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REVIEW

Synergistic Mechanisms of Traditional Chinese Medicine and Proteasome Inhibitors in Multiple Myeloma Therapy: A Comprehensive Review

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Background: Multiple myeloma (MM) is a clonal plasma cell malignancy characterized by bone marrow infiltration, monoclonal immunoglobulin production, and multisystem damage. Proteasome inhibitors (PIs) such as bortezomib, carfilzomib, and ixazomib have significantly improved progression-free and overall survival in MM patients. However, drug resistance and adverse effects—including peripheral neuropathy and cardiotoxicity—remain major limitations to long-term disease control.

Objective: This review aims to comprehensively evaluate the synergistic mechanisms and therapeutic potential of Traditional Chinese Medicine (TCM) in combination with PIs for the treatment of MM, from molecular insights to translational outcomes.

Methods and Scope: We synthesized findings from preclinical studies, pharmacological investigations, and cohort analyses that examine the interplay between TCM bioactives and PI-based regimens. Focus is given to the modulation of MM-related signaling pathways (eg, NF-κB, STAT3, PI3K/Akt), apoptotic cascades, proteasomal degradation processes, and the bone marrow microenvironment.

Results: Evidence suggests that specific TCM compounds—such as curcumin, baicalein, icariin, and berberine—can potentiate PI-induced cytotoxicity, reverse resistance mechanisms, reduce inflammatory damage, and protect against PI-associated toxicities. Several Chinese herbal formulations, including Fuzheng Peiyuan and Huanglian Jiedu decoctions, have demonstrated immunomodulatory and anti-myeloma effects in vivo and in human cohorts. These synergistic actions may enhance the efficacy and tolerability of PIs in MM therapy.

Conclusion: Integrating TCM with proteasome inhibitors represents a promising strategy to optimize MM treatment by simultaneously targeting malignant cells and the tumor microenvironment. Further mechanistic research and well-designed clinical trials are warranted to validate and standardize this combinational approach for broader clinical adoption.

Keywords: Multiple myeloma, proteasome inhibitors, traditional Chinese medicine treatment, drug synergy, NF-κB, apoptosis, bone marrow microenvironment, bortezomib resistance

Introduction

Multiple myeloma (MM) is an incurable plasma cell malignancy characterized by clonal proliferation in the bone marrow and the production of monoclonal immunoglobulins, leading to end-organ damage including bone lesions, anemia, renal failure, and hypercalcemia (the "CRAB" features).[1] Over the past two decades, the therapeutic landscape of MM has been revolutionized by novel agents, particularly proteasome inhibitors (PIs) like bortezomib, along with immunomodulatory drugs (IMiDs) and monoclonal antibodies. First-generation PI-based regimens have significantly prolonged progression-free survival (PFS) and overall survival (OS), transforming MM into a chronic disease with median survival now exceeding 5–6 years for many patients.[2]

Despite therapeutic advances, multiple myeloma (MM) remains an incurable malignancy. Most patients ultimately experience relapse or develop resistance to first-line agents, including proteasome inhibitors (PIs). Bortezomib, the first-in-class PI, revolutionized MM treatment; however, its clinical application is frequently limited by peripheral neuropathy,

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which occurs in 30–50% of patients and can lead to dose reduction or treatment discontinuation.[3] Although second-generation agents such as carfilzomib (an irreversible epoxyketone-based PI) and ixazomib (an oral PI) have partially addressed administration and resistance issues, they introduce new toxicities like cardiopulmonary complications and still face resistance in advanced disease settings.[4,5]

In this context, Traditional Chinese Medicine (TCM)—including both complex herbal formulas and purified compounds—has emerged as a promising adjunct to standard MM therapies. A nationwide retrospective matched-cohort study conducted in Taiwan[6] found that MM patients who received adjunctive Chinese herbal medicine (CHM) exhibited significantly improved overall survival compared to those who received conventional therapy alone (adjusted hazard ratio ~0.35), suggesting a survival benefit for integrative treatment. This clinical evidence is increasingly supported by preclinical research identifying bioactive TCM-derived molecules—such as celastrol, curcumin, and berberine—that can synergize with PIs to overcome drug resistance, enhance tumor apoptosis, and reduce treatment-related toxicity.[7,8]

Mechanistically, many of these compounds act on pathways central to MM biology, including the ubiquitin-proteasome system (UPS), NF-κB, JAK/STAT, and intrinsic apoptotic regulators, while also modulating the bone marrow microenvironment, thereby enhancing the cytotoxicity of PIs and protecting normal tissues. Given these complementary mechanisms, integrating TCM with PIs offers a promising strategy to enhance anti-myeloma efficacy and reduce toxicity. This review consolidates mechanistic and clinical evidence to clarify the translational potential of this combinational approach and its implications for improving patient outcomes (Figure 1 and Table 1).

Current Status of Proteasome Inhibitors in the Treatment of Multiple Myeloma

Proteasome inhibitors (PIs) have become a fundamental component of multiple myeloma (MM) therapy by exploiting the malignant plasma cells' reliance on the ubiquitin–proteasome system (UPS) to maintain protein homeostasis. The 26S proteasome is responsible for degrading misfolded, damaged, or regulatory proteins tagged with ubiquitin.[27] Due to their high production of abnormal immunoglobulins, MM cells place increased stress on this degradation pathway. Proteasome inhibition results in the accumulation of ubiquitinated proteins and misfolded proteins in the endoplasmic reticulum (ER), triggering ER stress and activation of the unfolded protein response (UPR), ultimately leading to apoptosis in MM cells.[28]

A critical mechanism underlying PI-induced apoptosis is suppression of the nuclear factor-κB (NF-κB) pathway.[29] For example, bortezomib, a first-generation boronic acid dipeptide, reversibly inhibits the chymotrypsin-like activity of the β5 subunit within the 20S core particle of the proteasome. This prevents IκBα degradation and subsequent NF-κB nuclear translocation, reducing transcription of anti-apoptotic and pro-proliferative genes.[30] Since NF-κB is often constitutively activated in MM, its inhibition leads to decreased cytokine production, proliferation, and drug resistance.[31]

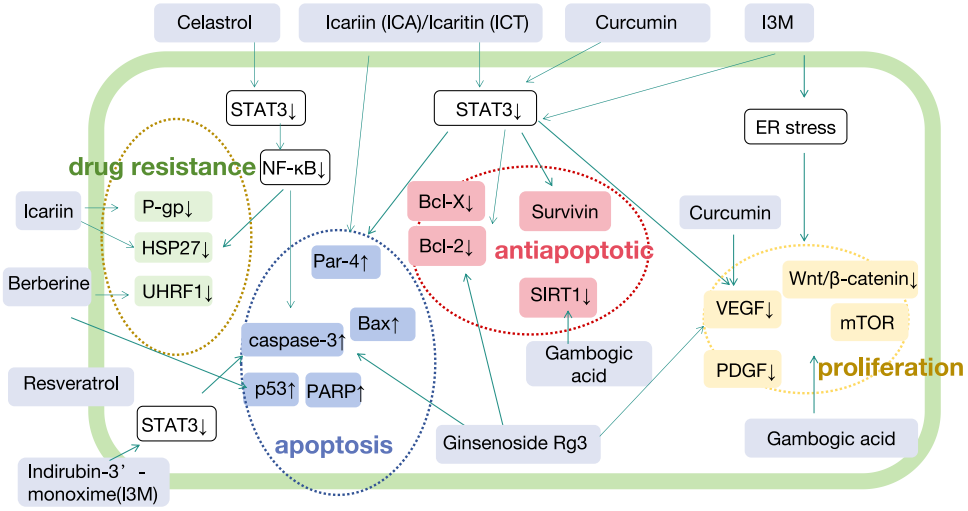

Figure 1 Integrated Mechanistic Pathways of Eight Key TCM Monomers Synergizing with Proteasome Inhibitors in Multiple Myeloma.

Table 1 Summary of TCM-Derived Compounds Synergizing with Proteasome Inhibitors in Multiple Myeloma

Ingredient	Herb Source	Proteasome Inhibitors Used in Combination	Primary Mechanism	Effects
Icariin / Icaritin[9–11]	Epimedii folium	Bortezomib	Inhibits JAK2/STAT3 cascade; upregulates Par-4; downregulates HSP27/P-gp; suppresses Bcl-2, Bcl-xL, survivin, COX-2, VEGF	Reverses PI resistance; enhances apoptosis and G0/G1 arrest; anti-angiogenic
Berberine[8,12,13]	Coptis chinensis	Bortezomib	Reactivates p53 via promoter hypomethylation; targets UHRF1; modulates miR-21/NF-κB/SET9/miR-106b/miR-19a clusters	Promotesapoptosis; overcomes resistance; inhibits proliferation
Celastrol[14–16]	Tripterygium wilfordii	Bortezomib	Inhibits NF-κB, IRAK4/ERK/p38 MAPK; induces ER stress/UPR; inhibits β5/β2/β1 proteasome subunits; increases Bax/Bcl-2 ratio	Induces apoptosis; inhibits migration/invasion; enhances BTZ efficacy
Ginsenoside Rg3[17,18]	Panax ginseng	Bortezomib	Induces mitochondrial apoptosis (Bax↑/Bcl-2↓/Caspase-3↑); suppresses IGF-1/IGF-1R; inhibits VEGF	Pro-apoptotic; anti-angiogenic; overcomes resistance
Curcumin[19,20]	Curcuma longa	Bortezomib	Inhibits STAT3, NF-κB, ERK1/2; suppresses Bcl-2, Bcl-xL, survivin; enhances PARP/caspase-3 cleavage; potentiatesproteasome inhibition	Promotes apoptosis; reverses resistance; cell cycle arrest
Resveratrol[21,22]	Polygonum cuspidatum	Carfilzomib	Induces ER stress and UPR; suppresses XBP1, mTOR, NEAT1, Wnt/β-catenin; activates AMPK/caspase-3; potentiates oxidative stress with PIs	Apoptosis; autophagy; chemosensitization with PIs; reduces toxicity
Indirubin-3'-monoxime[23,24]	Indigo naturalis (synthetic deriv).	Bortezomib	Inhibits STAT3 Tyr705 phosphorylation; suppresses survivin, Bcl-2, Mcl-1; directly inhibits β5 subunit of 20S proteasome	Induces apoptosis; restores BTZ sensitivity; dual mechanism
Gambogic acid[25,26]	Garcinia hanburyi	Bortezomib	ActivatesROS/caspase cascade; inhibits SIRT1, PI3K/Akt/mTOR, VEGF, HIF-1α, CXCR4; blocks osteoclastogenesis	Pro-apoptotic; anti-angiogenic; bone protection; overcomes resistance

Moreover, PIs modulate additional pathways by stabilizing pro-apoptotic proteins such as p53 and Bax and preventing the degradation of cell cycle inhibitors like p21 and p27.[32]

Currently approved PIs include bortezomib, carfilzomib (a second-generation irreversible epoxyketone inhibitor), and ixazomib (a second-generation orally bioavailable boronate). All of them primarily target the β5 subunit but differ in pharmacokinetic profiles and specificity.[33] These agents, especially when combined with immunomodulatory drugs (IMiDs) and glucocorticoids, form the basis of standard regimens such as VRd (bortezomib, lenalidomide, dexamethasone), which significantly improves overall response rates and survival in both newly diagnosed and relapsed/refractory MM patients.[34] Carfilzomib-based combinations are preferred in PI-relapsed cases, while ixazomib is widely used in maintenance settings due to its oral availability and favorable safety profile.[35]

Although proteasome inhibitors (PIs) have achieved remarkable efficacy in treating multiple myeloma (MM), drug resistance and toxicity remain major challenges. Mechanisms of PI resistance are multifaceted and include compensatory activation of the NF-κB pathway, mutations in proteasome subunits (e.g.PSMB5 G322A), epigenetic reprogramming (e.g.EZH2 upregulation), and activation of alternative protein degradation pathways, such as the HDAC6-mediated aggresome-autophagy system.[36] In

addition, mesenchymal stem cells (MSCs) in the bone marrow microenvironment contribute to resistance by transferring non-coding RNAs (e.g.PSMA3-AS1 lncRNA) to MM cells via exosomes or direct cell–cell contact.[37]

Among adverse effects, bortezomib-induced peripheral neuropathy (BIPN) is a major dose-limiting toxicity. Its pathogenesis involves proteasome inhibition and mitochondrial dysfunction in dorsal root ganglion neurons, resulting in decreased ATP production and axonal degeneration.[38] PIs also commonly cause hematologic toxicity, including thrombocytopenia and neutropenia, likely due to their inhibitory effects on hematopoietic stem cells.[39] While combination therapies (eg with the HDAC inhibitor panobinostat) may enhance efficacy, they can also exacerbate gastrointestinal side effects, fatigue, and infection risk.[40]

In summary, PIs remain the backbone of MM treatment and have significantly improved patient survival and remission rates. However, their clinical utility is constrained by both adverse events—particularly neurotoxicity and, in newer agents, potential cardiotoxicity—and the development of resistance. These challenges highlight the urgent need for adjuvant therapies that can enhance anti-myeloma efficacy or alleviate treatment-related toxicities.

Research Progress in the Treatment of Multiple Myeloma with Traditional Chinese Medicine Combined with Proteasome Inhibitors

Flavonoids

Icariin (ICA)/Icaritin (ICT)

Epimedii folium (EF), known as Yinyanghuo, is a traditional Chinese herb derived from several Epimedium species. Its major active flavonoid glycoside, icariin (ICA), and its intestinal metabolite icariside II (ICA II) exhibit diverse pharmacological properties, including anti-inflammatory, bone-strengthening, and anticancer effects. In modern pharmacology, both ICA and ICA II have attracted interest for their synergistic anti-myeloma potential when combined with proteasome inhibitors (PIs) such as bortezomib (BTZ).[7]

In bortezomib-resistant MM cell lines (eg, KM3/BTZ), ICA has been shown to partially reverse drug resistance by upregulating pro-apoptotic cytokine Par-4 and downregulating resistance-associated proteins such as HSP27 and P-glycoprotein (P-gp).[9] In U266 cells, co-treatment with ICA and BTZ significantly enhanced apoptosis and G0/G1 cell cycle arrest, which was mechanistically linked to inhibition of the JAK2/STAT3 signaling cascade and suppression of Bcl-2, Bcl-xL, and survivin.[10,41]

ICA II exhibits even stronger anti-myeloma activity than its parent compound, promoting BTZ-induced apoptosis through inhibition of STAT3 phosphorylation and its downstream effectors including cyclin D1, COX-2, and VEGF, which are critical for MM cell survival, angiogenesis, and drug resistance.[11,42] ICA II–induced apoptosis in U266 cells has been directly confirmed through modulation of JAK2/STAT3-mediated intrinsic pathways.[11]

Moreover, comparative pharmacokinetic studies reveal that ICA and ICA II differ significantly in absorption and bioavailability, offering distinct formulation strategies for clinical application.[43] Together, these findings underscore the potential of ICA and ICA II as natural, multi-targeted adjuvants in overcoming proteasome inhibitor resistance in multiple myeloma.

Alkaloids

Berberine

Berberine (BBR), a natural isoquinoline alkaloid derived from Coptis chinensis, has demonstrated promising anti-myeloma activity through multifaceted mechanisms involving epigenetic regulation, post-transcriptional modulation, and chemosensitization synergy with proteasome inhibitors.

At the epigenetic level, BBR reactivates tumor suppressor p53 by inducing hypomethylation of its promoter, thereby restoring p53-mediated transcriptional control and triggering intrinsic apoptotic pathways in MM cells.[12] Additionally, BBR directly targets UHRF1, a chromatin-associated epigenetic regulator involved in DNA methylation maintenance, further contributing to global reprogramming of the MM epigenome.[8]

BBR also exerts post-transcriptional regulation via modulation of oncogenic microRNAs that contribute to MM pathogenesis and drug resistance. Most notably, BBR downregulates miR-21, a key oncomiR in MM, by suppressing NF-κB signaling and modulating the activity of the histone methyltransferase SET9.[44,45] It also attenuates the miR-106b/25[46]

and miR-19a/92a[47] clusters, which are known to regulate proliferation, apoptosis, and therapeutic sensitivity, thereby reinforcing its broad transcriptomic influence.

From a therapeutic perspective, BBR has demonstrated synergistic cytotoxicity when combined with the proteasome inhibitor bortezomib. In vitro studies in U266 cells showed that this combination significantly enhances apoptosis and G0/G1 cell cycle arrest, suggesting its potential to overcome bortezomib resistance and improve treatment efficacy.[13] These findings align with the concept of integrating phytochemical adjuvants into MM therapy to potentiate standard regimens while minimizing toxicity.

Collectively, berberine's multi-targeted molecular profile, origin from traditional Chinese medicine, and capacity to overcome drug resistance establish it as a strong candidate for inclusion in combinatorial MM treatment strategies. Its preclinical efficacy across epigenetic, transcriptomic, and proteasome-targeted pathways supports further translational exploration in clinical contexts.

Quinones & Terpenoids

Celastrol

Celastrol, a quinone methide triterpenoid isolated from the root and bark of Tripterygium wilfordii (Thunder God Vine),[48] has emerged as a multi-targeted compound with substantial therapeutic potential in multiple myeloma (MM). Its pharmacological effects are mediated through a dual mechanism involving both inhibition of key oncogenic signaling cascades and direct interference with proteasomal activity.[49,50]

Mechanistically, celastrol attenuates MM cell proliferation and invasiveness by suppressing the NF-κB and IRAK4/ERK/p38 MAPK pathways.[14,15,50] These inhibitory actions lead to reduced transcription of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), as well as decreased expression of metastasis-related proteins including CXCR4 and matrix metalloproteinase-9 (MMP-9). Moreover, celastrol induces G0/G1 cell cycle arrest and promotes apoptosis via intrinsic mitochondrial pathways, evidenced by increased Bax/Bcl-2 ratio, and triggers endoplasmic reticulum stress through the activation of the PERK/eIF2α axis of the unfolded protein response (UPR).[14,49,51]

Importantly, celastrol has been identified as a direct inhibitor of the chymotrypsin-like (β5), trypsin-like (β2), and caspase-like (β1) subunits of the 20S proteasome. This interaction results in the accumulation of polyubiquitinated proteins and induction of proteotoxic stress, functionally resembling the mechanism of bortezomib. Such dual modulation renders celastrol particularly suitable for combinatorial strategies with proteasome inhibitors.[15,16]

In preclinical models, celastrol enhances bortezomib-induced apoptosis in MM cells by amplifying caspase-3 activation and DNA fragmentation.[14,51] In vivo, co-administration of celastrol significantly reduced tumor volume in SCID mouse xenografts bearing MM.1S or RPMI 8226 cells, thereby supporting its synergistic potential and translational relevance.[14,16]

Collectively, these findings underscore celastrol as a promising adjunct to proteasome inhibitor-based therapies in MM. Its dual targeting of pro-survival signaling and proteasomal degradation pathways offers a rational strategy to overcome drug resistance and potentiate therapeutic efficacy.

Ginsenoside Rg3

Ginsenoside Rg3, a bioactive saponin extracted from Panax ginseng, has demonstrated significant anti-myeloma activity through modulation of key survival, proliferation, and angiogenic pathways. Owing to its low toxicity profile and multi-targeted mechanisms, Rg3 has garnered interest as a natural adjuvant in proteasome inhibitor-based regimens.

Mechanistically, Rg3 induces mitochondrial-mediated apoptosis in MM cells. In U266 cells, treatment with Rg3 upregulates the pro-apoptotic protein Bax, downregulates Bcl-2, and activates caspase-3, culminating in programmed cell death.[17] Notably, this apoptotic response is selective to malignant cells, with minimal cytotoxicity observed in normal hematopoietic counterparts, supporting its potential as a safe pro-apoptotic enhancer.

In addition to its intrinsic cytotoxicity, Rg3 modulates growth factor signaling, particularly the IGF-1/IGF-1R axis, which is frequently implicated in MM progression and resistance to therapy. Rg3 has been shown to significantly reduce IGF-1 secretion, thereby attenuating downstream survival signaling and inducing cell cycle arrest in MM cells.[18] This suggests that Rg3 may overcome microenvironment-driven resistance mechanisms that limit proteasome inhibitor efficacy.

Moreover, Rg3 exerts anti-angiogenic effects through suppression of vascular endothelial growth factor (VEGF) expression. In vitro studies on U266 cells demonstrated that Rg3 reduced VEGF production in a dose-dependent manner, potentially disrupting the angiogenesis-dependent progression of MM within the bone marrow niche.[52]

Collectively, Ginsenoside Rg3 exhibits a tripartite mechanism of anti-MM action—namely, mitochondrial apoptosis induction, IGF-1/IGF-1R inhibition, and VEGF-mediated angiogenesis suppression. These combined effects support its development as a multifunctional phytotherapeutic agent suitable for combinatorial strategies with proteasome inhibitors or immunomodulatory drugs in MM treatment paradigms.

Polyphenols & Stilbenes

Curcumin

Curcumin, a polyphenolic compound derived from Curcuma longa (turmeric), has been extensively investigated for its anti-inflammatory, antioxidant, and anticancer properties. In the treatment of multiple myeloma (MM), curcumin exhibits pleiotropic antitumor activities, particularly when used in combination with proteasome inhibitors (PIs) such as bortezomib or carfilzomib, offering a strategy to enhance therapeutic efficacy and overcome drug resistance.

Mechanistically, curcumin inhibits several survival signaling pathways that are constitutively activated in MM. In U266 cells, curcumin was shown to block IL-6-induced phosphorylation of STAT3 and ERK1/2, leading to downregulation of anti-apoptotic proteins such as Bcl-2, Bcl-xL, and survivin.[19] This suppression promotes cleavage of poly(ADP-ribose) polymerase (PARP) and caspase-3 activation, thereby enhancing apoptosis when combined with PIs. Additionally, curcumin promotes cell cycle arrest at the G_0/G_1 phase and enhances proteotoxic stress by potentiating proteasome inhibition.[20]

Another critical mechanism involves inhibition of the nuclear factor-kappa B (NF-κB) pathway. Curcumin prevents the degradation of IκBα, resulting in decreased nuclear translocation of p65, reduced transcriptional activity of NF-κB, and subsequent downregulation of pro-survival genes such as IL-6, TNF-α, and COX-2.[53] These effects sensitize MM cells to the cytotoxic effects of bortezomib, as demonstrated in both RPMI 8226 and U266 cell lines.[54]

To improve its pharmacokinetic limitations, several curcumin analogs with better solubility and bioavailability have been developed. Notably, an amino acid-conjugated analog (compound 12) exhibited superior synergistic efficacy with bortezomib, as evidenced by enhanced caspase-3 and PARP cleavage in vitro.[55]

Collectively, these findings underscore curcumin as a promising adjuvant to proteasome inhibitor-based regimens in MM, acting through multi-pathway inhibition, apoptosis promotion, and reversal of resistance mechanisms.

Resveratrol

Resveratrol, a naturally occurring polyphenolic compound found in grapes, peanuts, and Polygonum cuspidatum, has demonstrated promising anti-myeloma activity through the modulation of multiple cellular pathways. In multiple myeloma (MM) models, it exerts both direct cytotoxicity and chemosensitizing effects when combined with conventional therapeutics, particularly proteasome inhibitors and mTOR-targeting agents.

Mechanistically, resveratrol induces endoplasmic reticulum (ER) stress by triggering the unfolded protein response, leading to apoptosis via downregulation of the X-box binding protein 1 (XBP1), a key transcription factor involved in MM cell survival.[21] In parallel, it activates autophagy and apoptosis by suppressing the AMPK/mTOR signaling pathway, disrupting energy metabolism and inhibiting cellular proliferation.[56]

Resveratrol has also been shown to synergize with proteasome inhibitors. For instance, its combination with carfilzomib significantly enhanced oxidative stress-mediated cell death and increased caspase-dependent apoptosis in MM cells, suggesting its potential in overcoming drug resistance.[22] Another pathway through which resveratrol inhibits MM progression is via NEAT1-mediated Wnt/β-catenin suppression, which reduces proliferation, migration, and invasion of MM cells.[57]

In terms of combination strategies beyond proteasome inhibition, resveratrol was shown to enhance the efficacy of rapamycin, a mammalian target of rapamycin (mTOR) inhibitor, in MM cells. This dual treatment significantly suppressed cell viability and promoted apoptosis through enhanced inhibition of the mTOR axis.[58] Furthermore, a novel clinical application has emerged with a resveratrol–copper pro-oxidant formulation (RESCU 001), which was found to reduce chemotherapy-related toxicities in MM patients undergoing high-dose melphalan therapy, marking a translational step toward supportive care in MM treatment.[59]

Collectively, these findings position resveratrol as a multi-targeted adjuvant capable of enhancing the anti-MM effects of both proteasome inhibitors and targeted agents, while also offering benefits in reducing treatment-related adverse effects.

Indole Derivatives

Indirubin-3'-Monoxime

Indirubin-3'-monoxime (I3M) is a potent synthetic derivative of indirubin, the major active compound extracted from Qingdai (Indigo naturalis), a traditional Chinese medicine historically used for hematologic malignancies and inflammatory disorders.[60,61] In the treatment of multiple myeloma (MM), I3M exerts multi-targeted anti-myeloma activity, acting through two principal mechanisms.

First, I3M inhibits the phosphorylation of STAT3 at Tyr705, thereby suppressing the transcription of downstream anti-apoptotic genes including Mcl-1, Bcl-2, and survivin. This suppression leads to the activation of the intrinsic apoptotic cascade, notably through caspase-3/9 cleavage.[23] Second, I3M directly inhibits the chymotrypsin-like activity of the β5 subunit of the 20S proteasome, leading to the accumulation of ubiquitinated proteins and proteotoxic stress—a mechanism mechanistically similar to that of bortezomib.[24,62]

Importantly, preclinical studies have shown that I3M can overcome bortezomib resistance in MM cells. This is likely due to its ability to simultaneously modulate the ubiquitin–proteasome system (UPS) and interfere with compensatory survival pathways such as STAT3 and NF-κB.[24,63] In bortezomib-refractory MM models, I3M restored drug sensitivity, suppressed tumor viability, and prolonged survival.[23,24] These findings underscore I3M as a promising synergistic candidate when used in combination with proteasome inhibitors.

Gambogic Acid

Gambogic acid (GA), a caged xanthone compound derived from the resin of Garcinia hanburyi, has emerged as a promising anti-myeloma agent due to its multifaceted molecular actions. GA exerts potent pro-apoptotic effects on MM cells by activating the caspase cascade and downregulating the SIRT1 pathway via the accumulation of reactive oxygen species (ROS), leading to enhanced mitochondrial dysfunction and cell death.[25] This redox-mediated cytotoxicity suggests GA's potential to overcome redox resistance often seen in MM.

Beyond direct apoptotic induction, GA also disrupts the PI3K/Akt/mTOR signaling axis, suppressing hypoxia-induced HIF-1α and VEGF expression in MM cells, thereby inhibiting tumor angiogenesis and growth under hypoxic conditions.[64] Additionally, it interferes with the CXCR4 chemokine receptor pathway, effectively blocking MM-induced osteoclastogenesis, a critical component of MM-related bone disease.[65] These effects highlight GA's dual role in both tumor cytotoxicity and modulation of the tumor microenvironment.

In combination regimens, GA has shown synergistic effects with bortezomib (BTZ) and nanomedicine strategies. For instance, dimercaptosuccinic acid (DMSA)-modified Fe_3O_4 nanoparticles co-delivering BTZ and GA synergistically induced G0/G1 cell cycle arrest and apoptosis in RPMI-8226 cells.[29] These findings point to the potential of GA in overcoming proteasome inhibitor resistance and improving drug delivery efficiency.

Collectively, the evidence positions gambogic acid as a multi-targeted phytochemical that not only enhances conventional chemotherapeutic efficacy but also interferes with MM-supporting pathways such as hypoxia response and bone resorption, making it a compelling adjunct candidate in MM integrative therapy.

Other TCM Formulas with Synergistic Potential

In addition to the single compound bioactive ingredients discussed previously, many traditional Chinese medicine (TCM) formulations have shown the potential to synergize with proteasome inhibitors (PIs) in the treatment of multiple myeloma (MM), although clinical studies of these regimens need to be further deepened. For example, Duhuo Jisheng Decoction combined with Fuyuan Huoxue Decoction combined with VCD/VAD regimen can reduce tumor burden (plasma cell ratio from 25.1% to 9.7%; M protein decreased by 61.5%) and alleviate chemotherapy-related gastrointestinal and nervous system toxicity without increasing bone marrow suppression or thrombosis.[66] Notably, Duhuo Jisheng Decoction also significantly improved bortezomib-induced peripheral neuropathy (BiPN), with a clinical symptom improvement rate of 80%, while only 40% in the methylcobalamin group, and nerve conduction velocity was also significantly

improved ($P < 0.01$). Bushen Huoxue Tongluo Decoction[67] combined with a modified Parkinson's disease (PD) regimen treats multiple myeloma (MM)-related bone disease by restoring RANKL/OPG balance, promoting osteoblast differentiation (Runx2 increased 2.1-fold), and increasing bone mineral density (+12.5% vs 4.8%, $P < 0.05$). In addition, Huanglian Jiedu Decoction[68] and its main component baicalin promoted MM cell apoptosis by inhibiting NF-κB signaling and downregulating XIAP and IL-6, with clinical data showing a higher ORR (89.47% vs 73.68%, $P = 0.03$) and a 35% reduction in the incidence of peripheral neuropathy. Finally, Huayu Jiedu Decoction[69] induced apoptosis by regulating the expression of Bax, Bcl-2, and Survivin, while downregulating HMGB1 (mRNA expression decreased by 58%) and IL-6, and inhibiting the TLR4/NF-κB axis - these actions together reversed the immunosuppressive state in the tumor microenvironment and improved PI sensitivity.

These findings provide a theoretical basis for further research on TCM-based compound preparations as an adjuvant strategy for optimizing PI therapy for multiple myeloma.

Conclusion

The integration of traditional Chinese medicine (TCM) with proteasome inhibitors (PIs) has emerged as a promising approach for enhancing therapeutic efficacy in multiple myeloma (MM). TCM-derived compounds—classified by chemical structure into flavonoids, indole derivatives, terpenoids, quinones, polyphenols, and alkaloids—demonstrate the ability to modulate multiple oncogenic pathways, including PI3K/AKT/mTOR, JAK/STAT3, and NF-κB. These compounds exert synergistic effects with PIs by promoting apoptosis, inhibiting proliferation, reversing drug resistance, and in some cases, directly inhibiting proteasomal catalytic subunits such as β5 and β2.

Despite robust preclinical evidence supporting these synergistic mechanisms, translation into clinical practice remains limited. Most existing studies focus on isolated monomers or simplified in vitro models, which do not fully reflect the complexity of multi-herbal TCM formulations commonly used in clinical settings. Additionally, safety concerns—such as hepatotoxicity or nephrotoxicity associated with high-dose administration—highlight the need for optimized dosing strategies and rigorous toxicity evaluation, particularly in elderly or comorbid MM populations.

High-quality clinical evidence is currently insufficient, with few randomized controlled trials (RCTs) or real-world studies (RWS) evaluating TCM–PI combination regimens. To address these gaps, future investigations should prioritize the systematic evaluation of multi-component herbal formulations, elucidate drug–herb and compound–compound interactions, and design translational studies that align traditional practices with modern standards of evidence-based oncology.

In summary, this review provides a mechanistic foundation for the rational integration of TCM with proteasome inhibitors in MM therapy. By mapping the synergistic molecular interactions between natural compounds and targeted agents, it offers a framework for the development of safer and more effective combinatorial strategies, with the ultimate goal of improving clinical outcomes in patients with relapsed, refractory, or treatment-resistant MM.

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Disclosure

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