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Exploring the Treatment of Chemotherapy-Induced Myelosuppression with the Kidney-Tonifying, Essence-Replenishing, and Marrow-Fortifying Method Based on the Hematopoietic Stem Cell Homing Theory

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Abstract: Chemotherapy-induced myelosuppression is a common dose-limiting toxicity of chemotherapy for malignant tumors, and its core mechanism is closely related to hematopoietic stem cell homing disorder. Chinese medicine attributes chemotherapy-induced myelosuppression to the category of "medullary labor" and believes that "deficiency of kidney essence and drying up of the medulla oblongata" is the main pathogenesis of chemotherapy-induced myelosuppression, which is precisely the same as that of hematopoietic stem cell homing disorders revealed by modern medicine, which involves chemokines such as CXCL12/CXCR4 axis, adhesion molecules such as very late antigen-4 (VLA-4)/vascular cell adhesion molecule (VCAM), and other factors such as the CXCL12/CXCR4 axis, and the CXCL4/VCAM axis. This is highly compatible with modern medicine's revelation of hematopoietic stem cell homing disorder. By activating signaling pathways such as *PI3K*/*Akt* and *Wnt*/β-catenin, up-regulating chemokine expression, enhancing cell adhesion, improving extracellular matrix remodeling, and alleviating oxidative stress, the method of tonifying the kidneys and filling in the marrow promotes the homing of hematopoietic stem cell through multiple pathways, which provides a new idea for the integration of Chinese and Western medicine in the treatment of chemotherapy-induced myelosuppression.

Keywords: Hematopoietic stem cell homing; Chemotherapy-induced myelosuppression; Kidney-tonifying; Essence-replenishing; Marrow-fortifying therapy

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1. Introduction

Malignant tumors constitute a major public health threat worldwide, with the evolving global disease burden attracting sustained attention from the international medical community [1]. According to GLOBOCAN data published by the WHO International Agency for Research on Cancer, China accounted for 25.5% of global new cancer cases and 26.5% of cancer-related deaths in 2022 [2].

As a primary treatment modality for malignancies, chemotherapy exerts its effects through broad-spectrum cytotoxic mechanisms. While effectively inhibiting the growth of malignant cells, it also causes non-selective damage to normal tissues with high metabolic activity. Among chemotherapy-related toxicities, myelosuppression stands out as a key dose-limiting factor due to its high incidence and complex clinical management. Typical manifestations include leukopenia, anemia, and thrombocytopenia [3]. Clinical studies report that the cumulative incidence of Grade ≥ 3 myelosuppression reaches 60.9% in small cell lung cancer patients treated with etoposide plus platinum-based regimens [4].

Current clinical management of Chemotherapy-induced myelosuppression (CIM) primarily follows NCCN guidelines, emphasizing growth factor support and blood component transfusion strategies. However, the time-sensitive limitations of pharmacological interventions and variations in patient tolerance remain significant therapeutic challenges. Consequently, exploring Traditional Chinese Medicine (TCM)-based prevention and treatment strategies for CIM holds considerable clinical importance.

Although bone marrow suppression following tumor chemotherapy is a concept derived from modern medicine, ancient TCM texts describe analogous conditions under the term "myelole" based on symptom location and clinical manifestations [5]. *Zhang's Medical Compendium* states, "The source of blood lies in the kidneys," elucidating the kidney's role as the foundation of innate constitution—storing essence, generating marrow, and transforming essence and marrow into blood. Thus, for CIM patients, a common TCM pathogenesis chain is: "Chemotherapy drug toxicity invades internally, depleting kidney essence → marrow sea becomes depleted → blood transformation lacks its source." Contemporary Western medical research on myelosuppression pathogenesis primarily focuses on impaired Hematopoietic Stem Cell (HSC) function and imbalances in the bone marrow microenvironment [6]. HSCs migrate directionally to injury sites via chemokine-mediated "homing" mechanisms, a process bearing substantial parallels with the TCM "kidney-essence-marrow-blood" pathogenesis chain. This paper explores the scientific rationale for treating CIM with kidney-tonifying, essence-replenishing, and marrow-nourishing therapy from this integrative perspective.

2. HSC homing impairment as a key mechanism in CIM

2.1. Definition of HSC homing

HSC homing refers to the biological process whereby endogenous human hematopoietic stem cells migrate from peripheral blood or the bone marrow microenvironment and colonize specific niches within the bone marrow during physiological homeostasis, tissue repair, or pathological injury. Its core mechanisms rely on chemokine signaling, adhesion molecule cascades, and precise regulation by the bone marrow microenvironment.

2.1.1. Chemokine guidance: the core role of the CXCL12-CXCR4 axis

The chemokine CXCL12, also known as stromal cell-derived factor-1 (SDF-1), secreted by bone marrow stromal cells (BMSCs), serves as the principal guiding signal for HSC homing. Binding of CXCL12 to the G protein-coupled receptor CXCR4 on HSC surfaces activates downstream signaling pathways, including *PI3K* and Rho

GTPases, driving cytoskeletal reorganization and polarization to facilitate directed migration [7]. A decreasing concentration gradient of CXCL12 from the bone marrow toward blood vessels establishes a chemotactic gradient that guides HSCs from the circulation into the bone marrow. Furthermore, CXCL12 enhances HSC adhesion to endothelial cells by increasing the affinity of chemokine receptors such as very late antigen-4 (VLA-4) on CXCR4 [8].

2.1.2. Cascade of adhesion molecules

HSC homing depends on the sequential activation of multiple adhesion molecules. The process initiates with the rolling phase, where HSCs reversibly adhere through L-selectin on their surface, binding to P-selectin and E-selectin on vascular endothelial cells [8]. This is followed by the stable adhesion phase, wherein integrins (e.g., VLA-4/ α4β1, αvβ3) bind to vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) on endothelial cell surfaces, enabling firm HSC adhesion to the vascular wall. The interaction between VLA-4 and VCAM-1 is particularly critical for HSC transendothelial migration [9]. Finally, during the transendothelial migration phase, integrin αvβ3 binds to fibronectin in the extracellular matrix, while matrix metalloproteinases degrade the basement membrane, collectively facilitating HSC penetration through the vascular wall into the bone marrow microenvironment [10].

2.1.3. Biomechanical regulation: corticotropin-releasing hormone (CRH)-THBS2-Integrin αvβ3 feedback loop

Emerging research highlights the importance of biomechanical properties such as HSC adhesion and deformability in homing. CRH binds to the CRHR1 receptor on HSC surfaces, activating a *RhoA*-dependent *YAP* nuclear translocation mechanism that upregulates the extracellular matrix protein THBS2. THBS2 binding to integrin αvβ3 promotes F-actin polymerization, further enhancing *YAP* nuclear translocation. This establishes a mechanical feedback loop that significantly improves HSC adhesion, migration, and deformability [11], offering a novel perspective on HSC mechanical remodeling within the bone marrow microenvironment.

2.1.4. Microenvironmental signal interactions

Various cells within the bone marrow microenvironment precisely regulate HSC homing through the secretion of specific factors. CXCL12-Abundant Reticular cells and arterial endothelial cells secrete CXCL12, multipotent growth factors, and insulin-like growth factor 1, providing crucial support for HSC migration and survival [12]. Osteoblasts maintain HSC pluripotency by secreting CXCL12 and Jagged-1 (a *Notch* signaling pathway ligand), while interacting with integrin αvβ3 on HSC surfaces to promote adhesion [12]. Additionally, endothelial cells not only express adhesion molecules like VCAM-1 and ICAM-1 but also secrete SDF-1, collectively guiding HSCs through the vascular wall into the bone marrow microenvironment [7].

2.1.5. Dynamic regulatory mechanisms

The HSC homing process is finely tuned by multiple dynamic mechanisms. Firstly, the local concentration of CXCL12 is tightly regulated: the G protein-coupled receptor GPR182 dynamically controls CXCL12 levels through endocytosis and degradation, thereby influencing HSC migration direction [13]. Concurrently, dipeptidyl peptidase IV cleaves CXCL12, reducing its activity and modulating HSC homing efficiency [14]. Secondly, adhesion molecule activity undergoes dynamic changes; for instance, proteases released by neutrophils (e.g., elastase) can cleave VCAM-1, disrupting HSC-endothelial adhesion and promoting HSC mobilization from bone

marrow into circulation [15]. Finally, synergistic interactions exist between mechanical and biochemical signals: the CRH-THBS2 pathway interfaces with the classical CXCL12-CXCR4 signaling axis, integrating mechanical stimuli with chemotactic signals to precisely coordinate HSC homing pathways [11].

2.2. HSC homing is closely linked to CIM

2.2.1. Chemotherapy-induced damage to the bone marrow microenvironment

Chemotherapeutic agents such as cytarabine and cyclophosphamide directly damage BMSCs and the extracellular matrix, disrupting vascular niche integrity and chemokine secretion, thereby impeding HSC homing. For example, cytarabine induces matrix cell apoptosis by inhibiting DNA synthesis, consequently reducing SDF-1 secretion [16]. The cyclophosphamide metabolite acrolein damages endothelial cells via oxidative stress, compromising niche integrity and impairing HSC migration and adhesion [17].

2.2.2. Abnormalities in chemokine signaling pathways

Chemotherapy significantly disrupts key signaling pathways essential for HSC homing. Firstly, the CXCL12/CXCR4 axis becomes dysregulated. CXCL12, secreted by BMSCs, binds to the CXCR4 receptor on HSCs, guiding their migration towards the bone marrow and maintaining their quiescent state. Chemotherapy disrupts this pathway through dual mechanisms: (1) Induction of stromal cell apoptosis, downregulating SDF-1 expression and weakening homing signals [18-19]; (2) Inhibition of CXCR4 function, potentially via direct suppression of its expression or interference with SDF-1 binding through phosphorylation [20]. For instance, cytarabine indirectly downregulates CXCR4 transcription by inducing DNA damage, thereby impairing HSC migration [16].

Secondly, adhesion molecule dysfunction occurs. HSC homing relies on the interaction between VLA-4 (integrin α4β1) on HSCs' surface and VCAM-1 in the bone marrow microenvironment. Chemotherapy downregulates the expression of VLA-4 on HSCs' surface and/or microenvironmental VCAM-1, disrupting HSC-stromal adhesion and causing HSC retention in peripheral blood [18].

2.2.3. Disruption of inflammatory responses

Chemotherapy-induced inflammatory responses release abundant proinflammatory cytokines (e.g., TNF-α, IL-6), which significantly interfere with HSC homing through multiple pathways. Inflammatory factors suppress SDF-1 secretion: TNF-α and IL-6 inhibit SDF-1 transcription in BMSCs by activating the *NF-κB* signaling pathway, thereby reducing its secretion and attenuating the key chemotactic homing signal [21]. Simultaneously, the inflammatory environment exerts complex effects on HSC survival and proliferation: acute inflammatory factors transiently activate HSC proliferation, whereas chronic inflammation persistently activates apoptotic pathways, ultimately reducing HSC numbers [22]. Furthermore, inflammatory mediators disrupt adhesion molecule function by downregulating VLA-4 expression on HSCs and VCAM-1 expression in the bone marrow microenvironment, further impairing HSC adhesion and migratory capacity [23].

2.2.4. Impairment of intrinsic HSC function

Chemotherapy drugs not only disrupt the bone marrow microenvironment but also directly impair intrinsic HSC functions. Firstly, chemotherapy induces HSC apoptosis and senescence. Chemotherapeutic agents activate the *p53* signaling pathway via DNA damage, triggering HSC apoptosis. For example, cytarabine inhibits DNA polymerase, leading to Caspase-3-dependent HSC apoptosis [24]. Additionally, chemotherapy induces oxidative stress, propelling

HSCs into a senescent state characterized by cell cycle arrest and functional decline. Concurrently, chemotherapy-induced autophagy dysfunction exacerbates HSC impairment: chemotherapeutic drugs inhibit Beclin1-dependent autophagy pathways, causing mitochondrial damage and increased HSC apoptosis. Moderate autophagy is crucial for clearing damaged organelles, thereby sustaining HSC survival and homing capacity [22].

2.2.5. Pathways of HSC homing impairment leading to bone marrow suppression

HSC homing impairment ultimately leads to bone marrow hematopoietic failure through a triple pathological network of "cell behavior disorder-molecular signaling dysregulation-microenvironment vicious cycle," specifically manifested as:

(1) Cascade of HSC Retention and Apoptosis

Homing impairment causes HSCs to persist in peripheral blood or the spleen, triggering a chain reaction. For instance, the cyclophosphamide metabolite acrolein downregulates VLA-4 expression via oxidative stress, disrupting HSCs' adhesion to VCAM-1 and impairing rolling and anchoring capacity [25]. Chemotherapy-induced iron overload and reactive oxygen species (ROS) accumulation inhibit the mitochondrial respiratory chain, reducing membrane potential, decreasing ATP production, and shifting metabolism toward inefficient glycolysis, thereby triggering caspase-3-dependent apoptosis [26]. Furthermore, chemotherapy induces HSC senescence via the p38 MAPK-*p16INK4a* pathway, and secreted inflammatory cytokines like IL-6 further suppress stromal repair [27].

(2) Molecular Networks Underlying Delayed Hematopoietic Reconstitution

Insufficient bone marrow HSCs lead to defective hematopoietic progenitor cells. Downregulation of the *Notch* ligand by stromal cells reduces Intracellular Notch nuclear translocation and Hes1 transcription in HSCs, causing premature differentiation and depletion of the stem cell pool [28]. Retained HSCs may undergo abnormal differentiation in ectopic microenvironments like the spleen, associated with dysregulated activation of the CXCL12/CXCR4 axis [29]. Chemotherapy also disrupts megakaryocyte-endothelial cell contacts, reducing thrombopoietin secretion; clinical studies confirm that thrombopoietin receptor agonists (e.g., eltrombopag) shorten platelet recovery time by activating the JAK2/STAT5 pathway [30].

(3) Vicious Cycle of Impaired Microenvironment Repair

Impaired homing suppresses microenvironment regeneration, creating a "damage-failed repair" positive feedback loop. Chemotherapy induces stromal cell senescence, increasing secretion of small extracellular vesicles carrying resistance proteins like ABCB4, which inhibit HSC homing and promote tumor resistance [31]. Increased numbers of bone marrow adipocytes secrete leptin or adiponectin, inhibiting HSC migration and proliferation; PPAR-γ agonists promote adipogenesis, further delaying reconstruction [32]. Chemotherapy disrupts sinusoidal endothelial integrity, reducing Ang-1/VEGF secretion; studies indicate that CRH activates the *RhoA*/*YAP* pathway to promote HSC secretion of THBS2, enhancing endothelial adhesion and improving vascular niche repair [25].

3. "Deficiency of kidney essence and drying of the sea of marrow" is the primary pathomechanism of CIM

3.1. Physiological relationship between the kidney and the bone marrow

The kidney, considered the foundation of innate constitution, governs storage and conservation. Its essence serves as the source for life's transformation and nurturing, embodying the capacity to refine essence into blood. As stated in *Suwen*: Great Treatise on Yin-Yang Correspondences and Manifestations, "The kidney generates bone marrow" [33], clearly indicating that kidney essence is the fundamental source for the transformation and generation

of the marrow sea. Kidney essence is the shared origin of both marrow and blood. *Ling Shu*: Decision on Qi notes, "The middle burner receives qi and extracts its essence, transforming it into red substance; this is called blood" [34]. However, this process fundamentally relies on the warming action of kidney yang and the nourishing power of kidney essence. The innate essence, inherited from parents, is stored within the kidneys; the acquired essence, derived from food and water, is transported by the spleen and also stored in the kidneys. These two essences intermingle and transform, descending into the bones to establish the mechanism of "essence transforming into marrow, marrow generating blood." This aligns with the principle in *Essentials of Integrating Chinese and Western Medical Classics*: "When essence is abundant, marrow is plentiful; when essence is deficient, marrow is depleted" [35], clearly demonstrating that the prosperity or decline of kidney essence is the pivotal mechanism governing bone marrow abundance or deficiency. The function of the kidney essence transforming into marrow and generating blood can also be understood through the theory of "essence and blood sharing the same origin." Bone marrow resides within bone cavities and is nourished and enriched by kidney essence.

3.2. Pathogenesis of medicinal toxins depleting kidney essence

Chemotherapy drugs fall under the category of "medicinal toxins" in TCM theory, characterized by a violent nature, heavy taste, and turbid substance. While such toxic substances possess potent efficacy in overcoming pathological obstacles, their indiscriminate action readily damages vital Qi. *Treatise on the Origins and Manifestations of Various Diseases*: Symptoms of Improper Medication Use states: "Medicines have both synergistic and antagonistic effects; if used improperly, they inevitably lead to disaster" [36]. This theory reveals that using toxic medicines to attack pathogens is a double-edged sword: excessive use may eliminate pathogens but will deplete vital qi. Chemotherapy toxicity first invades the Middle Jiao, impairing the pivotal functions of the spleen and stomach. It then descends along the Triple Burner pathways to the Shao Yin, ultimately depleting kidney essence. This progression aligns with the principle in *Jingyue Quanshu*: Deficiency and Debility that "injuries to the five Zang organs, when exhausted, inevitably reach the kidneys" [37], revealing the fundamental truth that organ deficiency ultimately stems from kidney essence depletion.

The mechanism by which drug toxicity injures the kidneys centers on the depletion of kidney yin, which impairs the storage of kidney essence. Drug toxins possess a violent nature: they exhibit fiery properties that readily scorch true yin and possess a destructive force that easily depletes vital qi. *Suwen*: The Great Treatise on the Five Constant Policies advises: "When treating disease with potent toxins, remove six parts out of ten... Do not overdo it, lest you injure the healthy Qi" [33]. Overuse of chemotherapy drugs is akin to removing the fuel from beneath the cauldron, damaging both yin and yang within the kidneys. The failure to contain the ministerial fire leads to depletion of kidney yin. Furthermore, as Ye Tianshi stated: "Initially, disease resides in the meridians; prolonged disease enters the collaterals" [38]. The cumulative toxicity of chemotherapy over time damages the kidney collaterals and impairs their storage and concealment functions.

The proliferation of secondary syndromes stems from kidney essence deficiency, triggering a chain reaction among the Zang-fu organs. Kidney essence, as the root of life, houses true Yin and true Yang. Chemotherapy damages kidney essence, disrupting the mutual support between Yin and Yang. When yin damage affects yang, symptoms include aversion to cold, cold limbs, and frequent nocturnal urination. When yang damage affects yin, symptoms manifest as restless insomnia, tidal fevers, and night sweats. Furthermore, depletion of essence and marrow leads to soreness in the lower back and knees, loose teeth, and hair loss. Failure of essence to transform into Qi manifests as mental fatigue, weakness, shortness of breath, and reluctance to speak. These diverse

symptoms all originate from kidney essence damage, causing Yin-Yang imbalance.

3.3. Pathological process of kidney essence deficiency leading to bone marrow exhaustion

Ling Shu: Treatise on the Sea states: "When the marrow sea is abundant, one becomes light and vigorous, possessing great strength" [34]. Although this refers specifically to cerebral marrow, bone marrow shares the same origin and is similarly derived from kidney essence. Chemotherapy drugs deplete the true yin within the kidneys, damaging both the innate essence and hindering the return of the acquired essence to its storehouse, thereby obstructing the transformation of essence into marrow. Clinically, patients often exhibit dry hair, loose teeth, and dull nails, indicating not merely blood deficiency but fundamentally reflecting essence depletion failing to generate marrow, resulting in insufficient marrow to nourish the body. Symptoms such as nighttime fever subsiding by morning and bone-steaming night sweats indicate essence depletion, marrow reduction, and the manifestation of floating deficient yang.

The toxic nature of these drugs, once they enter the collaterals, is violent and aggressive. Initially, they predominantly deplete qi and injure yin. Over time, they penetrate deeper into the Lower Jiao, plundering the kidney's true yin and severely damaging the innate essence. Deficiency of essence leads to a depleted source for marrow transformation, an empty marrow sea, and a failure of the marrow collaterals to receive nourishment from the essence. Kidney essence deficiency manifests in several ways: Firstly, the marrow channels become depleted, akin to a dried-up riverbed where water cannot flow, preventing the transport of vital substances through the marrow pathways to nourish bone marrow and generate new blood. Secondly, the mechanisms of transformation and production are obstructed. Kidney essence is the foundation for marrow generation; its depletion weakens the capacity to produce marrow, slows new marrow generation, and impairs the source for hematopoietic reconstruction. Thirdly, internal disturbance by deficient fire consumes vital substances, leading to concurrent essence and marrow depletion. Fourthly, the essence gate becomes unstable, disrupting opening and closing mechanisms, causing leakage of vital substances and ultimately resulting in the insidious depletion of marrow essence.

In summary, medicinal toxins deplete kidney essence, causing essence deficiency and marrow depletion alongside impaired storage functions. This core pathological outcome aligns closely with modern medical findings of bone marrow microenvironment disruption, signaling pathway dysfunction, and HSC functional failure—all manifestations of HSC homing disorders.

4. HSC homing impairment: the modern biological essence of "kidney essence deficiency and drying of the marrow sea"

4.1. Deep coupling between the kidney essence-to-marrow conversion mechanism and the HSC homing microenvironment

The classical assertion in *Suwen*: Yin-Yang Correspondence and Phenomenon Theory that "the kidney generates bone marrow" reveals scientific implications transcending its era in the field of hematopoietic regulation. When delving into the modern implications, we find that kidney essence, as the primordial source of life, nourishes bone marrow through a physiological process that fundamentally achieves precise regulation of HSCs by constructing the bone marrow microenvironment. Research by Tang Chao revealed that normal BMSCs secrete the chemokine SDF-1, forming molecular pathways that guide HSC homing. This aligns with the principle in Essentials of Medical Classics Integrating Chinese and Western Medicine: "When essence is abundant, marrow is plentiful."

Robust kidney essence ensures the functional integrity of the bone marrow microenvironment, comprising osteoblasts, endothelial cells, and others. The SDF-1/CXCR4 signaling axis, as a key chemotactic guidance system, effectively mediates the directed migration of HSCs toward bone marrow vascular niches and maintains their quiescent state [16]. Chemotherapy drugs damage stromal cells, significantly reducing SDF-1 secretion and disrupting the chemotactic gradient essential for HSC homing. This molecular-level alteration concretely embodies the TCM theory that "deficiency of essence leads to depletion of marrow." The TCM theory of "essence and blood sharing the same origin" also finds a new interpretation within the adhesion molecule system. The VLA-4/VCAM-1 interaction, essential for HSC homing, can be viewed as the biological vehicle through which kidney essence transforms into Qi and blood, sustaining normal intercellular communication and positioning. Chemotherapy downregulates VLA-4 and VCAM-1 expression, causing failure of HSC adhesion to stromal cells, resulting in HSC retention in peripheral blood and failure to return to their niche. This pathological process resonates with the theory in *Ling Shu*: Jue Qi that "the Middle Jiao requires kidney essence to nourish the transformation of fluids into blood" [34]: abundant kidney essence ensures the integrity of the adhesion molecule network, guaranteeing effective HSC homing; deficient kidney essence leads to inadequate marrow nourishment, causing disruption in adhesion molecule expression or function.

4.2. Cascading damage to the homing signal network via pathways of drug-induced kidney injury

The rampant toxicity of drugs, with its fierce nature akin to a blazing fire penetrating the Lower Jiao, not only scorches kidney yin but also directly depletes the essence within the kidneys. Pharmaceutical toxins directly damage HSCs' genetic material, activating *p53*-dependent apoptosis and senescence cascades, causing stem cell pool depletion [24], corresponding to the depletion of true yin and deficiency of essence and marrow. Simultaneously, the inflammatory cytokine storm persistently suppresses the secretion of the key homing factor SDF-1 by BMSCs via the *NF-κB* signaling axis, while disrupting the adhesion molecule network that anchors HSCs within the bone marrow niche [21,23]. This manifests as deficient fire disturbing the essence of the bone marrow.

The profound depletion of kidney essence and the emptying of the marrow sea represent the inevitable culmination of pathological progression. At the modern biological level, this manifests as a vicious cycle of failed HSC homing. HSCs trapped in peripheral blood, deprived of the nourishment and protection of the bone marrow microenvironment, become exposed to metabolic toxins such as iron overload and ROS accumulation, accelerating their apoptotic process [26]. The dwindling reserve of residual HSCs within the bone marrow leads to downregulation of critical signaling pathways like *Notch*, forcing them into abnormal differentiation to meet urgent hematopoietic demands, further depleting the stem cell pool [28]. Compounding this, the damaged bone marrow microenvironment becomes infiltrated by adipose tissue, which abnormally secretes factors like leptin. Rather than supporting repair, these factors become pathological signals inhibiting hematopoietic reconstruction [32]. These pathological mechanisms result in the failure of kidney essence to store and protect, profoundly suppressing and extinguishing the fundamental function of bone marrow hematopoiesis—a state recognized in TCM as "essence gate not secure, biochemical mechanisms suppressed."

4.3. Pathological resonance between essence deficiency and marrow exhaustion with HSC functional failure

Extreme deficiency of kidney essence ultimately diminishes HSC survival capacity. Cytarabine activates the

p53 pathway, triggering caspase-3-dependent apoptosis, corresponding to the depletion of true yin followed by false fire scorching the marrow, leading to a sharp reduction in the number of HSCs. Chemotherapy-induced iron overload and ROS accumulation cause collapse of the HSC mitochondrial membrane potential, shifting energy metabolism from efficient oxidative phosphorylation to inefficient glycolysis [23,26]. This phenomenon aligns with the traditional understanding of "insufficient transformation of kidney essence into Qi," diminished kidney qi fails to provide adequate warmth and propulsion, leading to functional decline of HSCs due to energy depletion. The activation of HSC senescence programs represents the ultimate manifestation of marrow depletion. The p38 MAPK-*p16INK4a* pathway-driven cell cycle arrest resembles marrow duct obstruction, causing HSCs to lose their self-renewal capacity. Furthermore, factors secreted by senescent cells, such as IL-6, further inhibit matrix repair [27]. This phenomenon resonates with Wang Qishi's admonition in *Li Xu Yuan Jian*: "When essence and blood cannot be rapidly replenished, the primordial energy must be urgently preserved." The abrupt depletion of kidney essence severs the root of marrow generation, leaving HSC homing and regenerative functions like water without a source. Ultimately, the marrow channels become depleted, leading to terminal decline.

5. Kidney-tonifying method to restore essence and enrich marrow for CIM treatment

The core pathological mechanism of CIM is closely linked to impaired HSC homing. TCM's theory of kidney essence deficiency offers a unique perspective to elucidate this pathogenesis. The kidneys govern bones and produce marrow; kidney essence serves as the material foundation for marrow generation. Chemotherapy drugs, as agents that attack pathogens, readily damage kidney essence, leading to depletion of the marrow sea and a lack of source for Qi and blood production. Modern research indicates that HSC homing relies on precise regulation of cytokine networks (e.g., CXCL12/CXCR4, SCF/*c-Kit* pathways) and stromal cell function within the bone marrow microenvironment [7]. The method of tonifying the kidneys, replenishing essence, and enriching marrow can promote HSC homing through multi-target regulation, thereby improving bone marrow suppression.

5.1. Pathological correlation between kidney essence deficiency and HSC homing impairment

In TCM theory, the physiological process of "the kidney stores essence, essence generates marrow, and marrow transforms into blood" exhibits functional homology with HSC proliferation, differentiation, and homing within the bone marrow microenvironment. As stated in *Ling Shu*: Decision on Qi, "Essence is the foundation of the body." Sufficient kidney essence nourishes the bone marrow microenvironment, ensuring normal HSC homing. Kidney essence deficiency disrupts BMSC function, leading to insufficient chemokine secretion and abnormal adhesion molecule expression, thereby hindering HSC-directed migration to bone marrow niches. Modern research reveals that chemotherapeutic agents like cyclophosphamide significantly downregulate CXCL12 expression in BMSCs and reduce the activity of the HSC homing receptor CXCR4, causing abnormal circulation of HSCs in peripheral blood and preventing their homing [17]. The method of "tonifying kidney essence and replenishing marrow" centers on "nourishing kidney essence and enriching the marrow sea." By replenishing kidney essence, this approach improves the secretory function of stromal cells and restores normal regulation of signaling pathways such as CXCL12/CXCR4, thereby creating a suitable microenvironment for HSC homing.

5.2. Molecular mechanisms of kidney-essence-replenishing and marrow-enhancing methods in promoting HSC homing

5.2.1. Chemokine system regulation: Activation of the SDF-1/CXCR4 axis

Kidney-tonifying formulas (e.g., Jisheng Shenqi Tang, Shenfu Tang) significantly upregulate the expression of SDF-1 and its receptor CXCR4 in the bone marrow microenvironment, forming a chemotactic gradient that guides the directed migration of HSCs. Animal studies demonstrate that after Jisheng Shenqi Tang intervention, SDF-1 and CXCR4 protein expression significantly increase in the liver tissue of cirrhotic rats. Concurrently, levels of hematopoietic factors such as EPO and G-CSF in peripheral blood are upregulated, promoting BMSC migration and homing. This process relies on activation of the *PI3K*/*Akt* signaling pathway, which enhances HSC migratory capacity by regulating actin reorganization and cytoskeletal remodeling [39]. Furthermore, SDF-1 binding to CXCR4 activates the *RhoA*/*YAP* pathway, promoting the expression of extracellular matrix proteins and further enhancing HSC adhesion and mechanical remodeling capabilities [25].

5.2.2. Enhanced adhesion molecule expression: CD44/CD62L-mediated cell adhesion

The kidney-tonifying method enhances HSC-myeloid endothelial cell interactions by modulating surface adhesion molecule expression. For instance, Shenshutang significantly increased the surface expression of CD44 and CD62L on HSCs, molecules that mediate HSC adhesion to and transendothelial migration through BMSCs, respectively. Flow cytometry analysis revealed that after Shenfu Tang intervention, the proportion of the Sca-1+ cells in the bone marrow of transplanted mice significantly increased, with CD44 and CD62L expression rates elevated by approximately 20%–30% compared to the control group [40].

5.2.3. Signal pathway activation: Synergistic effects of Wnt/β-Catenin and PI3K/Akt

Traditional Chinese kidney-tonifying herbs regulate HSC proliferation, migration, and differentiation by activating signaling pathways such as *Wnt*/β-catenin and *PI3K*/*Akt*. Zouguiwan-containing serum significantly upregulates *Wnt* and *Oct4* gene expression while suppressing tumor suppressor genes like *P16INK4a*, thereby maintaining stem cell self-renewal capacity [41]. Icariin promotes osteoblast differentiation of BMSCs by activating the *BMP-2*/*Smad* pathway while enhancing their migratory capacity [42]. Osteoblasts, as key components of the bone marrow microenvironment, when increased in number and function, help maintain and improve niche structures and signaling molecules that support HSC homing.

5.2.4. Epigenetic regulation: Interaction between miRNA and Notch pathway

Researchers studying the proprietary formula "Kidney-Tonifying, Blood-Activating, Nutrient-Regulating, Phlegm-Resolving Decoction" found it promotes BMSC homing and differentiation by downregulating *miRNA-139-5p* expression, thereby releasing its inhibition on the *Notch* pathway. Animal studies demonstrated that after intervention with this formula, *Notch* pathway activity in the bone marrow of asthma model mice significantly increased, with BMSC migration capacity improving by approximately 40% [43]. Additionally, Zuoguiwan can delay HSC senescence by regulating DNA methylation and histone modifications to maintain the expression of pluripotency-related genes [41].

6. Conclusion

CIM represents a common challenge in tumor therapy, with its core mechanism in modern medicine closely linked

to impaired HSC homing. Building upon the TCM pathogenesis theory of "kidney essence deficiency leading to depletion of the marrow sea," this paper substantiates the scientific rationale for treating CIM with the method of tonifying the kidney, replenishing essence, and nourishing marrow. This therapeutic approach cultivates innate essence and nourishes the marrow as the source of transformation. At the modern biological level, it manifests as multi-target regulation of the HSC homing microenvironment: upregulating SDF-1/CXCR4 chemotactic axis expression, enhancing the function of adhesion molecules like VLA-4/VCAM-1, activating key signaling pathways including *PI3K*/*Akt* and *Wnt*/β-catenin, improving bone marrow stromal function, and mitigating oxidative stress and inflammatory damage. These actions synergistically promote directed migration, anchoring, and homing of HSCs, thereby accelerating hematopoietic reconstitution. This study integrates the TCM theoretical chain of "kidney-essence-marrow-blood" with the modern mechanisms of HSC homing. It not only deepens the understanding of the action mechanisms of the kidney-tonifying, essence-nourishing, and marrow-strengthening method but also provides new theoretical foundations and research approaches for the integrated Chinese and Western medicine prevention and treatment of CIM.

Currently, this method is widely applied in treating CIM induced by cancers such as lung cancer, breast cancer, and lymphoma, with commonly used formulas including Liuwei Dihuang Wan, Guilu Erxian Tang, Zuogui Wan, and Yougui Wan. However, existing research still faces several critical issues: Firstly, studies on HSC homing mechanisms largely remain confined to animal experiments, with limited clinical monitoring data on HSC dynamic changes. Secondly, the complex composition of TCM formulations makes the synergistic interactions between individual compounds and compound combinations unclear. Finally, efficacy evaluation standards remain inconsistent, particularly lacking reliable quantitative indicators for assessing HSC homing efficiency.

Looking ahead, future research should integrate advanced technologies like single-cell sequencing and in vivo imaging to explore how kidney-tonifying herbs precisely regulate the HSC homing microenvironment. Concurrently, multi-center, large-scale clinical studies should be promoted to provide more robust evidence for standardizing this therapeutic approach. From the traditional theory of "the kidneys govern bone and produce marrow" to the modern biological mechanism of HSC homing, the method of tonifying the kidneys, replenishing essence, and nourishing marrow not only validates the foresight of TCM theory but also pioneers a distinctive pathway for supportive treatment in malignant tumors.

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Disclosure statement

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