Review Articles

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Metal ions as effectual tools for cancer with traditional Chinese medicine

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Abstract

Malignant tumor has become a major threat affecting human health, and is one of the main causes of human death. Recent studies have shown that many traditional Chinese medicines (TCM) have good anti-tumor activity, which may improve the therapeutic effect of routine treatment and quality of life with lower toxicity. However, the efficacy of TCM alone for the treatment of tumors is limited. Metal ions are essential substances for maintaining normal physiological activities. This article summarized the multiple mechanisms in which metal ions are involved in the prevention and treatment of tumors in TCM.

Keywords: Metal ions, Traditional Chinese medicine, Treatment modalities, Tumor development

Introduction

Cancer is considered to be one of the leading causes of human death in the world[1]. Cancer incidence and mortality are on the rise in some countries according to the statistics[2–3]. Studies have shown that traditional Chinese herbal medicine may improve the symptoms of disease, the quality of life with a better safety profile. Therefore, it is expected to play an essential role in cancer treatment[4–9]. However, there is limited high-quality evidence on the efficacy of traditional Chinese medicine (TCM) in treating cancer[10–11]. A study examined the potential mechanisms of some natural products in regulating cancer progression, suggesting that the natural product is a good way to reduce cancer cases and relevant cancer mortality[12]. Metal ions are essential elements for maintaining normal physiological activities in humans, and their role in biological processes was discovered for a long time[13–14]. Metal ions are involved in several biochemical reactions with multiple structural and functional types. Although they are essential for normal physiological processes, they appear to be toxic or even carcinogenic at higher concentrations[15–16]. The roles of metals are vary under different conditions[17–20].

In this review, we reviewed the role of metal ions in tumor progression, as well as the anti-tumor effects of TCM or natural products by regulating metal ions. We document the different therapeutic modalities, as well as the positive and negative aspects in the process. It is expected that this article will provide the latest research progress and establish new ideas and strategies for the development of therapeutic methods and ideas for cancer treatment with TCM targeting metal ions.

Advantages

Enhancing biological activity

Many compounds derived from TCM sometimes show only limited bioactivity for cancer treatment *in vivo*. Enhancing the bioactivity of potential anti-tumor natural products has been the focus of current research[21–22]. Metal ions mainly interact with the active compounds or form complexes, which enhance the biological activity of TCM (Table 1).

Interactions of TCM and metal ions

Thymol, widely found in many plants and used in the diet and traditional medicine, appears to have anti-tumor activity. Thymol-exposed human glioblastoma cells showed an increase in the Ca^{2+} level. The mechanism of Ca^{2+} rise was associated with phospholipase C release, which led to the release of Ca^{2+} from the ER and entry of Ca^{2+} by channels. Furthermore, thymol caused apoptosis and necrosis in a dose-dependent manner[23]. Baicalein, mainly derived from *Scutellaria baicalensis*, significantly impeded the growth of breast cancer cells Michigan Cancer Foundation-7 (MCF-7) cells. The intracellular redox cycling of Cu (II) and reactive oxygen species (ROS) formation play a synergistic effect with baicalein on cell growth inhibition[24]. A similar effect was found in catechins, a common dietary phytochemical. In cancer cells, catechins exhibit antioxidant capacity, leading to cytotoxic effects by inducing redox activity of endogenous transition metal copper to produce large amounts of ROS. Catechins cause cellular DNA breaks, which are remarkably improved when copper is present[25].

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Table 1

Metal ions enhance the anti-cancer biological activity of various natural products in different ways

Work way	Metal ions	Natural products	Action mechanism	Reference
Interactions of TCM and metal ions	Ca^{2+}	Thymol	Induction of apoptosis and necrosis in glioblastoma cells.	[23]
	Cu^{2+}	Baicalein; catechins	Baicalein induces apoptosis in MCF-7 cells through intracellular copper mobilization *via* accumulation of ROS and mitochondrial apoptotic pathways	[24–25]
Formation of TCM-metal complexes	Ni^{2+}	Curcumin	The curcumin-Ni (II) complex generates ROS under electron excitation at low energy visible light and induces cell death through apoptosis	[26]
	Ru^{2+}	Curcumin	The resulting complex induces apoptosis in cancer cells through DNA embedding and inhibition of the MEK/ERK signaling pathway	[27]
	Fe^{3+}	Curcumin	Iron-curcumin complexes inhibit cell proliferation of breast cancer cells at low doses	[28]
	Mg^{2+}, Zn^{2+}, Cu^{2+}, Mn^{2+}	Diacetylcurcumin	Anti-oxidant effect	[29]
	Pd^{2+}	Bisdemethoxy-curcumin	Enhanced anti-proliferative activity	[30]
	V^{4+}, Ru^{2+}, Ru^{3+}	Quercetin, Luteolin, Chrysin, Baicalein	Induces cell cycle arrest and induces apoptosis by upregulating p53, caspase-3, caspase-9 and Bax, followed by down-regulating Bcl-2, VEGF, mTOR and Akt	[31–35]
	La^{3+}	Quercetin	Inhibits the proliferation of cancer cells by binding to DNA	[36]
	Cu^{2+}	Myricetin, taxifolin, morin, kaempferol	Such complexes promote the formation of ROS and kill cancer cells by causing DNA damage	[37–38]
	Zn^{2+}, Fe^{2+}	Carboxymethyl pachymaran	Significantly inhibited the proliferation of human ovarian cancer cell line A2780 cells, promoted the production of reactive oxygen species and induced apoptosis	[39]
	Zn^{2+}	Butylsalicylate	By down-regulating STAT3 signaling through the SRC pathway, thereby affecting the migration and invasive ability of the cells	[40]

TCM: traditional Chinese medicine.

Formation of TCM-metal complexes

Ni(II) significantly enhances the stability of polyphenol curcumin as a co-ligand. Curcumin-Ni(II) complex shows an excellent photocytotoxity on cancer cells, such as HeLa and A549, compared with curcumin alone[26]. A novel curcumin-Zn dispersion inhibits liver cancer growth and can be used as a chemotherapeutic sensitizer *in vitro* and *in vivo*[41]. Li et al. prepared two types of Ruthenium(II)-polypyridyl complexes based on curcumin, which exhibited positive synergistic effects on cancer cells[27]. The iron-curcumin complex (10–100 μM) shows the highest cytotoxicity against MDA-MB-231, significantly decreasing proliferation of cells by 20% to 90%[28]. Diacetylcurcumin (DAC) could form complexes with the physiologically essential metals Zn, Mn, Cu, and Mg. The metal complexes of DAC were found to exhibit higher anti-cancer and antioxidant activities than DAC alone in three cancer cell lines, HCT-15, MCF-7, and SKLU-1[29]. Bisdemethoxycurcumin (BDMC) could suppress cancer cell proliferation, growth of malignancies, and metastasis, and showed improved anti-proliferative ability when binding with palladium (II) to form tight complexes[30].

Recently, flavonoid complexes with metal ions have been considered to be a new category of active agents with improved therapeutic ability and decreased toxicity. Quercetin, a main flavonoid, is considered to be a good antioxidant derived from herbs. *In vitro* tests have shown that vanadium (V)-quercetin complexes can arrest the cell cycle and induce apoptosis by upregulating pro-apoptotic proteins, such as caspases 3 and 9, p53, Bax, and further downregulate the expression of vascular endothelial growth factor (VEGF), B-cell lymphoma-2 (Bcl-2), protein kinase B (Akt) and mechanistic target of rapamycin (mTOR) of rat breast cancer and MCF-7 cells. Thus, V-quercetin induces apoptosis and inhibits cancer cell growth associated with the anti-angiogenic pathway[31]. Similarly, the Ru-quercetin, V-luteolin, and Ru-chrysin complexes induce cancer cells to undergo apoptotic cell death by activating p53 through activation of apoptotic factor Bax and caspase-3 while inhibiting the mTOR/Akt pathway[32–35]. Lanthanum (III), a rare-earth metal, forms a complex with quercetin which binds to DNA, inhibits tumor cells better than quercetin does[36]. In a study of a series of flavonoids-copper (II) complex, myricetin, morin, and taxifolin forms stable complexes with copper (II) and cause damage to DNA *via* ROS formation, which further kills cancer cells[37]. Kaempferol, another anti-tumor flavonoid, could also be ligated with redox-active Cu(II) ions to form complexes, which shows better anti-cancer properties *via* pro-oxidant activity[38].

Polysaccharides possess properties for the chelation of metal ions, which are commonly used for the synthesis of polysaccharides complexes with metal ions. A fungus from China, *Poria cocos*, is used for both medicinal and edible purposes. Carboxymethyl pachymaran has no inhibitory impact on the proliferation of the ovarian cancer cell line A2780 cells, while the complex with iron and zinc causes efficient inhibition of A2780 cell growth, production of ROS, and apoptosis[39]. The fruits of *Pyracantha fortuneana* are a high-quality natural plant resource for medicinal and edible purposes, with a polysaccharide content ranging from 10.59% to 13.40% in the fruit pulp. By characterizing of the Pyracantha polysaccharide-iron (PPI), a complex formed by this polysaccharide and iron, it was demonstrated that PPI has anti-oxidative activity *in vitro*. Furthermore, the mRNA of human ovarian cancer cells Skov3 was examined by high-throughput sequencing, and a total of 29,078

cancer-related genes were detected, with 873 genes differing between control and PPI groups. After PPI treatment, 455 genes were significantly upregulated and 418 genes downregulated, indicating significant anti-cancer activity[42].

Zinc 3,5-di-tert-butylsalicylate complexes, formed by salicylic acid and zinc ions, inhibit the activity of triple-negative breast cancer (TNBC) 4T1 cells by down-regulating STAT3 signaling *via* the SRC pathway, thereby affecting the migration of the cells and their invasive ability, thus meriting further investigation as potential therapeutic agents for TNBC[40].

Improving bioavailability

Many active compounds derived from TCM have good therapeutic potential for treating cancers[43–46]. However, clinical applications of these active compounds are not widely available due to the low bioavailability[47–50]. With the development of preparation technology, new drug delivery systems (DDS) was introduced to improve the efficacy of anti-cancer drugs or lower the side effects by improving the bioavailability of anti-tumor compounds[51–54].

Metal–organic framework-based DDSs

Metal–organic frameworks (MOFs) are composed of organic ligands clusters with metal ions/metal through coordination bonds, which turn them into crystalline porous material. Since MOFs are functional and tunable, efforts have been made to develop MOF-based stimulus-responsive systems and composites of MOFs for biomedical applications. MOF is often used as a drug carrier due to its special properties, such as great porosity, broad surface area, adjustable size of pore, structural stability, biocompatibility, and minimal toxicity[47–55].

Curcumin has anti-cancer and anti-oxidative activities, but the major issues with its delivery are the hydrophobicity and poor bioavailability. In a study, MIL-101 (Fe) was used as a pH-sensitive carrier for the loading and sustained release of the anti-cancer compound, curcumin. The results indicated that diffusion was the main driver of the release of curcumin[56]. MIL-101 (Fe)-NH2 chelates with tannic acid (TA) to form an iron-rich metal–organic framework, which efficiently loads adriamycin (DOX) into the inner lumen of MOF to form a tumor-targeted and acid-activated DSS with good tumoricidal effect and biosafety[57]. MIL-53(Fe) can also be used as a carrier for the drug against cancer, oridonin. The cytotoxicity of Ori@MIL-53(Fe)'s on HepG2 cells is high, as its anti-cancer ratio reached 90.62%[55]. Artemisinin, extracted from the *Artemisia annua*, shows significant anti-cancer activity on some cancer cell lines. Inspired by recent interest in supramolecular assembly of metal phenol ligand coatings on MOF surfaces, a TA-Fe(II)-based artemisinin (ART)-supplied iron-supplied nanocarrier was developed, coated on ZIF nanoparticles (NPs), and ART was self-assembled by ligand-driven encapsulation to enhance iron apoptosis in triple-negative breast tumor cells. Nanocarriers can dissolve and release ART and Fe(II) in a weak acidic microenvironment, causing high levels of intracellular ROS and MDA, which promoted a decrease in GSH and glutathione peroxidase 4 (GPX4), thus effectively inhibiting tumor growth and anti-cancer[58].

DDSs based on NP

With rapid advances in nanomedicine technology, nanotechnology has developed into cancer treatments such as radiotherapy, chemotherapy, imaging, and diagnostics. It shows the ability to enhance cancer therapy and improve patient care. Nanomaterials offer a wealth of adaptability and applications to design drugs for cancer, with nanomedicines designed to enhance the anti-tumor activity of drugs derived from plants. Both nanotechnology and metal NPs synthesized from plant extracts will be useful for the further development of anti-cancer therapies[59–63].

Carrageenan oligosaccharides (CAOs) are sulfated polysaccharides extracted from marine red algae, which could form stable and biocompatible AuNPs. The CAO-AuNPs were further utilized to deliver pH-triggered transport of epirubicin, enabling a new pH-triggered release of anti-cancer drugs[64]. Ginseng berries (GB) present advantageous pharmacological activities. The active compounds found in GB extract (GBE) effectively reduce and cap ions of silver (Ag) and gold (Au) to form GB-AgNPs and GBAuNPs. GBE contains phenolic compounds and polysaccharides that are believed to be important for the NPs' functionalization and stabilization. GBAuNPs are not toxic to both human dermal fibroblasts and mouse melanoma cells, whereas GB-AgNPs have cytotoxic effects on mouse melanoma cell lines[65]. To maximize delivery efficiency to tumors, PEG-PLGA NPs encapsulated with astragalus polysaccharide (APS) and Au nanorods were assembled to enhance focused ultrasound-induced immunity and achieve systemic durable anti-tumor immunity[66]. The biosynthesis of AuNPs using highly concentrated aqueous extract solutions of *Nigella sativa* and *Zingiber officinale* showed good cytotoxicity against both breast and colorectal cancer cell lines[67]. *Origanum vulgare* is a herb with multiple therapeutic properties. Biocompatible AuNPs synthesized from the aqueous extract of *O. vulgare* were well consumed by normal human dermal fibroblast (HDF) cells and more toxic effects on melanoma WM35 cancer cells, indicating the potential anti-cancer effects[68]. The Au and AgNPs loaded *Ginseng leaf extract* are applied to the *in vitro* study of cancer cells and inflammatory cells, which show great anti-cancer effects on lung cancer cells A549, B16BL6 Meno tumor, and B16BL6 black retinal cancer cells, and anti-inflammatory effects on the Raw 264.7 cell line[69]. *Lithospermum erythrorhizon* is a herb rich in shikonin and its derivatives. Modern pharmacological researches have shown that shikonin has a broad range of biological functions, such as anti-viral, anti-inflammatory, anti-cancer, immunomodulatory and anti-estrogenic activities[70]. The synthesized stable metal NPs of shikonin with AuNPs, AgNPs, and bimetallic Au-Ag NPs were found to have significant cytotoxicity but have little effect on migrated cells[71].

The leaves of *Cassia fistula* are a prominent medicinal Indian plant that is widely used against acute and

common diseases. By biosynthesizing AgNPs (AgNPs) with *C. fistula* leaf extract, a significant toxic effect was observed on A-431, a skin cancer cell, with little toxic effect on normal cells[72]. The AgNPs synthesized by the extract of *Perilla frutescens* shows pro-apoptosis effect against the colon cancer cell line COLO205 and the human prostate cancer LNCaP cell lines in a dose-dependent manner[53]. AgNPs synthesized with the extract of *Ginkgo biloba* (GB-AgNPs) shows anti-cancer ability against cervical cancer. GB-AgNPs NPs inhibit the proliferation of cancer cells and induce apoptosi by increasing the level of intracellular ROS production. They also promote the activation of cysteine-controlled mitochondrial apoptosis in cervical cancer cells[73]. The AgNPs with extract of *Cynara scolymus* leaf helped internalize the drug into cancer cells. The combination of synthesized AgNPs and photodynamic therapy showed effective anti-cancer activity by inducing the intrinsic apoptotic pathway through decreasing the levels of anti-apoptotic Bcl-2 protein and increasing the pro-apoptotic Bax protein in MCF-7 breast cancer cells[74]. AgNPs biosynthesized using the seaweed polysaccharide fucoidan, a polysaccharide isolated from brown seaweed with a variety of biological activities, remarkably impeded microbial growth and revealed potent anti-tumor activity against HeLa cells (human cervical cancer)[75]. The dihydromyricetin (DMY) is a natural flavonoid with anti-cancer and other properties. Compared with DMY, DMY-AgNP exhibits excellent biocompatibility and exhibits superior anti-tumor activity against cancer cell lines such as Hela, MDA-MB-231, and HepG2[50].

Among the NPs obtained from the safflower's aqueous extract with four metal ions, AgNPs and CuNPs showed effective activity against cancer cell lines, such as Caco-2, T47D, and HEPG2, with safflower CuNPs showing the higher anti-cancer activity as agents compared with the safflower extract[76]. Morin is a flavonol, and after encapsulating morin-Cu(II) into NPs based on HSA and PLGA, the NPs were able to deliver the morin-Cu (II) complex more efficiently in cells and microorganisms. Therefore, NPs showed better anti-cancer activity compared with morin-Cu(II) complexes and morin[54].

Emodin (EMO), a natural anthraquinone, has been widely used for the treatment of cancers, such as leukemia and colorectal cancer. The EMO was coupled with magnetic NPs to design a therapeutic diagnostic nanoplatform (Fe_3O_4-PEG-Cy7-EMO), which was demonstrated to provide therapy for pancreatic cancer cell lines and achieve magnetic resonance imaging/fluorescence imaging (MRI/FI) dual-modality imaging. Furthermore, the *in vivo* experiments using 12 *in situ* human pancreatic tumor xenograft models revealed that Fe_3O_4-PEG-Cy7-EMO showed the most pronounced inhibitory effect against the growth of cancer[77]. Paclitaxel (PTX) is an effective anti-cancer agent used in the treatment of several types of cancer. In order to improve the bioavailability of PTX, NPs made of iron oxide (IONP) were used to overcome the limitations of conventional therapy. The UV and visible absorption spectroscopy analysis revealed that IONP was loaded with PTX with a good release. The relative expression levels of IONP@PTX autophagy-associated proteins Beclin1 and LC3II to LC3I were upregulated, whereas the expression of p62 was downregulated. Compared with PTX alone, IONP@PTX inhibits U251 cells more strongly and suppresses glioblastoma invasion and cell migration, which is related to the activation of the autophagic pathway[78].

In a study to synthesize PTX-loaded Mn-doped ZnS NPs (Mn:ZnS NPs) encapsulated by cell-penetrating peptides, *in vivo* biodistribution, and anti-cancer efficacy were investigated on a breast cancer xenograft model. The developed Mn:ZnS NPs were found to show enhanced anti-cancer effects compared with PTX alone[79]. Curcumin-loaded ZnO NPs coupled with pH-sensitive (ZnO-PBA-curcumin) and phenyl boronic acid (PBA) caused apoptosis in the MCF-7 cells by inducing mitochondrial damage and oxidative stress. ZnO dissociated at low pH, that is, the release of curcumin was higher in cancer cells compared with normal cells. It resulted in a high drug loading and release profile with a significant advantage, and significantly enhanced the anti-tumor efficacy *in vitro* and *in vivo*[80].

A skeleton-type pre-drug copolymer of curcumin and platinum (IV) was designed and self-assembled into NPs. *In vitro* results demonstrated that Pt NPs showed high intracellular uptake and improved the inhibition of cell proliferation in the HeLa cells. Pt NPs showed the highest inhibitory effect on DDP and A549 cells, compared to curcumin[81].

APS, one of the highly active agents extracted from *Astragalus root*, is a prepared unique water-soluble NPs by chelating APS with sodium selenite. *In vitro* bioactivity of Se-APS-NP was investigated with good bioavailability. It not only increased the T lymphocytes' cell proliferation and showed high immunoprotective activity, but also inhibited the proliferation of the HepG2 cell line and reduced invasion and cell migration[82].

Metal-mediated regulation of herbzyme activity

Nanozymes, as a class of artificial enzymes, can consist of NPs made of metal and metal oxide, or nanoclusters of quantum and carbon dots, nanowires, nanotubes, or multiple MOFs[83]. Herbzymes are biocatalytic nanomaterials with nanozyme activity, combining the benefits of natural and artificial mimetic enzymes, which act through adjustable catalytic activity and nanostructure[84].

Processed herbs are widely used in medicine, yet the associated pharmacodynamic mechanisms are not clear. The nanostructures formed by the processing of *Rhizoma polygonati* (RP) or their assemblies were correlated with the enzyme activity shown in the last product by enzymatic assays and Fourier Transform infrared spectroscopy (FT-IR) spectroscopy together with quantum mechanical calculations. This article proposes a new term which is suggested here here to summarize the novel concept of enzymatic action in herbal processing, namely herbzyme, from the fusion of herbs and enzymes. Elemental and amino acid analyses revealed prominent levels of Ca^{2+} and glutamate, in which Ca^{2+} significantly inhibited alkaline phosphatase, but enhanced phosphatase-like activity of herbzyme. The addition of EthyleneDiamine Tetraacetic Acid (EDTA), which chelates metal ions and makes them unavailable, significantly inhibited the enzymatic activity of RP in a concentration dependent

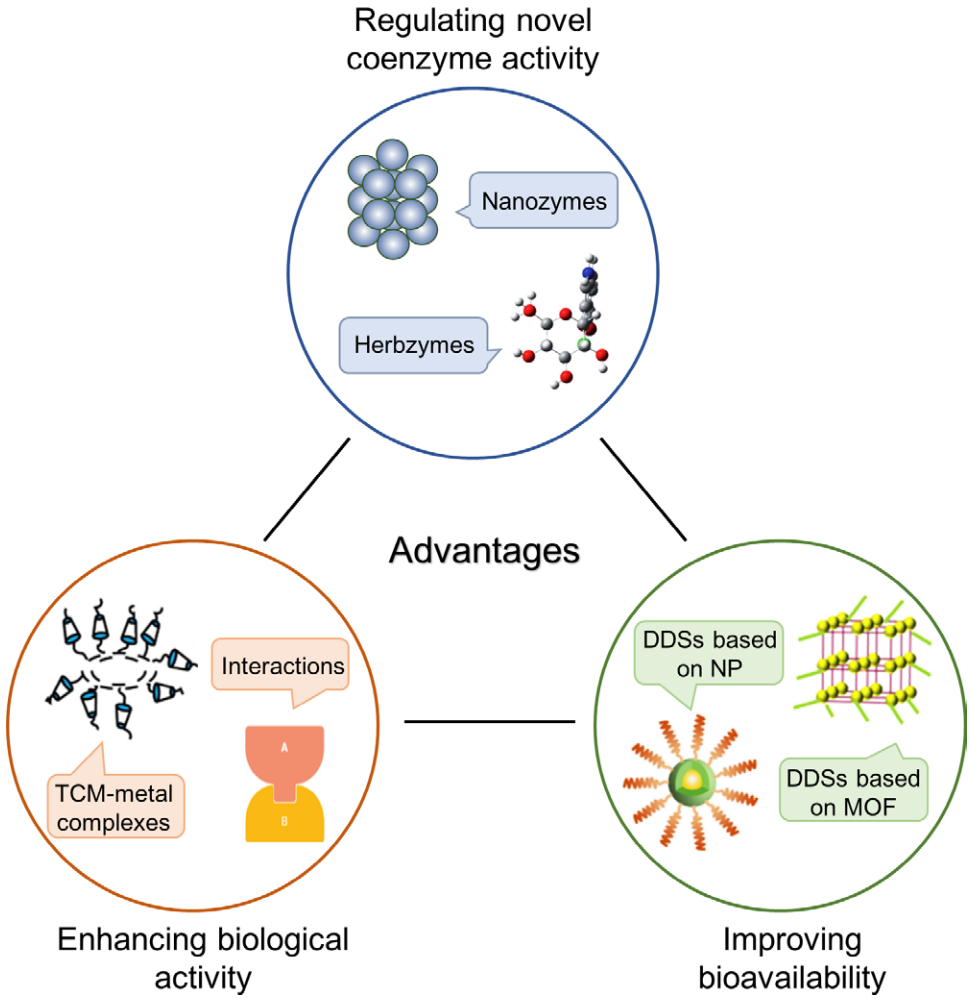

Figure 1. The advantages of metal ions in the treatment of tumors and prevention with TCM. TCM: Traditional Chinese medicine.

manner, demonstrating the importance of Ca^{2+} in nanozyme activity of the herb. The phosphatase-like activity shown by treated natural herb was observed to be effective in inhibiting the growth of cancer cells *via* phosphatase signaling through DNA damage[85].

Elemental analysis of nanozymes extracted from herbs revealed a high abundance of Fe, among other elements. The extracted proteins were divided into main six categories and their approximate evolutionary closeness was predicted. Nano-evolution of herb-based nanozymes showed conserved common types of enzymes, such as fructose-bisphosphate aldolase, which can be used to predict new types of herbzymes[86].

In another study, the anti-cancer effects of carbon NPs (CNPs), derived from food-herb-homology such as beet and soybean, was examined[87]. The treatment with NPs caused cell bursting, similar to cell death. The anti-cancer effect of CNPs was explained by its intrinsic phosphatase activity, as well as the enhancement of drug resistance against PARP inhibitors. Since the phosphatase activity of beet and soybean derived NPs was found to be similar to phospho-tyrosine phosphatases, the presence of metal ions could influence their phosphatase activity. In order to examine it, nanozyme activity should be compared with the activity of metal-dependent phosphatases as well, as the activity of metallophosphatases is based on the presence of at least two metal ions in their substrate[88].

Metal-based therapeutic agents are now commonly used in clinical treatment. Many nanoscale materials have been used to design enzyme-responsive systems over the past few years. In one study, it was discovered that the integration of nanomaterials with enzyme reactions could confer the biospecificity and selectivity of metal complexes. For example, Chen and colleagues developed a biocompatible DNA nanostructure for the transport of an anti-tumor ruthenium complex. The structure not only improved the loading efficiency of the therapeutic agent, but also upon internalization transferred to the nucleus and was degraded by DNase, leading to the release of the drug and induction of apoptosis *via* the signaling pathway mediated by ROS[89]. Relevant elements are shown in Figure 1.

Overcoming problems

Carcinogenicity of metal ions

Cadmium (Cd) is a transition metal with high toxicity that may accumulate in animals and plants, which poses a health risk to humans. Recent research has shown that Cd is capable of causing disease risk and the development of various cancers *in vivo* and *in vitro*. The International Agency for Research on Cancer considers Cd to be carcinogenic agent when inhaled[90].

Vanadium (V) has been a hot topic of research in many research centers because of its broad range of effects and various biological activities. Even though the use of vanadium in medicine increasing and the therapeutic activities reported, the accumulation and high toxicity are main limitation for application[91].

Chromium (Cr) is a metallic element, and although Cr(III) is evaluated as non-toxic, Cr(VI) has been identified as a class I carcinogen. The current resources suggest that Cr(VI) is capable of improving carcinogenesis through epigenetic and genetic mechanisms. Although the importance of oxidative stress in carcinogenesis caused by Cr(VI) has received much attention, future studies should focus on additional aspects in order to gain a complete understanding of carcinogenesis caused by Cr(VI)[92–93].

Nickel (Ni) is a recognized human carcinogen that does not directly induce DNA mutagenesis or construct DNA adducts. It demonstrates very small or no mutagenicity in mutagenicity assays. Ni exposure was found to result in a decrease in the level of DNA repair proteins that are important in mismatch repair and homologous DNA double-strand break repair in cancerogenic and non-cancerogenic human lung cells. It also inhibits DNA repair by transcriptional pathways which mimics acute hypoxia, and may contribute to carcinogenesis induced by nickel[94].

The iron is a key element of many biochemical reactions and is vital for the normal maintenance of human health. However, dysregulation of iron homeostasis caused by lifestyle and genetic factors may lead to a higher cancer risk[95]. Excess iron has an essential role in tumorigenesis, and iron deficiency can lead to increased oxidative stress that affects immune function and alters cellular oxidative metabolic conditions, leading to cancer development[96].

Zinc (Zn), a micronutrient, is involved in several functions in adequate amounts and is primarily important for human health. However, the deficiency of Zn is often associated with a high risk of cancer, such as acute myeloid leukemia. It has been shown that normal levels of Zn are cytotoxic to cancer cells, but a deficiency of Zn can promote cancer development[97].

Lack of specificity for target tissues

As Prasad et al. noted, that curcumin-metal complexes have better anti-inflammatory, antioxidant, antibacterial, and anti-viral properties compared to curcumin alone. Complexes can be used in the treatment of diseases such as arthritis, cancer, neurological disorders, osteoporosis, and other diseases. Some metals are more effective than others in certain health conditions, and finding out which metals together with curcumin show higher advantageous effects in certain diseases is the goal of future studies. However, which metal complexes are most effective in certain diseases is the main problem to be solved of future studies[98].

Chen et al. found that Zn-3,5-di-tert-butylsalicylate complexes formed by salicylic acid and Zn inhibited the invasion, viability, and migration of 4T1 cells, a TNBC cell line, and induced apoptosis *in vitro*. However, the compound did not have an anti-metastatic effect *in vivo*. Therefore, it was speculated that the anti-cancer agent was not properly transferred to the target tissues to act[40].

Lack of clinical research

Nagoor et al. pointed out that thymol has various pharmacological properties, such as anti-tumor, and has played a role in many types of diseases. There were several attempts to achieve higher bioavailability using many techniques, such as the preparation of NP formulations, to improve the DDS. However, the majority of information is pre-clinical data and further clinical studies are needed to validate the findings. In addition, to improve clinical studies, complete toxicological and safety research should be conducted to ensure the safety of thymol in animal models[23]. In a study based on a comprehensive review and perspective of DDSs for MOFs, various representative applications of MOFs are explained from the perspective of pharmacology, disease treatment, and applications in advanced DDS, while challenges in advanced DDS are discussed. All in all, *in vivo* data on MOFs are scarce and pre-clinical biosafety assessments are lacking. Thus the biomedical applications of MOFs still face many challenges[47].

Unclear specific mechanisms

Two phytoflavonoids, apigenin and lignan, could form complexes with ferrous or copper ions and change the stability and *in vitro* anti-cancer activity. However, the relevant molecular mechanisms remain unclear, and further studies are needed[99].

There is abundant evidence that bioactive compounds are found in large amounts of algae, such as fucoidan and sulfated polysaccharides. Despite the excellent antibacterial and anti-cancer efficacy of green-synthesized Ag and AuNPs, the mechanism regarding algal metal NPs remains unclear. Furthermore, extensive studies must be conducted to determine the role of specific biomolecules in the production of metal NPs mediated by algae[100].

Toxic effects

Flavonoids exert biological effects partly through complexation with ions of transition metal iron. On the one hand, the complexing ability of the complex is closely related to the potential beneficial preventive and therapeutic effects; on the other hand, complexed iron can greatly affect the biological properties of flavonoids and their potential toxicity risk must be considered[101].

As drug transport systems for oncology treatment, MOFs have shown great advantages due to their unique structural scalability, versatility, and biocompatibility. Despite impressive progress in the medical field, MOFs are still facing some problems to be solved in their practical application in the clinical field, such as systemic toxicity, early clearance by the immune system, and undesirable biodiseases[102].

In a recent research on the hybrids of curcumins with resveratrol, the results show that the hybrid products

formed by polyphenols and AuNP have implications in the treatment of tumor, offering a potential for the design of novel approaches for cancer treatment. However, when bioavailability altered, the potential toxicity associated with the active agent and the overall delivery system must be re-evaluated to ensure the safety[103]. The section is summarized in Figure 2.

Metal-mediated cell death modality

Up to now, the main forms of cell death mediated by metal identified by researchers have been ferroptosis and cuproptosis. These emerging forms of cell death have attracted keen attention, and are now a hot research topic in the field of cell death. Several attempts have been made to investigate the mechanisms involved in their induction of cell death to discover new potential therapeutic targets to treat several human diseases, like cancer, and to develop new therapeutic approaches. The relevant mechanisms are shown in Figure 3.

Ferroptosis

In 2012, after screening for small molecules responsible for inhibiting the growth of cancer cells with RAS-mutation, the "ferroptosis" term was introduced, which was defined as iron-dependent regulatory necrosis caused by massive lipid peroxidation-mediated membrane damage. Morphologically, intracellular iron death is mainly manifested as a decrease in cell size, a reduction or disappearance of mitochondrial cristae, and a condensation of the mitochondrial membrane. Biochemically, the main manifestations are depletion of glutathione and decreased activity of GPX4; lipid oxides cannot be reduced, and then divalent iron ions oxidize lipids to produce a large amount of reactive oxygen species, leading to iron death in cells[104]. The accumulation of iron and the further production of ROS causes ferroptosis, an unusual type of cell death triggered by several metabolic events, such as metabolism of iron ion, metabolism of amino acid, sugar and lipid, redox homeostasis, and numerous signaling pathways associated with it[105–106]. Recent research has demonstrated a close association of ferroptosis with pathological processes in several diseases, including neurological disorders, kidney injury, blood disorders, ischemia–reperfusion injury, and even cancer[107–110]. After the discovery of ferroptosis, convincing evidence showed that targeting iron apoptosis in experimental cancer models had an anti-cancer profile[111].

ART, extracted from *A. annua* plant, has been explored as a potent antimalarial drug, and together with its derivatives, they have also been studied for the treatment of several other diseases, including cancer[112]. Dihydroartemisinin (DAT), one of the ART derivatives, has high bioavailability and enhances the susceptibility of cancer cells to iron apoptosis induced by deprivation of cysteine and inhibition of GPX4. Ferritin, the major intracellular iron storage protein complex, degrades ferritin through autophagy to increase intracellular iron levels, leading to increased susceptibility to ferroptosis, a process called ferritinophagy[109,113–115]. DAT was found to increase the sensitivity of different types of ferroptosis inducers, such as the cystine transport inhibitor erastin and the GPX4 inhibitor RSL3, to promote cancer cell death, whereas cell death was inhibited when the ferroptosis inhibitor Ferrostatin-1 or the iron chelator desferrioxamine was added, confirming the DAT-induced cell death by ferroptosis nature of DAT-induced cell death. Mechanistically, DAT induces the lysosomal degradation of ferritin in an autophagy-independent manner, increasing the concentration of free iron in cells. In addition, DAT can affect ferroptosis by binding to cellular free iron and stimulating iron homeostasis regulated by iron regulatory proteins[116]. Phenol 6-gingerol, naturally found in ginger, showed to have several beneficial biological activities, such as anti-tumor, anti-inflammatory, and anti-oxidative properties. In a recent study, lotic mice and A549 were used to evaluated the anti-cancer effects

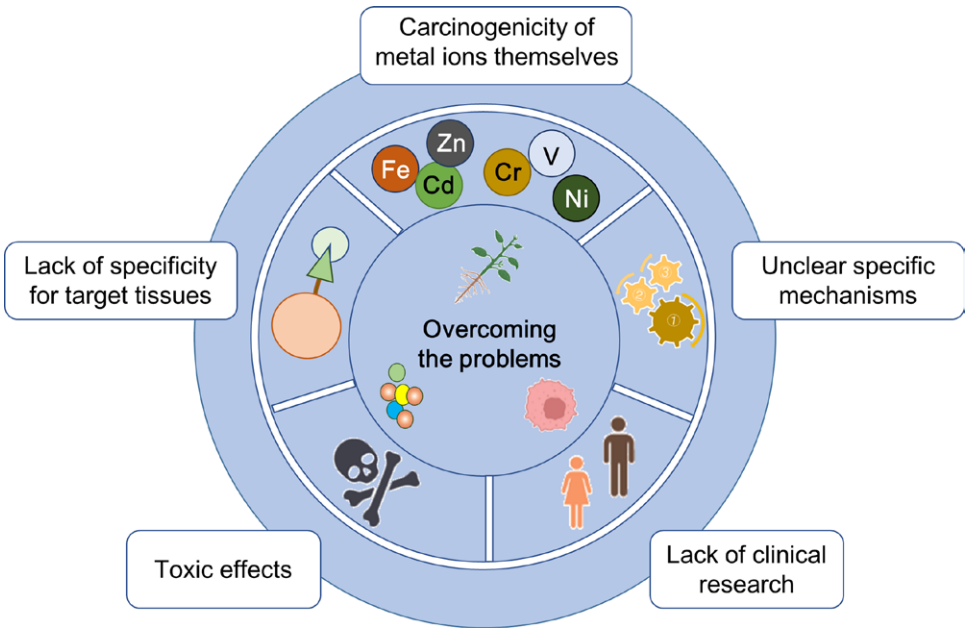

Figure 2. Overcoming the problems of metal ions in the treatment and prevention of tumors with TCM. TCM: Traditional Chinese medicine.

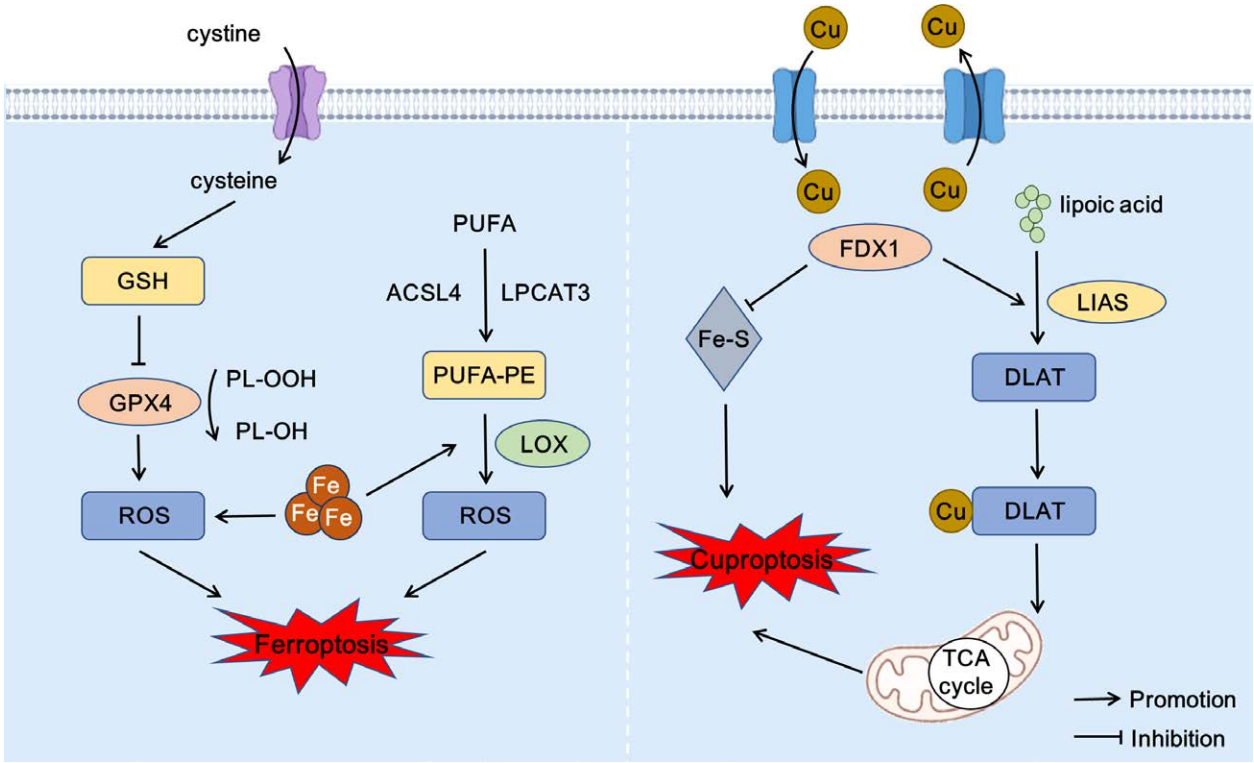

Figure 3. Metal-mediated cell death modality: ferroptosis and cuproptosis.

of 6-gingerol. The treatment with 6-gingerol resulted in numerous changes in the cell, such as a reduction in the expression of USP14, a highly increasing of auto-phagosomes, ROS, and the concentration of iron, which causes the lowering of proliferation and survival of A549 cells. This result suggests that 6-gingerol suppresses the growth of lung cancer cells through downregulation of USP14, and further affects autophagy-dependent ferroptosis, which is downstream regulated by USP14[117]. Erianin is a natural compound that derived from the *Dendrobium* and has anti-cancer activity against several cancers. Erianin was shown to cause ferroptosis in cancer cells by activating the Ca^{2+}/CaM pathway, and was supported by accumulation of ROS, depletion of GSH, and lipid peroxidation. It was also able to inhibit cell migration in the same lung cancer cell line, which never exerted anti-cancer effects. Therefore, Erianin was considered as a promising compound for treatment of lung cancer[118]. Cucurbitacin is a cyclic triterpenoid derived from the oriental herb tetra, which has anti-tumor activity against various human cancers. The cucurbitacin B is one of the most abundant and extensively studied cucurbitacin derivatives isolated from *Trichosanthes Kirilowii Maximowicz*. Cucurbitacin B was found to have excellent cytotoxicity against the human nasopharyngeal carcinoma cells, and its possible ferroptosis induced mechanism was explored. Morphological alterations in mitochondrial ultrastructure were first observed by transmission electron microscopy, suggesting that cells treated with cucurbitacin B underwent iron death. Furthermore, detailed molecular mechanistic studies have confirmed that cucurbitacin B may induce the accumulation of Fe and the depletion of GSH, leading to the excess lipid peroxides production. Furthermore, cucurbitacin B decreases GPX4 expression and promotes the multifaceted mechanism of iron death in CNE1 cells. Finally, it was established that cucurbitacin B exhibited tumor-suppressive effects both *in vivo* and *in vitro*, emphasizing its therapeutic potential as a ferroptosis inducer in nasopharyngeal carcinoma[119]. Baicalin, a major bioactive flavonoid derived from the extract of the *Scutellariae radix*, is reported to inhibit growth on bladder cancer cell lines (KU-19-19 and 5637 cells). The results demonstrated that baicalin exerted anti-tumor property by the promotion of apoptosis. Furthermore, *in vivo* and *in vitro* tests showed that baicalin-induced cellular ferroptosis was associated with an accumulation of ROS and intracellular chelated iron. While the heavy chain 1 domain of ferritin was a main determinant of ferroptosis induced by baicalein, overexpression of FTH1 was able to abrogate the anti-cancer effect of baicalein in 5637 and KU-19-19 cells. Specifically, the expression and transcript levels of transferrin were increased, while the expression and transcript levels of a negative ferroptosis-regulated protein (FTH1) were decreased when bladder cancer cells were treated with baicalin. Overexpression of FTH1 significantly abrogated the anti-cancer effect of baicalin in 5637 and KU-19-19 cells. Thus, FTH1 acted as a key regulator of baicalin-induced ferroptosis in bladder cancer cells[120].

Ferroptosis promotion is considered to be a potential cancer treatment, especially for the types of tumor which are highly sensitive to iron. Iron death research is progressing rapidly, and targeting ferroptosis is of great importance as a new anti-tumor treatment strategy[106]. However, it should not be ignored that a shortcoming of the current study is that there is no clear report showing the impact of ferroptosis inhibitors on the anti-tumor effects of TCM. This also suggests that subsequent studies would be better to introduce the combination

of ferroptosis inhibitors and TCM to further confirm the key role of ferroptosis in the efficacy of active compounds. The introduction of ferroptosis inducing drugs into the clinic could lead to the development of more targeted and effective anti-cancer iron chelators[121].

Cuproptosis

Tsvetkov et al. recently proposed a new type of copper-induced cell death. The study shows that cell death in human cells controlled by copper is a new type of cell death, which is different from already known mechanisms involved with direct bonding of Cu ions with lipidated molecules of the Krebs cycle from mitochondrial respiration. It decreased the expression of iron-sulfur cluster proteins and the aggregation of lipidated proteins, which resulted in rapid cell death and proteotoxic stress. The team named this form of cell death "cuproptosis"[122]. Briefly, the main process of copper death relies on the accumulation of intracellular copper ions, which directly bind to the lipoylated components of the tricarboxylic acid (TCA) cycle, leading to the aggregation and dysregulation of these proteins, blocking the TCA cycle, triggering a proteotoxic stress, and inducing cell death.

They found that the copper ion carrier used for cancer treatment, Elesclomol, when loaded with copper kills cells, but in the absence of copper, Elesclomol alone does not cause cell death, suggesting that toxicity is mainly caused by copper. They also found that caspase-3 activation did not happen after Elesclomol treatment, while inhibition of programmed cell death or apoptotic pathways did not cause prevention of cell death induced by copper. This suggests that the mechanism of cell death induced by copper is different from known mechanisms of apoptosis. *In vitro* and *in vivo* studies, Tsvetkov et al. elucidated a new mechanism through which cell death was caused by high intracellular concentrations of copper, showing that mitochondrial respiration-dependent cells have higher sensitivity to copper-induced apoptosis. In summary, the authors provide new insights into the essential correlation between copper-induced death and cellular metabolism in mitochondria. These findings are important to further understand how apoptosis is induced by copper[123–124].

Despite these significant advances, there remain additional challenges. It is still unclear, for example, whether copper apoptosis is induced by morphological features, whether it requires the activation of specific copper enzymes, or how protein degradation mechanisms regulate proteotoxic stress to control copper apoptosis. These questions require extensive future research[124].

For cancer therapy, the future development of drugs targeting various cell death pathways will be a challenging area. Incorporating the special importance of lipid-acylated protein modifications in copper-dependent death, and exploring targeted interventions based on cuproptosis have potential applications. Copper metabolic homeostasis and its mediated signaling pathways regulated by cell death could be potential targets for intervention in hazards or diseases associated with dysfunctional metabolism of copper, and could also provide a novel anti-tumor approach.

Conclusion

In conclusion, numerous studies have shown that metal ions are highly related to the treatment of malignant tumors of TCM. The importance of metal ions and their oxides in the treatment of diseases has been increasing recently. Due to their different redox properties, they can act under different conditions and in different ways. Most treatments for cancer of TCM focus on the natural products extracted from herbs. However, some limitations arising from the therapeutic process of most natural products, which limit their wide clinical application[125]. The use of metal ions improves TCM effects on cancer treatment with unexpected effects. Consequently, the use of metal ions may give rise to a unique perspective in the treatment and prevention of cancer in TCM.

Metal ions have multiple structural and functional roles, and they exist in different forms. Metal ions are essential elements for maintaining normal human life and play an important role in biological systems. However, Metal ions can also induce diseases due to its own toxic effects, which endanger human health. In a word, metal ions exhibit positive and negative aspects in the prevention and treatment of tumors in TCM. By interacting with active compounds or by forming metal complexes with them, metal ions can enhance the biological activity of natural products in the treatment of tumors. Moreover, metal ions can also be processed using nanotechnology to synthesize NPs or metal–organic skeletons with natural products green as new DDSs. This could result in an effective improvement of the bioavailability of the corresponding molecules to exert their therapeutic effects *in vivo*. It is worth mentioning that in these novel DDSs based on metal ions, such as NPs, metal–organic framework, liposomes, etc, the effects of carriers on metal ions should also be taken into account when designing and synthesizing them in the anti-tumor process of TCM. For example, with the change of valence of metal ions, their chemical properties and functions are likely to change and thus deviating from the expected results. Therefore, special attention should be paid to the impact of the change in the valence of metal ions in the process of binding, *in vivo* delivery and recognition of metal ions. Furthermore, the practical application of metal ions also faces challenges. Metal ions are limited in their wider application due to their own carcinogenicity, which is one of the reasons why researchers are currently interested in only limited metal ions (Au, Ag, Cu, Zn, etc.)[126]. Second, some problems need to be solved for metal ions to enhance the therapeutic effects of active compounds, such as the lack of specificity for target tissues, the lack of pre-clinical and clinical studies, the unclearness of the specific mechanisms, and safety assessment.

Conventional methods for tumor treatment include chemotherapy, radiotherapy, surgery, and drug therapy. Recent studies have developed new metal ion-based therapies, such as photodynamic therapy[127], photothermal therapy[128], immunotherapy[129], and targeted therapy[130], to achieve better therapeutic effects. However, single therapy seems to fail to achieve the desired purpose, so combined therapeutic approaches have quickly attracted the attention of researchers. In particular, in herbal medicine against tumors, most compounds have low

bioavailability and cannot precisely reach target tissues. Combination therapy makes these possible and provides more selectivity for future clinical treatment[131–136].

In personalized therapies, metal ions and active compounds have been realized not only for combined therapy, but also for diagnosis and treatment[137–140]. Furthermore, new perspectives on NP-based transport systems of drugs have emerged, such as supramolecular coordination complexes[141] and carrier-free nanomedicines[142–143]. Despite the emergence of novel therapeutics, there are still many challenges to be addressed, such as how to achieve high drug-loading rate and precise target, and the need to obtain a large amount of clinical data to verify the safety and efficacy.

Recently, it was reported that a herbzyme extracted from the RP of Mount Tai can enhance phosphatase activity as a co-enzyme and anti-cancer agent[144–146]. The herbzyme activity can be enhanced by $CaCl_2$ (0.25M), whereas control protein-based phosphatase ALP decreased enzyme activity at 0.75M by the metal calcium solution. This suggests that metal can enhance herbzyme activity but not for the protein-based enzyme in this reported case[84]. Other carbon dots derived from herbs, such as date, also showed the anti-cancer activity and how metal ion may regulate or involved in the regulation of carbon dots in anti-cancer to make a hybrid carbon-MOF for drug delivery of natural products from TCM[147–148]. As ionic regulation of metal ions on carbon dots has been reported, this area would be promising in application of metal ionic carbon dots derived from herbs.

This article mainly outlines the role of metal ions in the anti-tumor of TCM, but some ion receptors also deserve our attention. The receptors can be classified into ion channel receptors[149–154], G protein-coupled receptors[155–156], hormone-like receptors[149,157], etc, according to their mechanism, such as protein structure, information transduction process, and nature of effect. These receptors have been reported to be able to influence pathophysiological states in a variety of diseases, such as neurological disorders[149–152], cancer[152–156], hypertension[157], and vascular aging[149]. It is worth noting that although studies have shown that some receptors have therapeutic potential in anti-tumor, but whether they can become drug targets for cancer treatment is still unclear.

In summary, metal ions have obvious advantages in TCM for tumor prevention and treatment, although there are also certain drawbacks. With a thorough exploration of the design of new drug development methods and cancer pathology in general, the target of active compounds has been greatly improved by structural modification of natural products with metal ions and new DDSs based on metal ions. It is strongly believe that through an in-depth understanding of metal ions and the use of new technologies, the advantages of metal ions in various aspects should be fully utilized, and its limitations should be continuously broken through. Metal ions have a greatly indispensable importance in the future development of TCM. The rational use of metal ions in combination with TCM for the treatment of tumors will not only provides alternative options for cancer treatment but also promotes the development of TCM.

Conflict of interest statement

Yingqiu Xie is editorial board members of this journal. None of the other authors declare any conflicts of interest.

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Author contributions

Lei Wang, Sandugash Myrzagali, and Yingqiu Xie were responsible for the collection, collation of data, and writing of the original manuscript. Weiling Pu and Erwei Liu were responsible for concept development and manuscript revision. All authors reviewed and accepted the final version of the manuscript.

Ethical approval of studies and informed consent

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Data availability

All data generated or analyzed during this study are included in this published article.

References

[1] Arjmand B, Hamidpour SK, Tayanloo-Beik A, et al. Machine learning: a new prospect in multi-omics data analysis of cancer. *Front Genet* 2022;13:824451.
[2] Miller KD, Ortiz AP, Pinheiro PS, et al. Cancer statistics for the US Hispanic/Latino population, 2021. *CA Cancer J Clin* 2021;71(6):466–487.
[3] Xia C, Dong X, Li H, et al. Cancer statistics in China and United States, 2022: profiles, trends, and determinants. *Chin Med J (Engl)* 2022;135(5):584–590.
[4] Giordano A, Tommonaro G. Curcumin and cancer. *Nutrients* 2019;11(10):2376.
[5] Tomeh MA, Hadianamrei R, Zhao X. A review of curcumin and its derivatives as anticancer agents. *Int J Mol Sci* 2019;20(5):1033.
[6] Zhang L, Xu Q, Li Y, et al. Ameliorative effects of component Chinese medicine from Curcumae rhizoma and Sparganii rhizoma, a traditional herb pair, on uterine leiomyoma in a rat model. *Front Public Health* 2021;9:674357.
[7] Fu L, Han B, Zhou Y, et al. The anticancer properties of Tanshinones and the pharmacological effects of their active ingredients. *Front Pharmacol* 2020;11:193.
[8] Liskova A, Koklesova L, Samec M, et al. Flavonoids in cancer metastasis. *Cancers (Basel)* 2020;12(6):1498.
[9] Xu H, Van der Jeught K, Zhou Z, et al. Atractylenolide I enhances responsiveness to immune checkpoint blockade therapy by activating tumor antigen presentation. *J Clin Invest* 2021;131(10):e146832.
[10] Xu B, Cheng Q, So WKW. Review of the effects and safety of traditional Chinese medicine in the treatment of cancer cachexia. *Asia Pac J Oncol Nurs* 2021;8(5):471–486.
[11] Zhang X, Qiu H, Li C, et al. The positive role of traditional Chinese medicine as an adjunctive therapy for cancer. *Biosci Trends* 2021;15(5):283–298.
[12] G MS, Swetha M, Keerthana CK, et al. Cancer chemoprevention: a strategic approach using phytochemicals. *Front Pharmacol* 2022;12:809308.
[13] Wojtunik-Kulesza K, Oniszczuk A, Waksmundzka-Hajnos M. An attempt to elucidate the role of iron and zinc ions in development of Alzheimer's and Parkinson's diseases. *Biomed Pharmacother* 2019;111:1277–1289.
[14] Grzeszczak K, Kwiatkowski S, Kosik-Bogacka D. The role of Fe, Zn, and Cu in pregnancy. *Biomolecules* 2020;10(8):1176.

[15] Moustakas M. The role of metal ions in biology, biochemistry and medicine. *Materials (Basel)* 2021;14(3):549.
[16] Liu Y, Wang Y, Song S, et al. Cancer therapeutic strategies based on metal ions. *Chem Sci* 2021;12(37):12234–12247.
[17] Zhu Y, Costa M. Metals and molecular carcinogenesis. *Carcinogenesis* 2020;41(9):1161–1172.
[18] Stelling MP, Motta JM, Mashid M, et al. Metal ions and the extracellular matrix in tumor migration. *FEBS J* 2019;286(15):2950–2964.
[19] Wang C, Zhang R, Wei X, et al. Metalloimmunology: the metal ion-controlled immunity. *Adv Immunol* 2020;145:187–241.
[20] Xu J, Wang J, Ye J, et al. Metal-coordinated supramolecular self-assemblies for cancer theranostics. *Adv Sci (Weinh)* 2021;8(16):e2101101.
[21] Xu D, Hu MJ, Wang YQ, et al. Antioxidant activities of quercetin and its complexes for medicinal application. *Molecules* 2019;24(6):1123.
[22] Vervandier-Fasseur D, Latruffe N. The potential use of resveratrol for cancer prevention. *Molecules* 2019;24(24):4506.
[23] Nagoor Meeran MF, Javed H, Al Taee H, et al. Pharmacological properties and molecular mechanisms of thymol: prospects for its therapeutic potential and pharmaceutical development. *Front Pharmacol* 2017;8:380.
[24] Liu ZH, Yang CX, Zhang L, et al. Baicalein, as a prooxidant, triggers mitochondrial apoptosis in MCF-7 human breast cancer cells through mobilization of intracellular copper and reactive oxygen species generation. *Onco Targets Ther* 2019;12:10749–10761.
[25] Farhan M, Khan HY, Oves M, et al. Cancer therapy by catechins involves redox cycling of copper ions and generation of reactive oxygen species. *Toxins (Basel)* 2016;8(2):37.
[26] Banaspati A, Raza MK, Goswami TK. Ni(II) curcumin complexes for cellular imaging and photo-triggered in vitro anticancer activity. *Eur J Med Chem* 2020;204:112632.
[27] Li S, Xu G, Zhu Y, et al. Bifunctional ruthenium(II) polypyridyl complexes of curcumin as potential anticancer agents. *Dalton Trans* 2020;49(27):9454–9463.
[28] Mohammed F, Rashid-Doubell F, Taha S, et al. Effects of curcumin complexes on MDA-MB-231 breast cancer cell proliferation. *Int J Oncol* 2020;57(2):445–455.
[29] Meza-Morales W, Estévez-Carmona MM, Alvarez-Ricardo Y, et al. Full structural characterization of homoleptic complexes of diacetylcurcumin with Mg, Zn, Cu, and Mn: cisplatin-level cytotoxicity in vitro with minimal acute toxicity *in vivo*. *Molecules* 2019;24(8):1598.
[30] Miklášová N, Herich P, Dávila-Becerril JC, et al. Evaluation of antiproliferative palladium(II) complexes of synthetic bisdemethoxycurcumin towards in vitro cytotoxicity and molecular docking on DNA sequence. *Molecules* 2021;26(14):4369.
[31] Roy S, Banerjee S, Chakraborty T. Vanadium quercetin complex attenuates mammary cancer by regulating the p53, Akt/mTOR pathway and downregulates cellular proliferation correlated with increased apoptotic events. *Biometals* 2018;31(4):647–671.
[32] Roy S, Das R, Ghosh B, et al. Deciphering the biochemical and molecular mechanism underlying the in vitro and *in vivo* chemotherapeutic efficacy of ruthenium quercetin complex in colon cancer. *Mol Carcinog* 2018;57(6):700–721.
[33] Roy S, Chakraborty T. Deciphering the molecular mechanism and apoptosis underlying the *in vitro* and *in vivo* chemotherapeutic efficacy of vanadium luteolin complex in colon cancer. *Cell Biochem Funct* 2018;36(3):116–128.
[34] Roy S, Sil A, Chakraborty T. Potentiating apoptosis and modulation of p53, Bcl2, and Bax by a novel chrysin ruthenium complex for effective chemotherapeutic efficacy against breast cancer. *J Cell Physiol* 2019;234(4):4888–4909.
[35] Wang Y, Bian L, Chakraborty T, et al. Construing the biochemical and molecular mechanism underlying the *in vivo* and *in vitro* chemotherapeutic efficacy of ruthenium-Baicalein complex in colon cancer. *Int J Biol Sci* 2019;15(5):1052–1071.
[36] Zhou J, Wang LF, Wang JY, et al. Synthesis, characterization, antioxidative and antitumor activities of solid quercetin rare earth(III) complexes. *J Inorg Biochem* 2001;83(1):41–48.
[37] Jomová K, Hudecova L, Lauro P, et al. A switch between antioxidant and prooxidant properties of the phenolic compounds myricetin, Morin, 3',4'-dihydroxyflavone, taxifolin and 4-hydroxy-coumarin in the presence of copper(II) ions: a spectroscopic, absorption titration and DNA damage study. *Molecules* 2019;24(23):4335.
[38] Simunkova M, Barbierikova Z, Jomova K, et al. Antioxidant vs. prooxidant properties of the flavonoid, kaempferol, in the presence of Cu(II) Ions: a ROS-scavenging activity, fenton reaction and DNA damage study. *Int J Mol Sci* 2021;22(4):1619.
[39] Yan YY, Yuan S, Ma HH, et al. Structural modification and biological activities of carboxymethyl pachymaran. *Food Sci Nutr* 2021;9(8):4335–4348.
[40] Chen H, Wang D, Fan L, et al. Zinc complex of 3,5-di-tert-butyl salicylate inhibits viability, migration, and invasion in triple-negative breast cancer cells. *Sci Rep* 2022;12(1):4545.
[41] Wu R, Mei X, Ye Y, et al. Zn(II)-curcumin solid dispersion impairs hepatocellular carcinoma growth and enhances chemotherapy by modulating gut microbiota-mediated zinc homeostasis. *Pharmacol Res* 2019;150:104454.
[42] Li WF, Ma HH, Yuan S, et al. Production of pyracantha polysaccharide-iron(III) complex and its biologic activity. *Molecules* 2021;26(7):1949.
[43] Zeng P, Fang M, Zhao H, et al. A network pharmacology approach to uncover the key ingredients in Ginkgo Folium and their anti-Alzheimer's disease mechanisms. *Aging (Albany NY)* 2021;13(14):18993–19012.
[44] Zhao R, Wu X, Bi XY, et al. Baicalin attenuates blood-spinal cord barrier disruption and apoptosis through PI3K/Akt signaling pathway after spinal cord injury. *Neural Regen Res* 2022;17(5):1080–1087.
[45] Zhu T, Wang L, Feng Y, et al. Classical active ingredients and extracts of Chinese herbal medicines: pharmacokinetics, pharmacodynamics, and molecular mechanisms for ischemic stroke. *Oxid Med Cell Longev* 2021;2021:8868941.
[46] Wu M, Yu Z, Li X, et al. Paeonol for the treatment of atherosclerotic cardiovascular disease: a pharmacological and mechanistic overview. *Front Cardiovasc Med* 2021;8:690116.
[47] He S, Wu L, Li X, et al. Metal-organic frameworks for advanced drug delivery. *Acta Pharm Sin B* 2021;11(8):2362–2395.
[48] Du Y, Wan H, Huang P, et al. A critical review of Astragalus polysaccharides: from therapeutic mechanisms to pharmaceutics. *Biomed Pharmacother* 2022;147:112654.
[49] Lambrianidou A, Koutsougianni F, Papapostolou I, et al. Recent advances on the anticancer properties of Saffron (Crocus sativus L.) and its major constituents. *Molecules* 2020;26(1):86.
[50] Li Z, Ali I, Qiu J, et al. Eco-friendly and facile synthesis of antioxidant, antibacterial and anticancer dihydromyricetin-mediated silver nanoparticles. *Int J Nanomedicine* 2021;16:481–492.
[51] Wang L, Yin Q, Liu C, et al. Nanoformulations of ursolic acid: a modern natural anticancer molecule. *Front Pharmacol* 2021;12:706121.
[52] Szabo R, Bodolea C, Mocan T. Iron, copper, and zinc homeostasis: physiology, physiopathology, and nanomediated applications. *Nanomaterials (Basel)* 2021;11(11):2958.
[53] Reddy NV, Li H, Hou T, et al. Phytosynthesis of silver nanoparticles using Perilla frutescens leaf extract: characterization and evaluation of antibacterial, antioxidant, and anticancer activities. *Int J Nanomedicine* 2021;16:15–29.
[54] Ghosh P, Bag S, Parveen S, et al. Nanoencapsulation as a promising platform for the delivery of the morin-Cu(II) complex: antibacterial and anticancer potential. *ACS Omega* 2022;7(9):7931–7944.
[55] Leng X, Dong X, Wang W, et al. Biocompatible Fe-based micropore metal-organic frameworks as sustained-release anticancer drug carriers. *Molecules* 2018;23(10):2490.
[56] Karimi Alavijeh R, Akhbari K. Biocompatible MIL-101(Fe) as a smart carrier with high loading potential and sustained release of Curcumin. *Inorg Chem* 2020;59(6):3570–3578.
[57] Li H, Zhang Y, Liang L, et al. Doxorubicin-loaded metal-organic framework nanoparticles as acid-activatable hydroxyl radical nanogenerators for enhanced chemo/chemodynamic synergistic therapy. *Materials (Basel)* 2022;15(3):1096.
[58] Li Z, Wu X, Wang W, et al. Fe(II) and tannic acid-cloaked MOF as carrier of artemisinin for supply of serrous ions to enhance treatment of triple-negative breast cancer. *Nanoscale Res Lett* 2021;16(1):37.
[59] Kuppusamy P, Yusoff MM, Maniam GP, et al. Biosynthesis of metallic nanoparticles using plant derivatives and their new avenues in pharmacological applications – an updated report. *Saudi Pharm J* 2016;24(4):473–484.
[60] Alphandéry E. Natural metallic nanoparticles for application in nano-oncology. *Int J Mol Sci* 2020;21(12):4412.
[61] Zhang D, Ma XL, Gu Y, et al. Green synthesis of metallic nanoparticles and their potential applications to treat cancer. *Front Chem* 2020;8:799.
[62] Kemp JA, Kwon YJ. Cancer nanotechnology: current status and perspectives. *Nano Converg* 2021;8(1):34.

[63] Kaplan A. The nanocomposites designs of phytomolecules from medicinal and aromatic plants: promising anticancer-antiviral applications. *Beni Suef Univ J Basic Appl Sci* 2022;11(1):17.

[64] Chen X, Han W, Zhao X, et al. Epirubicin-loaded marine carrageenan oligosaccharide capped gold nanoparticle system for pH-triggered anticancer drug release. *Sci Rep* 2019;9(1):6754.

[65] Jiménez Pérez ZE, Mathiyalagan R, Markus J, et al. Ginsengberry-mediated gold and silver nanoparticle synthesis and evaluation of their in vitro antioxidant, antimicrobial, and cytotoxicity effects on human dermal fibroblast and murine melanoma skin cell lines. *Int J Nanomedicine* 2017;12:709–723.

[66] Xiong J, Jiang B, Luo Y, et al. Multifunctional nanoparticles encapsulating Astragalus polysaccharide and gold nanorods in combination with focused ultrasound for the treatment of breast cancer. *Int J Nanomedicine* 2020;15:4151–4169.

[67] Alkhathlan AH, Al-Abdulkarim HA, Khan M, et al. Evaluation of the anticancer activity of phytomolecules conjugated gold nanoparticles synthesized by aqueous extracts of Zingiber officinale (Ginger) and Nigella sativa seeds (Black Cumin). *Materials (Basel)* 2021;14(12):3368.

[68] Benedec D, Oniga I, Cuibus F, et al. Origanum vulgare mediated green synthesis of biocompatible gold nanoparticles simultaneously possessing plasmonic, antioxidant and antimicrobial properties. *Int J Nanomedicine* 2018;13:1041–1058.

[69] Singh P, Singh H, Ahn S, et al. Pharmacological importance, characterization and applications of gold and silver nanoparticles synthesized by Panax ginseng fresh leaves. *Artif Cells Nanomed Biotechnol* 2017;45(7):1415–1424.

[70] Wang J, Liu L, Sun XY, et al. Evidence and potential mechanism of action of Lithospermum erythrorhizon and its active components for psoriasis. *Front Pharmacol* 2022;13:781850.

[71] Shkryl Y, Rusapetova T, Yugay Y, et al. Biosynthesis and cytotoxic properties of Ag, Au, and bimetallic nanoparticles synthesized using Lithospermum erythrorhizon callus culture extract. *Int J Mol Sci* 2021;22(17):9305.

[72] Mohanta YK, Panda SK, Biswas K, et al. Biogenic synthesis of silver nanoparticles from Cassia fistula (Linn.): in vitro assessment of their antioxidant, antimicrobial and cytotoxic activities. *IET Nanobiotechnol* 2016;10(6):438–444.

[73] Xu Z, Feng Q, Wang M, et al. Green biosynthesized silver nanoparticles with aqueous extracts of Ginkgo biloba induce apoptosis via mitochondrial pathway in cervical cancer cells. *Front Oncol* 2020;10:575415.

[74] Erdogan O, Abbak M, Demirbolat GM, et al. Green synthesis of silver nanoparticles via Cynara scolymus leaf extracts: the characterization, anticancer potential with photodynamic therapy in MCF7 cells. *PLoS One* 2019;14(6):e0216496.

[75] Venkatesan J, Singh SK, Anil S, et al. Preparation, characterization and biological applications of biosynthesized silver nanoparticles with chitosan-fucoidan coating. *Molecules* 2018;23(6):1429.

[76] Ibrahim FY, El-Khateeb AY, Mohamed AH. Rhus and Safflower extracts as potential novel food antioxidant, anticancer, and antimicrobial agents using nanotechnology. *Foods* 2019;8(4):139.

[77] Ren S, Song L, Tian Y, et al. Emodin-conjugated PEGylation of Fe_3O_4 nanoparticles for FI/MRI dual-modal imaging and therapy in pancreatic cancer. *Int J Nanomedicine* 2021;16:7463–7478.

[78] Chen H, Wen J. Iron oxide nanoparticles loaded with paclitaxel inhibits glioblastoma by enhancing autophagy-dependent ferroptosis pathway. *Eur J Pharmacol* 2022;921:174860.

[79] Rejinold NS, Han Y, Yoo J, et al. Evaluation of cell penetrating peptide coated Mn: ZnS nanoparticles for paclitaxel delivery to cancer cells. *Sci Rep* 2018;8(1):1899.

[80] Kundu M, Sadhukhan P, Ghosh N, et al. PH-responsive and targeted delivery of curcumin via phenylboronic acid-functionalized ZnO nanoparticles for breast cancer therapy. *J Adv Res* 2019;18:161–172.

[81] Zhang H, Wu Y, Xu X, et al. Synthesis characterization of platinum (IV) complex curcumin backboned polyprodrugs: in vitro drug release anticancer activity. *Polymers (Basel)* 2020; 13(1):67.

[82] Meng Y, Zhang Y, Jia N, et al. Synthesis and evaluation of a novel water-soluble high Se-enriched Astragalus polysaccharide nanoparticles. *Int J Biol Macromol* 2018;118(Pt B):1438–1448.

[83] Wu Y, Darland DC, Zhao JX. Nanozymes-hitting the biosensing "target". *Sensors (Basel)* 2021;21(15):5201.

[84] Benassi E, Fan H, Sun Q, et al. Generation of particle assemblies mimicking enzymatic activity by processing of herbal food: the case of Rhizoma polygonati and other natural ingredients in traditional Chinese medicine. *Nanoscale Adv* 2021;3(8):2222–2235.

[85] Xie Y, Fan H, Lu W, et al. Nuclear MET requires ARF and is inhibited by carbon nanodots through binding to phospho-tyrosine in prostate cancer. *Oncogene* 2019;38(16):2967–2983.

[86] Nazarbek G, Kutzhanova A, Nurtay L, et al. Nano-evolution and protein-based enzymatic evolution predicts novel types of natural product nanozymes of traditional Chinese medicine: cases of herbzymes of Taishan-Huangjing (Rhizoma polygonati) and Goji (Lycium chinense). *Nanoscale Adv* 2021;3(23):6728–6738.

[87] Fan H, Sun Q, Dukenbayev K, et al. Carbon nanoparticles induce DNA repair and PARP inhibitor resistance associated with nanozyme activity in cancer cells. *Cancer Nano* 2022;13(1):39.

[88] Kamada R, Kudoh F, Ito S, et al. Metal-dependent Ser/Thr protein phosphatase PPM family: evolution, structures, diseases and inhibitors. *Pharmacol Ther* 2020;215:107622.

[89] Hu M, Ai X, Wang Z, et al. Nanoformulation of metal complexes: intelligent stimuli-responsive platforms for precision therapeutics. *Nano Res* 2018;11(10):5474–5498.

[90] Genchi G, Sinicropi MS, Lauria G, et al. The effects of cadmium toxicity. *Int J Environ Res Public Health* 2020;17(11):3782.

[91] Ścibior A, Pietrzyk L, Plewa Z, et al. Vanadium: risks and possible benefits in the light of a comprehensive overview of its pharmacotoxicological mechanisms and multi-applications with a summary of further research trends. *J Trace Elem Med Biol* 2020;61:126508.

[92] Chen QY, DesMarais T, Costa M. Metals and mechanisms of carcinogenesis. *Annu Rev Pharmacol Toxicol* 2019;59:537–554.

[93] Chen QY, Murphy A, Sun H, et al. Molecular and epigenetic mechanisms of Cr(VI)-induced carcinogenesis. *Toxicol Appl Pharmacol* 2019;377:114636.

[94] Scanlon SE, Scanlon CD, Hegan DC, et al. Nickel induces transcriptional down-regulation of DNA repair pathways in tumorigenic and non-tumorigenic lung cells. *Carcinogenesis* 2017;38(6):627–637.

[95] Morales M, Xue X. Targeting iron metabolism in cancer therapy. *Theranostics* 2021;11(17):8412–8429.

[96] Ying JF, Lu ZB, Fu LQ, et al. The role of iron homeostasis and iron-mediated ROS in cancer. *Am J Cancer Res* 2021;11(5):1895–1912.

[97] Costa MI, Lapa BS, Jorge J, et al. Zinc prevents DNA damage in normal cells but shows genotoxic and cytotoxic effects in acute myeloid leukemia cells. *Int J Mol Sci* 2022;23(5):2567.

[98] Prasad S, DuBourdieu D, Srivastava A, et al. Metal-curcumin complexes in therapeutics: an approach to enhance pharmacological effects of curcumin. *Int J Mol Sci* 2021;22(13):7094.

[99] Liu WN, Shi J, Fu Y, et al. The stability and activity changes of apigenin and luteolin in human cervical cancer Hela cells in response to heat treatment and Fe^{2+}/Cu^{2+} addition. *Foods* 2019;8(8):346.

[100] Mahmood Ansari S, Saquib Q, De Matteis V, et al. Marine macroalgae display bioreductant efficacy for fabricating metallic nanoparticles: intra/extracellular mechanism and potential biomedical applications. *Bioinorg Chem Appl* 2021;2021:5985377.

[101] Kejík Z, Kaplánek R, Masařík M, et al. Iron complexes of flavonoids-antioxidant capacity and beyond. *Int J Mol Sci* 2021;22(2):646.

[102] Yan C, Jin Y, Zhao C. Environment responsive metal-organic frameworks as drug delivery system for tumor therapy. *Nanoscale Res Lett* 2021;16(1):140.

[103] Micale N, Molonia MS, Citarella A, et al. Natural product-based hybrids as potential candidates for the treatment of cancer: focus on curcumin and resveratrol. *Molecules* 2021;26(15):4665.

[104] Tang D, Chen X, Kang R, et al. Ferroptosis: molecular mechanisms and health implications. *Cell Res* 2021;31(2):107–125.

[105] Jiang X, Stockwell BR, Conrad M. Ferroptosis: mechanisms, biology and role in disease. *Nat Rev Mol Cell Biol* 2021;22(4):266–282.

[106] Wang HT, Ju J, Wang SC, et al. Insights into ferroptosis, a novel target for the therapy of cancer. *Front Oncol* 2022;12:812534.

[107] Xu T, Ding W, Ji X, et al. Molecular mechanisms of ferroptosis and its role in cancer therapy. *J Cell Mol Med* 2019;23(8):4900–4912.

[108] Li J, Cao F, Yin HL, et al. Ferroptosis: past, present and future. *Cell Death Dis* 2020;11(2):88.

[109] Stockwell BR, Jiang X, Gu W. Emerging mechanisms and disease relevance of ferroptosis. *Trends Cell Biol* 2020;30(6):478–490.

[110] Chen X, Kang R, Kroemer G, et al. Ferroptosis in infection, inflammation, and immunity. *J Exp Med* 2021;218(6):e20210518.

[111] Hassannia B, Vandenabeele P, Vanden Berghe T. Targeting ferroptosis to iron out cancer. *Cancer Cell* 2019;35(6):830–849.

[112] Hu Y, Guo N, Yang T, et al. The potential mechanisms by which artemisinin and its derivatives induce ferroptosis in the treatment of cancer. *Oxid Med Cell Longev* 2022;2022:1458143.
[113] Gao M, Monian P, Pan Q, et al. Ferroptosis is an autophagic cell death process. *Cell Res* 2016;26(9):1021–1032.
[114] Chen X, Yu C, Kang R, et al. Cellular degradation systems in ferroptosis. *Cell Death Differ* 2021;28(4):1135–1148.
[115] Hou W, Xie Y, Song X, et al. Autophagy promotes ferroptosis by degradation of ferritin. *Autophagy* 2016;12(8):1425–1428.
[116] Chen GQ, Benthani FA, Wu J, et al. Artemisinin compounds sensitize cancer cells to ferroptosis by regulating iron homeostasis. *Cell Death Differ* 2020;27(1):242–254.
[117] Tsai Y, Xia C, Sun Z. The inhibitory effect of 6-Gingerol on ubiquitin-specific Peptidase 14 enhances autophagy-dependent ferroptosis and anti-tumor *in vivo* and *in vitro*. *Front Pharmacol* 2020;11:598555.
[118] Chen P, Wu Q, Feng J, et al. Erianin, a novel dibenzyl compound in dendrobium extract, inhibits lung cancer cell growth and migration *via* calcium/calmodulin-dependent ferroptosis. *Signal Transduct Target Ther* 2020;5(1):51.
[119] Huang S, Cao B, Zhang J, et al. Induction of ferroptosis in human nasopharyngeal cancer cells by cucurbitacin B: molecular mechanism and therapeutic potential. *Cell Death Dis* 2021;12(3):237.
[120] Kong N, Chen X, Feng J, et al. Baicalin induces ferroptosis in bladder cancer cells by downregulating FTH1. *Acta Pharm Sin B* 2021;11(12):4045–4054.
[121] Guo Q, Li L, Hou S, et al. The role of iron in cancer progression. *Front Oncol* 2021;11:778492.
[122] Tsvetkov P, Coy S, Petrova B, et al. Copper induces cell death by targeting lipoylated TCA cycle proteins. *Science* 2022;375:1254–1261.
[123] Wang Y, Zhang L, Zhou F. Cuproptosis: a new form of programmed cell death. *Cell Mol Immunol* 2022;19(8):867–868.
[124] Tang D, Chen X, Kroemer G. Cuproptosis: a copper-triggered modality of mitochondrial cell death. *Cell Res* 2022;32(5):417–418.
[125] Sun Q, He M, Zhang M, et al. Traditional Chinese medicine and colorectal cancer: implications for drug discovery. *Front Pharmacol* 2021;12:685002.
[126] Fnu G, Weber GF. Alterations of ion homeostasis in cancer metastasis: implications for treatment. *Front Oncol* 2021;11:765329.
[127] Zhang G, Cheng W, Du L, et al. Synergy of hypoxia relief and heat shock protein inhibition for phototherapy enhancement. *J Nanobiotechnology* 2021;19(1):9.
[128] Mukha I, Chepurna O, Vityuk N, et al. Multifunctional magneto-plasmonic Fe_3O_4/Au nanocomposites: approaching magnetophoretically-enhanced photothermal therapy. *Nanomaterials (Basel)* 2021;11(5):1113.
[129] Sun X, Zhang Y, Li J, et al. Amplifying STING activation by cyclic dinucleotide-manganese particles for local and systemic cancer metalloimmunotherapy. *Nat Nanotechnol* 2021;16(11):1260–1270.
[130] Zhang MK, Ye JJ, Li CX, et al. Cytomembrane-mediated transport of metal ions with biological specificity. *Adv Sci (Weinh)* 2019;6(17):1900835.
[131] Chen D, Cai L, Guo Y, et al. Cancer cell membrane-decorated zeolitic-imidazolate frameworks codelivering cisplatin and oleanolic acid induce apoptosis and reversed multidrug resistance on bladder carcinoma cells. *ACS Omega* 2020;5(2):995–1002.
[132] Grabarska A, Wróblewska-Łuczka P, Kukula-Koch W, et al. Palmatine, a bioactive protoberberine alkaloid isolated from Berberis cretica, inhibits the growth of human estrogen receptor-positive breast cancer cells and acts synergistically and additively with doxorubicin. *Molecules* 2021;26(20):6253.
[133] Zeng D, Wang L, Tian L, et al. Synergistic photothermal/photodynamic suppression of prostatic carcinoma by targeted biodegradable MnO_2 nanosheets. *Drug Deliv* 2019;26(1):661–672.
[134] Tan BL, Norhaizan ME. Curcumin combination chemotherapy: the implication and efficacy in cancer. *Molecules* 2019;24(14):2527.
[135] Zheng T, Wang W, Wu F, et al. Zwitterionic polymer-gated Au@TiO_2 core-shell nanoparticles for imaging-guided combined cancer therapy. *Theranostics* 2019;9(17):5035–5048.
[136] Gao L, Teng R, Zhang S, et al. Zinc ion-stabilized aptamer-targeted black phosphorus nanosheets for enhanced photothermal/chemotherapy against prostate cancer. *Front Bioeng Biotechnol* 2020;8:769.
[137] Coughlin AJ, Ananta JS, Deng N, et al. Gadolinium-conjugated gold nanoshells for multimodal diagnostic imaging and photothermal cancer therapy. *Small* 2014;10(3):556–565.
[138] Xi J, Da L, Yang C, et al. Mn^{2+}-coordinated PDA@DOX/PLGA nanoparticles as a smart theranostic agent for synergistic chemo-photothermal tumor therapy. *Int J Nanomedicine* 2017;12:3331–3345.
[139] Wu K, Zhao H, Sun Z, et al. Endogenous oxygen generating multifunctional theranostic nanoplatform for enhanced photodynamic-photothermal therapy and multimodal imaging. *Theranostics* 2019;9(25):7697–7713.
[140] Yu Z, He Y, Schomann T, et al. Achieving effective multimodal imaging with rare-earth ion-doped CaF_2 nanoparticles. *Pharmaceutics* 2022;14(4):840.
[141] Chen F, Li Y, Lin X, et al. Polymeric systems containing supramolecular coordination complexes for drug delivery. *Polymers (Basel)* 2021;13(3):370.
[142] Fu S, Li G, Zang W, et al. Pure drug nano-assemblies: a facile carrier-free nanoplatform for efficient cancer therapy. *Acta Pharm Sin B* 2022;12(1):92–106.
[143] Shao J, Fang Y, Zhao R, et al. Evolution from small molecule to nano-drug delivery systems: an emerging approach for cancer therapy of ursolic acid. *Asian J Pharm Sci* 2020;15(6):685–700.
[144] Kazybay B, Sun Q, Dukenbayev K, et al. Network pharmacology with experimental investigation of the mechanisms of Rhizoma polygonati against prostate cancer with additional herbzymatic activity. *ACS Omega* 2022;7(17):14465–14477.
[145] Xie Y, Mu C, Kazybay B, et al. Network pharmacology and experimental investigation of Rhizoma polygonati extract targeted kinase with herbzyme activity for potent drug delivery. *Drug Deliv* 2021;28(1):2187–2197.
[146] Xie Y, Filchakova O, Yang Q, et al. Inhibition of cancer cell proliferation by carbon dots derived from date pits at low dose. *Chem Select* 2017;2:4079–4083.
[147] Xie Y, Sun Q, Nurkesh AA, et al. Dysregulation of YAP by ARF stimulated with tea-derived carbon nanodots. *Sci Rep* 2017;7:16577.
[148] Kang W, Lee A, Tae Y, et al. Enhancing catalytic efficiency of carbon dots by modulating their Mn doping and chemical structure with metal salts. *RSC Adv* 2023;13(13):8996–9002.
[149] Pechlivanidou M, Ninou E, Karagiorgou K, et al. Autoimmunity to neuronal nicotinic acetylcholine receptors. *Pharmacol Res* 2023;192:106790.
[150] Terry AV, Jr, Jones K, Bertrand D. Nicotinic acetylcholine receptors in neurological and psychiatric diseases. *Pharmacol Res* 2023;191:106764.
[151] Wyllie DJA, Bowie D. Ionotropic glutamate receptors: structure, function and dysfunction. *J Physiol* 2022;600(2):175–179.
[152] Seo JS, Svenningsson P. Modulation of ion channels and receptors by p11 (S100A10). *Trends Pharmacol Sci* 2020;41(7):487–497.
[153] Chen CC, Krogsaeter E, Kuo CY, et al. Endolysosomal cation channels point the way towards precision medicine of cancer and infectious diseases. *Biomed Pharmacother* 2022;148:112751.
[154] Fiorio Pla A, Gkika D. Ca^{2+} channel toolkit in neuroendocrine tumors. *Neuroendocrinology* 2020;110(1-2):147–154.
[155] Cao B, Wang J, Feng J. Signaling pathway mechanisms of neurological diseases induced by G protein-coupled receptor 39. *CNS Neurosci Ther* 2023;29(6):1470–1483.
[156] Gottesman-Katz L, Latorre R, Vanner S, et al. Targeting G protein-coupled receptors for the treatment of chronic pain in the digestive system. *Gut* 2021;70(5):970–981.
[157] Kong D, Wan Q, Li J, et al. DP1 activation reverses age-related hypertension via NEDD4L-mediated T-Bet degradation in T cells. *Circulation* 2020;141(8):655–666.

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