The Application of Biomedicine in Chemodynamic Therapy: From Material Design to Improved Strategies

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Abstract: Chemodynamic therapy (CDT) has garnered significant interest as an innovative approach for cancer treatment, owing to its notable tumor specificity and selectivity, minimal systemic toxicity and side effects, and absence of the requirement for field stimulation during treatment. This treatment utilizes nanocatalytic medicines containing transitional metals to release metal ions within tumor cells, subsequently initiating Fenton and Fenton-like reactions. These reactions convert hydrogen peroxide (H₂O₂) into hydroxyl radical (•OH) specifically within the acidic tumor microenvironment (TME), thereby inducing apoptosis in tumor cells. However, insufficient endogenous H₂O₂, the overexpressed reducing substances in the TME, and the weak acidity of solid tumors limit the performance of CDT and restrict its application in vivo. Therefore, a variety of nanozymes and strategies have been designed and developed in order to potentiate CDT against tumors, including the application of various nanozymes and different strategies to remodel TME for enhanced CDT (e.g., increasing the H₂O₂ level in situ, depleting reductive substances, and lowering the pH value). This review presents an overview of the design and development of various nanocatalysts and the corresponding strategies employed to enhance catalytic drug targeting in recent years. Additionally, it delves into the prospects and obstacles that lie ahead for the future advancement of CDT.

Keywords: chemodynamic therapy; Fenton/Fenton-like reaction; nanomedicine materials; tumor microenvironment

1. Introduction

Cancer, as a major public health problem, causes approximately 10 million deaths worldwide every year due to its high incidence rate and mortality [1]. However, for patients with early-stage (stage I/II) cancer, traditional cancer treatments such as surgery, chemotherapy, and radiotherapy are less effective and have unavoidable side effects [2–4]. Therefore, the development of innovative and effective cancer therapies with improved efficacy and fewer side effects is both urgent and challenging.

Reactive oxygen species (ROS) is a general term for a class of chemically active molecules or ions with high oxidation activity, including hydrogen peroxide (H₂O₂), superoxide anion (O₂⁻), hydroxyl radical (•OH) and singlet oxygen (‘O₂), peroxy hydroxyl radical (•OOH), etc., which plays an important role in various physiological processes of biological systems [5]. A large number of studies have shown that the overgenerated ROS could break the redox hemostasis and cause a series of biochemical reactions, such as decreased
mitochondrial membrane potential, DNA breakage, cytoskeleton contraction, chromatin condensation, etc., leading to cancer cells death [6,7]. Since cancer cells are more sensitive to ROS levels, ROS generation is considered to be an effective way to kill tumor cells selectively.

Currently, the applications of ROS-based tumor therapies mainly including photodynamic therapy (PDT), chemodynamic therapy (CDT), and sonodynamic therapy (SDT) have attracted significant attention from researchers [8,9]. Among these treatment modalities, various methods can generate excessive ROS. In PDT treatment, the photosensitizer generates ROS under the action of near-infrared irradiation, and the local ROS burst promotes cell apoptosis. The cavitation effect, sonoluminescence, and piezoelectric effect are the main mechanisms of ROS generation in SDT. At the same time, there are other ways to increase ROS levels in tumors. For instance, Wang et al. reported a kind of ultrathin two-dimensional metal-organic framework (Cu-TCPP), which was endowed with selectively producing $^1\text{O}_2$ in the tumor microenvironment for tumor therapy [10]. Firstly, the acidic $\text{H}_2\text{O}_2$ peroxidized the tetrakis(4-carboxyphenyl) porphyrin (TCPP) ligand, and then it was reduced to peroxyl radicals under the action of peroxidase (POD)-like nanosheets and Cu$^{2+}$. Finally, a spontaneous recombination reaction based on the Russell mechanism occurred to generate $^1\text{O}_2$. In addition, Cu-TCPP also consumed glutathione (GSH) through a cyclic oxidation mechanism. Based on the above two “magic weapons”, Cu-TCPP nanosheets efficiently and selectively destroyed tumors.

CDT, proposed by Bu and co-workers in 2016, has emerged as a fascinating research area in recent years. This is primarily due to its remarkable specificity and selectivity for tumors, minimal systemic toxicity and side effects, and the absence of a requirement for field stimulation during treatment [11,12]. All the facts demonstrated that CDT not only had the potential to enhance the efficacy of cancer treatment but could also be used for bacterial infection treatments [13]. Generally, CDT utilizes peroxidase-like catalysis, metallic catalysis, or Fenton and Fenton-like reactions to significantly enhance intracellular ROS. Herein, transitional metal-based nanocatalytic medicines containing some metal ions (e.g., Fe, Cu, Mn, Co, V, Pd, Ag, Mo, Ru, W, and Ce) are utilized to release metal ions in tumor cells and then trigger Fenton and Fenton-like reactions to convert $\text{H}_2\text{O}_2$ into $\text{•OH}$ with higher toxicity in an acidic tumor microenvironment (TME), thus inducing the death of tumor cells [14]. However, the performance of CDT is limited by some natural factors, which makes it difficult to be widely applied. Firstly, there are insufficient endogenous $\text{H}_2\text{O}_2$ in tumors with a content of 50–100 µmol L$^{-1}$, which is insufficient to meet the ideal CDT therapeutic efficiency [15]. Secondly, the produced oxidative $\text{•OH}$ could be captured and neutralized by the overexpressed reducing substances in the TME, such as GSH and hydrogen sulfide (H-S), resulting in an unsatisfactory therapeutic efficiency [16,17]. Thirdly, the weak acidity (pH 6.5–7.0) of solid tumors is not suitable for Fenton and Fenton-like reactions, which are required to be remodeled to provide more suitable reaction conditions [18]. Up to now, a variety of nanozymes and strategies have been designed and developed in order to solve these problems (Scheme 1) [12,19]. This review aims to provide an overview of the design and development of different types of nanozymes as well as strategies to improve CDT in recent years. Finally, the opportunities and challenges for the future development of CDT are also discussed to promote clinical translation.
2. Fenton/Fenton-like Reagent

Nowadays, the research into efficient nanozymes for Fenton and Fenton-like reactions has attracted extensive attention due to the wide application of CDT in cancer therapy. The choice of nanomaterials (iron-based materials, copper-based materials, and other
metal-based materials) is crucial because of the irreplaceable role of catalysts in Fenton and Fenton-like reactions.

2.1. Iron-Based Fenton Reagent

In recent years, many nanozymes containing catalytically active ions have been designed based on the Fenton reaction and the Fenton-like reaction. So far, iron-based materials have been widely used in the biological field and have shown excellent biosafety and biocompatibility [20,21]. Various iron-based nanomaterials have been extensively studied to enhance the efficacy of CDT, such as ferroferri oxide (FeOx) [22], ferrous disulfide (FeS2) [23], ferric oxide (FeOx) [24], Fe-metal organic frameworks (Fe-MOFs) [25], and Fe-doped nanoagents [26]. A Fenton reaction is often catalyzed by Fe2+ or Fe3+, which decomposes H2O2 to produce radical •OH, resulting in the destruction of lipids, proteins, and DNA. The reactions (Equations (1) and (2)) are shown below:

\[
\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \cdot\text{OH} + \text{OH}^- \tag{1}
\]

\[
\text{Fe}^{3+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{2+} + \cdot\text{OOH} + \text{H}^+ \tag{2}
\]

As one of the most classical H2O2-responsive nanozymes, FeOx nanoparticles become an effective POD-like enzyme with the Fe2+/Fe3+ redox cycle. As the reaction site of nanozymes, Fe2+ on the surface of FeOx nanoparticles reacted with the overexpressed H2O2 in TME to produce •OH, which was then converted to Fe3+ in the oxidized state, leading to severe tumor damage. In this reaction process, the oxidation property of the generated •OOH was lower than that of the generated •OH, and the rate of the generated •OH was relatively faster [27,28]. For instance, Du et al. successfully constructed kinds of hollow FeOx mesocrystals to realize the high level of •OH in the tumor region and a low expression of heat shock proteins, resulting in a self-enhanced antitumor efficacy between magnetic hyperthermia and CDT [29]. The therapeutic efficiency of nanomaterials was greatly restricted due to the low iron loading and cumbersome releasing route. Polydopamine (PDA) has been widely studied as a CDT agent owing to its high biocompatibility and radical scavenging strong chelation with Fe2+. Recently, Xiao et al. prepared a multifunctional hybrid nanozyme (PDA/FeOx), which was retained in infected sites via an external magnet (Figure 1a) [30]. PDA with redox-active catechol moieties supplied oxygen with electrons to produce H2O2, which was then decomposed by decorated ultrasmall FeOx to generate more •OH. Surprisingly, PDA/FeOx was equipped with simultaneous H2O2-self-sufficient •OH generation and GSH depletion to improve the CDT efficacy. In another work, Luo et al. synthesized a novel nanoplatform of FeOx@PDA@BSA-BiS2 nanoparticles via the amidation between the carboxyl and amino groups to promote the efficiency of Fenton reaction in cancer cells [31]. In this system, the FeOx nanoparticles were not only capable of triggering Fenton reactions to generate highly •OH from the innate H2O2 in the TME but were also employed as the magnetic resonance imaging (MRI) contrast agent for the precise cancer diagnosis. Specifically, PDA promoted the long-term Fenton reactions and tumor apoptosis by preventing oxidation of FeOx, which reacted with intracellular H2O2 to produce •OH and further suppressed tumor growth. Moreover, computed tomography (CT) contrast was also enhanced due to the significant X-ray attenuation coefficient of BiS2, enabling the simultaneous CDT and PDT treatment of tumors. On the other hand, this also contributed to the regulation of the CDT treatment process, minimizing the biotoxicity and improving diagnostic and therapeutic capabilities. Eventually, the present study demonstrated a novel and viable approach for synthesizing composite theranostic nanoplatforms.

In addition to FeOx, other iron-based materials are also endowed with superb Fenton reaction catalysis. For instance, Wu et al. developed hollow porous carbon-coated FeS2 (HPFeS2@C) nanocatalysts for triple-modal imaging-guided synergistic tumor starvation therapy (ST), photothermal therapy (PTT), and CDT [32]. Interestingly, glucose oxidase (GOx) in the multifunctional nanocatalysts reacted with glucose in the TME to increase
the H$_2$O$_2$ concentration, which improved the production of •OH. Meanwhile, tannic acid (TA) was effectively released for reducing Fe$^{3+}$ to Fe$^{2+}$ under near-infrared (NIR) laser exposure, thereby accelerating the Fenton reaction. In addition, the photothermal effect induced by NIR lasers also increased the catalytic efficiency. Furthermore, our group reported a phthalocyanine-iron-based complex FeS$_2$@PcD, program-regulated by the dual factors of gluconic acid (H$^+$) and H$_2$O$_2$ in the TME (Figure 1b) [33]. After the efficient internalization into cancer cells, FeS$_2$@PcD reacted with excessive H$^+$ to generate Fe$^{2+}$. Fe$^{2+}$ then catalyzed intracellular H$_2$O$_2$ to produce •OH for CDT and simultaneously generate Fe$^{3+}$ for further MRI as well as activating the released building block PcD (Figure 1c). Interestingly, the nitrogen atom on the DPA group of PcD specifically chelated Fe$^{3+}$, thereby recovering fluorescence and sonosensitizing activity. Moreover, in vitro data showed that the fluorescence intensity of FeS$_2$@PcD increased 52.21-fold, resulting from the programable response, whereas the signal of the H$^+$ or H$_2$O$_2$ univariate factor was almost unchanged (Figure 1d). Moreover, FeS$_2$@PcD combined with ultrasound irradiation had a significant inhibitory effect on HepG2 tumor-bearing mice tumor, with an inhibition rate of 87.15% (Figure 1e). In summary, our work achieved precise sonodynamic and chemo-dynamic therapies, providing a novel strategy for CDT-related clinical research.

To date, dihydroartemisinin (DHA) has been regarded as a drug candidate for cancer therapy. This mechanism was based on the breakdown of weak endoperoxide bridges by Fe$^{2+}$ to produce toxic ROS, which resulted in facilitating H$_2$O$_2$-mediated Fenton reactions to generate abundant ROS for effective CDT [34]. Xu et al. prepared an antibacterial nanoagent Fe$_2$O$_3$@DHA@MPN (FDM) for dual-augmented NIR and DHA antibacterial CDT [35]. As the core, α-Fe$_2$O$_3$ mesoporous nanorods provided both efficient DHA transport and an additional source of Fe$^{2+}$ used for enhanced CDT. Furthermore, metal-polyphenol networks (MPN) shells released DHA in response to the microenvironment and led to the release of TA and Fe$^{3+}$ simultaneously due to bacterial infection. Consequently, TA reduced Fe$^{3+}$ to Fe$^{2+}$ under NIR laser exposure, which was favorable for H$_2$O$_2$-mediated CDT as well as DHA-mediated CDT.
Recently, MOFs, which are composed of metal ions and organic ligands, have attracted increasing attention in catalysis, energy storage, separation, and cancer therapy [36,37]. Owing to the large pore surfaces, good biodegradability, and biocompatibility, MOFs were widely used as nanoplatforms for drug delivery. Therein, Fe-MOFs (like MIL-101) showed an efficient catalytic effect as a Fenton nanocatalyst. For instance, Chen et al. prepared photosensitizer-integrated nanoagents of MIL-101(Fe)@TCPF for implementing the combined PDT and CDT [38]. In this system, the MIL-101(Fe) MOF transformed endogenous H₂O₂ into •OH via Fe ion-catalyzed Fenton reaction, resulting from the intrinsic POD-mimicking activity of MIL-101(Fe)@TCPF. Moreover, the photosensitizer TCPF was covalently connected with MIL-101(Fe) through amide bonds, leading to in situ ¹⁸O₂ evolution at the tumor region under light irradiation and amplifying ROS-induced oxidative damage. Similarly, Yin et al. successfully synthesized a cascade biomimetic nanoplatform of CPPO@Fe-porphyrin-MOF@Cancer cell membrane-GOD (C₈@M@C₉G) by loading harbors bis(2-carbopentlyoxy-3,5,6-trichlorophenyl) oxalate (CPPO) into the Fe-porphyrin-MOF nanoparticle, which was further coated with the cancer cell membrane and grafted GOD on the surface (Figure 2a) [39]. After accumulating in the tumor site, GOD-catalyzed
glucose oxidation activated the therapy of starvation, thereby consuming the local glucose and further generating H⁺ and H₂O₂, further greatly decreasing the pH of the microenvironment and promoting the massive generation of •OH for efficient CDT. Simultaneously, CPPO, as an energetic reagent, reacted with some other H₂O₂ to form high energy states, which excited porphyrin photosensitizers and produced ¹O₂ for PDT in situ. Overall, this work combined CPPO-induced PDT, Fenton reaction-based CDT, and GOD-catalyzed ST to synergistically enhance cancer therapy with effective cascade catalysis, and also broaden anticancer pathways.

Additionally, due to properties such as prominent molecular recognition ability and accurate addressability of nucleic acids, DNA-based hydrogels have outstanding advantages in controlling the release of encapsulated cargoes for controlled drug delivery [40-42]. Wang et al. prepared a kind of MOF-biomineralized DNA nanosphere (Fe-DNA@ZIF-8) via cascade reactions to implement the intracellular H₂O₂ level for enhanced CDT (Figure 2b) [43]. Fe-DNA was composed of Fe²⁺ and DNA molecules by coordination-driven self-assembly, which was then coated by zeolitic imidazolate framework-8 (ZIF-8) for mineralization. At the same time, GOx was encapsulated into ZIF-8 to further form Fe-DNA/GOx@ZIF-8. After being endocytosed by tumor cells, Fe-DNA and GOx were released in the acidic condition, providing Fe²⁺ and Fe⁴⁺ to activate the Fenton reaction and catalyzing glucose into H₂O₂ to enhance CDT effectiveness. In addition, multimetallic alloy nanostructures demonstrated higher catalytic activity than monometallic components owing to the electronic coordination effect, leading to its wide application. For example, Jana et al. fabricated a trimetallic (Pd, Cu, and Fe) alloy nanozyme (PCF-a NEs) with dynamic active-site synergism, which depleted intracellular overexpressed GSH and reduced the cellular self-defense antioxidant mechanism [44]. PCF-a NEs had the synergistic peroxidase-like property to promote •OH in the presence of Cu and Fe, thus boosting the effectiveness of CDT. This work pointed to the potential for using alloy nanozymes for tumor-specific treatments mediated by external stimulus.

To improve the application of iron-based nanoparticles for efficacious CDT, an effective method was to accelerate the conversion efficiency of Fe²⁺ and Fe⁴⁺. The low indirect band-gap (1.2–1.8 eV) of MoS₂ made it an effective co-catalyst for the Fenton reaction, which converted Fe(III) into Fe(II). For example, our group synthesized gallic acid (GA)-modified MoS₂ nanosheets coated with high Fe(III) (MoS₂@GA-Fe), which were used for photoacoustic (PA) imaging and MRI-guided combined cancer treatment integrating •OH and H₂O₂ (Figure 2c) [45]. Firstly, GA-Fe(III) reacted with overexpressed GSH to produce GA-Fe(II), which promoted the generation of •OH in the TME. Moreover, after Mo (IV) was oxidized to Mo (VI), 5-Mo-S was destroyed, exposing active sites for further reaction cycles and converting unsaturated sulfur atoms to H₂S with selective cytotoxicity to cancer cells. Additionally, PA imaging for BALB/c nude tumor-bearing mice after intravenous injection of MoS₂@GA-Fe showed that the signal of the tumor area was enhanced and remained for 24 h, resulting from the structure-based enhanced permeability and retention (EPR) effect (Figure 2d,e). Thus, the TME-responsive “Fenton Nanoreactor” was used as a promising nanomedicine to treat cancer or other diseases and improve patient health.
Figure 2. (a) Schematic representation of the fabrication procedure of C@M@C:G NSs and their working mechanism of CL–induced PDT, Fenton reaction–based CDT, and GOD–mediated ST. Reproduced with permission [39]. Copyright 2021, Royal Society of Chemistry. (b) Scheme of Fe–DNA/GOx@ZIF–8 for enhanced CDT. Reproduced with permission [43]. Copyright 2021, Elsevier Ltd. (c) Theranostic mechanism of the MoS2@GA–Fe NPs for PA/MR imaging–guided HCC treatment. (d) The PA images and (e) intensity of tumor–bearing mice after intravenous injection with MoS2@GA-Fe. Reproduced with permission [45]. Copyright 2021, Elsevier Ltd.

2.2. Copper-Based Fenton-like Reagent

In addition to ferrous iron ions, other transition metal ions like Cu2+ also have catalytic effects in Fenton and Fenton-like reactions. As a potential alternative to Fe-based nanomaterials, Cu-based nanomaterials have found a variety of applications in many CDT research fields. Cu-catalyzed Fenton-like reactions occur in neutral and very mild acidic conditions, which are less violent than that of Fe-catalyzed Fenton reactions [46]. Moreover, the valence transition between Cu2+ and Cu+ is usually accompanied by depletion of the excessive GSH in the TME, enhancing the production of •OH to achieve highly efficient CDT [47]. Hence, Cu-based nanomaterials have been extensively employed as Fenton reagents, such as copper sulfide (CuS), copper oxide (CuO), Cu-based MOF, and Cu-doped nanoagents [48–51]. The Cu-based catalytic reactions (Equations (3) and (4)) are shown below.

\[
\text{Cu}^+ + \text{H}_2\text{O}_2 \rightarrow \text{Cu}^{2+} + \bullet \text{OH} + \text{OH}^{-} \quad (3)
\]

\[
\text{Cu}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Cu}^+ + \bullet \text{OOH} + \text{H}^+ \quad (4)
\]

More and more attention has been paid to CuS nanoparticles because of their low toxicity, their ability to penetrate into biological tissues after being stimulated by NIR light, and their PA and Fenton-like properties [52–54]. For instance, Kong and co-workers reported a smart biomimetic enzyme system of CuGP/G, which was composed of the CuS nanoparticle, generation 5 poly (amidoamine) (G5) dendrimer, and GOD for the combination of CDT and PTT (Figure 3a) [55]. Specifically, CuS cores with Fenton-like catalysts were entrapped by positively charged G5, which simultaneously bonded to the negatively charged GOD via electrostatic interactions as a carrier. Additionally, H2O2 was produced by GOD to generate •OH in the sequential Fenton-like reaction, resulting in efficient tumor treatment. Moreover, the Michaelis–Menten kinetic curve demonstrated that the Michaelis–Menten constant (Km) was \(3.75 \times 10^{-3} \text{ M}\), and the maximum reaction velocity
(Vm) was calculated at $3.6 \times 10^{-7}$ M s$^{-1}$ after incorporating GOD with CuGP (Figure 3b,c), compared to a FeO$_3$-GOD system with the Km of $10.93 \times 10^{-3}$ M and the Vm of $4.22 \times 10^{-8}$ M s$^{-1}$, indicating that the Fenton-like catalytic activity of CuGP/G was better than the FeO$_3$-GOD-based system [56]. Nevertheless, CuS was usually trapped by the endothelial reticular system or rapidly cleared by the kidney, resulting in poor accumulation in tumors. To efficiently transport CuS to tumor cells, Li et al. used macrophages to phagocytose large supramolecular aggregates of CuS for the specific-release nanomedicines in the tumor region (Figure 3d) [57]. The supramolecular aggregates were composed of CuS nanoparticles, which were capped by β-cyclodextrin (β-CD) and ferrocene (Fc), respectively, and self-assembled via β-CD-Fc host–guest interactions. Since macrophages were attracted to tumor tissue with inflammatory properties, nanomedicines were successfully delivered through macrophages and then the β-CD-Fc host–guest pair were dissociated by the oxidation of ferrocene, inducing the disassemble of CuS aggregates into small CuS nanoparticles for further photothermal-enhanced CDT. This work proposed a feasible strategy for specific cancer therapy and new insights into new cell-based medicine carriers.

![Figure 3.](image)

**Figure 3.** (a) Synthetic route of CuGP/G. (b) The Michaelis–Menten kinetic curve and (c) Lineweaver–Burk plotting curve that indicate the catalytic activity of CuGP/G with the addition of GOD. Reproduced with permission [55]. Copyright 2020, WILEY–VCH. (d) Preparation of the supramolecular aggregates composed of CD–CuS and Fc–CuS and its action mechanism of tumor-targeted PTT/CDT. Reproduced with permission [57]. Copyright 2021, Royal Society of Chemistry.

CuO nanoparticles have aroused great interest in recent years, benefiting from the large surface area, reactive morphology, high catalytic reusability, and superb chemical and thermal stability [58,59]. As mentioned earlier, the rate of ⋅OH production was relatively faster relative to ⋅OOH in Cu-mediated CDT. As a representative CuO-based Fenton-like nanocatalyst in CDT, Jiang et al. reported the synthesis of semiconductor CuO and MoS$_2$ nanoflowers to construct MoS$_2$-CuO heteronanocomposites through a two-step hydrothermal method (Figure 4a) [60]. MoS$_2$-CuO heteronanocomposites were then loaded with bovine serum albumin (BSA) and immunoadjuvant imiquimod (R837) on its surface to further form MoS$_2$-CuO@BSA/R837 (MCBR) nanoplatorms, which had an excellent ability to eliminate the primary tumor and release tumor-associated antigens (TAAs). In this system, CuO responded to overexpressed H$_2$O$_2$ in tumor cells and produced a mass of ⋅OH through Fenton-like reactions. The reactions were further improved by the effect of MoS$_2$ due to its high photothermal conversion efficiency. And more importantly, MCBR released TAAs under 808 nm NIR laser irradiation, which combined with R837 to act as an immune-stimulating adjuvant to boost dendritic cells maturation
and the release of effector T cells from the lymph node. Consequently, this work achieved an efficient and tumor-specific therapy, providing a meaningful paradigm for future clinical applications. In another study, Xiao et al. prepared an intelligent nanoplatform of CuO@mPDA/DOX-HA (CPPDH) with self-sufficient H2O2 and GSH depletion for the synergistic chemotherapy, PTT, and CDT (Figure 4b) [61]. The surface of CuO nanoparticles was decorated with mesoporous polydopamine (mPDA) with seed-mediated microemulsion and further loaded with doxorubicin (DOX) via π-π stacking. Moreover, the obtained CuO@mPDA/DOX was constructed by hyaluronic acid (HA) using electrostatic adsorption to finally acquire CPPDH. After entering the intracellular HA environment, CuO was released to generate Cu²⁺ and H₂O₂ triggered by the acidic environment. The Cu²⁺ was then reduced to Cu⁺ by GSH, and subsequently Cu⁺ reacted with intracellular H₂O₂ to produce massive •OH for enhanced CDT. Interestingly, CPPDH had excellent targeting ability to tumor cells resulting from the specific binding affinity of HA, whose bonds overexpressed CD44 receptor in the tumor region. Furthermore, the nanoparticles were endowed with a superb effect of PTT due to the strong NIR absorption capacity of PDA, and the light-to-heat conversion efficiency was calculated as 20.8%, which was significantly higher than that of reported photothermal reagents like AuNRs@SiO₂ (20.8%) [62], MS-BSA (21.8%) [63], and Au-Cu₅S₅ nanoparticles (37%) [64].

In addition to the use of CuS and CuO, Cu-MOF also exhibited superb catalytic performance to achieve highly efficient CDT. For example, Tian et al. reported a nanoplatform integrating vitamin K3 into the MOF-199(Cu) to implement a CDT-mediated tumor therapy [65]. The hollow structures derived from MOFs have the virtue of drug loading and delivery with outstanding mass transfer and loading capacity. In a recent study, Cheng et al. proposed a strategy to incorporate Cu²⁺ into the precursors of ZIF-90 to form the Cu¹⁺²⁺ mixed-valence hollow porous structure (Cu/Zn-MOF) through heating treatment, and then Cu/Zn-MOF was integrated with Mn²⁺/MnO₂ using manganese(II) acetylacetonate(Mn(acac)₂) to construct a mixed-metal and mixed-valence (Cu¹⁺²⁺/Mn²⁺⁴⁺) structure, which was finally loaded by the photosensitizer indocyanine green (ICG) to prepare ICG@Mn/Cu/Zn-MOF@MnO₂(Figure 4c,d) [66]. After being endocytosed by tumor cells, Cu²⁺ and MnO₂ oxidized GSH to generate a great mass of ROS and Cu⁺ and produced Mn²⁺, which was used to “turn on” MRI. Subsequently, the obtained Cu⁺ and Mn²⁺ catalyzed H₂O₂ to produce •OH for effective CDT via the Fenton-like reaction and O₂ through a synergistic catalytic effect to relieve the hypoxia for the enhanced PDT. Then, the aggregated ICG in the system was not only employed for photothermal imaging (PTI) with excellent photothermal capacity, but also achieved “turn on” fluorescence imaging (FLI) after its release in tumor cells. Irradiated with a single 808 nm NIR, ICG@Mn/Cu/Zn-MOF@MnO₂ exhibited an obvious temperature increase with an excellent photothermal conversion efficiency of 30.1% and converted the O₂ generated in situ into O₃ for enhancing the effect of PDT. ICG@Mn/Cu/Zn-MOF@MnO₂ was expected as a versatile platform of PTI/FLI/MRI trimodality imaging due to the high photothermal conversion, ICG release capability, and the generation of Mn²⁺ that responded to TME.
2.3. Other Metal-Based Fenton-like Reagents

In addition to Fe- and Cu-based Fenton reagents, other metals have also been used in Fenton and Fenton-like reactions, such as Mn [67], Ti [68], Ag [69], Pt [70], V [71], and Ru [72]. For Mn-based Fenton reagents, manganese oxide (MnOx) triggers the generation of oxygen, a unique behavior that alleviates the hypoxia of TME, making it the most commonly used Mn-based Fenton nanomaterial in biological applications [73]. Moreover, as a classical Fenton-like reagent, MnOx can enhance CDT effectiveness by depleting intracellular GSH. Meanwhile, Mn$^{2+}$ has been demonstrated as an effective contrast agent for tumor $T_1$-weighted magnetic resonance imaging ($T_1$-MRI), and it also has excellent PTI, photoacoustic imaging (PAI), and ultrasound imaging capabilities [74–76].

In a recent study, Xiao and co-workers reported kinds of macrophage membrane-coated polymer nanogels (MPM@PNGs), which were co-loaded with MnO$_2$ nanoparticles and cisplatin to achieve specific targeted chemotherapy and CDT (Figure 5a) [77]. In this nanoplatform, redox-responsive poly (N-vinylcaprolactam) nanogels containing disulfide bond (S-S) cross-linkers were disintegrated in TME to specifically release cisplatin and consume GSH to enhance CDT. Furthermore, MnO$_2$ simultaneously consumed the highly concentrated endogenous GSH to promote the production of •OH, and the produced Mn$^{2+}$ catalyzed the decomposition of H$_2$O$_2$ to generate ROS for tumor apoptosis and was also employed for $T_1$-MRI (Figure 5b). In addition, the outer macrophage membrane enabled the polymer nanogels to penetrate the blood–brain barrier (BBB) due to the overexpressed macrophage-1 antigen, integrin $\alpha_4$, and $\beta_1$ on the surface for effective glioma targeting. Consequently, this nanoplatform represented a feasible way to enhance MRI-guided synergetic antitumor effect. To realize more accurate cancer imaging and effective treatment, Wang et al. employed poly(lactic-co-glycolic acid) (PLGA) nanoparticles with porous structure as templates to prepare hollow MnO$_2$ (HMnO$_2$) shells in situ, which were
further utilized to deliver bufalin and then cloaked with platelet membrane (Figure 5c) [78]. Bufalin and platelet modification were able to inhibit cancer angiogenesis, block cancer cell growth, and improve tumor targeting mediated by specific binding of P-selectin to the CD44 receptor of cancer cells. Moreover, under conditions of acidic tumor pH and relatively high GSH concentration, HMnO$_2$ nanoparticles were rapidly degraded to allow the controlled release of bufalin, while Mn$^{2+}$ was obtained for magnetic resonance monitoring and further targeted chemotherapy and CDT.

Recent reports have especially shown that multicomponent metallic composites improved activity and selectivity compared to single components, which was called the “synergetic catalytic effect” [79,80]. Zhou et al. synthesized cerium peroxide with good stability and then in situ doped Fenton-type metallic peroxides (Fe$^{2+}$, Cu$^{2+}$, Mn$^{2+}$, Ce$^{4+}$, Cr$^{3+}$, etc.) to successfully prepare cerium peroxide matrix (M-CeO$_x$) as a novel Fenton-type bimetallic peroxide nanomaterial [81]. Interestingly, the results of 3,3′,5,5′-tetramethylbenzidine (TMB) assays exhibited that the maximum absorbance increase of TMB increased 40–60-fold at pH 7.0 in the presence of M-CeO$_x$, suggesting that the relatively high pH stimulated the generation of •OH and M-CeO$_x$ had excellent catalytic performance. In this prepared M-CeO$_x$, 10% doping of Mn had much higher catalyst efficiency, and Mn-CeO$_x$ represented superb anticancer activity at the relatively high pH, due to the in situ self-generated H$_2$O$_2$ supplement and the multmetal-mediated synergistic-enhanced catalytic activity. In addition, in a recent work by Wu’s group, a novel type of organosilica hybrid micelles (Mn$_3$O$_4$@PDOMs-GOD) was designed and constructed by co-loading Mn$_3$O$_4$ and GOD for enhanced ST and CDT [82]. After the entry of Mn$_3$O$_4$@PDOMs-GOD in the tumor cells, GOD effectively depleted glucose and produced a large amount of H$_2$O$_2$ at the same time. Under the condition of acidic TME, H$_2$O$_2$ was decomposed into O$_2$ by Mn$_3$O$_4$, breaking the vicious cycle of hypoxia and simultaneously enhancing the GOD-mediated ST effect through the regeneration of H$_2$O$_2$. Meanwhile, Mn$_3$O$_4$ also reacted with
overexpressed GSH to release Mn\(^{2+}\), thereby converting the increased H\(_2\)O\(_2\) into highly toxic •OH. Eventually, the MnO\(_3\)@PDOMs-GOD nanosystem exhibited excellent cascade catalytic performance in the TME, which endowed it with a superior ability of sustained and stable delivery of O\(_2\) and H\(_2\)O\(_2\) in situ. Overall, the novel type of organosilica hybrid micelles was a promising approach to improve the efficiency of O\(_2\)-dependent ST and H\(_2\)O\(_2\)-dependent CDT.

3. Different Strategies to Improve CDT Performance

Although CDT has unique advantages over cancer treatments, its wide application in vivo is still limited by factors such as harsh Fenton reaction conditions, complex physiological environment, and limited reaction efficiency. Accordingly, to tackle the main obstacles existing in CDT, several strategies have been proposed to change this dilemma in the past few years. In general, the strategies to improve CDT performance are as follows: (1) CDT efficacy is improved by generating more H\(_2\)O\(_2\); (2) oxidative stress at the tumor cells is enhanced by decreasing the reducing substances amount; and (3) CDT efficiency is improved by reducing the pH value.

3.1. Increasing H\(_2\)O\(_2\) Level

The concentration of H\(_2\)O\(_2\) plays an important role in the efficiency of CDT. In response to the limitation of endogenous H\(_2\)O\(_2\) deficiency in the tumor region, an earlier approach was to directly deliver exogenous H\(_2\)O\(_2\) into the body [83]. For example, Li et al. prepared a PLGA polymersome to encapsulate H\(_2\)O\(_2\) into a hydrophilic core for direct delivery of exogenous H\(_2\)O\(_2\) [84]. However, supplementing H\(_2\)O\(_2\) from an external source had a risk of leakage and was difficult to implement. Therefore, several approaches for production in situ of endogenous H\(_2\)O\(_2\) have been designed to overcome the limitation of H\(_2\)O\(_2\) insufficiency in the tumor cells, such as the application of H\(_2\)O\(_2\)-related enzymes, metal peroxides, and photocatalysts.

GOx, which was able to specifically oxidize β-D-glucose into H\(_2\)O\(_2\) and H\(^+\), was ideal for increasing tumor acidity and H\(_2\)O\(_2\) level [85]. Zhang et al. synthesized an adenosine triphosphate (ATP)-responsive autocatalytic Fenton nanoagent (GOx@ZIF@MPN) for tumor therapy (Figure 6a) [86]. The nanoagents had cores which were formed by GOx and then incorporated with ZIF and MPN shells. Interestingly, the MPN shell was decomposed into TA and Fe\(^{3+}\) by the overexpression of ATP existing in the tumor cells, resulting in the exposure of internal GOx. Subsequently, the GOx consumed endogenous glucose to generate abundant H\(_2\)O\(_2\). And TA then reacted with Fe\(^{3+}\) to produce Fe\(^{2+}\), which converted H\(_2\)O\(_2\) to •OH and finally exerted good antitumor efficacy. It is widely known that GOx, as an aerobic enzyme, cannot efficiently catalyze the production of H\(_2\)O\(_2\) in situ due to the hypoxic condition of cancer cells. To address this situation, Feng et al. employed MnO\(_2\) as an oxygen donor to compose core-shell structured nanoplatfor Fe:Co-GOD@MnO\(_3\) which generated O\(_2\) through the weakly acidic TME-specific response, thereby enhancing the process of GOx to catalyze the production of H\(_2\)O\(_2\) from glucose and O\(_2\) (Figure 6b) [87]. Tao et al. designed a new CDT nanosystem of RBC@Hb@GOx that effectively overcame the restriction of BBB by using GOx to elevate H\(_2\)O\(_2\) concentration at the tumor site for the treatment of glioblastoma multiforme. Specifically, hemoglobin (Hb) and GOx were combined as an alternative synthetic Fenton catalyst and then encapsulated with red blood cell (RBC) membranes to achieve longer retention time and less immunogenic responses.

ROS-regulated nanozymes, such as superoxide dismutase (SOD) and POD, are employed to regulate intracellular and extracellular ROS concentrations. Hence, materials possessing SOD-like or POD-like enzyme activity are extensively utilized to enhance the level of ROS in TME [88,89]. In a study by Sang and her collaborators, the nanoparticle zeolitic imidazole framework-67 (ZIF-67) was constructed by assembling cobalt ions with 2-methylimidazole [90]. Subsequently, small-molecule inhibitor 3-amino-1,2,4-triazole (3-
AT) and COOH-PEG-COOH were modified on the surface of ZIF-67 to fabricate the final product PZIF67-AT. PZIF67-AT with SOD-like activity could break the homeostasis of H$_2$O$_2$ and convert plenty of O$_2$•⁻ into H$_2$O$_2$. At the same time, the small molecule inhibitors released in the acidic microenvironment effectively inhibited the activity of catalase (CAT) and reduced the self-consumption of H$_2$O$_2$. In a separate study, Dong et al. constructed a nanozyme with tunable multi-enzymatic activities named PHMZCO-AT, which was composed of a hollow mesoporous Mn/Zr-doped CeO$_2$ and 3-AT (Figure 6c) [91]. The nanozyme PHMZCO-AT, with enhanced SOD-like and POD-like activities, as well as inhibited CAT-like activity, allowed more H$_2$O$_2$ to participate in the Fenton reaction, thereby generating massive hydroxyl radicals to induce tumor cells apoptosis and death.

In addition to the SOD-like activity materials, cisplatin and β-Lapachone have also been demonstrated to be involved in affecting the related enzymes responsible for the generation of H$_2$O$_2$. For example, cisplatin was an extensively used broad-spectrum chemotherapy drug for cancer therapy. It was reported that nicotinamide adenine dinucleotide phosphate (NADPH) oxidase existing in cancer cells could be specifically activated by cisplatin and, subsequently, an O$_2$ molecule was converted into O$_2$•⁻ after accepting an electron provided by the oxidation of NADPH, which was further catalyzed by SOD to produce the final H$_2$O$_2$ [92]. Ren et al. utilized this mechanism to design and synthesize the nanodrug of PTCG, which was composed of phenolic platinum (IV) prodrug, epigallocatechin-3gallate, and copolymer (PEG-b-PPOH) [17]. The study demonstrated that activated cisplatin was employed to increase the intracellular H$_2$O$_2$ level obviously via a cascade reaction in vitro and in vivo. Moreover, β-Lapachone, a new antitumor drug, was catalyzed by NAD(P)H: quinone oxidoreductase1 (NQO1) to generate H$_2$O$_2$ [93]. For instance, Wang et al. combined β-Lapachone, iron oxide nanoparticles, and camptothecin (CPT) to form pH- and H$_2$O$_2$-dual-responsive nanoplatform LaCIONPs (Figure 6d) [94]. The research indicated that β-Lapachone could generate large amounts of H$_2$O$_2$ through tumor-specific NAD(P)H: NQO1 catalysis. Interestingly, the product H$_2$O$_2$ not only participated in the Fenton reaction but also specifically activated the release of camptothecin from LaCIONPs for chemotherapy.

**Figure 6.** (a) Schematic illustration of the synthesis of GOx@ZIF@MPN and its detailed therapeutic mechanisms for synergetic CDT and ST. Reproduced with permission [86]. Copyright 2018,
American Chemical Society. (b) Schematic illustration of the therapeutic mechanisms of FeC–GOD@MnO. Reproduced with permission [87]. Copyright 2018, American Chemical Society. (c) The action mechanism of PHMZCO–AT nanozymes. Reproduced with permission [91]. Copyright 2021, WILEY–VCH. (d) The detailed therapeutic mechanisms of LaCIONPs for chemo/chemodynamic combination therapy. Reproduced with permission [94]. Copyright 2019, WILEY–VCH.

Metal peroxides were conventionally composed of metal ions and peroxo groups. Previous studies have shown that metal peroxides, especially in acidic solutions, more easily react with H₂O to generate H₂O₂, which makes them more suitable for tumor therapy through the acidic TME response [95]. Meanwhile, with the rapid development of nanotheranostic technology in recent years, many nanostructured metal peroxides have been designed and fabricated for biomedical research and have achieved good therapeutic outcomes [49,96–98]. As a highly biocompatible metal peroxide, calcium peroxide (CaO₂) was rapidly hydrolyzed in the acidic TME to produce O₂ and H₂O₂ while releasing large amounts of Ca²⁺. The production of H₂O₂ not only strengthened the effect of CDT, but also caused the abnormal function of intracellular calcium channels, which eventually led to calcium overload-mediated cell necrosis. In addition, to prevent the disintegration of CaO₂ during blood circulation in vivo, Shen et al. utilized pH-responsive ZIF-90 as a protective layer to encapsulate CaO₂ (Figure 7a) [99]. CaO₂@ZIF-Fe/Ce₆@PEG was co-synthesized by Fe²⁺ and photosensitizer chlorin e₆ (Ce₆). CaO₂@ZIF-Fe/Ce₆@PEG achieved structural disassembly in the weakly acidic TME, and the exposed CaO₂ was further hydrolyzed to produce O₂ and H₂O₂, which enhanced Ce₆-mediated PDT and Fe²⁺-induced CDT. HA, another material that prevents the breakdown of CaO₂ during circulation, has been widely used as a tumor-targeting delivery carrier due to its good biocompatibility, biodegradability, and specific binding ability to CD44 receptors [100]. Meanwhile, HA exhibited strong affinity to CaO₂ and Fe₃O₄ based on the coordinating properties of carboxyl groups with Ca²⁺ and Fe³⁺. Therefore, Han et al. prepared CaO₂-Fe₃O₄@HA nanoparticles utilizing HA as a stabilizer and tumor-targeting block to deliver CaO₂ (Figure 7b) [101]. In addition, there are several other metal peroxides that have shown the ability to generate H₂O₂. For instance, ZnO nanoparticles generated exogenous H₂O₂ and Zn²⁺ under the weakly acidic TME, and the generated Zn²⁺ could further promote the generation of endogenous O₂•⁻ and H₂O₂ after entering cancer cells [96,97].

Figure 7. (a) The therapeutic mechanisms of pH–responsive CaZFCP for enhanced CDT/PDT. Reproduced with permission [99]. Copyright 2021, WILEY–VCH. (b) The action mechanism of CaO₂–Fe₃O₄@HA NPs in vivo. Reproduced with permission [101]. Copyright 2019, American Chemical
Society. (c) The synthesis of C$_3$N$_2$ photocatalyst via Schiff base reactions. (d) CB/VB positions of photocatalysts reported by C$_3$N$_2$ et al. (e) Photocatalytic generation of H$_2$O$_2$ by C$_3$N$_2$ or g-C$_3$N$_4$ in water. Reproduced with permission [102]. Copyright 2022, WILEY-VCH.

In the fields of energy and the environment, artificial photocatalysis is a common approach to produce H$_2$O$_2$. In order to apply the approach of photocatalytic synthesis of H$_2$O$_2$ to tumor treatment, it urgently needed to be considered that the low efficiency of existing photocatalysts to generate H$_2$O$_2$ under the low oxygen content, as well as the critical characteristic of the tumor microenvironment (pO$_2$ $\leq$ 5 mmHg), retrained its application. Therefore, Ma et al. proposed a C$_3$N$_2$ photocatalyst with a conjugated C=N chain by Schiff base reaction for stable and sufficient H$_2$O$_2$ production in both hypoxic and normoxic conditions (Figure 7c) [102]. The results showed that the CB/VB position of C$_3$N$_2$ was downshifted remarkably due to the reinforced delocalization of $\pi$-electrons, which contributed to a favorable CB and VB band position for H$_2$O$_2$ photosynthesis in kinetics and thermodynamics (Figure 7d). Encouragingly, the H$_2$O$_2$ production rate of C$_3$N$_2$ was 1550 $\mu$mol L$^{-1}$ per hour, which was approximately 298 times higher than that of traditional g-C$_3$N$_4$ (5.2 $\mu$mol L$^{-1}$ per hour), indicating that C$_3$N$_2$ had high photocatalytic H$_2$O$_2$ production performance (Figure 7e). Since H$_2$O$_2$ did not have a direct strong killing effect on cancer cells, the original C$_3$N$_2$: was exfoliated into nanosheets by ultrasonication, and then Fe$^{3+}$ was doped into C$_3$N$_2$: nanosheets to achieve effective CDT. Overall, this finding proposed a promising approach for improving CDT efficiency.

3.2. Decreasing the Level of Reducing Substances

The high expression of GSH in tumor cells hinders the production of ROS, further weakening the antitumor effect of CDT owing to the balance of oxidation and reduction being broken in the presence of high-level GSH in the TME. Therefore, downregulation of GSH in the TME was required to enhance the effectiveness of CDT.

One strategy for eliminating GSH was to deplete the existing GSH in tumor cells. Metals in the oxidized state were the most commonly used oxidants in existing GSH consumption because they could directly interact with GSH and consume it rapidly [103,104]. For instance, Chen et al. designed carrier-free Fe(III)-artemisinin (ART)-coordinated nanoparticles (Fe(III)-ART NPs) via coordination-driven self-assembly for self-enhanced MRI-guided CDT (Figure 8a) [105]. After cellular endocytosis, Fe(III)-ART NPs decomposed in an acidic and redox environment of endo/lysosomes to release Fe$^{3+}$ and ART. The Fe$^{3+}$ was then reduced to Fe$^{2+}$ by intracellular GSH, catalyzing the endoperoxide of ART to generate toxic C-centered free radicals for efficacious CDT. Moreover, significant toxicities were detected in A549 cells co-incubated with Fe(III)-ART NPs. In vitro studies demonstrated that after being treated with 200 $\mu$g mL$^{-1}$ Fe(III)-ART NPs for 24 h, the cell viability decreased to 34%, resulting from DNA damage and lipid and protein oxidation (Figure 8b). In addition, FLI was performed using ICG-labeled Fe(III)-ART NPs. The experiment showed that signals at the tumor site were detected within 8 h and maximized at 48 h. Furthermore, T2-weighted MRI signals in tumors were significantly enhanced at 32 h after intravenous administration of Fe(III)-ART NPs, proving that Fe(III)-ART NPs successfully accumulated in tumor cells (Figure 8c). Notably, the free radical generation process of Fe(III)-ART NPs was without reliance on pH or endogenous H$_2$O$_2$, thereby breaking through the bottlenecks of traditional CDT. Carbon dots (CDs) are small fluorescent carbon nanoparticles less than 10 nm in diameter, and have high chemical stability, luminescence, and broadband optical absorption. Existing studies have shown that CDs easily and rapidly formed iron-containing nanoparticles with Fe$^{3+}$ and then quench the fluorescence. Subsequently, GSH continues to react with the nanoparticles to restore fluorescence while oxidizing into GSSG. In this way, GSH in the tumor region was consumed, and CDs-based GSH FLI was realized for further cancer therapy [106,107]. In recent work, Li et al. combined fluorescence-imaging CD and Fe$^{3+}$ to produce a TME stimuli-responsive therapeutic nanodrug (Fe-C) for FLI of glutathione depletion and tumor therapy (Figure 8d) [108].
After the entry of Fe-CD into the tumor cells, Fe-CD reacted with GSH and then released Fe$^{3+}$, which not only acted as a quencher but was also an important factor in enhanced CDT. In this process, GSH was converted to GSSG, while Fe$^{3+}$ was simultaneously reduced to Fe$^{2+}$, making CDT more efficient. Moreover, this important process was also monitored by enhancing the fluorescence intensity of Fe-CD. In vitro data showed little change in GSH content when the A549 cells were treated with CD. However, when treated with Fe-CD, GSH content was significantly reduced, by 31.8%, due to the introduction of Fe$^{3+}$, suggesting that Fe-CD had a significant GSH consumption potential (Figure 8e). In addition, this process restored the bright fluorescence of CD, while the reduction of intracellular GSH content was qualitatively indicated by the increase of fluorescence intensity.

The other strategy for more effectively eliminating GSH was to inhibit the synthesis of GSH utilizing chemical inhibitors. However, the use of inhibitors was limited by their high toxicity to normal cells and short half-life. In order to overcome these shortcomings and more effectively eliminate GSH in the tumor, Huang et al. synthesized a multistage GSH exhaustion nanomedicine, named TDMH (TP/2-DG@HMnO$_2$@HMnO$_2$), to achieve high-efficiency CDT (Figure 9a) [109]. HA, which was modified on the surface of nanoparticles, enhanced tumor recognition by binding to the CD44 receptor on tumor cells. After HMnO$_2$ entered the TME, it underwent a redox reaction with GSH to generate Mn$^{2+}$ and GSSG, thereby quickly depleting the original GSH in the tumor. The generated Mn$^{2+}$ catalyzed the formation of •OH from H$_2$O$_2$ in the presence of bicarbonate (HCO$_3^-$), which was abundant in the physiological medium. On the other hand, TP and 2-DG were released due to the collapse of the HMnO$_2$ framework. Notably, the released TP targeted Nrf2 (nuclear factor (erythroid-derived 2)-like 2)/SLC7A11, thereby preventing de novo synthesis of GSH. As a commonly used glycolysis inhibitor, 2-DG blocked ATP production in the glycolytic pathway, which provides energy for tumor cells. Consequently, these reaction
processes enabled multistage GSH depletion and amplified differences in the susceptibility of tumor cells and normal cells to oxidative stress.

High endogenous H:\textsubscript{2}S expression is unique to the colon cancer tumor microenvironment compared to other tumor types [110]. As such, it is the target of many colon cancer treatments. The reducing capacity of endogenous H:\textsubscript{2}S (currently 0.3–3.4 mM) in colon cancer is much stronger than that of GSH [111]. Hence, the efficacy of CDT in colon cancer is limited by endogenous H:\textsubscript{2}S, which has a strong reducing ability and can scavenge the generated hydroxyl radicals. To solve the problem, Liu et al. synthesized H:\textsubscript{2}S-activated CuFe\textsubscript{2}O\textsubscript{4} nanoparticles using the characteristic that H:\textsubscript{2}S could react with metal oxides and accelerate the valence transformation of Fenton or Fenton-like reagents for efficacious CDT of colon cancer (Figure 9b) [112]. Firstly, CuFe\textsubscript{2}O\textsubscript{4} nanoparticles reacted with endogenous H:\textsubscript{2}S in situ in the TME, leading to the depletion of endogenous H:\textsubscript{2}S in colon cancer. Meanwhile, Cu\textsubscript{9}Fe\textsubscript{9}S\textsubscript{16} nanoparticles with strong NIR absorption were obtained by CuFe\textsubscript{2}O\textsubscript{4}, which were used as photothermal-enhanced CDT agents and intelligent PAI reagents (Figure 9c, d). In addition, parts of Cu\textsuperscript{2+} and Fe\textsuperscript{3+} in CuFe\textsubscript{2}O\textsubscript{4} nanoparticles were reduced to Cu\textsuperscript{+} and Fe\textsuperscript{2+} by endogenous H:\textsubscript{2}S to form hydroxyl radicals via Fenton or Fenton-like reactions. Eventually, CuFe\textsubscript{2}O\textsubscript{4} had a wide range of promising applications in anticancer drug delivery for colon cancer.

![Figure 9](image-url)

**Figure 9.** (a) The therapeutic mechanisms of TDMH nanomedicine. Reproduced with permission [109]. Copyright 2022, American Chemical Society. (b) The action mechanism of CuFe\textsubscript{2}O\textsubscript{4} nanoparticles in cancer cells. (c) Thermal imaging of different groups under 808 nm laser irradiation. (d) Corresponding PA signals of HCT116 tumor-bearing mice. Reproduced with permission [112]. Copyright 2021, Elsevier Ltd.

### 3.3. Lowering pH Value

The pH range of the TME was between 6.5 and 7.0, while the optimal pH for Fenton reactions ranged from 2 to 4 [113]. Since the high pH value inhibited the decomposition of nanomaterials and the release of metal ions with catalytic activity, lowering the pH value of TME could effectively improve the catalytic efficiency of the Fenton reaction and enhance the therapeutic efficiency of CDT. In general, introducing exogenous acids or
other substances was an efficient and common approach to regulating the pH of the TME. GOx was able to oxidize glucose to H$_2$O$_2$ and H$^+$, which effectively increased the acidity and hydrogen peroxide in the tumor region, thus improving the efficiency of CDT treatment [85]. For instance, Liu et al., for the first time, designed a ternary pillar[6]arene-based nanocatalyst (GOx@T-NPs) employing pillar[6]arene and ferrocene via host–guest interactions to realize the combination of chemotherapy, ST, and CDT (Figure 10a) [114]. After being internalized and endocytosed by cancer cells, the intratumoral glucose was catalyzed by GOx@T-NPs into H$^+$ and H$_2$O$_2$, thereby reducing the pH value inside cancer cells and further achieving high toxicity toward tumor cells. Meanwhile, overexpressed GSH in tumors was consumed by disulfide bonds of GOx@T-NPs, inducing the massive •OH production and the simultaneous release of the antitumor drug CPT. Li et al. reported a cascade catalytic nanoplatform (GOx-NCs/FeO$_4$) for antibacterial CDT toward *Escherichia coli* (Figure 10b) [115]. Specifically, GOx-NCs/FeO$_4$ was constructed by loading GOx onto the surface of covalent-assembled polymer capsules (NCs) through electrostatic interactions, which was successfully achieved to efficiently encapsulate FeO$_4$ and immobilize GOx. Furthermore, GOx was oxidized into H$_2$O$_2$ in the presence of glucose, increasing in H$^+$ concentration. After that, H$_2$O$_2$ was converted into •OH triggered by FeO$_4$ nanoparticles through the Fenton reaction, thereby destroying the lipoproteins of the bacterial cell wall and causing the death of pathogens. The results of plate counting showed that GOx-NCs/FeO$_4$ represented much higher inhibition efficiency compared with GOx and GOx-NCs, demonstrating its potential for efficient antimicrobial activity (Figure 10c). As a result, this strategy demonstrated that GOx-NCs/FeO$_4$ improved the efficacy of the FeO$_4$-mediated and GOx-introduced CDT for antibacterial applications.

Figure 10. (a) The therapeutic mechanisms of GOx@T-NPs. Reproduced with permission [114]. Copyright 2021, American Chemical Society. (b) The synthesis of Gox–NCs/FeO$_4$ and its antibacterial action mechanism. (c) Plate coating results. con, Control; (a) glucose; (b) NCs; (c) GOx (10 µg mL$^{-1}$) without glucose; (d and e) GOx–NCs (10 µg mL$^{-1}$) and GOx–NCs/FeO$_4$ (GOx: 10 µg mL$^{-1}$; FeO$_4$: 50 µg mL$^{-1}$) without glucose; (f and g) GOx (5 µg mL$^{-1}$ and 10 µg mL$^{-1}$) incubated with glucose; (h and i) GOx–NCs (5 µg mL$^{-1}$ and 10 µg mL$^{-1}$) incubated with glucose; (j) GOx–NCs/FeO$_4$(GOx: 5 µg mL$^{-1}$ and FeO$_4$: 25 µg mL$^{-1}$) and (k) GOx–NCs/FeO$_4$ (GOx: 10 µg mL$^{-1}$ and FeO$_4$: 50 µg mL$^{-1}$) incubated with glucose. Reproduced with permission [115]. Copyright 2021, Royal Society of Chemistry.
However, the uncontrollable reaction between Gox and glucose during blood circulation could cause damage to normal tissue, so Shi et al. synthesized an acidity-unlocked nanoplatform (FePt@FeOx@TAM-PEG) in order to selectively produce ROS within tumors while remaining silent in normal tissue (Figure 11a) [116]. Since FePt@FeOx@TAM-PEG had a hydrophobic shell, it remained silent in blood and normal tissues. After reaching the tumor area, FePt@FeOx@TAM-PEG was decomposed and further reacted with H$_2$O$_2$ to generate $\cdot$OH due to the pH-responsive transition from hydrophobic to hydrophilic tamoxifen (TAM). Notably, TAM, an anti-estrogen drug, inhibited mitochondrial complex I and further triggered the adenosine monophosphate-activated protein kinase signaling pathway. This process promoted the decomposition of glucose and the accumulation of lactic acid, which increased the acidity of the cancer cells, thus overcoming the limitations of the weak acidity of the tumor. The increased intracellular acidity boosted the release of Fe$^{2+}$ and Fe$^{3+}$ from FePt@FeOx nanoparticles, thereby accelerating the H$_2$O$_2$ degradation and enhancing the antitumor potential of the nanoplatform. Therefore, the problem of insufficient CDT efficiency and potential side effects on normal cells have been effectively solved by the design of the nanodrug.

Carbonic anhydrase IX (CA IX) is a pH-regulating enzyme overexpressed on the cell membrane of most hypoxic tumors and can catalyze the reversible hydration of CO$_2$ to generate H$_2$CO$_3$ and H$_+$, participate in tumor extracellular acidosis, and accelerate tumor metastases [117]. CA IX inhibitors (CAI) inhibit extracellular HCO$_3$/$\cdot$H$^+$ formation, leading to intracellular glycolytic H$^+$ accumulation. Inspired by this, Zuo et al. designed and constructed kinds of hollow mesoporous ferric oxide (HMFe) nanocatalysts (MM@HMFe@BS), which were camouflaged by macrophage membrane as well as loaded with CAI to decrease intracellular pH in the TME for self-amplified CDT (Figure 11b) [118]. The camouflage of macrophage cell membrane enabled the nanocatalysts to have immune evasion ability and recognize tumor endothelium cells and cancer cells via α4/VCAM-1 interaction, further promoting tumor chemotactic aggregation. After the efficient internalization into cancer cells, MM@HMFe@BS was specifically degraded to release HMFe and 4-(2-aminoethyl) benzene sulfonamide (BS). Interestingly, the released HMFe not only acted as a highly active atom-exposing Fenton agent to enhance CDT but was also used with high-efficiency MRI to monitor the biodistribution and treatment progress of MM@HMFe@BS. With the specific release of the CAI, CA IX was inhibited by BS, thus inducing intracellular H$^+$ accumulation to accelerate the Fenton reaction. Dong and co-workers reported a multifunctional nanosystem of TP@PP$_{CAI}$ to remodel the TME and reinforce the in situ Fenton reaction, which was composed of the inner TP micelles-loading iron-oxide nanoparticles (IONs) and the outer poly (dopamine-co-protocatechuc acid) (PDA-PA, PP) coating modified with the CAI [119]. Firstly, 4-(2-aminoethyl) benzene sulfonamide, a CA IX inhibitor, inhibited the overexpressed CA IX, thus leading to intracellular acidification. Next, the PP coating was degraded, triggered by the acidification and NIR irradiation, resulting in the disintegration of the inner micellar structure to further release TPGS-PPh$_3$ and IONs. Research showed that TPGS-PPh$_3$, as the endogenous ROS amplifier, was able to target the mitochondria and then interfere with the function, thereby increasing the intracellular ROS basal level for Fenton reactions [120–122]. Additionally, based on the good photothermal conversion performance of PDA, the temperature of TP@PP$_{CAI}$ nanoparticles solution increased by more than 15 °C and reached 46.5 °C at a concentration of 0.5 mg mL$^{-1}$ after NIR irradiation for 8 min, indicating that TP@PP$_{CAI}$ had good photothermal performance to enhance Fenton catalytic efficiency and improve the efficiency of CDT.

Jiang et al. synthesized a nanomedicine of FeCNB with high catalytic activity in acidic/neutral conditions, which overcame the limit of firm acidity required for the traditional Fenton reaction (Figure 11c) [123]. The nanomedicine FeCNB was composed of a Fe/FeC core and mesoporous graphite carbon shell modified by biotin to realize effective CDT by improving the efficiency of the Fenton reaction in acidic/neutral conditions. Specifically, graphitic carbon received electrons from Fe$^0$ via a reduction reaction based on the
principle of galvanic cells. Meanwhile, Fe⁰ in FeCNB as a reducing agent was oxidized to Fe²⁺, thus consuming H₂O₂ to produce •OH in neutral and acidic environments. Moreover, the experimental results confirmed that the photothermal conversion efficiency of FeCNB was 31.4% with 808 nm laser irradiation, revealing that it had an efficient photothermal conversion function to achieve effective PTT. This work offered a new perspective to remodel the pH in the TME for the development of ideal CDT nanomedicine.

Figure 11. (a) The therapeutic mechanisms of FePt@FeOx@TAM–PEG. Reproduced with permission [116]. Copyright 2021, WILEY–VCH. (b) Schematic diagram of the therapeutic mechanisms of MM@HMFe@BS nanomaterials in vivo. Reproduced with permission [118]. Copyright 2022, American Chemical Society. (c) Schematic illustrations of the construction and the therapeutic mechanism of FeCNB [123]. Copyright 2022, Elsevier Ltd.

4. Conclusions and Future Directions

Cancer has remained a major killer that endangers human life and health. However, traditional cancer treatment techniques such as chemotherapy, radiotherapy, and surgery suffer from poor treatment efficiency, large toxic side effects and easy recurrence, and metastasis, which limit their application in the clinic. Many researchers have focused on exploring more efficient and simpler cancer treatments with important clinical value. Based on Fenton/Fenton-like reactions, CDT is attracting increasing attention as a catalyst-driven modality for cancer therapy because of its remarkable specificity and selectivity for tumors, minimal systemic toxicity and side effects, and the absence of a requirement for field stimulation during treatment. So far, many studies have reported that a large number of metal-based nanocatalytic medicines have been developed to initiate in situ Fenton or Fenton-like reactions in tumor cells, while various nanomaterials have also been used to modulate the tumor microenvironment to improve the therapeutic efficiency of CDT and achieve better tumor treatment effects. Here, Table 1 shows commonly used metal-based catalysts and their applications in biomedicine.
<table>
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<th>Biological Model</th>
<th>Ref.</th>
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<td>PdD</td>
<td>HeLa tumor-bearing mice</td>
<td>[32]</td>
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<td></td>
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<td>dihydroartemisinin and metal-polyphenol networks</td>
<td>HepG2 tumor-bearing mice</td>
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<td>Fe-based nanocatalysts</td>
<td>Fe₃O₃</td>
<td>PDA</td>
<td>S. aureus-infected mice</td>
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<td>MIL-101(Fe)</td>
<td>TCPP</td>
<td>231 tumor-bearing mice</td>
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<td>Fe-porphyrin-MOF</td>
<td>CPPO, cancer cell membrane, and GOx</td>
<td>4T1 tumor-bearing mice</td>
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<td>Fe-DNA</td>
<td>GOx and ZIF-8</td>
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<td>PdCuFe alloy</td>
<td>DOPA-PIMA-PEG</td>
<td>4T1 tumor-bearing mice</td>
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<td>GA-Fe(III)</td>
<td>MoS₂</td>
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<td>4T1 tumor-bearing mice</td>
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<td>CuO₂</td>
<td>mesoporous polydopamine, DOX, and HA</td>
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<td>BSA-CuFeS₂</td>
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<td>4T1 tumor-bearing mice</td>
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<td>Manganese nanocatalysts</td>
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<td>HeLa and LO2 cell lines</td>
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</table>

PDA: polydopamine; GOx: glucose oxidase; TA: tannic acid; TCPP: tetrakis(4-carboxyphenyl) porphyrin; CPPO: bis(2-carboxypentoyloxy-3,5,6-trichlorophenyl) oxalate; ZIF-8: zeolitic imidazolate framework-8; DOPA-PIMA-PEG: dopamine and polyethylene glycol decorated poly(isobutylene-alt-maleic anhydride); GOD: glucose oxidase; BSA: bovine serum albumin; R837: immunoadjuvant imiquimod; DOX: doxorubicin; HA: hyaluronic acid; ICG: indocyanine green; PVCL: poly (N-vinylcaprolactam); Ce6: chlorin e6.

However, CDT is still in its early stages. More research is needed for the clinical translation of CDT, as several important scientific questions need to be addressed. Typical questions are listed below: (1) The target activity of anticancer medicines needs to improve. Metal-based compounds are widely utilized to enhance the performance of CDT based on Fenton and Fenton-like reactions. However, the targeted delivery via the EPR
effect is limited, so modifying the surface of nanoparticles for active targeting to recognize tumors selectively could be considered. (2) It is also an urgent issue to reduce the toxic side effects of CDT. Some of these metal ions remain in vivo after therapy, which has potential side effects on the body. Hence, it is necessary to improve the catalytic efficiency of the catalyst and to deepen its ADME (absorption, distribution, metabolism, and excretion) performance study. (3) New smart combinatorial therapeutic nanosystems with high therapeutic efficiency need to be developed. The efficiency of most nanocatalytic therapies depends largely on the tumor microenvironment. The H₂O₂ and reductive substances levels, and the pH value in the TME, greatly restrict the efficiency of CDT. Moreover, regulation of the CDT treatment process is also extremely important. Therefore, smart combinatorial therapeutic nanosystems with diagnostic and therapeutic capabilities capable of modulating the tumor microenvironment are a future prospect [28,126]. (4) The efficacy of a single treatment is limited. The further development and design of CDT-induced combination cancer therapies will, to some degree, overcome the shortcomings of CDT, which has a stronger therapeutic performance than any single therapy or their theoretical combinations, such as CDT-PTT, CDT-PDT, CDT-ST, CDT-chemotherapy, CDT-SDT, and CDT-immunotherapy. For example, the Fenton and Fenton-like reactions in CDT are used to produce large amounts of •OH in combination with immunotherapy, and the Russell mechanism in CDT is used to produce a number of 'O₂ to overcome the deficiencies of photodynamic therapy.

CDT is a fascinating research frontier that still requires further development. It is recommended to develop more metal-based and metal-free CDT nanomaterials and to improve the targeting and biological safety of these drugs. At the same time, metal-based nanocatalytic medicines are more likely to progress to the clinical stage, due to their multimodal diagnostic and therapeutic capabilities combined with advanced diagnostic methods like CT imaging and MRI. These nanomedicines could accurately diagnose diseases in real-time while simultaneously providing treatment. Moreover, the ability to monitor the therapeutic effect and adjust the dosage regimen during treatment enables optimal therapeutic outcomes and promotes the application of CDT nanomaterials in clinical transformation [126,127]. Additionally, an in-depth understanding and exploration of the anticancer pathways of CDT at the genetic and molecular levels are needed, which would help deepen the understanding of the anticancer mechanism of CDT and lead to the design of more effective agents.

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**Abbreviations**

- Reactive oxygen species: ROS
- Hydrogen peroxide: H₂O₂
- Superoxide anion: O₂⁻
- Hydroxyl radical: •OH
singlet oxygen
peroxy hydroxyl radical
photodynamic therapy
chemodynamic therapy
sonodynamic therapy
tetrakis(4-carboxyphenyl) porphyrin
peroxidase
glutathione
tumor microenvironment
hydrogen sulfide
ferroferric oxide
ferrous disulfide
ferric oxide
Fe-metal organic frameworks
polydopamine
magnetic resonance imaging
computed tomography
starvation therapy
photothermal therapy
glucose oxidase
glucose oxidase
tannic acid
near-infrared
gluconic acid
dihydroartemisinin
metal-polyphenol networks
bis(2-carbopentyloxy-3,5,6-trichlorophenyl) oxalate
zeolitic imidazolate framework-8
gallic acid
photoacoustic
enhanced permeability and retention
copper sulfide
copper oxide
bovine serum albumin
immunoadjuvant imiquimod
tumor-associated antigens
mesoporous polydopamine
doxorubicin
hyaluronic acid
generation 5 poly (amidoamine)
Michaelis–Menten constant
velocity
ß-cyclodextrin
ferrocene
indocyanine green
photothermal imaging
fluorescence imaging
manganese oxide
T1-weighted magnetic resonance imaging
photoacoustic imaging
blood–brain barrier
\(^1\)O_{2}
•OOH
PDT
CDT
SDT
TCPP
POD
GSH
TME
H$_2$S
FeO$_4$
FeS$_2$
FeO$_3$
Fe-MOFs
PDA
MRI
CT
ST
PTT
GOx
GOD
TA
NIR
H$^+$
DHA
MPN
CPPO
ZIF-8
GA
PA
EPR
CuS
CuO
BSA
R837
TAAs
mPDA
DOX
HA
G5
Km
Vm
ß-CD
Fc
ICG
PTI
FLI
MnOx
T$_1$-MRI
PAI
BBB
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