

Research on the Regulation of RNA by Traditional Chinese Medicine to Alleviate Chemotherapy Side Effects

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Abstract. Chemotherapy is the main treatment for tumors; however, its side effects, like bone marrow suppression, gastrointestinal reactions, and neurotoxicity, can seriously impact the patient's quality of life and the treatment process. Traditional Chinese medicine (TCM), which possesses the advantages of multi-component, multi-target, and overall regulation, appears quite promising in relieving the side effects brought about by chemotherapy. However, the molecular operating mechanism of it has not been fully figured out yet. In recent years, non-coding RNAs (including miRNAs, lncRNAs, and circRNAs) have been confirmed to play a key regulatory role in cell proliferation, apoptosis and damage repair and other aspects, thus providing a new perspective for us to understand the mechanism of chemotherapy-related adverse reactions. This article systematically reviews the research progress of how TCM active ingredients (such as ginsenosides, astragaloside IV and curcumin and the like) reduce chemotherapy side effects by regulating specific RNA molecules and regulating related signaling pathways, including protecting bone marrow hematopoiesis, reducing gastrointestinal toxicity and relieving neurotoxicity and the like. This article further delves into the challenges currently encountered in this domain and also envisions the future direction of precise TCM intervention combined with technologies like high-throughput sequencing and gene editing, with the purpose of offering a theoretical basis for integrating traditional Chinese and Western medicine in cancer supportive care.

Keywords: Traditional Chinese medicine, Chemotherapy side effects, Non-coding RNA, Multi-target regulation.

1. Introduction

Malignant tumors remain one of the major diseases that pose a serious threat to human health. According to the 2022 Global Cancer Statistics Report released by the International Agency for Research on Cancer (IARC) of the World Health Organization, there were approximately 19.965 million (about 20 million) new cancer cases and about 9.737 million (approximately 9.7 million) cancer deaths worldwide. In China, based on authoritative data published by the National Cancer Center in the Chinese Journal of Oncology in 2024, there were approximately 4.8247 million new cancer cases and about 2.5742 million cancer deaths in 2022. Cancer treatment needs to select appropriate treatment strategies according to the type, stage of the tumor as well as the condition of the patient, for example, surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy, endocrine therapy, and traditional Chinese medicine, etc. A multidisciplinary comprehensive treatment mode is indeed often adopted. Among these methods chemotherapy which is the core method for treating malignant tumors plays an indispensable role in inhibiting tumor growth and eliminating cancer cells. Yet, because chemotherapeutic drugs have little selectivity, they not only attack tumor cells but also cause severe damage to the normally proliferating cells in the body, for example, just like the hematopoietic cells in the bone marrow, the gastrointestinal mucosal cells, and the hair follicle cells), which gives rise to a large number of side effects. These include bone marrow suppression, nausea and vomiting, diarrhea, neurotoxicity, and liver and kidney dysfunction [1]. Such adverse effects not only cause a significant decrease in patients' quality of life; they may also cause them to have to discontinue treatment or reduce the dose. This directly affects the anti-tumor effect and the overall survival.

In recent years, with the development and progress of precision medicine and molecular biology, tumor treatment strategies are gradually shifting from traditional cytotoxic drugs to more targeted

treatment methods. Under such a large background, ribonucleic acid (RNA), which acts as a key regulator of biological processes, is playing an increasingly prominent role. Non-coding RNAs including microRNAs (miRNAs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) have been found to be extensively involved in such important pathophysiological processes as cell proliferation, cell apoptosis, DNA damage repair and immune response. Particularly miRNAs can bind to the 3' untranslated region (3'UTR) of the target gene messenger ribonucleic acid (mRNA), which causes mRNA degradation or the inhibition of translation, thus allowing for the precise post-transcriptional regulation of gene expression. This offers a new perspective for clarifying the molecular mechanism of the side effects caused by chemotherapy at the molecular level and for finding new intervention targets.

Traditional Chinese medicine (TCM) has accumulated quite a number of practical experience in the adjuvant treatment of tumors. Its core principles, namely "the overall concept" and "syndrome differentiation and treatment", are closely associated with such treatment objectives as alleviating the side effects caused by chemotherapy and reinforcing the body's resistance while eliminating healthy qi to eliminate the pathogenic factors. Numerous clinical researches have confirmed that the TCM formulas, single traditional Chinese medicines and their active components can effectively alleviate the chemotherapy-related adverse reactions and can also enhance the patients' tolerance levels. However, for a long time the specific mechanism of action has been expounded from a macroscopic perspective like immune regulation and antioxidant without in-depth understandings at the molecular biology level. Thus this article combines traditional Chinese medicine theory with modern RNA regulation research to systematically review and explore whether traditional Chinese medicine relieves the side effects of chemotherapy by regulating the expression of specific RNAs. This method not only offers modern biological evidence for the scientific basis of TCM but also has the potential to discover new drug targets and can facilitate the development of the combination of traditional Chinese and Western medicine in cancer adjuvant treatment.

The fundamental reason for the side effects brought about by chemotherapy is the non-specific damage inflicted on normal tissues. Traditional Chinese medicine, having the synergistic effect of multiple components and multiple targets, presents quite great potential in regulating the RNA network to safeguard normal tissues and facilitate damage repair

2. Regulating miRNA to Protect Bone Marrow Hematopoietic Function

Bone marrow suppression which is one of the most common and dangerous dose-limiting toxicities in chemotherapy mainly manifests as neutropenia thrombocytopenia and anemia. In severe cases it can induce infections and bleeding and may also force the reduction or interruption of chemotherapy thus directly affecting the anti-tumor efficacy. The core pathological mechanism includes the irreversible damage brought about by chemotherapeutic drugs to the proliferating hematopoietic stem/progenitor cells (HSPCs) in the bone marrow, which breaks the balanced state of the hematopoietic microenvironment. Recently, research has found that microRNAs (miRNAs), as important post-transcriptional regulatory factors, are widely involved in the precise regulatory network that controls the proliferation, differentiation, apoptosis, and aging of hematopoietic cells. Notably, various active components of traditional Chinese medicine and prescriptions are through precisely regulating these key miRNAs, coming up with new and promising strategies for the prevention and treatment of bone marrow suppression caused by chemotherapy. The mechanism by which traditional Chinese medicine protects bone marrow hematopoietic function by regulating miRNAs is shown in Figure 1.

2.1. Ginsenoside Rg1: Anti-apoptosis through the miR-423-5p/GPA33 axis

Ginsenoside Rg1 is an important active ingredient in ginseng, and has the obvious effect of "tonifying qi and generating blood". When chemotherapy induces myelosuppression, its protective effect has a corresponding explanation at the molecular level [2]. Studies have shown that 5-fluorouracil (5-FU) can activate excessive pro-apoptotic signals in bone marrow cells (such as the cysteinyl aspartate specific proteinase-3 (Caspase-3) pathway). After intervention with Rg1, the expression of miR-423-5p in bone marrow cells can be specifically up-regulated [3]. Bioinformatics and dual-luciferase assay confirmed that GPA33 is the direct target of miR-423-5p. GPA33 is a cell surface glycoprotein. Its overexpression is associated with higher apoptotic susceptibility. Ginsenoside Rg1 effectively reduces 5-FU-induced bone marrow cell apoptosis and maintains the number of hematopoietic pool cells through the pathway of "component to upregulation of miR-423-5p to target gene GPA33 inhibition to downstream apoptosis pathway blockade".

2.2. Astragaloside IV: Targeting the miR-34a/SIRT1 axis to prevent hematopoietic stem cell senescence

Different from simple apoptosis, chemotherapy can prematurely senesce hematopoietic stem cells (HSC), causing a permanent decline in self-renewal ability, which is the key to long-term bone marrow dysfunction. Astragaloside IV is the active ingredient in *Astragalus membranaceus* and plays a key role here. Studies have found that chemotherapy stimulation can increase miR-34a in hematopoietic stem cells, and miR-34a will play an opposite role, inhibiting SIRT1. SIRT1 is a longevity protein with deacetylase activity, which is very important for genome stability, resistance to oxidative stress, and delaying cellular senescence. After Astragaloside IV exerts its effect, miR-34a will decrease, no longer inhibiting SIRT1, SIRT1 will be activated, and downstream anti-aging pathways such as FoxO and p53 will also be activated. In the mechanism, astragaloside IV down-regulates miR-34a, then SIRT1 up-regulates, thereby inhibiting stem cell senescence, this process maintains the stemness and regenerative potential of hematopoietic stem cells, and lays a foundation for long-term hematopoietic recovery[3].

2.3. Formula "Bazhen Decoction": Multi-target reshaping of the hematopoietic microenvironment

Compound prescriptions have unique advantages in multi-target and systemic regulation, unlike single-component precision-targeted traditional Chinese medicine prescriptions that rely on the "jun, chen, zuo, shi" compatibility ratio. Take the classic qi and blood tonifying prescription "Bazhen Decoction" as an example; when improving myelosuppression caused by cyclophosphamide, it can comprehensively regulate the microRNA (miRNA) network. Through high-throughput sequencing analysis, it was found that Bazhen Decoction can synergistically regulate a series of functionally related miRNAs: down-regulate miR-146a; miR-146a is a key negative feedback regulator of the NF- κ B signaling pathway, and overexpression will inhibit the production of hematopoietic growth factors. Down-regulating miR-146a by Bazhen Decoction can relieve the inhibition of NF- κ B and promote bone marrow stromal cells to secrete hematopoietic stimulating factors such as G-CSF and SCF. It also regulates the miR-221/222 cluster; this cluster of miRNAs can target and inhibit the c-Kit receptor (stem cell factor receptor), thereby blocking the signal for hematopoietic stem/progenitor cell proliferation[4]. Bazhen Decoction helps restore c-Kit-mediated normal proliferation signal transduction by regulating expression. In the case of multi-gene and multi-pathway joint regulation, Bazhen Decoction directly acts on hematopoietic cells, and regulates bone marrow stromal cells and inhibits excessive inflammatory response, and remodels a supportive microenvironment for the survival, proliferation and differentiation of hematopoietic stem/progenitor cells.

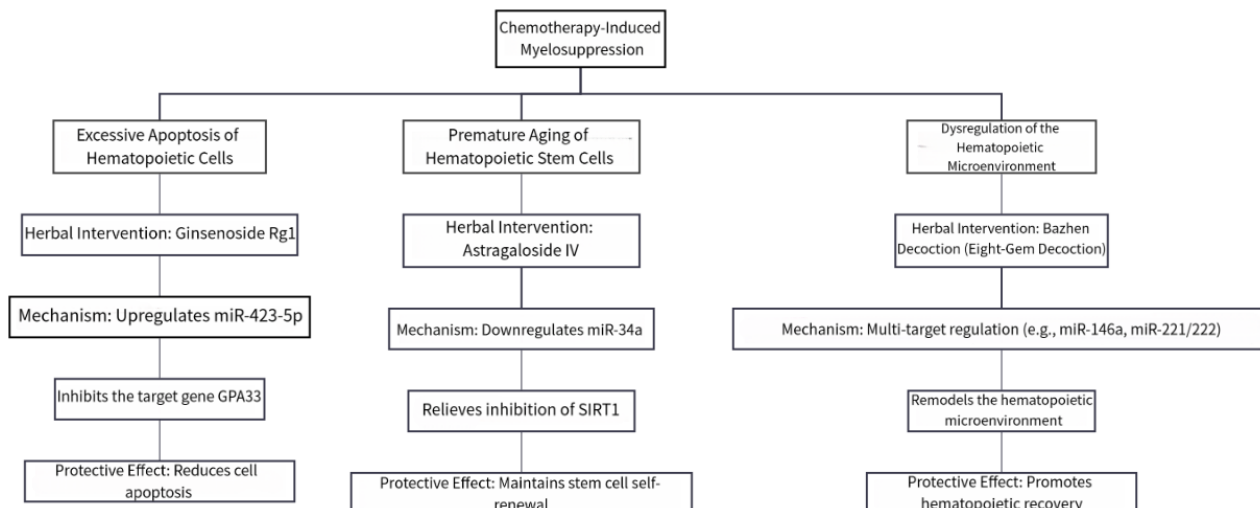


Figure 1. Flowchart of Traditional Chinese Medicine regulating miRNA to protect bone marrow hematopoietic function (Picture credit: Original)

3. Intervening in the lncRNA/circRNA network to alleviate gastrointestinal toxicity

Chemotherapy has side effects, such as gastrointestinal reactions like nausea, vomiting, diarrhea, which will affect the patient's quality of life. The rapid apoptosis of mucosal epithelial cells in the intestine and the destruction of barrier function are the key points.

Chemotherapy-induced gastrointestinal toxicity (CIGT), especially delayed diarrhea and mucositis, is the main obstacle limiting the clinical application of irinotecan and 5-fluorouracil. The pathological core is not only epithelial cell apoptosis, but also involves severe inflammatory storm, intestinal barrier collapse caused by destruction of tight junction proteins and subsequent ecological dysregulation. Long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) are the core of complex regulatory networks and play a key role in this process. Traditional Chinese medicine intervenes in this network through multi-component systems and has unique advantages in multi-target repair of intestinal mucosal barrier.

3.1. Curcumin: Targeting the LncRNA H19/miR-675 Axis for Synergistic Anti-Inflammatory and Anti-Apoptotic Effects

Curcumin is the key component in the traditional Chinese medicine turmeric, this component is famous for its anti-inflammatory and mucosal protection effects. Studies have found that chemotherapeutic drugs such as 5-FU will cause abnormal activation of LncRNA H19 in intestinal crypt cells. When H19 acts as a ceRNA, overexpression acts like a molecular sponge to absorb or inhibit miR-675, and the target of miR-675 is the pro-apoptotic protein PUMA. So the chemotherapy process is like this, H19 is up-regulated, miR-675 is inhibited, PUMA is elevated, thereby promoting cell apoptosis. Once curcumin intervenes, it can down-regulate the expression of LncRNA H19, release miR-675 to inhibit PUMA and also block apoptotic signals [5]. This pathway interacts with NF-κB downstream inflammatory signals. curcumin synergistically alleviates intestinal inflammation through this effect, and protects via the "apoptosis" and "inflammation" pathways.

3.2. Sijunzi Decoction: Regulating the CircRNA_0001292/miR-16-5p Network to Strengthen the Intestinal Barrier

Sijunzi Decoction is a classic prescription for invigorating the spleen and replenishing qi. It is often used clinically to relieve diarrhea caused by chemotherapy. Its modern mechanism is related to circRNA network regulation. Studies have found that in irinotecan-induced intestinal mucosal injury, the expression of circRNA_0001292, which stabilizes the circular structure, is significantly down-regulated. This circRNA acts as a "molecular sponge" to specifically adsorb miR-16-5p. After taking Sijunzi Decoction, the level of circRNA_0001292 can recover. miR-16-5p maintains the MLCK-related proteins of the cytoskeleton and tight junctions. Sijunzi Decoction upregulates circRNA_0001292, then adsorbs and inhibits miR-16-5p, then relieves the inhibition on barrier-related target genes, thereby promoting the expression and localization of tight junction proteins such as ZO-1 and Occludin, thus strengthening the intestinal mucosal barrier physically and reducing the translocation of pathogens and endotoxins.

3.3. Berberine: Intervening in the LncRNA H19/miR-29b-3p/P53 Axis to Promote Epithelial Repair

In addition to classic drugs, berberine in *Coptis chinensis* has an intestinal protective effect. Its mechanism is related to LncRNA H19. When the intestine is injured, H19 will increase, and then adsorb miR-29b-3p to indirectly activate P53. Over-activation of P53 will arrest the cell cycle, which is not conducive to repair. Berberine can inhibit LncRNA H19, enhance the activity of miR-29b-3p, thereby inhibiting excessive P53 signaling. Intestinal epithelial cells use this to escape damage stress, re-enter proliferation or repair state, and mucosal healing accelerates.

4. Regulating RNAs associated with oxidative stress and neurotoxicity

Chemotherapy drugs such as cisplatin and paclitaxel can cause organ damage and have neurotoxicity. Oxidative stress is the key. Cisplatin causes ferroptosis and apoptosis of renal tubular cells through reactive oxygen species. Paclitaxel activates neuroinflammatory signals in spinal dorsal horn and microglia, thereby causing neuropathy. Non-coding RNA networks regulate cellular stress. Traditional Chinese medicine accurately intervenes in oxidative damage and neuroinflammation by regulating RNA.

4.1. Ganoderma lucidum polysaccharides/Astragalus polysaccharides: Activation of the Nrf2 antioxidant system through the LncRNA/miRNA axis

Polysaccharides from traditional Chinese medicine, such as ganoderma lucidum polysaccharides and astragalus polysaccharides, are classic antioxidant ingredients. Their core mechanism is to activate the Nrf2/ARE signaling pathway, which is the master switch of cellular defense. Recent studies have found that there are more delicate regulatory mechanisms at the epigenetic level. Taking cisplatin-induced kidney injury as an example, polysaccharide components can significantly up-regulate the long non-coding RNA LINC00667 in renal tissues [6]. This long non-coding RNA acts as a ceRNA, adsorbing and spongily binding miR-449b. miR-449b directly targets and inhibits the translation of Nrf2 mRNA. The polysaccharide component promotes the nuclear translocation of Nrf2 through the pathways of "upregulating LINC00667, adsorbing miR-449b, and relieving the inhibition of Nrf2", then initiates downstream antioxidant enzymes such as HO-1, NQO1 and phase II detoxification enzymes to systematically clear excessive reactive oxygen species (ROS) produced by cisplatin, and protect renal tubular cells from oxidative damage.

4.2. Ligustrazine: Inhibition of miR-145-mediated glial cell activation

Chemotherapy drugs such as paclitaxel cause dose-limiting peripheral neuropathic pain. Its pathological core is not only peripheral neurotoxicity, but also persistent neuroinflammation mediated by spinal dorsal horn glial cells and central sensitization. In this process, microglia and astrocytes (guardians of central innate immunity) become abnormally activated, release pro-inflammatory mediators, and maintain the cycle of pathological pain. Piperazine ferulate in the traditional Chinese medicine Chuanxiong has the effect of promoting blood circulation and removing blood stasis, and has been confirmed to have neuroprotective and analgesic effects. It upregulates miR-145 in glial cells in paclitaxel-induced neuroinflammation or Parkinson's disease cell models. miR-145 is a fine regulator of cell signaling, targetedly inhibits the translation of TLR4 mRNA, and blocks the TLR4/MyD88/NF- κ B core pathway that drives neuroinflammation. Inhibiting the upstream central hub, NF- κ B nuclear translocation/activation is weakened, the transcription/synthesis and release of pro-inflammatory cytokines such as TNF- α , IL-1 β , IL-6 are reduced, the molecular-cellular cascade reaction transforms spinal microglia/astrocytes from a pro-inflammatory state to a homeostasis state, their abnormal activation/proliferation is inhibited, glia-neuron dysregulation leads to central sensitization being relieved, and animal models have significant improvements in neuropathic pain behaviors such as mechanical allodynia and cold hyperalgesia [7].

4.3. Salvianolic Acid B: Promoting Neural Repair via the miR-30c/BDNF Axis

In the treatment of neuropathic injury, inhibiting neuroinflammation and promoting neural structural repair are two goals [8]. Salvianolic acid B (Sal B), a water-soluble component of *Salvia miltiorrhiza*, is the key to repair. It not only has basic antioxidant effects, but also can regulate the miR-30c/BDNF axis, providing a repair approach for injuries such as chemotherapy-induced peripheral neuropathy.

Studies have shown that in neuropathy, BDNF is crucial for neuronal survival and axon growth, and synaptic plasticity in the CNS and PNS is often inhibited. The repair of salvianolic acid B starts from fine-tuning the miRNA network. It can specifically and significantly upregulate the expression of miR-30c in nerve tissues. As a key messenger, miR-30c indirectly relieves the inhibition of BDNF transcription and synthesis by directly targeting and inhibiting negative regulators of BDNF such as the deacetylase SIRT1, effectively stabilizing and increasing the local BDNF protein level.

The restoration of BDNF levels, which serves as the core of nerve repair as stated in [9], will cause BDNF to be enhanced and then combined with TrkB, thus activating the PI3K/Akt and MAPK/ERK pathways. With the anti-apoptotic function that the PI3K/Akt has, there are DRG sensory neurons that can survive. Genes related to MAPK/ERK activation are involved in promoting the regeneration of the damaged axons. Additionally, the axon system can also improve the functions of the Schwann cells, providing supportive microenvironments for axon regeneration as well [10].

In general, salvianolic acid B, through the "comp-miR-30c-BDNF-TrkB and downstream pathways", can promote nerve repair, increase neuron survival, can also promote axon regeneration, and at the same time optimize cell functions.

5. Challenges and Prospects

Current research has made some progress. However, many challenges still remain in this field. First, the composition of traditional Chinese medicine is relatively complex. Its role in RNA network regulation is multi-target and synergistic, which makes it difficult to analyze the compatibility rules of traditional Chinese medicine and the RNA regulatory network. Second, most studies are still at the stage of cellular or animal experiments, lacking validation from large-scale multicenter clinical studies. The sensitivity and specificity of specific RNA molecules as biomarkers need to be confirmed. Finally, RNA molecules have tissue specificity, and their regulatory networks are complex and redundant. How to perform precise intervention without destroying normal physiological functions is a problem that needs to be considered.

In the future, ① use high-throughput sequencing, bioinformatics and other systematic methods to map the RNA expression profile under the intervention of traditional Chinese medicine, and screen key regulatory points; ② combine gene editing technologies such as CRISPR/Cas9 to verify the functions of specific RNA molecules in animal models, and clarify the upstream and downstream pathways; ③ carry out rigorous clinical research, find the precise "syndrome-prescription-effect" correspondence based on RNA markers, and transform traditional Chinese medicine from "experience" to "science" in reducing chemotherapy side effects.

6. Conclusion

In summary, this review systematically expounds that Traditional Chinese medicine, by accurately regulating the non-coding RNA network (including miRNA, lncRNA, circRNA), provides a new multi-layer and multi-target strategy for preventing and treating chemotherapy side effects, has the advantage of "overall regulation" and is deeply connected with modern molecular biology.

To protect bone marrow hematopoietic function, Chinese medicine active ingredients like ginsenoside Rg1, astragaloside IV and compound prescriptions such as Bazhen Decoction, regulate miR-423-5p/GPA33, miR-34a/SIRT1, inhibit apoptosis or senescence of hematopoietic cells and remodel the blood microenvironment. To alleviate gastrointestinal toxicity, curcumin, Sijunzi Decoction and others via lncRNA H19/miR-675, circRNA_0001292/miR-16-5p, play roles in anti-apoptosis, anti-inflammation and repairing intestinal mucosal barrier. To relieve neurotoxicity and hepatotoxicity and nephrotoxicity, Chinese medicine ingredients such as ganoderma lucidum polysaccharide, tetramethylpyrazine, salvianolic acid B, regulate LINC00667/miR-449b/Nrf2, miR-155/SOCS1, miR-30c/BDNF, target oxidative stress and neuroinflammatory injury, protect organs or repair nerves.

This study reveals the modern scientific and technological basis of traditional Chinese medicine's "multi-target, networked" approach: regulating key RNA nodes to affect the network of downstream gene expression and signaling pathways, presenting TCM concepts such as "replenishing qi" and "treatment based on syndrome differentiation" at the molecular level. Mechanistic interpretation has made progress, and future research still needs to study the interaction between traditional Chinese medicine components and direct RNA targets, the association between compound compatibility and RNA regulatory network systems, and the clinical precise interpretation of basic RNA markers.

The theory of traditional Chinese medicine integrates with the cutting-edge of modern RNA biology, on one hand it blazes a new hopeful path for integrated traditional Chinese and western medicine in cancer supportive care but also treatment, on the other hand it marks the profound transformation of traditional Chinese medicine from empirical medicine to precision medicine. With the deepening and standardization of research, traditional Chinese medicine will play an increasingly important scientific role in global cancer treatment.

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