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REVIEW ARTICLE

# The thioredoxin system and cancer therapy: a review

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**Abstract**
Thioredoxin (Trx), thioredoxin reductase (TrxR), and NADPH are key members of the Trx system that is involved in redox regulation and antioxidant defense. In recent years, several researchers have provided information about the roles of the Trx system in cancer development and progression. These reports indicated that many tumor cells express high levels of Trx and TrxR, which can be responsible for drug resistance in tumorigenesis. Inhibition of the Trx system may thus contribute to cancer therapy and improving chemotherapeutic agents. There are now a number of effective natural and synthetic inhibitors with chemotherapy applications possessing antitumor activity ranging from oxidative stress induction to apoptosis. In this article, we first described the features and functions of the Trx system and then reviewed briefly its correlations with cancer. Finally, we summarized the present knowledge about the Trx/TrxR inhibitors as anticancer drugs.

**Keywords** Thioredoxin · Thioredoxin reductase · Cancer · Cancer therapy · Oxidative stress

## Introduction

Redox control processes have been established as a key regulatory factor in the activation of many cell signaling cascades in addition to their primary functions in the maintenance of cellular redox state [1, 2]. Research to date has determined that mitochondrial respiration is the major source of reactive oxygen species (ROS) influencing intracellular redox state [3]. Although ROS have a crucial role in mediating different signal transduction pathways, high levels of ROS can lead to oxidative stress, which appears to trigger apoptosis by various pathways. Many scientific investigators have reported that oxidative stress is a common feature of many cancers, and the thioredoxin (Trx) antioxidant system, as a key factor closely linked to the pathogenesis of several human diseases, is over-expressed in different tumors [4–9].

The Trx system is a main redox control system that is integral to scavenging ROS and protecting cells from the damages of free radicals [1, 5]. This system contains a Trx protein as a donor of hydrogen that is reduced by Trx reductase (TrxR) enzyme using NADPH to promote its activities [10]. It is well established that the Trx system is involved in cytoprotective processes, even though several researchers have noted its tumor-promoting features [5, 10–13]. In support of this view, a number of authors have reported the correlation between the over-expression of the Trx system and different hallmarks of cancer, for instance cancer cell drug resistance [11–13]. Considering these findings, targeting Trx/TrxR has been recognized as a promising strategy for cancer therapy as well as sensitizing tumor cells to chemotherapeutic drugs [14, 15]. In the present article, we summarize the Trx system functions and its relationship with tumor biology, and then we attempt to give an overview of the current knowledge of Trx/TrxR inhibitors.

## The thioredoxin system

The thioredoxin (Trx) system, consisting of Trx protein, nicotinamide adenine dinucleotide phosphate (NADPH) and Trx reductase (TrxR), has a cytoprotective activity and plays key roles in different cellular functions [5, 16–18]. Trx protein is an antioxidant which is known as a redox-sensitive molecule with a highly conserved active site (–Cys–Gly–Pro–Cys–) [5, 19]. The active site cysteine

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residues of Trx undergo reversible reduction to form a dithiol site during the transfer of reducing equivalents from NADPH to the active site disulfide of oxidized Trx by TrxR [19–21]. TrxR enzymes are selenocysteine-containing proteins and belong to the flavoprotein class of pyridine nucleotide-disulfide oxidoreductases that can catalyze the NADPH-dependent reduction of Trx proteins as well as a number of small-molecule substrates including hydrogen peroxide ($H_2O_2$), lipid hydroperoxides, ascorbic acid, and α-lipoic acid [1, 5, 20, 22]. Reduced Trx that is formed by TrxR activity, acts as a protein disulfide reductase and hydrogen donor for enzymes [10, 20]. The interaction of active site dithiol in reduced Trx with oxidized cysteines of many proteins induces the process of thiol/disulfide exchange reaction to form an oxidized Trx [10, 20, 23]. The complete catalytic cycles of Trx antioxidant system are schematically shown in Fig. 1. In mammalian cells, there are two isoforms of Trx including the cytosolic Trx1 (which is the dominant form) and the mitochondrial Trx2 [18]. In addition to these proteins, a report has described SpTrx as a new isoform, which is mainly expressed in spermatozoa cells [24]. Three confirmed mammalian isoforms of TrxR have also been identified that are the cytoplasmic flavoprotein TrxR1, the mitochondrial flavoprotein TrxR2 and TrxR3 [25–27]. The testis-specific TrxR3 isoform of this homodimeric enzyme also is called thioredoxin glutathione reductase (TGR) because of its ability to reduce glutathione disulfides as well as oxidized Trx protein [27]. Embryonic lethality of Trx knockout mice suggests that the existence of the Trx system members is essential for normal cellular functions [28]. The accumulating body of evidence also demonstrates the importance of the Trx system involvement in multiple processes of normal cells including redox homeostasis, cell growth, mutagenic DNA repair, and cell survival [10, 19–21]. Moreover, the consideration of many targets or substrates for the Trx and TrxR shows the true complexity of this system [10]. Some direct targets of Trx protein are methionine sulfoxide reductase and peroxiredoxin (Prx) which require disulfide bond reduction by the Trx system for their antioxidant defense functions [29–31]. Prx or Trx peroxidase is a Trx mediator which reduces peroxides using SH groups [20]. The ubiquitously expressed Trx protein also participates in the regulation of oxidative/nitrosative stress defense and metabolic states such as carbohydrate and lipid metabolism related to different diseases [18, 32, 33]. The protective role of Trx protein against oxidative stress can

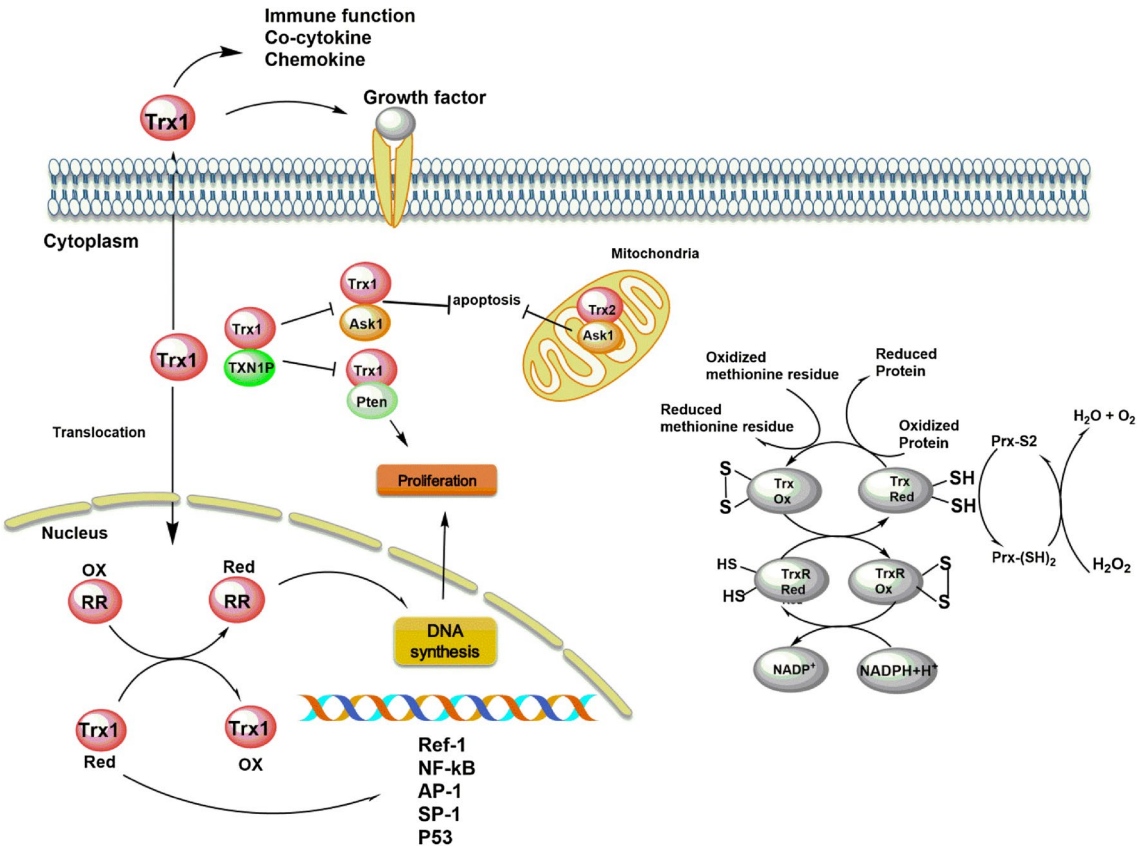


**Fig. 1** Catalytic processes and cellular functions of Thioredoxin family proteins. Complete details about this figure and the Trx system are available in "The theoredoxin system" section. *S–S* oxidized form, *SH* reduced form, *Ox* oxidized, *Red* reduced

be indirect through the reduction of ROS oxidized targets in addition to its direct role in scavenging singlet oxygen and hydroxyl radicals [34, 35]. This redox-active system has also a beneficial role in the maintenance of oxygen homeostasis and is responsible for the prevention of oxidative damage due to ROS formation such as lipid oxidation, protein oxidation, and DNA damage [1, 5, 36]. ROS are inherently unstable toxic intermediates that include free radicals with incomplete one-electron reduction, such as hydroxyl radicals, superoxide anion, and other oxidants [37]. It is well understood that the oxygen-free radicals induce and maintain the oncogenic phenotype through their ability to act as second messengers in intracellular signaling and produce mutagenic DNA lesions [10, 38]. Under certain conditions, the increased level of ROS induces the occurrence of a new consequence that is called oxidative stress, which is involved in the pathophysiology of many diseases [39–47].

Besides the profound antioxidant activity of Trx, it has been shown to have direct anti-apoptotic effects via binding to apoptosis signaling kinase1 (ASK1) that belongs to mitogen-activated protein kinase kinase kinase (MAPKKK) superfamily [48]. Only the reduced form of Trx protein can interact with the ASK1 N-terminal portion and inhibits apoptosis that is induced by ASK1 kinase activity [48]. The oxidation of cytosolic Trx1 protein by ROS leads to the dissociation of ASK1 pro-apoptotic molecule from Trx1 and activates ASK1-induced apoptosis via the c-Jun N-terminal kinase (JNK) and p38 MAP kinase pathways in the cytoplasm [48]. Trx2 has also been reported to keep ASK1 inactive in the mitochondria [49]. In contrast to the cytoplasm, the apoptotic signaling of ASK1 in the mitochondria is mediated through a JNK independent pathway [49]. Trx protein also induces the ubiquitin-mediated degradation of ASK1 in a redox-independent manner to inactivate the ASK1 apoptotic signaling pathway [50]. A recent investigation further showed that the catalyzation of procaspase-3 nitrosylation is the other manner of inhibiting apoptosis by Trx protein [51].

This 12 kDa protein has also been implicated in abnormal growth regulation through inactivation of phosphatase and tensin homolog (PTEN) and increasing Akt activity [23, 52]. The tumor suppressor PTEN negatively regulates phosphatidylinositol-3-kinase/Akt (PI3 K–Akt) pathway and its cell survival function [52]. The binding of Trx1 to the C2 domain of PTEN protein occurs through a disulfide bond and inhibits PTEN's lipid phosphatase activity [52].

It was furthermore recognized that Trx1 can translocate from cytoplasm to the nucleus and activate a number of transcription factors (TFs) [53]. TFs are the key proteins that are involved in transcriptional regulation as the first step of gene expression through binding to specific DNA sequences (promoters). Indeed, Trx1 regulates the DNA binding activity of different TFs, including nuclear factor kappa B (NF-κB), activator protein-1 (AP-1), p53, hypoxia-inducible factor-1 (HIF-1), and specificity protein 1 (sp-1) through either direct reduction of them and/or indirectly by a redox factor-1 (Ref-1)-dependent mechanism [5, 53–56]. Trx1 also provides the supply of DNA precursors by the transfer of reducing equivalents to ribonucleotide reductase (RR) [55, 57]. Although Trx1 has been reported to mostly exist in the cytoplasm and nucleus, there is a leaderless pathway that induces secretion of this cytosolic protein from cells to the extracellular environment [58]. The extracellular form of Trx1 can be full-length or shortened (truncated) [10]. The secreted form of Trx is involved in immunomodulatory activities and growth stimulation by enhancing the other growth factors functions [55, 59–61].

Besides the members of the Trx system, it has been shown that the existence of a Trx inhibitor molecule is also necessary to control the expression and activity of the Trx system [10]. Thioredoxin binding protein-2 (TBP2), also known as thioredoxin-interacting protein (TXNIP) or vitamin D3 up-regulated protein-1 (VDUP-1), is a critical negative regulator of Trx that belongs to the mammalian α-arrestin family [62]. This endogenous Trx inhibitor inactivates Trx functions by binding to its active site and competes with other proteins, such as ASK1 for occupancy [55, 63]. Finally, we would like to refer the readers to recent review articles for further information on any aspect of the current paper [20, 21, 64–66].

## The thioredoxin system in cancer

It is well known that the Trx system has different functions in normal physiological conditions, especially in antioxidant defense in protecting cells from cancer, even though a number of articles have reported that the Trx system is involved in tumor biology at different levels [4, 5, 9, 10]. This can be relevant to the condition of tumor cells which are under oxidative stress characterized by the overproduction of antioxidant proteins [5, 67, 68]. In this regard, several investigators have indicated that Trx expression is increased in different types of cancers, such as colorectal [9], lung [4], pancreatic [8] and gastric cancers [7]. The overexpression of Trx proteins has been shown to correlate with the enhancement of cancer cell growth, which occurs either through direct growth regulation or as a result of apoptosis inhibition. In line with this, it has been demonstrated that the cDNA cloning of Adult T cell leukemia-derived factor (ADF) shows great homology with Trx and ADF/Trx can promote transformed cell growth, as is the case with lymphocytes [69, 70]. Recently, an in vivo study indicated that subcutaneous injections of two human lung carcinoma cell lines with high and low expression of Trx protein into severe combined immunodeficient (SCID) mice, show the formation of wide

and small subcutaneous tumors that are dependent on the level of Trx expression in the injected cells [71]. Another investigation found that wild-type Trx transfected MCF-7 breast cancer cells show several times increase in cell proliferation and colony formation in soft agarose compared to redox-inactive mutant Trx transfected cells [72]. So far this section has shown that Trx has growth-promoting effects and its overexpression is not just a phenomenon associated with tumor progression. It is now necessary to explain briefly the anti-apoptotic functions of Trx system.

The anti-apoptotic effect of the Trx system is through different manners that one of them is ASK1 inhibition as mentioned above [10]. To date, a number of authors have also considered the influence of the Trx system on some TFs which can regulate the expression of anti-apoptotic genes [73, 74]. It is also well established that Trx protein could support the activities of Prx and other antioxidants which counteract oxidative stress as an apoptosis-inducing factor in cells [31, 66, 75, 76].

Moving on now to consider the correlation of Trx with another hallmark of cancer: unlimited replicative potential that provides a reasonable mechanism for the generation of extensive cell population. The possible correlation can partly be explained by the dependence of this cancer hallmark on selenium [10]. In this context, Gan et al. reported that the use of antisense approach for inhibition of TrxR overexpression in human hepatocellular carcinoma SMMC-7721 cells can arrest the cell cycle in G2/M phase [77]. Indeed, the accumulation of cells in G2/M phase can explain that Trx system is necessary for cancer cell proliferation and tumor progression [77, 78]. Besides the evidence presented here, it is known that Trx system contributes to several aspects of metastasis, for instance invasion and angiogenesis.

For example, in one investigation, ultraviolet A (UVA)-irradiated human dermal fibroblasts with high levels of Trx and TrxR, showed a significant increase in pro-matrix metalloproteinase-2 (proMMP-2) activity and a reduction in tissue inhibitor of metalloproteinase-2 (TIMP-2) activity [12]. It has also been revealed that the extracellular Trx can enhance human microvascular endothelial cells (HMEC-1) spreading through the reduction of disulfide bonds in the laminin and destabilization of laminin/galectin-3 complexes in a matrigel-based assay in vitro [79]. The literature on the high metastatic capacity of different tumors, such as breast and colorectal cancers, has also highlighted its correlation with increased expression of Trx protein [80].

For support of this view, there is also a large number of published studies describing that Trx overexpression is the consequence of hypoxia and can induce angiogenesis through increasing the expression of HIF-1 protein [13, 81, 82]. In addition, it has been revealed transfection of cells with Trx also causes the overexpression of vascular endothelial growth factor (VEGF) that is known as a protein product of hypoxia-responsive genes and an important factor for angiogenesis [13]. Together these studies provide important insights into the effects of Trx system on cancer.

## The Trx system as a therapeutic target in cancer

The Trx system is regarded as a potential anticancer target and the focus of some chemotherapeutic reagents [83–89]. The reasons for choosing the Trx system as a target of anticancer drugs are the integral role of this system in apoptosis regulation and the overexpression of its members in many cancer cells [14]. Inhibition of the Trx system can alter intracellular redox state and induce apoptosis through ROS accumulation, ASK1 activation, and inhibition of procaspase-3 nitrosylation [14, 48, 51]. By considering the growing interest in targeting the Trx system, we will discuss several Trx system inhibitors in the latter part of the present paper.

### Trx inhibitors

#### 1-Methyl-propyl-2-imidazolyl disulfide (PX-12)

1-Methyl-propyl-2-imidazolyl disulfide (IV-2) (also known as PX-12) is a small molecule inhibitor of Trx protein that was discovered originally using a cell line-directed screening approach (CDSA) [55, 85]. The approach was used to screen disulfide compounds due to their growth inhibitory effects on cancer cell lines in vitro [85]. The inhibitory mechanism of PX-12 appears to be through binding to the Cys73 residue of cytosolic Trx1, thereby rendering it inactive irreversibly and unable to act as TrxR1 substrate [90]. In an investigation into PX-12, Tan et al. (2014) highlighted evidence that this effective Trx1 inhibitor could induce apoptosis in acute myeloid leukemia (AML) cells and increase the expression of activated caspase-3 in a dose-dependent manner [91]. They also revealed that PX-12 treatment enhances AML cells sensitivity to arsenic trioxide (ATO) as another Trx system inhibitor [91]. In 1997, Kirkpatrick and colleagues reported that PX-12 is a potent apoptosis inducer in HL-60 human promyelocytic leukemia cells when is compared with known apoptotic reagents, such as dexamethasone [92]. Previous studies have also explored the correlation between PX-12 and angiogenesis [93, 94]. In these researches, they found evidence that PX-12 has inhibitory effects on angiogenesis through the regulation of VEGF expression that is dependent on Trx protein [93, 94]. In 2006, Baker et al. published a paper in which they examined the effects of PX-12 treatment on plasma concentration of Trx1 and VEGF in cancer patients with high mean plasma levels of them during a phase I study [93]. Their experiments showed that PX-12 treatment can reduce the concentration of both proteins in

plasma [93]. To date, it has been revealed that the expression of VEGF protein as a necessary factor for angiogenesis is regulated by HIF-1 transcription factor which is one of the downstream targets of Trx protein [95]. This view is supported by recent observations of Welsh (2003) who have shown that PX-12 decreases the levels of HIF-1α and subsequently VEGF protein in cultured cancer cells and human tumor xenografts by Trx1 inhibition [95]. PX-12 is the first Trx1 protein modulator that has been advanced into clinical trials for cancer treatment [96]. This drug has completed a phase I trial and now is in phase II for the treatment of pancreatic cancer [55, 96].

In addition to direct inhibition of Trx protein, there is an alternative approach that can lead to Trx inhibition through gene expression regulation of an endogenous inhibitor. Suberoylanilide hydroxamic acid (SAHA) is a cancer therapeutic agent which targets Trx protein indirectly.

#### Suberoylanilide hydroxamic acid (SAHA)

Histone deacetylase inhibitors (HDACis) are novel cancer therapeutic drugs that belong to the wide category of chromatin-modifying agents (CMAs) [97]. These chemical compounds have tumor-selective cytotoxic activity and inhibit deacetylation of lysine residues in histones [98]. Inhibition of histone deacetylation induces derepression of gene expression and is associated with the prevention of chromatin condensation [99]. The regulation of gene expression is dependent on histone acetylation and deacetylation that mediate the interaction between histone complexes and chromatin [100]. HDACis consist of different compounds which are categorized based on their chemical moieties that have the role of binding to the zinc-containing catalytic domain of HDAC enzymes [101]. SAHA is a hybrid polar compound (HPC) that belongs to the hydroxamate group of HDACis [102]. In 2006, this epigenetic modifying drug was the first FDA-approved HDACi that entered the clinical oncology market for the treatment of cutaneous T-cell lymphoma (CTCL) [103]. Now the effectiveness of SAHA is tested in clinical trials for the treatment of other malignancies [104]. This antitumor compound acts by binding to the catalytic site of HDAC enzymes (class I and II), causing the inhibition of their enzyme activity and thereby the accumulation of acetylated histones [105]. SAHA has been reported to induce growth arrest in a wide range of transformed cells in tumor-bearing animals and in vitro at concentrations that do not affect the growth of normal cells [102, 106, 107]. In 2005, Zhang and co-workers demonstrated that SAHA is a selective inducer of apoptosis in CTCL cell lines and can inhibit the growth of them in vitro [108]. Besides CTCL cells, prostate cancer cells growth is also inhibited completely by SAHA treatment [14]. An in vitro study indicated that transformed cells are more sensitive to SAHA compared to normal cells [109]. It has been shown that SAHA-mediated cancer cell death is related to its effects on the Trx system [83]. In 2002, Butler et al. used microarray analysis to detect gene expression profiles in prostate cancer cell lines that were treated with SAHA [83]. They showed SAHA could increase the gene expression of the endogenous Trx inhibitor, TBP-2, like other cancer cell types [83]. The upregulation of TBP-2 that was induced by SAHA's inhibition of HDACs could inactivate the functions of Trx by binding to it and thereby lead to oxidative stress condition [83]. In addition to TBP-2, the overexpression of ASK-1 is another consequence of SAHA treatment that leads to the activation of the apoptotic pathway [110]. The targeting of the Trx system by SAHA appears to be interesting due to its indirect Trx inhibition and tumor-selective cytotoxic activity.

### TrxR inhibitors

#### Gold-containing compounds

Gold salts are highly efficient ionic chemical compounds of gold that are used clinically to suppress different aspects of the inflammatory process and to prevent the progression of chronic diseases such as rheumatoid arthritis (RA) and human tuberculosis [111, 112]. Recently, these compounds have also been shown to be drug candidates in cancer chemotherapy due to their cytotoxic effects on different cell types [113, 114]. The proposed mechanism of their anticancer effects seems to be based on their interaction with DNA or other cellular targets, such as proteins [113]. It is known that gold has a high affinity for thiol groups and is able to target the reduced form of TrxR [15]. This is also supported by an in vitro study, in which therapeutic gold compounds are proved to have inhibitory effects on the reduced form of TrxR in the nanomolar range [115]. *S*-triethylphosphinegold (I)-2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (Auranofin) is a gold (I)-containing compound that was approved as an antiarthritic drug originally and has been developed for the treatment of cancer [113]. Auranofin could promote its cytotoxic effects in human ovarian cancer cells that they are resistant to cisplatin and show a higher activity of TrxR [116]. In isolated purified mitochondria, it is suggested that auranofin treatment could lead to mitochondrial malfunction and release of proapoptotic factors, like cytochrome *c* [117, 118]. It has been shown that auranofin is capable to induce the accumulation of mitochondrial $H_2O_2$ through the TrxR inhibition that decreases the rate by which the simplest peroxide is removed [88]. Lately, $[Au(d2\text{-}pypp)_2]Cl$ that is an interesting gold (I) phosphine complex led to advancement in anticancer therapy due to its ability to target the mitochondria in addition to the Trx system (both Trx and TrxR) [119]. The results of an in vitro study indicated that $[Au(d2\text{-}pypp)_2]Cl$ could induce

the mitochondria-mediated apoptosis through activation of caspases 3 and 9 in breast cancer cells [119]. Besides the increased mitochondrial membrane potential of tumor cells, the lipophilic cationic property of this gold (I) phosphine complex is another essential factor for its accumulation in mitochondria [119]. Apart from gold (I)-containing compounds, Omata et al. showed that TrxR1 is also the target of several other gold compounds (I and III) which have different potency and various levels of TrxR inhibition depending on ligand configuration [120].

#### Arsenic trioxide (ATO or $As_2O_3$)

ATO is known as a relatively safe and efficacious treatment for acute promyelocytic leukemia (APL) patients who have relapsed or newly diagnosed [121, 122]. In September 2000, this arsenic-containing compound was approved by FDA for the induction and consolidation therapy of APL patients [123]. ATO has been thought to mediate its biological effects by interactions with accessible cysteine residues on cell proteins [124]. An in vitro study conducted by Lu et al. showed that ATO could inhibit the reduced form of mammalian TrxR irreversibly by targeting its sulfhydryl groups with an $IC_{50}$ of 0.25 μM [86]. It has also been suggested that ATO could contribute to the induction of apoptosis and inhibition of proliferation through numerous pathways [125]. The growth inhibitory effects of ATO were determined by an investigation of human breast cancer cells [86]. Results have indicated that ATO treatment induces severe Trx oxidation and inhibits the growth of cells after 2 days [86].

#### Nitroaromatic compounds (DNCB)

1-Chloro-2,4-dinitrobenzene (DNCB) is a nitroaromatic compound which is used in trials as a sensitizing agent for chemotherapy of melanoma patients [126]. It has been shown that DNCB could inhibit TrxR irreversibly through dinitrophenyl-alkylation of both the cysteine and its adjacent selenocysteine in the carboxy-terminal motif of the enzyme [87]. The alkylation of TrxR enzyme by DNCB induces the loss of a Se-dinitrophenol group from the modified protein and subsequently leads to the dehydroalanine formation at the former selenocysteine position [87, 127]. DNCB is also capable to increase the generation of superoxide by induction a high NADPH oxidase activity of the modified enzyme [87]. Its mechanism for this activity involves the reduced FAD in the modified enzyme that can catalyze the transfer of one electron to a nitro group of the dinitrophenyl moieties of the dinitrophenyl-alkylated enzyme (dnp-TrxR) [87]. The electron transfer leads to the formation of nitro anion radical that consecutively reacts with oxygen to yield superoxide anion [87]. It seems that immunostimulation effects of this small electrophilic compound are mediated by increased extracellular level of oxidized Trx and induction of oxidative stress [128]. An in vitro study on DNCB-mediated cytotoxic properties has highlighted its ability to activate mitochondrial caspase (3/7) [129]. It has been proposed that dnp-TrxR might be a main target of the apoptotic events due to Bcl2 overexpressing cells which were astonishingly sensitive to apoptosis after treatment with DNCB [14]. In addition, other nitroaromatic compounds have been shown to have apoptosis-inducing effects as the consequences of TrxR inactivation in human cancer cells [15].

#### Platinum compounds

Cisplatin [*cis*-diamminedichloridoplatinum (II)] is a platinum compound that was approved by the FDA in 1978 for use in the treatment of cancer [130, 131]. This DNA-damaging compound inhibits TrxR in a dose- and time-dependent manner by targeting the highly reactive and very well-accessible selenocysteine residue on the flexible C-terminal arm of TrxR [14, 89, 132]. It has also been shown that the inhibition of TrxR by cisplatin is extremely specific and irreversible [133]. The platinum compound oxaliplatin as an analog of cisplatin also has similar effects on TrxR and can show the same extent of its inhibition [89].

#### Polyphenolic compounds

Data from several sources have recently identified the role of naturally occurring compounds, like polyphenols (curcumin and some flavonoids) as potential antitumor agents [134–137]. Curcumin (diferuloylmethane) is a widely consumed phytochemical compound, has been shown to inhibit TrxR irreversibly in a dose- and time-dependent manner [138]. Curcumin modification of cysteine 496 and selenocysteine 497 in the C-terminal TrxR redox-active site was confirmed to be its inhibitory mechanism [138]. Alkylation of TrxR enzyme by curcumin leads to increased oxidative stress through acquired NADPH oxidase activity [138]. Addition of curcumin to cultured human cervical HeLa cancer cells also led to TrxR inhibition with an $IC_{50}$ of 15 μM [138]. Flavonoids are a considerable family of plant and fungal secondary metabolites that possess diversity in their chemical structures [134, 139]. In a previous study on 3-hydroxyl-containing flavonoids, like quercetin and myricetin, it was shown that these active compounds also exert their TrxR inhibitory effects by a similar mechanism of action [134]. The TrxR inhibition by these compounds was found to be dependent on the concentration of flavonoids, time, and NADPH [134]. The analysis of adenocarcinomic human alveolar basal epithelial A549 cell lysate that was treated with myricetin $^{>}$50 μM showed a TrxR activity reduction coincided with Trx protein oxidization [134].

## Conclusions

It is widely accepted that the Trx system as an extremely major part of thiol regulating systems, is actively involved in redox homeostasis and maintenance of cell survival in normal cells. In addition, its overexpression has been shown in a variety of cancer cells and plays crucial roles in tumor development and maintaining tumor phenotypes. It is also currently clear that the Trx system is an important target for cancer therapy and chemoprevention trials. In this investigation, we aimed to describe some of the compounds that specifically inhibit Trx system members. Even though the insights gained from these reviewed studies demonstrated the mechanisms by which the agents suppress Trx system, further investigations are also required to improve the effectiveness and the overall antitumor treatment response. Furthermore, more researches should be performed for improving specificity and selectivity of Trx system inhibitors toward cancer cells and reducing their side effects.

### Compliance with ethical standards

**Conflict of interests** The authors have no competing interests to declare.

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