Novel strategies of glutathione depletion in photodynamic and chemodynamic therapy: A review

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D – writing the article; E – critical revision of the article; F – final approval of the article

Advances in Clinical and Experimental Medicine, ISSN 1899–5276 (print), ISSN 2451–2680 (online) *Adv Clin Exp Med*. 2025;34(7):1213–1221

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Funding sources
The study was supported by the SUM grant: PCN-1-040/N/1/F.

Conflict of interest
None declared

Received on September 14, 2023
Reviewed on May 31, 2024
Accepted on July 9, 2024

Published online on September 20, 2024

Abstract

Cancer remains a health problem worldwide; therefore, developing new therapies to increase the effectiveness of anticancer treatments is necessary. Two such methods are photodynamic therapy (PDT) and chemodynamic therapy (CDT). The intensive growth and increased metabolism of tumors lead to elevated levels of reactive oxygen species (ROS) within cancer cells. These cells develop several antioxidant mechanisms to protect them from this oxidative stress. Antioxidants also make tumors more resistant to chemotherapy and radiation. Glutathione (GSH) is an important and the most abundant endogenous cellular antioxidant. Photodynamic therapy and CDT are new methods that are based on the production of ROS,- therefore increasing oxidative stress in cancer cells. A significant problem with these therapies is the increased GSH levels, which is an adaptation of cancer cells to augmented metabolic processes. This paper presents various GSH depletion strategies that are used to improve PDT and CDT. While the main goal of GSH depletion in both PDT and CDT is to prevent its interaction with the ROS generated by these therapies, it should be remembered that the reduction of its level itself may initiate pathways leading to cancer cell death.

Key words: photodynamic therapy, chemodynamic therapy, glutathione depletion

Cite as
Wolny D, Stojko M, Zajdel A. Novel strategies of glutathione depletion in photodynamic and chemodynamic therapy: A review. *Adv Clin Exp Med*. 2025;34(7):1213–1221. doi:10.17219/acem/191025

DOI
10.17219/acem/191025

Introduction

The production of reactive oxygen species (ROS) is a natural consequence of oxygen metabolism and cellular biochemical reactions. As signaling molecules, ROS play an essential role in the activation of pathways that lead to cell proliferation and survival. However, in higher concentrations, they promote mutagenesis by damaging DNA, and in sufficiently high concentrations, they lead to oxidative stress, causing cell death. To prevent the adverse effects of high ROS levels, cells employ several antioxidant protective mechanisms to maintain cellular redox homeostasis and ensure normal functioning and survival.[1]

Contrary to normal cells, cancer cells are characterized by significantly increased levels of ROS owing to their unrestrained growth and increased metabolism.[2] Moreover, higher levels of ROS increase the proliferation of cancer cells and tumor aggressiveness, promoting their ability to invade and metastasize.[3] Increased ROS content forces cancer cells to intensify the antioxidant mechanisms that protect them from the negative effects of these oxidative stresses.[2] It has also been postulated that cancer cells maintain the concentration of ROS at a level that facilitates their progression.[4] The increased amount of antioxidants and constantly elevated levels of ROS found in cancer cells make them resistant to chemotherapeutic agents and radiation. It has also been shown that cancer cells are highly dependent on their antioxidant systems to maintain an appropriate redox level and are, therefore, sensitive to external factors disrupting these systems.[1]

Among the various endogenous cellular antioxidants, glutathione (GSH) is the most abundant. It is a major scavenger of ROS and plays an essential role in maintaining cell redox homeostasis. Although GSH plays an important role in the detoxification of carcinogens, its elevated concentration can be observed in many cancer types, which increases the resistance of such cells to the toxic effects of many chemotherapeutic agents and radiation.[1]

Due to the different amounts of ROS in cancer cells compared to normal cells, various tumor treatment strategies exacerbating oxidative stress have been developed.[2] Since GSH is a common cellular antioxidant whose main function is to remove free radicals and maintain cellular redox balance, it appears to be the optimal target for such anticancer therapies. There are many studies showing that GSH depletion increases oxidative stress, which leads to cancer cell death. Moreover, it has been shown that the reduction of GSH content in cancer cells makes them more susceptible to factors that increase ROS.[1]

Objectives

Here, we describe GSH depletion strategies that could improve the effectiveness of 2 promising ROS-based treatments for cancer: photodynamic therapy (PDT) and chemodynamic (CDT) therapy.

Glutathione depletion strategies

Increased concentrations of GSH in tumor tissues compared to normal tissues have been observed in many neoplastic diseases.[5] This increases the resistance of cancer cells to therapies based on potentiated oxidative stress.[6] Depletion of GSH in cancer cells makes them more sensitive to therapeutic agents. Therefore, it should come as no surprise that various strategies are being developed to lower intracellular GSH levels to inhibit tumor growth and increase the effectiveness of therapy. These approaches include a reduction in the availability of substrates for GSH biosynthesis, inhibition of GSH synthesis, GSH conjugation, or increases in its oxidized form (GSSG), as well as promotion of GSH cellular efflux (Fig. 1).[7–9]

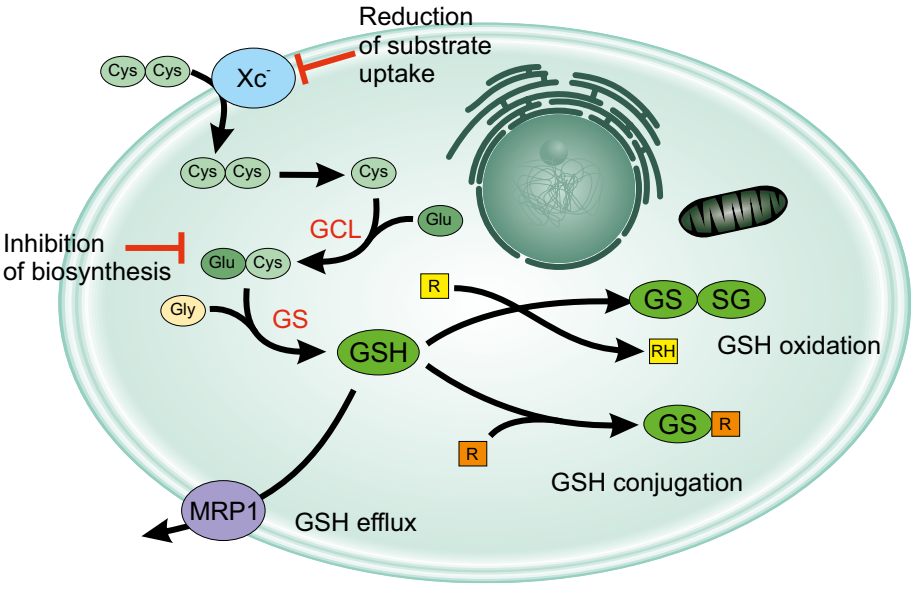

Fig. 1. Glutathione depletion strategies in cancer cells

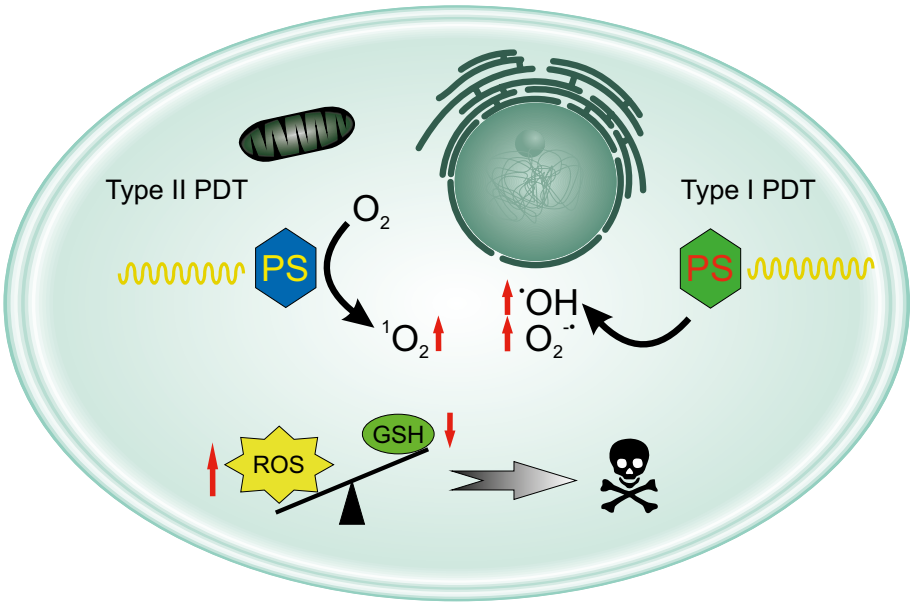

Fig. 2. The principles of photodynamic therapy

Glutathione depletion in photodynamic therapy

Photodynamic therapy (Fig. 2) is a new, developing anticancer therapy that is of great interest. The reasons for this are its undoubted advantages, such as low invasiveness, low toxicity, high effectiveness of therapy, and lack of drug resistance.[10–14] Reactive oxygen species play a key role in PDT. They oxidize biological macromolecules, such as nucleic acids, proteins and lipids, altering cell signaling pathways and gene expression, as well as destroying membrane structures.[15] This leads to apoptosis of cancer cells. Moreover, ROS within tumor tissues can also damage the microcirculation and cause immunogenic cell death.[16–18] In this therapy, a photosensitizer (PS) is administered to the patient and activated with an appropriate wavelength of light. Photodynamic reactions can be classified into 2 types. In type I, light energy is transferred from excited molecules to biomolecules through a direct contact reaction. The radicalization mechanism involves the transfer of an electron or hydrogen, and the resulting radicals can initiate a radical chain reaction. This also produces superoxide radicals ($O_2^{\bullet-}$) and hydroxyl radicals ($^{\bullet}OH$).[19] Type II PDT is based on an indirect reaction, in which the excited PS reacts with molecular oxygen. As a result, singlet oxygen ($^1O_2$) is generated, which is extremely electrophilic, causing damage to biomolecules and, consequently, destroying neoplastic cells.[20,21] Most PDT in clinical applications are based on the second type of reaction.[22]

Due to some limitations, PDT is not currently used as a first-line therapy in cancer treatment.[23,24] To function effectively, it requires large amounts of oxygen in the tumor microenvironment (TME), which is unfortunately hypoxic.[25] In addition, cells trigger several defense mechanisms in response to PDT, e.g., cancer cells increase the synthesis of various cytoprotective molecules. Redox-sensitive transcription factors are activated, which increases the amount of detoxification and antioxidant enzymes. Activation of anti-apoptotic pathways and overexpression of heat shock proteins prevent the formation of active apoptosomes.[26]

New strategies to increase the effectiveness of PDT are constantly being developed. These include an increase in ROS production by reducing hypoxia in the TME,[17,27] as well as reducing the efficiency of cancer cell antioxidant systems, with particular emphasis on GSH.[19,28]

Hu et al. used docosahexaenoic acid (DHA) and 2,2-dimethoxy-2-phenylacetophenone (DMPA) placed in a ROS-sensitive dendrimer nanocarrier (RSV) to reduce intracellular GSH concentrations and increase the effectiveness of PDT.[29] Zinc phthalocyanate (ZnPc) was used as the PS. Irradiated by 665 nm light in the presence of endogenous H_2O_2 or ROS resulting from PDT, RSV is decomposed, and DHA and DMPA are released. Under light irradiation, DMPA becomes the initiator of the thiol-ene click reaction, which consists of GSH conjugation to double bonds within the DHA molecule. This directly reduces the cellular concentration of GSH. Moreover, Hu et al. showed that their therapeutic system significantly decreased intracellular concentrations of ATP, which is a cofactor for γ-glutamylcysteine synthetase, resulting in inhibition of GSH synthesis.

Cao et al. synthesized nanoparticles from an amphiphilic branched copolymer (PEG) with pendant vinyl groups containing chlorine e6 (Ce6) as a PS.[30] The vinyl groups form a hydrophobic core as the nanoparticle reacts with GSH in the thiol-ene click reaction, lowering its intracellular concentration while Ce6 is released.

Li et al. proposed the use of S-nitrosated human serum albumin (HSA-SNO) to lower GSH concentrations and increase the effectiveness of PDT therapy.[31] HSA-SNO

binds GSH molecules, releasing nitric oxide (NO), which additionally occupies oxygen binding sites within the mitochondria, thus reducing cellular respiration of cancer cells and indirectly increasing the oxygen concentration needed for PDT.[14]

The use of 5-aminolevulinic acid (ALA) as a clinically approved PS has been attempted. Although it does not have the ability to photosensitize itself, it undergoes metabolism inside the cell, resulting in the formation of protoporphyrin IX (PpIX), which already possesses such properties.[32,33] Compared to other PSs, ALA has low toxicity and is quickly removed from the body. However, at physiological pH, it is largely hydrophilic and, therefore, hardly penetrates biological barriers.[34,35] The use of ester derivatives alleviates this drawback, but due to the presence of a nucleophilic amino group, these compounds are still not very stable under physiological conditions. Li et al. synthesized a number of ALA methyl ester derivatives in which the substituents were linked to the amino group via 2-hydroxyethyl disulfide.[36] After entering the cell, these derivatives react with GSH, which releases ALA and simultaneously lowers the intracellular GSH pool. Next, ALA was transformed into protoporphyrin IX.

An interesting solution was proposed by Meng et al., who created a metal-organic framework (MOF)-based nanocarrier using a disulfide-containing imidazole as an organic ligand and zinc (Zn^{2+}) as a coordination metal.[37] The nanocarrier was loaded with a PS (Ce6). To stabilize the MOF in an aqueous environment, its surface was covered with an amphiphilic polymer (pluronic F127). Glutathione depletion was accomplished through a disulfide-thiol exchange reaction and the decomposition of the MOF releases the PS. Meng et al. also demonstrated that the nanocarriers they used had a double therapeutic effect. The PS induces a typical PDT increase in ROS levels, leading to apoptosis. Glutathione depletion not only supports this process but also causes ferroptosis.[38]

Ferroptosis is a cell death pathway that includes an iron-dependent Fenton reaction and lipid peroxidation.[39] This process is characterized by the accumulation of Lipids-OOH due to the disruption of their scavenging systems. The scavenging of toxic Lipids-OOH is carried out by their reduction to Lipids-OH by GSH peroxidase 4 (GPX4).[40] Glutathione is the reducing co-substrate of GPX4; therefore, GSH depletion or GSH synthesis disorders can trigger ferroptosis.[41] There are many studies that have observed ferroptosis initiated by GSH depletion in both PDT and CDT.[37,42–46]

Curcumin, isolated from *Curcuma longa*, is a natural chemopreventive drug for cancer.[47] Many studies have shown that this compound significantly decreases the level of hypoxia-inducible factor 1α (HIF-1α), which is overexpressed in several neoplastic diseases. Moreover, curcumin depletes GSH.[48,49] Zhang et al. used a curcumin derivative (Cur-S-OA) to create a nanoparticle (ZnPc@Cur-S-OA), which decomposes in cancer cells in a ROS-responsive manner with the release of the PS (zinc phthalocyanate, ZnPC) and free curcumin.[50] The curcumin derivative serves 2 distinct purposes. First, it acts as a PS stabilizer. Second, following nanoparticle decomposition, it acts as a chemotherapeutic agent, thereby improving PDT efficiency.

Liu et al. designed an oxidative stress amplifier (OSA), that is activated in cancer cells by its interaction with H_2O_2.[51] It is a micelle (DPL@CC) consisting of cinnamaldehyde (Cin), a GSH scavenger, and Ce6, a PS, coated with a ROS-reactive amphiphilic polymer (DPL). Cinnamaldehyde conjugates with GSH and blocks its thiol group, which is required to react with ROS. After OSA application, the level of GSH decreased to 18.9% compared to control cells.

Cysteine is an essential substrate in GSH biosynthesis, and its deficiency significantly affects the formation rate and cellular concentration. Cystine, the oxidized form of cysteine, is present in the extracellular matrix (ECM) and is taken up by the cell through the X_c^- system. It is an anti-port glutamate/cystine transporter found in the cell membrane.[52] The light chain of the X_c^- system (xCT) is overexpressed in many types of neoplastic diseases, which correlates with resistance to treatment and a poor prognosis in patients.[53–56] A reduction in extracellular cystine uptake directly reduces the cellular concentration of GSH; thus, inhibiting the X_c^- system is another possible strategy for its depletion.[57] One of the compounds with the ability to inhibit the X_c^- system is erastin.[39] Zhul et al. designed a nanodrug containing erastin and Ce6 as the PS.[46] After entering cancer cells, erastin inhibited GSH biosynthesis, lowering the intracellular pool, enhancing Fe-induced lipid peroxidation, and inducing cell death via ferroptosis.[39,58–62]

Wang et al. synthesized nanoparticles consisting of pyropheophorbide (PPa) as a PS and clopidogrel, which was responsible for increasing the effectiveness of PDT by GSH depletion.[63] Clopidogrel is a classic antiplatelet drug that is metabolized by cytochrome P450 (CYP2C19) to form a thiol metabolite.[64] This metabolite conjugates with GSH, lowering its intracellular pool and increasing the effectiveness of PDT. The disadvantage of this approach is that it is limited to cancer cells that overexpress CYP2C19.

Depletion of glutathione in chemodynamic therapy

Chemodynamic therapy (Fig. 3) is highly selective towards cancer cells with minimal side effects.[65] It is based on Fenton or Fenton-like reactions in which transition metal ions (e.g., Fe, Co, Ni, Cu, and Mn) react with hydrogen peroxide to form highly cytotoxic hydroxyl radicals ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{\bullet}OH + OH^-$). This reaction is initiated in the TME, characterized by the overproduction of H_2O_2, low catalase activity and a weakly acidic pH.[66,67] Chemodynamic therapy is specific to cancer cells because the Fenton reaction is significantly limited in a weakly alkaline environment, and the limited amount of hydrogen peroxide is observed in normal cells.[68] The Fenton reaction

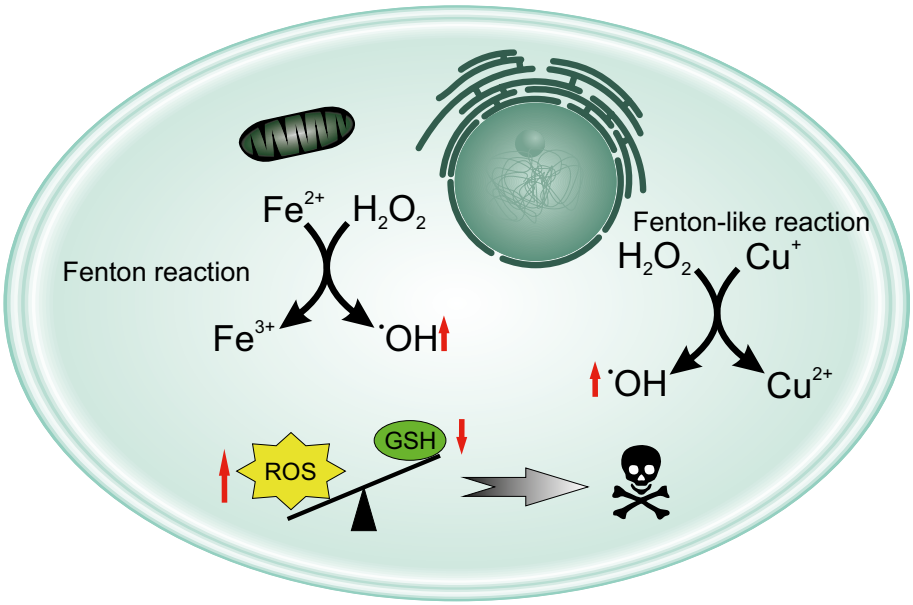

Fig. 3. Chemodynamic therapy basis

leads to oxidative stress, and the reactive hydroxyl radical reacts with proteins, lipids, and DNA, disrupting their function and leading to cancer cell death.[65]

Compared to PDT, CDT is more selective and is initiated by internal factors; therefore, it does not require external energy in the form of light and does not depend on local oxygen concentrations.[69,70] Nevertheless, some factors limit the effectiveness of CDT. The first is the limited amount of endogenous H_2O_2 in cancer cells and the low catalytic efficiency of chemodynamic agents.[65] Another limitation is the reaction environment. Most chemodynamic agents, such as iron-based nanomaterials, transition metal ions, and metal-organic frameworks, catalyze Fenton and Fenton-like reactions better in a more acidic environment (pH 3.0–5.0) than in the TME (pH 6.0–7.0).[65,71] Finally, overexpression of GSH in the TME significantly reduces the production of hydroxyl radicals, reducing the effectiveness of CDT.[65] Therefore, researchers have focused on designing new nanomaterials that increase the efficiency of CDT by modifying the TME, by lowering its pH, increasing H_2O_2 concentrations, and depleting GSH.

Lin et al. created nanoparticles consisting of mesoporous silica coated with manganese dioxide (MnO_2).[72] After internalization into cancer cells, the MnO_2 envelope undergoes a redox reaction with GSH, resulting in the formation of the oxidized form of GSH (GSSG) and Mn^{2+} ions. Manganese ions in the presence of carbonate ions (HCO_3^-) react with H_2O_2, forming hydroxyl radicals through a Fenton-like reaction. Therefore, MnO_2 plays a dual role. Its reaction with GSH lowers the intracellular pool, resulting in increased susceptibility of cancer cells to oxidative stress. The same reaction leads to the formation of Mn ions, which are responsible for ROS generation. The use of a mesoporous silica core, on the other hand, ensures the controlled release of the drug. It should be noted that a similar strategy has been used by many researchers.[73]

Compared with the classic Fenton reaction catalyzed by Fe^{2+} ions, a Fenton-like reaction is catalyzed by Cu^+ ions and can be carried out with greater efficiency in a weakly acidic environment. However, because of the low redox potential of Cu^+/Cu^{2+}, Cu^+ ions are easily oxidized to Cu^{2+}.[74,75] Ma et al. proposed the use of copper-amino acid mercaptide nanoparticles (Cu-Cys NPs).[76] After endocytosis into cancer cells, these nanoparticles oxidize GSH and the copper is reduced to Cu^+ ions. These ions react with hydrogen peroxide to form hydroxyl radicals. The use of Cu^{2+} ions not only increases the efficiency of ROS production but is also an effective way to reduce the ratio of GSH to oxidized GSH (GSSG). The GSH depletion strategy using transition metal ions, which are reduced by GSH to substrates for the Fenton-like reaction, has been used in many studies.[77–90]

Chen et al. designed nanoparticles containing Fe_3O_4 and β-lapachone (Lapa).[91] The first of these compounds is the source of Fe^{2+} ions, which participate in the Fenton reactions. Lapa undergoes a transition from quinone to hydroquinone in the futile cycle catalyzed by NADPH:quinone oxidoreductase-1 (NQO1). The overexpression of NQO1 in cancer cells, which occurs at a ratio of 2–100 times, results in greater selectivity for these cells when Lapa is used.[92] The futile cycle of Lapa not only generates H_2O_2, increasing the efficiency of CDT, but also significantly reduces the cellular concentration of NADPH (60 mol/Lapa mol/5 min).[93] Since NADPH is a coenzyme of GSH reductase, reduction in its amount interferes with the function of this GSSG-reducing enzyme. This leads to increased oxidative stress in cancer cells.

Limitations

Article selection bias is a possible limitation of this study. Due to the abundance of works on this review topic, despite every effort, some works that should have been cited may

Table 1. Glutathione depletion strategies during PDT and CDT

Type of therapy	Mode of action	Agent	References
PDT	conjugation with GSH	docohexaenoic acid	29
		pendant vinyl groups	30
		S-nitrosated human serum albumin	31
		curcumin	50
		cinnamaldehyde	51
		thiol metabolite of clopidogrel	63
		phenethyl isothiocyanate	94
		mesoporous polydopamine	95
		quinone methide	96
	GSH oxidation	ALA derivative with disulfide bond	36,97
		disulfide-containing imidazole	37
		hemin	98,99
		Cu^{2+}	87,88,100,101
		Mn^{4+}	89,102,103
		Fe^{3+}	84
		NO	104
	inhibition of GSH biosynthesis	erastin	46
		buthionine sulfoximine	105
CDT	conjugation with GSH	2-nitroimidazole and 1H-imidazole-4-carbonitrile	106
	GSH oxidation	Cu^{2+}	76,80,81,90,107,108
		Mn^{4+}	72,86,109
		Fe^{3+}	82,110
		NO	111
	decrease of GSH reductase activity	β-lapachone	91
	inhibition of GSH biosynthesis	triptolide	112

PDT – photodynamic therapy; CDT – chemodynamic therapy; GSH – glutathione; ALA – 5-aminolevulinic acid; $Cu2^{+}$ – cupric ion; $Mn4^{+}$ – tetravalent manganese ion; $Fe3^{+}$ – ferric ion; NO – nitric oxide.

have been omitted. In addition, many of the papers used the same GSH depletion strategies, so the authors decided not to cite some of them.

Conclusions

Cancer remains a global health problem despite the constant development of new medicines. Numerous studies focused on developing new therapeutic strategies to increase the effectiveness of anticancer treatment. Methods, such as PDT or CDT, are characterized by an increased specificity and selectivity for cancer cells and reduced side effects compared to traditional chemo- and radiotherapy. Despite the undoubted advantages of these oxidative stress-increasing therapies, they face certain problems in clinical applications. One of the most important obstacles is the adaptation of cancer cells to an increased concentration of ROS by increasing the production of GSH. This requires the development of effective strategies to reduce the concentration of this thiol compound in cancer cells (Table 1). A simple and direct way to deplete GSH is to use compounds that react with GSH to form stable derivatives or transform it into an oxidized form (GSSG). This is also the most common strategy used by scientists to develop new PDTs and CDTs, as presented in this paper. Although the main goal of GSH depletion in both PDT and CDT is to prevent its interaction with ROS generated by these therapies, it should be remembered that reductions in GSH levels by itself may initiate pathways leading to cancer cell death.

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