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INTEGRATIVE REVIEW ON BONE MARROW CANCER: RISK PROFILE, HERBAL INTERVENTIONS, AND ALTERATIONS IN RBC FUNCTION: A REVIEW

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ABSTRACT

Acute myeloid leukemia (AML) and multiple myeloma (MM) harm the bone marrow and lower normal blood cell production, which leads to anemia. Chemotherapy and targeted treatments kill cancer cells but also increase oxidative stress and reduce red blood cell (RBC) formation. Herbal compounds like curcumin, resveratrol, quercetin, EGCG, and withanolides show strong anti-leukemia and anti-myeloma effects by influencing NF-κB, STAT3, and PI3K/Akt pathways. Extracts from plants such as green tea, Withania somnifera, and Tinospora cordifolia help support RBC production and protect bone marrow cells. Combining herbal polyphenols with drugs like bortezomib improves treatment outcomes and lessens side effects. Plant-based compounds may also boost immunotherapy with monoclonal antibodies such as elotuzumab and daratumumab. These herbs activate pathways like Nrf2/HO-1 and JAK2/STAT5 to enhance antioxidant defenses and increase erythropoiesis. Research indicates that mixing herbal medicine with standard treatments may improve patient survival and tolerance while aiding bone marrow recovery.

Key Word:
Acute myeloid leukemia and multiple myeloma harm bone marrow, lower red blood cell production, and raise oxidative stress, leading to anemia [1][2]. Tumor growth is driven by changes in the microenvironment and the activation of NF-κB and STAT3/PI3K/Akt pathways [3][5][6]. Herbal medicines that are rich in bioactive compounds can block these pathways, cause tumor cell death, and boost antioxidant responses [7]. They also enhance immunity and red blood cell production through Nrf2/HO-1 and JAK2/STAT5 signaling [8][9]. When used alongside standard treatments, these herbs help lessen side effects related to therapy [10].

3. INTRODUCTION

Acute myeloid leukemia (AML) and multiple myeloma (MM) are the two main types of bone Acute myeloid leukemia (AML) and multiple myeloma (MM) are two examples of bone marrow cancers, which are aggressive hematologic malignancies characterized by the unchecked growth of immature or plasma cells in the bone marrow [1–3]. Anemia, immunosuppression, and thrombocytopenia are caused by these disorders' disruption of normal hematopoiesis, which significantly lowers patient survival and quality of life. Relapse and chemoresistance continue to be significant obstacles despite improvements in immunotherapy, targeted therapy, and chemotherapy, highlighting the need for more potent and less harmful therapeutic approaches [1, 2, 11].Despite their effectiveness, traditional chemotherapeutic medications such as melphalan, cytarabine, and bortezomib frequently result in erythropoietic dysfunction and marrow suppression [1, 9, 10]. Although hematologic toxicity and resistance have not been eradicated, the development of targeted agents and monoclonal antibodies, such as daratumumab and elotuzumab, has improved results [7, 8, 11, 13]. Due to their multi-targeted actions and reduced toxicity, herbal and natural compounds have become the focus of more research [4–8]. By altering oncogenic pathways (NF-κB, STAT3, PI3K/Akt), phytochemicals such as curcumin, resveratrol, quercetin, and epigallocatechin gallate (EGCG) prevent the growth of cancerous cells while preserving healthy erythroid cells and improving chemosensitivity [4–6, 8]. By activating the JAK2/STAT5, Nrf2/HO-1, and EPO pathways, herbal remedies like Withania somnifera, Tinospora cordifolia, and Camellia sinensis also encourage erythropoiesis [4, 6, 10, 14]. These phytocompounds exhibit enhanced red blood cell regeneration, decreased toxicity, and synergistic anticancer effects when used in conjunction with traditional medications [1, 5, 9, 18]. Herbal adjuvants have been shown in clinical trials to increase survival, reduce oxidative damage, and improve quality of life in patients with AML and MM [15–19]. Therefore, combining herbal remedies with contemporary cancer therapies presents a promising two-pronged strategy that targets tumor suppression while reestablishing hematopoietic balance and red blood cell function [1–20].

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4. PATHOPHYSIOLOGY OF BONE MARROW CANCER AND RBC DYSREGULATION

Bone marrow cancers like AML and MM cause major issues in red blood cell production due to low oxygen levels, oxidative stress, inflammatory cytokines, and the effects of chemotherapy. The low-oxygen environment in the bone marrow stabilizes HIF-1α. This stability promotes blood vessel growth, changes in metabolism, and makes treatment less effective. Oxidative stress and problems with mitochondria increase reactive oxygen species (ROS), which damage red blood cell precursors and lower red blood cell production. As the disease progresses, the suppression of erythroid colonies (BFU-E and CFU-E) becomes worse because of inhibitory cytokines like TNF-α and TGF-β. Myeloma-derived miRNAs, such as miR-21 and miR-29b, disrupt essential transcription factors, including GATA1 and KLF1, further hindering red blood cell production.

Chemotherapy drugs like cytarabine, anthracyclines, melphalan, and bortezomib increase bone marrow toxicity by causing mitochondrial damage, oxidative DNA harm, endoplasmic reticulum stress, and the death of progenitor cells. This leads to malignant anemia, which is marked by a poor reticulocyte response, even when erythropoietin (EPO) levels are normal or high. Kidney problems in MM also reduce EPO production, while inflammatory substances like IL-6 and TNF-α raise hepcidin levels and lead to iron sequestration, causing functional iron deficiency.

Oxidative stress speeds up damage to erythroid membranes and cell aging, worsened by a failure in the Nrf2/HO-1 antioxidant defense system. Phytochemicals like curcumin, quercetin, resveratrol, and withanolides help counteract these effects. They target pathways such as NF-κB, STAT3, and SIRT1/Nrf2, showing properties that promote red blood cell production and reduce inflammation. Withania somnifera has demonstrated the ability to restore bone marrow structure, increase red blood cell counts, and raise serum EPO levels.Modern methods based on omics are shedding light on how herbs and genes interact, making it possible to create better formulations with fewer side effects. However, large-scale randomized controlled trials, regulatory alignment, good manufacturing practices, and thorough toxicity assessments are crucial for clinical approval. In summary, standardized herbal therapies show promise as effective, low-toxicity, and cost-efficient options for restoring red blood cell production in patients with bone marrow cancers.

5. CONVENTIONAL THERAPIES AND LIMITATIONS

Conventional treatments for AML and MM include chemotherapy, targeted therapy, immunotherapy, corticosteroids, and supportive care. These aim to eliminate cancer cells and restore blood cell production. However, there are still significant challenges, such as myelotoxicity, treatment resistance, relapses, and suppression of red blood cell production. Chemotherapy regimens like cytarabine, anthracyclines, and alkylating agents, combined with corticosteroids, remain standard for AML and are crucial for MM treatment. Because these treatments act broadly, they can severely suppress bone marrow, lead to low blood counts, and cause cell death through p53-related mechanisms and oxidative stress. Prolonged use may result in reduced recovery of blood production, scarring, and treatment-related myelodysplasia. Drug resistance can arise from various mechanisms, including overexpression of P-glycoprotein and activation of ABC transporters, which lower the effectiveness of treatment.

Targeted therapies, such as FLT3 and IDH inhibitors, proteasome inhibitors, and IMiDs, block cancer pathways or influence blood vessel growth and immune responses, but their effectiveness can depend on specific mutations. Secondary resistance may develop due to reactivation of pathways and the emergence of compensatory mutations. FLT3 inhibitors may encounter resistance through the activation of AXL and KIT. Their long-term use can cause nerve damage, heart toxicity, and suppression of red blood cell production. Immunotherapies like CAR-T cells and monoclonal antibodies (daratumumab, elotuzumab) significantly improve outcomes, but they can lead to immune-related blood problems, cytokine release syndrome, antigen escape, and issues with accessibility due to high costs and infrastructure needs. Corticosteroids can improve the effectiveness of chemotherapy, yet they may lead to long-term immune suppression and bone marrow issues. Supportive agents such as EPO analogs and G-CSF can reduce low blood cell counts but do not tackle the underlying problems.Dormant stem-like cells can evade treatment through adhesion-mediated resistance involving pathways like BCL-2, MCL-1, and CXCR4/SDF-1, contributing to relapses and bone marrow failure over time. These challenges underline the potential of integrating plant-based treatments. Compounds like curcumin, resveratrol, quercetin, and withanolides activate pathways such as Nrf2/HO-1 and EPO/JAK2/STAT5. They help protect progenitor cells, improve the response to chemotherapy, and lessen multidrug resistance effects. Combining standard therapies with herbal approaches could bolster bone marrow resilience and lower blood-related toxicity while maintaining cancer-fighting effectiveness..

6. HERBAL DRUGS WITH ANTI-BONE MARROW CANCER PROPERTIES

The identification of novel anticancer drugs that exhibit selective cytotoxicity against malignant hematopoietic cells while maintaining normal bone marrow function has been greatly aided by the renewed interest in natural and plant-derived chemicals [1-3]. With their anti-proliferative, pro-apoptotic, antioxidant, and erythropoiesis-regulating properties, herbal medicines have the potential to be useful adjuncts or substitutes for traditional therapies in the treatment of acute myeloid leukemia (AML) and multiple myeloma (MM),

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according to an increasing amount of research [3–5]. These medicines provide a multi-targeted therapy approach against marrow malignancies by modulating important oncogenic and oxidative stress-related pathways like NF-κB, STAT3, PI3K/Akt/mTOR, and Nrf2/HO-1 [4–7].

6.1 Curcumin (Curcuma longa L.)

Fig. no. 6.1 curcumin [21]

Curcumin from Curcuma longa blocks NF-κB, STAT3, and AP-1, which decreases inflammation and cancer growth in AML and MM [5, 6]. It causes cell death by lowering Bcl-2 and activating caspase-3 [4]. Curcumin increases sensitivity to lenalidomide and bortezomib, reducing marrow toxicity [5, 7]. It also protects erythroid cells by activating Nrf2/HO-1, helping to restore erythropoiesis [6, 8].

6.2 Resveratrol (Vitis vinifera L.)

Fig. no. 6.2 vitis vinifera L. [22]

A naturally occurring stilbene present in red wine and fruits, resveratrol exhibits broad-spectrum anticancer activity with special effectiveness in hematological malignancies [6, 9]. It causes cell cycle arrest at the G1/S phase, suppresses PI3K/Akt and mTOR signaling, and encourages apoptosis in AML and MM cells [8–10]. Resveratrol improves mitochondrial function, lowers oxidative damage, and increases antioxidant enzymes including catalase and superoxide dismutase through SIRT1 activation [10]. Resveratrol increases sensitivity to chemotherapeutic drugs by downregulating Bcl-2 and Mcl-1 in leukemic cell lines [9]. Furthermore, it increases EPO receptor sensitivity and JAK2/STAT5 activation, which modifies erythropoietic signaling and aids in RBC recovery during myelosuppression [10, 11].

6.3. Quercetin (Allium cepa L., Ocimum sanctum L.)

Fig. no. 6.3 Ocimum sanctum L [23]

Strong anti-oxidant and anti-proliferative qualities of quercetin, a flavonoid found in many fruits and medicinal herbs, contribute to its potential as an anticancer agent [9, 12]. Quercetin suppresses the NF-κB and AKT pathways while inducing apoptosis in AML through caspase-9 activation and PARP cleavage [10, 13]. It has been demonstrated to decrease hypoxia-driven myeloma cell survival by downregulating HIF-1α and HSP70 [12]. Quercetin increases medication sensitivity and reduces chemoresistance when combined with cytarabine and doxorubicin [9, 14]. Furthermore, quercetin prevents erythrocyte hemolysis, scavenges reactive oxygen species (ROS), and maintains membrane integrity under chemotherapeutic stress to produce hematoprotective effects [11, 13].

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6.4. Withania somnifera (Ashwagandha)

Fig. no 6.4 Ashwagandha [24]

Withanolides, which have exceptional anti-leukemic and immunomodulatory qualities, are abundant in the adaptogenic herb Withania somnifera (Indian ginseng) [7, 10, 15]. Its main active component, withaferin A, causes AML and MM cells to undergo apoptosis by accumulating ROS, activating JNK, and blocking NF-κB signaling [15]. Additionally, it destabilizes oncogenic client proteins like BCR-ABL and Akt by upsetting the Hsp90 chaperone complex [14, 15]. Significantly, by promoting erythropoietin release and improving erythroid progenitor differentiation, W. somnifera aids in hematopoietic recovery [10, 15, 16]. Ashwagandha extracts have been shown in preclinical animals to increase hemoglobin levels and reduce cytopenias brought on by chemotherapy, confirming its dual function as an anticancer and marrow-protective drug [15, 16].

6.5. Tinospora cordifolia (Guduchi)

Fig. no 6.5 Guduchi [25]

The immunostimulant and anti-leukemic properties of Tinospora cordifolia are well known. By stopping cancerous cells in the G2/M phase and blocking DNA topoisomerase II, the alkaloids and diterpenoid lactones from this plant have cytostatic effects [10, 11, 17]. T. cordifolia extracts have been shown to improve immune surveillance by reducing leukemic blast growth and modifying the Th1/Th2 cytokine balance [17]. Additionally, it protects bone marrow from oxidative damage caused by chemotherapy by increasing antioxidant enzyme activity and increasing erythropoiesis through activation of the EPO/STAT5 axis [11, 17, 18].

6.6. Berberine (Berberis aristata DC).

Fig. no. 6.6 Berberis aristata DC [26]

In hematologic malignancies, berberine, an isoquinoline alkaloid extracted from Berberis aristata, exhibits strong anti-proliferative and pro-apoptotic actions [12, 14]. It suppresses leukemic cell survival and myeloma growth by blocking the Wnt/β-catenin and MAPK pathways [13, 14, 19]. By inhibiting AMPK/mTOR signaling, berberine also modifies energy metabolism and reduces glucose uptake in cancer cells [14, 19]. Additionally, by lowering oxidative burden and reinstating EPO signaling in erythroid precursors, berberine enhances hematological parameters [11, 18, 20].

7. MECHANISTIC INSIGHTS: HERBAL DRUGS AND RBC FORMATION

One important mechanistic domain in integrative oncology is the interaction of red blood cell (RBC) production, bone marrow microenvironment modification, and herbal remedies [1-3]. Through direct marrow invasion, oxidative stress, and dysregulation of cytokine signaling, bone marrow malignancies including multiple myeloma (MM) and acute myeloid leukemia (AML) severely inhibit

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erythropoiesis [1, 2]. Through hematopoietic signaling modulation, antioxidant pathways, and microenvironmental repair, herbal bioactives have complex mechanisms that not only prevent malignant growth but also restore erythropoietic activity [4–7].

7.1. Restoration of Hematopoietic Niche and Erythroid Differentiation

Leukemic and myeloma cells disrupt the HSC niche and block erythroid differentiation [2, 3]. Herbal compounds like curcumin, withaferin A, and tinocordifolin restore balance by improving stromal signaling and increasing EPO receptor expression [4, 6, 8]. Curcuma longa enhances GATA-1-mediated maturation of proerythroblasts into reticulocytes [4, 9]. Withania somnifera and Tinospora cordifolia boost erythropoiesis by increasing renal and hepatic EPO production [7, 10]. Under hypoxia, these herbs enhance HIF-1α-driven EPO transcription. This helps recover erythroid precursors and prevents chemotherapy-induced anemia [9, 11].

7.2. Modulation of Cytokine and Growth Factor Signaling

Bone marrow cancers produce too many inflammatory cytokines like IL-6, TNF-α, and TGF-β. This process suppresses erythropoiesis and helps tumors survive [12]. Herbal compounds counter this by changing cytokine signaling. For example, resveratrol inhibits IL-6/STAT3 and NF-κB, which reduces inflammation-driven erythroid suppression [5, 12]. EGCG protects progenitors from TGF-β-induced cell death during chemotherapy [6, 13]. Quercetin increases the release of SCF and GM-CSF, which helps maintain erythroid lineage [14]. Quercetin also boosts hemoglobin and reticulocyte counts in vitro and in vivo [14, 15]. This shows that phytochemicals work at the crossroads of anti-inflammatory and erythroid maturation pathways.

7.3. Activation of the JAK2/STAT5 and PI3K/Akt Pathways

The JAK2/STAT5 and PI3K/Akt signaling axes are critical regulators of erythropoiesis, mediating the response of erythroid progenitors to EPO and other growth stimuli [8]. Herbal compounds have been found to activate these pathways, leading to improved RBC formation. Curcumin and resveratrol directly enhance JAK2 phosphorylation, promoting STAT5 activation and transcription of erythroid-specific genes [8, 9]. Concurrently, PI3K/Akt signaling triggered by Withania somnifera and Tinospora cordifolia maintains cellular survival of erythroid progenitors under oxidative stress conditions [10, 11] These mechanisms are particularly important in bone marrow cancer, where chemotherapeutic agents such as bortezomib and melphalan suppress erythroid cell survival. Herbal co-administration enhances marrow resilience through Akt-dependent upregulation of Bcl-2 and downregulation of pro-apoptotic Bax, thereby preventing treatment-induced anemia [9, 11].

7.4. Role of Antioxidant and Anti-apoptotic Defense

Oxidative stress is a major cause of problems with red blood cell production in bone marrow cancers, with excess reactive oxygen species (ROS) leading to DNA damage and cell death. Herbal antioxidants activate Nrf2/HO-1 signaling. This boosts enzymes like catalase, superoxide dismutase (SOD), and glutathione peroxidase, which improves red blood cell survival. Resveratrol, EGCG, and curcumin increase glutathione (GSH) and HO-1, protecting bone marrow cells during chemotherapy. Polysaccharides from Panax ginseng and Ganoderma lucidum also reduce ROS and DNA damage. They help preserve red blood cell precursors and support the recovery of red blood cell counts after myelosuppression.

7.5. Epigenetic and Apoptotic Pathway Regulation

By altering DNA methylation and histone acetylation patterns, a number of herbal substances have epigenetic control on erythroid gene expression [12, 14]. As a SIRT1 activator, resveratrol improves the regulation of erythropoietic genes that is dependent on histone deacetylase (HDAC) [5, 12]. Curcumin reverses the hypermethylation of erythroid lineage promoters repressed in AML by inhibiting DNMT1 [4, 9]. Even after treatment is stopped, these epigenetic alterations promote long-term hematopoietic healing.Furthermore, a variety of phytochemicals enhance erythropoiesis by adjusting the ratio of survival signals to apoptosis. RBC progenitors are shielded from apoptosis caused by TNF-α or chemotherapeutic stress by withaferin A, a steroidal lactone from Withania somnifera that inhibits caspase-3 and PARP cleavage [10, 11]. This process has been confirmed in MM models, where Withaferin A retained erythroid lineages while simultaneously inhibiting the formation of malignant plasma cells [9–11].

8. COMBINATION AND SYNERGISTIC THERAPIES

The clinical necessity to overcome medication resistance, reduce systemic toxicity, and improve hematologic recovery gave rise to the idea of combination and synergistic therapy in the treatment of bone marrow cancer [1–3]. While traditional chemotherapeutics such bortezomib, melphalan, cytarabine, and dexamethasone are the mainstay of treatment for acute myeloid leukemia (AML) and multiple myeloma (MM), the addition of herbal bioactives provides multi-targeted efficacy with fewer side effects [2, 4, 5]. Phytochemicals, such as curcumin, resveratrol, quercetin, EGCG, and withanolides, have been shown in numerous trials over the past ten years to work in concert with conventional medications to improve tumor suppression while simultaneously promoting erythropoiesis and immunological balance [4–6].

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8.1. Rationale for Herbal–Conventional Synergy

Bone marrow cancers like AML and MM create major disruptions in red blood cell production due to low oxygen levels, oxidative stress, inflammatory cytokines, and the toxicity of chemotherapy. The low-oxygen environment in the marrow stabilizes HIF-1α, which helps blood vessel formation, changes in metabolism, and makes treatment less effective. Oxidative stress and issues with mitochondria increase reactive oxygen species (ROS), harming red blood cell precursors and lowering their production. The suppression of erythroid colonies (BFU-E and CFU-E) worsens as the disease progresses due to inhibitory cytokines such as TNF-α and TGF-β. Myeloma-derived miRNAs, like miR-21 and miR-29b, disrupt transcriptional regulators like GATA1 and KLF1, further hindering red blood cell generation. Chemotherapy drugs like cytarabine, anthracyclines, melphalan, and bortezomib increase marrow toxicity by causing mitochondrial damage, oxidative DNA harm, endoplasmic reticulum stress, and death of progenitor cells. This results in malignant anemia, which is marked by a weak reticulocyte response even when erythropoietin (EPO) levels are normal or high. Kidney problems in multiple myeloma reduce EPO production, while inflammatory factors like IL-6 and TNF-α raise hepcidin levels and cause iron to be sequestered, contributing to functional iron deficiency.

Oxidative stress speeds up damage to red blood cell membranes and cell aging, which is made worse by disrupted antioxidant defense mechanisms, particularly Nrf2/HO-1. Phytochemicals such as curcumin, quercetin, resveratrol, and withanolides help counter these effects by targeting NF-κB, STAT3, and the SIRT1/Nrf2 pathways, showing properties that support red blood cell production and reduce inflammation. Withania somnifera has been shown to restore marrow structure, increase red blood cell counts, and raise serum EPO levels. Combining herbs with conventional therapies improves outcomes since chemotherapy can lead to reduced bone marrow function while herbs help lower oxidative stress and repair the marrow environment. Curcumin enhances the effectiveness of bortezomib and dexamethasone by blocking NF-κB, STAT3, and PI3K/Akt, leading to better cancer cell killing with fewer side effects. Resveratrol enhances melphalan and daratumumab by promoting mitochondrial cell death and lowering ROS without harming red blood cell production.

8.2. Proteasome Inhibitors and Phytochemical Co-therapy

Although important medications in MM treatment, proteasome inhibitors (PIs) like bortezomib and carfilzomib are known to induce oxidative stress, neuropathy, and cytopenia [8]. Through reactive oxygen regulation and proteasomal degradation of carcinogenic substrates, such as cyclin D1 and Bcl-2, co-treatment with curcumin or EGCG (Epigallocatechin gallate) increases PI-induced apoptosis [6, 8, 11]. Preclinical research shows that curcumin-bortezomib combinations increase apoptosis in resistant myeloma clones by activating caspase-8 and Bid cleavage, while preserving erythroid progenitors through Nrf2 activation [4, 6]. Additionally, by binding to the proteasome β5 subunit and preferentially raising oxidative stress in malignant plasma cells, EGCG enhances the cytotoxicity of bortezomib [11]. Crucially, by focusing on NF-κB-regulated survival genes, which play a significant role in minimal residual illness, these combinations lower drug resistance and prevent relapse [8, 12].

8.3. Herbal–Immunotherapeutic Interactions

The development of monoclonal antibody (mAb) treatments, such as elotuzumab (anti-SLAMF7) and daratumumab (anti-CD38), has greatly improved the treatment of multiple myeloma [9]. However, cytokine imbalance and immunological fatigue can reduce the efficacy of these antibodies [10, 13]. Withania somnifera, Tinospora cordifolia, and Ganoderma lucidum are examples of herbal immunomodulators that improve immune cell activation, antibody-dependent cytotoxicity, and therapeutic response [7, 10, 14]. For instance, extracts from Withania somnifera increase T-cell and NK-cell activity while decreasing inflammatory cytokines (IL-6, TNF-α), which impede the effectiveness of antibodies [7, 10]. By boosting the expression of activating receptors such NKG2D, resveratrol and daratumumab further improve NK-cell-mediated cytolysis of MM cells [10, 13]. Potentiation of immunotherapy and restoration of immune surveillance mechanisms, which are essential for preventing relapse, are two benefits of these synergistic interactions [9, 14].

8.4. Targeted Therapies and Herbal Augmentation

Tyrosine kinase inhibitors (TKIs), BCL-2 inhibitors, and HDAC inhibitors are examples of contemporary targeted treatments that have better results but frequently cause oxidative damage and hematologic adverse effects [11]. Alkaloids and polyphenols found in herbs have demonstrated the ability to increase therapeutic efficacy while reducing these toxicities. By interfering with mitochondrial potential and increasing caspase-9 activation, curcumin amplifies the cytotoxic action of venetoclax, a BCL-2 inhibitor [4, 15]. Quercetin causes cell-cycle arrest in AML cells by increasing the expression of Bax and p21 when coupled with HDAC inhibitors [5, 11].Additionally, via modifying the Wnt/β-catenin and Notch pathways, resveratrol and withaferin A sensitize leukemic stem cells to TKI therapy [10, 15]. One of the most important obstacles to long-term leukemia treatment is medication resistance, which is overcome by these synergistic mechanisms [13, 16].

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8.5. Herbal Synergy in Hematoprotection and RBC Restoration

Herbal medicines are essential for maintaining RBC homeostasis during chemotherapy in addition to increasing anticancer activity [7, 9]. By boosting heme synthesis enzymes and activating JAK2/STAT5 signaling, Tinospora cordifolia and Panax ginseng extracts increase erythropoietin production and restore RBC count [7, 10, 17]. Co-administration of these extracts with chemotherapy medications promotes bone marrow regeneration and lessens the severity of anemia [16,17].By boosting Nrf2-mediated antioxidant defense and lowering ROS accumulation in erythroid progenitors, curcumin and resveratrol have been demonstrated to lessen bortezomib-induced myelosuppression [6, 9]. By boosting reticulocyte maturation and EPO receptor sensitivity, ashwagandha (Withania somnifera) promotes erythroid regeneration [7, 10]. These results demonstrate how herbal co-therapy promotes hematopoietic regeneration and tumor cytotoxicity, providing a biologically integrated therapeutic approach.

9. SAFETY, TOXICOLOGY, AND CLINICAL EVIDENCE

A thorough assessment of safety, toxicity, and clinical validation is necessary for moving herbal medicines from traditional use to evidence-based oncology. Many phytochemicals have strong anti-bone marrow cancer and hematopoietic restorative qualities, but in order to guarantee practical applicability, their pharmacological safety, pharmacokinetics, and interaction potential must be thoroughly determined [1-3]. A careful balance between safety and efficacy is required when combining herbal medications with traditional chemotherapeutics, especially in hematologic malignancies where immunological impairment and bone marrow damage are already significant clinical issues [2, 4].

9.1. Toxicological Evaluation of Herbal Compounds

Toxicological studies indicate that major herbal compounds like curcumin, resveratrol, quercetin, withaferin A, and EGCG have low systemic toxicity and are well-tolerated even at high doses [4, 5, 6]. Curcumin taken in doses up to 8 g per day does not cause liver or genetic toxicity [4, 5]. Resveratrol at 250–500 mg/kg shows no biochemical abnormalities [6, 7]. EGCG is generally safe, with hepatotoxicity occurring only above 1000 mg per day, while therapeutic doses provide protection for bone marrow [5, 8, 9]. Both withaferin A and W. somnifera extracts demonstrate no organ toxicity or cytogenetic damage up to 2 g/kg [7, 10]. There are risks of herb-drug interactions, as curcumin and quercetin may inhibit CYP enzymes and change the levels of chemotherapy drugs [4, 11]. However, controlled co-administration usually improves treatment tolerance instead of increasing toxicity [11, 12].

9.2. Hematological and Immunological Safety Profiles

Chemotherapy for bone marrow cancers often leads to immunotoxicity and myelosuppression. However, herbal co-therapies like Ashwagandha, Panax ginseng, and Tinospora cordifolia help reduce these side effects [10, 13, 14]. Tinospora cordifolia increases red blood cell (RBC) count and erythropoietin (EPO) while lowering oxidative damage to the marrow [10, 13]. Withania somnifera raises leukocyte levels and reduces marrow cell death in both animal and human studies [7, 10, 14]. Panax ginseng improves hemoglobin, neutrophil, and platelet levels in multiple myeloma (MM) patients without causing blood toxicity [15]. Ganoderma lucidum polysaccharides boost natural killer (NK) and macrophage activity, improving immune response during treatment [16].

9.3. Systemic Toxicity and Organ-Specific Safety

Major herbal anti-myeloma and anti-leukemic agents are non-mutagenic, non-teratogenic, and non-hepatotoxic within therapeutic ranges, according to systemic safety evaluations in both clinical and preclinical models [4, 7, 8]. Curcumin and resveratrol, in particular, protect against hepatic and renal toxicity caused by chemotherapy by increasing intracellular glutathione and triggering the Nrf2/HO-1 pathway [6, 8, 17]. Additionally, by lowering lipid peroxidation and reviving myocardial glutathione peroxidase activity, herbal antioxidants mitigate the cardiotoxicity caused by anthracyclines [9, 17]. Reduced serum ALT, AST, and creatinine levels demonstrate the hepatoprotective and nephroprotective effects of quercetin and EGCG in melphalan-induced oxidative stress models [5, 8, 18]. In both animal and human trials, safety evaluations of polyherbal formulations containing Withania somnifera (ashwagandha), ginseng, and Tinospora cordifolia confirm the absence of nephrotoxicity or hepatocellular degeneration [10, 13, 17]. Collectively, these findings validate the safe integration of standardized, quality-controlled herbal formulations into integrative oncologic care.

9.4. Pharmacokinetic and Drug Interaction Considerations

Herbal substances may change how chemotherapeutic drugs are absorbed and metabolized, according to pharmacokinetic studies. Nonetheless, the majority of interaction hazards are reduced by refined formulations and regulated dosage [11, 18, 19]. For instance, bortezomib or dexamethasone's plasma pharmacokinetics are unaffected by nanocurcumin formulations that increase bioavailability [12, 18]. Similar to this, resveratrol nanoparticles improve therapeutic delivery while preserving steady systemic drug levels [15, 19].Curcumin, quercetin, and EGCG have minor CYP inhibition, according to in vitro interaction studies, but these effects are dose-dependent and clinically negligible when given at nutritional or moderate therapeutic levels [5, 9, 19]. Therefore, safe combined usage

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of herbal and conventional medicines is ensured by sensible co-administration methods that emphasize appropriate time, dose, and patient monitoring [18, 19].

9.5. Regulatory and Clinical Translation Challenges

The absence of worldwide consistency in herbal preparation continues to be a significant obstacle to clinical translation despite rigorous safety validation [13, 19, 20]. Therapeutic response and toxicity profiles can be impacted by variations in phytochemical content, bioavailability, and extraction techniques [19, 20]. To guarantee reproducibility and patient safety, the European Medicines Agency (EMA) and the World Health Organization (WHO) have stressed the necessity of pharmacovigilance programs and herbal formulations recognized by Good Manufacturing Practice (GMP) [19, 20]. In order to create standardized dosage schedules and therapeutic indices, future directions will use phytopharmacokinetic profiling, multi-omics-based toxicity prediction, and controlled clinical trial designs. For herbal agents to be incorporated into supportive cancer care recommendations, they must adhere to a strict evidence-based system that guarantees both safety validation and regulatory compliance [18–20].

10. FUTURE PERSPECTIVES

The integration of herbal pharmacology into controlling blood cell production and treating bone marrow cancer has great potential. However, it requires improvements in standardization, understanding mechanisms, formulation, and regulation [1-3]. Standardization and Quality Control: It is essential to establish reliable phytochemical markers, authentication methods, and global good manufacturing practice standards for consistent results and safety [4-12]. Delivery Systems and Nanotechnology: Nanocarrier formulations can improve solubility, bioavailability, and targeted delivery to the bone marrow. This enhances effectiveness and reduces toxicity [11-16]. Mechanistic and Omics-Based Investigations: Multi-omics and bioinformatics methods can clarify how phytochemicals influence pathways such as NF-κB, STAT3, and JAK2/STAT5, supporting personalized medicine [5-19]. Clinical Translation and Evidence-Based Validation: Large-scale randomized controlled trials are important for confirming safety, optimal dosages, biomarkers, and long-term outcomes for blood cell production [7-19]. Combination Therapies and Systems Pharmacology: Combining phytochemicals with immunotherapy and AI-driven modeling may create personalized and multi-targeted treatment strategies for cancer [2-20].

11. CONCLUSION

Herbal pharmacology offers a promising way to treat bone marrow cancers like AML and MM by tackling issues related to blood cell production and anemia. Traditional therapies often lead to toxicity, resistance, and suppression of the bone marrow, which shows the need for alternative treatments. Bioactive compounds such as curcumin, resveratrol, quercetin, withaferin A, and berberine work through cancer-related and cell-death pathways, providing benefits like fighting leukemia, reducing oxidative stress, and lowering inflammation. Herbal extracts such as Eclipta alba, Tinospora cordifolia, and Withania somnifera boost red blood cell production and support bone marrow health. Nanocarrier systems, omics-based studies, and AI-driven models enhance how well these compounds work, improve their targeting, and promote their combined effects. While large-scale clinical validation is still needed, standardized herbal therapies offer a safe, multi-targeted, and cost-effective approach to managing cancer and restoring blood cell production

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