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Cuproptosis in prostate cancer: Molecular mechanisms, prognostic biomarkers and therapeutic frontiers of cuproptosis-related genes (Review)

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Abstract. Prostate cancer (PCa) is among the most prevalent malignancies in males globally and management remains complex. In recent years, cuproptosis, an emerging form of cell death, has offered novel insights for PCa treatment. Cuproptosis refers to a copper-mediated cellular death mechanism that is intricately associated with mitochondrial metabolism, with cuproptosis-related genes (CRGs) exerting a notable effect on both cuproptosis and PCa. CRGs and other cuproptosis-associated indicators have demonstrated efficacy as prognostic predictors of PCa and these predictors may exhibit potential as novel therapeutic targets in the treatment of PCa. The mechanisms underlying cuproptosis in PCa remain to be fully elucidated; thus, further research is required to validate the expression patterns of CRGs and their associated indicators and examine the potential association with the characteristics, treatment responses and prognoses of patients with PCa. The present study aimed to investigate novel therapeutic strategies that may enhance the prognosis and quality of life of patients with PCa.

Contents

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1. Introduction

Prostate cancer (PCa) is among the most prevalent malignancies in males globally and has emerged as a notable public health concern (1). The pathophysiology of PCa is intricate and early-stage symptoms often go undetected; however, as the condition progresses, it may markedly affect the prognosis of patients and treatment efficacy (2,3). Androgen pathway inhibitors and chemotherapeutic medicines act as first-line therapeutic options for PCa, while prostate-specific antigen testing, multi-parametric magnetic resonance imaging and positron emission tomography-computed tomography imaging function as first-line diagnostic techniques, considerably enhancing the survival rates and prognosis of patients. Despite advancements in medical technology and the growing complexity of diagnostic and therapeutic approaches for PCa, the treatment and prognosis remain poor due to delayed diagnosis, postoperative recurrence, complications, complexities in treatment and resistance (4-6). For example, the effectiveness of non-selective immune checkpoint inhibitor therapy in patients remains ambiguous and its application in the early stages of treatment-resistant clones may promote the emergence of highly cross-resistant clones, thereby diminishing the clinical efficacy of subsequent androgen pathway inhibitor therapy (7). Thus, further investigations are required, to determine the specific pathophysiology of PCa and identify novel treatment targets that may improve patient prognoses.

In ~1980, researchers demonstrated that copper may be associated with programmed cell death (8). In 2022, Tsvetkov *et al* (9) highlighted a novel mechanism of copper-induced cell death; namely, cuproptosis (9). The results of this previous study provided novel insights into the role of copper in tumor growth. Cuproptosis is an emerging form of cell death in PCa, with evidence suggesting that it suppresses tumor progression. Inducing cuproptosis or modulating cuproptosis-related genes (CRGs) may exhibit potential as novel anti-cancer therapies. Thus, further investigations are

required to determine the specific processes associated with cuproptosis and the potential role it may play in PCa.

2. Copper metabolism and mechanisms underlying cuproptosis

Copper is vital for numerous biological functions (10). In mammals, copper is derived from food and is absorbed by intestinal epithelial cells in the duodenum and small intestine (11), a process that is carried out by copper transporter 1 (CTR1). Notably, this protein is located at the tip of intestinal epithelial cells and is mediated by the metal-reducing enzyme prostate six transmembrane epithelial antigen (STEAP) with duodenal cytochrome *b* activity. This activity prompts the reduction of Cu^{2+} to Cu^+ (12,13), which is transferred to the bloodstream via the copper ion transport ATPase alpha peptide (ATP7A) (14). Upon entering the bloodstream, copper associates with soluble copper carrier proteins, referred to as copper chaperones (such as SLC31A1), which are transported by CTR1 and absorbed via the portal circulation system to reach the liver (15-19). Within hepatocytes, copper is released into the bloodstream via the ATPase copper ion transport, ATPase beta peptide (ATP7B), which subsequently binds to copper cyanoproteins and albumin, facilitating transport to other tissues in the body (20). Upon reaching target tissues, copper catalyzes reactions in various physiological processes (21-24). When copper levels in the body surpass the expected threshold, hepatocytes transport copper through ATP7B to bile and this travels through the bile ducts into the intestines, before being expelled in feces (25).

However, excessive accumulation of intracellular copper ions may be harmful to cells (26). Results of a previous study (27) indicated that excessively high copper levels promote the generation of reactive oxygen species (ROS), resulting in oxidative stress and DNA damage that may lead to cell death. Alterations in the valence state of copper ions result in harm to bio-organic molecules, including proteins, nucleic acids and lipids. These alterations may disrupt the production of iron-sulfur (Fe-S) clusters; thus, impacting enzyme activity (28). Excess copper ions associate with the lipoylated constituents of the tricarboxylic acid cycle (TCA) within mitochondria. Ferredoxin 1 (FDX1), a member of the ferredoxin protein family, co-regulates the proteolipoylation of proteins, such as dihydrolipoic acid S-acetyltransferase (DLAT) and lipoic acid synthetase (LIAS). FDX1 reduces Cu^{2+} to Cu^+, which exhibits higher levels of toxicity. This ion subsequently binds to lipoylated proteins, causing DLAT aggregation, resulting in proteotoxic stress and cellular apoptosis. Moreover, Cu^+ may destabilize the architecture of Fe-S cluster proteins and impede the synthesis of Fe-S proteins, which are integral to mitochondrial stability. The depletion of Fe-S cluster proteins markedly compromises cellular metabolic functions and energy maintenance, leading to an escalation of oxidative free radicals and the production of ROS, thereby increasing cytotoxicity and culminating in cell death (Fig. 1). In addition, FDX1 and LIAS may be affected by cuproptosis, resulting in reduced expression (9,29,30). Thus, the homeostatic management of copper is crucial to avert cytotoxicity and sustain overall health. Notably, the processes and attributes of cuproptosis may exhibit potential in the treatment of specific disorders.

3. Role of copper in tumor metabolism

The identification of cuproptosis has offered novel insights into the initiation and advancement of tumor pathologies. Copper participates in the biological mechanisms of tumor proliferation and migration during the initial stages, activating metastasis-associated enzymes and signaling pathways to facilitate the spread of cancer (26). Notably, it binds to and activates critical molecules within various tumor signaling pathways (31,32), thereby influencing cancers directly or indirectly, and is intricately associated with the regulation of anti-tumor immunity (33). Moreover, copper directly influences or indirectly modifies the activity of key components, such as the Notch system; thus, affecting tumor angiogenesis, metabolism and inflammatory response (34). Copper also plays a key role in cancer cell proliferation (35) and results of a previous study (36) revealed that metallothionein, which is associated with copper storage, was markedly diminished in tumor tissues. Collectively, these results suggest that the capacity of cancer cells for regulating copper levels may be compromised. Moreover, copper facilitates angiogenesis, which is intricately associated with the advancement of malignant tumors (37,38). Results of previous studies (39-41) demonstrate that copper may activate numerous angiogenic factors and stabilize nuclear hypoxia-inducible factor-1, thereby augmenting the expression of pro-angiogenic factors. In addition, copper facilitated angiogenesis in numerous *in vitro* and *in vivo* models, whereas copper chelators inhibited tumor angiogenesis (42). Results of a further previous study (43) revealed that increased copper concentrations in tumor cells facilitated tumor angiogenesis, resulting in tumor advancement and spread. Consequently, increased copper concentrations may facilitate tumor development and progression. Excess copper levels may lead to cytotoxicity and trigger cuproptosis, which suppress tumor progression. Notably, excess copper-induced cuproptosis may exert inhibitory effects in numerous types of cancer (44). Copper exerts a dual influence on tumors and their metabolism, facilitating tumor cell proliferation and differentiation, while simultaneously suppressing proliferation and triggering apoptosis. This phenomenon is intricately associated with its biochemical characteristics and the complex tumor microenvironment (45).

4. Current status of cuproptosis research in PCa

Cuproptosis and the progression of PCa. Elevated copper concentrations in PCa cell tissues are a hallmark of patients with PCa (46), as demonstrated using *in vitro* cell line studies (47-49) and a xenograft mouse model (49,50). Notably, patients with PCa exhibit higher than expected serum copper levels (51-53) and elevated serum copper levels may be associated with a poor prognosis in patients with PCa (54). The RNA interference-mediated knockdown of CTR1 decreased copper ion absorption in PCa cells, resulting in the substantial inhibition of tumor growth (50). Collectively, these findings highlighted the role that increased copper ion concentrations may play in sustaining the biological processes of PCa cells, while diminished copper ion levels may fail to support the physiological functions of tumor cells.

Table I. Targets and roles of PCa-related CRGs in the cuproptosis process.

First author/s, year	Designation (of an object)	Target of action	Role in cuproptosis	(Refs.)
Yang, 2022; Yang, 2024	FDX1	Sites of lipoylation modification, Cu^{2+}	Engaged in the lipoylation modification of proteins (DLAT, among others); Reduction of Cu^{2+} to the more hazardous Cu^+ resulting in cuproptosis	(61,62)
Yang, 2023	DLAT	Lipoylated protein, Cu^{2+}	Cuproptosis triggered by lipoylation oligomerization	(63)
Yang, 2022	LIAS	Lipoylated protein	Regulated by FDX1, involved in lipid acylation pathway	(61)
Li, 2024	DLD		Engaged in TCA, wherein lipid acylation interacts with copper ions to trigger cuproptosis	(64)
Xiao, 2023	GCSH			(65)
Li, 2024	PDHA1			(64)
Li, 2024	DBT		Key enzyme in TCA, binds to copper ions to induce cuproptosis	(64)
Zhang, 2023	CDKN2A	Cellular cycle and p53 signaling pathway	Regulates the cell cycle and copper metabolism while inhibiting cuproptosis	(66)
Li, 2024	GLS	Metabolic route of glutamine	Oxidative stress in the TCA cycle mitigates tumors and prevents the occurrence of cuproptosis	(64)
Lin, 2024	NUDT21	Genes associated with DHA biosynthesis and copper ion transport-related proteins	Demethylation of these genes/proteins induces shortening of the 3'UTR, thereby suppressing DHA biosynthesis and conferring insensitivity to cuproptosis	(67)

PCa, prostate cancer; CRGs, cuproptosis-related genes; TCA, tricarboxylic acid cycle; FDX1, ferredoxin 1; DLAT, dihydrolipoamide S-acetyltransferase; LIAS, lipoic acid synthase; DLD, dihydrolipoamide dehydrogenase; GCSH, glycine cleavage system protein H; PDHA1, pyruvate dehydrogenase E1 subunit alpha 1; DBT, dihydrolipoamide branched-chain transacylase E2; CDKN2A, cyclin-dependent kinase inhibitor 2A; GLS, glutaminase; NUDT21, nudix hydrolase 21; DHA, docosahexaenoic acid; 3'UTR, 3' untranslated region.

Results of a previous study (31) reveal that the expression levels of CRGs in several types of tumor were markedly associated with patient prognosis, indicating that cuproptosis may play a key role in tumor biology and therapeutic response. Results of previous studies (51,55-60) indicate that individuals with malignant tumors, including PCa, exhibit markedly altered levels of Cu in both serum and tumor tissues. Moreover, CRGs play a role in PCa through predicting prognosis, modulating the tumor microenvironment and affecting therapeutic response (54). A range of CRGs may affect the progression of PCa, with CRGs and corresponding functions associated with cuproptosis detailed in Table I. At present, research is focused on the potential of cuproptosis in preventing tumor growth. Consequently, the manipulation of cuproptosis or CRGs has emerged as a viable anti-cancer therapy.

Mechanisms underlying cuproptosis in PCa. Mitochondrial dysfunction is pivotal for cuproptosis, resulting in oxidative damage to the mitochondrial membrane and compromised enzyme performance in the TCA cycle (29). By contrast, excessive copper accumulation in cellular mitochondria initiates cuproptosis (68), producing substantial amounts of ROS. During PCa progression, ROS levels are increased in PCa cells (69), resulting in DNA mutations, oncogene activation and tumor suppressor gene inactivation. This cascade facilitates malignant cell transformation and the activation

of stress-responsive survival pathways, thereby exacerbating the aberrant proliferation of PCa cells (70). In addition, the process of cuproptosis generates ROS, further advancing PCa progression (71). Notably, a requisite level of ROS is essential for tumor cell growth and DNA mutation; however, severe oxidative stress may deplete the capabilities of the antioxidant system, resulting in apoptosis (72). In cuproptosis, ROS are continuously generated, leading to toxic concentrations in PCa cells and notable effects on tumor growth. Results of previous studies (73-75) indicate that the excessive creation and accumulation of ROS are employed to impede PCa progression. Moreover, soy isoflavones, such as genistein and soy glycosides, may elevate copper concentrations in PCa cells through mobilizing endogenous copper and disrupting the expression of copper transporter protein genes, CTR1 and ATP7A, in cancer cells. This process subsequently induced high levels of ROS production, ultimately resulting in apoptosis in PCa cells (76). Moreover, curcumin analogs (77) and felicidin (78) exhibit analogous mechanisms of action to impede PCa cell proliferation. Results of a previous study (79) reveal that alterations in the ATP7B gene inhibits the regulation of copper ion distribution *in vivo*, resulting in increased copper levels in PCa cells. Similarly, ATP7B protein levels were markedly enhanced in docetaxel-resistant PCa cell lines, resulting in diminished intracellular copper levels. Notably, these levels may be promoted through silencing ATP7B
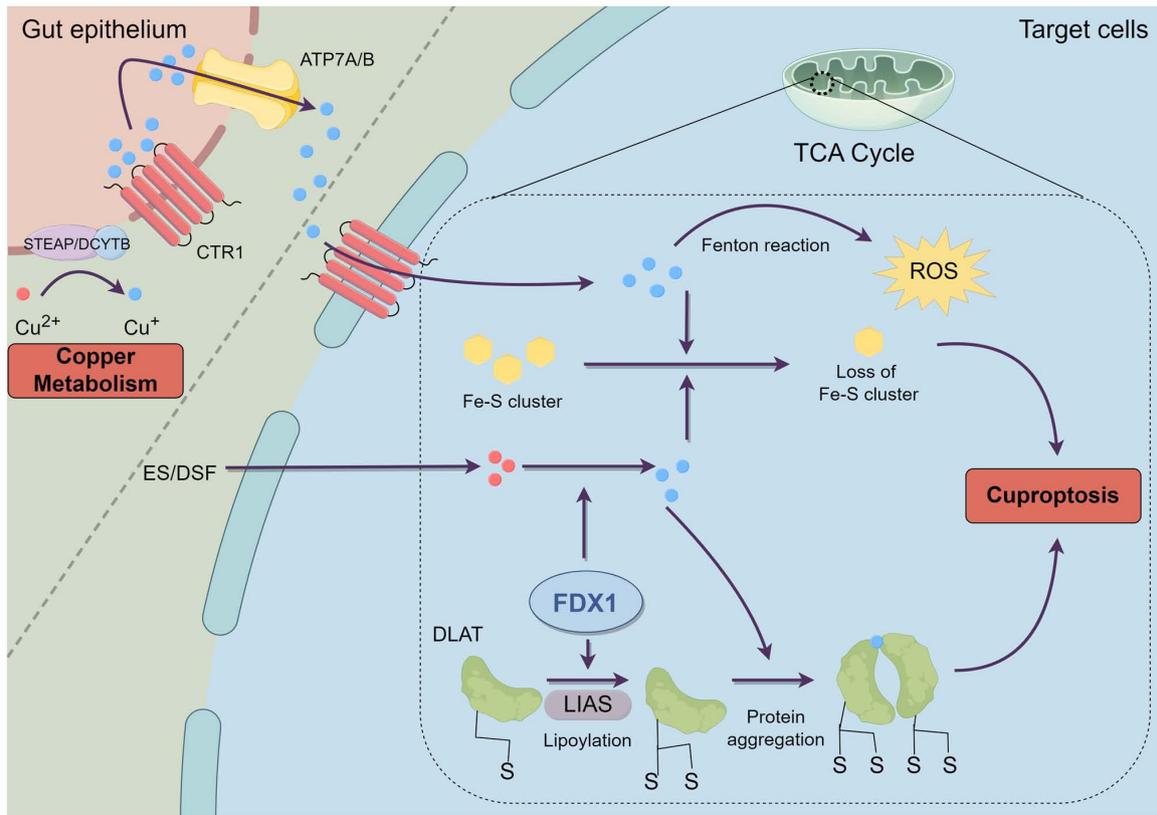
Figure 1. Processes of copper metabolism and cuproptosis. Cu^{2+} are reduced to Cu^+ by STEAP/DCYTB in the gut epithelium and transported into cells via CTR1. Inside target cells, Cu^+ interferes with Fe-S clusters, generates ROS and leads to mitochondrial dysfunction. Excess Cu^+ induces protein aggregation via lipoylated proteins, mediated by FDX1 and LIAS, ultimately causing cuproptosis. STEAP, prostate six transmembrane epithelial antigen; DCYTB, duodenal cytochrome *b*; CTR1, copper transporter 1; TCA, tricarboxylic acid cycle; Fe-S, iron-sulfur; ROS, reactive oxygen species; FDX1, ferredoxin 1; DLAT, dihydrolipoamide S-acetyltransferase; LIAS, lipoic acid synthetase.

expression or using a combination of disulfiram and copper to enhance intracellular copper concentrations (80). This modified intra- and extracellular copper distribution results in a substantial inhibitory effect on PCa growth, which may be associated with the excessive production of ROS due to copper ion carriers entering PCa cells, as well as antioxidant deficiencies present in these cells (79). Results of a previous study (81) highlight a reciprocal interaction between cuproptosis and copper-induced oxidative stress. The accumulation of ROS may facilitate the progression of PCa and exert an inhibitory effect on it. Cuproptosis may induce excessive ROS production to promote tumor cell death; however, investigations surrounding this dual mechanism are limited (Fig. 2). The specific impact of cuproptosis on PCa requires further validation through relevant experiments to elucidate the mechanism underlying cuproptosis in the context of PCa development.

Copper participates in tumor metabolism and promotes tumor progression. Notably, copper is associated with the progression and spread of PCa (82,83) and it also facilitates tumor angiogenesis (37,38). Angiogenesis markedly contributes to the progression and metastasis of PCa (84), primarily driven by angiogenic factors, including vascular endothelial growth factor, fibroblast growth factor, hypoxia-inducible factor (HIF) and interleukin (85). Results of a previous study (79) reveal that a reduction in copper levels diminishes HIF activity and obstructed tumor angiogenesis. Moreover, restrictions in angiogenesis may limit PCa progression (86).

Copper chelators may also diminish intracellular copper ion concentrations and lower copper bioavailability, thereby reducing copper-induced angiogenesis (42). Therefore, lowering copper concentrations to impede tumor angiogenesis may mitigate tumor advancement.

Complexities in lipid metabolism may contribute to carcinogenesis and disease progression. Results of a previous study (87) reveal that disturbances in lipid metabolism are associated with disease advancement and the development of castration-resistant prostate cancer (CRPC). In addition, cholesteryl esters (CE) are excessively accumulated in high-grade PCa and metastatic sites (88). The Wnt/β-catenin signaling pathway plays an important role in the metastasis of PCa and the depletion of CE markedly obstructs Wnt3a secretion through reducing unsaturated fatty acid levels, which inhibit the activation of the Wnt/β-catenin signaling pathway and restrict the acylation of Wnt3a, thereby inhibiting the metastasis of PCa (89). Copper ions also activate the Wnt/β-catenin signaling pathway, resulting in augmented cancer stem cell characteristics and increased resistance to numerous therapies (90). Elevated serum copper levels may be associated with increased serum total cholesterol and HDL cholesterol levels, as well as a heightened risk of dyslipidemia characterized by high serum total cholesterol and LDL cholesterol (91). Results of previous studies (92,93) reveal that zebrafish and grass carp exhibit elevated copper concentrations in their livers when subjected to excess copper, resulting in increased lipid accumulation and
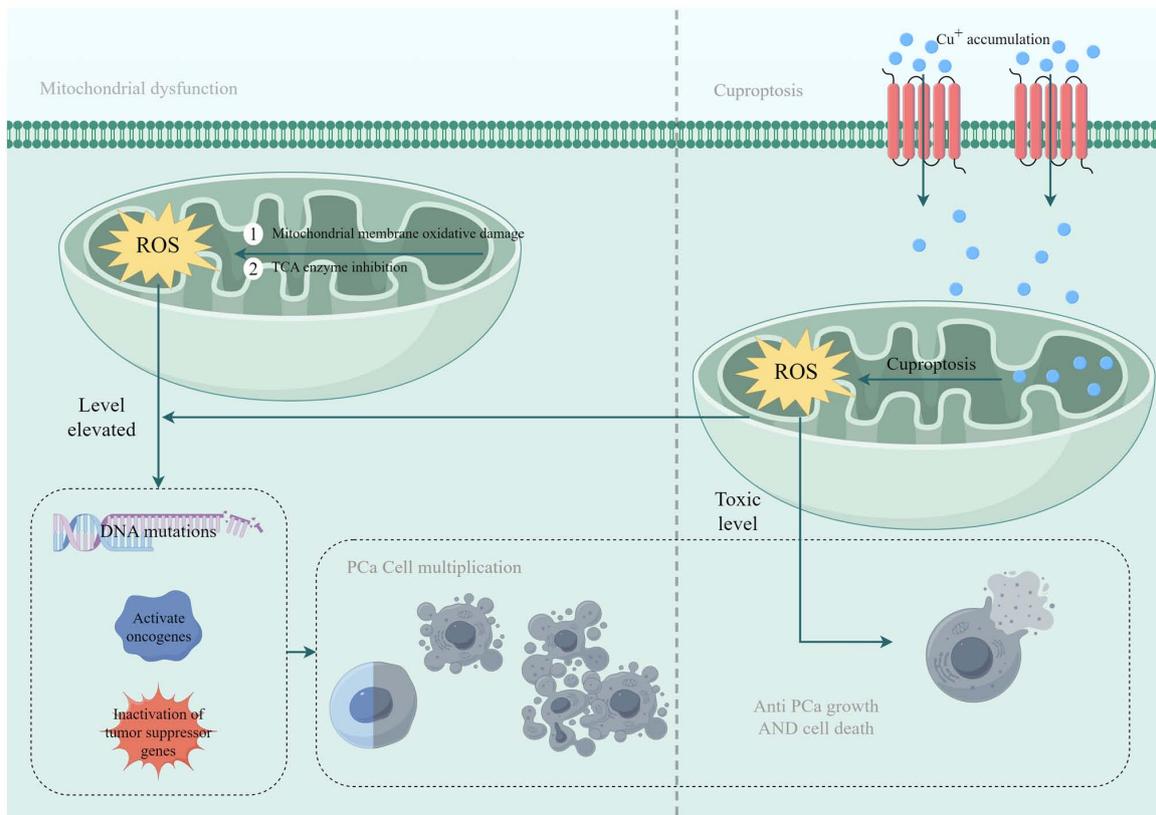
Figure 2. Dual mechanisms underlying copper and cuproptosis in PCa. Mitochondrial dysfunction is central to cuproptosis, leading to oxidative damage and inhibition of the TCA cycle. Excess copper accumulation in mitochondria triggers cuproptosis and sustained ROS production. Moderate ROS levels promote DNA mutations and oncogenic signaling, driving tumor progression. In contrast, excessive ROS overwhelm antioxidant defenses and induce tumor cell death. The specific involvement in PCa requires further validation. PCa, prostate cancer; TCA, tricarboxylic acid cycle; ROS, reactive oxygen species.

levels of triglycerides. These findings indicate that alterations in copper levels, particularly in excess, may influence the progression of PCa by affecting lipid metabolism and signaling system activity; however, further molecular or animal studies are required to validate these mechanisms.

In conclusion, the mechanisms underlying cuproptosis in PCa primarily encompass oxidative stress, intracellular copper distribution, angiogenesis and lipid metabolism dysregulation. Further investigations into these mechanisms may facilitate a deeper comprehension of cuproptosis in PCa and aid in identifying potential therapeutic targets.

Integrated therapeutic approaches for PCa predicated on cuproptosis, including carriers of copper ions. Elesclomol (ES) is a copper ion transporter that facilitates the entry of copper ions into cells, often targeting mitochondria. The entry of copper into cells leads to the accumulation of ROS, consequently impeding tumor growth. In cancer therapy, ES may leverage its capacity to produce cuproptosis to eliminate malignant cells. Disulfiram (DSF) functions as a copper ion transporter through binding to copper ions and facilitating entry into the cell. Notably, DSF has previously been investigated for the treatment of specific types of cancer, particularly those with elevated levels of lipoylated proteins (94). The two aforementioned copper ion carriers have been extensively researched for their ability to carry Cu^{2+} into cells or mitochondria to facilitate copper-dependent cell death (Fig. 3). Copper exerts a multifaceted impact on PCa growth and

proliferation; however, results of *in vitro* studies (61,62) consistently demonstrate that ES diminishes PCa cell viability via a reduction in FDX1 expression levels. Moreover, ES promotes keratin formation in tumor cells, inhibits autophagy in PCa via the DLAT/mammalian target of rapamycin pathway and enhances sensitivity to docetaxel and paclitaxel chemotherapy (95). In addition, DSF compounds combined with copper have demonstrated efficacy in breast cancer treatment through downregulating the expression of the phosphatase and tensin homolog (PTEN) associated with human chromosome 10 deletion and activating protein kinase B (AKT) signaling. This indicates a potential for combination therapy utilizing phosphatidylinositol 3-kinase (PI3K)/AKT inhibitors (96). Results of further previous studies (97,98) reveal that PCa may involve the same PTEN and PI3K/AKT signaling pathways for targeted therapy, highlighting that these pathways may inhibit PCa progression. However, previous investigations focused on the role of PTEN and PI3K/AKT signaling pathways in PCa progression remain limited.

Moreover, ES may exhibit potential in the treatment of PCa. Results of a previous study (99) revealed that DSF may inhibit the proliferation of PCa cell lines and this mechanism may be mediated by other pharmacological agents or specific sensitizers, such as copper (100). Thus, copper may be used to suppress the growth of PCa cells (49,101), ultimately improving the survival rate of patients (80).

Collectively, these results revealed that although copper ion carrier-induced cell death is a key form of cell death, few
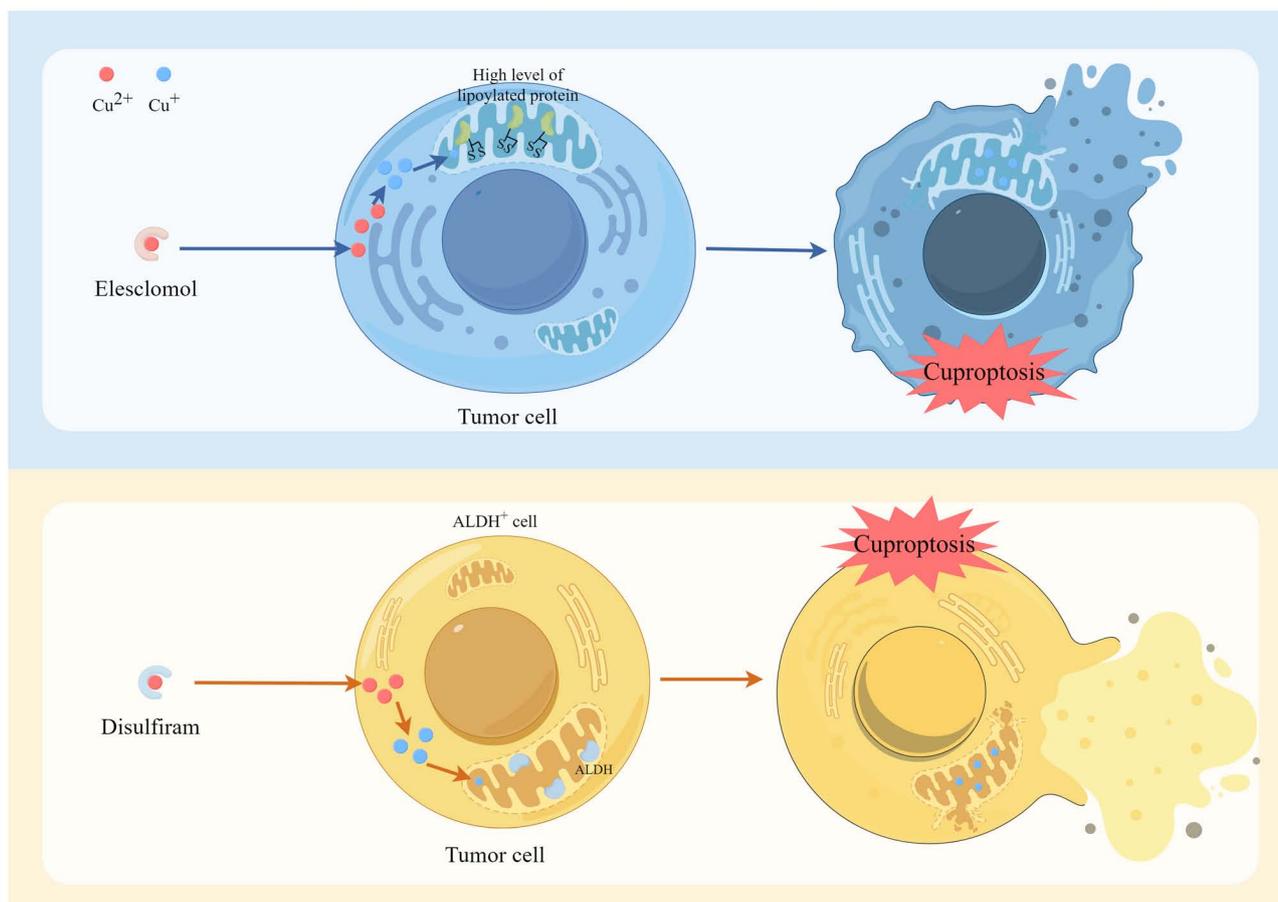
Figure 3. Mechanism of copper ion carriers. Elesclomol and disulfiram enhance intracellular Cu$^+$ accumulation in tumor cells. In the presence of elevated lipoylated proteins or ALDH expression (such as PCa), Cu$^+$ induces toxic stress within mitochondria, triggering cuproptosis and resulting in tumor cell death. ALDH, acetaldehyde dehydrogenase; PCa, prostate cancer.

studies have confirmed the efficacy in PCa using *in vitro* investigations. Results of previous research demonstrated that several substances may elevate intracellular copper ion concentrations, including the aforementioned copper ion carriers, copper ion compounds and several copper chelators that inhibit the increase in copper ion levels. Triethylenetetramine dihydrochloride (102), 8-hydroxyquinoline (103), penicillamine (104), methanobactin (105), Bathocuproine disulphonate (106) and choline tetrathiomolybdate (107) are key compounds that regulate intracellular copper ion concentrations, thereby facilitating or obstructing copper ion-associated biological functions. The aforementioned drugs are theoretically capable of stimulating cell proliferation; however, no previous investigations have been undertaken regarding cuproptosis in PCa. Preliminary experiments should be performed to substantiate this hypothesis and to aid in the development of novel cuproptosis-associated therapies.

Chelators of copper ions. A reduction in glutathione (GSH), a natural chelator of intracellular copper ions, results in an elevation of intracellular copper concentration, ultimately culminating in cell death (9). In healthy prostate cells, GSH neutralizes ROS produced by increased copper ion levels from copper ion carriers; thus, providing an antioxidant effect and reducing sensitivity to ROS. Conversely, PCa cells possess diminished levels of GSH and are deficient in antioxidants, rendering them susceptible to ROS generated by copper ion carriers. Subsequently, this may result in PCa cell mortality (79). In addition, elevated copper concentrations facilitate tumor angiogenesis and disrupt lipid metabolism. Steroid-based compounds impede PCa progression through the inhibition of CTR, thereby decreasing copper absorption by PCa cells and mitigating the proliferative effects of copper. These results indicate that the aforementioned compounds may represent innovative anticancer agents targeting anti-copper therapy (35). Results of a further study (108) reveal that the pro-drug, gamma-glutamyl transferase-activated prochelator releasing dithiocarbamate (GGTDTC), is activated by gamma-glutamyl transferase (GGT) in PCa cells. The release of dithiocarbamate (DTC), which chelates with copper ions to form a Cu-DTC complex, is highly toxic and promotes PCa cell death by triggering oxidative stress to generate large amounts of ROS. Ultimately, this interferes with protein ubiquitination. In PCa cells, GGT is often overexpressed and the concentration of copper ions is high. In addition, GGT exhibits a decreased antioxidant capacity, leading to metabolic disorders. This compound is more selective to cancer cells and therefore less toxic to non-tumor cells. In addition, GGT exhibits improved selectivity (108). Thus, the use of copper chelators, in addition to elevated copper ion concentrations that mediate cuproptosis and impede tumor advancement, may diminish intracellular copper levels and initiate cuproptosis.

These compounds may be used to leverage the highly toxic characteristics of copper-chelator complexes, which may further inhibit tumor progression to some degree. However, the specific mechanisms remain to be fully elucidated.

Copper nanoparticles. Nanotechnology facilitates the targeted delivery of copper ions to tumor sites via modifying responsive groups that coordinate with copper compounds. This process enhances the concentration of copper ions within tumor cells, leading to the toxic oligomerization of lipoylated proteins and the degradation of Fe-S cluster proteins. This ultimately induces cuproptosis in tumor cells and produces a therapeutic effect against cancer (109). Researchers presented a novel nanoparticle, DCM@GDY-CuMOF@DOX, capable of releasing Cu^+ in the presence of GSH, ultimately facilitating the onset of cuproptosis (110). Concurrently, doxorubicin (DOX) generates high levels of hydrogen peroxide (H_2O_2), which, when catalyzed by Cu^+, is transformed into cytotoxic ROS via a Fenton-like reaction. Notably, this process induces cancer cell death. ROS produced via this method may trigger apoptosis, resulting in oxidative DNA damage and mitochondrial impairment. By contrast to the administration of DOX alone, nanoparticles enveloped within the PCa cell membranes (DU145 cell membrane; DCM) exhibit isotypic targeting capabilities, allowing them to specifically identify and target identical PCa cells. This process may diminish the likelihood of non-specific targeting during blood circulation. The non-specific adsorption and elimination in the bloodstream extend circulation time within the body, thereby minimizing toxicity to healthy tissues and enhancing the precision of targeting PCa cells for treatment. Haemolysis experiments, histopathological assessments and serum biochemical analyses demonstrated that nanoparticles did not induce notable damage to healthy cells and tissues; however, they did exhibit targeting capabilities and biocompatibility. Thus, these may exhibit potential in clinical practice (110). Results of a previous study (111) demonstrate that cuprous oxide nanoparticles (CONPs) selectively inhibited the proliferation of CRPC cells. Toxicological investigations revealed that CONPs elevate copper demand and uptake capacity and induce cell cycle arrest and apoptosis in cancer cells. In addition, CONPs suppressed stem cell properties and the Wnt signaling pathway and exhibited minimal effects on healthy prostate epithelial cells. Moreover, $Cu(DDC)_2$ nanoparticles facilitate the transport of Cu^{2+} into cells, elevate intracellular copper levels and mediate the apoptosis of paclitaxel-resistant PCa cells (112). These nanoparticles facilitated tumor site-specific accumulation and induce cuproptosis through loading copper ions and employing a responsive release mechanism, offering a novel, targeted and biocompatible therapeutic alternative for PCa treatment.

Moreover, liposomal copper (LpCu) effectively transports copper ions into PCa cells via encapsulating copper salts within liposomes. PCa cells treated with LpCu exhibit metabolic toxicity comparable with that of free copper salts, indicated by increased intracellular copper levels and increased levels of ROS, apoptosis and necrosis (113). Specific steroid-based compounds form complexes with copper ions, diminishing the concentration of free copper ions within the cell. Thus, the influx of copper ions into PCa cells via CTR1 is reduced, effectively impeding copper absorption by PCa cells and disrupting their biosynthesis to inhibit PCa cell proliferation (35).

Adjuvant therapy and targeted prediction of cuproptosis in PCa. Surgery remains the primary treatment option for localized PCa and androgen deprivation therapy is effective for patients with biochemically recurrent and metastatic hormone-sensitive PCa. However, resistance and progression to CRPC may still occur, along with suboptimal therapeutic outcomes following chemotherapy and immunotherapy (54). At present, research is focused on the role of cuproptosis in malignancies, to determine the effects on cell growth and the specific underlying mechanisms.

Cuproptosis affects treatment resistance and contributes to the management of PCa. Notably, enzalutamide augments the susceptibility of CRPC cells to copper ion carriers and improves treatment efficacy through facilitating copper-dependent cell death. This combination therapy efficiently suppresses the proliferation of CRPC cells and reverses the resistance of enzalutamide-resistant cells both *in vitro* and *in vivo* (43). By contrast, enzalutamide-resistant PCa cells demonstrate high levels of resistance to cuproptosis and the alteration of NUDT21 activity or the addition of PDHA improve the effectiveness of the copper ionophore, potentially leading to treatment resistance in PCa (67). Results of a further previous study revealed that a combination of disulfiram and copper led to a notable reduction in the expression of ATP7B and the elevation of intracellular copper levels in PCa cell lines, rendering resistant cells sensitive to the growth-inhibitory and apoptotic effects of docetaxel (80). Results of both *in vivo* and *in vitro* studies demonstrate that a combination of DSF and copper markedly reduces cell proliferation and the induction of apoptosis, indicative of the increased antitumor efficacy of docetaxel (80). Moreover, DSF and copper directly interact with ATP7B, leading to the downregulation of its downstream proteins, including copper metabolism MURR1 Domain containing 1, α-clusterin and S-phase kinase associated protein 2. Simultaneously, DSF and copper promote upregulation of cyclin-dependent kinase inhibitor 1 thus inhibiting tumor growth (80). Results of a previous study (95) reveal that a combination of ES and $CuCl_2$ (ES-Cu) effectively induces copper-mediated cytotoxicity in PCa cells, inhibits autophagy via DLAT upregulation and subsequently promotes cell retention in the G_2/M phase, thereby augmenting the chemotherapeutic efficacy of docetaxel. *In vivo* experiments further demonstrate that the combination of ES-Cu and docetaxel markedly suppresses tumor growth in a PCa transplantation model using nude mice, where tumor proliferation was markedly inhibited (95). Collectively, these data indicated that copper-induced cell death may impact the sensitivity of PCa to pharmacological agents.

Complanatoside A (CA) is a flavonoid derived from the Traditional Chinese Medicine, *Semen Astragali Complanati*. Results of a previous study (114) reveal that CA downregulates the expression of the copper efflux-associated protein, ATOX1, promotes the accumulation of intracellular copper ions, inhibits mitochondrial activity and induces copper-mediated cell death. Notably, this agent markedly suppresses the proliferation, invasion and growth of PCa cells both *in vivo* and *ex vivo*, with no notable damage to major organs in

Table II. Correlation between CRGs and PCa.

First author/s, year	CRGs	Sources for screening	Association with PCa	(Refs.)
Yang, 2022; Yang, 2024; Wang, 2023	FDX1	Genome-wide screening utilizing CRISPR/Cas9 technology	Elevated expression correlates with unfavorable prognosis; Inverse connection with immune cell infiltration, cellular autophagy and drug sensitivity	(61,62,117)
Yang, 2023; Wang, 2023	DLAT		Elevated expression correlates with favorable prognosis and positively connected with immune cell infiltration	(63,117)
Yang, 2024; Wang, 2023	LIAS		Elevated expression correlates with a favorable outcome	(62,117)
Li, 2024; Wang, 2023; Cheng, 2023	PDHA1		Elevated expression correlates with diminished bad prognosis, treatment resistance and DFS	(64,117,118)
Wang, 2023	CDKN2A DLD		Elevated expression correlated with unfavorable prognosis and decreased DFS	(117)
Li, 2024; Wang, 2023	GLS		Elevated expression correlates with unfavorable prognosis	(64,117)
Xiao, 2023	GCSH	Analysis of expression levels using the StarBase and GEPIA databases		(65)
Yang, 2024; Li, 2024	DBT	Analysis of differential expression in TCGA and GEO datasets	Elevated expression correlates with a favorable outcome	(62,64)

CRGs, cuproptosis-related genes; PCa, prostate cancer; FDX1, ferredoxin 1; DLAT, dihydrolipoamide S-acetyltransferase; LIAS, lipoic acid synthase; PDHA1, pyruvate dehydrogenase E1 subunit alpha 1; CDKN2A, cyclin-dependent kinase inhibitor 2A; DLD, dihydrolipoamide dehydrogenase; GLS, glutaminase; GCSH, glycine cleavage system protein H; DBT, dihydrolipoamide branched-chain transacylase E2; CRISPR/Cas9, clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9; DFS, disease-free survival; GEPIA, Gene Expression Profiling Interactive Analysis; TCGA, The Cancer Genome Atlas; GEO, Gene Expression Omnibus.

experimental animal models (114). Nuclear factor-activated T cell 5 (NFAT5) is a transcription factor that activates T cells and plays a key role in cellular stress response, immunological response and cell proliferation. Results of previous study revealed that NFAT5 acts as a target gene of microRNA (miR)-206 through bioinformatics analysis and database predictions. In addition, results of a previous study (115) reveal that the long-chain non-coding RNA (lncRNA), AP000842.3, acts as a target gene of miR-206, functioning as a competitive endogenous RNA (ceRNA) that modulates the expression levels of NFAT5. Thus, this lncRNA affects the sensitivity of PCa cells to copper death inducers. In cellular experiments, NFAT5 knockdown markedly increases the sensitivity of PCa cells to copper-induced cytotoxicity and this was highlighted by elevated intracellular copper ion concentrations and reduced ROS levels (115). Therefore, the interaction of lncRNA AP000842.3 with miR-206 may play a key role in regulating NFAT5 expression. Notably, this regulatory mechanism may be partly dependent on miR-206, providing a novel potential target for PCa diagnosis and treatment (115).

Resveratrol, a polyphenol compound mainly located in red grapes and pomegranates, is an antioxidant that inhibits PCa cells through interacting with copper ions. This process contributes to the redox of copper ions and the generation of ROS, leading to an increase in intracellular oxidative stress and interference with intracellular signaling pathways, such as MAPK, PI3K/Akt and NF-κB pathways. Moreover, results of a this study (116) reveal that resveratrol inhibits cell cycle progression, thus inhibiting PCa cell proliferation. This compound also activates key intracellular apoptotic signaling pathways, such as the mitochondrial pathway and death receptor pathway, to promote the apoptosis of PCa cells. By contrast, copper ion chelation reverses the anticancer effects of resveratrol, further confirming the key role of copper ions in the action of resveratrol. In addition, the observed elevation of copper ions may facilitate their absorption and storage, promoting the harmful effects of resveratrol through the upregulation of the copper transporter protein, CTR (116). Collectively, results of these investigations indicated that copper and copper-induced cytotoxicity may serve as viable therapeutic approaches for the treatment of PCa.

Despite the limited number of studies on cuproptosis in PCa, previous studies revealed that CRGs may act as novel therapeutic targets, playing a key role in the progression of PCa (Table II). Moreover, cuproptosis may be associated with key predictors of PCa, exhibiting potential as a novel indicator of the prognosis of patients with PCa and their responsiveness to treatment (Table III).

Table III. Summary of PCa prediction models based on cuproptosis.

First author/s, year	Forecasting model	Construction methods	Forecasting metrics	Prominent application domains in PCa	(Refs.)
Yang, 2024; Li, 2024; Wang, 2023	CRGs	Sequential LASSO Cox regression	FDX1, DLAT, DLD, PDHA1, CDKN2A, DBT, GLS and others	Assessment of relapse risk, treatment efficacy and DFS	(62,64,117)
Jin, 2022	CRGs evaluations	Univariate Cox regression	DLAT, FDX1, DLD, LIAS, GLS, PDHA1, CDKN2A and others	Recommendations for individualized immunotherapy approaches	(119)
Wang, 2024	Gleason scores and CRGs	LASSO Cox and multifactorial Cox regression	Five particular genes (STX3, CABLES2, E2F5, RALA and POLE3)	Personalized therapy and administration	(120)
Yao, 2023	Cuproptosis-related immunization risk score		Three immune-related CRGs (PRLR, DES and LECT2)	Evaluation of OS and DFS	(121)
Zhang, 2023	CRGs and PCa expression correlate		Five particular genes (B4GALNT4, FAM83D, COL1A, CHRM3 and MYBPC1)	Prediction of responsiveness to chemotherapy and immunotherapy	(122)
Ma, 2024	Necrosis and CRGs		CDI	Assessment of survival and recurrence risk	(123)
Cheng, 2023	CRLs related with cuproptosis		Six CRLs	DFS prognosis, evaluation of the immune microenvironment	(124)
Ma, 2023			Twelve CRLs	Evaluation of OS and DFS	(125)
Jiang, 2022			Six CRLs	DFS evaluation	(126)
Zhong, 2025					(127)
Ren, 2023				Assessment of relapse risk	(128)
Yu, 2024					(129)
Lu, 2024			Three CRLs	Prognostic assessment for progression-free survival	(130)

CRGs, cuproptosis-related genes; PCa, prostate cancer; FDX1, ferredoxin 1; DLAT, dihydrolipoamide S-acetyltransferase; DLD, dihydro-lipoamide dehydrogenase; PDHA1, pyruvate dehydrogenase E1 subunit alpha 1; CDKN2A, cyclin-dependent kinase inhibitor 2A; DBT, dihydrolipoamide branched-chain transacylase E2; GLS, glutaminase; LIAS, lipoic acid synthase; STX3, syntaxin 3; CABLES2, Cdk5 and Abl enzyme substrate 2; E2F5, E2F transcription factor 5; RALA, RAS-like proto-oncogene A; POLE3, DNA polymerase epsilon 3; PRLR, prolactin receptor; DES, desmin; LECT2, lectin-like transcript 2; B4GALNT4, beta-1,4-galactosyltransferase 4; FAM83D, family with sequence similarity 83 member D; COL1A, collagen type I alpha; CHRM3, cholinergic receptor muscarinic 3; MYBPC1, myosin binding protein C 1; DFS, disease-free survival; OS, overall survival; CDI, cell death index; CRLs, cuproptosis-related long non-coding RNAs.

Irrespective of the trajectory of predictive modeling, research is focused on the development of novel molecular instruments for prognostic evaluation and clinical decision-making in PCa. Cuproptosis-based prognostic models exhibit efficacy in predicting outcomes of patients with PCa; however, the recurrence prediction mediated by CDI surpasses that of the cuproptosis-based prognostic models (123). CRLs obtained from bioinformatics analysis not only aid in the establishment of a prognostic prediction model for patients with PCa, but also the results of cellular experiments reveal that the knockdown of CRLs, particularly AC106820.5, may inhibit the proliferation, migration and invasive capabilities of PCa cells (127). Collectively, these data illustrate that bioinformatics analyses may be used to identify potential therapeutic targets in the treatment of PCa. Notably, the aforementioned models may also be used to predict responsiveness to immunotherapy, leading to the development of personalized treatment options that improve patient outcomes and quality of life.

5. Discussion

The redox activity of copper represents a dual purpose in cellular viability; for example, it acts as a crucial cofactor for enzymes that facilitate vital physiological processes in

cellular metabolism and may induce oxidative stress and cell death when present in excess (131,132). The initial discovery of cuproptosis elucidated the association between copper-induced cell death and mitochondrial metabolism, thus furthering investigations in copper biology and offering novel insights for future investigations into cell death pathways. In PCa, increased copper concentrations and a disruption of copper transporters result in the accumulation of copper ions within tumor cells, facilitating the initiation of cuproptosis. The activation of cuproptosis facilitates the elimination of surplus copper ions, mitigates cellular damage resulting from copper metabolism disorders and suppresses the proliferation, invasion and metastasis of PCa cells, thereby inhibiting tumor progression induced by copper metabolism disorders. However, further investigations are required to determine the specific underlying mechanisms.

In recent years, cuproptosis has become a novel focus within PCa research, demonstrating potential in various tumors to markedly impact the proliferation, invasion and metastasis of tumor cells. Despite novel insights into the role of cuproptosis in PCa, this field of study exhibits certain limitations. Cuproptosis may inhibit the progression of PCa; however, PCa requires elevated copper levels for its physiological functions. In addition, FDX1 expression in PCa cells remains low to prevent the initiation of cuproptosis. Androgens may enhance the transcriptional levels of CTR1, ATP7B and STEAP in PCa cells via androgen receptor activation, thereby increasing copper uptake and facilitating PCa progression (49). Moreover, the hypothesis regarding increased copper demand in PCa and the approaches to alleviate levels of toxicity remain ambiguous and the specific molecular mechanisms underlying cuproptosis have yet to be fully elucidated. Thus, further investigations should focus on the specific signaling pathways and regulatory mechanisms underlying this phenomenon. Notably, these processes may include the accumulation of copper ions in PCa cells, the functions of pivotal proteins and the activation of signaling pathways associated with the onset of cuproptosis. To date, previous research has focused on CRGs and CRLs and the use of bioinformatics analyses, predictive model development and *in vitro* experimentation. The aforementioned studies have primarily utilized public databases for analysis, which may result in limitations in the validity of studies, through large-scale clinical samples and a lack of investigation into clinical applications. Thus, further investigations should focus on the use of genetic analysis of clinical samples to validate prior findings and inform subsequent studies. Notably, the AlphaFold (https://deepmind.google/science/alphafold/) suite of tools constitutes a robust, integrated platform for structural prediction. It is used to accurately predict the structures of proteins interacting with various biomolecules (133). Thus, the development of novel prediction models using AlphaFold 3 tools may further the understanding of PCa at the molecular level and aid in the identification of additional therapeutic targets. Further investigations into drug sensitivity may lead to the development of novel therapeutic targets, while analyses of immune cells inside the tumor microenvironment may clarify the role of cuproptosis in modulating their activity and the potential impact on tumor proliferation and metastasis. Moreover, a multidisciplinary research approach is required to elucidate the specific role of cuproptosis in PCa, thereby establishing a foundation for the advancement of novel therapies aimed at enhancing the prognosis and quality of life of patients.

In conclusion, the present review article demonstrated that cuproptosis may exhibit potential in the treatment of PCa. Notably, copper-based nanomedicines, as well as traditional copper ion carriers and chelators, may elicit more potent anti-tumor effects. Additional investigations into the transformation of conventional pharmaceuticals into nanoparticles, alongside additional clinical trials, may aid in the development of a novel therapeutic approach. However, these trials should be preceded by a comprehensive understanding of the mechanisms underlying copper metabolism and cuproptosis, aiming to determine distinct interactions between copper and the tumor microenvironment, as well as immune responses, which are essential for drug design and efficacy prediction. Notably, the identification of cuproptosis has prompted extensive investigations into novel treatment options for PCa and this newly recognized mechanism of regulatory cell death may contribute to theoretical advancements and practical implementations in the field.

Availability of data and materials

Not applicable.

Authors' contributions

ZL was responsible for writing the original draft, reviewing and editing, project administration, supervision and conceptualization. YC was responsible for writing the original draft, reviewing and editing, supervision and visualization. KZ was responsible for writing the original draft, supervision and conceptualization. ZC was responsible for writing the original draft and resources. YY was responsible for funding acquisition, supervision, project administration, writing, reviewing and editing. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
2. Siegel DA, O'Neil ME, Richards TB, Dowling NF and Weir HK: Prostate cancer incidence and survival, by stage and race/ethnicity - United States, 2001-2017. MMWR Morb Mortal Wkly Rep 69: 1473-1480, 2020.
3. Zhang Z, Garzotto M, Davis EW II, Mori M, Stoller WA, Farris PE, Wong CP, Beaver LM, Thomas GV, Williams DE, et al: Sulforaphane bioavailability and chemo-preventive activity in men presenting for biopsy of the prostate gland: A Randomized controlled trial. Nutr Cancer 72: 74-87, 2020.
4. Tilki D, van den Bergh RCN, Briers E, Van den Broeck T, Brunckhorst O, Darraugh J, Eberli D, De Meerleer G, De Santis M, Farolfi A, et al: EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines on prostate cancer. Part II-2024 update: Treatment of relapsing and metastatic prostate cancer. Eur Urol 86: 164-182, 2024.
5. Cornford P, van den Bergh RCN, Briers E, Van den Broeck T, Brunckhorst O, Darraugh J, Eberli D, De Meerleer G, De Santis M, Farolfi A, et al: EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines on prostate cancer-2024 update. Part I: Screening, diagnosis, and local treatment with curative intent. Eur Urol 86: 148-163, 2024.
6. Gillessen S, Bossi A, Davis ID, de Bono J, Fizazi K, James ND, Mottet N, Shore N, Small E, Smith M, et al: Management of patients with advanced prostate cancer. Part I: Intermediate-/high-risk and locally advanced disease, biochemical relapse, and side effects of hormonal treatment: Report of the advanced prostate cancer consensus conference 2022. Eur Urol 83: 267-293, 2023.
7. Sandhu S, Moore CM, Chiong E, Beltran H, Bristow RG and Williams SG: Prostate cancer. Lancet 398: 1075-1090, 2021.
8. Halliwell B and Gutteridge JM: Oxygen toxicity, oxygen radicals, transition metals and disease. Biochem J 219: 1-14, 1984.
9. Tsvetkov P, Coy S, Petrova B, Dreishpoon M, Verma A, Abdusamad M, Rossen J, Joesch-Cohen L, Humeidi R, Spangler RD, et al: Copper induces cell death by targeting lipoylated TCA cycle proteins. Science 375: 1254-1261, 2022.
10. Francque SM, Marchesini G, Kautz A, Walmsley M, Dorner R, Lazarus JV, Zelber-Sagi S, Hallsworth K, Busetto L, Frühbeck G, et al: Non-alcoholic fatty liver disease: A patient guideline. JHEP Rep 3: 100322, 2021.
11. Mason KE: A conspectus of research on copper metabolism and requirements of man. J Nutr 109: 1979-2066, 1979.
12. Dancis A, Roman DG, Anderson GJ, Hinnebusch AG and Klausner RD: Ferric reductase of Saccharomyces cerevisiae: molecular characterization, role in iron uptake, and transcriptional control by iron. Proc Natl Acad Sci USA 89: 3869-3873, 1992.
13. Georgatsou E, Mavrogiannis LA, Fragiadakis GS and Alexandraki D: The yeast Fre1p/Fre2p cupric reductases facilitate copper uptake and are regulated by the copper-modulated Mac1p activator. J Biol Chem 272: 13786-13792, 1997.
14. Guan D, Zhao L, Shi X, Ma X and Chen Z: Copper in cancer: From pathogenesis to therapy. Biomed Pharmacother 163: 114791, 2023.
15. Boyd SD, Ullrich MS, Skopp A and Winkler DD: Copper sources for Sod1 activation. Antioxidants (Basel) 9: 500, 2020.
16. Luza SC and Speisky HC: Liver copper storage and transport during development: Implications for cytotoxicity. Am J Clin Nutr 63: 812S-820S, 1996.
17. Pufahl RA, Singer CP, Peariso KL, Lin SJ, Schmidt PJ, Fahrni CJ, Culotta VC, Penner-Hahn JE and O'Halloran TV: Metal ion chaperone function of the soluble Cu(I) receptor Atx1. Science 278: 853-856, 1997.
18. Heaton DN, George GN, Garrison G and Winge DR: The mitochondrial copper metallochaperone Cox17 exists as an oligomeric, polycopper complex. Biochemistry 40: 743-751, 2001.
19. Gromadzka G, Tarnacka B, Flaga A and Adamczyk A: Copper dyshomeostasis in neurodegenerative diseases-therapeutic implications. Int J Mol Sci 21: 9259, 2020.
20. La Fontaine S and Mercer JFB: Trafficking of the copper-ATPases, ATP7A and ATP7B: Role in copper homeostasis. Arch Biochem Biophys 463: 149-167, 2007.
21. Lutsenko S, LeShane ES and Shinde U: Biochemical basis of regulation of human copper-transporting ATPases. Arch Biochem Biophys 463: 134-148, 2007.
22. Lutsenko S, Bhattacharjee A and Hubbard AL: Copper handling machinery of the brain. Metallomics 2: 596-608, 2010.
23. Lutsenko S: Copper trafficking to the secretory pathway. Metallomics 8: 84-852, 2016.
24. Csiszar K: Lysyl oxidases: A novel multifunctional amine oxidase family. Prog Nucleic Acid Res Mol Biol 70: 1-32, 2001.
25. Pierson H, Yang H and Lutsenko S: Copper transport and disease: What can we learn from organoids? Annu Rev Nutr 39: 75-94, 2019.
26. Chen L, Min J and Wang F: Copper homeostasis and cuproptosis in health and disease. Signal Transduct Tar 7: 378, 2022.
27. Gaetke LM and Chow CK: Copper toxicity, oxidative stress, and antioxidant nutrients. Toxicology 189: 147-163, 2003.
28. Wang Z, Jin D, Zhou S, Dong N, Ji Y, An P, Wang J, Luo Y and Luo J: Regulatory roles of copper metabolism and cuproptosis in human cancers. Front Oncol 13: 1123420, 2023.
29. Tang D, Chen X and Kroemer G: Cuproptosis: A copper-triggered modality of mitochondrial cell death. Cell Res 32: 417-418, 2022.
30. Sun L, Zhang Y, Yang B, Sun S, Zhang P, Luo Z, Feng T, Cui Z, Zhu T, Li Y, et al: Lactylation of METTL16 promotes cuproptosis via m(6)A-modification on FDX1 mRNA in gastric cancer. Nat Commun 14: 6523, 2023.
31. Xie J, Yang Y, Gao Y and He J: Cuproptosis: Mechanisms and links with cancers. Mol Cancer 22: 46, 2023.
32. Feng Q, Huo C, Wang M, Huang H, Zheng X and Xie M: Research progress on cuproptosis in cancer. Front Pharmacol 15: 1290592, 2024.
33. Liu WQ, Lin WR, Yan L, Xu WH and Yang J: Copper homeostasis and cuproptosis in cancer immunity and therapy. Immunol Rev 321: 211-227, 2024.
34. Nowell CS and Radtke F: Notch as a tumour suppressor. Nat Rev Cancer 17: 145-159, 2017.
35. Xie F and Peng F: Reduction in copper uptake and inhibition of prostate cancer cell proliferation by novel steroid-based compounds. Anticancer Res 41: 5953-5958, 2021.
36. Si M and Lang J: The roles of metallothioneins in carcinogenesis. J Hematol Oncol 11: 107, 2018.
37. Baldari S, Di Rocco G and Toietta G: Current biomedical use of copper chelation therapy. Int J Mol Sci 21: 1069, 2020.
38. Ilyechova EY, Bonaldi E, Orlov IA, Skomorokhova EA, Puchkova LV and Broggini M: CRISP-R/Cas9 mediated deletion of copper transport genes CTR1 and DMT1 in NSCLC cell line H1299. Biological and pharmacological consequences. Cells 8: 322, 2019.
39. Shao S, Si J and Shen Y: Copper as the target for anticancer nano-medicine. Adv Ther 2: 2019. https://doi.org/10.1002/adtp.201800147
40. Li Y: Copper homeostasis: Emerging target for cancer treatment. IUBMB Life 72: 1900-1908, 2020.
41. Lelièvre P, Sancey L, Coll JL, Deniaud A and Busser B: The multifaceted roles of copper in cancer: A trace metal element with dysregulated metabolism, but also a target or a bullet for therapy. Cancers (Basel) 12: 3594, 2020.
42. Li S, Zhang J, Yang H, Wu C, Dang X and Liu Y: Copper depletion inhibits CoCl2-induced aggressive phenotype of MCF-7 cells via downregulation of HIF-1 and inhibition of Snail/Twist-mediated epithelial-mesenchymal transition. Sci Rep 5: 12410, 2015.
43. Gao X, Zhao H, Liu J, Wang M, Dai Z, Hao W, Wang Y, Wang X, Zhang M, Liu P, et al: Enzalutamide sensitizes castration-resistant prostate cancer to copper-mediated cell death. Adv Sci (Weinh) 11: e2401396, 2024.
44. Wang Y, Chen Y, Zhang J, Yang Y, Fleishman JS, Wang Y, Wang J, Chen J, Li Y and Wang H: Cuproptosis: A novel therapeutic target for overcoming cancer drug resistance. Drug Resist Update 72: 101018, 2024.
45. Ge EJ, Bush AI, Casini A, Cobine PA, Cross JR, DeNicola GM, Dou QP, Franz KJ, Gohil VM, Gupta S, et al: Connecting copper and cancer: From transition metal signalling to metalloplasia. Nat Rev Cancer 22: 102-113, 2022.
46. Stanislawska IJ, Figat R, Kiss AK and Bobrowska-Korczak B: Essential elements and isoflavonoids in the prevention of prostate cancer. Nutrients 14: 1225, 2022.

47. Cater MA and Haupt Y: Clioquinol induces cytoplasmic clearance of the X-linked inhibitor of apoptosis protein (XIAP): Therapeutic indication for prostate cancer. Biochem J 436: 481-491, 2011.
48. Chen D, Cui QC, Yang H, Barrea RA, Sarkar FH, Sheng S, Yan B, Reddy GP and Dou QP: Clioquinol, a therapeutic agent for Alzheimer's disease, has proteasome-inhibitory, androgen receptor-suppressing, apoptosis-inducing, and antitumor activities in human prostate cancer cells and xenografts. Cancer Res 67: 1636-1644, 2007.
49. Safi R, Nelson ER, Chitneni SK, Franz KJ, George DJ, Zalutsky MR and McDonnell DP: Copper signaling axis as a target for prostate cancer therapeutics. Cancer Res 74: 5819-5831, 2014.
50. Cai H, Wu JS, Muzik O, Hsieh JT, Lee RJ and Peng F: Reduced 64Cu uptake and tumor growth inhibition by knockdown of human copper transporter 1 in xenograft mouse model of prostate cancer. J Nucl Med 55: 622-628, 2014.
51. Saleh SAK, Adly HM, Abdelkhaliq AA and Nassir AM: Serum levels of selenium, zinc, copper, manganese, and iron in prostate cancer patients. Curr Urol 14: 44-49, 2020.
52. Kaba M, Pirincci N, Yuksel MB, Gecit I, Gunes M, Ozveren H, Eren H and Demir H: Serum levels of trace elements in patients with prostate cancer. Asian Pac J Cancer Prev 15: 2625-2629, 2014.
53. Ozmen H, Erulas FA, Karatas F, Cukurovali A and Yalcin O: Comparison of the concentration of trace metals (Ni, Zn, Co, Cu and Se), Fe, vitamins A, C and E, and lipid peroxidation in patients with prostate cancer. Clin Chem Lab Med 44: 175-179, 2006.
54. Wu J, He J, Liu Z, Zhu X, Li Z, Chen A and Lu J: Cuproptosis: Mechanism, role, and advances in urological malignancies. Med Res Rev 44: 1662-1682, 2024.
55. Baszuk P, Marciniak W, Derkacz R, Jakubowska A, Cybulski C, Gronwald J, Dębniak T, Huzarski T, Białkowska K, Pietrzak S, *et al*: Blood copper levels and the occurrence of colorectal cancer in Poland. Biomedicines 9: 1628, 2021.
56. Baltaci AK, Dundar TK, Aksoy F and Mogulkoc R: Changes in the serum levels of trace elements before and after the operation in thyroid cancer patients. Biol Trace Elem Res 175: 57-64, 2017.
57. Jin Y, Zhang C, Xu H, Xue S, Wang Y, Hou Y, Kong Y and Xu Y: Combined effects of serum trace metals and polymorphisms of CYP1A1 or GSTM1 on non-small cell lung cancer: A hospital based case-control study in China. Cancer Epidemiol 35: 182-187, 2011.
58. Aubert L, Nandagopal N, Steinhart Z, Lavoie G, Nourreddine S, Berman J, Saba-El-Leil MK, Papadopoli D, Lin S, Hart T, *et al*: Copper bioavailability is a KRAS-specific vulnerability in colorectal cancer. Nat Commun 11: 3701, 2020.
59. Lener MR, Scott RJ, Wiechowska-Kozlowska A, Serrano-Fernández P, Baszuk P, Jaworska-Bieniek K, Sukiennicki G, Marciniak W, Muszyńska M, Kładny J, *et al*: Serum concentrations of selenium and copper in patients diagnosed with pancreatic cancer. Cancer Res Treat 48: 1056-1064, 2016.
60. Pavithra V, Sathisha TG, Kasturi K, Mallika DS, Amos SJ and Ragunatha S: Serum levels of metal ions in female patients with breast cancer. J Clin Diagn Res 9: BC25-BC27, 2015.
61. Yang L, Zhang Y, Wang Y, Jiang P, Liu F and Feng N: Ferredoxin 1 is a cuproptosis-key gene responsible for tumor immunity and drug sensitivity: A pan-cancer analysis. Front Pharmacol 13: 938134, 2022.
62. Yang L, Tang Y, Zhang Y, Wang Y, Jiang P, Liu F and Feng N: Comprehensiveness cuproptosis related genes study for prognosis and medication sensitiveness across cancers, and validation in prostate cancer. Sci Rep 14: 9570, 2024.
63. Yang Q, Zeng S and Liu W: Roles of cuproptosis-related gene DLAT in various cancers: A bioinformatic analysis and preliminary verification on pro-survival autophagy. PeerJ 11: e15019, 2023.
64. Li C, Xiao Y, Cao H, Chen Y, Li S and Yin F: Cuproptosis regulates microenvironment and affects prognosis in prostate cancer. BIOL Trace Elem Res 202: 99-110, 2024.
65. Xiao S and Lou W: Integrated analysis reveals a potential cuproptosis-related ceRNA axis SNHG17/miR-29a-3p/GCSH in prostate adenocarcinoma. Heliyon 9: e21506, 2023.
66. Zhang D, Wang T, Zhou Y and Zhang X: Comprehensive analyses of cuproptosis-related gene CDKN2A on prognosis and immunologic therapy in human tumors. Medicine (Baltimore) 102: e33468, 2023.
67. Lin SC, Tsai YC, Chen YL, Lin HK, Huang YC, Lin YS, Cheng YS, Chen HY, Li CJ, Lin TY and Lin SC: Un-methylation of NUDT21 represses docosahexaenoic acid biosynthesis contributing to enzalutamide resistance in prostate cancer. Drug Resist Update 77: 101144, 2024.
68. Tang D, Kroemer G and Kang R: Targeting cuproplasia and cuproptosis in cancer. Nat Rev Clin Oncol 21: 370-388, 2024.
69. Di Meo S, Reed TT, Venditti P and Victor VM: Role of ROS and RNS sources in physiological and pathological conditions. Oxid Med Cell Longev 2016: 1245049, 2016.
70. Han C, Wang Z, Xu Y, Chen S, Han Y, Li L, Wang M and Jin X: Roles of reactive oxygen species in biological behaviors of prostate cancer. Biomed Res Int 2020: 1269624, 2020.
71. Liu Y, Chen A, Wu Y, Ni J, Wang R, Mao Y, Sun N and Mi Y: Identification of mitochondrial carrier homolog 2 as an important therapeutic target of castration-resistant prostate cancer. Cell Death Dis 16: 70, 2025.
72. Khandrika L, Kumar B, Koul S, Maroni P and Koul HK: Oxidative stress in prostate cancer. Cancer Lett 282: 125-136, 2009.
73. Baohai X, Shi F and Yongqi F: Inhibition of ubiquitin specific protease 17 restrains prostate cancer proliferation by regulation of epithelial-to-mesenchymal transition (EMT) via ROS production. Biomed Pharmacother 118: 108946, 2019.
74. Lee W, Kim KY, Yu SN, Kim SH, Chun SS, Ji JH, Yu HS and Ahn SC: Pipernonaline from Piper longum Linn. induces ROS-mediated apoptosis in human prostate cancer PC-3 cells. Biochem Biophys Res Commun 430: 406-412, 2013.
75. Kim SH, Kim KY, Yu SN, Park SG, Yu HS, Seo YK and Ahn SC: Monensin induces PC-3 prostate cancer cell apoptosis via ROS production and Ca2+ homeostasis disruption. Anticancer Res 36: 5835-5843, 2016.
76. Farhan M, El Oirdi M, Aatif M, Nahvi I, Muteeb G and Alam MW: Soy isoflavones induce cell death by copper-mediated mechanism: Understanding its anticancer properties. Molecules 28: 2925, 2023.
77. Alhasawi M, Aatif M, Muteeb G, Alam MW, Oirdi ME and Farhan M: Curcumin and its derivatives induce apoptosis in human cancer cells by mobilizing and redox cycling genomic copper ions. Molecules 27: 7410, 2022.
78. Farhan M, Rizvi A, Ali F, Ahmad A, Aatif M, Malik A, Alam MW, Muteeb G, Ahmad S, Noor A and Siddiqui FA: Pomegranate juice anthocyanidins induce cell death in human cancer cells by mobilizing intracellular copper ions and producing reactive oxygen species. Front Oncol 12: 998346, 2022.
79. Denoyer D, Pearson HB, Clatworthy SA, Smith ZM, Francis PS, Llanos RM, Volitakis I, Phillips WA, Meggyesy PM, Masaldan S and Cater MA: Copper as a target for prostate cancer therapeutics: copper-ionophore pharmacology and altering systemic copper distribution. Oncotarget 7: 37064-37080, 2016.
80. Song L, Nguyen V, Xie J, Jia S, Chang CJ, Uchio E and Zi X: ATPase copper transporting beta (ATP7B) is a novel target for improving the therapeutic efficacy of docetaxel by disulfiram/copper in human prostate cancer. Mol Cancer Ther 23: 854-863, 2024.
81. Vo T, Peng TY, Nguyen TH, Bui TNH, Wang CS, Lee WJ, Chen YL, Wu YC and Lee IT: The crosstalk between copper-induced oxidative stress and cuproptosis: A novel potential anticancer paradigm. Cell Commun Signal 22: 353, 2024.
82. Onuma T, Mizutani T, Fujita Y, Yamada S and Yoshida Y: Copper content in ascitic fluid is associated with angiogenesis and progression in ovarian cancer. J Trace Elem Med Biol 68: 126865, 2021.
83. Oliveri V: Selective targeting of cancer cells by copper ionophores: An overview. Front Mol Biosci 9: 841814, 2022.
84. Melegh Z and Oltean S: Targeting angiogenesis in prostate cancer. Int J Mol Sci 20: 2676, 2019.
85. Ioannidou E, Moschetta M, Shah S, Parker JS, Ozturk MA, Pappas-Gogos G, Sheriff M, Rassy E and Boussios S: Angiogenesis and anti-angiogenic treatment in prostate cancer: mechanisms of action and molecular targets. Int J Mol Sci 22: 9926, 2021.
86. Fang J, Ding M, Yang L, Liu LZ and Jiang BH: PI3K/PTEN/AKT signaling regulates prostate tumor angiogenesis. Cell Signal 19: 2487-2497, 2007.
87. Marin-Aguilera M, Pereira MV, Jimenez N, Reig Ò, Cuartero A, Victoria I, Aversa C, Ferrer-Mileo L, Prat A and Mellado B: Glutamine and cholesterol plasma levels and clinical outcomes of patients with metastatic castration-resistant prostate cancer treated with taxanes. Cancers (Basel) 13: 4960, 2021.

88. Yue S, Li J, Lee SY, Lee HJ, Shao T, Song B, Cheng L, Masterson TA, Liu X, Ratliff TL and Cheng JX: Cholesteryl ester accumulation induced by PTEN loss and PI3K/AKT activation underlies human prostate cancer aggressiveness. Cell Metab 19: 393-406, 2014.

89. Lee HJ, Li J, Vickman RE, Li J, Liu R, Durkes AC, Elzey BD, Yue S, Liu X, Ratliff TL and Cheng JX: Cholesterol esterification inhibition suppresses prostate cancer metastasis by impairing the wnt/β-catenin pathway. Mol Cancer Res 16: 974-985, 2018.

90. Liu YT, Chen L, Li SJ, Wang WY, Wang YY, Yang QC, Song A, Zhang MJ, Mo WT, Li H, et al: Dysregulated Wnt/β-catenin signaling confers resistance to cuproptosis in cancer cells. Cell Death Differ 31: 1452-1466, 2024.

91. Song X, Wang W, Li Z and Zhang D: Association between serum copper and serum lipids in adults. Ann Nutr Metab 73: 282-289, 2018.

92. Pan YX, Zhuo MQ, Li DD, Xu YH, Wu K and Luo Z: SREBP-1 and LXRα pathways mediated Cu-induced hepatic lipid metabolism in zebrafish Danio rerio. Chemosphere 215: 370-379, 2019.

93. Xu YC, Xu YH, Zhao T, Wu LX, Yang SB and Luo Z: Waterborne Cu exposure increased lipid deposition and lipogenesis by affecting Wnt/β-catenin pathway and the beta-catenin acetylation levels of grass carp Ctenopharyngodon idella. Environ Pollut 263(Pt B): 114420, 2020.

94. Yang L, Yang P, Lip GYH and Ren J: Copper homeostasis and cuproptosis in cardiovascular disease therapeutics. Trends Pharmacol Sci 44: 573-585, 2023.

95. Wen H, Qu C, Wang Z, Gao H, Liu W, Wang H, Sun H, Gu J, Yang Z and Wang X: Cuproptosis enhances docetaxel chemosensitivity by inhibiting autophagy via the DLAT/mTOR pathway in prostate cancer. FASEB J 37: e23145, 2023.

96. Zhang H, Chen D, Ringler J, Chen W, Cui QC, Ethier SP, Dou QP and Wu G: Disulfiram treatment facilitates phosphoinositide 3-kinase inhibition in human breast cancer cells in vitro and in vivo. Cancer Res 70: 3996-4004, 2010.

97. Bergez-Hernandez F, Irigoyen-Arredondo M and Martinez-Camberos A: A systematic review of mechanisms of PTEN gene down-regulation mediated by miRNA in prostate cancer. Heliyon 10: e34950, 2024.

98. Marques RB, Aghai A, de Ridder CMA, Stuurman D, Hoeben S, Boer A, Ellston RP, Barry ST, Davies BR, Trapman J and van Weerden WM: High efficacy of combination therapy using PI3K/AKT inhibitors with androgen deprivation in prostate cancer preclinical models. Eur Urol 67: 1177-1185, 2015.

99. Lin J, Haffner MC, Zhang Y, Lee BH, Brennen WN, Britton J, Kachhap SK, Shim JS, Liu JO, Nelson WG, et al: Disulfiram is a DNA demethylating agent and inhibits prostate cancer cell growth. Prostate 71: 333-343, 2011.

100. Iljin K, Ketola K, Vainio P, Halonen P, Kohonen P, Fey V, Grafström RC, Perälä M and Kallioniemi O: High-throughput cell-based screening of 4910 known drugs and drug-like small molecules identifies disulfiram as an inhibitor of prostate cancer cell growth. Clin Cancer Res 15: 6070-6078, 2009.

101. Tesson M, Rae C, Nixon C, Babich JW and Mairs RJ: Preliminary evaluation of prostate-targeted radiotherapy using 131I-MIP-1095 in combination with radiosensitising chemotherapeutic drugs. J Pharm Pharmacol 68: 912-921, 2016.

102. Castoldi F, Hyvonen MT, Durand S, Aprahamian F, Sauvat A, Malik SA, Baracco EE, Vacchelli E, Opolon P, Signolle N, et al: Chemical activation of SAT1 corrects diet-induced metabolic syndrome. Cell Death Differ 27: 2904-2920, 2020.

103. Vetrik M, Mattova J, Mackova H, Kucka J, Pouckova P, Kukackova O, Brus J, Eigner-Henke S, Sedlacek O, Sefc L, et al: Biopolymer strategy for the treatment of Wilson's disease. J Control Release 273: 131-138, 2018.

104. Mao L, Huang CH, Shao J, Qin L, Xu D, Shao B and Zhu BZ: An unexpected antioxidant and redox activity for the classic copper-chelating drug penicillamine. Free Radic Biol Med 147: 150-158, 2020.

105. Kenney GE and Rosenzweig AC: Chemistry and biology of the copper chelator methanobactin. ACS Chem Biol 7: 260-268, 2012.

106. Lenartowicz M, Moos T, Ogorek M, Jensen TG and Moller LB: Metal-dependent regulation of ATP7A and ATP7B in fibroblast cultures. Front Mol Neurosci 9: 68, 2016.

107. Lee K, Briehl MM, Mazar AP, Batinic-Haberle I, Reboucas JS, Glinsmann-Gibson B, Rimsza LM and Tome ME: The copper chelator ATN-224 induces peroxynitrite-dependent cell death in hematological malignancies. Free Radic Biol Med 60: 157-167, 2013.

108. Bakthavatsalam S, Sleeper ML, Dharani A, George DJ, Zhang T and Franz KJ: Leveraging γ-Glutamyl transferase to direct cytotoxicity of copper dithiocarbamates against prostate cancer cells. Angew Chem Int Ed Engl 57: 12780-12784, 2018.

109. Wei C and Fu Q: Cell death mediated by nanotechnology via the cuproptosis pathway: A novel horizon for cancer therapy. VIEW-CHINA 4: 20230001, 2023.

110. Xie W, Zhang Y, Xu Q, Zhong G, Lin J, He H, Du Q, Tan H, Chen M, Wu Z, et al: A Unique approach: biomimetic graphdiyne-based nanoplatform to treat prostate cancer by combining cuproptosis and enhanced chemodynamic therapy. Int J Nanomedicine 19: 3957-3972, 2024.

111. Wang Y, Yang QW, Yang Q, Zhou T, Shi MF, Sun CX, Gao XX, Cheng YQ, Cui XG and Sun YH: Cuprous oxide nanoparticles inhibit prostate cancer by attenuating the stemness of cancer cells via inhibition of the Wnt signaling pathway. Int J Nanomedicine 12: 2569-2579, 2017.

112. Chen W, Yang W, Chen P, Huang Y and Li F: Disulfiram copper nanoparticles prepared with a stabilized metal ion ligand complex method for treating drug-resistant prostate cancers. ACS Appl Mater Interfaces 10: 41118-41128, 2018.

113. Wang Y, Zeng S, Lin TM, Krugner-Higby L, Lyman D, Steffen D and Xiong MP: Evaluating the anticancer properties of liposomal copper in a nude xenograft mouse model of human prostate cancer: Formulation, in vitro, in vivo, histology and tissue distribution studies. Pharm Res 31: 3106-3119, 2014.

114. Zhao Y, Wang R, Hu C, Wang Y, Li Z, Yin D and Tan S: Complanatoside A disrupts copper homeostasis and induces cuproptosis via directly targeting ATOX1 in prostate cancer. Toxicol Appl Pharmacol 496: 117257, 2025.

115. Zhou G, Chen C, Wu H, Lin J, Liu H, Tao Y and Huang B: LncRNA AP000842.3 triggers the malignant progression of prostate cancer by regulating cuproptosis related gene NFAT5. Technol Cancer Res Treat 23: 15330338241255585, 2024.

116. Farhan M: Cytotoxic activity of the red grape polyphenol resveratrol against human prostate cancer cells: A molecular mechanism mediated by mobilization of nuclear copper and generation of reactive oxygen species. Life (Basel) 14: 611, 2024.

117. Wang X, Chen X, Xu C, Zhou W and Wu D: Identification of cuproptosis-related genes for predicting the development of prostate cancer. Open Med (Wars) 18: 20230717, 2023.

118. Cheng B, Tang C, Xie J, Zhou Q, Luo T, Wang Q and Huang H: Cuproptosis illustrates tumor micro-environment features and predicts prostate cancer therapeutic sensitivity and prognosis. Life Sci 325: 121659, 2023.

119. Jin L, Mei W, Liu X, Sun X, Xin S, Zhou Z, Zhang J, Zhang B, Chen P, Cai M and Ye L: Identification of cuproptosis-related subtypes, the development of a prognosis model, and characterization of tumor microenvironment infiltration in prostate cancer. Front Immunol 13: 974034, 2022.

120. Wang H, Xie M, Zhao Y and Zhang Y: Establishment of a prognostic risk model for prostate cancer based on Gleason grading and cuprotosis related genes. J Cancer Res Clin Oncol 150: 376, 2024.

121. Yao K, Zhang R, Li L, Liu M, Feng S, Yan H, Zhang Z and Xie D: The signature of cuproptosis-related immune genes predicts the tumor microenvironment and prognosis of prostate adenocarcinoma. Front Immunol 14: 1181370, 2023.

122. Zhang J, Jiang S, Gu D, Zhang W, Shen X, Qu M, Yang C, Wang Y and Gao X: Identification of novel molecular subtypes and a signature to predict prognosis and therapeutic response based on cuproptosis-related genes in prostate cancer. Front Oncol 13: 1162653, 2023.

123. Ma S, Xu M, Zhang J, Li T, Zhou Q, Xi Z, Wang Z, Wang J and Ge Y: Analysis and functional validations of multiple cell death patterns for prognosis in prostate cancer. Int Immunopharmacol 143 (Pt 1): 113216, 2024.

124. Cheng X, Zeng Z, Yang H, Chen Y, Liu Y, Zhou X, Zhang C and Wang G: Novel cuproptosis-related long non-coding RNA signature to predict prognosis in prostate carcinoma. BMC Cancer 23: 105, 2023.

125. Ma Z, Liang H, Cui R, Ji J, Liu H, Liu X, Shen P, Wang H, Wang X, Song Z and Jiang Y: Construction of a risk model and prediction of prognosis and immunotherapy based on cuproptosis-related LncRNAs in the urinary system pan-cancer. Eur J Med Res 28: 198, 2023.

126. Jiang S, Li Z, Dou R, Lin Z, Zhang J, Zhang W, Chen Z, Shen X, Ji J, Qu M, et al: Construction and validation of a novel cuproptosis-related long noncoding RNA signature for predicting the outcome of prostate cancer. Front Genet 13: 976850, 2022.

127. Zhong H, Lai Y, Ouyang W, Yu Y, Wu Y, He X, Zeng L, Qiu X, Chen P, Li L, *et al*: Integrative analysis of cuproptosis-related lncRNAs: Unveiling prognostic significance, immune microenvironment, and copper-induced mechanisms in prostate cancer. Cancer Pathog Ther 3: 48-59, 2024.
128. Ren L, Yang X, Wang W, Lin H, Huang G, Liu Z, Pan J and Mao X: A cuproptosis-related LncRNA signature: Integrated analysis associated with biochemical recurrence and immune landscape in prostate cancer. Front Genet 14: 1096783, 2023.
129. Yu Z, Deng H, Chao H, Song Z and Zeng T: Construction of a cuproptosis-related lncRNA signature to predict biochemical recurrence of prostate cancer. Oncol Lett 28: 526, 2024.
130. Lu Y, Wu J, Li X, Leng Q, Tan J, Huang H, Zhong R, Chen Z and Zhang Y: Cuproptosis-related lncRNAs emerge as a novel signature for predicting prognosis in prostate carcinoma and functional experimental validation. Front Immunol 15: 1471198, 2024.
131. Nyvltova E, Dietz JV, Seravalli J, Khalimonchuk O and Barrientos A: Coordination of metal center biogenesis in human cytochrome c oxidase. Nat Commun 13: 3615, 2022.
132. Xue Q, Kang R, Klionsky DJ, Tang D, Liu J and Chen X: Copper metabolism in cell death and autophagy. Autophagy 19: 2175-2195, 2023.
133. Abramson J, Adler J, Dunger J, Evans R, Green T, Pritzel A, Ronneberger O, Willmore L, Ballard AJ, Bambrick J, *et al*: Accurate structure prediction of biomolecular interactions with AlphaFold 3. Nature 630: 493-500, 2024.