

Review Article

Targeting Reactive Oxygen Species Capacity of Tumor Cells with Repurposed Drug as an Anticancer Therapy

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Accumulating evidence shows that elevated levels of reactive oxygen species (ROS) are associated with cancer initiation, growth, and response to therapies. As concentrations increase, ROS influence cancer development in a paradoxical way, either triggering tumorigenesis and supporting the proliferation of cancer cells at moderate levels of ROS or causing cancer cell death at high levels of ROS. Thus, ROS can be considered an attractive target for therapy of cancer and two apparently contradictory but virtually complementary therapeutic strategies for the regulation of ROS to treat cancer. Despite tremendous resources being invested in prevention and treatment for cancer, cancer remains a leading cause of human deaths and brings a heavy burden to humans worldwide. Chemotherapy remains the key treatment for cancer therapy, but it produces harmful side effects. Meanwhile, the process of de novo development of new anticancer drugs generally needs increasing cost, long development cycle, and high risk of failure. The use of ROS-based repurposed drugs may be one of the promising ways to overcome current cancer treatment challenges. In this review, we briefly introduce the source and regulation of ROS and then focus on the status of repurposed drugs based on ROS regulation for cancer therapy and propose the challenges and direction of ROS-mediated cancer treatment.

1. Introduction

As a common and frequently occurring disease worldwide, cancers increasingly continue to produce serious clinical and socioeconomic issues [1, 2]. Reducing cancer mortality is the primary challenge globally, and the study on cancer treatment has increasingly been a hot spot in the field of scientific research [1, 2]. Despite the progress made in cancer therapy, the growing burden of the most common cancers in low-income and middle-income countries remains to be a major challenge [3]. More importantly, global cancer mortality is not much decreased compared with those in the past decades, though many new anticancer drugs have been approved for tumor prevention or treatment [4]. Unfortunately, the commonly used chemotherapeutics are accompanied with severe adverse effects [5]. Extensive efforts have been made to develop novel and highly efficacious tumor-targeting agents [6]. However, it is not only the frequent

appearance of resistance concomitant with targeted therapies but also the higher budgets of targeted drugs that account for the limited use clinically, which lead to the classical cytotoxic drugs to remain the first choice for patients [7, 8]. Therefore, there is still a need to develop more effective and less toxic anticancer drugs worldwide to prevent and treat cancer.

Over the past few decades, the challenges of drug discovery facing the global pharmaceutical industry are multifold and stagnant, including the escalating cost and length of time required for new drug development and high risk of research and development failure [9, 10]. Currently, the cost of discovering and developing a drug from scratch is traditionally about 2.5 billion US dollars on average, and it takes about 10 to 15 years to enter the market and the success rate is only 2% [11, 12]. Few new anticancer drugs are approved by the FDA annually (Figure 1), though more than 10,000 clinical trials have been completed to evaluate cancer drug

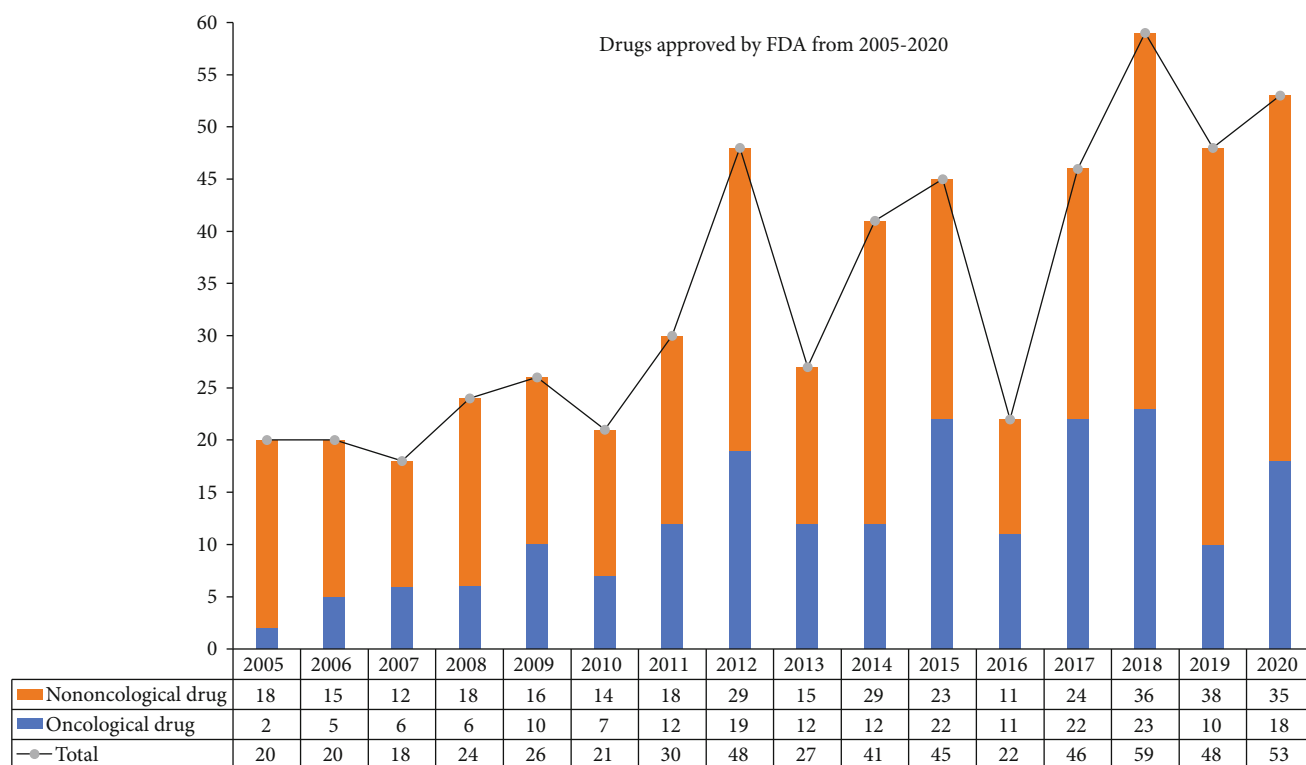


FIGURE 1: The number of the FDA approved drugs for oncology from 2005 to 2020.

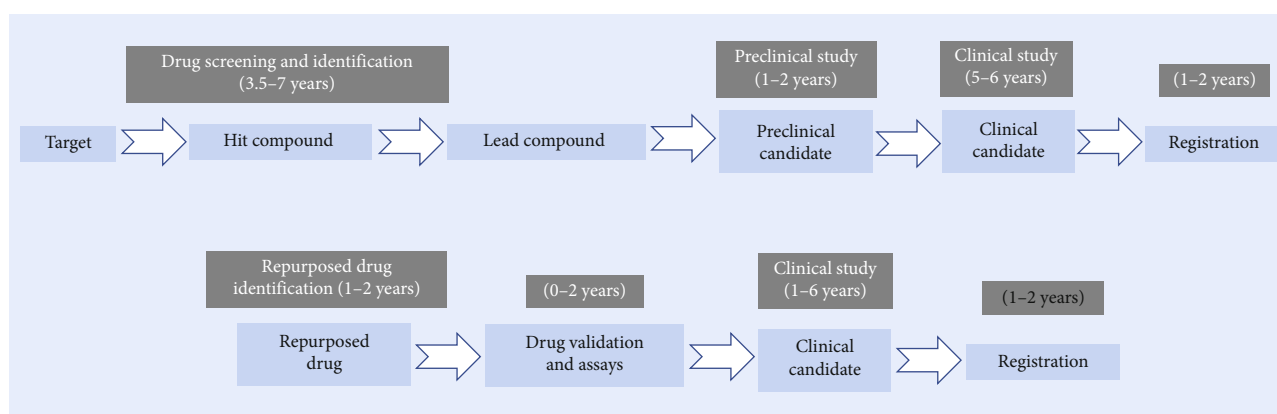


FIGURE 2: A comparison of the estimated time and main steps in de novo drug development and drug repurposing tactics.

interventions [13]. Hence, alternative approaches to drug development are direly needed.

In light of these challenges, drug repurposing may be an alternative approach to overcome obstructions and has gained much attention and momentum in recent years. Drug repurposing is the practice of discovering novel effects or targets of the approved drugs beyond their initial approval, which can expand the indications for marketed drugs [14]. Drug repurposing has many advantages over developing an entirely new drug for a specific indication. For example, repurposed drugs have been found to be safe enough in preclinical models and humans; it is unlikely to fail in early-stage trials and subsequent efficacy trials based on the safety standpoint [15]. Additionally, the time frame and investment for drug development can be reduced; that

is, the return on investment in the development of repurposed drugs for new uses is more rapid (Figure 2) [15]. Finally, repurposed drugs may reveal new anticancer targets and pathways that can be further developed [15]. Historically, drug repurposing was largely discovered by accident by researchers [15]. Once it is discovered that repurposed drugs have off-target effects or newly discovered target effects, they will be developed commercially [15]. The most dramatic examples of repurposed drug are thalidomide and sildenafil citrate. Thalidomide was initially used to treat morning sickness, but it was found to cause severe skeletal birth defects in newborns [16]. However, it was successfully repositioned for use in erythema nodosum leprosum and multiple myeloma therapy [17]. Sildenafil citrate was originally developed as an antihypertension drug, but when

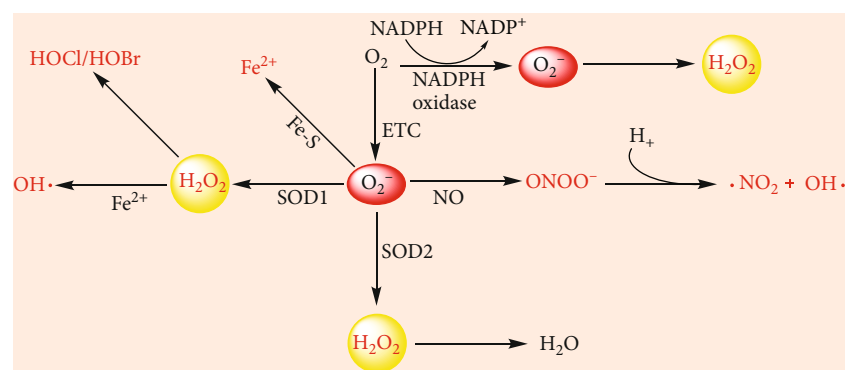


FIGURE 3: General scheme for ROS production by cellular enzymes and electron transport chain. The major sources of intracellular ROS include the mitochondrial ETC and NADPH oxidases. SOD1 and SOD2 can convert O_2^- into H_2O_2 ; then H_2O_2 can be converted into H_2O . Meanwhile, H_2O_2 can also be converted into OH^\cdot , HOCl, and HOBr by Fe^{2+} and myeloperoxidase, respectively. NO is responsible for the conversion of O_2^- into $ONOO^-$ and OH^\cdot .

Pfizer reintroduced it to treat erectile dysfunction and marketed it as Viagra [18]. Surprisingly, it captured vast majority of the erectile dysfunction drug market [15]. Such successes have encouraged the global pharmaceutical industry and drug researchers to identify repurposed drugs. Indeed, there is no systematic approach to predict which drugs can be used as repurposed drugs. The strategies towards identifying drug repurposing opportunities based on a number of promising candidate drugs roughly include computational and experimental approaches [15, 19]. A full account of the comprehensive strategies used for drug repurposing is beyond the scope of this review, and readers are directed elsewhere [15, 19].

2. Overview Biological Characteristics of Reactive Oxygen Species (ROS)

2.1. The Types and Sources of ROS. In recent years, the understanding of tumor pathophysiology and pathogenesis has witnessed an unprecedented explosion. A large number of pleiotropic physiological signaling pathway factors regulating tumor occurrence and development have been emerged. Reactive oxygen species (ROS), the inevitable product of cell metabolism in aerobic life, are broadly defined as oxygen-containing chemical species with reactive properties, and they can be divided into nonradical and free radical [20, 21]. ROS are constantly produced by both enzymatic reaction and the mitochondrial electron transport chain (ETC) from molecular oxygen [20–22]. Complexes I, II, and III of mitochondrial ETC account for a great amount of the intracellular ROS production [23]. The enzyme-catalyzed reactions involve NADPH oxidase (NOX), xanthine oxidase, uncoupled endothelial nitric oxide synthase (eNOS), arachidonic acid, and metabolic enzymes such as the cytochrome P450 enzymes, lipoxygenase, and cyclooxygenase; indeed, NOX has primarily evolved to produce ROS [22, 24]. During the process of aerobic respiration and cellular metabolism, superoxide (O_2^-) is generated either intracellularly by $1 e^-$ transfer to O_2 from the ETC or extracellularly by NOX. In the mitochondria, O_2^- damages iron-sulfur (Fe-S) clusters to release iron (Fe^{2+}) into

the extracellular matrix and reduces ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}), which leads to inactivation of protein function [25, 26]. The O_2^- is dismutated to hydrogen peroxide (H_2O_2) in a buffer or catalyzed by superoxide dismutases (SOD1 and SOD2) [22]. Moreover, H_2O_2 is also generated by various other oxidases present in subcellular localizations, prominently including the endoplasmic reticulum (ER) lumen [27, 28]. Meanwhile, O_2^- is converted into peroxynitrite ($ONOO^-$) and hydroxyl radical (OH^\cdot) through a reaction with nitric oxide (NO) [29]. OH^\cdot is generated by a ferrous iron-mediated reduction of H_2O_2 and the decomposition of $ONOO^-$ [29]. Additionally, H_2O_2 can be converted into hypochlorous acid and hypobromous acid (HOCl and HOBr) through myeloperoxidase in the phagocytic vacuole in neutrophils for pathogen defense [22, 30, 31] (Figure 3). Meanwhile, biologically relevant ROS are also derived from the exogenous environment, which includes air pollutants, stress, ultraviolet rays, toxicants, tumor chemotherapy, and radiotherapy [24, 32–35]. However, these exposures are highly variable; it is challenging to measure ROS directly in cells and tissues.

2.2. The Impact and Damage Outcomes of ROS. Among the radical and nonradical oxygen species, H_2O_2 is recognized as the key redox signaling agent in redox regulation of biological activities, and a total of 37 H_2O_2 -generating enzymes have been found [36, 37]. It is now clear that H_2O_2 plays a fundamental role in physiology as a functional signaling entity [38]. H_2O_2 first occurred at low homeostasis levels in normally breathing eukaryotic cells, and it was the primary ROS responsible for protein oxidation [39]. Generally, the generation of H_2O_2 was constantly stimulated by metabolic cues or various stressors intracellularly, and the concentration of H_2O_2 is maintained in the low nanomolar range, which is important for signaling by redox signaling via oxidation and called “oxidative eustress” [40, 41]. The overall cellular concentration of the O_2^- is maintained at about 10^{-11} M, which is much lower than the 10^{-8} M of H_2O_2 [42]. Diffusible H_2O_2 contributes to orchestration of various processes including cell proliferation, differentiation, and angiogenesis through oxidation of sulfur

(thiolate groups) in target proteins and further activates stress responsive survival pathways [43, 44]. Meanwhile, H_2O_2 acts as signal transduction molecules that induce proinflammatory cytokines and the nuclear factor- κ B (NF- κ B) pathway [45, 46].

In contrast to low levels of H_2O_2 , supraphysiological concentrations of H_2O_2 cause “oxidative distress,” which can induce a plethora of irreversible damaging effects to proteins, DNA, and lipids and ultimately cause cell death [47]. At the cellular level, oxidation of proteins by ROS is more common than that of DNA and lipids [48]. When proteins are exposed to ROS, amino acid side chains are modified, and consequently, the protein structure is altered [48]. ROS can cleave peptide bonds through α -amidation, diamidation, proline residue oxidation, glutamine residue oxidation, and aspartyl residue oxidation [49]. ROS-induced protein oxidation may contribute to the following: (1) hydroxylation of aromatic groups and aliphatic amino acid side chains, nitration of aromatic amino acid residues, nitrosation of sulfhydryl groups, and sulfonation of methionine residues; (2) polypeptide chain breaking to form cross-linked protein aggregates; and (3) the functional groups of proteins reacting with oxidation products of polyunsaturated fatty acids or carbohydrate derivatives, which affects normal physiological function [48, 49]. It is equally well known that sustained exposure to high ROS levels can damage DNA through single strand break, point mutations, mis-coding, and abnormal amplification [48]. DNA is complexed as chromatin with histones; ROS can further affect the oxidation and reduction of adduct radicals of DNA [48]. Besides, toxic concentrations of ROS also induce mitochondrial DNA mutations [48, 50]. Lipids have the functions of energy storage, signal transduction, transport, and cell membrane composition in cells, and many types of lipids are easily oxidized by ROS [48, 51]. The reaction of ROS with lipid molecules can activate the lipid peroxidation free radical cascade, which is generally very fast [48]. The hydrogen atom abstraction forms a methylene carbon of a polyunsaturated fatty acid by a lipid hydroperoxyl radical, forming a new carbon centered radical that propagates the peroxidative chain reaction and a hydroperoxide [52]. Moreover, the more double bonds in the lipid, the easier it is for hydrogen atoms to be taken away [53]. Excessive ROS can cause lipid peroxidation in biofilms, which would result in loss of fluidity, abnormal membrane potential, and rupture and leakage of cell contents [54]. Therefore, it is challenging and important to determine the precise role and maintain a safe cellular ROS gradient and regulate redox signaling pathways.

2.3. Intracellular Clearance of ROS. Excess ROS production induces a plethora of damaging effects to cellular biomacromolecules. Hence, supraphysiological gradients of ROS are showcased as harmful species, and buffering ROS to maintain redox homeostasis is required. In order to prevent the unrestricted accumulation of ROS, a series of antioxidant defense systems have been discovered and can act independently or synergistically to neutralize ROS. Antioxidants can be divided into two groups, that is, noncatalytic small molecules and catalytic antioxidants [29]. Glutathione

(GSH) is the most abundant nonenzymatic antioxidant molecule and is essential for cell survival and redox homeostasis [55]. GSH is a tripeptide that synthesis catalyzed by glutamate-cysteine ligase (GCL) and GSH synthetase (GSS), and it is used as a cofactor by GSH S-transferases (GSTs) and GSH peroxidases (GPxs) to eliminate ROS [56]. Besides, endogenously synthesized bilirubin, melatonin, α -lipoic acid, and uric acid are other nonenzymatic antioxidant molecules that mitigate the excess level of ROS produced in cells [29, 57]. Enzymatic antioxidants include SOD, catalase (CAT), peroxiredoxins (PRxs, also called PRxs), glutathione peroxidases (GPxs), thioredoxin reductases (TrxRs), and thioredoxins (Trxs) [29]. Enzymatic antioxidants with high catalytic activity are uncovered as handling ROS levels in cells [29]. SODs are a family of metalloenzymes catalyzing the dismutation of O_2^- to H_2O_2 , which utilizes metal ions, including copper (Cu^{2+}), ferrous iron (Fe^{2+}), manganese (Mn^{2+}), and zinc (Zn^{2+}) as cofactors [58]. CAT is primarily localized in the cytosol and cell organelles called the peroxisome, which can convert H_2O_2 into O_2 and H_2O [59]. In addition, Trxs promote PRDX-mediated H_2O_2 detoxification and reduction of lipid by GPx requires GSH [56]. More importantly, GSH and Trxs generate oxidized forms through detoxification of ROS [56]. Oxidized GSH and Trxs are both regenerated by GSH reductase (GSR) and Trxs reductase 1 using NADPH as a cofactor, respectively [60]. GSH and Trxs, and TrxRs are noncatalytic and catalytic antioxidants, which are critically involved in different stages of cancers [61–63].

In addition, it is established that many transcription factors, including nuclear factor erythroid 2-related factor 2 (NRF2), the forkhead box O (FOXO), hypoxia-inducible factor (HIF), NF- κ B, and tumor protein p53 (TP53 or Trp53 in mice), are activated by ROS and regulate intracellular redox environment of cells [64]. NRF2 is the most important transcription factor for the activation of a number of genes that have antioxidant functions within the cell [65, 66]. However, under resting conditions, NRF2 is degraded through interacting with Kelch-like ECH-associated protein 1- (KEAP1-) Cullin 3 (CUL3) E3 ligase complex. Under conditions of oxidative stress or electrophilic addition, cysteine residues on KEAP1 are modified, thus blocking NRF2 interaction and subsequent degradation [67]. Then, NRF2 translocated into the nucleus, where it serves as a transcription factor for expression of the antioxidant responsive element-(ARE-) driven genes, including hemeoxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO1), glutathione S-transferases (GSTs), and UDP-glucuronosyltransferases (UGTs) [67]. In addition, sestrins (SESN1, 2, and 3) exert indirect antioxidant activity, in part by activation of transcription factor NRF2 [68, 69]. The FOXO family of transcription factors contributes to the maintenance of cellular and organismal homeostasis in various ways [70]. For example, FOXO improves mitochondrial redox, suppresses the levels of free transition metal ions, and promotes antioxidant defense system [71]. Hypoxia has been associated with an increase in O_2^- and H_2O_2 generation through inhibition of the mitochondrial ETC [72]. HIF is a transcription factor that serves as the master regulator of transcriptional

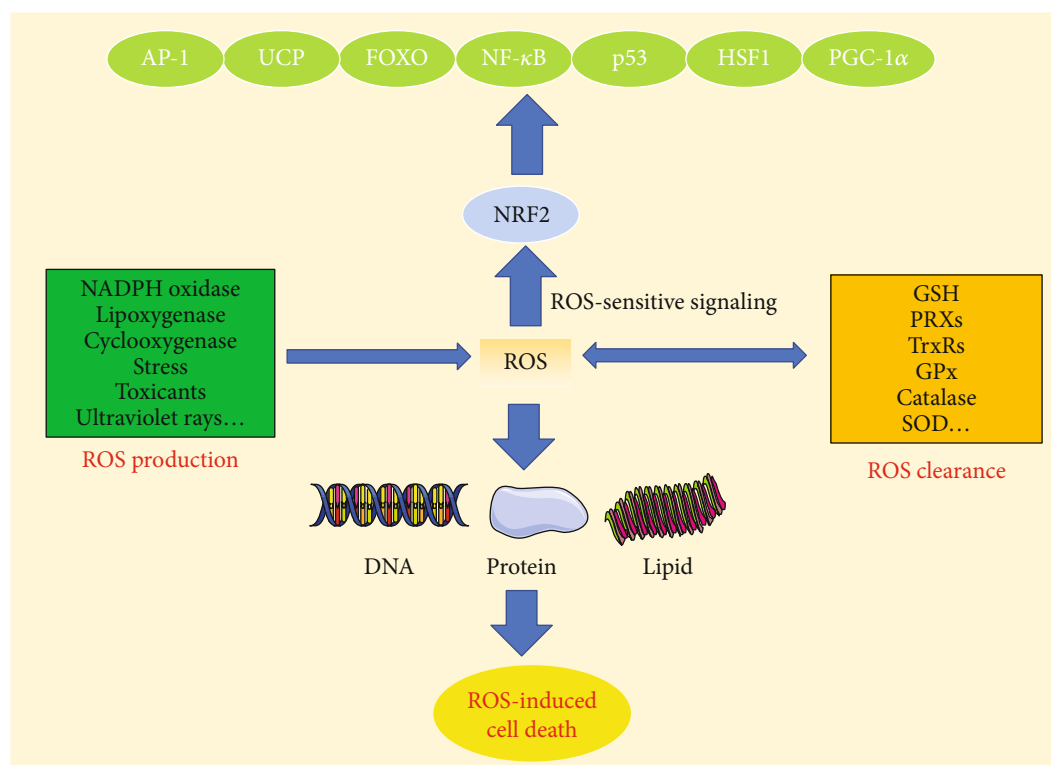


FIGURE 4: ROS balance and their roles in regulating transcription factors and cell death. ROS can be produced by NADPH oxidases, lipoxygenase, cyclooxygenase, stress, toxicants, and ultraviolet rays. On the other hand, ROS can be eliminated via activation of the GSH, PRXs, TrxRs, GPx, catalase, and SOD. Extremely high levels of ROS are dangerous for the DNA, protein, and lipid and eventually cause cell death. Cells first adapt to the increase in ROS by activating NRF2 and then trigger other members of the antioxidant transcription factor when the excess levels of ROS that are not countered by the NRF2-directed defenses.

responses to hypoxia [73]. Oxidants can stabilize HIF during hypoxia, thereby helping to increase the hypoxia response [73]. NF-κB serves as a master switch of inflammation, which is associated with extensive H_2O_2 production [74]. In different context, H_2O_2 has different roles in NF-κB function [74]. H_2O_2 activates NF-κB pathway and then negatively controls the stability of IκB in the cytosol [75], while H_2O_2 also directly modulates NF-κB due to the presence of oxidizable cysteines in the DNA-binding region of NF-κB [76]. The tumor suppressor protein p53 was considered the transcription factor that has a major role in regulating antioxidant gene expression [77, 78]. Under the control of H_2O_2 , it regulates the selective transcription activation of p53 target genes through the oxidation of p53 cysteine residues. Reciprocally, p53 regulates the expression of antioxidant genes to maintain cellular redox balance [79]. Other transcription factors, such as AMP-activated protein kinase (AMPK), activator protein 1 (AP-1), heat shock factor 1 (HSF1), peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1 α), uncoupling protein (UCP), and protein-tyrosine phosphatase 1B (PTP1B), also contribute to redox status [80–85].

However, the extents to which individual members of the above network of antioxidant transcription factors are differentially activated by oxidative stress are uncertain, although it is improbable that all of them are activated simultaneously. However, different transcription factors

may respond to distinct threshold levels of ROS. When cells suffered from moderate levels of ROS, NRF2 first was activated, and then a series of genes encoding detoxification enzymes were further induced, which provided a floodgate to protect against ROS [20]. When cells further adapt to sustained exposure to high ROS levels, which causes activation of Krüppel-like transcription factor 9 (KLF9) and downregulation of NRF2, the NRF2-induced defense cannot counteract the excess ROS, then triggering additional redox switches that activate other members of the antioxidant transcription factor network [20] (Figure 4). Therefore, intracellular ROS regulation is closely related to the above complex processes, and there is no constant boundary between prooxidants and antioxidants in the regulation of ROS.

3. ROS Paradox and Contradictory Strategies Based on ROS for Cancer Treatment

Under normal physiological conditions, the redox system is in good coordination and well-balanced. However, in the presence of obvious stimuli, the balance would be disrupted, triggering oxidative stress and in turn increasing ROS levels, implicated in various human diseases including cancer. Interestingly, oxidative stress can activate cell survival or death mechanisms depending on the severity and exposure time of ROS excess. In general, ROS act as mitogens to induce proliferation and differentiation of normal and

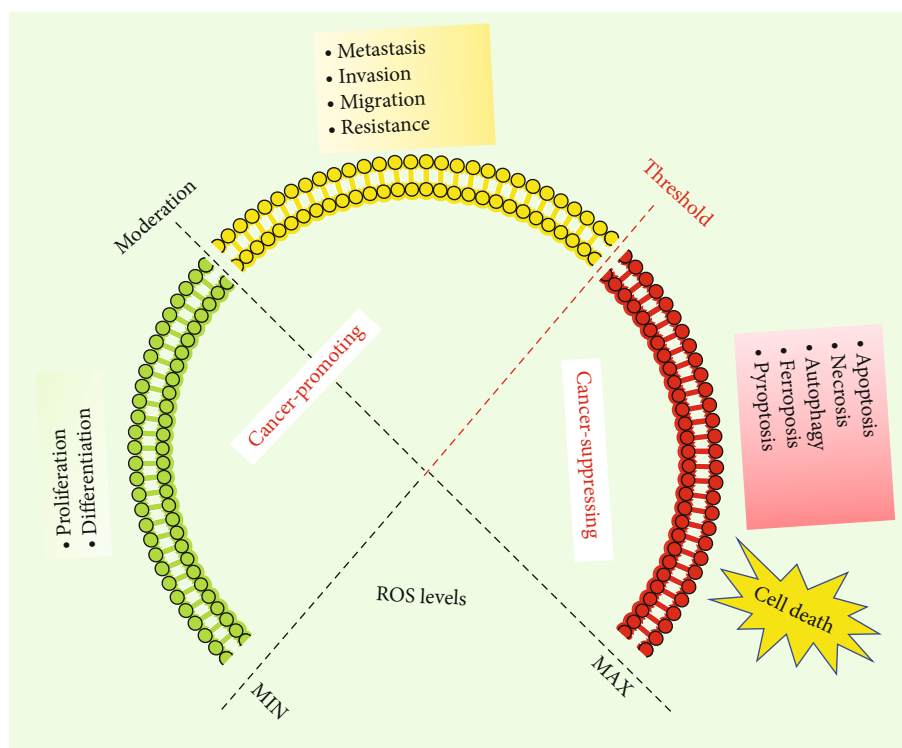


FIGURE 5: The cancer-promoting activities and cancer-suppressing activities of ROS in cancer. Low ROS (green) is the basic need to maintain normal cellular proliferation, and differentiation. Moderate ROS (yellow) is the signal for the increased cellular metastasis, invasion and migration, and resistance. When the ROS level exceeds threshold (red), ROS can induce cancer cell death via the activation of cell apoptosis, necrosis, autophagy, ferroptosis, and pyroptosis.

cancer cells at low concentrations (usually submicromolar concentrations) [48]. At moderate concentrations, ROS have been implicated in tumor initiation and progression, malignant conversion, and resistance to chemotherapy. The higher concentrations of ROS result in damage cellular biomolecules and cause gene mutations, thus promoting canceration of normal cells or inducing cancer cell apoptosis, necrosis, autophagy, ferroptosis, and pyroptosis [48, 86] (Figure 5). Therefore, the roles of ROS are complicated, and ROS operate as a diversified biochemical entity in cancer progression.

Because the influence of ROS on cancer development is contradictory, reducing or increasing intracellular ROS levels would be a potential strategy to prevent or treat cancer [87]. Namely, reducing the intracellular ROS content by inhibiting ROS production pathway and using exogenous supplementation of antioxidants is an effective strategy, and it could effectively prevent the early stage of tumor occurrence. Cancer cells are more sensitive to enhanced intracellular ROS than normal cells; thus, cancer cells can be preferentially killed by enhancing the cellular ROS levels, which might be another puissant strategy to selectively kill cancer cells. Moreover, the expression level of antioxidant enzymes and oxidative stress environment in drug-resistant tumor cells are usually higher; ROS-modulating drugs may have a better therapeutic effect on the intervention of drug-resistant tumor cells. The use of small molecules to increase the production of ROS or/and inhibit the antioxi-

dant defense system is one of the most effective anticancer methods [87]. In recent years, several clinical trials have been made in the research of therapeutic drugs targeting ROS regulation in cancer cells [88]. Moreover, small molecules regulating ROS homeostasis for cancer therapy have been comprehensively reviewed [24, 87]. However, most small molecules described in the literature or on the clinical development stages have not entered into clinical treatment for cancer. Several FDA-approved drugs based on ROS regulation have led to repurposing of cancer indications, which may be considered a novel and valid cancer therapeutics [89]. Therefore, in this paper, we will focus on repurposed drugs for cancer therapy by the regulation of ROS homeostasis.

4. Repurposed Drug-Regulated ROS Homeostasis as a Novel Cancer Therapeutics in Oncology

4.1. Repurposed Drugs as a ROS Scavenger in Cancer. ROS accumulation is one of the initiating factors in the early stage of the neoplastic process. To this extent, ROS can lead to more metabolic adaptations and more levels of DNA damage and genetic instability in normal cells, consequently promoting the cancer cell proliferation and growth [90, 91]. Numerous epidemiological data and preclinical/clinical studies suggest that small molecule ROS inhibitors can

TABLE 1: Repurposed clinical candidates for cancer.

Drug	Original indication	Clinical trials
Vitamin C	Antioxidant	<p>(1) Effect of vitamin C and E in breast cancer patients undergoing chemotherapy (nct04463459)</p> <p>(2) Preoperative IMRT with concurrent high-dose vitamin C and mFOLFOX6 in locally advanced rectal cancer (nct04801511)</p> <p>(3) Intravenous (IV) vitamin C with chemotherapy for cisplatin-ineligible bladder cancer patients (nct04046094)</p> <p>(4) Intravenous ascorbic acid supplementation in neoadjuvant chemotherapy for breast cancer (nct03175341)</p> <p>(5) Ph 2 trial of vitamin C & G-FLIP (low doses of gemcitabine, 5FU, leucovorin, irinotecan, and oxaliplatin) for pancreatic cancer (nct01905150)</p> <p>(6) Other clinical trials are available at clinicaltrials.gov</p>
Vitamin E	Antioxidant	<p>(1) Vitamin E supplements in preventing cancer in patients at risk of prostate cancer or who have prostate cancer (nct00895115)</p> <p>(2) Vitamin E supplements in treating patients undergoing surgery for colorectal cancer (nct00905918)</p> <p>(3) Selenium and vitamin E in preventing cancer progression and recurrence in patients with early-stage bladder cancer (nct00553345)</p> <p>(4) S0000 selenium and vitamin E in preventing prostate cancer (nct00006392)</p> <p>(5) A pilot clinical trial with tocotrienol on breast cancer (nct01157026)</p> <p>(6) Other clinical trials are available at clinicaltrials.gov</p>
Tigecycline	Antibacterial	<p>(1) Personalized treatment of urogenital cancers depends on the microbiome (nct03962920)</p> <p>(2) Safety study evaluating intravenous infusions of tigecycline to treat acute myeloid leukemia (nct01332786)</p> <p>(3) In vitro study of tigecycline to treat chronic myeloid leukemia (nct02883036)</p>
Doxycycline	Antibacterial	<p>(1) Metformin hydrochloride and doxycycline in treating patients with localized breast or uterine cancer (nct02874430)</p> <p>(2) Doxycycline for the treatment of cutaneous T-cell lymphoma (nct02341209)</p> <p>(3) Combining doxycycline with bone-targeted therapy in patients with metastatic breast cancer (nct01847976)</p> <p>(4) Doxycycline in lymphangioliomyomatosis (lam) (nct00989742)</p> <p>(5) Doxycycline, temozolomide, and ipilimumab in melanoma (nct01590082)</p> <p>(6) A phase II study of doxycycline in relapsed NHL (nct02086591)</p>
Clarithromycin	Antibacterial	<p>(1) Is clarithromycin a potential treatment for cachexia in people with lung cancer? (nct02416570)</p> <p>(2) A trial with metronomic low-dose treosulfan, pioglitazone, and clarithromycin versus standard treatment in NSCLC (nct02852083)</p> <p>(3) Chemoprevention therapy in treating patients at high risk of developing multiple myeloma (nct00006219)</p> <p>(4) Clarithromycin in multiple myeloma induction therapy (nct02573935)</p> <p>(5) Clinical trial of clarithromycin, lenalidomide, and dexamethasone in the treatment of the first relapsed multiple myeloma (nct04063189)</p> <p>(6) Other clinical trials are available at clinicaltrials.gov</p>
Nicosamide	Antiparasitic	<p>(1) A study of nicosamide in patients with resectable colon cancer (nct02687009)</p> <p>(2) Drug trial to investigate the safety and efficacy of nicosamide tablets in patients with metastases of a colorectal cancer progressing after therapy (nct02519582)</p> <p>(3) Enzalutamide and nicosamide in treating patients with recurrent or metastatic castration-resistant prostate cancer (nct03123978)</p> <p>(4) Nicosamide and enzalutamide in treating patients with castration-resistant, metastatic prostate cancer (nct02532114)</p> <p>(5) Abiraterone acetate, nicosamide, and prednisone in treating patients with hormone-resistant prostate cancer (nct02807805)</p>
Hydroxychloroquine	Antimalarial	<p>(1) Phase I/II study of hydroxychloroquine with itraconazole with biochemically recurrent prostate cancer (nct03513211)</p> <p>(2) Hydroxychloroquine in previously treated patients with metastatic pancreatic cancer (nct01273805)</p> <p>(3) Hydroxychloroquine to increase tumor suppressor par-4 levels in oligometastatic prostate cancer (nct04011410)</p>

TABLE 1: Continued.

Drug	Original indication	Clinical trials
Simvastatin	Antihyperlipidemic	(4) Hydroxychloroquine in metastatic estrogen receptor-positive breast cancer progressing on hormonal therapy (nct02414776)
		(5) Hydroxychloroquine and gefitinib to treat lung cancer (nct00809237)
		(6) Other clinical trials are available at clinicaltrials.gov
		(1) Simvastatin plus dual anti-HER2 therapy for metastatic breast cancer (nct03324425)
		(2) Trial of xp (capecitabine/cddp) simvastatin in advanced gastric cancer patients (nct0109908)
		(3) Simvastatin in preventing a new breast cancer in women at high risk for a new breast cancer (nct00334542)
Digoxin	Antiheart failure	(4) Metformin and simvastatin use in bladder cancer (nct02360618)
		(5) A phase I study of high-dose simvastatin in patients with gastrointestinal tract cancer who failed to standard chemotherapy (nct03086291)
		(6) Other clinical trials are available at clinicaltrials.gov
		(1) Potentiation of cisplatin-based chemotherapy by digoxin in advanced unresectable head and neck cancer patients (nct02906800)
		(2) Digoxin for recurrent prostate cancer (nct01162135)
		(3) Capecitabine with digoxin for metastatic breast cancer (nct01887288)
Fluphenazine	Antipsychotics	(4) Phase IB metformin, digoxin, and simvastatin in solid tumors (nct03889795)
		(5) Phase II multicenter study of digoxin per os in classic or endemic Kaposi's sarcoma (nct02212639)
		(6) Other clinical trials are available at clinicaltrials.gov
		(1) Fluphenazine in treating patients with refractory advanced multiple myeloma (nct00335647)
		(2) Study of fluphenazine in relapsed or relapsed-and-refractory multiple myeloma (nct00821301)

effectively prevent tumorigenesis. Therefore, repurposed drugs that act as ROS scavengers have the potential to modulate levels of ROS for therapeutic benefit in cancer.

4.1.1. Vitamin C. Vitamin C, known as ascorbic acid, is an antioxidant converted from glucose, which is abundant in fresh fruits and vegetables [92]. At physiological concentrations, vitamin C prevents gene mutations caused by peroxidation by removing ROS, and it also blocks oxidative modification of amino acids to maintain protein integrity and protects lipids from peroxidation [93]. In a cohort study, Wright et al. analyzed the comprehensive intake of individual selenium, flavonoids, vitamin C, and carotenoids to predict the risk of lung cancer. They proved that integration of dietary antioxidants can significantly reduce lung cancer incidence in male smokers [94]. However, it has been nearly half of a century since the beginning of researches of anticancer mechanism of vitamin C, and its role was challenged and verified repeatedly. Moreover, the controversy about the anticancer efficiency of vitamin C may depend on the administration ways (oral or intravenous), which can result in different concentrations in the plasma of cancer subjects [92]. High-dose vitamin C alone or in combination can inhibit tumor growth in various cancer models through regulation the level of ROS [95–97]. Furthermore, high-dose intravenous vitamin C in cancer patients has led to increased quality of life with minimal side effects [98, 99]. Several excellent reviews have recently described that vitamin C is used for cancer chemoprevention and clarified that the anticancer mechanism of high doses of vitamin C is targeting excessive ROS generation and/or epigenetic regulators

and/or hypoxia-inducible factor 1 (HIF-1) [92, 100, 101]. Moreover, vitamin C has also been extensively tested in clinical trials of cancer for many years (Table 1).

4.1.2. Vitamin E. Vitamin E is a hydrophobic fat-soluble compound that exists in a variety of food sources, and it in nature occurs as 8 isoforms (tocopherols and tocotrienols, both as α , β , γ , and δ forms); however, only α -tocopherol is considered to be essential for human [102, 103]. Vitamin E protects cells from cell damage caused by ROS, thereby attenuating DNA damage and cancer development [102]. Vitamin E has been extensively studied, and much data indicates that it has a role in cancer prevention [103]. For example, it is found that vitamin E can interfere phosphatidylinositol-3-kinase/protein kinase B (PI3K/PKB) and protein kinase C (PKC) signaling pathways by scavenging ROS, which may be one of the antitumor mechanisms [102, 104–106]. Moreover, clinical trials of vitamin E in cancer treatment have been detailed in some review and research articles [107, 108], although it was found that the development and metastasis of lung tumors were increased in vitamin E-treated mouse models [109].

4.2. Repurposed Drugs as a ROS Inducer in Cancer. Interestingly, repurposed drugs are more likely to act as ROS inducers in the treatment or prevention of cancer. ROS-inducing repurposed drugs by mechanisms of inhibiting intracellular antioxidant systems and/or producing ROS generation in cells were reported to selectively kill cancer phenotypes. Several reviews on the small molecules regulating ROS homeostasis for cancer therapy have been

published [24, 87, 89]. In the review, we will classify and describe repurposed drugs that induce the excessive production of ROS in the cancer cells to exert antitumor effects.

4.2.1. Antibacterial

(1) *Tigecycline*. Tigecycline is a broad-spectrum antibiotic approved by the FDA for the treatment of multidrug-resistant bacterial infections, complicated intra-abdominal infections, complicated skin structure infections, and community-acquired pneumonia [110]. Its antibacterial mechanism involves killing bacteria by binding to the 30S bacterial ribosomal subunit, thereby preventing tRNA and its codons from linking to the A site of the ribosomal complex, which result in inhibiting protein synthesis [111, 112]. Recent studies have found that tigecycline is identified as one of the effective anticancer agents by enhancing the levels ROS. For example, tigecycline inhibited mitochondrial respiration, mitochondrial membrane potential, and adenosine triphosphate (ATP) levels and caused an increase in intracellular ROS in a dose-dependent manner, which induced death of non-small-cell lung cancer cells [113]. Additionally, tigecycline was found to selectively kill leukemic stem and progenitor cells by inhibiting mitochondrial translation [114]. Besides, tigecycline significantly enhanced conventional cisplatin activity against human hepatocellular carcinoma through inducing mitochondrial dysfunction and increasing the levels of mitochondrial superoxide, hydrogen peroxide, and ROS levels [115]. More importantly, a phase I clinical trial evaluating the safety and biologic activity of intravenous infusions of tigecycline to treat acute myeloid leukemia was completed (NCT01332786) (Table 1).

(2) *Levofloxacin*. Levofloxacin is a third-generation fluoroquinolone antibacterial drug, which can kill bacterial through preventing DNA replication [116]. It is often used clinically for some moderate and severe infections caused by sensitive bacteria [116]. With the further study, repurposed antibiotic levofloxacin is an attractive candidate for cancer treatment. It was found that levofloxacin effectively inhibited lung cancer cell proliferation and induces apoptosis [117]. Mechanistically, levofloxacin inhibited the activity of the mitochondrial electron transport chain complex, which in turn blocked mitochondrial respiration, reduced ATP production, and increased the levels of ROS, mitochondrial superoxide, and hydrogen peroxide [117]. Moreover, levofloxacin effectively targeted breast cancer cells and acted synergistically with 5-fluorouracil through inhibiting mitochondrial biogenesis and was accompanied by the deactivation of PI3K/PKB/mammalian target of rapamycin (mTOR) and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) signaling pathways [118].

(3) *Doxycycline*. Doxycycline (DOXY), a derivative of tetracycline, is a broad-spectrum antibiotic that exhibits many therapeutic activities in addition to its antibacterial properties [116, 119]. Doxycycline has recently carved out a role in cancer therapy. It was found that doxycycline triggered cell death in different cancer cells, including cervical, breast,

lung, and prostate cancer cells [120]. A further study found that doxycycline was effective in targeting glioblastoma through inducing mitochondrial dysfunctions and oxidative stress [121]. Moreover, the ROS-apoptosis signal regulating kinase 1- (ASK1-) Jun N-terminal kinase (JNK) pathway is involved in doxycycline-induced melanoma cell death [122]. Amplification of tumor-associated ROS has been used as a boosting strategy to improve tumor therapy. A recent study has shown that prodrug chlorin e6 (Ce6) and zoledronic acid (ZA)/mesoporous silica nanoparticles (MSN)/doxorubicin- (DOX-) thioketal- (TK-) DOXY can be used for the chemodynamic therapy of osteosarcoma [123]. Upon laser irradiation, the loaded Ce6 produced in situ ROS and subsequently resulted in DOX/DOXY release. The released DOXY promoted ROS production and further induced ROS burst, which increased the sensitivity of the osteosarcoma to chemotherapy and resulted in enhancing tumor cell inhibition and apoptosis [123]. Furthermore, some clinical trials are ongoing, including a phase II trial study of how well metformin hydrochloride works together with doxycycline in treating patients with localized breast or uterine cancer (NCT02874430) and a study of doxycycline for the treatment of cutaneous T-cell lymphoma (NCT02341209) (Table 1).

(4) *Clarithromycin*. Clarithromycin belongs to a family of 14-membered ring macrolide antibiotics, but several clinical investigations showed that clarithromycin was highly efficient for multiple myeloma (MM) when used in combination with conventional chemotherapy since 1997 [124]. This finding highlights the importance of clarithromycin on the treatment of MM and offers a new regimen for the relapsed/refractory MM patients. Moreover, the results of Zhou et al. showed that clarithromycin plus cisplatin had a synergetic effect against ovarian cancer cell viability and induced the apoptosis rate, which was linked to the increase of ROS levels *in vitro* and *in vivo* [125]. This result proved that clarithromycin augmented cisplatin response via a ROS-mediated synergistic effect. However, no clinical trials have investigated the activity of clarithromycin against ovarian cancer. Indeed, a phase II clinical trial evaluating clarithromycin treatment for cachexia (the loss of muscle mass) in people with non-small-cell lung cancer was terminated due to having not enough participants (NCT02416570) (Table 1).

4.2.2. Anthelmintic

(1) *Niclosamide*. Niclosamide, an FDA-approved oral agent, belongs to the antiparasitic disease drug and has been used in the clinical treatment of intestinal parasitic infections for nearly 50 years [126]. In recent studies, it had been documented that niclosamide had antitumor effects and can increase the sensitivity of tumor cells to chemotherapy and radiotherapy through regulating redox homeostasis. For example, niclosamide inhibited the NF- κ B pathway and increased ROS levels to induce apoptosis in acute myelogenous leukemia cells [127]. Niclosamide also suppressed renal cell carcinoma by inhibiting Wnt/beta-catenin and inducing

mitochondrial dysfunctions [128]. Moreover, niclosamide was found to sensitize the responsiveness of cervical cancer cells to paclitaxel via ROS-mediated mTOR inhibition [129]. Also, niclosamide was chosen based on a cell-based high-throughput viability screen and it had a radiosensitizing effect on H1299 human lung cancer cells [130]. A further study had demonstrated that niclosamide plus gamma-ionizing radiation can produce ROS and promote c-Jun and its phosphorylation [130]. Moreover, niclosamide also acted as a potent radiosensitizer through inhibiting signal transducer and activator of transcription 3 (STAT3) and B-cell lymphoma-2 (Bcl-2) and increasing ROS generation in triple-negative breast cancer cells [131]. The therapeutic effect of combination valproic acid and niclosamide was investigated on human lung cancer cell line [132]. The results showed that combination therapy caused a dramatic decrease in cell viability by inducing the extrinsic apoptotic pathway and stimulating endoplasmic reticulum stress and mitochondrial membrane potential loss associated with increased ROS levels [132]. Based on these encouraging results, the evaluation of niclosamide in several clinical trials has been investigated (Table 1).

(2) *Albendazole*. Albendazole is a broad-spectrum, low-toxic antiparasitic drug that kills susceptible parasites by reducing the glycogen stores and the formation of ATP [133]. There are several evidences supporting albendazole repositioning for cancer therapy against tumor cell lines [133]. Further studies have shown that oxidative stress was one of anticancer mechanisms that mediated albendazole. Castro et al. had demonstrated that albendazole treatment could trigger apoptosis and induce MCF-7 cell death through ROS generation, which was related to depletion of reduced glutathione levels, augmented important oxidative biomarkers, and increased the activity of antioxidant enzymes [134]. It was found that ROS can induce p38 MAPK activation in U937 cells treated with albendazole. Pretreatment with SB202190 (p38 MAPK inhibitor) increased the activity of cells treated with albendazole, indicating that ROS-induced P38 MAPK activation was associated with albendazole-mediated cell death [135]. However, no clinical trials have been conducted to investigate the antitumor effects of the albendazole.

4.2.3. Antimalarial

(1) *Artemisinin*. Artemisinin and its derivatives are natural synthetic antimalarial drugs [136]. With the deepening of research, artemisinin not only has strong antimalarial activity but also has obvious antitumor effects. Artemisinin harbors an endoperoxide bridge whose cleavage results in the generation of ROS and/or artemisinin carbon-centered free radicals, further promoting cell apoptosis, inhibiting cell proliferation and damaging DNA, cell membrane, protein, and organelles to play an antitumor effect [137]. The ROS-mediated antitumor properties of artemisinin on numerous cancer types have been reported [138–142]. Compared with traditional chemotherapeutic drugs, artemisinin has the advantages of broad antitumor spectrum, less toxicity, and

side effects, so it can be identified as an intriguing candidate for repurposing. However, there are no clinical trials investigating the antiproliferative effects of artemisinin; an additional study is necessary for optimal clinical efficacy.

(2) *Hydroxychloroquine*. Hydroxychloroquine, a chloroquine derivative, is originally developed to treat patients with malaria, but it has been further investigated because of its antiproliferative effects on different types of tumors [143]. In general, hydroxychloroquine has a better oral bioavailability and safety profile than chloroquine, which makes it a suitable candidate to evaluate its potential therapeutic applications in cancer [143]. Hence, hydroxychloroquine was under investigation in cell level, animal models, and clinical trials for a variety of cancers. Many studies found that hydroxychloroquine was capable of killing tumor cells by different pathways accompanied by the massive production of ROS. In-depth evaluation of hydroxychloroquine, it revealed that it could be considered an effective autophagy inhibitor [144]. Autophagy is a self-degrading intracellular process involving tumor suppression and promotion [145]. However, inhibition of autophagy with hydroxychloroquine can not only hinder the autophagic protective effect but also increase dysfunctional mitochondria and ROS production, and a further study found that ROS was the main mechanism of enhanced cytotoxicity with autophagy inhibition [144]. Moreover, hydroxychloroquine exhibited a good synergism with microtubule polymerization inhibitor CYT997 on the induction of ROS-associated apoptosis in human head and neck squamous cell carcinoma [146]. In addition, breast cancer cell apoptosis induced by hydroxychloroquine was related to the inhibition of the autophagic flux and accumulation of damaged mitochondria and ROS [147]. Hence, the inhibition of autophagy is, at least partially, responsible for hydroxychloroquine-mediated upregulation of ROS in cancer cell death.

4.2.4. Cardiovascular

(1) *Simvastatin*. Simvastatin is an antihigh cholesterol drug widely used in the prevention and treatment of cardiovascular diseases by inhibiting the 3-hydroxy-3-methylglutaryl-coenzyme a (Hmg-CoA) reductase in the mevalonate pathway and blocking the formation of intermediary products in the biosynthesis of cholesterol [148]. Simvastatin has recently been considered a potential sensitizer to chemotherapy and radiotherapy and exhibits inhibitory effects on amounts of types of cancer [149]. For example, simvastatin alone or in combination with doxorubicin significantly increased ROS levels and suppressed breast cancer MCF-7 cell proliferation [150]. Moreover, a combined therapy of simvastatin and pentoxifylline effectively activated ERK/AKT, upregulated ROS levels, downregulated p-p38, and inhibited NF- κ B signaling pathway, thereby promoting triple-negative breast cancer cell apoptosis [150]. Additionally, simvastatin administration alone also could induce ROS formation in the KKV-100 cells [151]. Due to the excellent antitumor effect of simvastatin *in vitro*, a large number of clinical studies have been conducted (Table 1).

(2) *Digoxin*. Digoxin, an inhibitor of Na^+/K^+ ATPase, is widely used to treat heart failure. The clinical tests of digoxin as an anticancer drug, alone or in combination with chemotherapeutic drug, were reported [152]. Anticancer effects of digoxin involve various mechanisms. For example, Wang et al. reported that digoxin inhibited p53 synthesis by activating Src/MAPK signaling pathways and suppresses tumor growth [153]. In addition, digoxin induced apoptosis and cell cycle arrest and had antitumor effects on Burkitt lymphoma cells *in vitro* and *in vivo* [154]. Many studies also reported that digoxin promoted ROS generation via inhibiting hypoxia-inducible factor-1 α (HIF-1 α), a key regulator of angiogenesis, to block cell growth in a multiple tumor model [155–157]. Moreover, digoxin was found to inhibit activity of the NRF2-ARE luciferase reporter gene in A549-ARE cells, which suggested that digoxin may be a potent NRF2 inhibitor [158]. Zhou et al. found that digoxin could reverse drug resistance of gemcitabine in SW1990/Gem and Panc-1/Gem cells [159]. Mechanistically, digoxin inhibited the activity of NRF2 by suppressing PI3K/Akt signaling pathway in gemcitabine-resistant pancreatic cancer cells [159]. To date, digoxin has been investigated in clinical trials for cancer therapy (Table 1).

4.2.5. Antipsychotics

(1) *Fluphenazine*. Fluphenazine is a phenothiazine antipsychotic drug, which is an antagonist of dopamine D1 and D2 receptors and has a high affinity with 5-HT receptors [160]. It is used in the treatment of schizophrenia and bipolar disorder [160]. Studies have shown an overall decreased cancer incidence in schizophrenic patients using antipsychotics, implying that antipsychotics may have anticancer potentials [161]. As expected, research found that fluphenazine may play an important role in the treatment of cancer [161]. It was found that the ROS levels in triple negative breast cancer cells were significantly increased after fluphenazine treatment, which could impair the mitochondria membrane integrity and further induce cancer cell death [162]. Moreover, HeLa cancer cells treated with fluphenazine in combination with UVA light demonstrated a consistent ROS production in a clearly concentration-dependent manner, indicating a significant photodynamic mechanism involved in the photocytotoxic effect of fluphenazine [163]. Moreover, a clinical trial of fluphenazine in treating patients with refractory advanced multiple myeloma was completed (NCT00335647) (Table 1).

(2) *Pimozide*. Pimozide is an FDA-approved antipsychotic, and it is used to treat clinical Tourette syndrome and schizophrenia [164]. In 1979, pimozide was first found to act as a dopamine antagonist with antimelanoma cancer effect [165]. After that, pimozide had been investigated in a number of cancer cells, and a further study found that pimozide inhibited the cancer cells through the generation of ROS [166]. For example, pimozide induced ROS generation by downregulating the expression of the antioxidant enzyme catalase to suppress osteosarcoma and prostate cancer [166, 167]. Moreover, recently, the ability of ROS generation

to suppress hepatocellular carcinoma cells has been reported [168]. However, to date, pimozide has not been investigated in clinical trials to clarify the antitumor activity.

5. Research Perspectives and Discussion

Despite the fact that traditional approaches of looking for differences in the transcriptome or the proteome in cancer have many benefits, much attention has been focused on significant changes in function, such as regulating ROS level, which may be an effective anticancer strategy [169, 170]. Certainly, many clinical chemotherapeutic drugs, such as doxorubicin, daunorubicin, and epirubicin, can kill cancer cells by enhancing ROS production. However, the uses of these drugs are accompanied by indiscriminate cytotoxicity and adverse events and chemoresistance. Repurposed drugs with established safety profiles that are developed based on clearing ROS generation or increasing ROS production may be a novel strategy for the treatment of cancers. However, repurposed drugs may be the lack of specificity for cancer. Moreover, ROS are considered a double-edged sword in cancer. The molecular action of ROS is multidirectional, which in turn produces many uncertainties. There are still some key issues that need to be resolved in the development of ROS-related repurposed drugs.

It is necessary to first understand whether repurposed drugs based on ROS regulation can really be used clinically to treat cancer. The benefits of antioxidant drugs for early cancer therapies by reducing ROS level have been widely recognized. However, several studies have demonstrated antioxidant drugs produced the paradoxical results. Long-term supplementation with the antioxidants N-acetylcysteine and vitamin E promotes KRAS-driven lung cancer metastasis [109]. In addition, it has been shown that the administration of antioxidants, such as N-acetylcysteine, accelerates the progression of lung cancers and melanomas [171]. Thus, whether antioxidants inhibit or promote tumors needs further support by solid trials performed on a large scale. Meanwhile, raising ROS to cytotoxic levels can kill cancer cells; this strategy may inevitably damage normal cells. Since the dose of chemotherapy drugs clinically is much higher than the dose required for the original effect of the repurposed drugs, it may be difficult to obtain an effective and safe dose clinically. Repurposed drugs may produce ultrahigh ROS levels that the human body cannot tolerate when administered rapidly and at a high concentration, which can significantly induce systemic toxicity to cancer patients. In this regard, ROS-related repurposed drugs are more suitable for use as chemotherapy sensitizers or adjuvant drugs in tumor treatment, which may lead to unexpected response. Moreover, further elucidation of ROS-related cysteine modifications and their functional consequences will be the basis for improving our understanding of the selective effects of ROS on cancer and normal cells.

Another major challenge is increasing the selectivity of ROS-related repurposed drugs as therapeutic drugs. Cancer cells thrive on levels of ROS that are moderately higher than those in their normal counterparts; this feature renders ROS-responsive photodynamic therapy can reach good results. Up to now, new ROS-responsive prodrugs, probes,

theranostic prodrugs, and nanotheranostics that allow for the monitoring of ROS with temporal and spatial specificity have been developed for the targeted treatment and precise diagnosis of cancer and selectively killing tumor cells [172, 173]. In fact, ROS-responsive prodrug strategies have been successfully used to modify clinically platinum-based drugs, showing enhanced therapeutic efficacy and reduced side effects [174, 175]. Therefore, the development of repurposed drugs inspired ROS-responsive groups/probes/nanoparticles would be a significant improvement in cancer treatment selectively.

In future research, before adopting the treatment method, there should be advanced inspection and real-time monitoring of the ROS status in the body, and ROS-related repurposed drugs should be taken appropriately to increase or decrease the ROS level in the body, so as to obtain a better treatment effect.

Ethical Approval

This review article does not contain any original studies with animals or human participants.

Conflicts of Interest

All authors declare that they have no conflict of interest.

Authors' Contributions

Jiabing Wang and Dongsheng Sun contributed equally to this work.

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