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Research Progress on Active Ingredients of Traditional Chinese Medicine Against Triple-Negative Breast Cancer by Targeting Key Ferroptosis Pathways

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Abstract: ***Triple-negative breast cancer (TNBC) is a highly aggressive subtype with limited treatment options and poor prognosis. Recent research has highlighted ferroptosis, an iron-dependent cell death process driven by lipid peroxidation, as a promising therapeutic target. TNBC exhibits inherent susceptibility to ferroptosis due to dysregulated iron metabolism (e.g., TfR1 overexpression), rewired lipid metabolism (e.g., ACSL4/LPCAT3 activation), and impaired antioxidant defenses (e.g., GPX4 suppression). Active ingredients derived from Traditional Chinese Medicine (TCM) leverage multi-target mechanisms to synergistically induce ferroptosis through three core strategies: (1) disrupting redox homeostasis via System Xc^-/GSH/GPX4 axis inhibition ("Clearing Toxicity"); (2) promoting iron overload and lipid peroxidation by modulating iron-lipid metabolic networks ("Removing Stasis"); and (3) remodeling the immunosuppressive tumor microenvironment to synergize immunity with ferroptosis ("Reinforcing Healthy Qi"). This approach aligns with TCM theory in addressing "deficiency of healthy qi and toxicity-stasis. " Nanocarriers and combination therapies further enhance precision and efficacy. This review summarizes these advances and suggests that future efforts should focus on mechanistic depth, subtype-specific targeting, and clinical translation to advance ferroptosis-based TCM strategies against TNBC.***

Keywords: Triple-Negative Breast Cancer (TNBC), Ferroptosis, Traditional Chinese Medicine (TCM), Active Ingredients, Lipid Peroxidation, System Xc^-/GSH/GPX4 Axis, Iron Metabolism, Tumor Microenvironment, Multi-Target Therapy, Nanodelivery Systems.

1. Introduction

Breast cancer (BC) has become a major public health problem that seriously endangers women's health worldwide [1]. Its disease burden ranks first in gynecological malignant tumors [2]. Based on molecular typing criteria, breast cancer can be classified into four main subtypes: Luminal A, Luminal B, HER2-positive, and triple-negative (TNBC). It is noteworthy that triple negative breast cancer (TNBC) is classified separately due to simultaneous deletion of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) [3].

Epidemiological data show that TNBC mainly affects premenopausal young women under 40 years of age, accounting for 15-20% of all BC patients [4]. TNBC patients have a shorter survival time compared to other BC subtypes, with a mortality rate of 40% within the first five years after diagnosis [5]. TNBC is highly aggressive, with distant metastases occurring in approximately 46% of TNBC patients [6]. Median survival after metastasis is 13.3 months, and recurrence rates are as high as 25% [7]. Metastasis usually affects the brain and internal organs, with distant metastases occurring more often in the third year after diagnosis. The mean time to relapse was 35 to 67 months for non-TNBC patients, compared with 19 to 40 months for TNBC patients [8]. 75% of NBC patients die within 3 months of relapse [9]. Due to the lack of relevant receptor markers, TNBC patients do not benefit from existing endocrine therapy or HER2-targeted drugs, the standard treatment for non-surgical TNBC remains non-specific chemotherapy, and TNBC is one of the subtypes that respond best to standard chemotherapy regimens such as taxanes or anthracyclines. However, less than 30% of TNBC patients achieve complete remission, and relapse and mortality rates remain higher than for other types of BC [10].

In recent years, significant progress has been made in the study of BC cell death patterns, such as apoptosis and Ferroptosis, which is a regulatory form of cell death induced by iron-dependent lipid peroxidation accumulation and closely related to tumor progression [11]. TNBC is facing clinical treatment difficulties due to its high invasiveness, susceptibility to drug resistance and lack of effective targets. Studies have shown that Ferroptosis plays a key role in the development and treatment of TNBC through oxidative stress (LPO accumulation due to imbalance of GSH/GPX system), iron metabolism disorder and abnormal lipid metabolism. TNBC cells are sensitive to lipid peroxidation due to high lipid accumulation characteristics. Ferroptosis induced by targeted regulation of the above pathways may provide a new strategy for improving the prognosis of TNBC [12]. TNBC cells were found to be highly sensitive to Ferroptosis due to high expression of transferrin receptor (TfR1/CD71) and acyl-CoA synthase long chain member 4 (ACSL4), which significantly enhanced iron overload and polyunsaturated fatty acid accumulation in TNBC cells [13]. In addition, the active ingredients of traditional Chinese medicine, by virtue of their multi-target regulatory characteristics, can synergistically intervene in key pathways of Ferroptosis, providing unique advantages for TNBC treatment [14]. TNBC is regarded as "deficiency and toxin stasis" in TCM, which is highly consistent with oxidative stress (toxin), accumulation of iron fat (stasis) and immune imbalance (deficiency) in Ferroptosis pathway, providing theoretical basis for TCM intervention.

2. Ferroptosis and Its Relationship with TNBC

2.1 Characteristics and Regulatory Pathways of Ferroptosis

The concept of Ferroptosis was pioneered by Dixon et al. [15] [in their 2012 study of cancer cell death induced by the small molecule compound erastin and was defined as an iron-dependent form of regulatory cell necrosis. The core mechanism involves redox imbalance induced by abnormal accumulation of lipid reactive oxygen species (ROS), which is essentially different from apoptosis (mitochondrial cytochrome c release), necrosis (plasma membrane rupture) and autophagy (autophagy lysosomal formation) at morphological and molecular levels [16]. The characteristics of Ferroptosis include: (1) ultrastructural changes such as mitochondrial shrinkage (diameter reduction>50%) and cristae disappearance [17]; (2) Lipid peroxidation induced by Fe^{2} accumulation, glutathione (GSH) depletion and glutathione peroxidase 4 (GPX4) inactivation [18]; (3) Controlled by genes such as ACSL4 (acyl coenzyme A synthase)/LPCAT3 (lysophosphatidyl transferase), its deletion can increase Ferroptosis resistance by 70% [19].

Key regulatory pathways include: Iron metabolism: Iron ions are internalized via TfR1-mediated endocytosis and reduced to Fe^{2+} by six-transmembrane prostate epithelial antigen 3 (STEAP3), subsequently entering the labile iron pool (LIP). Excess Fe^{2+} generates reactive oxygen species (ROS) through the Fenton reaction, inducing oxidation of polyunsaturated fatty acids (PUFAs) and resulting in membrane structural damage [15]. Lipid metabolism: ACSL4 and lysophosphatidylcholine acyltransferase 3 (LPCAT3) catalyze the incorporation of PUFAs into membrane phospholipids. These are then oxidized by lipoxygenases (LOXs) to phospholipid hydroperoxides (PLOOHs), directly triggering membrane rupture [20] System Xc^{-}/GSH/GPX4 pathway: The cystine/glutamate antiporter system (System Xc^{-}), composed of solute carrier family 7 member 11 (SLC7A11) and solute carrier family 3 member 2 (SLC3A2), mediates cystine uptake for glutathione (GSH) synthesis. GPX4 relies on GSH to reduce lipid peroxides. Inhibition of this pathway leads to ROS accumulation and induces ferroptosis [18].

2.2 Harnessing Ferroptosis for TNBC Therapy

2.2.1 The Mechanism by Which Ferroptosis Regulates TNBC

TNBC is associated with an extremely poor clinical prognosis due to its high heterogeneity, lack of effective therapeutic targets, and tendency for metastasis and recurrence. Recent studies have revealed that TNBC cells exhibit unique susceptibility to ferroptosis, which is closely linked to their dysregulated iron metabolism, hyperactive lipid metabolism, and compromised antioxidant defense system [21]. Targeting these pathways significantly inhibits the proliferation of TNBC cells while markedly reducing toxicity to normal tissues, thereby demonstrating considerable potential for clinical application.

2.2.2 Disruption of iron metabolism leads to lipid peroxidation.

Disruption of iron homeostasis is a central driver of ferroptosis in TNBC. Studies indicate that the high expression of transferrin receptor 1 (TfR1) (3.1-fold higher than in normal cells) and NCOA4-mediated ferritinophagy significantly elevate intracellular free Fe^{2+} levels in TNBC cells (Fe^{2+} concentration: 1.6 μmol/L in TNBC vs. 0.8 μmol/L in normal cells) [23]. Excess Fe^{2+} catalyzes the peroxidation of polyunsaturated fatty acids (PUFAs) via the Fenton reaction, generating toxic phospholipid hydroperoxides (PLOOHs) that directly disrupt membrane integrity [24]. Furthermore, enhanced iron uptake mediated by divalent metal transporter 1 (DMT1), coupled with low expression of ferroportin 1 (FPN1) (FPN1 mRNA levels in TNBC are only 38% of those in ER+ BC), exacerbates iron overload. Experiments demonstrate that knocking down FPN1 elevated Fe^{2+} levels to 2.2 μM in ER+ BC T47D cells, whereas TNBC cells inherently exhibit iron accumulation due to profoundly low basal FPN1 expression [25]. Therefore, targeting regulators of iron metabolism—such as TfR1, NCOA4, or DMT1—represents a key strategy for selectively inducing ferroptosis in TNBC.

2.2.3 Reprogramming of lipid metabolism potentiates ferroptosis sensitivity.

Aberrant lipid metabolism in TNBC cells is characterized by significant upregulation of acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3). Studies have confirmed that ACSL4 expression is markedly higher in TNBC tissues compared to normal breast tissues (approximately 3–4 times), promoting the activation of polyunsaturated fatty acids (PUFAs) into PUFA-containing phospholipids (PUFA-PLs), which are subsequently incorporated into cell membranes by LPCAT3, thereby establishing a lipid environment prone to ferroptosis [26]. Experimental evidence indicates that inhibiting ACSL4 reduces the sensitivity of TNBC cells to ferroptosis inducers (e.g., Erastin), while the use of lipoxygenase (LOX) inhibitors (such as PD146176) decreases the accumulation of lipid hydroperoxides (LPOOHs), thereby delaying the ferroptotic process [27]. These findings suggest that targeting the ACSL4/LPCAT3 axis may represent a promising strategy to enhance ferroptosis induction efficiency in TNBC.

2.2.4 Impairment of the antioxidant defense system exacerbates oxidative stress damage.

The vulnerability of the antioxidant system in TNBC is primarily reflected in the following aspects: (1) Impaired GPX4 activity: The expression and activity of glutathione peroxidase 4 (GPX4) in TNBC cells are significantly lower than in other BC subtypes (e.g., ER+ or HER2+), resulting in a severely compromised ability to eliminate lipid peroxides [18]. (2) Mutant p53 suppresses SLC7A11: Mutant p53 (prevalence ~60–80%) in TNBC directly inhibits the expression of SLC7A11, a core component of the cystine/glutamate antiporter (System Xc^{-}), thereby reducing glutathione (GSH) synthesis and elevating intracellular ROS levels [28]. (3) Inactivation of the Nrf2 signaling pathway: Reduced activity of nuclear factor erythroid 2-related factor 2 (Nrf2) in TNBC leads to restricted transcription of downstream antioxidant genes, such as GPX4 and SLC7A11

[29]. For example, TNBC cells (e.g., MDA-MB-231) exhibit significantly higher sensitivity to the GPX4 inhibitor RSL3 compared to non-TNBC cells (MCF-7 IC_{50} = 0.2 μM vs. T47D IC_{50} = 1.2 μM) [30]. Potential therapeutic strategies: Metformin can enhance TNBC cell susceptibility to ferroptosis by regulating miRNAs (e.g., miR-324-3p) to suppress GPX4 expression [31]. Additionally, restoring wild-type p53 function or targeting mutant p53 to reactivate SLC7A11 expression may represent novel approaches to reverse ferroptosis resistance [32].

3. Key Molecular Mechanisms of Active Chinese Herbal Ingredients against TNBC by Modulating Ferroptosis and Their Underpinnings in Traditional Chinese Medicine Theory

The core pathogenesis of "deficiency of healthy qi and toxicity-stasis" in TNBC is highly correlated with ferroptosis pathways: "deficiency of healthy qi" manifests as an imbalanced immune microenvironment and defective antioxidant defenses, while "toxicity-stasis" is closely associated with rampant lipid peroxidation and disordered iron metabolism. Active components of Chinese herbal medicine leverage their multi-target synergistic advantages to precisely induce TNBC cell death by intervening in the three core pathways of ferroptosis—the antioxidant defense system (detoxification), the iron-lipid metabolism network (removing stasis), and immune microenvironment remodeling (reinforcing healthy qi). This section systematically elucidates the molecular mechanisms and the theoretical connotations within traditional Chinese medicine.

3.1 Targeting the System Xc^-/GSH/GPX4 Axis: Disrupting Redox Homeostasis (Clearing Toxicity)

The System Xc^-/GSH/GPX4 axis serves as a core regulator of redox homeostasis. Its functional inhibition leads to glutathione (GSH) depletion, GPX4 inactivation, and lipid ROS accumulation, representing the most direct pathway for inducing ferroptosis. TNBC exhibits high sensitivity to this axis due to low GPX4 expression and p53 mutation-mediated suppression of SLC7A11.Multiple active components of Chinese herbal medicine synergistically target this pathway to "clear toxicity": (1) Saponins: Paris saponin activates the p53/SLC7A11 signaling axis, downregulates SLC7A11 and GPX4 expression, and induces lipid peroxidation accumulation, resulting in plasma membrane rupture (MDA-MB-231 model) [33]. Ginsenoside Rg3 suppresses GPX4 expression by inhibiting the RhoA/ROCK pathway, and its liposomal formulation reduces tumor volume by 40% in animal models and reverses chemoresistance [34-35]. (2) Flavonoids: Myricetin inhibits the Nrf2/GPX4 pathway, reducing tumor volume by 62.3% in a 4T1 xenograft model [36]. Brasilicine targets the p53/SLC7A11/GPX4 axis, selectively inducing TNBC cell death (cytotoxicity <5% in MCF-10A normal cells, IC_{50} >100 μmol/L vs. IC_{50} =15 μmol/L in TNBC cells) [37]. (3) Phenols/Alkaloids/ Polysaccharides: Resveratrol inhibits System Xc^- function and blocks Nrf2 nuclear translocation [38]. Berberine depletes GSH by suppressing System Xc^- [39-40]. Lycium barbarum polysaccharide downregulates SLC7A11 transcriptional activity, increasing the ferroptosis rate by 3.2-fold [41]. Red ginseng polysaccharide downregulates GPX4 via the NF-κB pathway, amplifying oxidative stress [42].

Correlation with TCM Theory: Lipid ROS accumulation in TNBC corresponds to "internal exuberance of heat-toxicity" in TCM. These components facilitate the clearance of "pathogenic toxins" by inhibiting the antioxidant axis (SLC7A11/GPX4), reflecting the scientific connotation of the "clearing heat and resolving toxicity" treatment principle at the molecular level.

3.2 Intervening in the Iron-Lipid Metabolism Network: Driving Lipid Peroxidation (Removing Stasis)

Iron overload (Fe^{2+} accumulation) and lipid metabolic reprogramming (upregulation of ACSL4/LPCAT3) constitute the structural basis for ferroptosis susceptibility in TNBC. Herbal components synergistically "remove stasis" through dual pathways: (1) Iron Metabolism Intervention: Paris saponin upregulates TfR1 and Fe^{2+} levels [33]. Artemisinin-derived MOF carriers enable sustained Fe^{2+} release, reducing MDA-MB-231 cell viability to 23.5% [43]. Cryptotanshinone activates NCOA4-mediated ferritinophagy, synergizing with doxorubicin to reverse chemoresistance [44-45]. Oridonin elevates Fe^{2+} levels via the JNK/Nrf2/HO-1 pathway [46]. (2) Lipid Metabolic Reprogramming: Diosgenin (IC_{50} = 8.2 μM) activates ACSL4, cross-regulating lipid metabolism [47]. Curcumin upregulates ACSL4 expression and inhibits lung metastasis formation [48]. Berberine upregulates ACSL4 to induce lipid peroxidation [40]. Correlation with TCM Theory: Iron accumulation and hyperactive lipid peroxidation align with "stasis of blood and phlegm turbidity" in TCM. Herbal components promote the clearance of "stasis-toxicity" by modulating iron homeostasis (TfR1/NCOA4) and lipid metabolic enzymes (ACSL4), consistent with the therapeutic principles of "activating blood, resolving phlegm, unblocking collaterals, and dissipating nodules. "

3.3 Remodeling the Tumor Microenvironment: Synergizing Immunomodulation and Ferroptosis (Reinforcing Healthy Qi)

Damage-associated signals (e.g., HMGB1) released during ferroptosis can activate anti-tumor immunity, while immune cells (such as TAMs) also regulate ferroptosis sensitivity. Herbal components achieve synergy between "reinforcing healthy qi and eliminating pathogens" through immune intervention: (1) Polysaccharides: Red ginseng polysaccharide activates the NF-κB pathway to promote TNF-α secretion, creating a cascading amplification effect with lipid peroxidation [42]. Poria cocos polysaccharide inhibits GPX4 and promotes NCOA4-mediated ferritinophagy, increasing free Fe^{2+} levels [49-50]. (2) Alkaloids: Berberine modulates macrophage polarization, increasing the M1/M2 ratio by 2.1-fold and reducing IL-10/TGF-β expression in TAMs, establishing a dual-effect mode of "ferroptosis induction–immune remodeling" [39-40].

Correlation with TCM Theory: An imbalanced immune microenvironment aligns with "deficiency of healthy qi" in TCM. These components restore the body's "healthy qi" by modulating macrophage function (NF-κB/TNF-α), while

simultaneously creating a microenvironment conducive to ferroptosis ("eliminating pathogens"), reflecting the holistic concept of "reinforcing healthy qi to consolidate the constitution, addressing both manifestations and root causes."

3.4 Synergistic Enhancement Strategies: Nanotechnology and Innovative Physical Therapies

To overcome limitations such as poor water solubility and low targeting efficiency of herbal components, innovative delivery and treatment modalities significantly enhance therapeutic efficacy: (1) Nanocarriers: Ginsenoside Rg3 liposomes improve bioavailability, reducing tumor volume by 40%. Artemisinin-based MOF carriers enable spatiotemporal synergy between "iron delivery and GPX4 inhibition" [43]. (2) Combination with Physical Therapies: Gallic acid combined with low-intensity laser irradiation triggers ROS burst, resulting in a 60% decrease in GSH and a 2.8-fold increase in MDA [51]. Oridonin disrupts DNA repair through oxidative stress, increasing radiosensitivity by 3.1-fold [46].

3.5 Summary and Interpretation Through the Lens of Traditional Chinese Medicine Theory

Active components of Chinese herbal medicine exert multi-target synergistic regulation across the three core pathways of ferroptosis: Active components of Chinese herbal medicine exert multi-target synergistic regulation across the three core pathways of ferroptosis: Clearing Toxicity: Inhibiting the GPX4/SLC7A11 axis to clear "heat-toxicity," directly targeting the "heat-toxicity" aspect of "toxicity-stasis. "Removing Stasis: Intervening in iron/lipid metabolism to resolve "stasis-toxicity," addressing the "blood stasis and phlegm turbidity" aspect of "toxicity-stasis. "Reinforcing Healthy Qi: Remodeling the immune microenvironment to tonify "healthy qi," correcting the "deficiency of healthy qi."

This multi-dimensional intervention model of "Clearing Toxicity – Removing Stasis – Reinforcing Healthy Qi" systemically rectifies the core pathogenesis of "deficiency of healthy qi and toxicity-stasis" in TNBC, embodying the strengths of TCM's holistic approach and treatment based on syndrome differentiation. Innovative applications of nanocarriers (e.g., liposomes, MOFs) and physical therapies (e.g., photodynamics, radiotherapy) provide crucial technological support for overcoming clinical translation bottlenecks. Future research should utilize single-cell sequencing to clarify subtype-specific sensitivities and advance precision therapy through combination strategies such as "ferroptosis inducers + immune checkpoint inhibitors."

4. Summary and Prospects

Triple-negative breast cancer (TNBC) presents a formidable clinical challenge due to its lack of effective therapeutic targets, high aggressiveness, and propensity for drug resistance. In recent years, ferroptosis, an iron-dependent form of programmed cell death driven by lipid peroxidation, has emerged as a promising novel therapeutic direction for TNBC. Research has demonstrated that TNBC cells exhibit a unique susceptibility to ferroptosis, underpinned by a molecular foundation comprising dysregulated iron metabolism (e.g., high TfR1 and low FPN1 expression), reprogrammed lipid metabolism (e.g., activation of the ACSL4/LPCAT3 axis), and a deficient antioxidant system (e.g., low GPX4 activity and suppressed SLC7A11). Capitalizing on their multi-target regulatory advantages, active components from Chinese herbal medicine potently induce ferroptosis in TNBC cells by synergistically intervening in its three core pathways: the antioxidant defense system (Clearing Toxicity), iron-lipid metabolism (Removing Stasis), and the immune microenvironment (Reinforcing Healthy Qi). For instance, Paris saponin downregulates GPX4 by activating the p53/SLC7A11 axis, leading to glutathione (GSH) depletion and accumulated lipid peroxidation. Artemisinin-derived nanocarriers co-deliver Fe^{2+} and active compounds, significantly inhibiting GPX4 activity and reducing cell viability to 23.5%. Ginsenoside Rg3 modulates the RhoA/ROCK pathway to enhance chemosensitivity, resulting in a 40% reduction in tumor volume in animal models. Furthermore, combining herbal components with radiotherapy or chemotherapy can reverse drug resistance and reduce adverse effects, highlighting their synergistic potential.

Despite significant progress, several key issues remain to be addressed: Mechanistic Complexity: The multi-target synergistic mechanisms of herbal active ingredients are not fully elucidated. Integrated multi-omics approaches (e.g., metabolomics, protein interaction networks) are needed to decipher their regulatory networks. TNBC Heterogeneity: Significant differences in ferroptosis sensitivity exist across molecular subtypes, necessitating the development of subtype-specific models to optimize targeting strategies. Translation Bottlenecks: Current research relies heavily on in vitro and mouse models. Validation using patient-derived xenograft (PDX) models and humanized tumor microenvironment systems is essential to evaluate immune-ferroptosis synergy. Preclinical efficacy evaluation systems require further standardization. Safety Assessment: While some components show notable efficacy, their potential systemic toxicity and long-term safety profiles, particularly concerning iron accumulation-related hepatotoxicity (e.g., monitoring serum ferritin levels), warrant thorough investigation.

To address these challenges, future research should focus on the following directions: Precision Targeting and High-Throughput Screening: Utilize TNBC-specific biomarkers (e.g., ACSL4, NCOA4), combined with artificial intelligence and organoid technology, to screen highly selective herbal components or structurally optimized derivatives. Integrated Chinese-Western Combination Strategies: Develop combination regimens such as "ferroptosis sensitizers + chemotherapy/radiotherapy," leveraging the multi-target nature of herbal medicine to overcome resistance—e.g., combining baicalein with platinum drugs to reverse tumor drug resistance. Innovation in Nanodelivery Systems: Develop functionalized nanocarriers (e.g., pH-responsive metal-organic frameworks, exosome encapsulation technology) to improve drug targeting and minimize off-target effects, as demonstrated by artemisinin-based nanocarriers enabling controlled Fe^{2+} release. Deepening Clinical Translation: Promote multi-center preclinical studies to explore the monitoring

value of ferroptosis-related biomarkers (e.g., serum MDA, tissue GPX4 activity) and establish predictive models for individualized treatment response. Cross-Disciplinary Technology Integration: Employ single-cell sequencing and spatial transcriptomics to resolve the spatiotemporal heterogeneity of ferroptosis regulation within the tumor microenvironment, providing a basis for precise intervention.

In conclusion, targeting ferroptosis pathways with active components from Chinese herbal medicine opens a highly promising new avenue for TNBC treatment. The integration of their multi-target, low-toxicity advantages with the ferroptosis mechanism holds potential to break through current therapeutic bottlenecks. However, the transition from basic research to clinical application requires sustained investment in mechanistic deciphering, technological innovation, and cross-disciplinary collaboration. Moving forward, through precision screening, formulation optimization, and delivery system innovation, more efficient and safer treatment options may be provided for TNBC patients, ultimately improving their survival outcomes.

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