Harnessing copper: Innovative approaches to combat neurodegenerative diseases and cancer (Review)

TAO DUAN[1*], HANHAI MAO[1*], XINGYUE JIANG[1], YING TIAN[2], JIDONG ZHANG[3] and JUN TAN[1]

[1]Department of Histology and Embryology, Zunyi Medical University, Zunyi, Guizhou 563000, P.R. China; [2]Morphology Laboratory, Zunyi Medical University, Zunyi, Guizhou 563000, P.R. China; [3]Department of Immunology, Zunyi Medical University, Zunyi, Guizhou 563000, P.R. China

Received May 29, 2025; Accepted October 3, 2025

DOI: 10.3892/ijmm.2025.5678

Abstract. Copper is an important trace element in the human body and plays an essential role in cells, where it is involved in synthesizing copper-dependent enzymes, including superoxide dismutase, cytochrome c oxidase, tyrosinase, lysyl oxidase, dopamine-β-hydroxylase and other related copper-containing enzymes. Copper overload or deficiency affects cell activity, leading to the development of neurodegenerative diseases or cancer. Neurodegenerative diseases, including Alzheimer's, Parkinson's and Huntington's disease, as well as cancer, represent significant chronic health burdens. The complexity of their pathophysiological mechanisms, coupled with the limitations of current targeted therapies, complicates the development of effective treatments. This review provides a comprehensive overview of the current understanding of copper's regulatory mechanisms in health and disease, with particular emphasis on its roles in neurodegenerative disorders and cancer. Recent advances in copper-targeted therapeutic strategies, including copper chelators, ionophores and copper-based nanoparticles, were highlighted. Furthermore, the clinical potential, key challenges and future prospects of these interventions were assessed. By synthesizing recent preclinical and clinical evidence, this review aims to contribute novel perspectives for improving the treatment of copper-associated diseases.

Correspondence to: Dr Jun Tan, Department of Histology and Embryology, Zunyi Medical University, 6 Xuefu West Road, Xinpu New District, Zunyi, Guizhou 563000, P.R. China
E-mail: juntan_zmu@126.com

Professor Jidong Zhang, Department of Immunology, Zunyi Medical University, 6 Xuefu West Road, Xinpu New District, Zunyi, Guizhou 563000, P.R. China
E-mail: jidongzhang@zmu.edu.cn

*Contributed equally

Key words: copper, neurodegenerative diseases, cancer, therapeutic approach, copper-targeting approaches, cognitive dysfunction

Contents

1. Introduction

Copper is an essential trace element and the recommended daily intake for adults ranges from 0.8 to 2.4 mg per day (1). Copper is required for almost all the functions of tissues and organs, in particular for oxidative phosphorylation in the heart and brain, scavenging of free radicals (2), angiogenesis (3), bone formation and regeneration (4,5), modulation of bone strength (6,7) and the regulation of rest-activity cycles (8) (Fig. 1). Copper also participates in the synthesis of copper-dependent enzymes, including superoxide dismutase (SOD) (9), cytochrome c oxidase (10), tyrosinase (11), lysyl oxidase and dopamine (DA) β-hydroxylase (12,13). Copper enzymes play a crucial role in key physiological processes such as energy metabolism, antioxidant defense and neurotransmitter synthesis. Their dysfunction directly leads to a variety of genetic and acquired diseases (14,15) (Table I).

Copper homeostasis regulation can be classified into three processes: Absorption, utilization/storage and excretion. Disruptions in copper homeostasis can result in impaired physiological functions and the onset of various related diseases (Fig. 1). In response to these challenges, researchers have developed a range of copper-targeted therapeutic strategies designed to manage such conditions. These interventions specifically address pathological states caused by copper deficiency, copper overload or disturbances in copper metabolism, and they exert their effects by modulating copper concentration, distribution or biological activity within the body. These therapeutic approaches show significant potential in the treatment of hereditary copper metabolism disorders, neurodegenerative diseases and cancers. This article provides a

comprehensive and timely review of the dual role of copper in human biology, with a particular emphasis on its implications for health, neurodegenerative diseases and cancer. This review provides a theoretical foundation and offers diverse perspectives for the development of treatments for related diseases.

2. Maintenance of copper homeostasis

Absorption and transport of copper. Copper absorption primarily occurs in the small intestine, particularly in the duodenum, which serves as the key site for this process (16). In dietary sources, copper is predominantly present as Cu(II). The six-transmembrane epithelial antigen of the prostate proteins (17), localized on the apical membrane of small intestinal epithelial cells, possess reductase activity that facilitates the reduction of Cu(II) to Cu(I). Subsequently, Cu(I) is taken up by the copper transporter 1 (CTR1), also known as solute carrier family 31 member 1 (SLC31A1) (18,19), which is expressed on the intestinal epithelial membrane. Once Cu(I) enters the enterocytes, it is transported into the bloodstream through vesicular transport mediated by ATPase copper transporting α (ATP7A) (Fig. 2). In the bloodstream, copper binds to various proteins, including human serum albumin (20), ceruloplasmin (21), albumin, α-2-macroglobulin (22), histidine and transcupreins. These complexes either support copper's physiological functions through the systemic circulation or enable its uptake and storage by the liver (23-25).

The high-affinity copper transporter protein CTR1 facilitates the transfer of extracellular Cu(I) into the cell (26). In mice, intestinal-specific knockout of CTR1 resulted in severe growth and developmental defects, leading to embryonic lethality by mid-gestation. These findings indicate that CTR1-mediated copper uptake is essential for mammalian copper homeostasis and embryonic development (27). Additionally, CTR1 gene expression is regulated by changes in specificity protein 1 (Sp1) activity and extracellular copper concentrations (28,29). Specifically, the human high-affinity copper transporter hCTR1 is transcriptionally upregulated during copper deficiency and downregulated under copper-replete conditions. Elevated hCTR1 levels also suppress its own expression. Notably, Sp1 modulates hCTR1 expression under copper stress (30).

Copper utilization and storage in cells. Once inside the cell, copper rapidly binds to co-chaperone proteins such as antioxidant 1 copper chaperone (Atox1), copper chaperone for SOD (CCS) and cytochrome c oxidase copper chaperone COX17 (COX17). This interaction is essential for the safe and targeted delivery of copper to its specific functional sites, thereby supporting and maintaining critical cellular processes (29).

Atox1 functions as a key cytoplasmic copper chaperone, directly binding Cu(I) and mediating its delivery to the copper-transporting ATPases ATP7A and ATP7B located on the Golgi membrane (Fig. 2). This process is essential for the systemic distribution of copper ions and the maintenance of copper homeostasis (31,32). Importantly, research by Lutsenko has revealed that Atox1 promotes the synthesis of ceruloplasmin, a protein critical for iron metabolism, as well as tyrosinases (33).

The CCS is localized in compartments such as the cytoplasm and the mitochondrial intermembrane space (34), binds copper and activates SOD1 (Cu/Zn SOD), a copper/zinc-dependent enzyme. In eukaryotes, SOD is expressed as SOD1 in the cytoplasm and extracellularly, and as Mn-SOD2 in the mitochondria. The SOD enzymes catalyze the disproportionation of superoxide ($O_2^{\bullet-}$) to produce hydrogen peroxide (H_2O_2), and the balance between copper and reactive oxygen species (ROS) is physiologically crucial (35,36). Furthermore, CCS expression is strongly negatively correlated with copper levels, serving as a feedback regulatory mechanism to prevent excessive activation of SOD1 under conditions of copper overload (37).

The COX is associated with oxidative phosphorylation in mitochondria, and its function is mainly mediated by five proteins: COX17, synthesis of cytochrome C oxidase 1 (SCO1), SCO2, cytochrome c oxidase assembly factor 6 (COA6) and COX11, each of which is essential. COX17 transfers copper ions from the cytoplasm to the mitochondrial intermembrane space (38), and then, through the formation of a disulfide bond, transfers them to SCO1 (39). Copper is transported primarily through the action of COA6 with SCO2 in the maintenance of redox homeostasis within mitochondria or through COX11 (40).

In addition to these chaperones, copper can be transported into the mitochondria by the mitochondrial phosphate transporter SLC25A3 (41). Another key component is the intracellular copper storage proteins metallothionein 1 (MT1) and MT2, which have a high affinity for copper (40), while copper, as a catalyst for the Fenton reaction, is also capable of binding to glutathione (GSH) (42). These proteins are essential for the effective utilization of copper and the synthesis of key copper enzymes, including SOD, cytochrome c oxidase, tyrosinase, lysyl oxidase, DA β-hydroxylase, ATPase copper-transporting α (ATP7A) and ATP7B to maintain normal cellular functions (40).

Regulation by intracellular copper levels. The regulation of copper homeostasis is fundamentally dependent on the copper-transporting ATPases ATP7A and ATP7B. In response to elevated intracellular copper [Cu(I)] levels, ATP7A and ATP7B translocate from the trans-Golgi network (TGN) to vesicles that subsequently fuse with the plasma membrane, thereby facilitating the efflux of Cu(I) from the cell. Conversely, when intracellular Cu(I) levels are reduced, these ATPases are retained within the TGN, where they actively transport Cu(I) into the TGN lumen to support the maturation of copper-dependent proteins. Once physiological Cu(I) levels are restored, ATP7A and ATP7B are recycled back to the TGN, re-establishing their basal localization and maintaining responsiveness to fluctuations in cellular copper concentrations (43). ATP7A can mediate copper transport across polarized cellular barriers, such as the blood-brain barrier (BBB) and the blood-placenta barrier, thereby enabling copper export and ensuring that the fetus receives adequate copper during development. ATP7B, predominantly expressed in the liver, becomes active under conditions of elevated hepatic copper concentrations (33). In hepatic cells, ATP7B plays a crucial role in the regulation of copper homeostasis by mediating the transport of excess copper into bile, leading to its excretion via feces, a process essential for maintaining the systemic copper balance (44). This protein facilitates copper

Table I. Enzymes and mechanisms of action related to copper.

Copper-related enzymes	Mechanism of action	Related diseases	(Refs.)
Cytochrome c oxidase	Catalyzes electron transfer to generate ATP in the mitochondrial respiratory chain	Infantile mitochondrial myopathy	(10)
Lysyl oxidase	Collagen cross-linking enzyme	Ehlers-Danlos syndrome	(12)
Dopamine β-hydroxylase	Converts dopamine to norepinephrine	DBH deficiency	(13)
ATP7A	Mediates copper transport across cellular membranes	Menkes disease	(14)
ATP7B	Mediates copper transport across cellular membranes	Wilson's disease	(15)
SOD1	Specific mutations in SOD1 lead to familial ALS (associated with the loss of dismutase function and/or an increase in toxic aggregation)	Familial ALS	(9)
Tyrosinase	Melanin synthesis	Albinism, vitiligo, melanoma	(11)

ALS, amyotrophic lateral sclerosis; SOD, superoxide dismutase; ATP7a, ATPase copper transporting α; DBH, dopamine β-hydroxylase.

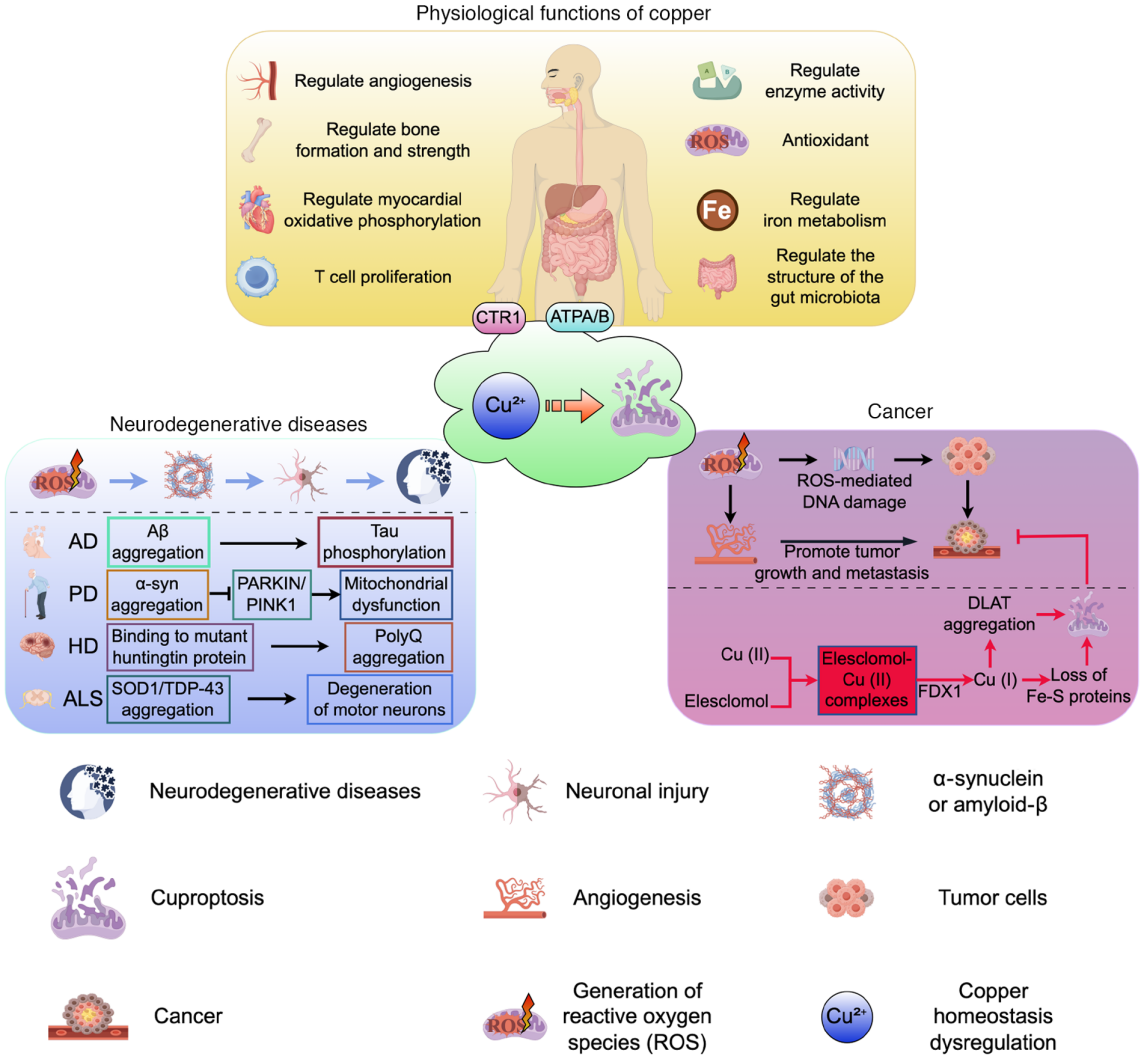

Figure 1. Schematic overview of copper homeostasis: Physiological functions and pathological implications in neurodegenerative diseases and cancer. Copper plays a critical role in maintaining normal physiological functions by supporting essential cellular processes such as oxidative phosphorylation and the biosynthesis of copper-dependent enzymes. Cellular copper homeostasis is tightly regulated through transporters, including CTR1 and ATP7A/B. Dysregulation of copper homeostasis has been implicated in the pathogenesis of neurodegenerative disorders, where it promotes the aggregation of pathogenic proteins and contributes to cancer progression by enhancing tumor cell proliferation and angiogenesis. Notably, cuproptosis, an emerging form of regulated cell death driven by copper and mediated by mitochondrial proteins FDX1 and DLAT, has emerged as a promising therapeutic target in oncology. Conversely, restoration of copper homeostasis via copper chelators or ionophores represents a potential treatment strategy for neurodegenerative diseases. AD, Alzheimer's disease; PD, Parkinson's disease; HD, Huntington's disease; ALS, amyotrophic lateral sclerosis; FDX1, ferredoxin 1; DLAT, dihydrolipoyl transacetylase; SOD1, superoxide dismutase 1; TDP-43, TAR DNA-binding protein 43; CTR1, copper transporter 1; ATP7A, ATPase copper-transporting α.

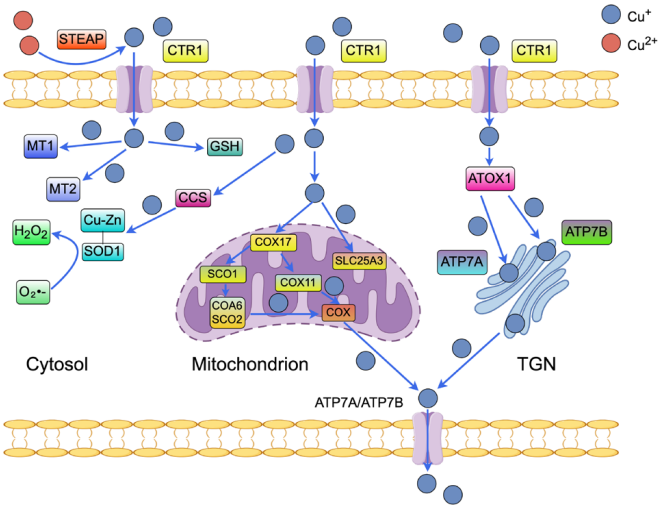

Figure 2. The intracellular transport pathway of copper. STEAP, Six-transmembrane epithelial antigen of the prostate; GSH, glutathione; CCS, copper chaperone for superoxide dismutase; MT1, metallothionein-1; CTR1, copper transporter 1; ATOX1, antioxidant protein 1; ATP7A, ATPase copper-transporting α; TGN, trans-Golgi network; COA6, cytochrome c oxidase assembly factor 6; SCO1, synthesis of cytochrome c oxidase 1; COX11, cytochrome c oxidase assembly protein 11; SLC25A3, solute carrier family 25 member 3.

elimination via bile secretion or through binding to soluble proteins for delivery to specific tissues and organs (45).

3. Impact of copper on health

Copper deficiency. Copper deficiency is associated with impaired immune function and reduced T-cell proliferation, which leads to decreased production of interleukin-2 (IL-2). The capacity of immune cells to generate superoxide anions and eliminate bacteria is diminished in mild copper deficiency, and the number of neutrophils in the peripheral blood is reduced in severe copper deficiency (46,47). Menkes syndrome (MD) is an X-linked recessive disorder caused by mutations in ATP7A and is characterized by systemic copper deficiency, primarily due to impaired intestinal copper uptake, progressive neurodegeneration, connective tissue disorders, and brittle, kinky hair (48). Infants with severe MD often do not survive beyond the third year of life, with neurological deficits, matted hair, developmental delays, genitourinary abnormalities, skin abnormalities, vascular abnormalities, skeletal abnormalities and spasticity of the limbs that transform into muscle weakness of the limbs along with other abnormal signs. Most patients die within the third year of life from cerebral hemorrhage due to vascular fragility or infection-related complications (49). This indicates that copper plays a crucial role in infant development: Copper imbalance driven by ATP7A mutations leads to extensive multi-organ dysfunction in MD, which is manifested as multi-system abnormalities and fatal outcomes in infants. Another disorder caused by mutations in ATP7A leading to copper deficiency is occipital horn syndrome (OHS), which is a phenotype of MD but with milder symptoms than those of MD (50). Bone exostoses, radial head dislocations, keloid-like skin lesions and dental abnormalities are specific to OHS, which can also present with developmental delay and mild neurological symptoms (14). An early study indicated that the ATP7A transcript lacking exon 10 encodes a partially functional protein, and this residual function is associated with a milder form of occipital horn syndrome (OHS), which is caused by mutations at the ATP7A splicing site. Unlike the loss-of-function mutations observed in classical Menkes disease (MD), OHS is characterized by relatively mild clinical symptoms (50). In 2022, Batzios *et al* (51) identified a genetic disorder of brain copper metabolism caused by CTR1 deficiency, which presents with hypotonia, global developmental delay, seizures and rapid cerebral atrophy. Brain CTR1, ATP7A and ATP7B protein levels may be affected by factors other than gene expression, such as the rate of copper transport mediated by these proteins. The key to treating MD is supplementation with additional copper (52-54), which is not replenished orally because of impaired intestinal absorption caused by ATP7A deficiency. The most widely used treatment is parenteral or subcutaneous supplementation with copper histidine (55,56).

Copper overload. Copper overload disrupts the expression and function of antioxidant enzymes and induces oxidative stress, while oxidative stress and increased ROS levels are thought to be the main cause of Cu-induced cytotoxicity (57,58). When copper is overloaded, hydrogen peroxide can be converted into highly reactive hydroxyl radicals, which can cause DNA and membrane damage (59,60). Excessive copper intake has also been linked to alterations in the gut microbiota, which in turn can lead to a range of conditions such as polycystic ovary syndrome (61). Studies have shown that increased intracellular Cu activates autophagy through unc-51 like autophagy activating kinase 1 (ULK1)/ULK2 signaling, thereby promoting cancer cell growth and survival (62,63). Wilson disease (WD) is an autosomal recessive disorder caused by mutations in ATP7B that is primarily due to ATP7B mutations that result in impaired copper excretion from hepatocytes into bile, a significant increase in copper levels in hepatocytes and subsequent liver injury; excess copper is released into the circulation, where it is deposited in areas such as the brain or the eyeballs, causing damage. WD is clinically heterogeneous and may present with neurological dysfunction, acute liver failure and the presence of hemolysis, rhabdomyolysis, renal tubular injury, leukopenia and thrombocytopenia (64-66). Long-term management of WD includes chelating agents such as tetrathiomolybdate (TM) (67), trientine or d-penicillamine (68-70), as well as zinc salts to reduce copper absorption (40,71,72).

4. Neurodegenerative diseases

Alzheimer's disease (AD). AD is a neurodegenerative disorder characterized by the presence of β-amyloid (Aβ) plaques and tau protein tangles in the brain (Fig. 3A). Initially, these pathological features were regarded as the primary pathogenic drivers of AD, prompting a focus on therapeutic strategies aimed at reducing the accumulation of Aβ or tau proteins (73,74). However, drug development targeting these proteins has faced substantial challenges: >30 Phase III clinical trials have shown that Aβ inhibitors do not significantly improve cognitive function in patients with AD, and some interventions have even

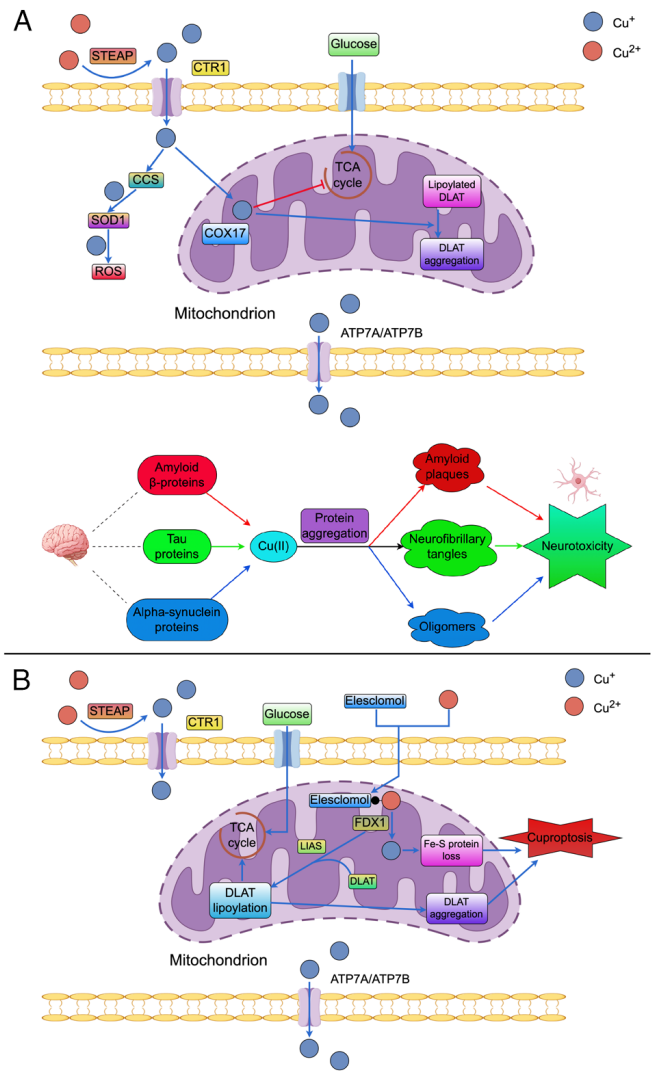

Figure 3. Copper ions contribute to the pathogenesis of neurodegenerative diseases and induce cuproptosis. (A) Copper ions contribute to neurodegenerative diseases: Dysregulation of copper ion metabolism leads to the misfolding of SOD1, resulting in the loss of its normal antioxidant function and promoting the generation of ROS. This disrupts the balance of intracellular ROS levels, triggering oxidative stress. Concurrently, copper ions inhibit the TCA cycle, impairing cellular energy metabolism by both increasing ROS production and reducing its clearance. This exacerbates oxidative stress, ultimately accelerating neuronal degeneration. In patients with neurodegenerative diseases, copper ions bind to amyloid β-protein, Tau protein and α-synuclein, promoting the formation of neurotoxic oligomers. The abnormal interaction between copper ions and amyloid β-protein induces protein aggregation, leading to the formation of oligomers, protofibrils and amyloid plaques. These aggregated species are neurotoxic and can disrupt synaptic connections, interfere with neuronal signaling, and impair cognitive and memory functions. Copper ions also bind to Tau proteins, facilitating the formation of neurofibrillary tangles. Furthermore, copper ions alter the conformation and aggregation state of α-synuclein, further contributing to the accumulation of neurotoxic oligomers. (B) Copper ions induce cuproptosis: Elesclomol forms a complex with extracellular Cu(II), known as the elesclomol-Cu(II) complex, which facilitates the transport of copper ions into mitochondria. Within the mitochondria, FDX1 reduces Cu(II) to Cu(I). On one hand, Cu(I) induces the loss of Fe-S proteins, thereby triggering cuproptosis. On the other hand, FDX1 and LIAS mediate the lipoylation of DLAT, and Cu(I) promotes DLAT aggregation, which also leads to cuproptosis. STEAP, six-transmembrane epithelial antigen of the prostate; CCS, copper chaperone for superoxide dismutase; Fe-S, iron-sulfur; CTR1, copper transporter 1; COX17, cytochrome c oxidase assembly protein 17; FDX1, ferredoxin 1; TCA, tricarboxylic acid; SOD1, superoxide dismutase 1; ROS, reactive oxygen species; DLAT, dihydrolipoyl transacetylase; LIAS, lipoic acid synthase.

led to adverse effects following plaque removal (75-77). This research and development predicament not only highlights the limitations of traditional target therapy but also prompts researchers to re-examine and explore the pathogenesis of AD.

While the precise molecular mechanisms underlying AD remain elusive, accumulating evidence suggests that dysregulation of brain metal ions, particularly copper and zinc, may contribute to the hallmark Aβ neuropathology associated with the disease (78,79). Transition metals such as copper, iron and zinc are essential for normal physiological functions; however, copper has been specifically implicated in promoting Aβ aggregation and the formation of harmful species. Notably, individuals with AD exhibit reduced copper levels in brain tissue, yet elevated concentrations in serum and age-related pigments (80-82). Copper's role in promoting Aβ precipitation and generating redox-active species warrants further investigation. Serum levels of both free and total copper are significantly elevated in individuals with AD, and increased copper deposition is observed in the age-related pigments of these patients (82,83). Following the observation that copper promotes Aβ precipitation under acidic conditions, the interactions between copper and Aβ have been increasingly explored in detail (84-86). Critically, copper can form complexes with Aβ that drive redox reactions, involving lipids to induce oxidative stress, ultimately leading to cellular apoptosis and contributing to cognitive decline (87-89).

Research on the treatment of AD with copper. In early animal studies, inhibition of CTR1 in *Drosophila* was found to improve AD-like symptoms caused by Aβ42 (90). In the preventive paradigm of the Tg2576 mouse model of AD, TM treatment reduced brain copper levels and lowered Aβ concentrations (91,92). Excessive circulating copper may impair brain function in wild-type mice and worsen neurodegenerative changes in AD mouse models (93,94). Another study demonstrated that long-term oral exposure to very high levels of copper or zinc resulted in only minimal alterations in brain metal homeostasis. Specifically, in transgenic APP-C100 mice (engineered to express a mutant form of the human amyloid precursor protein without the typical Aβ deposition characteristic of AD), high-level metal exposure does not induce Aβ protein formation (95). These findings suggest that modulating copper transport or levels - such as through CTR1 inhibition and the use of copper regulators - may alleviate Aβ-related AD pathology. However, excessive copper exposure can worsen the condition, and therapeutic efficacy may depend on the presence of Aβ deposition, as copper shows little effect in models without amyloid deposits. In the brain, high extracellular copper levels promote amyloid formation, and low intracellular copper levels also lead to amyloid formation (96-98), suggesting that the symptoms of AD are complex and difficult to treat with copper chelators or copper ion carriers alone (99,100). Therefore, enhancing copper transport to the brain to increase its bioavailability has become a key strategy for the treatment of AD (101), for instance, with quinolones (clioquinol and PBT2) or bis(thiosemicarbazones) (BTSCs) (102-104). BTSCs restore cognitive function by increasing copper bioavailability and inhibiting the formation of neurotoxic Aβ trimers and phosphorylated Tau (105), whereas clioquinol and PBT2 act as Zn^{2+}-Cu^{2+} ion carriers (106,107), regulating the intracellular concentration and distribution of zinc and copper ions, leading

to the reduction of Aβ along with high intracellular levels of copper and zinc (73,108). The mechanism of action of PBT2 has also been investigated, but the results of the clinical trials (no. ACTRN12611001008910) for AD therapy have not been satisfactory, as Pittsburgh compound-B standardized uptake value ratios in the placebo group exhibited a surprising decline, obscuring statistically significant differences compared to the treatment group and even showing a more pronounced reduction. Recently, it was concluded that Aβ peptides associated with AD form a unique Cu(Aβ) complex to which PBT2 cannot effectively bind. Further study has shown that the chelator PBT2 forms a ternary Cu(II) complex with Aβ that is highly stable but has low specificity (109). This remains a major challenge in the treatment of AD with copper.

Huntington's disease (HD). HD is an inherited neurodegenerative disorder characterized by neuropsychiatric symptoms, movement disorders (most commonly choreoathetosis) and progressive cognitive impairment. HD is currently treated symptomatically and scientists have struggled to identify effective disease-modifying therapies. Metal homeostasis is disrupted during the progression of HD, although its exact role in the pathogenesis of the disease remains elusive. Meanwhile, some researchers have observed tissue abnormalities and deposition of copper (Cu) and zinc (Zn) in HD-affected brain regions, which may contribute to disease initiation and progression through mechanisms including mitochondrial dysfunction, oxidative stress and BBB dysfunction (110). It has been reported that copper-regulated genes are upregulated in HD and that copper binds to the N-terminal fragment of huntingtin, supporting the involvement of aberrant copper metabolism in HD. Copper has been shown to accelerate fibril formation of the N-terminal fragment of huntingtin *in vitro* via the expanded polyglutamine (polyQ) stretch (httExon1). Copper has also been found to enhance polyQ aggregation and toxicity in mammalian cells expressing httExon1. Studies in a yeast model of HD demonstrated that overexpression of several genes involved in copper metabolism reduced polyQ-mediated toxicity. The MT3 gene belongs to the metallothionein family and is mainly expressed in the central nervous system. It regulates zinc and copper homeostasis and acts as a neuronal growth inhibitory factor (111). Overexpression of MT3 in mammalian cells significantly reduced polyQ aggregation and toxicity (112). Animal studies have also shown that copper chelators modulate the early events of Htt misfolding and reduce neurotoxicity in the *Drosophila* HD model (90,113,114). Despite the promising therapeutic potential of MT3 in HD, its clinical translation remains limited by technical and mechanistic challenges.

Parkinson's disease (PD). PD is an age-related neurodegenerative disease, and the role of oxidative stress and mitochondrial dysfunction in the progression of PD has been widely recognized in relation to the selective loss of DA neurons in the substantia nigra pars compacta (SNpc) of the nigrostriatal DA pathway and the reduction of DA levels in the striatum (115). The normal substantia nigra contains twice as much copper as other brain regions, suggesting that copper plays an important role in this brain area (116). Autopsy brain samples from patients with PD show increased iron and decreased copper in the substantia nigra and basal ganglia (117,118).

At the cellular level, PD is associated with the overproduction of ROS. While copper may contribute to intracellular oxidative stress by participating in the Fenton and Haber-Weiss reactions or by interfering with iron homeostasis, either directly or indirectly through the formation of hydroxyl radicals, experimental evidence linking copper deficiency and the formation of SOD1 aggregates to the progression of PD is also discussed in terms of its therapeutic implications (119,120). Copper causes a decrease in SOD1 activity by interfering with SOD1 synthesis, leading to a loss of cellular protection against neuronal oxidative damage (121,122).

It is important to note that mitochondrial dysfunction represents a central mechanism driving oxidative stress in PD. Mutations in the phosphatase and tensin homolog-induced kinase 1 (PINK1) and PARKIN RBR E3 ubiquitin ligase (PARKIN) genes are associated with familial forms of the disease. Parkin and PINK1 play critical roles in mitochondrial quality control, particularly in the process of mitophagy, and are essential for the survival of dopaminergic neurons. Under normal physiological conditions, PINK1 accumulates on damaged mitochondria by sensing changes in the mitochondrial membrane potential. This accumulation promotes Parkin recruitment and activates its E3 ubiquitin ligase activity, resulting in the ubiquitination of damaged mitochondria and the initiation of autophagic degradation. This pathway limits the release of ROS and reduces mitochondrial toxicity (123,124).

Dysregulation of copper homeostasis interferes with the PARKIN/PINK1 pathway through multi-layered mechanisms (125). Excessive copper downregulates the transcription of PINK1 and PARKIN in cellular models, although the exact regulatory mechanism (e.g., involvement of NF-κB) remains to be fully elucidated. Importantly, copper can also impair the activity of PINK1 and PARKIN proteins by inducing conformational changes, specifically through binding to the kinase domain of PINK1 and the RING finger domain of PARKIN. Notably, the role of copper in regulating PINK1/PARKIN is context-dependent: It inhibits PINK1/PARKIN function under pathological conditions (e.g., copper excess), while promoting their transcriptional regulation and autophagic processes under physiological conditions (125,126). It further impairs PINK1 kinase activity and Parkin E3 ubiquitin ligase activity by coordinating with cysteine/histidine residues within their respective functional domains, the kinase domain of PINK1 and the RING finger domain of Parkin, thereby inducing conformational changes (125). These disruptions prevent Parkin recruitment to damaged mitochondria, inhibit mitochondrial substrate ubiquitination and perturb the PARKIN/PINK1-regulated balance of mitochondrial dynamics, ultimately leading to the accumulation of dysfunctional mitochondria and exacerbated oxidative stress. This cascade reflects the pathological shift in copper's regulatory role in mitophagy under homeostatic imbalance, which contrasts with its physiological role in promoting mitophagy-mediated tissue regeneration (126). However, the underlying mechanisms remain incompletely understood and require further investigation. In addition, exposure to elevated copper levels has been shown to accelerate the formation of toxic α-synuclein aggregates, a key pathological contributor to neuronal loss in PD (127).

Second, microglia-mediated neuroinflammation is an important component of the pathogenesis of PD. In animal studies, researchers have observed inflammatory changes in mouse brain tissue, including activation of microglia, loss of dopaminergic neurons and aggregation of α-syn in the substantia nigra. Copper has been shown to activate BV2 cells via the NF-κB pathway and to increase ROS levels in BV2 cells (128,129). Sustained copper accumulation in BV2 cells resulted in a decrease in mitochondrial membrane potential, a reduction in Parkin and PINK1 expression, an increase in P62 expression and light chain 3BII/I ratio, and upregulation of NLR family pyrin domain containing 3/caspase-1/gasdermin D axis proteins (130,131).

Research on the treatment of PD with copper-based compounds, such as 8-hydroxyquinoline-2-carboxaldehyde isonicotinoylhydrazine, a moderate metal-binding compound that binds to copper ions, has been shown to efficiently compete with ortho-nucleosides for Cu(I) and Cu(II) binding and to inhibit protein aggregation *in vitro* and in cells (132). Copper(II) diacetylbis(4-methylthiosemicarbazone), also known as CuII(atsm), is an orally available, biologically active BBB-penetrant compound that is widely used to selectively label hypoxic tissues in cellular imaging experiments (133). It has been shown to accumulate in the striatum of patients with PD at levels that positively correlate with disease stage (134). Furthermore, CuII(atsm) has demonstrated therapeutic potential in rescuing dopaminergic neuron loss and alleviating motor dysfunction in PD models (119,135). In addition, CuII(atsm) supplementation has been shown to significantly reduce the misfolding and deposition of wild-type SOD1 protein associated with PD in a novel mouse model, enhance DA neuron survival and improve motor function, suggesting its potential as a novel therapeutic strategy for PD treatment (136). However, further research and clinical trials are necessary to validate these findings.

Amyotrophic lateral sclerosis (ALS). ALS is a progressive neurodegenerative disease of the motor neurons that leads to the worsening of casual muscle weakness until death from respiratory failure ~3 years after onset (137). Numerous symptoms of ALS are associated with signs of copper deficiency, leading to defects in the vasculature, antioxidant system and mitochondrial oxidative respiration, but there are also signs of copper toxicity, such as increased ROS generation and protein aggregation (138).

About 2% of ALS cases have mutations in SOD1, which neutralizes harmful reactive oxygen superoxide (139). Familial ALS is at times linked to the gene encoding Cu/Zn-binding SOD. Mutations in ALS are thought to result in functional enhancement of dismutase activity (140). Mutations in human SOD1 are found in ~20% of patients with familial ALS. They are characterized by a conformational dysfunction of the electrostatic and zinc-binding elements (mutant SOD1-mediated pathogenesis of ALS). A study using transgenic mice expressing wild-type or mutant human SOD confirmed that dominant mutations in SOD and the acquisition of function are important factors in the pathogenesis of familial ALS (141).

Previous studies have shown that CuII(atsm) in ALS can restore SOD1 dysfunction caused by copper deficiency (135). Therefore, the use of Cu as a new target for treating familial progressive ALS becomes possible. However, further studies are necessary to validate these findings.

Overall, for copper-related diseases, including both the copper metabolism disorders discussed earlier and the neurodegenerative conditions addressed in this chapter, therapeutic strategies targeting copper homeostasis have been developed, with drug selection guided by the underlying disease etiology (deficiency, overload or imbalance). This establishes a clear pathophysiological and etiological foundation for clinical intervention (Table II).

5. Copper and cancer

Epidemiological context of cancer incidence. According to the most recent estimates provided by the International Agency for Research on Cancer, ~20 million new cancer cases, including non-melanoma skin cancers, and 9.7 million cancer-related deaths were reported globally in 2022. Lung cancer emerged as the most frequently diagnosed cancer, accounting for nearly 2.5 million new cases, representing approximately one in eight cancer diagnoses worldwide (12.4% of all cancers). This was followed by female breast cancer (11.6%), colorectal cancer (9.6%), prostate cancer (7.3%) and gastric cancer (4.9%). Furthermore, lung cancer was identified as the leading cause of cancer-related mortality, with an estimated 1.8 million deaths (18.7% of total cancer deaths), followed by colorectal cancer (9.3%), liver cancer (7.8%), female breast cancer (6.9%) and stomach cancer (6.8%) (142).

Abnormal accumulation or deficiency of trace elements plays a significant role in cancer pathogenesis and progression, with dysregulation of copper metabolism being particularly notable (143,144). Research suggests that there is an increased demand for copper during tumor proliferation and metastasis (40,145). Elevated serum copper levels have been reported in various cancers, including breast cancer (146,147), lung cancer (148) and prostate cancer (149). By contrast, reduced serum copper levels have been observed specifically in hepatocellular carcinoma and endometrial cancer (150,151), although the underlying mechanisms remain to be fully elucidated.

Molecular mechanisms of copper in promoting carcinogenesis. Copper can promote tumorigenesis by promoting oxidative stress that damages DNA and related molecular structures (152), and contributes to tumor development by promoting angiogenesis, metastasis and cell proliferation through multiple mechanisms: Increased intracellular copper enhances oxidative stress caused by the formation of ROS, leading to elevated intracellular ROS levels (153), DNA damage and activation of oncogenes (59), whereas reduced intracellular copper results in decreased SOD1 activity, nearly complete loss of resistance to oxidative damage and impaired maintenance of normal cellular life activities (121).

McAuslan and Reilly (154) were the first to discover that copper promotes migration of vascular endothelial cells. Narayanan *et al* (155) found that angiogenesis is inhibited after silencing CTR1 using small interfering RNAs. Furthermore, copper has been shown to regulate the secretion of vascular growth factors, including fibroblast growth factor (FGF) and IL-1α (156,157), and to modulate endothelial cell affinity by binding to angiogenic factors (158). TM-induced copper deficiency leads to reduced transcriptional activity of NF-κB and

Table II. Copper-related therapeutic agents for copper metabolism disorders and neurodegenerative diseases.

Disease	Etiology	Drugs	Mechanism of action	(Refs.)
Menkes disease	Mutations in the ATP7A gene	Copper-histidine	Supplementation of copper ions to correct copper deficiency	(52)
Wilson's disease	ATP7B deficiency and copper accumulation	Bis-choline, tetrathiomolybdate	Regulation of copper metabolism, reduction of copper accumulation and its toxicity	(53,54)
		Penicillamine, trientine	Increase of urinary excretion of copper	(70)
		Tetrathiomolybdate	Formation of a tripartite complex with copper and protein, block of intestinal copper absorption and reduction of toxic copper in blood	(67)
		D-penicillamine	Enhancement of copper excretion in urine by eliminating copper deposits	(101)
Alzheimer's disease	Aβ deposition	Clioquinol	Metal chelation reduces the aggregation of Aβ	(102)
		PBT2	Decrease of the formation of soluble Aβ aggregates	(103)
HD	CAG expansion in the HD gene	PBT2	Regulation of the homeostasis of copper/zinc ions in the brain to reduce the accumulation of mHTT	(114)

Aβ, amyloid β; HD, Huntington's disease; ATP7A, ATPase copper-transporting α; mHTT, mutant huntingtin.

suppressed expression of the angiogenic factors FGF (159), VEGF (160), IL-6, IL-8 and IL-1α (161-163); copper activates hypoxia-inducible factor (HIF)-1, and when copper is chelated, HIF-1-mediated VEGF expression is blocked (164,165).

Copper has also been found to directly bind ULK1/ULK2 and activate autophagy by Tsang *et al* (62). Cellular autophagy is inhibited when CTR1 is deficient, which can suppress oncogene-induced cancer cell proliferation; autophagosomes are reduced and tumor size is significantly decreased in mice in which CTR1 is knocked out using single-guide RNA (62). Copper promotes cancer by stimulating the MAPK pathway (166). Copper binds to MAPK kinase (MEK)1/2 and activates downstream ERK1/2 phosphorylation, thereby promoting tumor proliferation. MEK1/2 activity was inhibited in BRAFV600E-positive cancer cells, and proliferation was significantly suppressed after TM treatment, suggesting that MEK1/2 activity is highly correlated with copper levels (167,168). The epidermal growth factor receptor (EGFR), as a key upstream regulator of the MAPK pathway, is overexpressed or mutated in various cancers (including ovarian cancer), driving cell proliferation, survival and metastasis. Copper binds to and inhibits protein tyrosine phosphatase N2 (PTPN2), leading to the loss of its phosphatase activity. This inhibition relieves the suppression of EGFR dephosphorylation, thereby activating EGFR signaling. In turn, activated EGFR suppresses the transcription of CTR1 via the cAMP responsive element binding protein (CREB) signaling pathway, forming a closed-loop regulatory circuit: 'copper-PTPN2-EGFR-CREB-CTR1'. Fluctuations in intracellular copper levels can thus modulate EGFR activity through this feedback axis, highlighting a mechanistic link between copper homeostasis and EGFR signaling (169). Research by Jakhmola *et al* (147) revealed the significant role of EGFR in ovarian cancer through computational simulation methods and pointed out that the DADETL segment (including the self-phosphorylated tyrosine 992) is the key region leading to receptor overexpression. This is similar to the copper-mediated activation mechanism of the MAPK pathway, suggesting that copper may indirectly affect tumor development by regulating EGFR activity or downstream signal transduction. Future studies are necessary to deeply explore the direct association between copper and the EGFR pathway, providing new ideas for the combined application of copper-targeted therapy and EGFR inhibitors (147).

Copper also mediates the activation of programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) in cancer cells, enabling immune evasion. When copper chelators are used, phosphorylation of STAT3 and EGFR is inhibited, promoting ubiquitination-mediated degradation of PD-L1, and slowing tumor growth by increasing the number of $CD8^+$ T cells and NK cells (170,171).

Mechanisms and implications of cuproptosis for cancer therapy. It has been shown that the metabolic profile of cancer cells differs from that of normal cells in that cancer cells maintain a higher metabolic rate to support a higher proliferation rate and to resist cell death signals (172). Cell death involves proteins and lipids and includes apoptosis (173,174), necroptosis (175), pyroptosis (176) and ferroptosis (177,178). The demand for copper is high during cell growth and abnormal accumulation of excess copper within the cell leads to cellular dysfunction and ultimately cell death (179,180). Mechanisms of copper-induced toxicity

include induction of apoptosis (181-183), caspase-independent cell death pathways (184-186), induction of ROS or inhibition of the ubiquitin-proteasome system (129,187-189).

However, the mechanism underlying copper-induced cell death remained unclear until a study published in Science in 2022 by Tsvetkov *et al* (190) proposed the concept of cuproptosis - a novel form of copper-induced cell death that is distinct from other known forms of cell death (Fig. 3B). This study demonstrated that copper ionophore-induced cell death is predominantly dependent on the accumulation of intracellular copper (191,192). Notably, treatment with inhibitors targeting other established mechanisms of cell death, including ferroptotic apoptosis (ferrostatin-1), necroptosis (necrostatin-1) and oxidative stress (N-acetylcysteine), did not abolish copper ionophore-induced cytotoxicity (190). Genome-wide CRISPR/Cas9 knockdown experiments identified seven specific genes that significantly mitigated the cytotoxic effects associated with the copper ionophore elesclomol (193). Among the identified genes was ferredoxin 1 (FDX1), a reductase known for its role in reducing Cu(II) to the more toxic Cu(I) and serving as a direct target for elesclomol (194,195). Additionally, six genes encoding components of the lipoic acid pathway - specifically lipoyltransferase 1, lipoic acid synthase (LIAS) and dihydrolipoamide dehydrogenase - or targets associated with lipoylated proteins within the pyruvate dehydrogenase complex [including dihydrolipoyl transacetylase (DLAT), pyruvate dehydrogenase E1 subunit α1 (PDHA1) and PDHB] were also identified (196). Importantly, single gene knockout analyses revealed that FDX1 and LIAS were particularly effective at diminishing cytotoxicity associated with copper ion carriers. Furthermore, inhibition of complex I was found to obstruct copper-induced cell death. This finding suggests that applying an electron transport chain inhibitor can prevent the cytotoxic effects induced by copper when administered alongside elesclomol in both serum-containing and serum-free media. Under serum-free conditions, cells exhibited significant resistance to elesclomol-mediated cytotoxicity; substantial toxicity was observed only when elesclomol-Cu(II) complexes were present. This effect was inhibited by the addition of TM. Furthermore, buthionine sulfoximine has been demonstrated to sensitize cells to copper-induced cell death by inhibiting glutamate cysteine ligase, which results in a direct depletion of the endogenous copper chelator GSH. The underlying mechanism involves the role of FDX1 in promoting the lipoylation of DLAT and dihydrolipoamide S-succinyltransferase proteins (190,197). Cu(II) binds to lipoylated DLAT, facilitating the production of insoluble DLAT that promotes cell death. Conversely, the conversion of Cu(II) to the more toxic Cu(I) induces cell death and intracellular oxidative stress, leading to an increase in heat shock protein 70 expression levels (190).

P53 activity maintains the functional integrity of mitochondrial morphology and structure, and mutations or deficiencies in p53 lead to significant reductions in cytochrome c oxidase (COX) activity and respiratory metabolism (198-200). P53 also promotes the conversion of pyruvate to acetyl coenzyme A by promoting lactate dehydrogenase A to maintain high pyruvate levels and by promoting dephosphorylation to activate PDH complexes (201,202). Copper-induced cell death is also highly dependent on cellular oxidative phosphorylation, the circulating component that targets tricarboxylic acid, and cells are more susceptible to copper death when glycolysis is inhibited. Studies have shown that cells dependent on mitochondrial oxidative phosphorylation for energy are 1,000-fold more sensitive to copper ion carriers than glycolysis-dependent cells (190).

Potential of copper-targeted cancer therapy. New studies have also shown that advanced clear cell renal cell carcinoma (ccRCC) accumulates Cu and allocates it to CuCOX. Copper promotes ccRCC growth through a combination of bioenergetics, biosynthesis and redox oncogenic remodeling of body homeostasis (203).

Through bioinformatics analysis, more and more researchers are focusing on the important link between cuproptosis and the cancer process (128,204). With the discovery of cuproptosis (205-207), the interactions between copper ionophores (208,209), copper and mitochondria, and drugs that had previously been considered as potential anti-tumor therapies (71), have become increasingly clear. This has accelerated research into copper-targeting therapies, with numerous studies on copper chelators and ionophores demonstrating significant therapeutic efficacy across various cancer types (Table III).

6. Clinical translation and challenges of copper-targeting approaches

Copper-targeted therapies exhibit promising potential in the treatment of cancer and neurodegenerative diseases, while their immunomodulatory properties merit comprehensive investigation. Copper ions serve as cofactors for various enzymes and are involved in the regulation of immune cell activity and oxidative stress responses, thereby potentially affecting the functions of critical immune cells, such as dendritic cells (DCs). A copper-manganese (Cu-Mn) nanocomposite demonstrates therapeutic potential by selectively releasing Cu^{2+} in the acidic tumor microenvironment (TME). The localized accumulation of Cu^{2+} induces cuproptosis in cancer cells, promotes the release of damage-associated molecular patterns, enhances DC activation - evidenced by a 2.3-fold increase in CD80/CD86 expression - and facilitates increased infiltration of $CD8^+$ T cells (1.8-fold) in murine melanoma models, thereby augmenting anti-tumor immune responses. Utilizing the enhanced permeability and retention effect, the nanocomposite achieves intratumoral Cu^{2+} concentrations 5.2-fold higher than those attained with free chelators, without inducing off-target toxicity, as indicated by normal liver enzyme levels (210).

Importantly, DCs also play a critical role in maintaining immune tolerance and their dysfunction has been associated with the development of autoimmune disorders. In recent years, exogenously derived tolerogenic DCs (tolDCs) have emerged as a novel cell-based immunotherapy approach, designed to restore immune tolerance in patients with autoimmune disorders. For instance, Jonny *et al* (47) conducted a systematic review on the therapeutic potential of tolDCs in autoimmune diseases, including systemic lupus erythematosus, demonstrating that the induction of tolDCs *in vitro* can effectively modulate T-cell responses and promote antigen-specific

Table III. Role of copper ion carriers and copper chelators in cancer therapy.

System	Type of cancer	Drugs	Function	(Refs.)
Respiratory	Lung cancer	Disulfiram	Inhibition of proteasome (copper-dependent)	(129,189)
			Induction of cuproptosis	(191)
		Tetrathiomolybdate	Enhancement of chemosensitivity (reduce intratumoral Cu)	(162)
	Mesothelioma	Penicillamine, trientine, tetrathiomolybdate	Antiangiogenic	(163)
	Nasopharyngeal cancer	Clioquinol	Enhancement of radiosensitivity	(232)
		Disulfiram	Induction of ROS accumulation	(153)
			Triggering of ferroptosis	(153)
Digestive	Liver cancer	Elesclomol	Triggering of ferroptosis	(241)
			Induction of cuproptosis	(241)
		Trientine	Antiangiogenic	(233)
		Clioquinol	Induction of cell-cycle arrest	(180)
	Colorectal cancer	Elesclomol	Induction of Cu-dependent ferroptosis (degradation of ATP7A)	(178)
		Tetrathiomolybdate	Inhibition of cell proliferation (suppression of MAPK activation)	(166)
	Stomach cancer	Elesclomol	Induction of cuproptosis	(194)
	Pancreatic cancer	Tetrathiomolybdate	Antiangiogenic	(159)
Nervous	Glioma	Disulfiram	Inhibition of glioma stem cell self-renewal (suppression of NF-κB)	(128,129)
	Glioblastoma	Disulfiram	Inhibition of DNA repair	(152)
		Elesclomol	Induction of ROS accumulation	(195)
			Inhibition of TIC and CSC	(195)
		Penicillamine	Antiangiogenic	(165)
Reproduction	Breast cancer	Disulfiram	Block of radiation-induced breast CSC formation (inhibit proteasome)	(235)
			Inhibition of TIC and CSC	(235-237)
			Induction of cuproptosis	(205,206)
		Elesclomol	Induction of cuproptosis	(207)
		Tetrathiomolybdate	Antiangiogenic	(160)
			Enhancement of chemosensitivity (target, ATP7A)	(243)
			Modulates tumor immune microenvironment (reduction of MDSCs)	(253)
			Induction of mitochondrial toxicity	(57)
		Clioquinol	Enhancement of radiosensitivity	(104)
	Ovarian cancer	Disulfiram	Cuproptosis	(204)
	Triple negative breast cancer	Casiopeínas	Inhibition of random and chemotactic migration of MDA-MB-231 cells	(26)
	MCF-7 breast cancer cells	Triethylenetetramine	Modulation of polyamine and energy metabolism and inhibition of cancer-cell proliferation	(145)
	JEG-3 choriocarcinoma cells	Triethylenetetramine	Modulation of polyamine and energy metabolism and inhibition of cancer-cell proliferation	(145)
	Prostate cancer	Clioquinol	Inhibition of the proteasome	(106,107)
	DU145 prostate cancer cells	Triethylenetetramine	Modulation of polyamine and energy metabolism and inhibition of cancer-cell proliferation	(145)
	Bladder cancer	Elesclomol	Induction of cuproptosis	(193)
Blood	Leukaemia	Disulfiram	Induction of ROS accumulation	(58)

Table III. Continued.

System	Type of cancer	Drugs	Function	(Refs.)
Other sites	Thyroid cancer	Tetrathiomolybdate	Inhibition of the expression of MEK1/2 and reduction of the metastasis and growth of BRAFV600E-positive PTC	(171)
	Neuroendocrine tumours	Disulfiram	Induction of cuproptosis	(192)

ROS, reactive oxygen species; CSC, cancer stem cell; PTC, papillary thyroid carcinoma; ATP7A, ATPase copper-transporting α; TIC, tumor-initiating cell.

immune tolerance. This approach aligns with the objectives of copper-regulating therapies (47).

Recent reviews have highlighted the importance of metabolic complications in cancer (211-213), such as hypercalcemia, which affect a significant proportion of patients with advanced malignancies and contribute to morbidity and treatment challenges. While hypercalcemia involves dysregulation of calcium homeostasis often mediated by parathyroid hormone-related protein and osteoclast activation, it shares with copper dysregulation a common theme of metal ion imbalance in cancer pathophysiology. Understanding these parallel mechanisms may provide synergistic insights into targeting ion homeostasis as a therapeutic strategy. For instance, just as bisphosphonates and denosumab are used to manage cancer-related hypercalcemia by inhibiting bone resorption (143), copper-chelation and ionophore-based therapies are being explored to modulate copper levels and induce selective cancer cell death (214,215). This complementary approach underscores the broader potential of metal-targeting therapies in oncology.

Among metal elements that perform essential biological functions, such as iron, zinc, and copper, copper demonstrates distinct advantages due to its unique chemical properties. Copper, iron and zinc fulfil distinct roles in cellular redox processes. The Cu^{+}/Cu^{2+} redox couple functions at a high reduction potential, facilitating efficient catalytic activity in essential enzymatic reactions such as cytochrome c oxidase-mediated mitochondrial respiration and SOD-dependent antioxidant defence. Unlike iron - which can induce non-specific oxidative damage through Fenton reactions - or zinc, which contributes to structural and catalytic stability without participating in redox cycling, copper supports tightly regulated electron transfer and dynamic, chaperone-mediated signaling processes via proteins such as Atox1. These unique properties position copper as a specialized redox messenger capable of mediating compartmentalized signaling pathways that are inaccessible to iron or zinc (216,217).

Research status of copper adjustment therapy. Copper-based targeted therapeutic strategies, including chelators, ionophores, and copper nanoparticles (CuNPs) (218,219), have made notable progress in clinical translational research (Table IV). Chelators primarily correct copper metabolic imbalances by sequestering excess copper ions (189), ionophores exploit copper-dependent pathological processes by facilitating the transport of copper ions across biological membranes (220) and CuNPs integrate the biological activity of controlled copper ion release with the targeted delivery capabilities of nanocarriers, thereby expanding their application scenarios in precision therapy (221).

Copper chelators. TM is a primary copper chelator under investigation for its role in copper-induced cell death. Preclinical studies indicate that TM exerts antitumor effects by inhibiting angiogenesis and directly suppressing tumor cell proliferation (222-224). Mechanistically, copper depletion - achieved either through TM treatment or knockdown of the copper transporter SLC31A1 - inhibits the progression of oral squamous cell carcinoma (OSCC) by selectively targeting cancer stem-like cells and reducing the stability of the histone methyltransferase EZH2. This identifies a novel 'copper-dependent proliferation' pathway that is essential for tumor growth. Notably, a recent clinical study evaluating TM combined with anti-PD-1 therapy in patients with locally advanced OSCC reported an objective response rate (ORR) of 57.8% and a 12-month overall survival (OS) rate of 80.0%, highlighting its potential to overcome immunotherapy resistance (225).

Beyond cuproptosis, copper also modulates ferroptosis. In pancreatic cancer models, copper promotes ferroptosis by inducing Tax1 binding protein 1-mediated autophagic degradation of GSH peroxidase 4 (GPX4). By contrast, copper chelators such as TM protect against ferroptosis-related tissue damage (e.g., in acute pancreatitis) by promoting GPX4 ubiquitination and aggregation through direct binding to cysteine residues (C107/C148) (226). Consistent with these findings, the chelator bathocuproine sulfonic acid enhances ferroptosis via copper depletion-mediated mitochondrial dysfunction and impairment of antioxidant defense (227).

Given copper's involvement in fibrosis and angiogenesis, TM has also been evaluated in related pathological conditions. In a bleomycin-induced pulmonary fibrosis model, TM downregulated VEGF expression and improved lung function (228). Its anti-inflammatory effects, mediated by the inhibition of copper-dependent cytokines, may further contribute to its antitumor efficacy by reducing the infiltration of pro-angiogenic immune cells (229). Additionally, NRF2 activation suppresses angiogenesis by inducing autophagy in vascular endothelial cells, thereby disrupting the energy supply to cancer cells (230).

The therapeutic potential of copper chelation extends beyond oncology. In patients with WD with reproductive dysfunction, engineered extracellular vesicles delivering a copper-chelating ligand significantly reduced

Table IV. Comparison of different copper-targeting strategies in terms of efficacy, safety and disease relevance.

Category	Representative drugs	Core mechanism	Features	Adverse reactions	Indications	(Refs.)
Copper chelators	D-penicillamine, trientine	Specific binding to free/excessive copper ions in the body, reduction of copper load and promotion of its excretion.	High copper affinity and selectivity. They are mainly taken orally and are suitable for regulating copper throughout the body.	Neurotoxic reactions, hematological toxicity, immune-related adverse reactions.	Indicated for copper metabolic disorders: Wilson's disease.	(99,100)
Copper ionophores	Elesclomol, disulfiram	Penetration of the biological membrane barrier and regulation of the distribution and concentration of copper ions inside and outside cells.	Their affinity and selectivity for Cu^{2+} are higher than those for Zn^{2+} and Fe^{2+}. Mainly taken orally.	Oxidative stress-related injury, disulfiram-like reactions.	Suitable for anti-tumor treatment. Disulfiram is also used for anti-alcohol dependence.	(214,215)
Copper NPs	CuNPs (e.g., CuO, CuS NPs)	Regulation of intracellular copper levels by dissolving or releasing Cu^{2+} in the biological environment.	Environment-dependent; can be administered locally or intravenously.	Skin/mucous membrane irritation, oxidative stress damage, hematological toxicity (e.g., hemolysis, copper-induced anemia), immunotoxicity.	Anti-tumor (e.g., solid tumors), antibacterial/ wound repair (local infection/ wounds), immune regulation (immune-related disorders).	(218,219)

NPs, nanoparticles.

non-ceruloplasmin-bound copper (42.7%) and urinary copper (47.7%), normalized gonadotropin levels in 87.5% of patients and exhibited a favorable safety profile (6.25% mild gastrointestinal events) (231). In oncology clinical settings, trientine combined with radiotherapy improved the ORR in hepatocellular carcinoma (65.5 vs. 37.9% with radiotherapy alone) and achieved a 12-month OS rate of 75.9% (232-234). For HER2-negative metastatic breast cancer (235-237), a polymer-based nano-copper chelator delivering paclitaxel achieved an ORR of 44.4% and a 6.8-fold increase in intratumoral drug accumulation (238). In case of drug-resistant *Pseudomonas aeruginosa* pneumonia, nebulized copper-chelator nanoparticles achieved an 82.1% sputum bacterial clearance rate and significantly shortened antipyretic time, while maintaining a favorable safety profile (239).

Copper ionophores. Elesclomol, a highly selective copper ionophore, binds Cu(II) to form a complex that is rapidly transported into mitochondria (184). Within the mitochondria, FDX1 facilitates the reduction and dissociation of the elesclomol-Cu(II) complex, leading to the generation of ROS (240). Notably, elesclomol also operates through an FDX1-independent pathway that enables an extracellular Cu(II) release pathway, distinguishing it from other ionophores (241). This sustained copper delivery mechanism results in a chronic elevation of intracellular copper and ROS levels, ultimately inducing cell death (242).

The anticancer effects of elesclomol have been demonstrated across various malignancies. In colorectal cancer (CRC) models, elesclomol promotes ATP7A degradation (243), leading to mitochondrial copper accumulation, oxidative stress and the subsequent degradation of SLC7A11 - a key component of the cystine/glutamate transporter - thereby inducing ferroptosis (178,184). Beyond CRC, a novel natural copper ionophore, Pochonin D (PoD), was identified in triple-negative breast cancer (TNBC). PoD covalently binds to Cys173 on peroxiredoxin 1 (PRDX1), inhibiting its peroxidase activity, promoting copper accumulation and ROS generation, and ultimately triggering copper-dependent cell death. This study unveils PRDX1 as a critical mediator in copper-induced cell

death and highlights a new regulatory axis between copper metabolism and oxidative stress (244).

CuNPs. CuNPs have emerged as promising agents for therapeutic applications due to their tunable physicochemical properties and multifunctional capabilities. For instance, a CuO nanoplatform co-loaded with elesclomol potently induces copper-dependent cell death and enhances antitumor immunity. When combined with PD-1 inhibitors, this strategy achieves an 85% tumor suppression rate in melanoma models (219). In prostate cancer, the combination of elesclomol and $CuCl_2$ induces DLAT aggregation and inhibits protective autophagy through mTOR activation, thereby synergizing with docetaxel chemotherapy (245). The application of CuNPs extends beyond oncology. Electrospun nanofiber membranes embedded with CuNPs exhibit broad-spectrum antibacterial activity against pathogenic *Escherichia coli* (246). Furthermore, CuNPs have demonstrated neuroprotective effects in models of AD by improving cognitive function (247), and ultra-small CuNPs embedded in hydrogels have been shown to significantly accelerate diabetic wound healing (248). Despite these promising findings, the clinical translation of CuNPs requires further optimization to address challenges related to long-term stability (249), targeting specificity and scalable manufacturing (250,251).

Challenges of copper adjustment therapy. In summary, copper-targeting approaches introduce novel concepts and hold substantial promise in disease diagnosis and treatment, representing a potential therapeutic strategy. However, further comprehensive research and validation are required for its clinical application to refine therapeutic protocols, enhance treatment efficacy and minimize adverse effects.

Dependence on transporters for drug uptake. The cellular uptake of copper-related therapeutics is tightly regulated by key transporters: CTR1 and the P-type ATPases ATP7A and ATP7B. As the primary mediator of copper influx, CTR1 also facilitates the entry of platinum-based drugs into tumor cells, a process that is critical for achieving therapeutic concentrations. By contrast, ATP7A and ATP7B act as copper efflux transporters, regulating the extrusion and subcellular sequestration of excess copper and platinum drugs (250). Dysregulation of CTR1 and ATP7A/B, whether through altered expression (e.g., CTR1 downregulation in drug-resistant tumors) or genetic mutations, disrupts copper homeostasis and impairs drug accumulation. For instance, ATP7A loss-of-function mutations cause MD (48), whereas ATP7B mutations underlie WD (251). In neurodegenerative diseases (such as AD), abnormal activity of copper-related transporters can disrupt brain copper homeostasis. Excess copper promotes Aβ protein aggregation and ROS overproduction, thereby exacerbating neuronal damage (79,252).

TME limitations. Copper-targeted therapy is significantly limited by the TME. In the hypoxic microenvironment of solid tumors (253), HIF-1α biaxially induces resistance to copper-dependent cell death by upregulating pyruvate dehydrogenase kinase 1/3-mediated degradation of DLAT and promoting MT2A-mediated chelation of free copper. This results in resistance to copper ionophores in nearly 60% of clinical samples, with the IC_{50} of elesclomol increasing by 7.2-fold under hypoxic conditions (254). Meanwhile, vascular abnormalities, elevated interstitial pressure and infiltration of immunosuppressive cells within the TME significantly impair drug delivery. For instance, in hepatocellular carcinoma, multidrug resistance mechanisms, such as the overexpression of ATP-binding cassette transporters, act synergistically with these TME-associated barriers to reduce intratumoral drug accumulation (255).

Long-term toxicity risks of chronic copper exposure. Copper, an essential micronutrient, maintains precise systemic homeostasis through coordinated regulatory mechanisms. However, long-term administration of copper-related therapeutics (e.g., copper ionophores and chelators), disrupts this balance. Excess copper catalyzes the generation of ROS via the Fenton reaction, causing oxidative damage to lipids, proteins and DNA, and ultimately leads to cytotoxicity (249).

Although cuproptosis induced by copper ionophores exhibits anti-tumor potential, preclinical studies have demonstrated that prolonged high-dose treatment elicits severe toxicity in normal tissues. For instance, mitochondrial-targeted copper-depleting nanoparticles effectively inhibit the growth of TNBC but still pose toxicity risks to healthy mice, thereby narrowing the therapeutic window (256). Additionally, the hypoxic TME promotes resistance to cuproptosis through HIF-1α activation, which further compromises therapeutic efficacy (254).

7. Conclusions

Copper is the third most abundant trace element in the body after iron and zinc. It is essential for processes such as oxidative phosphorylation, free radical scavenging, angiogenesis, bone metabolism, neurotransmission and the synthesis of copper-dependent enzymes. On the other hand, both copper overload and deficiency can lead to impaired cellular function or even cell death, and their prolonged presence can trigger associated dysfunctions or neurodegenerative disorders such as hepatomegaly, MD, AD and PD.

It has been found that there are interactions among copper, iron and zinc, and the use of combination drug formulations for the treatment of related diseases may represent a new therapeutic strategy. In the treatment of diseases associated with copper overload, strategies such as reducing dietary copper intake, administering oral zinc to inhibit copper absorption or employing copper chelators to decrease intracellular copper levels may represent promising therapeutic approaches.

In the context of cancer, copper levels in cancer cells can exceed the tolerance threshold of normal cells, leading to significant adverse effects. Conversely, reducing intracellular copper levels can diminish the synthesis of the copper-dependent enzyme SOD1, thereby substantially impairing the organism's antioxidant capacity. Copper-induced cell death exhibits greater sensitivity in cells reliant on oxidative phosphorylation than in those dependent on glycolysis for energy production. Thus, converting the metabolic pathway of cancer cells from glycolysis to oxidative phosphorylation, coupled with exploiting the characteristic of elevated intracellular copper, may offer a promising new approach to cancer therapy. Comprehensive studies of the mechanisms of copper-induced cell death may help to identify more effective therapeutic agents, thus providing new insights and approaches for the

treatment of related diseases and improving the prognosis of affected patients.

Copper regulation therapy has demonstrated significant potential in the diagnosis and treatment of diseases. Copper chelating agents, copper ion carriers and copper-based nanoparticles have shown therapeutic effects across various disease models. For instance, clinical studies have shown that the combination of the copper chelating agent TM with anti-PD-1 therapy achieves promising outcomes in the treatment of locally advanced OSCC. The copper ion carrier elesclomol exhibits anticancer effects in multiple malignant tumor models. CuNPs have yielded remarkable results in cancer therapy, antibacterial applications, neuroprotection and wound healing. However, the clinical application of this therapeutic approach faces several challenges. These include drug uptake dependence on key transporters such as CTR1, ATP7A and ATP7B, whose dysregulation can compromise therapeutic efficacy; the influence of the TME, including hypoxia and vascular abnormalities, which may limit treatment outcomes; and the potential toxicity associated with long-term copper exposure, which also narrows the therapeutic window.

Acknowledgements

Not applicable.

Funding

This work was supported by the Science and Technology Support Program of Guizhou Province [grant nos. QKH-ZK (2023)506 and QKH-MS(2025)373], the Education Department of Guizhou Province [grant no. QJJ(2022)242] and Zunyi City Science and Technology and Big Data Bureau & Zunyi Medical University joint project [grant nos. HZ(2023)175, HZ(2023)189, (2021)1350-011 and (2021)1350-025].

Availability of data and materials

Not applicable.

Authors' contributions

All authors contributed to the study conception and design. TD and HM were responsible for article design and manuscript writing. TD and XJ were involved in the design of the images. JT, JZ and YT were involved in the design of the study and funding application. All authors read and approved the final manuscript. Data authentication is not applicable.

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. Bost M, Houdart S, Oberli M, Kalonji E, Huneau JF and Margaritis I: Dietary copper and human health: Current evidence and unresolved issues. J Trace Elem Med Biol 35: 107-115, 2016.
2. Huang F, Lu X, Kuai L, Ru Y, Jiang J, Song J, Chen S, Mao L, Li Y, Li B, *et al*: Dual-Site Biomimetic Cu/Zn-MOF for atopic dermatitis catalytic therapy via suppressing FcγR-mediated phagocytosis. J Am Chem Soc 146: 3186-3199, 2024.
3. Ash D, Sudhahar V, Youn SW, Okur MN, Das A, O'Bryan JP, McMenamin M, Hou Y, Kaplan JH, Fukai T and Ushio-Fukai M: The P-type ATPase transporter ATP7A promotes angiogenesis by limiting autophagic degradation of VEGFR2. Nat Commun 12: 3091, 2021.
4. Ding H, Gao YS, Wang Y, Hu C, Sun Y and Zhang C: Dimethyloxaloylglycine increases the bone healing capacity of adipose-derived stem cells by promoting osteogenic differentiation and angiogenic potential. Stem Cells Dev 23: 990-1000, 2014.
5. Akhtar H, Alhamoudi FH, Marshall J, Ashton T, Darr JA, Rehman IU, Chaudhry AA and Reilly G: Synthesis of cerium, zirconium, and copper doped zinc oxide nanoparticles as potential biomaterials for tissue engineering applications. Heliyon 10: e29150, 2024.
6. Han J, Luo J, Wang C, Kapilevich L and Zhang XA: Roles and mechanisms of copper homeostasis and cuproptosis in osteoarticular diseases. Biomed Pharmacother 174: 116570, 2024.
7. Wei M, Huang Q, Dai Y, Zhou H, Cui Y, Song W, Di D, Zhang R, Li C, Wang Q and Jing T: Manganese, iron, copper, and selenium co-exposure and osteoporosis risk in Chinese adults. J Trace Elem Med Biol 72: 126989, 2022.
8. Xiao T, Ackerman CM, Carroll EC, Jia S, Hoagland A, Chan J, Thai B, Liu CS, Isacoff EY and Chang CJ: Copper regulates rest-activity cycles through the locus coeruleus-norepinephrine system. Nat Chem Biol 14: 655-663, 2018.
9. Benatar M, JRobertson J, and Andersen PM: Amyotrophic lateral sclerosis caused by SOD1 variants: From genetic discovery to disease prevention. Lancet Neurol 24: 77-86, 2025.
10. Horvath R, Kemp JP, Tuppen HA, Hudson G, Oldfors A, Marie SK, Moslemi AR, Servidei S, Holme E, Shanske S, *et al*: Molecular basis of infantile reversible cytochrome c oxidase deficiency myopathy. Brain 132 (Pt 11): 3165-3174, 2009.
11. Qu Y, Zhan Q, Du S, Ding Y, Fang B, Du W, Wu Q, Yu H, Li L and Huang W: Catalysis-based specific detection and inhibition of tyrosinase and their application. J Pharm Anal 10: 414-425, 2020.
12. Foehr R, Anderson K, Dombrowski O, Foehr A and Foehr ED: Dysregulation of extracellular matrix and lysyl oxidase in Ehlers-Danlos syndrome type IV skin fibroblasts. Orphanet J Rare Dis 19: 9, 2024.
13. Wassenberg T, Deinum J, van Ittersum FJ, Kamsteeg EJ, Pennings M, Verbeek MM, Wevers RA, van Albada ME, Kema IP, Versmissen J, *et al*: Clinical presentation and long-term follow-up of dopamine beta hydroxylase deficiency. J Inherit Metab Dis 44: 554-565, 2021.
14. De Feyter S, Beyens A and Callewaert B: ATP7A-related copper transport disorders: A systematic review and definition of the clinical subtypes. J Inherit Metab Dis 46: 163-173, 2023.
15. Stalke A, Behrendt A, Hennig F, Gohlke H, Buhl N, Reinkens T, Baumann U, Schlegelberger B, Illig T, Pfister ED and Skawran B: Functional characterization of novel or yet uncharacterized ATP7B missense variants detected in patients with clinical Wilson's disease. Clin Genet 104: 174-185, 2023.
16. Li Y, Ma J, Wang R, Luo Y, Zheng S and Wang X: Zinc transporter 1 functions in copper uptake and cuproptosis. Cell Metab 36: 2118-2129 e6, 2024.
17. Ohgami RS, Campagna DR, McDonald A and Fleming MD: The Steap proteins are metalloreductases. Blood 108: 1388-1394, 2006.
18. Wyman S, Simpson RJ, McKie AT and Sharp PA: Dcytb (Cybrd1) functions as both a ferric and a cupric reductase in vitro. FEBS Lett 582: 1901-1906, 2008.
19. Kleven MD, Dlakic M and Lawrence CM: Characterization of a Single b-type Heme, FAD, and metal binding sites in the transmembrane domain of six-transmembrane epithelial antigen of the prostate (STEAP) family proteins. J Biol Chem 290: 22558-22569, 2015.
20. Kirsipuu T, Zadorožnaja A, Smirnova J, Friedemann M, Plitz T, Tõugu V and Palumaa P: Copper(II)-binding equilibria in human blood. Sci Rep 10: 5686, 2020.

21. Linder MC: Ceruloplasmin and other copper binding components of blood plasma and their functions: An update. Metallomics 8: 887-905, 2016.
22. Moriya M, Ho YH, Grana A, Nguyen L, Alvarez A, Jamil R, Ackland ML, Michalczyk A, Hamer P, Ramos D, *et al*: Copper is taken up efficiently from albumin and alpha2-macroglobulin by cultured human cells by more than one mechanism. Am J Physiol Cell Physiol 295: C708-C721, 2008.
23. Liu N, Lo LS, Askary SH, Jones L, Kidane TZ, Trang T, Nguyen M, Goforth J, Chu YH, Vivas E, *et al*: Transcuprein is a macroglobulin regulated by copper and iron availability. J Nutr Biochem 18: 597-608, 2007.
24. Wang Y, Hodgkinson V, Zhu S, Weisman GA and Petris MJ: Advances in the understanding of mammalian copper transporters. Adv Nutr 2: 129-137, 2011.
25. Chen L, Li N, Zhang M, Sun M, Bian J, Yang B, Li Z, Wang J, Li F, Shi X, *et al*: APEX2-based proximity labeling of Atox1 Identifies CRIP2 as a nuclear copper-binding protein that regulates autophagy activation. Angew Chem Int Ed Engl 60: 25346-25355, 2021.
26. González-Ballesteros MM, Sánchez-Sánchez L, Espinoza-Guillén A, Espinal-Enríquez J, Mejía C, Hernández-Lemus E and Ruiz-Azuara L: Antitumoral and antimetastatic activity by mixed chelate copper(II) Compounds (Casiopeínas®) on triple-negative breast cancer, in vitro and in vivo models. Int J Mol Sci 25: 8803, 2024.
27. Kuo YM, Gybina AA, Pyatskowit JW, Gitschier J and Prohaska JR: Copper transport protein (Ctr1) levels in mice are tissue specific and dependent on copper status. J Nutr 136: 21-26, 2006.
28. Vizcaíno C, Mansilla S and Portugal J: Sp1 transcription factor: A long-standing target in cancer chemotherapy. Pharmacol Ther 152: 111-124, 2015.
29. Xue Q, Kang R, Klionsky DJ, Tang D, Liu J and Chen X: Copper metabolism in cell death and autophagy. Autophag 19: 2175-2195, 2023.
30. Liang ZD, Tsai WB, Lee MY, Savaraj N and Kuo MT: Specificity protein 1 (sp1) oscillation is involved in copper homeostasis maintenance by regulating human high-affinity copper transporter 1 expression. Mol Pharmacol 81: 455-464, 2012.
31. Ohse VA, Klotz LO and Priebs J: Copper homeostasis in the model organism C. elegans. Cells 13: 727, 2024.
32. Hatori Y, and Lutsenko S: The role of copper chaperone Atox1 in coupling redox homeostasis to intracellular copper distribution. Antioxidants (Basel) 5: 25, 2016.
33. Lutsenko S, Barnes NL, Bartee MY and Dmitriev OY: Function and regulation of human copper-transporting ATPases. Physiol Rev 87: 1011-1046, 2007.
34. Sturtz LA, Diekert K, Jensen LT, Lill R and Culotta VC: A fraction of yeast Cu,Zn-superoxide dismutase and its metallochaperone, CCS, localize to the intermembrane space of mitochondria. A physiological role for SOD1 in guarding against mitochondrial oxidative damage. J Biol Chem 276: 38084-38089, 2001.
35. Wang Y, Branicky R, Noë A and Hekimi S: Superoxide dismutases: Dual roles in controlling ROS damage and regulating ROS signaling. J Cell Biol 217: 1915-1928, 2018.
36. Miriyala S, Spasojevic I, Tovmasyan A, Salvemini D, Vujaskovic Z, St Clair D and Batinic-Haberle I: Manganese superoxide dismutase, MnSOD and its mimics. Biochim Biophys Acta 1822: 794-814, 2012.
37. Boyd SD, Calvo JS, Liu L, Ullrich MS, Skopp A, Meloni G and Winkler DD: The yeast copper chaperone for copper-zinc superoxide dismutase (CCS1) is a multifunctional chaperone promoting all levels of SOD1 maturation. J Biol Chem 294: 1956-1966, 2019.
38. Ding Y, Chen Y, Wu Z, Yang N, Rana K, Meng X, Liu B, Wan H and Qian W: SsCox17, a copper chaperone, is required for pathogenic process and oxidative stress tolerance of Sclerotinia sclerotiorum. Plant Sci 322: 111345, 2022.
39. Banci L, Bertini I, Ciofi-Baffoni S, Hadjiloi T, Martinelli M and Palumaa P: Mitochondrial copper(I) transfer from Cox17 to Sco1 is coupled to electron transfer. Proc Natl Acad Sci USA 105: 6803-6808, 2008.
40. 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.
41. McCann C, Quinteros M, Adelugba I, Morgada MN, Castelblanco AR, Davis EJ, Lanzirotti A, Hainer SJ, Vila AJ, Navea JG and Padilla-Benavides T: The mitochondrial Cu(+) transporter PiC2 (SLC25A3) is a target of MTF1 and contributes to the development of skeletal muscle in vitro. Front Mol Biosci 9: 1037941, 2022.
42. van Rensburg MJ, van Rooy M, Bester MJ, Serem JC, Venter C and Oberholzer HM: Oxidative and haemostatic effects of copper, manganese and mercury, alone and in combination at physiologically relevant levels: An ex vivo study. Hum Exp Toxicol 38: 419-433, 2019.
43. Ruturaj, Mishra M, Saha S, Maji S, Rodriguez-Boulan E, Schreiner R and Gupta A: Regulation of the apico-basolateral trafficking polarity of the homologous copper-ATPases ATP7A and ATP7B. J Cell Sci 137: jcs261258, 2024.
44. Guttmann S, Nadzemova O, Grünewald I, Lenders M, Brand E, Zibert A and Schmidt HH: ATP7B knockout disturbs copper and lipid metabolism in Caco-2 cells. PLoS One 15: e0230025, 2020.
45. Dmitriev OY, and Patry J: Structure and mechanism of the human copper transporting ATPases: Fitting the pieces into a moving puzzle. Biochim Biophys Acta Biomembr 1866: 184306, 2024.
46. Percival SS: Copper and immunity. Am J Clin Nutr 67 (5 Suppl): 1064S-1068S, 1998.
47. Jonny, Sitepu EC, Nidom CA, Wirjopranoto S, Sudiana IK, Ansori ANM and Putranto TA: Ex vivo-generated tolerogenic dendritic cells: Hope for a definitive therapy of autoimmune diseases. Curr Issues Mol Biol 46: 4035-4048, 2024.
48. Backal A, Velinov M, Garcia J and Louis CL: Novel, likely pathogenic variant in ATP7A associated with Menkes disease diagnosed with ultrarapid genome sequencing. BMJ Case Rep 17: e259792, 2024.
49. Tümer Z and Møller LB: Menkes disease. Eur J Hum Genet 18: 511-518, 2010.
50. Moller LB, Mogensen M, Weaver DD and Pedersen PA: Occipital horn syndrome as a result of splice site mutations in ATP7A. no activity of ATP7A splice variants missing exon 10 or exon 15. Front Mol Neurosci 14: 532291, 2021.
51. Batzios S, Tal G, DiStasio AT, Peng Y, Charalambous C, Nicolaides P, Kamsteeg EJ, Korman SH, Mandel H, Steinbach PJ, *et al*: Newly identified disorder of copper metabolism caused by variants in CTR1, a high-affinity copper transporter. Hum Mol Genet 31: 4121-4130, 2022.
52. Garnica A, Chan WY and Rennert O: Copper-histidine treatment of Menkes disease. J Pediatr 125: 336-338, 1994.
53. Moini M, To U and Schilsky ML: Recent advances in Wilson disease. Transl Gastroenterol Hepatol 6: 21, 2021.
54. Weiss KH, Członkowska A, Hedera P and Ferenci P: WTX101 - an investigational drug for the treatment of Wilson disease. Expert Opin Investig Drugs 27: 561-567, 2018.
55. Kreuder J, Otten A, Fuder H, Tümer Z, Tønnesen T, Horn N and Dralle D: Clinical and biochemical consequences of copper-histidine therapy in Menkes disease. Eur J Pediatr 152: 828-832, 1993.
56. Christodoulou J, Danks DM, Sarkar B, Baerlocher KE, Casey R, Horn N, Tümer Z and Clarke JT: Early treatment of Menkes disease with parenteral copper-histidine: Long-term follow-up of four treated patients. Am J Med Genet 76: 154-164, 1998.
57. Ramchandani D, Berisa M, Tavarez DA, Li Z, Miele M, Bai Y, Lee SB, Ban Y, Dephoure N, Hendrickson RC, *et al*: Copper depletion modulates mitochondrial oxidative phosphorylation to impair triple negative breast cancer metastasis. Nat Commun 12: 7311, 2021.
58. Xu B, Wang S, Li R, Chen K, He L, Deng M, Kannappan V, Zha J, Dong H and Wang W: Disulfiram/copper selectively eradicates AML leukemia stem cells in vitro and in vivo by simultaneous induction of ROS-JNK and inhibition of NF-κB and Nrf2. Cell Death Dis 8: e2797, 2017.
59. Theophanides T, and Anastassopoulou J: Copper and carcinogenesis. Crit Rev Oncol Hematol 42: 57-64, 2002.
60. Zhong CC, Zhao T, Hogstrand C, Chen F, Song CC and Luo Z: Copper (Cu) induced changes of lipid metabolism through oxidative stress-mediated autophagy and Nrf2/PPARγ pathways. J Nutr Biochem 100: 108883, 2022.
61. Wang Q, Sun Y, Zhao A, Cai X, Yu A, Xu Q, Liu W, Zhang N, Wu S, Chen Y and Wang W: High dietary copper intake induces perturbations in the gut microbiota and affects host ovarian follicle development. Ecotoxicol Environ Saf 255: 114810, 2023.
62. Tsang T, Posimo JM, Gudiel AA, Cicchini M, Feldser DM and Brady DC: Copper is an essential regulator of the autophagic kinases ULK1/2 to drive lung adenocarcinoma. Nat Cell Biol 22: 412-424, 2020.

63. Conforti RA, Delsouc MB, Zorychta E, Telleria CM and Casais M: Copper in gynecological diseases. Int J Mol Sci 24: 17578, 2023.
64. Compston A: Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver, by S. A. Kinnier Wilson, (From the National Hospital, and the Laboratory of the National Hospital, Queen Square, London) Brain 1912: 34; 295-509. Brain 132: 1997-2001, 2009.
65. Kipker N, Alessi K, Bojkovic M, Padda I and Parmar MS: Neurological-type wilson disease: Epidemiology, clinical manifestations, diagnosis, and management. Cureus 15: e38170, 2023.
66. Członkowska A, Litwin T, Dusek P, Ferenci P, Lutsenko S, Medici V, Rybakowski JK, Weiss KH and Schilsky ML: Wilson disease. Nat Rev Dis Primers 4: 21, 2018.
67. Kirk FT, Munk DE, Swenson ES, Quicquaro AM, Vendelbo MH, Larsen A, Schilsky ML, Ott P and Sandahl TD: Effects of tetrathiomolybdate on copper metabolism in healthy volunteers and in patients with Wilson disease. J Hepatol 80: 586-595, 2024.
68. Bruha R, Marecek Z, Pospisilova L, Nevsimalova S, Vitek L, Martasek P, Nevoral J, Petrtyl J, Urbanek P, Jiraskova A and Ferenci P: Long-term follow-up of Wilson disease: natural history, treatment, mutations analysis and phenotypic correlation. Liver Int 31: 83-91, 2011.
69. Członkowska A, Litwin T, Karliński M, Dziezyc K, Chabik G and Czerska M: D-penicillamine versus zinc sulfate as first-line therapy for Wilson's disease. Eur J Neurol 21: 599-606, 2014.
70. Brewer GJ: Practical recommendations and new therapies for Wilson's disease. Drugs 50: 240-249, 1995.
71. Xie J, Yang Y, Gao Y and He J: Cuproptosis: Mechanisms and links with cancers. Mol Cancer 22: 46, 2023.
72. Członkowska A and Litwin T: Wilson disease - currently used anticopper therapy. Handb Clin Neurol 142: 181-191, 2017.
73. Lambert C, Beraldo H, Lievre N, Garnier-Suillerot A, Dorlet P and Salerno M: Bis(thiosemicarbazone) copper complexes: Mechanism of intracellular accumulation. J Biol Inorg Chem 18: 59-69, 2013.
74. Ayton S and Bush AI: β-amyloid: The known unknowns. Ageing Res Rev 65: 101212, 2021.
75. Egan MF, Kost J, Voss T, Mukai Y, Aisen PS, Cummings JL, Tariot PN, Vellas B, van Dyck CH, Boada M, *et al*: Randomized Trial of Verubecestat for Prodromal Alzheimer's Disease. N Engl J Med 380: 1408-1420, 2019.
76. Doody RS, Thomas RG, Farlow M, Iwatsubo T, Vellas B, Joffe S, Kieburtz K, Raman R, Sun X, Aisen PS, *et al*: Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. N Engl J Med 370: 311-321, 2014.
77. Salloway S, Sperling R, Fox NC, Blennow K, Klunk W, Raskind M, Sabbagh M, Honig LS, Porsteinsson AP, Ferris S, *et al*: Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. N Engl J Med 370: 322-333, 2014.
78. Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chételat G, Teunissen CE, Cummings J and van der Flier WM: Alzheimer's disease. Lancet 397: 1577-1590, 2021.
79. Mazur T, Malik M and Bienko DC: The impact of chelating compounds on Cu(2+), Fe(2+)/(3+), and Zn(2+) ions in Alzheimer's disease treatment. J Inorg Biochem 257: 112601, 2024.
80. Xu J, Church SJ, Patassini S, Begley P, Waldvogel HJ, Curtis MA, Faull RLM, Unwin RD and Cooper GJS: Evidence for widespread, severe brain copper deficiency in Alzheimer's dementia. Metallomics 9: 1106-1119, 2017.
81. Rembach A, Hare DJ, Lind M, Fowler CJ, Cherny RA, McLean C, Bush AI, Masters CL and Roberts BR: Decreased copper in Alzheimer's disease brain is predominantly in the soluble extractable fraction. Int J Alzheimers Dis 2013: 623241, 2013.
82. Scholefield M, Church SJ, Xu J and Cooper GJS: Metallomic analysis of brain tissues distinguishes between cases of dementia with Lewy bodies, Alzheimer's disease, and Parkinson's disease dementia. Front Neurosci 18: 1412356, 2024.
83. Squitti R, Simonelli I, Ventriglia M, Siotto M, Pasqualetti P, Rembach A, Doecke J and Bush AI: Meta-analysis of serum non-ceruloplasmin copper in Alzheimer's disease. J Alzheimers Dis 38: 809-822, 2014.
84. Jiao Y and Yang P: Mechanism of copper(II) inhibiting Alzheimer's amyloid beta-peptide from aggregation: A molecular dynamics investigation. J Phys Chem B 111: 7646-7655, 2007.
85. Gomes LM, Vieira RP, Jones MR, Wang MC, Dyrager C, Souza-Fagundes EM, Da Silva JG, Storr T and Beraldo H: 8-Hydroxyquinoline Schiff-base compounds as antioxidants and modulators of copper-mediated Aβ peptide aggregation. J Inorg Biochem 139: 106-116, 2014.
86. Pedersen JT, Østergaard J, Rozlosnik N, Gammelgaard B and Heegaard NH: Cu(II) mediates kinetically distinct, non-amyloidogenic aggregation of amyloid-beta peptides. J Biol Chem 286: 26952-26963, 2011.
87. Reybier K, Ayala S, Alies B, Rodrigues JV, Bustos Rodriguez S, La Penna G, Collin F, Gomes CM, Hureau C and Faller P: Free Superoxide is an intermediate in the production of H2O2 by Copper(I)-Aβ Peptide and O2. Angew Chem Int Ed Engl 55: 1085-1089, 2016.
88. Fanlo-Ucar H, Picón-Pagès P, Herrera-Fernández V, Ill-Raga G and Muñoz FJ: The dual role of amyloid beta-peptide in oxidative stress and inflammation: Unveiling Their connections in Alzheimer's disease etiopathology. Antioxidants (Basel) 13: 1208, 2024.
89. Xia Y, Dore V, Fripp J, Bourgeat P, Laws SM, Fowler CJ, Rainey-Smith SR, Martins RN, Rowe C, Masters CL, *et al*: Association of basal forebrain atrophy with cognitive decline in early Alzheimer disease. Neurology 103: e209626, 2024.
90. Lang M, Fan Q, Wang L, Zheng Y, Xiao G, Wang X, Wang W, Zhong Y and Zhou B: Inhibition of human high-affinity copper importer Ctr1 orthologous in the nervous system of Drosophila ameliorates Aβ42-induced Alzheimer's disease-like symptoms. Neurobiol Aging 34: 2604-2612, 2013.
91. Ceccom J, Coslédan F, Halley H, Francès B, Lassalle JM and Meunier B: Copper chelator induced efficient episodic memory recovery in a non-transgenic Alzheimer's mouse model. PLoS One, 2012. 7: e43105, 2012.
92. Quinn JF, Harris CJ, Cobb KE, Domes C, Ralle M, Brewer G and Wadsworth TL: A copper-lowering strategy attenuates amyloid pathology in a transgenic mouse model of Alzheimer's disease. J Alzheimers Dis 21: 903-914, 2010.
93. Chen C, Jiang X, Li Y, Yu H, Li S, Zhang Z, Xu H, Yang Y, Liu G, Zhu F, *et al*: Low-dose oral copper treatment changes the hippocampal phosphoproteomic profile and perturbs mitochondrial function in a mouse model of Alzheimer's disease. Free Radic Biol Med 135: 144-156, 2019.
94. Yao D, Jing T, Niu L, Huang X, Wang Y, Deng X and Wang M: Amyloidogenesis induced by diet cholesterol and copper in a model mouse for Alzheimer's disease and protection effects of zinc and fluvastatin. Brain Res Bull 143: 1-8, 2018.
95. Maynard CJ, Cappai R, Volitakis I, Laughton KM, Masters CL, Bush AI and Li QX: Chronic exposure to high levels of zinc or copper has little effect on brain metal homeostasis or Abeta accumulation in transgenic APP-C100 mice. Cell Mol Neurobiol 29: 757-767, 2009.
96. Acevedo KM, Hung YH, Dalziel AH, Li QX, Laughton K, Wikhe K, Rembach A, Roberts B, Masters CL, Bush AI and Camakaris J: Copper promotes the trafficking of the amyloid precursor protein. J Biol Chem 286: 8252-8262, 2011.
97. Borchardt T, Camakaris J, Cappai R, Masters CL, Beyreuther K and Multhaup G: Copper inhibits beta-amyloid production and stimulates the non-amyloidogenic pathway of amyloid-precursor-protein secretion. Biochem J 344: 461-467, 1999.
98. Afsar A, Chacon Castro MDC, Soladogun AS and Zhang L: Recent development in the understanding of molecular and cellular mechanisms underlying the etiopathogenesis of Alzheimer's disease. Int J Mol Sci 24: 7258, 2023.
99. 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 Updat 72: 101018, 2024.
100. Kumar V, Singh AP, Wheeler N, Galindo CL and Kim JJ: Safety profile of D-penicillamine: A comprehensive pharmacovigilance analysis by FDA adverse event reporting system. Expert Opin Drug Saf 20: 1443-1450, 2021.
101. Lee EJ, Woo MH, Moon JS and Ko JS: Efficacy and safety of D-penicillamine, trientine, and zinc in pediatric Wilson disease patients. Orphanet J Rare Dis 19: 261, 2024.
102. Perez DR, Sklar LA and Chigaev A: Clioquinol: To harm or heal. Pharmacol Ther 199: 155-163, 2019.
103. Relkin N: Testing the mettle of PBT2 for Alzheimer's disease. Lancet Neurol 7: 762-763, 2008.
104. Daniel KG, Chen D, Orlu S, Cui QC, Miller FR and Dou QP: Clioquinol and pyrrolidine dithiocarbamate complex with copper to form proteasome inhibitors and apoptosis inducers in human breast cancer cells. Breast Cancer Res 7: R897-R908, 2005.
105. Crouch PJ, Hung LW, Adlard PA, Cortes M, Lal V, Filiz G, Perez KA, Nurjono M, Caragounis A, Du T, *et al*: Increasing Cu bioavailability inhibits Abeta oligomers and tau phosphorylation. Proc Natl Acad Sci USA 106: 381-386, 2009.

106. Schimmer AD: Clioquinol - a novel copper-dependent and independent proteasome inhibitor. Curr Cancer Drug Targets 11: 325-331, 2011.
107. Costello LC and Franklin RB: A proposed efficacious treatment with clioquinol (Zinc Ionophore) and Cabergoline (Prolactin Dopamine Agonist) for the treatment of terminal androgen-independent prostate cancer. Why and How? J Clin Res Oncol: Feb 27, 2019 (Epub ahead of print).
108. Donnelly PS, Caragounis A, Du T, Laughton KM, Volitakis I, Cherny RA, Sharples RA, Hill AF, Li QX, Masters CL, *et al*: Selective intracellular release of copper and zinc ions from bis(thiosemicarbazonato) complexes reduces levels of Alzheimer disease amyloid-beta peptide. J Biol Chem 283: 4568-4577, 2008.
109. Drew SC: Chelator PBT2 forms a ternary Cu(2+) Complex with β-Amyloid That has high stability but low specificity. Int J Mol Sci 24: 9267, 2023.
110. Scholefield M, Patassini S, Xu J and Cooper GJS: Widespread selenium deficiency in the brain of cases with Huntington's disease presents a new potential therapeutic target. Ebiomedicine 97: 104824, 2023.
111. Upadhyay A, Chhangani D, Rao NR, Kofler J, Vassar R, Rincon-Limas DE and Savas JN: Amyloid fibril proteomics of AD brains reveals modifiers of aggregation and toxicity. Mol Neurodegener 18: 61, 2023.
112. Hands SL, Mason R, Sajjad MU, Giorgini F and Wyttenbach A: Metallothioneins and copper metabolism are candidate therapeutic targets in Huntington's disease. Biochem Soc Trans 38: 552-558, 2010.
113. Zhu Z, Song M, Ren J, Liang L, Mao G and Chen M: Copper homeostasis and cuproptosis in central nervous system diseases. Cell Death Dis 15: 850, 2024.
114. Cherny RA, Ayton S, Finkelstein DI, Bush AI, McColl G and Massa SM: PBT2 Reduces Toxicity in a C. elegans Model of polyQ aggregation and extends lifespan, reduces striatal atrophy and improves motor performance in the R6/2 mouse model of Huntington's disease. J Huntingtons Dis 1: 211-219, 2012.
115. Rodriguez-Oroz MC, Jahanshahi M, Krack P, Litvan I, Macias R, Bezard E and Obeso JA: Initial clinical manifestations of Parkinson's disease: Features and pathophysiological mechanisms. Lancet Neurol 8: 1128-1139, 2009.
116. Davies KM, Hare DJ, Cottam V, Chen N, Hilgers L, Halliday G, Mercer JF and Double KL: Localization of copper and copper transporters in the human brain. Metallomics 5: 43-51, 2013.
117. Dexter DT, Wells FR, Lees AJ, Agid F, Agid Y, Jenner P and Marsden CD: Increased nigral iron content and alterations in other metal ions occurring in brain in Parkinson's disease. J Neurochem 52: 1830-1836, 1989.
118. Ayton S, Lei P, Duce JA, Wong BX, Sedjahtera A, Adlard PA, Bush AI and Finkelstein DI: Ceruloplasmin dysfunction and therapeutic potential for Parkinson disease. Ann Neurol 73: 554-559, 2013.
119. Bisaglia M and Bubacco L: Copper ions and Parkinson's disease: Why Is homeostasis so relevant? Biomolecules 10: 195, 2020.
120. Hemmati-Dinarvand M, Saedi S, Valilo M, Kalantary-Charvadeh A, Alizadeh Sani M, Kargar R, Safari H and Samadi N: Oxidative stress and Parkinson's disease: Conflict of oxidant-antioxidant systems. Neurosci Lett 709: 134296, 2019.
121. Trist BG, Davies KM, Cottam V, Genoud S, Ortega R, Roudeau S, Carmona A, De Silva K, Wasinger V, Lewis SJG, *et al*: Amyotrophic lateral sclerosis-like superoxide dismutase 1 proteinopathy is associated with neuronal loss in Parkinson's disease brain. Acta Neuropathol 134: 113-127, 2017.
122. Zhang MS, Liang JH, Yang MJ, Ren YR, Cheng DH, Wu QH, He Y and Yin J: Low serum superoxide dismutase is associated with a high risk of cognitive impairment after mild acute ischemic stroke. Front Aging Neurosci 14: 834114, 2022.
123. Quinn PMJ, Moreira PI, Ambrósio AF and Alves CH: PINK1/PARKIN signalling in neurodegeneration and neuroinflammation. Acta Neuropathol Commun 8: 189, 2020.
124. Cummins N and Götz J: Shedding light on mitophagy in neurons: What is the evidence for PINK1/Parkin mitophagy in vivo? Cell Mol Life Sci 75: 1151-1162, 2018.
125. Aschner M, Skalny AV, Lu R, Martins AC, Tizabi Y, Nekhoroshev SV, Santamaria A, Sinitskiy AI and Tinkov AA: Mitochondrial pathways of copper neurotoxicity: Focus on mitochondrial dynamics and mitophagy. Front Mol Neurosci 17: 1504802, 2024.
126. Ling Z, Ge X, Jin C, Song Z, Zhang H, Fu Y, Zheng K, Xu R and Jiang H: Copper doped bioactive glass promotes matrix vesicles-mediated biomineralization via osteoblast mitophagy and mitochondrial dynamics during bone regeneration. Bioact Mater 46: 195-212, 2024.
127. Synhaivska O, Bhattacharya S, Campioni S, Thompson D and Nirmalraj PN: Single-particle resolution of copper-associated annular α-synuclein oligomers reveals potential therapeutic targets of neurodegeneration. ACS Chem Neurosci 13: 1410-1421, 2022.
128. Triscott J, Rose Pambid M and Dunn SE: Concise review: Bullseye: Targeting cancer stem cells to improve the treatment of gliomas by repurposing disulfiram. Stem Cells 33: 1042-1046, 2015.
129. Kannappan V, Ali M, Small B, Rajendran G, Elzhenni S, Taj H, Wang W and Dou QP: Recent advances in repurposing disulfiram and disulfiram derivatives as copper-dependent anticancer agents. Front Mol Biosci 8: 741316, 2021.
130. Zhou Q, Zhang Y, Lu L, Zhang H, Zhao C, Pu Y and Yin L: Copper induces microglia-mediated neuroinflammation through ROS/NF-κB pathway and mitophagy disorder. Food Chem Toxicol 168: 113369, 2022.
131. Chidambaram SB, Anand N, Varma SR, Ramamurthy S, Vichitra C, Sharma A, Mahalakshmi AM and Essa MM: Superoxide dismutase and neurological disorders. IBRO Neurosci Rep 16: 373-394, 2024.
132. Cukierman DS, Pinheiro AB, Castiñeiras-Filho SL, da Silva AS, Miotto MC, De Falco A, de P Ribeiro T, Maisonette S, da Cunha AL, Hauser-Davis RA, *et al*: A moderate metal-binding hydrazone meets the criteria for a bioinorganic approach towards Parkinson's disease: Therapeutic potential, blood-brain barrier crossing evaluation and preliminary toxicological studies. J Inorg Biochem 170: 160-168, 2017.
133. Vavere AL and Lewis JS: Cu-ATSM: A radiopharmaceutical for the PET imaging of hypoxia. Dalton Trans: 4893-4902, 2007.
134. Ikawa M, Okazawa H, Kudo T, Kuriyama M, Fujibayashi Y and Yoneda M: Evaluation of striatal oxidative stress in patients with Parkinson's disease using [62Cu]ATSM PET. Nucl Med Biol 38: 945-951, 2011.
135. Hung LW, Villemagne VL, Cheng L, Sherratt NA, Ayton S, White AR, Crouch PJ, Lim S, Leong SL, Wilkins S, *et al*: The hypoxia imaging agent CuII(atsm) is neuroprotective and improves motor and cognitive functions in multiple animal models of Parkinson's disease. J Exp Med 209: 837-854, 2012.
136. Rowlands BD, Trist BG, Karozis C, Schaffer G, Mor D, Harwood R, Rosolen SA, Cottam V, Persson-Carboni F, Richardson M, *et al*: Copper supplementation mitigates Parkinson-like wild-type SOD1 pathology and nigrostriatal degeneration in a novel mouse model. Acta Neuropathol Commun 13: 133, 2025.
137. Al-Chalabi A and Hardiman O: The epidemiology of ALS: A conspiracy of genes, environment and time. Nat Rev Neurol 9: 617-628, 2013.
138. Min JH, Sarlus H and Harris RA: Copper toxicity and deficiency: The vicious cycle at the core of protein aggregation in ALS. Front Mol Neurosci 17: 1408159, 2024.
139. Moriyama H and Yokota T: Recent progress of antisense oligonucleotide therapy for superoxide-dismutase-1-mutated amyotrophic lateral sclerosis: Focus on tofersen. Genes (Basel) 15: 1342, 2024.
140. Jerusalem F, Pohl C, Karitzky J and Ries F: ALS. Neurology 47 (Suppl 4): S218-S220, 1996.
141. Gurney ME, Pu H, Chiu AY, Dal Canto MC, Polchow CY, Alexander DD, Caliendo J, Hentati A, Kwon YW, Deng HX, *et al*: Motor neuron degeneration in mice that express a human Cu, Zn superoxide dismutase mutation. Science 264: 1772-1775, 1994.
142. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74: 229-263, 2024.
143. Ansori ANM, Widyananda MH, Antonius Y, Murtadlo AAA, Kharisma VD, Wiradana PA, Sahadewa S, Durry FD, Maksimiuk N, Rebezov M and Zainul R: A review of cancer-related hypercalcemia: Pathophysiology, current treatments, and future directions. J Med Pharm Chem Res 6: 944-952, 2024.
144. Wu T, Sempos CT, Freudenheim JL, Muti P and Smit E: Serum iron, copper and zinc concentrations and risk of cancer mortality in US adults. Ann Epidemiol 14: 195-201, 2004.

145. Hyvönen MT, Ucal S, Pasanen M, Peräniemi S, Weisell J, Khomutov M, Khomutov AR, Vepsäläinen J, Alhonen L and Keinänen TA: Triethylenetetramine modulates polyamine and energy metabolism and inhibits cancer cell proliferation. Biochem J 473: 1433-1441, 2016.
146. 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-c27, 2015.
147. Jakhmola V, Parashar T, Ghildiyal P, Ansori ANM, Sharma RK, Rao NGR, Kalra K, Singh N, Nainwal N, Singh RK, *et al*: An in silico study to explore the role of EGFR in ovarian cancer. Pharmacog J 14: 817-821, 2022.
148. Zhang X and Yang Q: Association between serum copper levels and lung cancer risk: A meta-analysis. J Int Med Res 46: 4863-4873, 2018.
149. 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.
150. Atakul T, Altinkaya SO, Abas BI and Yenisey C: Serum copper and zinc levels in patients with endometrial cancer. Biol Trace Elem Res 195: 46-54, 2020.
151. Fang AP, Chen PY, Wang XY, Liu ZY, Zhang DM, Luo Y, Liao GC, Long JA, Zhong RH, Zhou ZG, *et al*: Serum copper and zinc levels at diagnosis and hepatocellular carcinoma survival in the Guangdong liver cancer cohort. Int J Cancer 144: 2823-2832, 2019.
152. Lun X, Wells JC, Grinshtein N, King JC, Hao X, Dang NH, Wang X, Aman A, Uehling D, Datti A, *et al*: Disulfiram when combined with copper enhances the therapeutic effects of temozolomide for the treatment of glioblastoma. Clin Cancer Res 22: 3860-3875, 2016.
153. Li Y, Chen F, Chen J, Chan S, He Y, Liu W and Zhang G: Disulfiram/copper induces antitumor activity against both nasopharyngeal cancer cells and cancer-associated fibroblasts through ROS/MAPK and ferroptosis pathways. Cancers (Basel) 12: 138, 2020.
154. Mcauslan BR and Reilly W: Endothelial cell phagokinesis in response to specific metal ions. Exp Cell Res 130: 147-157, 1980.
155. Narayanan G, R BS, Vuyyuru H, Muthuvel B and Konerirajapuram Natrajan S: CTR1 Silencing inhibits angiogenesis by limiting copper entry into endothelial cells. PLoS One 8: e71982, 2013.
156. Mandinov L, Mandinova A, Kyurkchiev S, Kyurkchiev D, Kehayov I, Kolev V, Soldi R, Bagala C, de Muinck ED, Lindner V, *et al*: Copper chelation represses the vascular response to injury. Proc Natl Acad Sci USA 100: 6700-6705, 2003.
157. Nurzynska A, Klimek K, Swierzycka I, Palka K and Ginalska G: Porous curdlan-based hydrogels modified with copper ions as potential dressings for prevention and management of bacterial wound infection-an in vitro assessment. Polymers (Basel) 12: 1893, 2020.
158. Badet J, Soncin F, Guitton JD, Lamare O, Cartwright T and Barritault D: Specific binding of angiogenin to calf pulmonary artery endothelial cells. Proc Natl Acad Sci USA 86: 8427-8431, 1989.
159. Zhao YN, Chen LH, Yang XL, Dong JY, Wu WB, Chen D, Geng RM, Ke NW and Liu J: Inhibition of copper transporter-1 by ammonium tetrathiocarbolybdate in the treatment of pancreatic cancer. Sichuan Da Xue Xue Bao Yi Xue Ban 51: 643-649, 2020 (In Chinese).
160. Pan Q, Bao LW and Merajver SD: Tetrathiomolybdate inhibits angiogenesis and metastasis through suppression of the NFkappaB signaling cascade. Mol Cancer Res 1: 701-706, 2003.
161. Pan Q, Kleer CG, van Golen KL, Irani J, Bottema KM, Bias C, De Carvalho M, Mesri EA, Robins DM, Dick RD, *et al*: Copper deficiency induced by tetrathiomolybdate suppresses tumor growth and angiogenesis. Cancer Res 62: 4854-4859, 2002.
162. Li Y, Fang M, Xu Z and Li X: Tetrathiomolybdate as an old drug in a new use: As a chemotherapeutic sensitizer for non-small cell lung cancer. J Inorg Biochem 233: 111865, 2022.
163. Crowe A, Jackaman C, Beddoes KM, Ricciardo B and Nelson DJ: Rapid copper acquisition by developing murine mesothelioma: Decreasing bioavailable copper slows tumor growth, normalizes vessels and promotes T cell infiltration. PLoS One 8: e73684, 2013.
164. Cosimo RD, Scarpelli A, Lappano R, Pisano A, Santolla MF, De Marco P, Cirillo F, Cappello AR, Dolce V, Belfiore A, *et al*: Copper activates HIF-1α/GPER/VEGF signalling in cancer cells. Oncotarget 6: 34158-34177, 2015.
165. Mammoto T, Jiang A, Jiang E, Panigrahy D, Kieran MW and Mammoto A: Role of collagen matrix in tumor angiogenesis and glioblastoma multiforme progression. Am J Pathol 183: 1293-1305, 2013.
166. Baldari S, Di Rocco G, Heffern MC, Su TA, Chang CJ and Toietta G: Effects of copper chelation on BRAF(V600E) positive colon carcinoma cells. Cancers (Basel) 11: 659, 2019.
167. Brady DC, Crowe MS, Turski ML, Hobbs GA, Yao X, Chaikuad A, Knapp S, Xiao K, Campbell SL, Thiele DJ and Counter CM: Copper is required for oncogenic BRAF signalling and tumorigenesis. Nature 509: 492-496, 2014.
168. Brady DC, Crowe MS, Greenberg DN and Counter CM: Copper chelation inhibits BRAFV600E-driven melanomagenesis and counters resistance to BRAFV600E and MEK1/2 inhibitors. Cancer Res 77: 6240-6252, 2017.
169. Ross MO, Xie Y, Owyang RC, Ye C, Zbihley ONP, Lyu R, Wu T, Wang P, Karginova O, Olopade OI, *et al*: PTPN2 copper-sensing relays copper level fluctuations into EGFR/CREB activation and associated CTR1 transcriptional repression. Nat Commun 15: 6947, 2024.
170. Voli F, Valli E, Lerra L, Kimpton K, Saletta F, Giorgi FM, Mercatelli D, Rouaen JRC, Shen S, Murray JE, *et al*: Intratumoral copper modulates PD-L1 expression and influences tumor immune evasion. Cancer Res 80: 4129-4144, 2020.
171. Xu M, Casio M, Range DE, Sosa JA and Counter CM: Copper chelation as targeted therapy in a mouse model of oncogenic BRAF-Driven papillary thyroid cancer. Clin Cancer Res 24: 4271-4281, 2018.
172. Akins NS, Nielson TC and Le HV: Inhibition of glycolysis and glutaminolysis: An emerging drug discovery approach to combat cancer. Curr Top Med Chem 18: 494-504, 2018.
173. Carneiro BA and El-Deiry WS: Targeting apoptosis in cancer therapy. Nat Rev Clin Oncol 17: 395-417, 2020.
174. Achmad AB, Proboningrat A, Ansori ANM, Fadholly A, Rochmi SE, Samsudin RR, Hidayatik N, Hendarti GA and Jayanti S: Stem bark ethanolic extract of Pinus merkusii induces caspase 9-mediated apoptosis in HeLa cells. Open Vet J 14: 2628-2633, 2024.
175. Weinlich R, Oberst A, Beere HM and Green DR: Necroptosis in development, inflammation and disease. Nat Rev Mol Cell Biol 18: 127-136, 2017.
176. Bergsbaken T, Fink SL and Cookson BT: Pyroptosis: Host cell death and inflammation. Nat Rev Microbiol 7: 99-109, 2009.
177. Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, Patel DN, Bauer AJ, Cantley AM, Yang WS, *et al*: Ferroptosis: An iron-dependent form of nonapoptotic cell death. Cell 149: 1060-1072, 2012.
178. Gao W, Huang Z, Duan J, Nice EC, Lin J and Huang C: Elesclomol induces copper-dependent ferroptosis in colorectal cancer cells via degradation of ATP7A. Mol Oncol 15: 3527-3544, 2021.
179. Pan C, Ji Z, Wang Q, Zhang Z, Wang Z, Li C, Lu S and Ge P: Cuproptosis: Mechanisms, biological significance, and advances in disease treatment-A systematic review. CNS Neurosci Ther 30: e70039, 2024.
180. Huang Z, Wang L, Chen L, Zhang Y and Shi P: Induction of cell cycle arrest via the p21, p27-cyclin E,A/Cdk2 pathway in SMMC-7721 hepatoma cells by clioquinol. Acta Pharm 65: 463-471, 2015.
181. Tsvetkov P, Detappe A, Cai K, Keys HR, Brune Z, Ying W, Thiru P, Reidy M, Kugener G, Rossen J, *et al*: Mitochondrial metabolism promotes adaptation to proteotoxic stress. Nat Chem Biol 15: 681-689, 2019.
182. Tardito S, Bassanetti I, Bignardi C, Elviri L, Tegoni M, Mucchino C, Bussolati O, Franchi-Gazzola R and Marchiò L: Copper binding agents acting as copper ionophores lead to caspase inhibition and paraptotic cell death in human cancer cells. J Am Chem Soc 133: 6235-6242, 2011.
183. Tardito S, Barilli A, Bassanetti I, Tegoni M, Bussolati O, Franchi-Gazzola R, Mucchino C and Marchiò L: Copper-dependent cytotoxicity of 8-hydroxyquinoline derivatives correlates with their hydrophobicity and does not require caspase activation. J Med Chem 55: 10448-10459, 2012.
184. Nagai M, Vo NH, Shin Ogawa L, Chimmanamada D, Inoue T, Chu J, Beaudette-Zlatanova BC, Lu R, Blackman RK, Barsoum J, *et al*: The oncology drug elesclomol selectively transports copper to the mitochondria to induce oxidative stress in cancer cells. Free Radic Biol Med 52: 2142-2150, 2012.

185. Shimada K, Reznik E, Stokes ME, Krishnamoorthy L, Bos PH, Song Y, Quartararo CE, Pagano NC, Carpizo DR, deCarvalho AC, *et al*: Copper-binding small molecule induces oxidative stress and cell-cycle arrest in glioblastoma-patient-derived cells. Cell Chem Biol 25: 585-594 e7, 2018.
186. Yip NC, Fombon IS, Liu P, Brown S, Kannappan V, Armesilla AL, Xu B, Cassidy J, Darling JL and Wang W: Disulfiram modulated ROS-MAPK and NFκB pathways and targeted breast cancer cells with cancer stem cell-like properties. Br J Cancer 104: 1564-1574, 2011.
187. Chen D, Cui QC, Yang H and Dou QP: Disulfiram, a clinically used anti-alcoholism drug and copper-binding agent, induces apoptotic cell death in breast cancer cultures and xenografts via inhibition of the proteasome activity. Cancer Res 66: 10425-10433, 2006.
188. Liu N, Huang H, Dou QP and Liu J: Inhibition of 19S proteasome-associated deubiquitinases by metal-containing compounds. Oncoscience 2: 457-466, 2015.
189. Baldari S, Di Rocco G and Toietta G: Current biomedical use of copper chelation therapy. Int J Mol Sci 21: 1069, 2020.
190. 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.
191. Li P, Sun Q, Bai S, Wang H and Zhao L: Combination of the cuproptosis inducer disulfiram and anti-PD-L1 abolishes NSCLC resistance by ATP7B to regulate the HIF-1 signaling pathway. Int J Mol Med 53: 19, 2024.
192. Huang N, Feng Y, Liu Y, Zhang Y, Liu L, Zhang B, Zhang T, Su Z, Xue L and Wu ZB: Disulfiram mediated anti-tumour effect in pituitary neuroendocrine tumours by inducing cuproptosis. Int Immunopharmacol 134: 112159, 2024.
193. Guo B, Yang F, Zhang L, Zhao Q, Wang W, Yin L, Chen D, Wang M, Han S, Xiao H and Xing N: Cuproptosis induced by ROS responsive nanoparticles with elesclomol and copper combined with αPD-L1 for enhanced cancer immunotherapy. Adv Mater 35: e2212267, 2023.
194. 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.
195. Buccarelli M, D'Alessandris QG, Matarrese P, Mollinari C, Signore M, Cappannini A, Martini M, D'Aliberti P, De Luca G, Pedini F, *et al*: Elesclomol-induced increase of mitochondrial reactive oxygen species impairs glioblastoma stem-like cell survival and tumor growth. J Exp Clin Cancer Res 40: 228, 2021.
196. Solmonson A and DeBerardinis RJ: Lipoic acid metabolism and mitochondrial redox regulation. J Biol Chem 293: 7522-7530, 2018.
197. Harris IS, Endress JE, Coloff JL, Selfors LM, McBrayer SK, Rosenbluth JM, Takahashi N, Dhakal S, Koduri V, Oser MG, *et al*: Deubiquitinases maintain protein homeostasis and survival of cancer cells upon glutathione depletion. Cell Metab 29: 1166-1181.e6, 2019.
198. Zhou S, Kachhap S, and Singh KK: Mitochondrial impairment in p53-deficient human cancer cells. Mutagenesis 18: 287-292, 2003.
199. Matoba S, Kang JG, Patino WD, Wragg A, Boehm M, Gavrilova O, Hurley PJ, Bunz F and Hwang PM: p53 regulates mitochondrial respiration. Science 312: 1650-1653, 2006.
200. Saleem A, Adhihetty PJ and Hood DA: Role of p53 in mitochondrial biogenesis and apoptosis in skeletal muscle. Physiol Genomics 37: 58-66, 2009.
201. Zhang C, Lin M, Wu R, Wang X, Yang B, Levine AJ, Hu W and Feng Z: Parkin, a p53 target gene, mediates the role of p53 in glucose metabolism and the Warburg effect. Proc Natl Acad Sci USA 108: 16259-16264, 2011.
202. Contractor T and Harris CR: p53 negatively regulates transcription of the pyruvate dehydrogenase kinase Pdk2. Cancer Res 72: 560-567, 2012.
203. Bischoff ME, Shamsaei B, Yang J, Secic D, Vemuri B, Reisz JA, D'Alessandro A, Bartolacci C, Adamczak R, Schmidt L, *et al*: Copper drives remodeling of metabolic state and progression of clear cell renal cell carcinoma. Cancer Discov 15: 401-426, 2025.
204. Gan Y, Liu T, Feng W, Wang L, Li LI and Ning Y: Drug repositioning of disulfiram induces endometrioid epithelial ovarian cancer cell death via the both apoptosis and cuproptosis pathways. Oncol Res 31: 333-343, 2023.
205. Liu X, Luo B, Wu X and Tang Z: Cuproptosis and cuproptosis-related genes: Emerging potential therapeutic targets in breast cancer. Biochim Biophys Acta Rev Cancer 1878: 189013, 2023.
206. Liu T, Zhou Z, Zhang M, Lang P, Li J, Liu Z, Zhang Z, Li L and Zhang L: Cuproptosis-immunotherapy using PD-1 overexpressing T cell membrane-coated nanosheets efficiently treats tumor. J Control Release 362: 502-512, 2023.
207. Lu X, Deng W, Wang S, Zhao S, Zhu B, Bai B, Mao Y, Lin J, Yi Y, Xie Z, *et al*: PEGylated Elesclomol@Cu(II)-based Metal-organic framework with effective nanozyme performance and cuproptosis induction efficacy for enhanced PD-L1-based immunotherapy. Mater Today Bio 29: 101317, 2024.
208. Hasinoff BB, Wu X, Yadav AA, Patel D, Zhang H, Wang DS, Chen ZS and Yalowich JC: Cellular mechanisms of the cytotoxicity of the anticancer drug elesclomol and its complex with Cu(II). Biochem Pharmacol 93: 266-276, 2015.
209. Jiao Y, Hannafon BN, and Ding WQ: Disulfiram's anticancer activity: Evidence and mechanisms. Anticancer Agents Med Chem 16: 1378-1384, 2016.
210. Xie L, Gong J, He Z, Zhang W, Wang H, Wu S, Wang X, Sun P, Cai L, Wu Z and Wang H: A copper-manganese based nanocomposite induces cuproptosis and potentiates anti-tumor immune responses. Small 21: e2412174, 2025.
211. Deng L, Liu T, Liu CA, Zhang Q, Song MM, Lin SQ, Wang YM, Zhang QS and Shi HP: The association of metabolic syndrome score trajectory patterns with risk of all cancer types. Cancer 130: 2150-2159, 2024.
212. Song M, Liu T, Liu H, Zhang Q, Zhang Q, Wang Y, Ma X, Cao L and Shi H: Association between metabolic syndrome, C-reactive protein, and the risk of primary liver cancer: A large prospective study. BMC Cancer 22: 853, 2022.
213. Gathirua-Mwangi WG, Song Y, Monahan PO, Champion VL and Zollinger TW: Associations of metabolic syndrome and C-reactive protein with mortality from total cancer, obesity-linked cancers and breast cancer among women in NHANES III. Int J Cancer 143: 535-542, 2018.
214. Springer C, Humayun D and Skouta R: Cuproptosis: Unraveling the mechanisms of copper-induced cell death and its implication in cancer therapy. Cancers (Basel) 16: 647, 2024.
215. Chen Z, Li Y, Yin Y, Song M, Wang F and Jiang G: Cu Nanowires trigger efficient cuproptosis via special intracellular distribution and excessive Cu Ion release. Nano Lett 24: 11446-11453, 2024.
216. Shao R, Visser I, Fros JJ and Yin X: Versatility of the zinc-finger antiviral protein (ZAP) As a modulator of viral infections. Int J Biol Sci 20: 4585-4600, 2024.
217. Zhang N, Yu X, Xie J and Xu H: New insights into the role of ferritin in iron homeostasis and neurodegenerative diseases. Mol Neurobiol 58: 2812-2823, 2021.
218. Ermini ML and Voliani V: Antimicrobial nano-agents: The copper age. ACS Nano 15: 6008-6029, 2021.
219. Lu X, Chen X, Lin C, Yi Y, Zhao S, Zhu B, Deng W, Wang X, Xie Z, Rao S, *et al*: Elesclomol loaded copper oxide nanoplatform triggers cuproptosis to enhance antitumor immunotherapy. Adv Sci (Weinh) 11: e2309984, 2024.
220. Zheng P, Zhou C, Lu L, Liu B and Ding Y: Elesclomol: A copper ionophore targeting mitochondrial metabolism for cancer therapy. J Exp Clin Cancer Res 41: 271, 2022.
221. Woźniak-Budych MJ, Staszak K, and Staszak M: Copper and copper-based nanoparticles in medicine-perspectives and challenges. Molecules 28: 6687, 2023.
222. Brewer GJ: Tetrathiomolybdate anticopper therapy for Wilson's disease inhibits angiogenesis, fibrosis and inflammation. J Cell Mol Med 7: 11-20, 2003.
223. Kim YJ, Tsang T, Anderson GR, Posimo JM and Brady DC: Inhibition of BCL2 family members increases the efficacy of copper chelation in BRAFV600E-Driven melanoma. Cancer Res 80: 1387-1400, 2020.
224. Ishida S, McCormick F, Smith-McCune K and Hanahan D: Enhancing tumor-specific uptake of the anticancer drug cisplatin with a copper chelator. Cancer Cell 17: 574-583, 2010.
225. Lin X, Chen W, Li B, Zhao Z, Yu Z, Zhao XY, Zhou X, Feng Z, Lin C and Cao W: Targeting intratumoral copper inhibits tumor progression via p62-Mediated EZH2 degradation and potentiates Anti-PD-1 immunotherapy in oral squamous cell carcinoma. Adv Sci (Weinh): Jul 28, 2025 (Epub ahead of print).
226. Xue Q, Yan D, Chen X, Li X, Kang R, Klionsky DJ, Kroemer G, Chen X, Tang D and Liu J: Copper-dependent autophagic degradation of GPX4 drives ferroptosis. Autophagy 19: 1982-1996, 2023.

227. Li F, Wu X, Liu H, Liu M, Yue Z, Wu Z, Liu L and Li F: Copper depletion strongly enhances ferroptosis via mitochondrial perturbation and reduction in antioxidative mechanisms. Antioxidants (Basel) 11: 2084, 2022.
228. Derseh HB, Perera KUE, Dewage SNV, Stent A, Koumoundouros E, Organ L, Pagel CN and Snibson KJ: Tetrathiomolybdate treatment attenuates bleomycin-induced angiogenesis and lung pathology in a sheep model of pulmonary fibrosis. Front Pharmacol 12: 700902, 2021.
229. Brewer GJ: The promise of copper lowering therapy with tetrathiomolybdate in the cure of cancer and in the treatment of inflammatory disease. J Trace Elem Med Biol 28: 372-378, 2014.
230. Zhang M, Qiu H, Mao L, Wang B, Li N, Fan Y, Weng P, Hu S, Dong X, Qin X, *et al*: Ammonium tetrathiomolybdate triggers autophagy-dependent NRF2 activation in vascular endothelial cells. Cell Death Dis 13: 733, 2022.
231. Wang T, Lu W, Cheng Z, Wang L, Jiang Z, Yue Y, Jiang P, Xia Z, He L, Wang F, *et al*: Oral engineered extracellular vesicles based on ion exchange strategy for multipronged management of Wilson's disease complicated with reproductive dysfunction therapy. Adv Sci (Weinh) 12: e01689, 2025.
232. Ke Y, Wu C, Zeng Y, Chen M, Li Y, Xie C, Zhou Y, Zhong Y and Yu H: Radiosensitization of clioquinol combined with zinc in the nasopharyngeal cancer stem-like cells by inhibiting autophagy in vitro and in vivo. Int J Biol Sci 16: 777-789, 2020.
233. Yoshiji H, Kuriyama S, Yoshii J, Ikenaka Y, Noguchi R, Yanase K, Namisaki T, Yamazaki M, Tsujinoue H, Imazu H and Fukui H: The copper-chelating agent, trientine, attenuates liver enzyme-altered preneoplastic lesions in rats by angiogenesis suppression. Oncol Rep 10: 1369-1373, 2003.
234. Yang M, Wu X, Hu J, Wang Y, Wang Y, Zhang L, Huang W, Wang X, Li N, Liao L, *et al*: COMMD10 inhibits HIF1α/CP loop to enhance ferroptosis and radiosensitivity by disrupting Cu-Fe balance in hepatocellular carcinoma. J Hepatol 76: 1138-1150, 2022.
235. Wang Y, Li W, Patel SS, Cong J, Zhang N, Sabbatino F, Liu X, Qi Y, Huang P, Lee H, *et al*: Blocking the formation of radiation-induced breast cancer stem cells. Oncotarget 5: 3743-3755, 2014.
236. Wu L, Meng F, Dong L, Block CJ, Mitchell AV, Wu J, Jang H, Chen W, Polin L, Yang Q, *et al*: Disulfiram and BKM120 in combination with chemotherapy impede tumor progression and delay tumor recurrence in tumor initiating cell-rich TNBC. Sci Rep 9: 236, 2019.
237. Sun T, Yang W, Toprani SM, Guo W, He L, DeLeo AB, Ferrone S, Zhang G, Wang E, Lin Z, *et al*: Induction of immunogenic cell death in radiation-resistant breast cancer stem cells by repurposing anti-alcoholism drug disulfiram. Cell Commun Signal 18: 36, 2020.
238. Zhou P, Qin J, Zhou C, Wan G, Liu Y, Zhang M, Yang X, Zhang N and Wang Y: Multifunctional nanoparticles based on a polymeric copper chelator for combination treatment of metastatic breast cancer. Biomaterials 195: 86-99, 2019.
239. Hu H, Hua S, Lu F, Zhang W, Zhang Z, Cui J, Lei X, Xia J, Xu F and Zhou M: Mucous permeable nanoparticle for inducing cuproptosis-like death in broad-spectrum bacteria for nebulized treatment of acute pneumonia. Adv Sci (Weinh) 12: e2408580, 2025.
240. Wu A, Yin N, Li Z, Zhang X, Zhang Z, Zhong T, Xia F, Pan J, Wang D, Liu L and Dong J: FDX1 facilitates elesclomol-induced cuproptosis and promotes glioblastoma development via transcription factor NFKB1. Biochem Pharmacol 241: 117186, 2025.
241. Wang W, Lu K, Jiang X, Wei Q, Zhu L, Wang X, Jin H and Feng L: Ferroptosis inducers enhanced cuproptosis induced by copper ionophores in primary liver cancer. J Exp Clin Cancer Res 42: 142, 2023.
242. Zulkifli M, Spelbring AN, Zhang Y, Soma S, Chen S, Li L, Le T, Shanbhag V, Petris MJ, Chen TY, *et al*: FDX1-dependent and independent mechanisms of elesclomol-mediated intracellular copper delivery. Proc Natl Acad Sci USA 120: e2216722120, 2023.
243. Chisholm CL, Wang H, Wong AH, Vazquez-Ortiz G, Chen W, Xu X and Deng CX: Ammonium tetrathiomolybdate treatment targets the copper transporter ATP7A and enhances sensitivity of breast cancer to cisplatin. Oncotarget 7: 84439-84452, 2016.
244. Feng L, Wu TZ, Guo XR, Wang YJ, Wang XJ, Liu SX, Zhang R, Ma Y, Tan NH, Bian JL and Wang Z: Discovery of natural resorcylic acid lactones as novel potent copper ionophores covalently targeting PRDX1 to induce cuproptosis for triple-negative breast cancer therapy. ACS Cent Sci 11: 357-370, 2025.
245. 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.
246. Ahire JJ, Neveling DP and Dicks LMT: Polyacrylonitrile (PAN) nanofibres spun with copper nanoparticles: An anti-Escherichia coli membrane for water treatment. Appl Microbiol Biotechnol 102: 7171-7181, 2018.
247. Cendrowska-Pinkosz M, Krauze M, Juśkiewicz J, Fotschki B and Ognik K: The influence of copper nanoparticles on neurometabolism marker levels in the brain and intestine in a rat model. Int J Mol Sci 24: 11321, 2023.
248. Geng X, Liu K, Wang J, Su X, Shi Y and Zhao L: Preparation of ultra-small copper nanoparticles-loaded self-healing hydrogels with antibacterial, inflammation-suppressing and angiogenesis-enhancing properties for promoting diabetic wound healing. Int J Nanomedicine 18: 3339-3358, 2023.
249. Li L, Tai Z, Liu W, Luo Y, Wu Y, Lin S, Liu M, Gao B and Liu JX: Copper overload impairs hematopoietic stem and progenitor cell proliferation via prompting HSF1/SP1 aggregation and the subsequently downregulating FOXM1-Cytoskeleton axis. iScience 26: 106406, 2023.
250. Petruzzelli R and Polishchuk RS: Activity and trafficking of copper-transporting ATPases in tumor development and defense against platinum-based drugs. Cells 8: 1080, 2019.
251. Nayagam JS, Jeyaraj R, Foskett P, Dhawan A, Ala A, Joshi D, Bomford A and Thompson RJ: ATP7B genotype and chronic liver disease treatment outcomes in wilson disease: Worse survival with loss-of-function variants. Clin Gastroenterol Hepatol 21: 1323-1329.e4, 2023.
252. Wang Y, Li D, Xu K, Wang G and Zhang F: Copper homeostasis and neurodegenerative diseases. Neural Regen Res 20: 3124-3143, 2025.
253. Chan N, Willis A, Kornhauser N, Ward MM, Lee SB, Nackos E, Seo BR, Chuang E, Cigler T, Moore A, *et al*: Influencing the tumor microenvironment: A phase II study of copper depletion using tetrathiomolybdate in patients with breast cancer at high risk for recurrence and in preclinical models of lung metastases. Clin Cancer Res 23: 666-676, 2017.
254. Yang Z, Su W, Wei X, Pan Y, Xing M, Niu L, Feng B, Kong W, Ren X, Huang F, *et al*: Hypoxia inducible factor-1α drives cancer resistance to cuproptosis. Cancer Cell 43: 937-954.e9, 2025.
255. Zhang J, Han H, Wang L, Wang W, Yang M and Qin Y: Overcoming the therapeutic resistance of hepatomas by targeting the tumor microenvironment. Front Oncol 12: 988956, 2022.
256. Chen L, Ma S, Wu H, Zheng L, Yi Y, Liu G, Li B, Sun J, Du Y, Wang B, *et al*: Zonated copper-driven breast cancer progression countered by a copper-depleting nanoagent for immune and metabolic reprogramming. Adv Sci (Weinh) 12: e2412434, 2025.