Potential therapeutic effects of natural extracts in multiple myeloma

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Received: April 14, 2016
Published online: June 06, 2016

Introduction

MM is an incurable malignant tumor of B-cell origin. The malignant clone expands in the bone marrow, causing lytic bone lesions, anemia, hypercalcemia and renal failure [1]. Despite the advance in current clinical treatment and new therapeutic agents, including thalidomide, lenalidomide, and bortezomib, MM is still incurable and patients eventually relapse and become resistant with 5-7 years median survival time [2]. Therefore, there is a need for novel therapeutic strategies to improve patient outcome.

Over half a century, phytochemicals have been an important part of antineoplastic drugs and new chemotherapy adjuvants to enhance the efficacy of chemotherapy in multiple myeloma. Because of their capacity to bind multiple targets, natural products may have an advantage over rationally designed mono-targeted agents in the treatment of multiple myeloma with multi-aspect abnormalities [3]. Most importantly, they show no or minor toxicity towards normal epithelial and normal peripheral blood and myeloid cells, indicating a therapeutic window. For example, Taxol and Vinblastine have been widely used in the treatment or in
combination with other cancer chemotherapeutic drugs for a variety of cancers \cite{4}. More than 48% of antineoplastic drugs are actually being either natural products or directly derived therefrom from 1940s \cite{5}. This review will focus on the natural compounds such as Gambogic Acid, Curcumin, Resveratrol and Scutellaria extracts, which are proved to have anti-myeloma activities.

Gambogic acid (GA) is the main active component of Gamboge resin derived from the resin of Garcinia hanburyi, a plant that mainly grows in Southeast Asian. Recent in vitro and in vivo studies demonstrated that GA has extensive anti-tumor activities in several types of tumors, such as hepatocellular carcinoma, oral squamous cell carcinoma, breast cancer, malignant melanoma, gastric carcinoma, and leukemia \cite{6-11}. These lines of evidence prove that GA has the potential to be an agent in MM treatment.

Curcumin is a polyphenol derived from Curcuma longa and has being used as an anti-inflammatory agent for a variety of illnesses thousands of years in Asia. The anti-tumor effects have been well described in various types of cancers \cite{12}. Curcumin suppress transformantion, proliferation, metastasis and osteoclastogenesis through regulating multiple cellular targets in MM cells.

Resveratrol is a polyphenolic phytoalexin present in wine, grape and peanut. It has recently attracted considerable interests because of its inhibitory activity on multiple cellular and molecular events associated with several tumor developments, including breast and colon cancer cells, cervical tumor cells, and gastric adenocarcinoma cells \cite{13-17}.

Baicalein and wogonin are the main bioflavones isolated from Scutellaria root. The flavones have been shown to exert antioxidant, anti-viral, anti-inflammatory, anticancer, and neuroprotection \cite{18-22}. They are also highly effective in protecting against MM cells through inducing apoptosis, suppressing cell cycle and decreasing the proportion of side population cells. The topic of this review will discuss the pharmacological properties and mechanisms of these natural drugs and their therapeutic potential for treating MM, so as to provide views for further research.

**Apoptosis induction**

Apoptosis is a morphologically and biochemically distinct form of eukaryotic cell death that occurs under a variety of physiological and pathological conditions \cite{23}. Apoptosis is executed via both extrinsic (receptor-mediated) and intrinsic (mitochondria-mediated) pathways that lead to the activation of caspases. It has been established that apoptosis in plasma cells plays an important role in pathogenesis and drug resistance in MM \cite{24, 25}. Many studies have shown that natural agents can suppress MM cells proliferation by inducing apoptosis. They selectively kill MM cells but not normal peripheral blood cells. Nature products always induce apoptosis in MM cells through mitochondrial pathway because the regulating mechanisms for apoptosis are associated with members of the Bcl-2 family, which comprises both proapoptotic and antiapoptotic proteins. However, the molecular mechanisms how they trigger apoptosis are complex and multiple.

**STAT3 inhibition**

Among all STAT family members, STAT3 is most often correlated to tumorigenesis, and is considered as an oncogene as it is the point of convergence of many signaling pathways triggered by cytokines, growth factors and oncogenes. It has been found that most MM cells harboring persistent both constitutive and inducible activation of STAT3 have elevated levels of anti-apoptotic (Mcl-1 and Bcl-XL) and cell cycle regulating proteins (cyclin D1 and c-Myc) \cite{26}. Several cytokines and growth factors like IL-6 and insulin-like growth factor (IGF) family members, as well as hepatocyte growth factor (HGF) mediate activation of STAT3 by phosphorylation \cite{27}. As one of the central MM survival factors, IL-6 induces the differentiation of normal B cells to antibody-secreting plasma cells and promotes MM cell growth \cite{28}. In addition, IL-6 production is associated with a resistance to chemical agent-induced apoptosis of MM cells \cite{29}. In MM, Initiation of STAT3 activation through ligand (such as IL6)-receptor interaction induces dimerization of gp130 chains, then results in activation of the associated Janus kinase (JAKs). JAKs phosphorylate gp130, leading to the recruitment and activation of the STAT3, and results in STAT3-mediated transcriptional regulation \cite{30, 31}. These observations highlight the potential importance of STAT3 gene for antiapoptotic signaling and made it a prime target for therapeutic intervention.

Over the last decade, studies show that GA \cite{3}, Curcumin \cite{32}, Resveratrol \cite{33} and Icaritin \cite{28} have shown significant efficacy in blocking STAT3 activation and thereby inducing apoptosis in multiple myeloma cells. Prasad et al. \cite{3} found that GA induced MM cell apoptosis that correlated with inhibition of both constitutive and IL-6-induced STAT3 activation in a dose- and time-dependent manner. STAT3 suppression is mediated through the inhibition of activation of JAK1 and JAK2. Meanwhile, GA induced the expression of the PTP SHP-1, and silencing of the SHP-1 gene abolished the ability of GA to inhibit STAT3 activation. Then, GA down-regulates the expression of
Icaritin has been reported to inhibit proliferation and induce apoptosis in MM model both in vitro and in vivo. Icaritin induces U266 cells and CD138+ primary MM cells apoptosis with concentration-dependent way. The regulating mechanisms for apoptosis are associated with a cleaved activation of caspase 9 and 3; up-regulated the expression of Bax, Bak proteins and down-regulated expression of Bcl-xL, which mainly involve in the inhibition of IL-6 driven-JAK2/STAT3 signaling pathway. Upon administration of Icaritin, the growth of human multiple myeloma xenograft tumors in female NOD/SCID mice is inhibited [28]. Zhu et al. [28] also found that Icaritin evidently inhibits IL-6/STAT3 activities, associated with upstream p-JAK2 inhibition. The inhibition of JAK2 or signal blocking of STAT3 mostly abolish the effect of Icaritin on growth-inhibiting and apoptosis-inducement of U266 cells.

In a previous study, baicalein was found to suppress the proliferation of IL-6 and inhibit IL-6 gene expression in myeloma cells. Liu [34] and Zhang [35] further found that baicalein abrogates IL-6-induced phosphorylation of JAK, STAT3, MAPK, and Akt in myeloma cell lines. Myeloma cells studied are all sensitive to baicalein, regardless of whether or not they are IL-6 dependent, and whether or not they are Dex-sensitive.

**NF-κB inhibition**

NF-κB, as an inducible transcription factors that controls over one hundred gene expression, plays a pivotal role development, proliferation, and survival of MM cells. When activated, NF-κB proteins trans-activate target genes encoding regulators of the cell cycle (eg, cyclin D1 and cyclin D2), anti-apoptosis genes (eg, Bcl-2 and Bcl-DR1) [36]. In MM cells, NF-κB is highly activated and thus contributes to the anti-apoptosis gene overexpression, which inhibits cell apoptosis [37]. GA [36], Curcumin [38], Baicalein [39] and Resveratrol [33] could downregulate expression of many anti-apoptotic gene products e.g. TRAF1, Bcl-2, Bcl-xL, IAP-1 and IAP-2 by inhibiting NF-κB activation, leading to MM cell apoptosis.

Numerous studies have shown that curcumin is pharmacologically safe. Curcumin suppresses constitutively IκBα phosphorylation in all MM cell lines through the inhibition of IκK activity. This leads to inactivation of NF-κB and down-regulation of expression of NF-κB-regulated gene products, including Bcl-2, Bcl-xL, cyclin D1 and IL-6, thus suppressing proliferation and inducing apoptosis in MM cells. Suppression of NF-κB by curcumin also induces apoptosis of MM cells by activation of caspases and cleavage of PARP. Additionally, down-regulation of NF-κB by curcumin also sensitizes MM cells to vincristine, melphalan [38].

GA suppresses NF-κB activation induced by various inflammatory agents and carcinogens (e.g. TNF, LPS, PMA). Manoj’s group first showed that GA suppresses TNF-mediated IκK activation and subsequent NF-κB activation through disrupting the interaction between TAK1 and TAB and this, accompanied by the inhibition IκBα phosphorylation and degradation, and finally abrogates NF-κB-dependent reporter gene expression including c-Myc, TRAF1, Bcl-2, Bcl-xL, IAP-1, and IAP-2 [36].

Baicalein is reported to inhibit the production of IL-6 and induce apoptosis in myeloma cell lines through suppression the phosphorylation of IκB-α. Baicalein selectively affects the survival of MPC-1 immature myeloma cells but not MCP-1 mature myeloma cells, and this effect would contribute to the inhibition of relapse during maintenance therapy in multiple myeloma [39]. Otsuyama [40] found that baicalein shows strong PPARβ-stimulating activity and suppresses the NF-κB activity. The mechanism for its down-regulation of NF-κB activity is associated with the up-regulation of IκB gene expression and the inhibitory physical interaction between the p65 subunit of NF-κB and PPAR in the nucleus.

Resveratrol down-regulates NF-κB expression in all MM cell lines and leads to down-regulation of the expression of gene products (IL-6, Bcl-2, Bcl-xL, XIAP, c-IAP, VEGF and MMP-9) regulated by NF-κB, thus inhibiting cell proliferation and invasion, and inducing apoptosis in MM cells. Meanwhile, results from preclinical studies in rats suggested that resveratrol conjugates seem to reach much higher plasma levels than the parent agent. Validation of in vitro findings with an in vivo model system is warranted for the potential clinical application of resveratrol in the management of patients with MM [41].
**ROS accumulation**

ROS, including free radicals such as superoxide and hydrogen peroxide, are mainly produced by mitochondrial oxidative respiratory chain. Overproduced ROS and free radicals can specifically regulate the process involved in the initiation of apoptotic signaling cascades, such as caspases, which induce apoptosis by cleaving substrates, such as cell cycle and DNA repair-related proteins, and thus contribute to cell apoptosis. ROS could also induce the depolarization of the mitochondrial membrane potential (MMP), leading to the release of factor cytochrome c from the inner mitochondrial membrane into the cytosol, which activates the pro-apoptosis molecules (caspase-3, caspase-9) [42, 43]. Therefore, it is believed that anticancer activity of some chemotherapy may involve the increased ROS concentration. Yang et al. [44] reported that GA induces MM cell apoptosis and inhibits proliferation in a dose-dependent manner, and these changes are accompanied by the activation of caspase-3, cleavage of PARP-1 and deregulation of ROS. The ROS scavenger N-acetylcysteine (NAC) blocks GA-induced MM cell apoptosis. The activation of caspase-3 and the cleavage of PARP caused by GA is also inhibited by the pretreatment of NAC. This result indicates that GA could induce apoptosis in MM cells via ROS accumulation.

**Inhibition of osteoclastogenesis**

Bone disease caused by an imbalance in the function of osteoblasts and osteoclasts is the hallmark of MM [45]. The high receptor activator of NF-κB ligand (RANKL)/osteoprotegerin (OPG) ratio leads to an increase of osteoclasts and enhancement of bone resorption [46]. At the same time, increased osteoclasts allow proliferation and survival of MM cells [47]. Bone disease in MM cannot be repaired because decreased osteoblast makes the function of bone formation deficient. Clinical drug like bisphosphonates are used to cure bone disease [48]. However, harmful side effects preclude the use of these drugs and not all patients respond to bisphosphonates [49]. This problem may be solved by using the low toxic natural products like GA [50] and resveratrol [51].

Through the interaction with each other, MM cells and invading plasma cells stimulate production of numerous cytokines, such as IL-6, SDF-1α, MCP-1, that stimulate RANKL, leading to osteoclasts development and function [52]. As a regulator of bone resorption, high levels of SDF-1α in bone marrow can up-regulate IL-6 expression and osteoclastogenesis through CXCR4 and NF-κB activation [53]. Pandey and his colleagues [50] found that GA directly interacts with CXCR4 on MM cells and subsequently inhibits NF-κB DNA binding. This inhibition of CXCR4 leads to the inhibition of IL-6 expression and osteoclastogenesis. The effect of GA in IL-6 inhibition is specific because GA does not affect other OC-related growth factors. GA abrogates the RANKL-and MM-induced differentiation of macrophages to osteoclasts. The results suggest that GA, which is highly affordable and safe, can suppress osteoclast formation induced by MM.

Resveratrol has been reported to inhibit myeloma cell growth, prevent osteoclastogenesis and bone resorption, and promote osteoblast differentiation. The mechanisms are associated with down-regulation of RANK expression at both mRNA and cell surface levels and reduction of NF-κB nuclear translocation. Moreover, Resveratrol stimulates the mRNA expression of osteocalcin and osteopontin, the late markers of osteoblast differentiation. Because 1,25(OH)2D3 directly activates transcriptional promoters of osteocalcin and osteopontin genes. Dr Patrice examined the relative gene expression of the nuclear receptor of 1,25(OH)2D3 (vitamin D receptor (VDR)). Interestingly, he found up-regulates the expression of VDR, the nuclear receptor of 1,25(OH)2D3 and thereby stimulates osteoblast differentiation. In accordance with the in vitro data, rat studies shown that oral administration of resveratrol prevents decrease in bone femur strength and increases epiphysis bone mineral density in the same manner as the bisphosphonate alendronate. Thus, the in vitro and in vivo studies suggest that resveratrol may prevent increased bone degradation by osteoclasts or may stimulate compensative bone formation by osteoblasts [51].

**Angiogenesis repression**

Angiogenesis, supporting the growth, survival, progression, and drug resistance acquisition of the MM cells, plays a critical role in the pathophysiology and progression of MM [54]. Hypoxia, a key feature of the most MM microenvironment, is a leading cause of angiogenesis [55]. In the tumor cells, hypoxia-inducible factor-1α (HIF-1α) has been regarded as the most important transcriptional factor promoting angiogenesis. Under hypoxia, HIF-1α can escape the Von Hippel-Lindau tumor suppressor protein (VHL) binding and proteasome degradation, translocate to the nucleus, heterodimerize with HIF-1β, and induce transcription of pro-angiogenic genes such as vascular endothelial growth factor (VEGF, PDGF, bFGF ), which can enhance the microvascular density of bone marrow and accounts for the abnormal structure of myeloma tumor vessels [56]. The previous studies have demonstrated the bone marrow microenvironment is hypoxic in MM patients and determined the role of hypoxia and HIF-1α in angiogenesis in MM mouse models [57]. Recent studies have shown many mechanisms regulate the HIF-1α expression at the level of transcription, translation and protein stability, such as NF-κB,
PI3K/Akt, and c-Myc-dependent mechanisms. These signaling pathways can activate HIF-1α expression in non-hypoxic and hypoxic cells. Clinical studies have also indicated that MM cells often exhibit increased rates of angiogenesis, even in the presence of adequate oxygen concentration. Wang et al. demonstrated that GA dramatically downregulates the expression of HIF-1α protein and vascular endothelial growth factor in U266 cells via suppression of PI3K/Akt/mTOR pathway under hypoxia. BALB/C nude mice model showed that GA can prevent the development of myeloma growth that may be attributed to inhibition of tumor angiogenesis and growth, possibly by attenuating HIF-1α and VEGF expression inside the tumors. Last year, our group reported wogonin has the ability to inhibit expression/secretion of the main pro-angiogenic factors (VEGF, PDGF, bFGF) in MM cells via c-Myc/HIF-1α signaling pathway, leading to the reduction in MM-stimulated angiogenesis and thus prevents tumor growth in vivo. Unexpectedly, we discovered that overexpression of c-Myc in MM cells impairs function of VHL ubiquitin complex via disrupting the balance between VHL SUMOylation and ubiquitination, which consequently inhibits HIF-1α degradation through the ubiquitin-proteasome pathway. Meanwhile, c-Myc-mediated unbalance between VHL SUMOylation and ubiquitination in MM cells is normalized by wogonin, resulting in the activation of HIF-1α-VHL interaction and eventually HIF-1α degradation in MM cells.

Reversal of drug resistance

Common front line agents used in the induction therapy of MM are either two drug or three drug combinations of melphalan, dexamethasone, thalidomide, lenalidomide and bortezomib. Although most patients show very good response to standard and high dose chemotherapeutics at first, they will relapse eventually due to the development of the multidrug resistance (MDR), which leads to the failure of chemotherapy. Several biological mechanisms are implicated in chemoresistance, including enhancement of DNA damage repair, e.g. Fanconianemia (FA)/BRCA pathway, and NF-κB.

Inhibition of FA/BRCA

It is reported that the MDR has a relation with the enhanced DNA damage repair in MM cells. Many chemotherapeutic drugs are DNA cross-linking agents, such as mitomycin C, cisplatin (DDP), cyclophosphamide (CTX), and melphalan. Melphalan induces interstrand cross-links (ICLs) and it is widely used in MM treatment. Several studies suggested that enhanced interstrand cross-link (ICL) repair is enhanced through the FA/BRCA pathway and regulates the cellular response to melphalan in myeloma cell lines. There is a significant activation of FA/BRCA pathway in drug-resistant MM cells compared with drug-sensitive MM cells, which suggesting that activation of FA/BRCA pathway may contribute to enhanced DNA ICL repair capacity in drug-resistant cells, and disruption of FA/BRCA pathway reverses drug resistance. In Xiao’s study, curcumin reverses multidrug resistance of MOLP-2/R cells to melphalan via suppression of FA/BRCA pathway by the inhibition of FANCD2 monoubiquitination. Curcumin reduces DNA damage repair and induced apoptosis through inhibition of FA/BRCA pathway. Curcumin also increases the intracellular concentration of melphalan and thus effectively blocking the MDR of MOLP-2/R cells.

Regulation of NF-κB

Current therapeutic approaches, such as bortezomib and IMiD, target core components of NF-κB pathway, and so, although they are potentially capable of abrogating the cancer-promoting activities of NF-κB, they fail to preserve their efficient antitumor effects. The best documented function of NF-κB in cancer is to induce genes that block apoptosis and, despite its ubiquitous nature, NF-κB signaling elicits highly tissue- and context-specific transcriptional programs. When compared to chemosensitive MM cell lines chemoresistant MM cells express higher levels of NF-κB, suggesting a link between NF-κB and development of chemoresistance. Thus targeting deregulated NF-κB activation can be an important strategy pharmacological strategy to overcome chemoresistance in MM patients. Sung suggested that the ability of curcumin can overcome the chemoresistance of MM cells to chemotherapeutic agents and potentiate the effects of Thalidomide and Bortezomib via suppression activation of NF-κB pathway and expression of NF-κB-regulated antiapoptotic gene products. Moreover, when combined with bortezomib in vivo, there is a higher antmyeloma effect than either agent alone in human multiple myeloma xenograft in nude mice.

Regulation of ABCG2

Increasing evidence indicates that cancer stem cells (CSCs) resist current standard chemotherapeutics in multiple myeloma and repair DNA after treatment and that these CSCs are responsible for the recurrence of tumors after treatment. SP cells are considered as an enriched source of CSCs with the stem cell characteristics, e.g. proliferative potential, self-renewal, and differentiation, which are considered to contribute to chemoresistance and tumorigenicity in vivo. Several recent reports have also demonstrated the presence of SP cells in multiple myeloma, and these SP cells could survive in standard...
chemotherapeutics for MM [71]. The ATP-binding cassette, subfamily G, isoform 2 protein (ABCG2) is a molecular determinant of the SP phenotype, and has been suggested to be involved in multidrug resistance in cancer. The ABCG2 acts as efflux proteins to transport a variety of molecules, including certain chemotherapeutic drugs [72]. Data suggested that ABCG2 is a promising molecular marker for identification of CSCs in tumors. ABCG2 possesses a relatively conserved structure, which contains a combination of conserved nucleotide binding (NB) and transmembrane (TM) domains. Between NB and TM, it's a linker region. The NB domain is the ATP-binding subunit, which is located at the N-terminus of the polypeptide chain. The close interaction of the two NB units can bind ATP, which then activates the both catalytic sites [73]. The TM domains are the crucial binding regions for substrates, where most of the amino acid residues were predicted to form helices, TM1–TM6. The six α-helices result in the formation of the central substrate translocation pathway and mediate substrate transfer through the membrane [74]. A few equilibrium for kinetic binding studies suggested that most chemotherapeutic agent bind clustered in one region, such as doxorubicin, daunomycin and prazosin, which eventually leads to MDR [75]. Lin et al. [76] found for the first time that baicalein and wogonin stongly modify the proportion of SP cells through the way of modulating the ABCG2 expression in myeloma cells. The results imply that baicalein and wogonin perform their anticancer effect mainly targeting CSCs of tumors. That might clarify the reason why baicalein and wogonin were found to target specifically to malignant cells with low toxicity to corresponding dormant or normal plasma cells. From this point, baicalein and wogonin were suggested to be used as adjuvant agents for conventional chemotherapeutic.

Gu’s group [73] further clarified the molecular mechanism linked between baicalein and ABCG2 expression. Gu [73] investigated baicalein could dock into all the TM five binding sites of ABCG2 and diminish side population proportion in RPMI 8226.Baicalein shared the similar features with as specific inhibitors of ABCG2 (FTC) to bind to ABCG2. The data suggest that baicalein and wogonin may possess the potential to overcome MDR by targeting SP cells, and thus they can enhance effect of chemotherapy in multiple myeloma.

Conclusions

In summary, natural products have been shown to possess multiple anti-myeloma activities, including induction of apoptosis, inhibition of cell cycle, inhibition of osteoclastogenesis, suppression of angiogenesis and reversal of drug resistance, both in vivo and in vitro. Compared with existing anti-myeloma chemotherapy and agents, natural products present two major advantages, minimizing side-effects towards normal cells and reversal of drug resistance. Therefore, these studies suggest that natural products, used either alone or in combination with other drugs, represent a promising novel targeted approach to overcome drug resistance and improve patient outcome in MM.

Conflicting interests

The authors have declared that no conflict of interests exist.

Acknowledgments

This work was supported by a Startup Fund from China Pharmaceutical University, a grant from the Program for Jiangsu Province Innovative Research Team and a grant from State Key Laboratory of Natural Medicines, China Pharmaceutical University (SKLNMZZJQ201604).

Author Contributions

Rong Fu and Wen-Cong Lv drafted and revised the manuscript, Zhao-Qiu Wu and Qing-Long Guo contributed to the conception of the paper and proved the final version.

Abbreviations

MM: multiple myeloma; GA: gambogic acid; IGF: insulin-like growth factor; HGF: hepatocyte growth factor; JAK: Janus kinase; Dex: dexamethasone; MPP: mitochondrial membrane potential; NF-κB: nuclear factor kappa-B; NAC: N-acetylcysteine; RANKL: receptor activator for nuclear factor-κB ligand; OPG: osteoprotegerin; VDR: vitamin D receptor; HIF-1α: hypoxia-inducible factor-1α; VHL: Von Hippel-Lindau tumor suppressor protein; MDR: multidrug resistance; FA: Fanconianemia; DDP: Cisplatin; CTX: cyclophosphamide; ICL: interstrand cross-link; CSC: cancer stem cells; ABCG2: ATP-binding cassette subfamily G isoform 2 protein; NB: nucleotide binding; TM: transmembrane; STAT: signal transducers and activators of transcription; PTP: protein tyrosine phosphatase; MAPK: mitogen-activated protein kinase; ROS: reactive oxygen species.

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