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Research progress on the anti-colorectal cancer effect of traditional Chinese medicine active ingredients based on ferroptosis

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Author contributions

Hui Gong collected the data and contributed to the drafting of the manuscript. Qiang Sun conceived the work and revised the manuscript.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

CRC, colorectal cancer; 5-Fu, 5-fluorouracil; TCM, traditional Chinese medicine; ROS, reactive oxygen species; GSH, glutathione.

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Abstract

Ferroptosis is defined as an iron-dependent form of regulated cell death that is initiated by the toxic accumulation of lipid peroxides on cellular membranes. In the past decade, ferroptosis has aroused considerable interest in comprehensive treatment of colorectal cancer, mainly as it is a specific cell death mode that is mechanistically and morphologically differ from other forms of cell death such as autophagy, apoptosis, and pyroptosis, following by holding a giant potential for the therapy of colorectal cancer. Research has found that various active ingredients in traditional Chinese medicine possess the ability of inducing ferroptosis in colorectal cancer cells through pathways such as lipid metabolism, iron metabolism, or cysteine/glutamate transporter system, which demonstrating enormous clinical therapeutic potential. In this review, the metabolic regulatory network of ferroptosis is introduced from the perspective of ferroptosis mechanism, and the information on the induction of ferroptosis in colorectal cancer cells by active ingredients of traditional Chinese medicine is also be retrospected, which the purpose is to provide novel strategies for the anti-colorectal cancer therapy of active ingredients in traditional Chinese medicine.

Keywords: traditional Chinese medicine; colorectal cancer; ferroptosis; lipid peroxidation; iron metabolism

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Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors worldwide, which the global burden of CRC will continue to increase with the intensification of population aging [1, 2]. According to statistics released by the International Agency for Research on Cancer, the incidence of CRC accounts for approximately 10% of all annual diagnosed malignant tumors, which causing 881, 000 and 94, 000 deaths in 2018 and 2020, respectively [3, 4]. Due to the absence of obvious early symptoms, most patients are already in the advanced stage after diagnosis. Unfortunately, this malignant tumor not only induce damage to the human digestive system, but also, if accompanied by tumor metastasis, can corrupt areas such as lymph nodes, liver, lungs, and bones [5, 6]. Therefore, it is extremely urgent to exploit effective treatment schemes to address the current predicament.

Currently, although the development of modern multidisciplinary technology continues to promote significant progress in the diagnosis and treatment of CRC, the adverse effects of chemotherapy agents are still worrisome [7]. 5-fluorouracil (5-Fu) is currently a classic chemotherapeutant for palliative and adjuvant systemic chemotherapy of CRC. In the past few decades, various therapeutic strategies such as the combined implementation of 5-Fu and the development of precursor drugs have been extensively applied in clinical settings to enhance anti-cancer activity and reduce the occurrence of drug resistance [8–10]. However, the response of most patients to treatment regimens based on the combination of 5-Fu and precursor agents is far from optimistic, accompanied by various toxicity, side effects and drug resistance [11]. Consequently, excavating more effective treatment strategies and medical intervention approaches, especially formulating agents with beneficial therapeutic effects and minimal adverse reactions, is an urgent issue in clinical practice. Traditional Chinese medicine (TCM) is an important medium for nurturing human life and treating diseases with less or no side effects and thus play a pivotal role in improving human health. In recent years, researches have demonstrated that various active ingredients in TCM endow favorable anti-CRC effects, which could postpone or hinder tumor growth through multiple pathways [12–14].

Ferroptosis, a novel form of cell death driven by iron-dependent lipid peroxidation, was identified as a distinct phenomenon and named a decade ago [15]. Specifically, it is triggered by unrestricted phospholipid peroxidation, which mainly depends on the increase of reactive oxygen species (ROS), phospholipids containing polyunsaturated fatty acid chains, and iron accumulation. Besides, intracellular and intercellular signals, as well as environmental pressure, could indirectly affect ferroptosis by regulating cell metabolism and ROS levels [16, 17]. Ferroptosis has been implicated in a broad set of biological contexts, from development to aging, inflammation, immune regulation, especially the malignant tumors [18, 19]. For instance, microvascular invasion mediated cancer cell metastasis is a significant characteristic of the malignancy of CRC, and is considered to be one of the main triggers of recurrence and death in CRC patients. Interestingly, in recent years, a series of investigations have confirmed that ferroptosis inducers can serve as microvascular invasion inhibitors, which can be applied to restrain the distant metastasis of CRC [20–22]. In addition, ferroptosis regulatory factors have also been proven to build a robust theoretical foundation for mRNA vaccine and personalized immunotherapy [23]. Recently, multiple investigations have confirmed that active ingredients in TCM exerts an remarkable therapeutic effects on CRC by inducing ferroptosis mediated cell death [24–26]. This review describes key mechanism framework of ferroptosis biology. A brief overview of progress in the anti-CRC effect of TCM monomers based on ferroptosis is also highlighted.

Mechanism of ferroptosis

Ferroptosis endows distinctive morphological changes and molecular mechanisms that are completely differ from other procedural deaths. As cells undergo ferroptosis, the mitochondrial and mitochondrial cristae morphology are observed to shrink or disappear, mitochondrial membrane density significantly increases, and mitochondrial outer membrane rupture occurs, which these morphological changes are based on inherent genetic molecular biology and cellular metabolic processes that constantly change [27].

Classic cystine/glutathione (GSH)/GPX4 regulatory pathways

System xc^- is a heterodimer composed of two subunits, SLC7A11 and SLC3A2, widely distributed on human cell membranes. With the action of system xc^-, cysteine and glutamic acid exchange in an equal proportion on the cell membrane, and the exchanged cysteine is reduced to cysteine within the cell and subsequently participates in the synthesis of GSH. In terms of biological function, GSH reduce intracellular ROS through the action of GPX4 to impede the occurrence of ferroptosis. When system xc^- encounter with suppressed, followed by the exchange inhibition of cysteine, which triggering a decrease in GPX activity and accumulation of lipids and ROS, ultimately resulting in oxidative damage and ferroptosis. Erastin and RSL3 represent typical ferroptosis inducing compounds. The former touch off ferroptosis by inhibiting system xc^- triggering intracellular cysteine depletion and membrane structure damage [28], while the latter spark off ferroptosis by targeting GPX4 to accumulate peroxidized phospholipids [29].

Non-dependent GPX4 regulatory pathway

Unlike GPX4, which serves as a regulatory pathway for iron dependent cell death, it has been corroborated that the FSP1/CoQ10, DHODH, and GCH1/BH4 pathways possess the ability to regulate the occurrence of ferroptosis independently of GPX4.

NAD(P)H/FSP1/CoQ10 pathway. FSP1, an NAD(P)H-ubiquinone oxidoreductase that blocks ubiquinone to ubiquinol, has emerged as an important participant in the management of ferroptosis. It operates independently of the canonical system xc^-/GPX4 signaling pathway, making it a prospective therapeutic target for triggering ferroptosis in cancer cells and conquering ferroptosis resistance [30]. From the mechanistic perspective, FSP1 reduces the ubiquinone to ubiquinol via obvious reductase activity, directly reducing the generation of lipid free radicals or promoting the regeneration of vitamin E, thereby regulating lipid peroxidation and ferroptosis.

DHODH pathway. DHODH has recently been identified as a novel ferroptosis defender independently of GPX4 or FSP1 [31]. As a rate-limiting enzyme in de novo pyrimidine nucleotide biosynthesis, DHODH complements mitochondrial GPX4 in decreasing peroxidized membrane phospholipids. In the process of ferroptosis inhibition, DHODH inhibitors could display unique mechanisms of action against tumors. Specifically, as CoQH2 could act as a free radical trapping antioxidant to prevent lipid peroxidation, it has been proven to induce the production of CoQH2 in the inner membrane of mitochondria, thereby inhibiting ferroptosis in mitochondria [32].

GCH1/BH4/DHFR pathway. As is known to all, various malignant tumor cells can acquire massive endogenous antioxidant capacity for defense anti cell death when suffering persistent oxidative stress. It have substantiated that another effective GPX4-independent antioxidative mechanism exists in tumor cells. The GCH1/BH4/DHFR axis has been proven to prevent lipid peroxidation damage in cells during the process of ferroptosis, which the specific process includes: (1) GCH1 produces lipophilic antioxidant BH4, which functions similarly to CoQ10 to prevent lipid peroxidation; (2) GCH1 mediates the remodeling of the lipid membrane environment, thereby increasing the abundance of reduced CoQ10 while consuming the inducer of ferroptosis [33].

Iron metabolism pathway

Iron is one of the essential trace elements for human body. In vivo, Fe^{3+} commonly bind to transferrin in the form of trivalent iron and enter cells through transferrin channels, subsequently reduced to Fe^{2+} by the metal reductase STEAP3 and participate in various

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physiological and biochemical processes. The lack of iron element in the body possibly initiate various iron deficiency diseases, such as anemia and weakened immunity [34]. In addition, digestive system diseases such as indigestion and neurological diseases such as memory loss are also important diseases induced by iron deficiency [35]. As iron overload occurs, excess Fe^{2+} accumulates in cells to form unstable iron pools, which induce ROS production and promote lipid peroxidation by participating in the Fenton reaction, ultimately triggering the occurrence of ferroptosis.

Lipid metabolism pathway

The essence of ferroptosis is ultimately driven by the peroxidation of specific membrane lipids, and the tendency of lipids to undergo peroxidation depends on the strength of carbon hydrogen bonds. Due to the extremely weak C-H bonds between adjacent C = C double bonds, the polyunsaturated fatty acids is particularly prone to peroxidation. Under the action of enzymes ACSL4 and LPCAT3, polyunsaturated fatty acids binds with phosphatidylethanolamine to form polyunsaturated fatty acid-containing phosphatidylethanolamine, which are susceptible to oxidation induced by free radicals mediated by LOX and induce ferroptosis [36].

Monomer components of TCM targeting ferroptosis to combat CRC

Based on current investigations, a series of active ingredients derived from TCM, such as artemisinin, luteolin, osthole, glycyrrhetinic acid have been proven to restrain the growth and proliferation of cancer cells by inducing ferroptosis (Figure 1). In an investigation exploring the crosstalk effect between ferroptosis induced endoplasmic reticulum stress and tumor necrosis factor-related apoptosis-inducing ligand induced cell apoptosis, the combined treatment of ferroptosis inducers artemisinin and erastin with tumor necrosis factor-related apoptosis-inducing ligand could enhance the activation of caspase-8 and increase the truncation of Bid in human CRC HCT116 cells [37]. In SW480 cells, treatment with curcumin increased the expression of ferroptosis-related factors such as SLCA5 and caveolin 1, which this result indicate that natural ingredient curcumin could induce ferroptosis in CRC and possess the potential to be applied as a therapeutic agent for treating CRC [38].

The drug resistance of 5-Fu emphasize the demand for novel therapeutic strategies that offer ameliorated efficacy and assist conquer acquired chemoresistance, followed by increasing anti-cancer efficacy of conventional chemotherapies. Research has shown that, andrographolide treatment markedly promoted the sensitiveness of HCT116 cells and SW480 cells to 5-Fu, as evidenced by increased the apoptosis and suppressed proliferation, which the microarray-based gene expression profiling analysis suggested that the mechanism may involve inducing cell ferroptosis [39]. Unfavorable aqueous solubility and needy bioavailability restrict the clinical efficacy of natural products, simultaneously carbon dots, as an emerging 0D material, endows specific properties in pharmaceutical field. Research has confirmed that carbon dots prepared with glycyrrhetinic acid, ursolic acid, and oleanolic acid could stimulate green fluorescence, induce high sensitivity to ROS damage and internal oxidative stress, as well as induce cell death through ferroptosis and autophagy [40]. Additional details involved ferroptosis-induction effects and mechanisms of TCM active ingredients anti-CRC are displayed as Table 1.

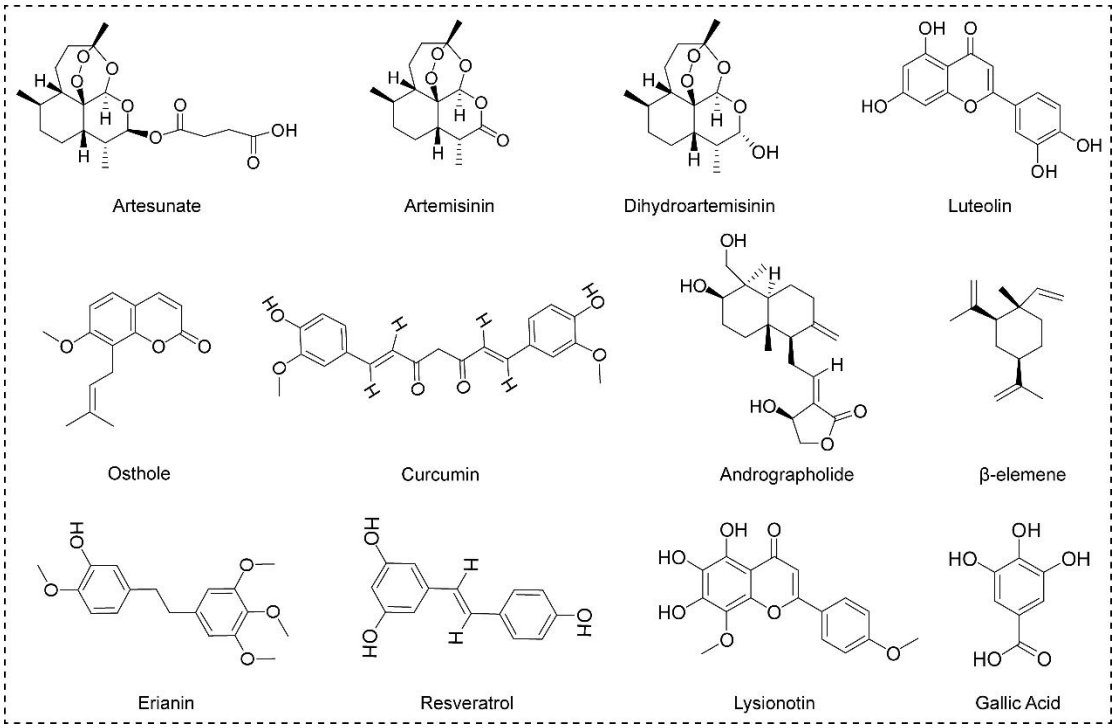

Figure 1 Active ingredients of TCM with the ability to induce ferroptosis in CRC cells. TCM, traditional Chinese medicine; CRC, colorectal cancer.

Table 1 Ferroptosis-induction mechanisms of TCM active ingredients anti-CRC

Ingredients	Main sources	Detail information	Models	Dose	Ref.
Artesunate	*Artemisia annua L.*	Inhibit CRC cell growth and proliferation through iron dependent pathways	HCT116 cells	10–160 μM	[41]
Artesunate	*Artemisia annua L.*	Induce endoplasmic reticulum stress and promote PUMA expression via CHOP	HCT116 cells	5–50 μM	[42]
			Balb/c nude mice	200 mg/kg	

TCM, traditional Chinese medicine; CRC, colorectal cancer.

Table 1 Ferroptosis-induction mechanisms of TCM active ingredients anti-CRC (*Continued*)

Ingredients	Main sources	Detail information	Models	Dose	Ref.
Artemisinin Dihydroartemisinin	*Artemisia annua L.*	Induce iron dependent lipid peroxidation mediated ferroptosis	SW480 cells SW620 cells	1–8 μM 1–8 μM	[43]
Luteolin	*Lonicera japonica* Thunb.	Reduce glutathione and elevate lipid peroxides, inhibit the expression of GPX4	HCT116 cells SW480 cells Balb/c nude mice	1.56–50 μM 1.56–50 μM 60 mg/kg	[44]
Osthole	*Cnidium monnieri* (L.) Cuss.	Inhibit malignant phenotypes and induce ferroptosis via suppressing AMPK/Akt signaling	HCT116 cells SW480 cells Balb/c nude mice C57BL/6 J mice	25–100 μM 25–100 μM 10–40 mg/kg 10–40 mg/kg	[45]
Curcumin	*Curcuma Longa* L.	Downregulate GSH, SLC7A11, and GPX4, increase levels of iron, MDA, and ROS	HCT8 cells Balb/c nude mice	5–50 μM 100 mg/kg	[46]
Curcumin Andrographis	Curcuma Longa L. *Andrographis paniculata* (Burm. f.) Nee	Inhibit the expression levels of GPX4 and FSP1 proteins	HCT116 cells SW480 cells	2–10 μg/mL 20–100 μg/mL	[47]
β-elemene	*Curcuma phaeocauLis* Val.	Induce iron-dependent ROS accumulation, GSH depletion, lipid peroxidation, HO-1 and transferrin upregulation, downregulate GPX4, SLC7A11 and FTH1 expressions	HCT116 cells Lovo cells CaCO2 cells Balb/c nude mice	125 μg/mL 125 μg/mL 125 μg/mL 50 mg/kg	[48]
Erianin	*Dendrobium nobile* Lindl	Inhibit the growth and metastasis via autophagy-dependent ferroptosis	LoVo cells HCT116 cells DLD1 cells HCT8 cells Balb/c nude mice	20–100 nM 20–100 nM 20–100 nM 20–100 nM 100 mg/kg	[49]
Erianin	*Dendrobium nobile* Lindl	Increase the expression of FDX1 and induce the lipoylation of DLAT and DLST protein	SW480 cells SW620 cells Balb/c nude mice	40 nM 40 nM 20 mg/kg	[50]
Resveratrol	*Polygonum cuspidatum*	Downregulate the expression of SLC7A11 and GPX4	HT29 cells HCT116 cells Balb/c nude mice	10–60 μg/mL 10–60 μg/mL 10 mg/kg	[51]
Pt3R5G	*Lycium ruthenicum* Murray	Down-regulate the expression of SLC7A11	RKO cells HCT116 cells Balb/c nude mice	100–500 μg/mL 100–500 μg/mL 25, 50 mg/kg	[52]
Lysionotin	*Lysinonotus pauciflorus* Maxim.	Induces ferroptosis to suppress development of CRC via promoting Nrf2 degradation	HCT116 cells SW480 cells Athymic nude mice	1–100 μM 1–100 μM 20 mg/kg	[53]
Timosaponin AIII	*Anemarrhena asphodeloides* Bge.	Trigger lipophagy via the Rab7 gene and promote ferroptosis	HCT116 cells SW480 cells Balb/c nude mice	1.25–40 μM 1.25–40 μM 6 mg/kg	[54]
Gallic acid	*Rhus chinensis* Mill.	Target regulation of ferroptosis related factors expression	HCT116 cells SD rats	0.2–0.6 μM 10 mg/kg	[55]
Tagitinin C	*Tithonia diversifolia* (Hemsl.) A. Gray	Attenuate GSH levels and increase lipid peroxidation	SW480 cells DLD1 cells HCT116 cells	5–20 μM 5–20 μM 5–20 μM	[56]

TCM, traditional Chinese medicine; CRC, colorectal cancer; ROS, reactive oxygen species; GSH, glutathione.

Discussions and prospects

With the features of multiple-components and targets as well as multifunction, TCM has been extensively utilized in the prevention and treatment of various diseases for a long time. The clinical intervention of TCM could significantly ameliorate the quality of life and survival of CRC patients, which setting a favorable pattern for the combined treatment of Chinese and Western medicine in related diseases. As a novel form of cell death identified in recent years, ferroptosis exhibits significant characteristic differences from traditional cell death modes in terms of morphology, pharmacology, mechanism and so on. The review of the molecular mechanisms of ferroptosis and understanding of the targeted application of TCM active ingredients in the treatment of CRC, is conducive to expedite clarify the key role of ferroptosis in the progression of this malignant tumor, as well as provide innovative strategy for clinical treatment of CRC.

Although a series of active ingredients in TCM have been found to induce ferroptosis in CRC cells, there are still a series of issues that need to be addressed urgently at present. Firstly, the understanding of ferroptosis remains elusive. The specific mechanism by which ferroptosis leads to cell death is not yet clear, which limits further research on agents that induce ferroptosis in CRC cells. In addition, there is still a lack of research on the therapeutic effects and safety of drugs based ferroptosis in vivo, and further improvement is necessary in the investigation of drug properties, drug delivery, distribution characteristics, pharmacokinetics, and targeted drug carrier modification. Therefore, revealing the mechanism of ferroptosis induction in CRC cells based on the TCM theory, may become a leading-edge direction for the anti-tumor research of active ingredients in TCM.

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