenol network was reported to enable cascade catalysis between glucose oxidation and Fenton for cancer therapy.\textsuperscript{54} In this work, human serum albumin (HSA), GOx, and tirapazamine (TPZ) were mixed to obtain TPZ-loaded protein mixture. Then Fe$^{3+}$ and TA were introduced to the mixture to form the nanoreactor. Nanoclustered cascaded enzymes that were synthesized by covalently cross-linking GOx, catalase, and BSA were reported to induce cascade catalysis for oxygen exhaustion.\textsuperscript{55} In this work, the cascade catalysis of glucose oxidization by GOx and H$_2$O$_2$ decomposition by catalase could rapidly exhaust oxygen to trigger the reductase-activated prod drug TPZ and avoid harmful H$_2$O$_2$ accumulation. Zhang et al.\textsuperscript{56} conjugated GOx on the surface of Janus-type $\gamma$-Fe$_2$O$_3$/SiO$_2$ nanoparticles. The close distance between GOx and $\gamma$-Fe$_2$O$_3$ enables adequate cascade catalytic effect of glucose oxidation and Fenton reaction, which finally enhanced synergistic cancer therapy. Chen et al.\textsuperscript{57} reported GOx-conjugated SrCuSi$_4$O$_{10}$ nanosheets to achieve enhanced CDT with cascade catalysis.

Biominer alization is another way to obtain enzyme delivery nanomaterials to enable a cascade for cancer therapy. Liu et al.\textsuperscript{58} anchored ultrasmall Fe$^0$ nanoparticles in GOx as nanocatalyst (GOx–Fe$^0$) to enable cascade catalytic therapy. Fe$^0$ nanoparticles were synthesized by in situ reduction in GOx and then the resulting nanocatalyst and ICG were coated with tumor-targeted erythrocyte membrane (EM). After accumulated in tumor sites, NIR light irradiation was applied for PTT to trigger the rupture of erythrocyte membrane and GOx–Fe$^0$ release.
Further self-activated cascade catalysis involving glucose oxidation and Fenton reaction could eradicate tumor effectively. Fu et al.\textsuperscript{59} fabricated copper-doped calcium phosphate (CuCaP) nanoparticles, which are mineralized with GOx as a template to achieve enhanced cascade chemodynamic therapy.

Local administration into tumors was reported by encapsulating GOx and gallic acid–ferrous (GA–Fe) nanocomplexes with hydrogels.\textsuperscript{60} Such hydrogels were formed by in situ gelation, allowing long-term tumor retention of GOx and GA–Fe, thus leading to superior tumor inhibition by cascade production of •OH and rapid glucose depletion-mediated starvation therapy.

Gas therapy is an alternative treatment that could be augmented by a cascade strategy. Fan et al.\textsuperscript{61} utilized the generated H\textsubscript{2}O\textsubscript{2} and acids with GOx to oxidize L-arginine (L-Arg) and then produced NO for gas therapy. To achieve such cascade-triggered gas therapy, GOx and L-Arg are separately conjugated on the surface, loaded in hollow mesoporous organosilica nanoparticles (HMONs), and codeivered to tumor sites. Glucose oxidation provides H\textsubscript{2}O\textsubscript{2} and elevated acidity for further reaction between L-Arg and H\textsubscript{2}O\textsubscript{2}, which would produce NO for gas therapy. Similarly, Ling et al.\textsuperscript{62} loaded L-Arg and immobilized GOx on the surface of Co–TCPP(Fe) metal organic framework (MOF). Abundant H\textsubscript{2}O\textsubscript{2} could be generated by oxidation of endogenous glucose to achieve starvation-like therapy, and involved in the generation of NO by L-Arg with TCPP(Fe) as the catalyst.

### LOx-involved cascade enhancing cancer therapy

LA is another potential source of hydrogen peroxide, which is a remarkable metabolite in tumor sites. Tang et al.\textsuperscript{63} reported a one-pot synthesis of dendritic mesoporous silica nanoparticles loaded with LOx to deplete lactate accumulated in the TME for cancer therapy (Figure 1E). The effective depletion of intratumoral LA could cause essential changes including downregulation of vascular endothelial growth factor (VEGF), inhibition of vascularization, and exacerbation of tumor hypoxia. Tian et al.\textsuperscript{64} utilized LOx-immobilized Ce–benzenetricarboxylic

| Enzymes | Nanomaterials | Immobilized method | Ref |
|---------|---------------|--------------------|-----|
| GOx     | GOx–Fe\textsubscript{3}O\textsubscript{4}@DMSNs | Physical encapsulation | 27  |
|         | Fe-conjugated DMSNs@GOx@HA | Physical encapsulation | 53  |
|         | HSA–GOx–TPZ–Fe\textsuperscript{3+}–TA | Physical encapsulation | 54  |
|         | Hydrogels encapsulating GOx and (GA–Fe) nanocomplexes | Physical encapsulation | 60  |
|         | L-Arg–HMON–GOx | Physical encapsulation | 61  |
|         | BSA-conjugated enzymes (GOx+catalase) | Covalently conjugation | 55  |
|         | GOx-conjugated Janus-type γ–Fe2O3/SiO2 nanoparticles | Covalently conjugation | 56  |
|         | SrCuSi\textsubscript{6}O\textsubscript{10}–GOx | Covalently conjugation | 57  |
|         | GOx@Co–FeMOF | Covalently conjugation | 58  |
|         | GOx–Fe\textsuperscript{0} | Covalently conjugation | 58  |
|         | PEG–GOx encapsulated CuCaP nanoparticles | Covalently conjugation | 59  |
| LOx     | ODMSN–LOX | Physical encapsulation | 63  |
|         | LOx–Ce–BTC | Physical encapsulation | 64  |
| Catalase | H\textsubscript{2}O\textsubscript{2}-activatable and O\textsubscript{2}-evolving PDT (HAOP) nanoparticles | Physical encapsulation | 65  |
|         | UCNP/TAPP@ZIF-8@Catalase | Physical encapsulation | 66  |
|         | Mn-doped CaP mineralized GOx nanoparticles with catalase | Physical encapsulation | 67  |
|         | BQ-MIL@cat–MIL | Physical encapsulation | 68  |
|         | Zeolite–catalase–MB nanocapsule | Physical encapsulation | 69  |
|         | CAT@liposome | Physical encapsulation | 70  |
|         | ICG/AuNR@BCNP | Physical encapsulation | 71  |
|         | Catalase-entrapped nanocapsules (CAT–THPP–PEG) | Covalently cross-linked | 72  |
|         | CAT–TCPP/F–PEI CS | Covalently cross-linked | 73  |
| CPO     | GOx/CPO-embedded ZIF-8 | Physical encapsulation | 74  |
|         | MNPs–CPO | Physical encapsulation | 75  |
| AAO     | AAO@HFe–TA | Physical encapsulation | 76  |
acid MOFs (Ce–BTC) to enable CDT by intratumoral cascade reactions: (1) the overexpressed LA is catalyzed to generate \( \text{H}_2\text{O}_2 \); and (2) the generated \( \text{H}_2\text{O}_2 \) is catalyzed by POD-mimicking nanozyme Ce–BTC to generate \( \cdot\text{OH} \). Consequently, selective tumor therapy is ensured by utilizing tumor metabolism and overexpressed LA to preferentially induce tumor cell apoptosis with negligible side effects.

### 3.3 | Catalase-involved cascade enhancing cancer therapy

Catalase, a natural enzyme that can decompose \( \text{H}_2\text{O}_2 \) to \( \text{O}_2 \), has been delivered to tumor sites for oxygen generation to improve the efficacy of PDT, radiotherapy and SDT. Since Chen et al.\(^{65}\) reported catalase as an \( \text{O}_2 \)-evolving agent to augment PDT, numerous nanomaterials utilizing catalase or catalase-mimicking nanzymes have been developed. You et al.\(^{66}\) coloaded catalase and GOx in zeolitic imidazolate framework-8 (ZIF-8) after coating onto upconversion nanoparticles (UCNPs). Consequently, the cascade catalytic reactions of glucose oxidation and \( \text{H}_2\text{O}_2 \) decomposition improved the efficacy of PDT. Fu et al.\(^{67}\) loaded catalase and photosensitizer in calcium phosphate mineralized glucose oxidase to achieve catalytic therapy. Oxygen produced by \( \text{H}_2\text{O}_2 \) decomposition involving PDT and cascade catalytic reaction of glucose oxidation and Fenton reaction. Consequently, such long-term cascade catalytic reactions that enhanced synergetic therapy with PDT were verified to improve therapeutic effects on tumor bearing mice.

Liu et al.\(^{68}\) reported a tendem catalyst with heterostructure through stepwise in situ growth. Black phosphorus quantum dots (BQ) was encapsulated inside Materials of Institute Lavoisier (MIL-101)-type MOF, and then outer MIL-101 was grown and conjugated with catalase. In this way, \( \text{O}_2 \) produced by decomposition of \( \text{H}_2\text{O}_2 \) would enter MOF and supply to PDT. Yang et al.\(^{69}\) reported biomimetic catalase-integrated albumin nanoprobes (BCNPs) to achieve diagnosis and treatment for glioma after penetrating the blood–brain barrier. Indocyanine green (ICG) and gold nanorods (AuNRs) were encapsulated in BCNPs as photosensitizer and photothermal agents. Benefiting from catalytic decomposition of endogenous hydrogen peroxide, the nanoprobes could effectively promote the level of \( \text{I}_2\text{O}_2 \) to amplify phototherapy. A catalase and methylene blue (MB)-coloaded hierarchical zeolite (ZCM) have been developed to treat pancreatic cancer.\(^{70}\) The porous zeolite architecture could provide confined nanochannels to enable high loading capacity, catalytic activity, and cascade between \( \text{O}_2 \) production and PDT. Modification of catalase with a photosensitizer by in situ polymerization is another method to ensure cascade-enhancing PDT.\(^{71}\) In this work, polyethylene glycol (PEG) short chains are grafted onto the surface of catalase as a permeable brush-like safeguard. Mesotetra (phenoxophenyl) porphine (THPP) plays multiple roles: photosensitizer, crosslinker between catalase and PEG, and chelating agent for \( {}^{99}\text{mTc}^{4+} \) (a radioisotope ion). Consequently, such an enzyme modification strategy endows cascade-promoted PDT and in vivo single-photon emission computed tomography (SPECT) imaging.

Song et al.\(^{72}\) reported their contribution to cascade-promoted radiotherapy, which employs liposomes modified with polyethylene glycol (PEG) as carriers. Catalase or \( \text{H}_2\text{O}_2 \) was loaded in liposomes to obtain catalase@liposome or \( \text{H}_2\text{O}_2@\text{liposome} \) separately. Further sustainable released \( \text{H}_2\text{O}_2 \) can be decomposed by catalase@liposomes to provide sufficient \( \text{O}_2 \) for radiotherapy. Consequently, remarkable synergistic effect could be observed in a mouse tumor model and patient-derived xenograft tumor model.

Catalase catalyzed \( \text{H}_2\text{O}_2 \) decomposition and was also developed to achieve highly efficient SDT. Li et al.\(^{73}\) reported a transmucosal delivery system with assembly of fluorinated chitosan (FCS) and meso-tetra(4-carboxyphenyl) porphine-conjugated catalase (catalase–TCP). The assembled catalase–TCP/FCS nanoparticles can cross mucosal barrier and penetrate into tumors. Further \( \text{O}_2 \) generated from endogenous \( \text{H}_2\text{O}_2 \) catalyzed by catalase could ablate intratumoral hypoxia to improve the therapeutic efficacy of SDT.

### 3.4 | Other natural enzymes applied in cascade-enhanced cancer therapy

Recently, neutrophil-inspired catalytic therapy with CPO has been reported in two separate studies. Inspired by the immune system of organisms, nanoplateform could generate HClO by cascade catalysis and inhibit tumor progression as “artificial neutrophils.” Zhang et al.\(^{74}\) embedded GOx and CPO into ZIF-8 to mimic neutrophil for tumor eradication. The porous zeolite architecture could provide confined nanochannels to enable high loading capacity, catalytic activity, and cascade between \( \text{O}_2 \) production and PDT. Modification of catalase with a photosensitizer by in situ polymerization is another method to ensure...
### Table 3: Nanomaterials integrated nanozyme for cascade promoted catalytic cancer therapy

| Nanoyzes | Nanomaterials | Integration | Ref |
|----------|---------------|-------------|-----|
| **Metal clusters/hybrids** | rGO–MnO₂–PEG | Chemical deposition | 78 |
| | CuS@CeO₂ core–shell nanoparticles | Chemical deposition | 81 |
| | Pb@ periodic mesoporous organosilica–Ce6 | In situ grown organosilica on Pb | 82 |
| | RuO₂@BSA@IR-808-Br̂ | Biomineralization | 83 |
| | Hydrogenated hollow Pt–TiO₂ Janus | Physical vapor deposition | 84 |
| | Cu₂Mo₄ | Hydrothermal | 85 |
| | Au/Pt star | In situ grown | 86 |
| | Bi₃Se₆@ hemin–(G–H)–HA NPs | Self-assemble with host–guest and electrostatic interaction | 87 |
| **Mesoporous nanomaterials** | Mesoporous copper/manganese silica nanospheres | In situ grown (hydrothermal deposition of copper/manganese silica) | 80 |
| | DMSN–Au–Fe₃O₄ NPs | In situ grown and physisorption | 88 |
| | MSNR@MnO₂–Au | Chemical deposition | 89 |
| **MOFs** | NMIL–100@ Gox@C | Physical encapsulation | 91 |
| | Co–Fc NMOF@Gox | Physical encapsulation | 93 |
| | Au/FeMOF@CPT NPs | In situ grown | 94 |
| | Gold nanoparticles doped iron-based MOFs | In situ grown | 95 |
| | MnCoO–PDA–PEG–Ce6 | Physical encapsulation | 96 |
| | PCN@Pt@PCN–Au–FA | In situ grown | 97 |
| | Dox@MOF–Au–PEG | In situ grown | 98 |
| | UCNP–iron porphyrinic MOF NPs@Au | In situ grown | 99 |
| | DBBC–UiO | Coordination | 100 |
| **Two-dimensional materials** | GOx/CoFe–LDHs | Physisorption | 92 |
| | MoS₂@CGTC NCR | Self-assemble | 101 |
| | N-GQD@HMSN@C₃N₄ | In situ grown | 102 |
| **Supramolecular complex** | GOx@ZIF@MPN | Supramolecular interaction | 103 |
| **Macromolecules based nanomaterials** | (PCL–b–PArg)–Lapa–Fc | Physical encapsulation | 104 |
| | Cy5–dHeme–BPNS–FA | Self-assemble | 105 |

incorporated AAO in Fe³⁺/tannic acid nanocapsules (HFe–TA).⁷⁶ AAO could catalyze oxidative deamination of L-amino acids to produce acid, amino, and H₂O₂. Then HFe–TA could utilize H₂O₂ to initiate CDT by Fenton reaction in a cascade manner.

### 4 | INTEGRATION OF NANOZYME FOR CANCER THERAPY

Artificial nanozymes were emerging nanomaterials with prior catalytic performance, stability, and low cost, which obtain considerable applications in cancer therapy. Benefit from the superior stability, most nanozymes could be integrated into nanomaterials various methods like in situ grown, chemical deposition, hydrothermal method, etc. (Table 3). Various categories of nanomaterials, including metal clusters/hybrids, mesoporous nanomaterials, MOFs, two-dimensional materials, supramolecular complex, and macromolecule-based nanomaterials as integrated nanozymes, were integrated as part or main body of nanomaterials with different designs.

#### 4.1 | Metal clusters/hybrids as integrated nanozymes for cancer therapy

Similar to catalase, manganese is an alternative choice to catalase to catalyze H₂O₂ decomposition, which has been utilized for catalytic cascade-enhanced radiotherapy, PDT and SDT.⁷⁷ Tao et al.⁷⁸ designed a ternary nanocomposite, polyethylene glycol (PEG)-reduced nanographene
oxide–MnO₂ (denoted as rGO–MnO₂–PEG), to improve tumor hypoxic microenvironments for enhanced radiotherapy. Additionally, most of the nanomaterials for radiotherapy were merely focused on maximizing tumor eradication but neglected radiation protection for normal tissues. Lv et al.⁷⁹ reported atomically precise Mn₁₂ clusters with different catalytic activities under different pH conditions, which could achieve different functions in radiotherapy. In the acidic TME, Mn₁₂ clusters catalyze the enormous production of O₂ to enhance the radioactive therapeutic efficiency of tumors; meanwhile, in neutral normal tissue sites, Mn₁₂ clusters switch on the reduction pathway to protect normal organs from radiation.

As shown in Figure 2A, Liu et al.⁸⁰ prepared mesoporous copper/manganese silicaspheres (CMSNs) coated with cancer cell membrane to integrate MRI imaging, CDT, and PDT. Specifically, the CMSNs catalyze H₂O₂ decomposition as catalase-mimicking nanozyme, then release Cu(I) and Mn (II) with POD activity, which could convert H₂O₂ to •OH for CDT. The H₂O₂ decomposition could improve PDT efficiency by supplying O₂ to enhance anticancer effects in a cascade manner. Other catalase-mimicking nanozymes, such as CeO₂,⁸¹ Pb,⁸² RuO₂,⁸³ Pt,⁸⁴ and Cu₂MoS₄,⁸⁵ have been reported to enable cascade-promoted radiotherapy, PDT, and SDT. For instance, Zhang et al.⁸⁶ reported a multifunctional probe with core-shell structure involving a gold/platinum star-shaped (Au/Pt star) core as nanozyme and HAS conjugates shell as carrier for tumor imaging and eradication. In the shell carrier, folic acid (FA), near-infrared fluorophores (IR780), and GOx were conjugated to HSA as target head, PDT agent, and catalyst with glutathione (GSH)-sensitive disulfide bonds. After the disulfide linker is cleaved by intracellular GSH, functional IR780, GOx, and Au/Pt stars are released and cause cascade catalysis and PDT. GOx catalyzes glucose oxidization to produce H₂O₂, and then POD-mimicking Pt stars generate physiologically toxic •OH to induce oxidative damage in tumor cells.

Beside of nanozymes, hemin also presents catalytic activity as a prosthetic group of various proteins and enzymes (such as catalase and hemoglobin). Niu et al.⁸⁷ composed β-cyclodextrin–modified hyaluronic acid (HA) and adamantane–modified hemin complex via guest–host (G–H) interaction. Then Bi₂Se₃ NPs were wrapped with result complex to obtain a nanoreactor (Bi₂Se₃@hemin–(G–H)–HA NPs) via electrostatic interactions (Figure 2B). Once irradiated by NIR (near infrared) light, hemin assists Bi₂Se₃ in separating electron–hole pairs and catalyzes endogenous H₂O to generate vast H₂O₂, resulting in H₂O₂ generation that is several times higher than that of individual Bi₂Se₃. Further generation of toxic •OH and O_2⁻ is catalyzed by aggregation-limited hemin subsequently, which could augment intratumoral ROS level.
4.2 | Mesoporous nanomaterials as integrated nanozymes for cancer therapy

As mentioned above, mesoporous nanomaterials are excellent carriers for biocatalysts. Gao et al. reported a binary inorganic nanozyme-involved cascade reaction for tumor treatment with ultrasmall Au and Fe₃O₄ NP-loaded DMSNs (DMSN–Au–Fe₃O₄ NPs). Ultrasmall gold nanoparticles (AuNPs) are GOx-mimicking nanozymes that have been found in recent years. GOx-mimicking nanozymes and POD-mimicking Fe₃O₄ NPs catalyze glucose oxidation to produce H₂O₂ and subsequently decompose H₂O₂ to liberate highly toxic ⋅OH. As a result, endogenous cascade reactions for tumor-specific and effective catalytic tumor therapy could be achieved in a noninvasive and "toxic-drug-free" way. Liu et al. developed cell membrane-coated mesoporous copper/manganese silicate nanospheres (mCMSNs) that present catalase-mimicking catalytic activity and GSH-activated Fenton reactions. Yang et al. integrate MnO₂ and ultrasmall AuNPs by depositing them on mesoporous silica nanorods and developed biomimetic hybrid inorganic MnO₂–Au nanozymes (MSNR@MnO₂–Au). Such MSNR@MnO₂–Au nanozymes could catalyze cascade catalysis of H₂O₂ decomposition with MnO₂ and glucose oxidation with ultrasmall AuNPs. The decomposition of H₂O₂ could produce O₂ for glucose oxidation; in turn, glucose oxidation would produce H⁺ and H₂O₂ and augment MnO₂ catalyzed H₂O₂ decomposition. Consequently, the mutually reinforcing enzymatic cycle could improve the catalytic efficiency to alleviate oxygen-deprived conditions to enhance radiotherapy efficacy.

Prussian blue is one kind of biocompatible substance with catalytic activity and photothermal effect. Recently, porous hollow Prussian blue nanoparticles (PHPBNs) were developed as mesoporous nanocarriers. For instance, Zhou et al. utilized PHPBNs as carriers of GOx with a HA coating linked by redox-cleavable linkage for synergetic cascade catalytic therapy and photothermal therapy (PTT). Such PHPBNs nanocarriers could catalyze intratumoral H₂O₂ decomposition to provide O₂ for glucose oxidation. Thus GOx-mediated starvation therapy could be enhanced and cause further suppressed expression of heat shock proteins (HSPs), which could improve PTT efficiency.

4.3 | MOFs as integration of nanozymes for cancer therapy

MOFs are also a family of distinguished functional porous materials that are suitable for drug delivery and synergetic therapy. Additionally, various MOF hybrids with other metals, such as Fe, Ce, and Au, showed catalytic activity that could be utilized for cascade-promoted cancer therapy.

4.3.1 | MOFs with Fenton/Fenton-like catalytic activity for cancer therapy

In previous studies, iron-based MOFs (NMIL100, GIM, Co–ferrocene MOF, etc.) have been developed as nanocarriers and nanozymes for cancer therapy. Liu et al. reported their work on AuNP-doped iron-based MOFs (GIMs) for cascade chemodynamic therapy. Fe-based MOFs play two important roles: (1) as the source of Fe(II) for the Fenton reaction and (2) as shield to prevent adsorption of AuNPs by protein in biological fluids. Additionally, the porous architecture of MOFs are confinement sites for catalytic reactions that could also favor mass transport. Ding et al. utilized iron-based porphyrin-MOFs (FeMOFs) as matrices, anchored ultrasmall AuNPs as GOx-mimicking nanozymes, and encapsulated camptothecin (CPT); the resulting sophisticated nanomedicine was named Au/FeMOF@CPT NPs. As shown in Figure 3A, 1-dodecanethiol (C₁₂SH) and methoxy polyethylene glycol thiol (PEG–SH) were modified on AuNPs to improve the stability and long blood circulation time. After being internalized by tumor cells, Au/FeMOF@CPT NPs would collapse completely by intracellular phosphate due to their stronger coordination with zirconium. Then cascade catalytic reactions and drug release would be initiated.

In addition to Fe-based MOFs, other metal-based MOFs with POD activity have been studied for cancer therapy. For instance, Ce–BTC have been utilized to immobi­lize LOx for cascade catalytic therapy. Specifically, LOx could catalyze intratumoral overexpressed LA oxidized into H₂O₂. Then Ce–BTC with POD activity would produce ⋅OH with H₂O₂ to induces tumor apoptosis.

4.3.2 | MOF-based catalase-mimicking nanozymes for cancer therapy

It is known that Mn-based nanozymes present catalase-mimicking catalytic activity; therefore, Mn-based MOFs have been designed as catalase-mimicking nanozymes in catalytic therapy. Wang et al. utilized mesoporous Mn₃[Co(CN)₆]₂ MOFs, which modified with polydopamine (PDA) and PEG, as nanozymes and nanocarriers to load chlorin e6 (Ce6). Mn₃[Co(CN)₆]₂ MOFs play the role of H₂O₂-activated oxygen supplier to alleviate hypoxia for enhancing PDT in a cascade manner.
Based on massive studies of individual nanozymes applied in tumor therapy, Yu et al. proposed a dual-nanozyme-engineered porphyrin MOF to enable cascade-enhanced synergistic therapy. Specifically, catalase-mimicking platinum nanoparticles (Pt NPs) were sandwiched by porous coordination network (PCN) MOFs. Then GOx-mimicking ultrasmall AuNPs were anchored within the outer shell of MOFs, which is further coordinated with folic acid (FA). The Pt NPs catalyzed \( \text{H}_2\text{O}_2 \) decomposition to generate \( \text{O}_2 \) for further \( \text{O}_2 \)-dependent PDT and starving-like therapy catalyzed by ultrasmall AuNPs, which deplete glucose. Consequently, synergistic PDT and starving-like therapy could be enhanced by cascade catalytic strategy to prevent recurrence and metastasis.

Porphyrinic MOF–gold (MOF–Au) hybrid nanoparticles with catalase-mimicking activity have also been reported to achieve \( \text{O}_2 \)-evolving radiotherapy. As shown in Figure 3B, AuNPs were in situ grown on the surface of porphyrinic MOF to achieve MOF–Au artificial enzyme with PEGylation. Such MOF–Au nanoparticles catalyze \( \text{H}_2\text{O}_2 \) into \( \text{O}_2 \) to improve hypoxic TME for enhancing \( \text{O}_2 \)-dependent radiotherapy.

Similarly, He et al. developed ultrasmall Au NP–decorated zirconium TCPP(Fe) MOFs coated on UCNPs (UMOF NPs) to utilize dual nanozymes to achieve cascade
catalytic reactions for O₂ supply. GOx-mimicking ultra-small AuNPs and catalase-mimicking porphyrin (Fe) in UMOFs construct an effective cascade system for tumor treatment.

4.3.3 | MOF-based superoxide dismutase (SOD)-mimicking nanozymes for cancer therapy

SOD is one kind of natural enzyme that could catalyze O₂⁻ into O₂. Zhang et al. reported versatile MOFs as SOD-mimicking nanozymes to improve PDT efficacy by alleviating the limitation of hypoxic TME. The versatile MOFs (DBBC–UiO) were composed of bacteriochlorin ligands (DBBC) and Hf₆(μ₃-O)₄(μ₃-OH)₄ clusters and could enable massive O₂⁻ under NIR laser irradiation. Furthermore, part of O₂⁻ was transformed into O₂ by SOD-mimicking activity to underhypoxic TME, and enhanced O₂⁻ generation.

4.4 | Two-dimensional materials as integrated nanozymes for cancer therapy

Two-dimensional materials are attractive to be applied in catalytic therapy because of their high specific surface area and convenient surface modification. For instance, molybdenum sulfide (MoS₂) nanozymes present POD activity that has been reported to obtain nanocatalytic reactor for cascade chemocatalytic therapy. In this work, GOx (G), TPZ (T), and chitosan (C) were anchored on the surface of MoS₂ by self-assembly to compose MoS₂@CGTC nanocatalytic reactor. The self-supplied H⁺ and H₂O₂ generated by glucose oxidation augment POD activity remarkably to yield abundant ·OH for catalytic therapy. Layered double hydroxides (LDHs) are a class of typical lamellar 2D nanomaterials that can be designed by regulating the compositions of both the hydroxide layer and interlayer anions. Mei et al. reported CoFe-layered double hydroxides (CoFe–LDHs) for cascade-promoted CDT. GOx is assembled onto CoFe–LDH monolayer nanosheets to trigger massive H₂O₂ generation. Further Fenton reaction was catalyzed by highly dispersed Fe³⁺ in the host layer with H₂O₂ to enable cascade catalytic therapy.

Synergistic cancer therapy with PDT and other catalytic therapies has also been studied widely. With catalytic therapy, ·OH produced by the Fenton reaction, POD and SOD catalytic reactions, and water decomposition were reported to combine PDT. As shown in Figure 3C, hierarchical structural nanomaterials were designed as three parts: a mesoporous carbon nitride (C₃N₄) layer as outer coating, nitrogen-doped graphene quantum dots (N-GQDs) as inner core, and hollow mesoporous silica nanospheres (HMSNs) as shell of N-GQDs inside C₃N₄ coating. Finally, the polymer with RGD was decorated on N-GQDs@HMSN@C₃N₄ to obtain nanomaterials named R-NCNPs. Such R-NCNP NPs could catalyze water decomposition to produce O₂ for PDT.

4.5 | Supramolecular complex as an integration of nanozymes for cancer therapy

Zhang et al. incorporated GOx in ZIF-8, coated it with a metal polynphenol network (MPN), and named it GOx@ZIF@MPN. Intracellular degradation of outer shell MPN produces Fe(III) as well as tannic acid (TA) and releases internal GOx in ATP-overexpressing tumor cells. Endogenous glucose could be degraded to produce plenty of H₂O₂ catalyzed by GOx; then, self-produced H₂O₂ would be catalyzed by Fe(II), which originated from Fe(III) reduced by TA, to generate highly toxic ·OH. However, the stability and high catalytic activity of GOx are two incompatible factors that inhibit the effectiveness of cascade-promoted CDT.

4.6 | Macromolecule-based nanomaterials as integrated nanozymes for cancer therapy

Macromolecules were widely applied in cancer therapy to deliver therapeutic molecules or materials into tumor because of their stability and flexible structural design. Cao et al. designed L-Arg-rich poly(ε-caprolactone)-block poly(L-arginine) (PCL-b-PArg) to enable gas therapy. Such design could provide stable protection to L-Arg during in vivo transportation. A pH-sensitive coating based on polyethylene glycol–block–polydimethylmaleic anhydride (PEG–b–PDMA) was assembled with PCL–b–PArg to enable precise control on L-Arg release. Then β-lapachone (Lapa) was assembled on PCL–b–PArg nanoparticles to produce H₂O₂ for NO generation. Consequently, ROS generation and NO release were connected with acidity-triggered nanosystems in a cascade way to provide effective gas therapy.

Inspired by the natural enzyme POD, Liu et al. utilized Fe–protoporphyrin IX (natural heme) as catalyst to integrate with black phosphorus nanosheet (BPNS)-based PDT agent to enable cascade catalytic therapy. Specifically, heme could catalyze H₂O₂ decomposition locally to provide O₂ for further PDT. A heme dimer (dHeme) with mild POD activity was obtained by designing conjugates containing heme monomers
and heme-labeled oligonucleotides. Consequently, the sustained O₂ supply improved in situ PDT in hypoxic TME.

5 | CONCLUSIONS AND PERSPECTIVES

Catalytic chemical reactions have been studied widely to achieve tumor-specific therapy or synergistic therapy with other treatments. Benefiting from the differences in the catalytic activity of catalysts and microenvironments in tumor sites or normal tissues, tumor-specific therapy is enabled with negligible side effects. Catalysis of oxygen generation, glucose, or lactate oxidation enhances chemotherapy, chemodynamic therapy, radiotherapy, PDT, and gas therapy by providing O₂ or H₂O₂. Cascade strategies are helpful to augment therapeutic efficacy by rational integration of nanomaterials. Herein, we summarized the catalytic reactions, catalysts (Table 1), and cascade strategies that promote catalytic cancer therapy. Furthermore, more issues are considerable for nanomaterials applied in cascade-promoted catalytic cancer therapy.

1. The catalytic activity of nanomaterials shall be further improved. On the one hand, the poor stability of natural enzymes in the physiological environment limited their application, which requires protection and delivery of nanomaterials with better design. On the other hand, the catalytic activity of nanozymes is still limited by the TME like pH, redox conditions, etc. In previous studies, enormous experience has provided specific instructions to design nanomaterials with high catalytic activity, including element valence, crystallinity, and hybridization of nanomaterials. Prospectively, sophisticated structural design of nanozymes shall be considered to obtain biocompatible and highly effective catalysts.

2. The unsatisfied therapeutic efficacy of cascade promoted catalytic cancer therapy required novel strategies for materials design. For instance, the catalytic generation of O₂ is beneficial for augmenting sonodynamic therapy with nanozymes. Emerging electrodynamic therapy, which can generate ROS by nanomaterials under an alternating electric field, is considered to be combined with cascade catalytic therapy for effective tumor ablation. Artificial “superneutrophils” were reported to generate HClO, which could eliminate malignant tumor cells with a cascade reaction catalyzed by CPO and GOx. Additionally, immunomodulation is a considerable issue that could be utilized by improving the O₂ environment or changing the ROS level in tumors.

3. Biosafety of nanomaterials for cascade promoted catalytic cancer therapy is a significant factor that shall be verified to ensure plausible clinic application. Besides regular cytotoxicity and histocompatibility, studies on long-term retention of nanomaterials including metals and polymers are necessary before clinic trials. Moreover, nanomaterials with selective catalytic properties in TME are worthy of being developed to achieve tumor-specific therapy and avoid damage to normal tissue. For instance, nanozymes with tardy activity in neutral conditions and high activity in acidic environment are worthy of investigation. Meanwhile, some nanozymes could act as ROS scavengers in normal tissues and cell killers in tumor sites because of the difference catalytic activity under different pH conditions. Furthermore, special substances (such as glutathion) overexpressed in tumor sites could be utilized for efficient cancer therapy.

4. The development of nanomaterials that are available for large-scale production with low cost and mild condition is considerable. Even though most nanomaterials in previous studies are cost-effective in lab scale preparation, expensive equipment, complicated process, and difficulty in scale-up are common problems limited the large-scale production and subsequent application of nanomaterials.

In summary, nanomaterials for cascade strategies have been proposed to enable synergistic effects of different therapeutic treatments and are expected to be more efficient and tumor-specific.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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