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评 述

益气活血类中药调控铁死亡机制研究进展

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摘要 铁死亡(ferroptosis)是一种铁依赖的细胞死亡方式, 主要特征为铁过载、脂质过氧化物和活性氧蓄积. 中医中"气血"是构成人体的重要组成部分, 也是生命活动的动力和源泉. 当"气血"失调时, 会引发严重的疾病, 所以调节"气血"是临床治疗疾病的基本原则和核心思想. 研究表明, 益气活血类中药可以通过调节铁稳态和抑制铁死亡在防治重大疾病方面发挥着积极作用. 本文综述了益气活血类中药调控铁死亡防治各类重大疾病的研究进展, 梳理现有的益气活血类中药防治铁死亡引发重大疾病的相关药物, 为中药防治铁死亡引发的重大疾病提供新的思路.

关键词 铁死亡, 铁稳态, 中药, 益气活血

中药研究拥有悠久的文化历史, 其在预防和治疗各类重大疾病中具有重要地位. 在中医理论中"气血"是人体重要组成部分, 也是生命活动的动力和源泉, 《黄帝内经·素问》曰: "人之所有者, 血与气耳"[1]. 《素问·至真要大论》中将调节"气血"作为临床治疗疾病的基本原则和核心思想[2]. 同时"气血"在人体中可以通过流动的形式将五脏六腑联系起来, 以此来调节各器官之间的正常运作与代谢[3]. 《素问·调经论》中记载: "血气不和, 百病乃变化而生", 当人体中"气血"出现异常变化时, 器官之间会产生相应的疾病[4]. 因此, 调节"气血"对于治疗各类疾病具有十分重要的作用.

在中医辨证理论中将"气血"归属于"阴阳"范畴, 其核心思想为"阴阳为纲, 气血为本". 当机体阴阳失衡时, 则会引发疾病. 根据中医理论将运动、上升、增殖的状态定义为"阳"; 而相对静止、下降、凋亡则定义为"阴". 铁死亡(ferroptosis)作为一种特殊的细胞死亡方式, 在中医理论范畴中属于"阴". 因此, 抑制铁死亡能够有效地保护正常组织免受损伤, 这与中医的抑阴扶阳理论不谋而合[5~7]. 益气活血类中药复方及中药有效成分可以通过靶向不同信号通路对铁死亡产生双向调控作用, 这意味着调控铁死亡可能是中药治疗各类疾病的重要机制之一, 其总体原则是调节阴阳平衡[5,8]. 近年来, 关于中药及有效成分参与铁死亡引发各类疾病发生发展的报道较多, 但具体机制尚不清楚. 研究表明益气活血类中药能够参与调节体内铁稳态来预防和治疗多种疾病.本文从益气活血类中药调控铁

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死亡进而防治各类重大疾病的角度，梳理了该类中药在防治重大疾病中的研究进展并提出新的见解.

1. 铁死亡的基本特征

铁死亡是2012年发现的一种铁依赖的新型细胞死亡方式，其主要特征为铁过载(iron overload)、脂质过氧化(lipid peroxidation)和活性氧(reactive oxygen, ROS)蓄积[9,10]. 另外，铁死亡的三个代谢因素分别为: 铁、谷胱甘肽以及脂质. 其中，铁代谢紊乱在脂质过氧化的产生和运行中具有关键作用[11]. 后者能够有效增加细胞膜的通透性，并影响细胞膜的流动性和离子功能，促进了非射程孔的形成，从而导致铁蛋白信号的传播和铁死亡[12~14]. 同时铁作为人体必需的微量元素之一，是人生长发育的重要组成部分[15]. 人体中的铁大部分是以血红素铁的形式分布在血红蛋白和肌红蛋白中，其余的铁则以铁蛋白的形式储存在肝脏细胞和小肠细胞中. 铁在人体维持吸收、转运、储存中起到了重要的作用[16]. 当人体铁稳态代谢紊乱时，会引发严重的疾病，铁缺乏时会引发缺铁性贫血，铁过载时则会引发血色病. 其中，铁过载是引发铁死亡的关键因素之一. 越来越多的研究发现铁死亡参与各类重大疾病的发生发展，但具体机制尚不清楚. 目前铁死亡调控机制(图1)主要从以下几方面展开研究.

1.1 铁代谢

人体中的铁元素是以Fe^{2+}及Fe^{3+}的形式存在，其中转铁蛋白(transferrin, TF)可以与Fe^{3+}结合并通过细胞膜上的转铁蛋白受体-1(transferrin receptor-1, Tfr1)将Fe^{3+}转运到细胞中[17,18]，而细胞核中的Fe^{2+}则能够通过二价金属转运蛋白1(divalent metal transporter 1, DMT1)将其释放到细胞质中去[19]. 此外，溶质载体家

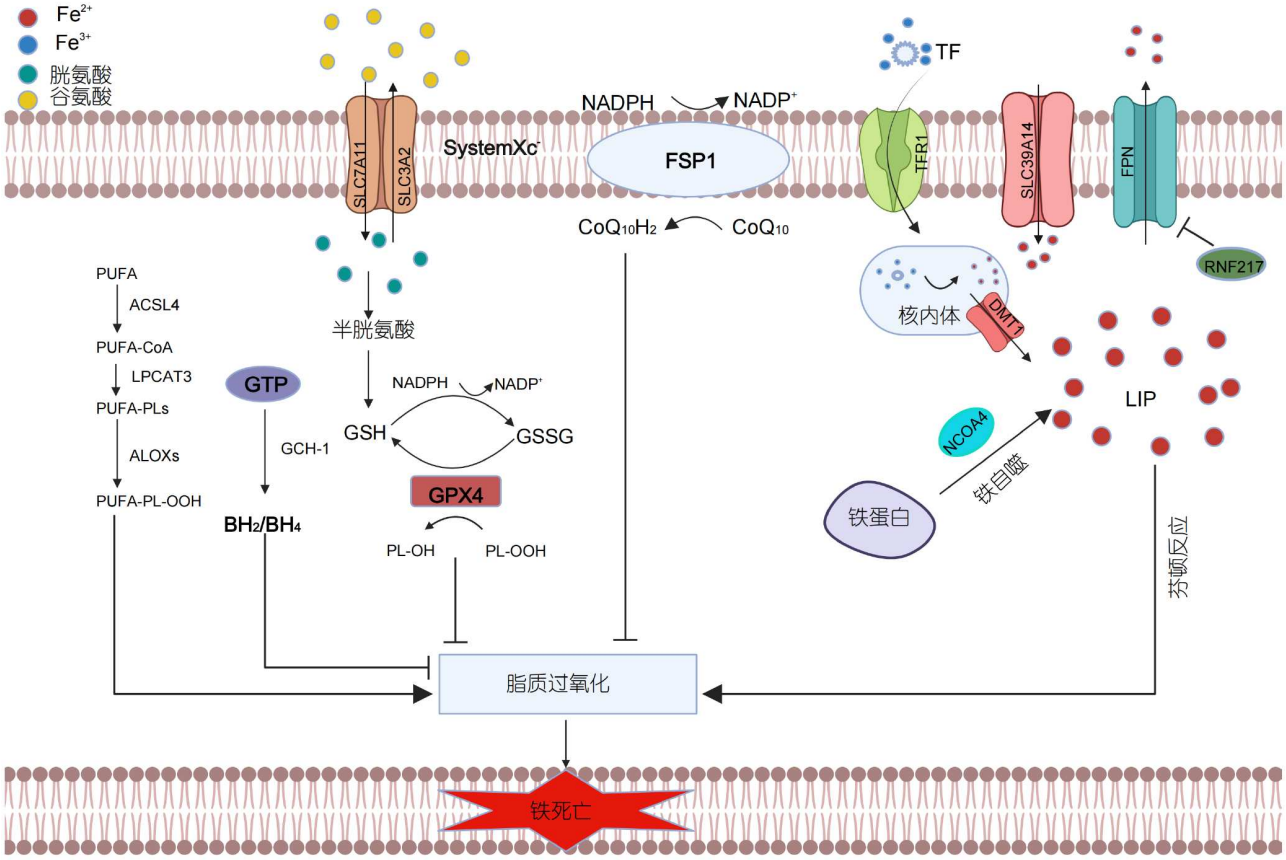


图 1 铁死亡调控机制图
Figure 1 Regulatory mechanisms of ferroptosis

族39成员14(solute carrier family 39 member 14, SLC39A14)[17]和铁转运蛋白(ferroportin, FPN)[20,21]都可以参与Fe^{2+}的转运. 本团队首次报道了一种E3泛素连接酶RNF217, 可以通过调控FPN降解从而维持体内铁稳态[22]. 核受体辅活化因子4 (nuclear receptor coactivator 4, NCOA4)可以将铁蛋白(ferritin)以铁自噬方式传送到不稳定铁池(labile iron pool, LIP)[23]. 不稳定铁池中的Fe^{2+}能够参与芬顿反应并生成羟基自由基, 进而促进脂质过氧化积累, 并最终引发铁死亡[14,24].

1.2 抗氧化通路

抗氧化通路分为System Xc^-/GSH/GPX4、GCH1/BH4和FSP1/CoQ_{10}. 其中胱氨酸/谷氨酸逆向转运体, 又称System Xc^-是由(SLC7A11/SLC3A2)两个亚基组成, 能够以1:1的比例将胱氨酸(cystine)转入细胞和谷氨酸(glutamate)转出细胞, 并在细胞内将胱氨酸还原为半胱氨酸(cysteine)[25]. 同时谷胱甘肽过氧化物酶4 (glutathione peroxidase 4, GPX4)作为一种硒蛋白, 能够将细胞内的谷胱甘肽(glutathione, GSH)转化为氧化型谷胱甘肽(oxidized glutathione, GSSG), 并可以把细胞内具有毒性的脂质过氧化物还原为惰性的脂质醇. 当细胞内GSH消耗殆尽时, 会导致脂质过氧化物的积累, 从而引发GPX4的失活, 进而导致铁死亡的发生[26~28]. GTP环氢化酶1/四氢生物蝶呤(GTP cyclohydrolase 1/tetrahydrobiopterin, GCH-1/BH4)通路是一种独立于GPX4的抑制铁死亡的通路. 其中BH4是芳香族氨基酸羟化酶和一氧化氮的重要辅助因子. GCH-1能够催化产生BH2/BH4并引起脂质重塑, 防止两个多不饱和脂肪酰尾磷脂的消耗, 从而保护铁死亡[29,30]. 此外, 铁死亡抑制蛋白1(Ferroptosis suppressor protein 1, FSP1)作为烟酰胺腺嘌呤二核苷磷酸(nicotinamide adenine dinucleotide phosphate, NAD(P)H)依赖的氧化还原酶, 能够将辅酶Q_{10}(也称为泛醌, CoQ_{10})还原为二氢泛醌($CoQ_{10}H_2$), 同时$CoQ_{10}H_2$可以清除脂质过氧自由基, 进而抑制脂质过氧化和铁死亡[31~34].

1.3 脂质过氧化

铁死亡是由多不饱和脂肪酸磷脂(polyunsaturated fatty acid binding phospholipids, PUFA-PLs)脂质过氧化而引发的. 在PUFA-PLs形成过程中, 长链脂酰辅酶A合成酶4(acyl-CoA synthetase long-chain family member 4, ACSL4)发挥着重要作用, ACSL4作为一种脂肪酸CoA合成酶, 能够将游离多不饱和脂肪酸(polyunsaturated fatty acids, PUFA)与CoA连接生成PUFA-CoA, 随后在溶血卵磷脂酰基转移酶3(recombinant lysophosphatidylcholine acyltransferase 3, LPCAT3)催化下形成PUFA-PLs. 经过脂氧合酶(arachidonate lipoxygenase, ALOXs)催化发生脂质过氧化, 从而引发铁死亡[35~38].

2. 铁死亡与疾病

目前为止, 大量研究表明铁死亡参与了心脏疾病、肝脏疾病、肾脏疾病等多种疾病的发生发展, 因此靶向铁死亡可能是防治各类重大疾病的一种新的思路和策略[30].

2.1 铁死亡与心脏疾病

阿霉素(doxorubicin, DOX)作为一种抗癌药物, 在临床中主要用于治疗恶性肿瘤, 其主要副作用为心脏毒性, 严重时能够引发心力衰竭. 方学贤等[39]首次发现使用铁死亡抑制剂Fer-1(ferrostatin-1, Fer-1)和铁螯合剂右雷佐生可以保护DOX引发的心脏损伤. 同时方学贤等[40]还发现当心肌细胞铁蛋白缺乏的情况下, 会导致心肌细胞中铁含量的升高, 进而加剧心脏损伤, 通过构建SLC7A11过表达小鼠发现, 当SLC7A11过表达时可以促进GSH合成, 进而逆转FTH小鼠铁死亡和心衰表型, 这表明SLC7A11可以作为铁死亡相关心脏疾病的治疗靶点. 此外, Jonghan kim团队[41]发现镰刀性贫血(sickle cell diease, SCD)引发的心肌病与Hmox-1上调有关, 抑制铁死亡可以改善SCD引发的心肌损伤, 该研究为SCD引发的心脏疾病与铁死亡相关机制提供理论依据, 并且为治疗SCD相关的心脏疾病提供治疗策略.

2.2 铁死亡与肝脏疾病

肝脏在机体的合成与代谢中发挥重要作用, 研究显示肝脏损伤、肝脏纤维化, 脂肪肝等多种肝脏疾病中均发现不同程度的铁代谢紊乱和脂质过氧化物集聚等铁死亡特征. 王浩等[42]首次发现了铁过载能够诱导铁死亡从而引发血色病肝脏损伤, 并阐明了SLC7A11在调控铁死亡和铁过载中的重要作用. 余盈盈等[17]发

现抑制SLC39A14可以显著改善肝脏非转铁蛋白结合铁(Non-transferrin bound iron, NTBI)蓄积, 减轻脂质过氧化能够缓解铁死亡引发的肝损伤和肝脏纤维化. 方学贤、孟红恩等[43,44]发现了苹果酸酶1型(ME1)和组蛋白去乙酰化酶3(HDAC3)等关键基因均能够调控铁死亡引发的肝脏损伤. 同时杨磊等[45]发现低剂量金诺芬能够提高小鼠肝脏铁调素(hepcidin)表达从而有效减轻铁过载, 但高剂量金诺芬会抑制硫氧还蛋白还原酶活性, 导致细胞膜脂质过氧化累积诱导铁死亡, 说明了金诺芬毒副作用与肝脏铁死亡有着密切关联.

2.3 铁死亡与肾脏疾病

铁死亡在调控肾脏疾病中也发挥着重要作用. 本团队最近在*Cell Discovery*杂志上发表论文, 发现使用二甲双胍能加重急性肾损伤, 铁死亡可以使中性粒细胞增加进而加重二甲双胍对肾脏的损伤, 同时研究人员发现了低铁水平对急性肾损伤具有保护作用[46]. Zhang等[47]发现血小板激活因子乙酰水解酶2(PAFAH2)能够抑制铁死亡并缓解小鼠缺血再灌注引发的急性肾损伤. Mässenhausen等[48]发现地塞米松可以通过糖皮质激素受体(glucocorticoid recepto, GR)依赖的方式使GSH失活进而引发铁死亡, 同时发现使用Fer-1和DPEP1抑制剂西司他丁能够逆转地塞米松诱导的肾脏损伤, 这是由于地塞米松可以通过GR介导DPEP1表达增加和GSH耗竭使铁死亡变得敏感, 该研究成果具有临床和治疗意义. 上述研究体现了铁死亡相关基因在防治疾病中具有重要意义, 同时靶向铁死亡能够在防治重大疾病中发挥着至关重要的作用.

3 益气活血类中药调控铁死亡防治重大疾病

3.1 益气类中草药

3.1.1 益气类中药复方

人体中的“气”遍布于各个器官之间, 能够为生命活动提供能量[49]. 当机体内的“气”失调时, 就会产生疾病. 《素问·调经论》曰: “血之与气, 并走于上, 则为大厥, 厥则暴死, 气复反则生, 不反则死”. 当人体中气血不顺时, 轻则引发疾病, 重则导致死亡. 因此, 治疗的首要方向就是补精益气. 具有益气功能的中药复方主要有: 芪参益气丸、加味涤痰汤、参附注射液等. 其中芪参益气丸具有“益气通脉”的功效, 能够改善血液循环、提高心血管功能、抗炎止痛等. Wu等[50]研究发现使用芪参益气丸能够减轻线粒体动力学紊乱和心肌缺血性损伤, 通过调节线粒体的生物合成和动态平衡来抑制心肌细胞铁死亡. 加味涤痰汤服用之后可以显著降低心脏肌酸激酶同工酶和乳酸脱氢酶的水平, 还可以通过抑制铁死亡来减轻低氧型大鼠心肌损伤[51]. 参附注射液和益气活血方均能够通过调节铁代谢、 降低体内丙二醛(malondialdehyde, MDA)水平和减轻氧化应激损伤, 同时减少心肌纤维化与胶原蛋白沉积, 减轻心肌细胞的炎性浸润, 改善心功能和心室重构, 通过调控SLC7A11/GPX4/Nrf2/FTH等信号通路减缓慢性心力衰竭和心肌缺血再灌注的发生发展[52,53]. 参苓白术散和丹蒌片能够有效缓解酒精性肝脏损伤和非酒精性脂肪肝, 调节脂肪变性和降低脂肪沉积, 同时发挥抗炎抗氧化等作用, 通过抑制肝脏细胞中铁死亡来治疗肝脏疾病[54,55]. 其中人参、黄芪、党参等中药是上述复方的核心有效成分.

3.1.2 益气类单味中药及中药有效成分

具有益气功能中草药有: 人参、黄芪、党参、黄精、黄皮、甘草等. 其中人参作为一种使用最广泛的治疗药物, 在中国历代医书中记载的别名分别为: 鬼盖、地精、神草、血参等, 被誉为“百草之王”. 其衍生物已超过近百种, 广泛用于治疗多种疾病. 研究发现人参皂苷Rb1、Rg1可以抑制脂质过氧化和降低脑部炎症水平, 通过减轻脑组织中线粒体损伤来抑制脑内铁死亡发生, 进而对缺血性脑损伤起到保护作用[56,57]. 人参皂苷Rh2、Rd[58,59]能够通过减少体内ROS、MDA和铁含量来缓解肝脏纤维化和肝脏损伤的发生. 此外, 人参皂苷和人参皂苷Rg3可以通过激活SLC7A11/Nrf2/HO-1来缓解心脏缺血再灌注和急性胰腺炎的发展[60,61]. 红参多糖作为一种从人参中提取的多糖类化合物, 可以通过靶向GPX4来达到抗肺癌和乳腺癌的作用[62].

黄芪甲苷作为一种具有抗氧化功效的黄芪提取物, 可以通过激活Nrf2/HO-1/SLC7A11/GPX4来缓解DOX引发的心肌损伤, 还能够减轻脑卒中和肺损伤的发病进程[63~66]. 另外, 黄芪多糖(a-stragalus polysaccharide, APS)作为一种多糖类衍生物, 有抗炎、抗肿瘤等作用[67~70], 同时APS对胃肠道疾病也有良好的治疗效果. 有研究发现高剂量APS可以减轻结肠炎小鼠的疾病活

动指数评分, 减轻组织损伤和结肠中炎性细胞因子的表达, 通过调控Nrf2/HO-1信号通路抑制铁死亡从而缓解结肠炎小鼠的病变, 为治疗结肠炎提供了新的思路[71].

党参具有补中益气的作用, 研究发现使用党参能够通过抑制肠黏膜细胞线粒体动力学失衡和铁死亡氧化应激损伤来治疗溃疡性结肠炎[72]. 刘赫等[73]发现黄精多糖可以通过调控FTH/TF/GPX4来抑制铁死亡, 从而发挥治疗糖尿病的作用. 黄皮作为一种生长在中国南方的一种常见的可食用性水果, 其根、茎、叶、果实、种子皆可入药, 具有一定药用价值, Wang等[74]发现黄皮提取物黄皮酰胺能逆转药物引发的肝脏损伤, 使用黄皮酰胺之后能够有效降低GSH的含量和减少MDA的产生, 并通过发挥其抗氧化的作用来降低脂质过氧化的发生从而抑制铁死亡.

甘草作为一种豆科(*Leguminosae*)植物, 具有补气益中等疗效, 其拥有“中药之王”的美誉. 有研究表明使用甘草和异甘草酸镁可以通过调控Nrf2/HO-1缓解肝脏纤维化和溃疡性肠炎的发病过程[75,76]. Huang等[77]首次在斑马鱼和小鼠双模型实验中发现异甘草素能抑制GPX4并上调Tfr/DMT1, 从而诱导肝星状细胞(hepatic stellate cells, HSCs)铁死亡, 同时还发现窖蛋白-1(Cav-1)也能够诱导HSCs铁死亡, 从而发挥治疗肝脏纤维化作用.

五味子素可以减轻线粒体障碍, 降低细胞内Fe^{2+}、ROS和MDA水平, 通过抑制铁死亡来缓解肝脏损伤及纤维化、肾结石和糖尿病心肌病等疾病的发病过程[78~81].

通过上述研究, 益气类中药复方和中药有效成分主要是通过调节线粒体动态紊乱和减轻氧化应激损伤的方式来抑制铁死亡从而治疗各类疾病. 益气活血类中药有效成分及中药复方调控铁死亡防治各类重大疾病见表1、表2和表3.

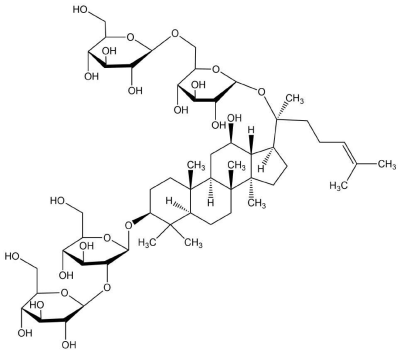
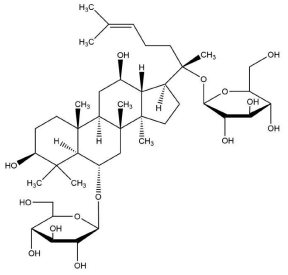
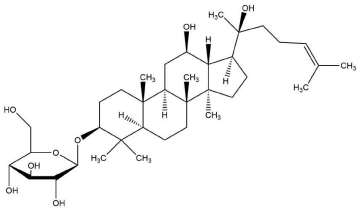
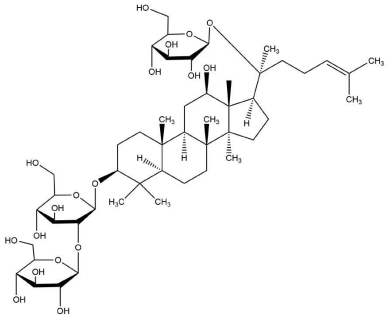
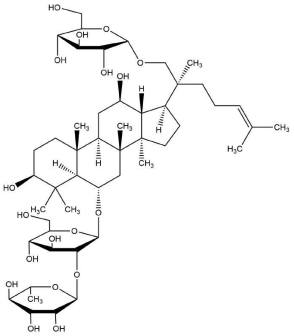
表 1　益气活血类中药复方与铁死亡研究

Table 1　Herbal compounds with qi-invigorating and blood-activating functions and ferroptosis research

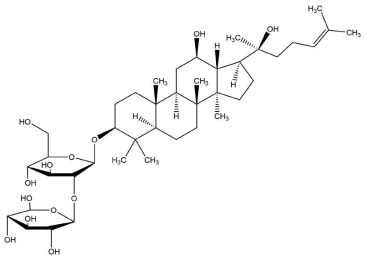
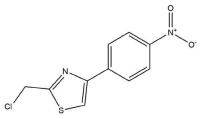
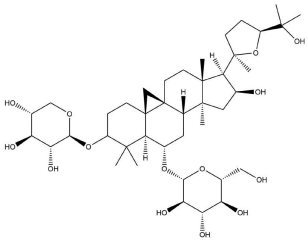
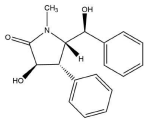
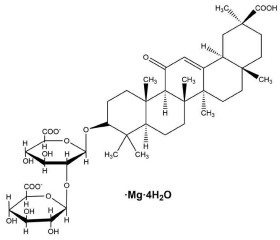
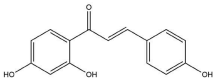
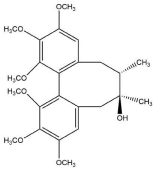
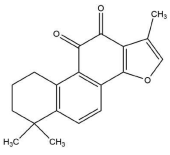
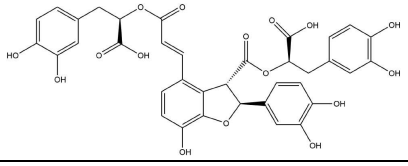
名称	功效	调控铁死亡研究有效中药组分	治疗疾病	调控通路机制	参考文献
芪参益气滴丸	益气	黄芪、丹参	心肌缺血再灌注/心肌梗死	SLC7A11/GPX4/ACSL4	[50]
加味涤痰汤	益气	黄芪、党参	心肌缺血再灌注/心肌梗死	Keap1/Nrf2	[51]
参附注射液	益气	红参	慢性心力衰竭	SLC7A11/GPX4/Nrf2/FTH	[52]
益气活血方	益气	黄芪、丹参、三七	心肌缺血再灌注/心肌梗死	SLC7A11/GPX4/FTH	[53]
参苓白术散	益气	白术、甘草、人参	酒精性肝损伤	Nrf2	[54]
丹蒌片	益气	川芎、丹参、黄芪	非酒精性脂肪肝	GPX4/FTH	[55]
片仔癀	活血	麝香、三七	肝脏纤维化	SLC7A11/GPX4	[83]
丹红注射液	活血	丹参、红花	缺血性脑卒中	SATB1/SLC7A11/HO-1	[84]
健脾生血片	活血	黄芪	慢性心力衰竭	Hepcidin	[85,86]
心阳片	活血	黄芪	慢性心力衰竭	MLK3/JNK/p53/System Xc^-/GPX4/FTH	[87,88]
二陈汤合桃红四物汤	活血	当归、生地黄	动脉粥样硬化	SLC7A11/p53	[89]
佛手撒	活血	当归、川芎	认知障碍	Nrf2/HO-1	[90]
通心络胶囊	益气/活血	人参	动脉粥样硬化	ACSL4/GPX4/FSP1	[139]
清心解淤颗粒	益气/活血	黄芪、丹参、三七	动脉粥样硬化	SLC7A11/GPX4	[140]
补阳还五汤	益气/活血	黄芪、当归	糖尿病	SLC7A11/GPX4/ACSL4	[141]
补肾活血颗粒	益气/活血	丹参	帕金森病	ACSL4/SLC7A11/GPX4	[144]
鹿红方	益气/活血	红花	心肌缺血再灌注/心肌梗死	Keap-1/Nrf2/ARE	[142]
益糖康	益气/活血	黄芪、红参、五味子、丹参、甘草	糖尿病	SLC7A11/GPX4	[143]
脑泰方	益气/活血	黄芪	急性脑缺血	DMT1/Tfr1/GPX4/SLC7A11	[145]

表 2 益气活血类中药有效成分化学结构与作用位点

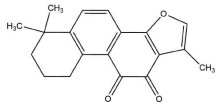
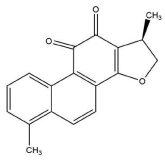
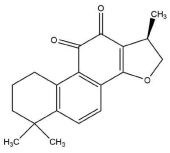
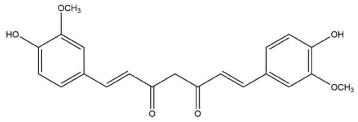
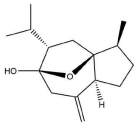
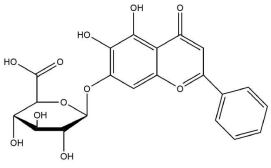
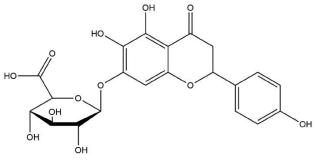
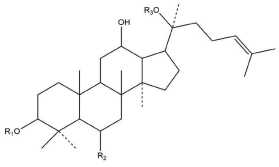
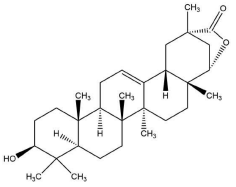
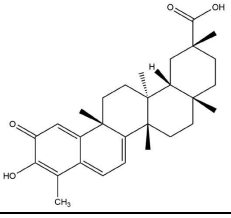
Table 2 Chemical structures and action sites of active components in herbal medicines with qi-invigorating and blood-activating effects

中药活性成分名称	化学结构式	作用位点	参考文献
人参皂苷Rb1		System Xc^-、GPX4	[56]
人参皂苷Rg1		System Xc^-、GPX4、Nrf2	[57]
人参皂苷Rh2		IRF1、SLC7A11	[58]
人参皂苷Rd		cGAS、STING	[59]
人参皂苷Re		SLC7A11	[60]

(表2续)

中药活性成分名称	化学结构式	作用位点	参考文献
人参皂苷Rg3		Nrf2、HO−1	[61]
黄芪多糖		Nrf2、HO-1	[71]
黄芪甲苷		Nrf2、SLC7A11、GPX4、HO-1	[63~66]
黄皮酰胺		Nrf2	[74]
异甘草酸镁		HO-1	[75]
异甘草素		Cav-1	[77]
五味子素		Nrf2、ACSL4、GPX4、SLC7A11	[78~81]
丹参酮IIA		VDAC1、Nrf2、HO-1、SLC7A11、GPX4	[96]
丹酚酸B		Nrf2	[97]

(表2续)

中药活性成分名称	化学结构式	作用位点	参考文献
丹参酮		NQO1	[98]
二氢丹参酮I		GPX4	[102]
隐丹参酮		Tfr1	[103]
姜黄素		HO-1、Nrf2、GPX4	[108,109]
姜黄醇		NCOA4、FTH1	[110,111]
黄芩苷		FTH1、SLC7A11、GPX4、ACSL4	[112~114]
野黄芩苷		ALOX15	[115]
三七总皂苷		GPX4	[123]
雷公藤甲素		p53、SLC7A11	[117]
雷公藤素		HO-1	[116]

(表2续)

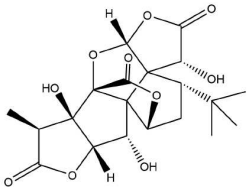
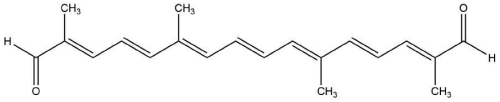
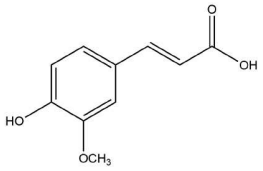
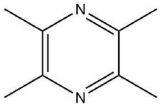
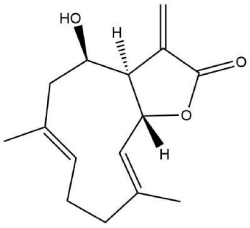
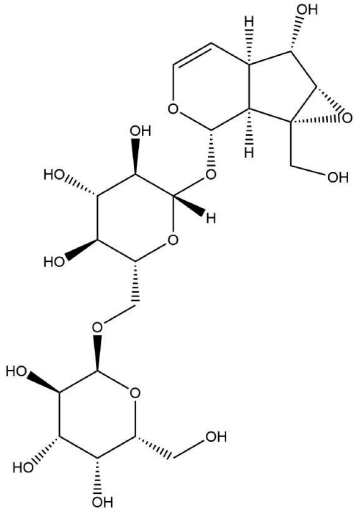
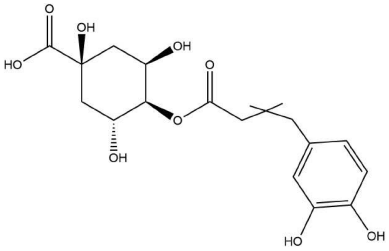
中药活性成分名称	化学结构式	作用位点	参考文献
银杏内酯B		Nrf2、HO-1、GPX4、FTH1	[119~121]
西红花酸		Nrf2、HO-1	[125,126]
阿魏酸		SLC7A11、GPX4	[129]
川芎嗪		Nrf2、NQO1、HO-1、FTH1、FTL	[131~133]
泽兰内酯		p53、SLC7A11	[130]
地黄苷A		Akt、Nrf2、GPX4	[135]
隐绿原酸		System Xc⁻、GPX4、Nrf2、NCOA4	[136]

表 3 益气活血类中药及有效成分与铁死亡研究

Table 3 Herbs and Active components with qi-invigorating and blood-activating functions and ferroptosis Research

名称	四气五味	功效	已有中药及有效成分	治疗疾病	调控通路机制	参考文献
人参	温、苦、甘	益气	人参皂苷Rb1、Rg1、Rh2、Rd、Rg3、红参多糖	脑缺血、肝脏纤维化、心肌缺血再灌注、胰腺炎、肿瘤	Nrf2/HO-1/System Xc^-/GPX4/cGAS/STING/IRF1	[56~62]
黄芪	甘、温	益气	黄芪多糖、黄芪甲苷	脑卒中、肺损伤、心肌损伤	Nrf2/HO-1/SLC7A11/GPX4	[63~71]
党参	甘、平	益气	党参	溃疡性结肠炎	Keap1/Nrf2/GPX4	[72]
黄精	甘、平	益气	黄精多糖	糖尿病	FTH/TF/GPX4	[73]
黄皮	酸	益气	黄皮酰胺	药物性肝脏损伤	Nrf2	[74]
甘草	甘、平	益气	甘草、异甘草酸镁、异甘草素	肝脏纤维化、溃疡性肠炎	Nrf2/HO-1/GPX4/Tfr/DMT1	[75~77]
五味子	酸、甘、温	益气	五味子素	肝脏纤维化、肾结石、糖尿病心肌病	Nrf2/ACSL4/GPX4/SLC7A11	[78~81]
丹参	苦、寒	活血	丹参、丹参酮IIA、丹酚酸B、丹参酮、二氢丹参酮I、隐丹参酮	认知障碍、心肌缺血再灌注/心肌梗死、肝脏损伤、神经系统疾病、肿瘤	NQO1/Nrf2/GPX4/ACSL4/VDAC1/FPN/HO-1/Tfr1	[95~103]
姜黄	辛、苦、温	活血	姜黄素、姜黄醇	急性肾损伤、糖尿病心肌病、肝脏纤维化、肿瘤	Nrf2/HO-1/GPX4/NCOA4/FTH	[108~111]
黄芩	苦、寒	活血	黄芩苷、野黄芩苷	肿瘤、脑出血、心肌缺血、癫痫	FTH/ACSL4/SLC7A11/GPX4/ALOX15	[112~115]
雷公藤	辛、苦、凉	活血	雷公藤甲素、雷公藤素	肝脏纤维化、肿瘤	HO-1/SLC7A11/p53	[116,117]
银杏叶	甘、苦、涩、平	活血	银杏内酯B	非酒精性脂肪肝、糖尿病、炎症	Nrf2/HO-1/GPX4/FTH	[119~121]
三七	甘、苦、温	活血	三七粉、三七总皂苷	脑缺血、胃溃疡	Nrf2/GPX4	[122,123]
红花	辛、温	活血	西红花酸	糖尿病肾病	Nrf2/HO-1	[124,125]
麝香	辛、温	活血	麝香保心丸	心肌缺血再灌注	miR-144-3p/SLC7A11	[126]
益母草	苦、辛、寒	活血	益母草	急性肾损伤	p62/Nrf2/HO-1	[127,128]
当归	甘、辛、温	活血	阿魏酸	肿瘤	SLC7A11/GPX4	[129]
川芎	辛、温	活血	川芎嗪	药物性肝损伤、脊髓损伤	Nrf2/NQO1/HO-1/FTH/FTL	[131~133]
泽兰	苦、辛、温	活血	泽兰内酯	肿瘤	p53/SLC7A11	[130]
地黄	甘、苦、寒	活血	地黄、地黄苷A	肝脏、心脏缺血再灌注	Nrf2/GPX4/SLC7A11/SLC39A14/Akt/PCBP2	[134,135]
桑叶	甘、苦、寒	活血	隐绿原酸	糖尿病	System Xc^-/GPX4/Nrf2/NCOA4	[136]
红景天	甘、苦、平	活血	红景天	肾脏纤维化	SLC7A11/GPX4	[137]
延胡索	辛、苦、温	活血	延胡索	肝脏纤维化	PI3K/Akt/p53	[138]

3.2 活血类中草药

3.2.1 活血类中药复方

“气”与“血”在人体中的关系是相互依存，相互影响[82]. 《仁斋直指方》曰:“气为血帅,气行则血行,气滞则血止”. 张仲景《金匮要略》记载: “妇人则经水不通，经为血，血不利则为水”. 当人体中血气淤血过多时, 会引发严重的疾病. 所以活血化瘀也是一种常规的治疗手段. 其中具有活血化瘀功效的中药复方有: 片仔癀、健脾生血片、心阳片等. 片仔癀主要功效为凉血化瘀、消肿止痛. 使用片仔癀可以通过抑制铁死亡缓解肝脏纤维化，并且可以有效地预防肝癌[83]. 丹红注射液可以通过激活SATB1/SLC7A11/HO-1通路来减轻神经元铁死亡, 治疗缺血性脑卒中[84]. 健脾生血片作为一种治疗贫血的中药复方能够调节慢性心力衰竭伴贫血患者体内hepcidin的表达[85,86]. 心阳片作为一种临床上治疗慢性心力衰竭的药物, 具有活血利水等功效, 使用心阳片可以抑制小鼠心肌细胞肥大和减少心肌胶原

纤维面积, 同时心阳片还可以通过抑制MLK3/JNK/p53信号通路从而抑制心肌细胞铁死亡并改善慢性心力衰竭的发病进程[87,88]. 何信用等[89]发现使用二陈汤合桃红四物汤后, 动脉粥样硬化小鼠氧化应激得到改善, SLC7A11、GPX4 mRNA表达增加. Wang等[90]研究发现佛手散可以通过调控Nrf2/HO-1通路来进一步改善小鼠的认知障碍. 其中上述复方中核心中药有效成分为: 丹参、姜黄、黄芩等.

3.2.2 活血类单味中药及中药有效成分

铁作为生理过程中至关重要的元素, 日常生活中饮食铁的缺乏会导致缺铁性贫血, 鸡血藤作为活血类中药在临床上主要治疗贫血、风湿病等疾病. 本团队早期研究发现鸡血藤可以有效抑制hepcidin的表达, 研究结果显示鸡血藤可以作为一种新型且低副作用的hepcidin抑制剂, 可以用于改善hepcidin过表达引发的相关疾病[91], 该研究成果荣获2014年浙江大学十大学术进展. 本团队还发现黑豆作为一种日常膳食药品, 具有抗炎、活血等功效, 使用黑豆可以减少小鼠肝脏hepcidin的表达来调节铁代谢, 同时黑豆能够作为一种潜在的日常饮食补充剂和治疗剂来治疗慢性病贫血和缺铁性贫血[92]. 该项研究成果被国际著名营养学家James P. McClung教授在知名营养学期刊*British Journal of Nutrition*发表评论[93], 高度赞扬该研究成果为发展中国家治疗贫血提供了中国方案, 具有良好的临床转化前景. 除此之外, 具有活血功能的中药还有: 丹参、姜黄、黄芩、雷公藤、三七等.

丹参作为这一种唇形科(*Lamiaceae*)植物, 有活血祛瘀, 通经止痛等功能, 在临床中用于抗炎、抗肿瘤、缓解糖尿病和改善心血管等疾病[94]. Ko等[95]在使用了丹参后发现它可以有效地缓解脑组织的氧化应激失调和炎症水平, 并改善认知障碍. 此外丹参酮、丹参酮IIA和丹酚酸B均能够有效地减轻体内铁过载和氧化应激水平从而抑制铁死亡引发的心脏缺血再灌注和心肌梗死[96~98]. 同时丹参酮IIA还能通过调节铁稳态, 抑制ROS和MDA的生成, 降低细胞脂质过氧化进而保护肝脏和治疗神经系统疾病[99~101]. 隐丹参酮和二氢丹参酮I均能够有效地诱导铁死亡进而达到抗肿瘤的效果[102,103].

姜黄属姜科(*Zingiberaceae*)植物, 药用部位为根茎, 一般有降血脂、抗炎、抗肿瘤、改善心血管功能、增强血小板聚集等功效[104~107]. Guerrero-Hue等[108]发现姜黄素可以有效改善血清肌酐水平、缓解急性肾损伤和抑制肾小管细胞铁死亡. 同时姜黄素还可以治疗铁死亡诱导的心肌细胞损伤, 并改善糖尿病引发的心肌损伤的心室重构, 包括心脏纤维化和心肌组织紊乱[109]. 姜黄醇可以诱导HSCs和肿瘤细胞中的铁死亡并调控FTH的表达来达到抗肿瘤和抗肝脏纤维化的目的[110,111].

黄芩的主要功效为清热、止血. 黄芩苷可以通过诱导肿瘤细胞铁死亡来抑制肿瘤的生长, 通过下调FTH来缓解膀胱癌的发病进程[112]; 同时黄芩苷还对脑出血和心肌缺血具有治疗作用, 可以有效地降低小鼠的氧化应激和组织内的铁含量, 减轻小鼠的脑组织损伤程度和心肌损伤程度[113,114]; 野黄芩素可以参与调控ALOX15抑制铁死亡从而治疗创伤性癫痫[115].

雷公藤素是从卫矛科(*Euonymus japonicus Thunb*)植物雷公藤中提取出的一种化合物, 具有抗炎、抗肿瘤等作用, Luo等[116]发现雷公藤素可以通过诱导HSCs铁死亡来发挥抗纤维化的作用, 通过上调HO-1来缓解肝脏纤维化的发生发展; 另有研究表明雷公藤甲素参与调控p53/SLC7A11通路从而发挥抗肿瘤的作用[117].

银杏内酯B是从银杏叶中提取得到, 具有抗血小板聚集、抗炎、抗氧化等多种药理作用, 它可以减少自由基损伤、缓解炎症并通过抑制铁死亡来达到治疗非酒精性脂肪肝、糖尿病和抗炎症的目的[118~121].

三七具有散瘀止血, 消肿定痛等功效, 使用三七粉和三七总皂苷可以显著地改善脑缺血和降低胃黏膜溃疡指数, 降低体内Fe^{2+}、MDA和ROS的水平, 并能够增强SOD活性[122,123]. 红花具有活血通经, 散瘀止痛的功效, 使用西红花酸可以显著改善糖尿病小鼠肾损伤, 减少细胞内ROS生成, 抑制细胞铁死亡[124,125].

麝香具有开窍醒神, 活血通经的功效. 叶健等[126]研究表明麝香保心丸可以通过调控miR-144-3p/SLC7A11信号通路来减轻心肌缺血再灌注损伤. 益母草可以通过激活Nrf2信号通路抑制铁死亡并能够缓解急性肾损伤和抑制肾小管上皮细胞铁死亡[127,128]. 阿魏酸是一种当归提取物, 具有抗肿瘤的作用, 可以诱导铁死亡并抑制食管癌细胞增殖[129]. 另外, 泽兰内酯也具有抗肿瘤的作用, 研究人员发现泽兰内酯可以通过调控p53/SLC7A11表达来抑制肺癌细胞的增殖[130].

川芎是一种活血类的药物, 研究表明川芎嗪可通

过降低肝组织中MDA的含量及肝纤维化中不同类型胶原进而抑制肝纤维化, 同时川芎嗪还能改善药物性肝损伤和脊髓损伤后铁代谢紊乱[131~133].

地黄具有清热凉血, 养阴生津的作用, 地黄、地黄苷A能够抑制铁死亡改善肝脏、心脏缺血再灌注损伤[134,135].

桑叶的主要功效为凉血明目、平抑肝阳等. Zhou等[136]研究表明使用桑叶提取物隐绿原酸, 发现隐绿原酸可以有降低糖尿病大鼠血糖和保护胰腺的功能, 并通过激活System Xc^-/GPX4/Nrf2/NCOA4等通路来抑制铁死亡从而达到治疗糖尿病的目的. 红景天具有益气活血的功效, 可以显著地降低衰老型小鼠肾脏脂质过氧化, 并且通过调控SLC7A11/GPX4来延缓铁死亡引发的肾脏纤维化[137]. 白瑜[138]发现延胡索可以抑制铁死亡并治疗肝纤维化.

上述研究进展说明了活血类中药复方及中药单体不仅能够对缺血引发的各类器官损伤和缺铁性贫血有很好的治疗效果, 还能够通过调控铁代谢、抗氧化和脂质过氧化等铁死亡相关通路来抑制铁死亡从而治疗各类疾病.

3.3 益气活血类中药复方

中医理论认为人体疾病的发生是血气失调的结果, 《黄帝内经·灵枢》记载: “夫百病之生也, 皆生于风雨寒暑……, 则血气分离……血气不次, 乃失其常”. 因此, 调节血气是治疗疾病的基本原则. 目前具有益气活血功效的复方有: 通心络胶囊、清心解淤颗粒、补阳还五汤、鹿红方、益糖康等, 它们除了常规的益气和活血双重功效之外, 在治疗心血管疾病、肾病糖尿病等疾病方面也有良好的治疗效果. Wang等[139]发现使用通心络胶囊可以通过调控ACSL4/GPX4/FSP1来达到抑制铁死亡和保护肺微血管屏障功能的目的, 从而缓解慢性肺部疾病和动脉粥样硬化发病进程. 另外, 清心解淤颗粒也能够有效抑制动脉粥样硬化的脂质过氧化水平, 增强机体抗氧化能力, 并通过激活GPX4/System Xc^-通路抑制铁死亡从而达到治疗动脉粥样硬化的目的[140]. 补阳还五汤在临床上多用于气虚血瘀证的治疗, 郑琳琳等[141]研究发现使用补阳还五汤可以减轻糖尿病肾病小鼠肾脏指数、血糖指标和体内Fe^{2+}含量, 能够显著缓解小鼠肾脏纤维化. 鹿红方和益糖康可以通过调控Keap-1/Nrf2/ARE和SLC7A11/GPX4等铁死亡相关蛋白表达量来缓解急性心肌梗死及肾病糖尿病的发病进程[142,143]. 补肾活血颗粒具有补肾益气、活血化瘀通经脉的功效, 同时可以提高血液中血红素的含量, 使用补肾活血颗粒可以有效地降低帕金森模型小鼠脑黑质Fe^{2+}水平, 通过抑制帕金森模型小鼠脑黑质铁死亡, 发挥对神经系统的保护作用[144]. 脑泰方可以有效降低大鼠体内的ROS、MDA和Fe^{2+}含量, 通过抑制铁死亡和改善急性脑缺血引发的神经损伤[145].

综上所述, 我们发现益气活血类中药不仅可以将益气类和活血类中药的优势紧密地结合起来, 还可以在调控铁死亡治疗各类疾病中具有可观的价值, 有望成为治疗各类疾病的新靶点, 但是由于不同疾病在不同病理时期的作用机制各不相同, 如何正确使用使益气活血类中药在不同病理时期有效地调控铁死亡和治疗相关疾病两者维持在最佳水平, 是目前急需解决的关键问题[146,147].

4 结论与展望

铁死亡在各类重大疾病发生发展过程中发挥着重要作用, 益气活血类中药可以通过调控铁死亡相关的通路来缓解重大疾病的发生和发展. 目前中药靶向铁死亡防治重大疾病已成为研究热点, 但仍然处于起步阶段. 现阶段面临的问题与挑战体现在以下几个方面: (i)中药基础研究缺乏良好的临床转化; (ii)研究一般采用药物诱导动物模型的方法研究疾病, 无法体现出中医辨证论治思想; (iii)中药复方包含多种有效组分,但对其中某些特定组分的作用机制尚未充分理解; (iv)对中药复方及单体的研究不够深入且缺乏创新性. 总而言之, 今后要加强中药机制研究, 并且推进临床转化, 为“中西医结合”创造有利的结合点, 为中药治疗各类疾病提供更有力的理论依据.

参考文献

1 Guan H Q, Han X W, Liang H Z. Trial discussion on immunologic concept in “qi-blood” theory of traditional chinese medicine (in Chinese).

Guiding J Tradit Chin Med Pharmacol, 2008, 14: 7–8, 25 [关洪全, 韩晓伟, 梁洪志. 试论中医“气血”学说中的免疫学思想. 中医药导报, 2008, 14: 7–8, 25]
2 Li W B. Adjusting qixue is the fundamental method for all kinds of diseases (in Chinese). Dissertation for Master’s Degree. Jinan: Shandong University of Traditional Chinese Medicine, 2005 [李万斌. 百病皆在调气血. 硕士学位论文. 济南: 山东中医药大学, 2005]
3 Ji Z P.On the theory of qi and blood in traditional Chinese medicine(in Chinese). Chin J Int Tradit and West Med, 1987, 4: 237–241 [季钟朴. 略论中医气血学说. 中西医结合杂志, 1987, 4: 237–241]
4 Huang W, Yu J W, Yu G J, et al. The clinical guidance of “qi-blood” theory in “Huang Di Neijing”(in Chinese). Cardiovasc Dis J Int Tradit Chin West Med, 2018, 6: 17, 19 [黄玮, 余江维, 余国君, 等.《黄帝内经》中气血学说在临床的指导. 中西医结合心血管病电子杂志, 2018, 6: 17, 19]
5 Yang Y, Zhong Y Y, Su C, et al. Traditional Chinese medicine intervention of ferroptosis based on Yin-yang theory(in Chinese). Chin J Exp Tradit Med Formulae, 2022, 28: 227–237 [杨漾, 钟园园, 苏畅, 等. 基于阴阳理论探讨中医药干预铁死亡的研究进展. 中国实验方剂学杂志, 2022, 28: 227–237]
6 Luo J, Shen S, Xia J, et al. Mitochondria as the Essence of Yang Qi in the Human Body. Phenomics, 2022, 2: 336–348
7 Yan Q. Stress and systemic inflammation: Yin-yang dynamics in health and diseases. Meth Mol Biol, 2018, 1781: 3–20
8 Xiao M Y, Luo Y L, Qi X F, et al. Study on prevention and treatment of hypoxic-ischemic diseases by traditional Chinese medicine regulating ferroptosis(in Chinese). J Basic Chin Med, 2024, 30: 162–167 [肖孟勇, 骆亚莉, 齐晓风, 等. 中医药调节铁死亡防治缺血缺氧性疾病的研究. 中国中医基础医学杂志, 2024, 30: 162-167]
9 Dixon S J, Lemberg K M, Lamprecht M R, et al. Ferroptosis: An iron-dependent form of nonapoptotic cell death. Cell, 2012, 149: 1060–1072
10 Zheng J, Conrad M. The metabolic underpinnings of ferroptosis. Cell Metab, 2020, 32: 920–937
11 Liang D, Minikes A M, Jiang X. Ferroptosis at the intersection of lipid metabolism and cellular signaling. Mol Cell, 2022, 82: 2215–2227
12 Riegman M, Sagie L, Galed C, et al. Ferroptosis occurs through an osmotic mechanism and propagates independently of cell rupture. Nat Cell Biol, 2020, 22: 1042–1048
13 Nishizawa H, Matsumoto M, Shindo T, et al. Ferroptosis is controlled by the coordinated transcriptional regulation of glutathione and labile iron metabolism by the transcription factor BACH1. J Biol Chem, 2020, 295: 69–82
14 Yang X, Kawasaki N K, Min J, et al. Ferroptosis in heart failure. J Mol Cell Cardiol, 2022, 173: 141–153
15 Cai Z, Min J, Wang H, et al. Role of iron overload and ferroptosis in heart disease (in Chinese). Chin Sci Bull, 2019, 64: 2974–2987 [方学贤, 蔡昭贤, 王浩, 等. 铁过载及铁死亡在心脏疾病中的研究进展. 科学通报, 2019, 64: 2974–2987]
16 Andrews N C, Schmidt P J. Iron homeostasis. Annu Rev Physiol, 2007, 69: 69–85
17 Yu Y, Jiang L, Wang H, et al. Hepatic transferrin plays a role in systemic iron homeostasis and liver ferroptosis. Blood, 2020, 136: 726–739
18 Ganz T. Systemic iron homeostasis. Physiol Rev, 2013, 93: 1721–1741
19 Fang X, Ardehali H, Min J, et al. The molecular and metabolic landscape of iron and ferroptosis in cardiovascular disease. Nat Rev Cardiol, 2023, 20: 7–23
20 Li D H, Xu S, Jiang L, et al. Physiological functions of iron exporter ferroportin and its regulatory mechanism(in Chinese). Chin Bull Life Sci, 2022, 34: 754–777 [李大航, 徐杉, 蒋丽, 等. 铁泵蛋白Ferroportin生理功能及其调控机制研究进展. 生命科学, 2022, 34: 754–777]
21 Zhang Z, Zhang F, An P, et al. Ferroportin1 deficiency in mouse macrophages impairs iron homeostasis and inflammatory responses. Blood, 2011, 118: 1912–1922
22 Jiang L, Wang J, Wang K, et al. RNF217 regulates iron homeostasis through its E3 ubiquitin ligase activity by modulating ferroportin degradation. Blood, 2021, 138: 689–705
23 Ito J, Omiya S, Rusu M C, et al. Iron derived from autophagy-mediated ferritin degradation induces cardiomyocyte death and heart failure in mice. eLife, 2021, 10: e62174
24 Cheng X, Yu C, Yang X, et al. A panoramic view of ferroptosis in cardiovascular disease. Kidney Dis, 2023, 9: 173–186
25 Stockwell B R, Friedmann Angeli J P, Bayir H, et al. Ferroptosis: a regulated cell death nexus linking metabolism, redox biology, and disease. Cell, 2017, 171: 273–285
26 Yang W S, SriRamaratnam R, Welsch M E, et al. Regulation of ferroptotic cancer cell death by GPX4. Cell, 2014, 156: 317–331
27 Yang W S, Stockwell B R. Ferroptosis: death by Lipid Peroxidation. Trends Cell Biol, 2016, 26: 165–176
28 Xie Y, Kang R, Klionsky D J, et al. GPX4 in cell death, autophagy, and disease. Autophagy, 2023, 19: 2621–2638

29 Kraft V A N, Bezjian C T, Pfeiffer S, et al. GTP cyclohydrolase 1/tetrahydrobiopterin counteract ferroptosis through lipid remodeling. ACS Cent Sci, 2020, 6: 41–53

30 Shen X, Yu Y Y, Chen J Y, et al. Targeting ferroptosis as a potential prevention and treatment strategy for human diseases(in Chinese). Sci Sinica Vitae, 2022, 52: 1818–1826 [沈馨, 余盈盈, 陈峻逸, 等. 靶向铁死亡防治重大疾病的转化医学研究. 中国科学: 生命科学, 2022, 52: 1815–1826]

31 Doll S, Freitas F P, Shah R, et al. FSP1 is a glutathione-independent ferroptosis suppressor. Nature, 2019, 575: 693–698

32 Yang M, Tsui M G, Tsang J K W, et al. Involvement of FSP1-CoQ10-NADH and GSH-GPx-4 pathways in retinal pigment epithelium ferroptosis. Cell Death Dis, 2022, 13: 468

33 Bersuker K, Hendricks J M, Li Z, et al. The CoQ oxidoreductase FSP1 acts parallel to GPX4 to inhibit ferroptosis. Nature, 2019, 575: 688–692

34 Li W, Liang L, Liu S, et al. FSP1: A key regulator of ferroptosis. Trends Mol Med, 2023, 29: 753–764

35 Doll S, Proneth B, Tyurina Y Y, et al. ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition. Nat Chem Biol, 2017, 13: 91–98

36 Bai Y, Meng L, Han L, et al. Lipid storage and lipophagy regulates ferroptosis. Biochem Biophys Res Commun, 2019, 508: 997–1003

37 Kagan V E, Mao G, Qu F, et al. Oxidized arachidonic and adrenic PEs navigate cells to ferroptosis. Nat Chem Biol, 2017, 13: 81–90

38 Wenzel S E, Tyurina Y Y, Zhao J, et al. PEBP1 wardens ferroptosis by enabling lipoxygenase generation of lipid death signals. Cell, 2017, 171: 628–641.e26

39 Fang X, Wang H, Han D, et al. Ferroptosis as a target for protection against cardiomyopathy. Proc Natl Acad Sci USA, 2019, 116: 2672–2680

40 Fang X, Cai Z, Wang H, et al. Loss of cardiac ferritin H facilitates cardiomyopathy via Slc7a11-mediated ferroptosis. Circ Res, 2020, 127: 486–501

41 Menon A V, Liu J, Tsai H P, et al. Excess heme upregulates heme oxygenase 1 and promotes cardiac ferroptosis in mice with sickle cell disease. Blood, 2022, 139: 936–941

42 Wang H, An P, Xie E, et al. Characterization of ferroptosis in murine models of hemochromatosis. Hepatology, 2017, 66: 449–465

43 Fang X, Zhang J, Li Y, et al. Malic enzyme 1 as a novel anti-ferroptotic regulator in hepatic ischemia/reperfusion injury. Adv Sci, 2023, 10: e2205436

44 Meng H, Yu Y, Xie E, et al. Hepatic HDAC3 regulates systemic iron homeostasis and ferroptosis via the Hippo signaling pathway. Research, 2023, 6: 0281

45 Yang L, Wang H, Yang X, et al. Auranofin mitigates systemic iron overload and induces ferroptosis via distinct mechanisms. Sig Transduct Target Ther, 2020, 5: 138

46 Cai Z, Wu X, Song Z, et al. Metformin potentiates nephrotoxicity by promoting NETosis in response to renal ferroptosis. Cell Discov, 2023, 9: 104

47 Zhang Q, Sun T, Yu F, et al. PAFAH2 suppresses synchronized ferroptosis to ameliorate acute kidney injury. Nat Chem Biol, 2024, 20: 835–846

48 von Mässenhausen A, Zamora Gonzalez N, Maremonti F, et al. Dexamethasone sensitizes to ferroptosis by glucocorticoid receptor–induced dipeptidase-1 expression and glutathione depletion. Sci Adv, 2022, 8: eabl8920

49 Wu Y J, Liu J X. Research progress of the mechanism of Yiqi huoxue traditional Chinese medicine on improving chronic heart failure with Xinqixu syndromoe(in Chinese). Pharmaco Clin Chin Mater Med, 2021, 37: 234–239 [吴昱杰, 刘建勋. 益气活血中药改善慢性心衰心气虚证作用机制研究进展. 中药药理与临床, 2021, 37: 234–239]

50 Wu L, Fan Z, Gu L, et al. QiShenYiQi dripping pill alleviates myocardial ischemia-induced ferroptosis via improving mitochondrial dynamical homeostasis and biogenesis. J EthnoPharmacol, 2023, 308: 116282

51 李 荣良. Experience of TCM differentiation and treatment of primary sjogren's syndrome complicated with depression (in Chinese). TCM, 2022, 11: 370–373 [廖燃, 陈沁, 王丰, 等. 加味涤痰汤对慢性间歇低氧模型大鼠心肌组织损伤及Keap1-Nrf2信号通路的影响. 中医杂志, 2022, 63: 370–376]

52 Wang Z Y, Zhang Q, Guo J, et al. Pathogenesis of chronic heart failure in rats based on ferroptosis-mediated oxidative stress and intervention effect of Shenfu injection(in Chinese). China J Chin Mater Med, 2023, 48: 5285–5293 [王梓仪, 张倩, 郭瑾, 等. 基于铁死亡介导的氧化应激探讨慢性心力衰竭大鼠的发病机制及参附注射液的干预作用. 中国中药杂志, 2023, 48: 5285–5293]

53 Wang Y Y. Experimental study on the protective effect of Yiqi huoxue recipe on ventricular remodeling after myocardial infarction from the "cell autophagy-ferroptosis" interaction(in Chinese).Dissertation for Master's Degree. Tianjin: Tianjin University of Traditional Chinese

Medicine,2022 [王玥瑶. 从“细胞自噬-铁死亡”交互作用探讨益气活血方干预心肌梗死后心室重构保护作用的实验研究. 硕士学位论文, 天津: 天津中医药大学, 2022]

54 Zhou X Y, Zhou S F, Li Y R, et al. Effect of Shenling baizhusan on alcoholic liver injury in rats by regulating ferroptosis based on Nrf2 signaling pathway(in Chinese). Chin J Exp Tradit Med Formulae, 2023, 29: 104–113 [周相宇, 周素芳, 李玉茹, 等. 基于Nrf2信号通路探究参苓白术散调节铁死亡对酒精性肝损伤大鼠的影响. 中国实验方剂学杂志, 2023, 29: 104–113]

55 Zhang X, Chen W N, Song N, et al. Danlou tablets attenuate oxidative damage of liver in mice with non-alcoholic fatty liver disease through ferroptosis pathway(in Chinese). Chin J Pathophysiol, 2021, 37: 2180–2188 [张新, 陈文娜, 宋囡, 等. 丹蒌片通过铁死亡途径减轻非酒精性脂肪性肝病模型小鼠肝脏氧化损伤. 中国病理生理杂志, 2021, 37: 2180–2188]

56 Zhang M, Lin W, Tao X, et al. Ginsenoside Rb1 inhibits ferroptosis to ameliorate hypoxic-ischemic brain damage in neonatal rats. Int Immunopharmacol, 2023, 121: 110503

57 Hu K C, Gao Y, He J Q, et al. Ginsenoside Rg1 inhibits neuronal ferroptosis caused by ischemic stroke through activating of Nrf2 / xCT /GPX4 axis(in Chinese). Chin Pharmacol Bull, 2023, 39: 1902–1913 [胡凯超, 高岩, 何佳琦, 等. 人参皂苷Rg1通过激活Nrf2/xCT/GPX4通路抑制神经元铁死亡改善缺血性脑卒中损伤. 中国药理学通报, 2023, 39: 1905–1913]

58 Lang Z, Yu S, Hu Y, et al. Ginsenoside Rh2 promotes hepatic stellate cell ferroptosis and inactivation via regulation of IRF1-inhibited SLC7A11. Phytomedicine, 2023, 118: 154950

59 Li Y, Yu P, Fu W, et al. Ginsenoside Rd inhibited ferroptosis to alleviate CCl_4-induced acute liver injury in mice via cGAS/STING pathway. Am J Chin Med, 2023, 51: 91–105

60 Ye J, Lyu T J, Li L Y, et al. Ginsenoside Re attenuates myocardial ischemia/reperfusion induced ferroptosis via miR-144-3p/SLC7A11. Phytomedicine, 2023, 113: 154681

61 Shan Y, Li J, Zhu A, et al. Ginsenoside Rg3 ameliorates acute pancreatitis by activating the Nrf2/HO−1−mediated ferroptosis pathway. Int J Mol Med, 2022, 50: 89

62 Zhai F, Liang Q, Wu Y, et al. Red ginseng polysaccharide exhibits anticancer activity through GPX4 downregulation-induced ferroptosis. Pharm Biol, 2022, 60: 909–914

63 Wang X, Wang Y, Huang D, et al. Astragaloside IV regulates the ferroptosis signaling pathway via the Nrf2/SLC7A11/GPX4 axis to inhibit PM2.5-mediated lung injury in mice. Int Immunopharmacol, 2022, 112: 109186

64 Zhang C, Shi Z, Xu Q, et al. Astragaloside IV alleviates stroke-triggered early brain injury by modulating neuroinflammation and ferroptosis via the Nrf2/HO-1 signaling pathway. Acta Cir Bras, 2023, 38: e380723

65 Liu Z, Zhou Z, Ai P, et al. Astragaloside IV attenuates ferroptosis after subarachnoid hemorrhage via Nrf2/HO-1 signaling pathway. Front Pharmacol, 2022, 13: 924826

66 Luo L F, Guan P, Qin L Y, et al. Astragaloside IV inhibits adriamycin-induced cardiac ferroptosis by enhancing Nrf2 signaling. Mol Cell Biochem, 2021, 476: 2603–2611

67 Bamodu O A, Kuo K T, Wang C H, et al. Astragalus polysaccharides (PG2) enhances the M1 polarization of macrophages, functional maturation of dendritic cells, and T cell-mediated anticancer immune responses in patients with lung cancer. Nutrients, 2019, 11: 2264

68 Liu T, Zhang M, Niu H, et al. Astragalus polysaccharide from Astragalus Melittin ameliorates inflammation via suppressing the activation of TLR-4/NF-κB p65 signal pathway and protects mice from CVB3-induced virus myocarditis. Int J Biol Macromol, 2019, 126: 179–186

69 Xue H, Gan F, Qian G, et al. Astragalus polysaccharides attenuate PCV2 infection by inhibiting endoplasmic reticulum stress in vivo and in vitro. Sci Rep, 2017, 7: 40440

70 Li W, Hu X, Wang S, et al. Characterization and anti-tumor bioactivity of astragalus polysaccharides by immunomodulation. Int J Biol Macromol, 2020, 145: 985–997

71 Chen Y, Wang J, Li J, et al. Astragalus polysaccharide prevents ferroptosis in a murine model of experimental colitis and human Caco-2 cells via inhibiting NRF2/HO-1 pathway. Eur J Pharmacol, 2021, 911: 174518

72 Li F, Chen Z J, Ge J L, et al. Intervention of codonopsis radix on ferroptosis and mitochondrial dynamics imbalance in mucosal cells of ulcerative colitis via PI3K/Akt(in Chinese). Chin Tradit Herb Drugs 2023, 54: 3865–3877 [李芳, 陈正君, 葛俊李, 等. 党参经PI3K/Akt干预溃疡性结肠炎黏膜细胞铁死亡-线粒体动力学失衡的机制研究. 中草药, 2023, 54: 3865–3877]

73 Liu H, Li H Z, Zhang H, et al. Effects of Polygona-polysaccharose on ferroptosis in diabetic nephropathy rats(in Chinese). Chin J Inf Tradit Chin Med, 2023, 30: 126–130 [刘赫, 李函舟, 张辉等. 黄精多糖对糖尿病肾病大鼠铁死亡的影响. 中国中医药信息杂志, 2023, 30: 126–130]

74 Wang M, Liu C Y, Wang T, et al. (+)-Clausenamide protects against drug-induced liver injury by inhibiting hepatocyte ferroptosis. Cell Death Dis, 2020, 11: 781

75 Sui M, Jiang X, Chen J, et al. Magnesium isoglycyrrhizinate ameliorates liver fibrosis and hepatic stellate cell activation by regulating ferroptosis signaling pathway. Biomed Pharmacother, 2018, 106: 125–133

76 Kong J R, Shi G X, Hou J, et al. Effect of Glycyrrhizae radix et rhizoma-containing serum on LPS-induced inflammation in Caco2 cells based on inhibition of ferroptosis by Nrf2/HO-1 pathway(in Chinese). Chin J Exp Tradit Med Formulae, 2023, 29: 144–153 [孔金融, 施高翔, 侯静, 等. 基于Nrf2/HO-1通路抑制铁死亡探究甘草含药血清对LPS诱导的Caco2细胞炎症的影响. 中国实验方剂学杂志, 2023, 29: 144–153]

77 Huang S, Wang Y, Xie S, et al. Isoliquiritigenin alleviates liver fibrosis through caveolin-1-mediated hepatic stellate cells ferroptosis in zebrafish and mice. Phytomedicine, 2022, 101: 154117

78 Shi H, Yan Y, Yang H, et al. Schisandrin B diet inhibits oxidative stress to peduce ferroptosis and lipid peroxidation to prevent pirarubicin-induced hepatotoxicity. Biomed Res Int, 2022, 2022: 5623555

79 Li X, Jiang F, Hu Y, et al. Schisandrin B Promotes Hepatic Stellate Cell Ferroptosis via Wnt Pathway-Mediated Ly6C^{lo} Macrophages. J Agric Food Chem, 2023, acs.jafc.3c03409

80 Dong C, Song C, He Z, et al. Protective efficacy of Schizandrin B on ameliorating nephrolithiasis via regulating GSK3β/Nrf2 signaling-mediated ferroptosis in vivo and in vitro. Int Immunopharmacol, 2023, 117: 110042

81 Yang S Q, He T L, Su J H, et al. Study on the mechanism of Schizandrin B regulating Nrf2 / HO-1/ GPX4 iron death pathwayto reduce myocardial injury in diabetes mellitus mice(in Chinese). J Chin Med Mater, 2022, 45: 1705–1713 [杨素清, 何天乐, 苏军华, 等. 五味子乙素调控Nrf2/HO-1/GPX4铁死亡途径减轻糖尿病小鼠心肌损伤的机制研究. 中药材, 2022 ,45: 1705–1713]

82 Zhao C, Wang Y Y. Research progress on mechanism of benefiting qi for activating blood circulation Chinese medicine(in Chinese). Chin Med Mod Distance Educ China, 2017, 15: 139–140 [赵闯, 王艳艳. 益气活血类中药治疗心衰病作用机制的研究进展. 中国中医药现代远程教育, 2017, 15: 139–140]

83 Yan X, Liu Y, Li C, et al. Pien-Tze-Huang prevents hepatocellular carcinoma by inducing ferroptosis via inhibiting SLC7A11-GSH-GPX4 axis. Cancer Cell Int, 2023, 23: 109

84 Zhan S, Liang J, Lin H, et al. SATB1/SLC7A11/HO-1 axis ameliorates ferroptosis in neuron cells after ischemic stroke by danhong injection. Mol Neurobiol, 2023, 60: 413–427

85 Li G P, Ou Y H, Yang X Y. Clinical observation on Jianpi shengxue tablets in the treatment of anemia referred to heart failure(in Chinese). World Chin Med, 2019, 14: 149–153 [李贵平, 欧阳慧, 杨晓云. 健脾生血片治疗慢性心力衰竭伴贫血的临床效果. 世界中医药, 2019, 14: 149–153]

86 Zhu L, Min J, Chen Y Z. Clinical observation on Jianpi shengxue tablet in the treatment of COPD related anemia(in Chinese). World Chin Med, 2018, 13: 1148–1151, 1155 [朱林, 闵捷, 陈亚忠. 健脾生血片治疗COPD相关性贫血的临床观察. 世界中医药, 2018, 13: 1148–1151, 1155]

87 Wang J Y, Huang Y S, Liu Q, et al. Effects and mechanism of Xinyang tablet on inhibiting cardiomyocyte cell ferroptosis mediated by MLK3/JNK/p53 and preventing chronic heart failure(in Chinese). China J Tradit Chin Med Pharm, 2020, 35: 2604–2607 [王俊岩, 黄育生, 刘青, 等. 心阳片抑制MLK3/JNK/p53介导的心肌细胞铁死亡抗慢性心力衰竭的作用及机制研究. 中华中医药杂志, 2020, 35: 2604–2607]

88 Wang J Y, Yu Z Yang, Guo Y N, et al. Protective effect and mechanism of Xinyang tablet containing serum regulating MLK3－mediated ferroptosis on cardiomyocytes(in Chinese). Chin Arch Tradit Chin Med, 2022, 40: 32-35, 261–262 [王俊岩, 于忠杨, 郭依宁, 等. 心阳片含药血清调控MLK3介导的铁死亡对心肌细胞的保护作用及机制研究. 中华中医药学刊, 2022, 40: 32-35, 261–262]

89 He X Y, Wang J Y, Song N, et al. Effects and mechanism of Erchen decoction and Taohong siwu decoction on the regulation of p53/SLC7A11 mediated oxidative damage and ferroptosis on atherosclerosis(in Chinese). China J Tradit Chin Med Pharm, 2020, 35: 2344–2348 [何信用, 王俊岩, 宋囡, 等. 二陈汤合桃红四物汤调控p53/SLC7A11介导的氧化损伤及铁死亡抗动脉粥样硬化的作用及机制研究. 中华中医药杂志, 2020, 35: 2344–2348]

90 Wang J, Shi J, Xiao Y, et al. Fo-Shou-San ameliorates chronic cerebral hypoperfusion-induced cognitive impairment in mice by regulating NRF2/HO-1 pathway against ferroptosis. J Integr Neurosci, 2023, 22: 41

91 Guan Y, An P, Zhang Z, et al. Screening identifies the Chinese medicinal plant caulis spatholobi as an effective HAMP expression inhibitor1–3. J Nutr, 2013, 143: 1061–1066

92 Mu M, Wu A, An P, et al. Black soyabean seed coat extract regulates iron metabolism by inhibiting the expression of hepcidin. Br J Nutr, 2014, 111: 1181–1189

93 McClung J P. Nutrition is medicine: Dietary inhibition of hepcidin expression. Br J Nutr, 2014, 111: 1145–1146

94 MEIm X D, Cao Y F, Che Y Y, et al. Danshen: a phytochemical and pharmacological overview. Chin J Nat Med, 2019, 17: 59–80

95 Ko G, Kim J, Jeon Y J, et al. Salvia miltiorrhiza alleviates memory deficit induced by ischemic brain injury in a transient MCAO mouse model by inhibiting ferroptosis. Antioxidants, 2023, 12: 785

96 Hu T, Zou H X, Le S Y, et al. Tanshinone IIA confers protection against myocardial ischemia/reperfusion injury by inhibiting ferroptosis and apoptosis via VDAC1. Int J Mol Med, 2023, 52: 109

97 Shen Y, Shen X, Wang S, et al. Protective effects of Salvianolic acid B on rat ferroptosis in myocardial infarction through upregulating the Nrf2 signaling pathway. Int Immunopharmacol, 2022, 112: 109257

98 Wang T X, Duan K L, Huang Z X, et al. Tanshinone functions as a coenzyme that confers gain of function of NQO1 to suppress ferroptosis. Life Sci Alliance, 2022, 6: e202201667

99 Qin Z, Zhou M. Tanshinone ⅡA inhibits ferroptosis via Nrf2 signaling pathway to protect liver in rats of non-alcoholic fatty liver disease(in Chinese). China J Chin Mater Med, 2024, 49: 1611–1620 [秦智, 周敏. 丹参酮ⅡA通过Nrf2信号通路抑制肝组织铁死亡对非酒精性脂肪肝大鼠肝脏的保护作用. 中国中药杂志, 2024, 49: 1611–1620]

100 Wu Y, Song N, Jia L Q, et al. Effect of Tanshinone ⅡA on liver lipid deposition and ferroptosis-related protein expression in ApoE$^{-/-}$ mice(in Chinese). Chin J Pathophysiol, 2020, 36: 1261–1268 [吴瑶, 宋囡, 贾连群, 等. 丹参酮ⅡA对ApoE~(-/-)小鼠肝脏脂质沉积及铁死亡相关蛋白表达的影响. 中国病理生理杂志, 2020, 36: 1261–1268]

101 Xu Lu, Tang Q Q. Research on the mechanism of Tanshinone ⅡA inhibiting ferroptosis in HT22 hippocampus cells(in Chinese). Acta Univ Med Anhui, 2019, 54: 833–839 [许璐, 汤其强. 丹参酮ⅡA抑制HT22海马神经元发生铁死亡的机制研究. 安徽医科大学学报, 2019, 54: 833–839]

102 Wu C Y, Yang Y H, Lin Y S, et al. Dihydroisotanshinone I induced ferroptosis and apoptosis of lung cancer cells. Biomed Pharmacother, 2021, 139: 111585

103 Tan G Y, Cai P H, Cao L, et al. Effect of Cryptotanshinone on ferroptosis-related gene expression in lung cancer cells(in Chinese). Chin Pharmaco Bull, 2019, 35: 1654–1659 [谭国耀, 蔡珮蘅, 曹霖, 等. 隐丹参酮对肺癌细胞铁死亡相关基因表达的影响. 中国药理学通报, 2019, 35: 1654–1659]

104 Prasad S, Gupta S C, Tyagi A K, et al. Curcumin, a component of golden spice: From bedside to bench and back. Biotechnol Adv, 2014, 32: 1053–1064

105 Kunnumakkara A B, Bordoloi D, Padmavathi G, et al. Curcumin, the golden nutraceutical: Multitargeting for multiple chronic diseases. Br J Pharmacol, 2017, 174: 1325–1348

106 Prasad S, Tyagi A K, Aggarwal B B. Recent developments in delivery, bioavailability, absorption and metabolism of curcumin: the golden pigment from golden spice. Cancer Res Treat, 2014, 46: 2–18

107 Pagano E, Romano B, Izzo A A, et al. The clinical efficacy of curcumin-containing nutraceuticals: An overview of systematic reviews. Pharmacol Res, 2018, 134: 79–91

108 Guerrero‐Hue M, García‐Caballero C, Palomino‐Antolín A, et al. Curcumin reduces renal damage associated with rhabdomyolysis by decreasing ferroptosis-mediated cell death. FASEB J, 2019, 33: 8961–8975

109 Zhang W, Qian S H, Pinfang K, et al. Curcumin attenuates ferroptosis-induced myocardial injury in diabetic cardiomyopathy through the Nrf2 pathway. Cardiovasc Ther, 2022, 2022: 3159717

110 Zhang R, Pan T, Xiang Y, et al. Curcumenol triggered ferroptosis in lung cancer cells via lncRNA H19/miR-19b-3p/FTH1 axis. Bioact Mater, 2021, 13: 23–36

111 Zheng Y, Zhao T, Wang J, et al. Curcumol alleviates liver fibrosis through inducing autophagy and ferroptosis in hepatic stellate cells. FASEB Journal, 2022, 36: e22665

112 Kong N, Chen X, Feng J, et al. Baicalin induces ferroptosis in bladder cancer cells by downregulating FTH1. Acta Pharm Sin B, 2021, 11: 4045–4054

113 Duan L, Zhang Y, Yang Y, et al. Baicalin inhibits ferroptosis in intracerebral hemorrhage. Front Pharmacol, 2021, 12: 629379

114 Fan Z, Cai L, Wang S, et al. Baicalin prevents myocardial ischemia/reperfusion injury through inhibiting ACSL4 mediated ferroptosis. Front Pharmacol, 2021, 12: 628988

115 Liu L, Zhang Y, Wang L, et al. Scutellarein alleviates chronic obstructive pulmonary disease through inhibition of ferroptosis by chelating iron

and interacting with arachidonate 15-lipoxygenase. PhytoTher Res, 2023, 37: 4587–4606

116 Luo P, Liu D, Zhang Q, et al. Celastrol induces ferroptosis in activated HSCs to ameliorate hepatic fibrosis via targeting peroxiredoxins and HO-1. Acta Pharm Sin B, 2022, 12: 2300–2314

117 Xu J H, Lu X G. Triptolide induces ferroptosis by modulating the p53/slc7a11 axis in colon cancer cells(in Chinese). Zhejiang J Int Tradit Chin West Med, 2023, 33: 502–505, 511 [徐嘉韩, 陆新刚. 雷公藤甲素调控p53/SLC7A11轴诱导结肠癌细胞铁死亡. 浙江中西医结合杂志, 2023, 33: 502–505, 511]

118 Nash K M, Shah Z A. Current Perspectives on the Beneficial Role of *Ginkgo biloba* in Neurological and Cerebrovascular Disorders. Integr MedInsights, 2015, 10: 1–9

119 Shao L, Dong C, Geng D, et al. Ginkgolide B protects against cognitive impairment in senescence-accelerated P8 mice by mitigating oxidative stress, inflammation and ferroptosis. Biochem Biophys Res Commun, 2021, 572: 7–14

120 Yang Y, Chen J, Gao Q, et al. Study on the attenuated effect of Ginkgolide B on ferroptosis in high fat diet induced nonalcoholic fatty liver disease. Toxicology, 2020, 445: 152599

121 Chen J, Ou Z, Gao T, et al. Ginkgolide B alleviates oxidative stress and ferroptosis by inhibiting GPX4 ubiquitination to improve diabetic nephropathy. Biomed Pharmacother, 2022, 156: 113953

122 An K, Guo P R, Sun Y F. Panax nnotoginseng powder ameliorates gastric mucosal injury via Nrf2 / Gpx4-mediated iron death in rats with cerebral hemorrhagic stress ulcers(in Chinese). Hebei Med, 2023, 29: 1267–1274 [安凯, 郭沛然, 孙玉凤. 三七白及粉通过Nrf2/Gpx4介导的铁死亡改善脑出血型应激性溃疡大鼠的胃黏膜损伤. 河北医学, 2023, 29: 1267–1274]

123 Wang L L, Kang Z N, Liu W P, et al. Panax notoginseng saponins attenuate cerebral ischemia reperfusion injury in rats by inhibiting ferroptosis and inflammation(in Chinese). Chin J Immuno, 2022, 38: 296–300 [王林琳, 康智能, 刘文鹏, 等. 三七总皂苷抑制铁死亡和炎症反应减轻大鼠脑缺血再灌注损伤. 中国免疫学杂志, 2022, 38: 296–300]

124 Lu J H, Liu A J. Crocetin inhibits high glucose-induced ferroptosis in human glomerular mesangial cells through regulating Nrf2/HO-1 pathway (in Chinese). Tradit Chin Drug Res Clin Pharmaco, 2023, 34: 8–15 [陆江华, 刘爱军. 西红花酸调控Nrf2/HO-1通路抑制高糖诱导人肾小球系膜细胞铁死亡. 中药新药与临床药理, 2023, 34: 8–15]

125 Xiang M, Qian Z Y, Zhou C H. Effects of Crocetin on formation of advanced glycation end products and expression of releptor for advanced glycation and prodmts protein in diabetic rats(in Chinese). Chin J Clin Pharmaco Therap, 2006, 448–452 [向敏, 钱之玉, 周成华. 西红花酸对糖尿病大鼠体内晚期糖基化终产物的形成及其受体表达的影响. 中国临床药理学与治疗学, 2006, 448–452]

126 Ye J, Wang X, Xi X, et al. Experimental study of Shexiang baoxin pill on alleviating myocardial ischemia-reperfusion injury by regulating miR-144-3p/SLC7A11(in Chinese). Chin J Integr Med Cardio-Cerebrovasc Dis, 2023, 21: 2396–2399 [叶健, 汪谞, 席鑫, 等. 麝香保心丸通过调控miR-144-3p/SLC7A11减轻心肌缺血再灌注损伤的实验研究. 中西医结合心脑血管病杂志, 2023, 21: 2396–2399]

127 Hu J Q. Leonurine alleviates ferroptosis in cisplatin-induced acute kidney injury by activating the Nrf2 signalling pathway(in Chinese). Dissertation for Master's Degree, Jilin: Jilin university, 2023 [胡健强. 益母草碱通过激活Nrf2信号通路抑制铁死亡减轻顺铂诱导的急性肾损伤. 硕士学位论文, 吉林: 吉林大学, 2023]

128 Wu A J, Chen N Q, Huang L H, et al. Leonurine inhibits ferroptosis in renal tubular epithelial cells by activating p62 / Nrf2 / HO-1 signaling pathway(in Chinese). China J Chin Mater Med, 2023, 48: 2176–2183 [吴爱君, 陈乃清, 黄丽华, 等. 益母草碱激活p62/Nrf2/HO-1信号通路抑制肾小管上皮细胞铁死亡的作用机制. 中国中药杂志, 2023, 48: 2176–2183]

129 Cao Y, Zhang H, Tang J, et al. Ferulic acid mitigates growth and invasion of esophageal squamous cell carcinoma through inducing ferroptotic cell death. Dis Markers, 2022, 2022: 4607966

130 Wei Y, Zhu Z, Hu H, et al. Eupaformosanin induces apoptosis and ferroptosis through ubiquitination of mutant p53 in triple-negative breast cancer. Eur J Pharmacol, 2022, 924: 174970

131 Tang W C, He Q, Li J F. Ligustrazine alleviates acetaminophen-induced liver injury by inhibiting inflammatory response and ferroptosis(in Chinese). World Chin Med, 2023, 18: 3512–3517 [唐文诚, 何清, 李俊峰, 等. 川芎嗪通过抑制炎症反应和铁死亡减轻对乙酰氨基酚所致肝损伤. 世界中医药, 2023, 18: 3512–3517]

132 Fan X, Tao JW, Jiang S Y, et al. Effect of tetramethylpyrazine on iron metabolism after spinal cord injury in rats(in Chinese). Chin J Tiss Eng Res, 2023, 27: 3561–3566 [范筱, 陶经纬, 蒋昇源, 等. 川芎嗪对大鼠脊髓损伤后铁代谢的影响. 中国组织工程研究, 2023, 27: 3561–3566]

133 Pan F Z, Liu D. Research progress on the mechanism of ligustrazine in anti-liver fibrosis from the method of promoting blood circulation to remove meridian obstruction(in Chinese).China Med Her, 2021, 18: 34–37 [潘富珍, 刘定. 从活血通络法探讨川芎嗪抗肝纤维化的作用机制

研究进展. 中国医药导报, 2021, 18: 34–37]

134 Zhang Y H, Jia K X, Luo R Y, et al. Comparative pharmacodynamic study of aqueous extract of rehmanniae radix praeparata and drying rehmannia root for amelioration of hepatic ischemia-reperfusion injury by inhibiting ferroptosis process(in Chinese). Drug Eval Res, 2024, 47:46–56 [张银浩, 贾可欣, 罗苒艺, 等. 生地黄　熟地黄水提取物通过抑制铁死亡进程改善肝缺血再灌注损伤的药效对比研究. 药物评价研究, 2024, 47: 46–56]

135 Liu P, Wang X Y, Han D. Rehmannioside a improves myocardial ischemia-reperfusion injury in rats by regulating ferroptosis mediated by AKT/Nrf2/GPX4 signaling pathway(in Chinese). Chin J Integr Med Cardio-Cerebrovasc Dis, 2023, 21: 4112–4119 [刘盼, 王晓英, 韩丹. 地黄苷A通过调节AKT/Nrf2/GPX4信号通路介导的铁死亡改善大鼠心肌缺血再灌注损伤. 中西医结合心脑血管病杂志, 2023, 21: 4112–4119]

136 Zhou Y. The Protective Effects of Cryptochlorogenic Acid on β-Cells Function in Diabetes in vivo and vitro via Inhibition of Ferroptosis. DMSO, 2020, Volume 13: 1921–1931

137 Yang S, Pei T, Wang L, et al. Salidroside alleviates renal fibrosis in SAMP8 mice by inhibiting ferroptosis. Molecules, 2022, 27: 8039

138 Bai Yu. Mechanism of Rhizoma corydalis in prevention and treatment of liver fibrosis was researched by regulating ferroptosis based on PI3K/Akt/P53 signal axis(in Chinese). Dissertation for Master's Degree. Xianyang: Shaanxi University of Chinese Medicine, 2023 [白瑜. 基于PI3K/Akt/P53信号轴调控铁死亡探讨延胡索防治肝纤维化的作用机制.硕士学位论文. 咸阳: 陕西中医药大学, 2023]

139 Wang Y, Kuang X, Yin Y, et al. Tongxinluo prevents chronic obstructive pulmonary disease complicated with atherosclerosis by inhibiting ferroptosis and protecting against pulmonary microvascular barrier dysfunction. Biomed Pharmacother, 2022, 145: 112367

140 Zhang J, Wang X, Guan B, et al. Qing-Xin-Jie-Yu Granule inhibits ferroptosis and stabilizes atherosclerotic plaques by regulating the GPX4/xCT signaling pathway. J EthnoPharmacol, 2023, 301: 115852

141 Zheng L L, Guo D Z. Effect of Buyang-huanwutang on ferroptosis in diabetic kidney disease mice(in Chinese). Chin J Exp Tradit, 2023, 29: 34–41 [郑琳琳, 郭登洲. 补阳还五汤对糖尿病肾病小鼠铁死亡的影响. 中国实验方剂学杂志, 2023, 29: 34–41]

142 Cai W, Ge W, Wang J, et al. The Protective effect of Luhong recipe on ischemia/reperfusion lnjury of myocardial cells regulated by Nrf2(in Chinese). Chin J Integr Med Cardio-Cerebrovasc Dis, 2022, 20: 4257–4264 [蔡婉, 葛文, 王婧, 等. 鹿红方调控Nrf2因子保护缺血/再灌注损伤心肌细胞的机制研究. 中西医结合心脑血管病杂志, 2022, 20: 4257–4264]

143 Li Y C.The mechanism of Yitangkang regulating SLC7A11 / GPX4-mediated ferroptosis in the prevention and treatment of diabetic kidney injury(in Chinese). Dissertation for Master's Degree.Shenyang: Liaoning University of Traditional Chinese Medicine, 2022 [李艳春. 中药复方益糖康调控SLC7A11/GPX4介导的铁死亡防治糖尿病肾脏损伤的机制研究. 硕士学位论文. 沈阳: 辽宁中医药大学, 2022]

144 Li C, Wang P, Wang L, et al. Effeet of Bushen-huoxue granule on ferroptosis of dopamine neurons in substantia nigra of subacute parkinson's disease model mice(in Chinese). J Tradit Chin Med, 2022, 63:1463–1469 [李晨, 王鹏, 王亮, 等. 补肾活血颗粒对亚急性帕金森病模型小鼠脑黑质多巴胺神经元铁死亡的影响. 中医杂志, 2022, 63: 1463–1469]

145 Lan B, Ge J, Cheng S, et al. Extract of Naotaifang, a compound Chinese herbal medicine, protects neuron ferroptosis induced by acute cerebral ischemia in rats. J Integr Med, 2020, 18: 344–350

146 Zhang X Y, Wan S Q, Liu W J, et al. Stepping into the new age of efficiency and precision: review and prospect of evidence-based research on traditional Chinese medicine for major diseases prevention and treatment(in Chinese). Sci Sinica Vitae, 2022, 52: 823–831 [张晓雨, 万思琦, 刘文静, 等. 迈入高效精准新时代:中医药防治重大疾病循证研究的回顾与展望. 中国科学:生命科学, 2022, 52: 823–831]

147 Xiang Y Z. Integrating traditional Chinese medicine and western medicine for cardiovascular disease(in Chinese). Sci Sinica Vitae, 2022, 52: 832–839 [项耀祖. 中西医结合防治冠心病. 中国科学:生命科学, 2022, 52: 832–839]

Research progress on regulating mechanism of ferroptosis by traditional Chinese medicines for qi-invigoration and blood-activation

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Ferroptosis is an iron-dependent type of cell death, which mainly characterized by iron overload, lipid peroxidation and reactive oxygen species accumulation.In Chinese medicine “qi and blood” are an important part of the human body, as well as the power and source of life activities. Imbalance in “qi and blood” can lead to serious diseases, therefore, regulation of “qi and blood” serves as the fundamental principle and core concept in clinical disease treatment. Traditional Chinese medicine for qi-invigorating and blood-activating play an active role in regulating iron homeostasis and inhibiting ferroptosis, thereby contributing to the prevention and treatment of major diseases. This review not only summarize recent research progress in regulating ferroptosis-induced major diseases using traditional Chinese medicine, but also categorize existing traditional Chinese medicine interventions that invigorate qi and activate blood circulation, providing new insights for preventing and treating ferroptosis-induced major diseases.

ferroptosis, iron homeostasis, traditional Chinese medicine, qi-invigoration and blood-activation

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