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Review Article

Molecular Basis and Potential Molecular Mechanisms of Action in Natural Products as Therapeutic Agents Towards Multiple Myeloma

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ABSTRACT

Multiple myeloma (MM) is a bone marrow-based neoplasm of clonal plasma cells resulting in substantial mortality and morbidity. It is classified as a mature B-cell neoplasm in which clonal plasma cell proliferation results in anaemia, hypercalcaemia and organ/tissue damage such as kidneys and skeletal system. The response rates of myeloma improved significantly following the introduction of novel therapies such as immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), monoclonal antibodies (MoAbs), hematopoietic stem cell transplant and cellular therapies such as chimeric antigen receptor (CAR) T-cells. However, MM remains incurable. In addition, adverse effects, exorbitant costs, and problems with accessibility to drugs and therapeutic modalities prevent many patients from reaping the potential benefits of these novel therapies. Therefore, it is essential to investigate new therapeutic targets and agents. Many cell-signalling pathways are described in MM. Some facilitate the evasion of apoptosis and long periods of cell survival. Natural products contain a variety of secondary metabolites targeting these signalling pathways responsible for anti-MM activities such as apoptosis, cell cycle arrest, anti-angiogenesis, and miRNA modulation. The role of natural compounds as therapeutic agents in the treatment of multiple myeloma has drawn a considerable interest in research in recent past. This review attempts to collate available information on natural products from terrestrial plants, animals, and macrofungi, and their potential molecular mechanisms in MM.

Keywords: Multiple Myeloma, Natural Products, Anticancer, Apoptosis, Cell Signalling

Introduction

Multiple myeloma (MM) is a malignancy in plasma cells based on bone marrow. It has multifocal proliferation of neoplastic plasma cells that is incurable, resulting in substantial mortality and morbidity rates worldwide. It is classified as a mature B-cell neoplasm per the World Health Organisation (WHO) classification of 2016.[1] It spans a broad clinical spectrum from asymptomatic to highly aggressive. MM is commoner in males and very infrequent in adults <30 years of age, accounting for about 1% of all malignant tumours and 10-15% of hematopoietic malignancies. Age affects the prevalence of MM, with patients over 50 accounting for 90% of cases. It accounts for about 20% of deaths from haematological malignancies.[1] Incidence of multiple myeloma was 1.78 per 100,000 people in 2020, while death was 1.14 per 100,000 persons worldwide.[2] Although the incidence of MM varies significantly among countries and regions, increasing trend was observed in high-income countries.[2] Incident cases have increased from 1990 to 2016 by 126% globally.

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Chronic diseases and exposure to some specific industrial or agricultural toxic substances/radiation have contributed to the increased incidence of MM.[2]

As cancer, MM can be considered somewhat unique for two reasons. Firstly, it can be diagnosed with a panel of basic diagnostic tests, commonly accessible for free in low- and middle-income nations. Secondly, treatment can be given exclusively as an outpatient except for autologous hematopoietic stem cell transplantation (auto-HSCT).

Method

Published articles in Google Scholar, PubMed, Scopus, Springer, ScienceDirect and electronically available books were searched from the earliest to 2022 to gain relevant information to conduct this review. A literature survey was performed using the keywords "multiple myeloma", along with "natural products", "therapeutic agents", "molecular mechanism", "novel therapies", and "signalling pathways". Resulted articles were sorted according to their relevance and suitability for writing the review.

The information gained about natural products was analysed, and the sources were sorted as terrestrial plants, animal toxins and macro-fungi. Chemical structures of the particular natural product compounds were verified using the PubChem NCBI database, and the structures were drawn using ChemDraw JS. Chemical structures and their mechanisms of action were tabulated. Scientific illustrations were created using BioRender platform to depict the signalling interactions between myeloma cells, other bone marrow cells, microenvironment and therapeutic targets of some active compounds, and novel therapeutic agents.

Current treatment options in myeloma and their limitations

Treatment of myeloma has evolved and improved substantially during the past decade or two due to so-called modern treatment options such as immunomodulatory (IMiDs) followed by proteasome inhibitors (PIs), and more recently, monoclonal antibodies (MoAbs), histone deacetylating agents, and cellular therapies (Figure 1).[3] Auto-HSCT is the standard of care post-remission induction in all transplant eligible (<70-75 years with a good performance status and acceptable co-morbidities patients). Immunomodulatory drugs (IMiDs), analogues of thalidomide, have many antimyeloma properties due to the down-regulation of crucial cytokines. In addition, properties such as immune modulation, anti-angiogenesis and anti-inflammation are mainly due to their anti-tumour necrosis factor (TNF) α activity.[4] In 1999, the first IMiD, thalidomide, was introduced and has since made way for newer generations of IMiDs, such as lenalidomide and pomalidomide.[5] The proteasome is a protein complex which maintains cellular homeostasis by selectively degrading the cellular regulatory proteins.[6] Bortezomib is the first generation of PIs.[7] Newer PIs such as carfilzomib and ixazomib are also used regularly in countries where available and affordable. MoAbs, once called 'magic bullets', are considered less toxic than conventional chemotherapy because they are target-oriented and bind directly to antigens expressed on tumour cells. They act by directly blocking the functional activity of the specific antigen. Other mechanisms of action include cell death via complement activation, antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP).[8] The widely used MoAb for MM is daratumumab, a humanized IgG1-kappa monoclonal antibody that targets CD38 expressed on plasma cells and other cells such as lymphocytes and engenders cellular toxicity in MM cells[5], followed by elotuzumab, a humanized IgG1 monoclonal antibody against SLAMF7 also referred to as CS1. More recently, IgG chimeric MoAb isatuximab, which binds selectively to a specific epitope on human CD38, has been demonstrated to have antimyeloma activity by direct apoptosis, ADCC, and ADCP.[9] Adverse effects such as acute anaphylaxis, serum sickness, cardiotoxicity, and cytokine release syndrome (CRS) have been reported with MoAbs.[10,11]

However, more importantly, even with all the available therapeutic modalities, MM patients can only be offered significantly better survival rates (disease-free survival and overall survival) yet not a "cure". Furthermore, many new modalities, such as MoAbs and chimeric antigen receptor T-cell (CART) therapy, are unavailable for most patients worldwide, one reason being their exorbitant cost.

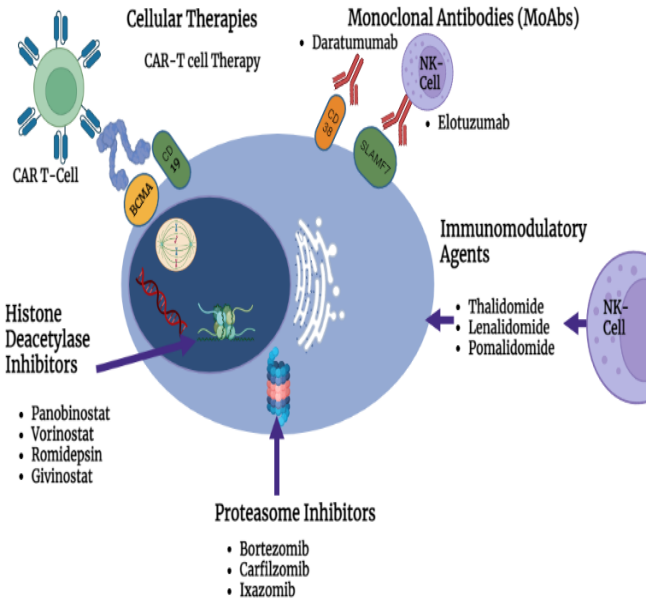

Figure 1: Novel therapeutic agents in multiple myeloma

Therefore, much is being done to investigate the role of natural products as an adjuvant to current MM therapies or to add more widely accessible, cost-effective products to the available armament of anti-MM agents.

Role of natural products as therapeutic agents

Over thousands of years, nature has provided a vast array of medicines for the health benefits of humankind. Sorokina and Steinbeck have recently published a review on natural product information compiling over 120 databases.[12] Natural products are significant sources of new pharmaceuticals and pharmaceutical lead compounds.[13] They involve in a significant role in the survival of interspecies competition in an organism,[14,15] and provide defensive mechanisms against stress.[16] Secondary metabolites have been shown to act as antibacterial[17] or antifungal agents,[18] anticancer drugs,[19] cholesterol-reducing agents,[17] immunosuppressants,[20]anti-parasitic agents[21] and herbicides.[22] Natural products are not only drugs but also serve as structural models for developing synthetic analogues and use as models in structure-based mechanism studies.[23] From drugs introduced based on natural products during 1981-2014 globally, 63% are natural product or their synthetic derivatives.[24]

Recently, a rapid increase in published data regarding anticancer agents from natural resources has appeared. The development of analytical techniques, computerized technologies, and robotics employed in drug screening have paved the path for increased effectiveness and speed up the screening process of natural products in the rapid evaluation of drug candidates and to interpret the mechanism of action.[25]

Publications and databases published on natural products reflect the enthusiasm for exploring natural products for drug discovery and other purposes. However, new active compounds remain unexplored and are still to be unearthed in drug discovery.

Chemotherapeutic agents derived from terrestrial plants with antimyeloma activity

Drug discovery programs with anticancer activity began with World War II.[26] The potential anticancer effects of natural products were identified by the National Cancer Institute (NCI) in the 1950s. Since then, many studies have offered insightful information on discovering new anticancer agents from natural origin.[27]

Natural products from terrestrial plants have been discovered as key sources in anticancer drug areas. Some plant-derived anticancer agents are vinblastine and vincristine, etoposide, paclitaxel, docetaxel, topotecan, and irinotecan which contain effective cancer chemotherapeutics.[28] Several new therapies exist that can improve the response rate and the survival rate of MM patients. However, limited solubility in aqueous media [29] and convincing toxic side effects still prevail.[30] Accordingly, it is necessary to continue searching for novel therapies from natural products and their analogues to minimize these issues targeting MM (Table 1).

Gambogic acid (GA) and fisetin are secondary plant metabolites that induce apoptosis in MM cells through the activation of caspase-3 and poly(ADP-ribose) polymerase (PARP) cleavage.[30,31,32] Moreover, the authors demonstrated that N-acetylcysteine, a reactive oxygen species (ROS) scavenger, inhibits apoptosis induced by both GA and fisetin via ROS accumulation.[32] Prasad et al. revealed that GA induces MM cell apoptosis by inhibiting the activation of signal transducer and activator of transcription-3 (STAT3).[33] Further, GA inhibits the phosphorylation of STAT3 at both tyrosine residue 705 and serine residue 727.[33] In the same study, the authors manifest that GA downregulates the utterance of STAT3-regulated proteins such as cyclin D1, cyclo-oxygenase 2 (COX-2), vascular endothelial growth factor (VEGF) and the antiapoptotic gene products, including cellular inhibitor of apoptosis (c-IAP), mantle cell lymphoma 1 (Mcl-1), survivin, B-cell lymphoma gene 2 (Bcl-2), and B-cell lymphoma-extra-large (Bcl-XL) (Figure 2).[33]

Pandey and co-workers found that GA inhibits nuclear factor kappa B (NF-κB) DNA binding by suppressing C-X-C chemokine receptor type 4 (CXCR4) expression in MM cells.[34] They further reported that GA suppresses stroma-derived factor-1 (SDF-1α) induced chemotaxis of MM cells (Figure 2) and downstream signalling of CXCR4 by

inhibiting phosphorylation of Ak strain transforming factor (Akt), p38, and extracellular signal-regulated kinase 1 and 2 (ErK1/2) and suppression of osteoclastogenesis mediated through interleukin 6 (IL-6) inhibition in MM cells (Figure 2).[34] GA also forbids the differentiation of macrophages to osteoclasts through receptor activator nuclear factor kappa B ligand (RANKL) (Figure 2).[34] Wang and co-workers showed that GA down-regulates the pronouncement of hypoxia-inducible factor 1α (HIF-1α) protein and VEGF in U266 cells (Figure 2).[35] In addition, they found that hypoxic conditions induce activation of phosphatidylinositol 3-kinase (PI3K) / Akt / mammalian target of rapamycin (mTOR) signalling pathway in U266 cells. [35] BALB/c nude mice model shows that GA can arrest the growth of myeloma, which could be assigned to the inhibition of tumour angiogenesis and growth, perhaps by attenuating HIF-1α and VEGF expression inside tumours.[36]

Resveratrol is a potentially active compound as it affects the physiological functions in MM, such as inhibition of myeloma cell growth, inhibition of osteoclast differentiation and bone resorption, and promotion of osteoblast differentiation (Figure 2).[37] These cause the down-regulation of RANK levels and lowering of NF-κB nuclear translocation.[37] Further, resveratrol induces the mRNA expression of osteocalcin and osteopontin, which are late markers of osteoblast differentiation.[37] Resveratrol suppresses STAT3 initiation and induces apoptosis in MM cells.[38] Sun et al. have shown that resveratrol suppresses the expression of IL-6, Bcl-2, Bcl-Xl, x-link inhibitor of apoptosis (XIAP), a cellular inhibitor of apoptosis (c-IAP), VEGF, and matrix metalloproteinase 9 (MMP-9) gene product and this is accompanied by the inhibition of activation of NF-κB in MM cells (Figure 2).[39] Low doses of the proteasome inhibitor carfilzomib and low concentrations of resveratrol worked together to cause myeloma cells apoptosis. To boost the formation of ROS, resveratrol was combined with carfilzomib. Additionally, after the resveratrol /carfilzomib combination, in MM cells, the activity of the deacetylase enzyme, a stress sensor known as SIRT1, was substantially downregulated, sharply decreasing its target protein, survivin. In myeloma cells, the resveratrol /carfilzomib combination therapy simultaneously induced autophagy.[39]

Curcumin inhibits the NF-κB pathway in MM cells by suppressing IκB-α phosphorylation, inhibiting IκB kinase (IKK) activity and downregulating NF-κB-regulated gene products such as Bcl-2, Bcl-XL, and cyclin D1 in Human MM U266, RPMI 8226, MM.1, and MM.1R cell lines inducing apoptosis (Figure 2).[40]

Icariin is one of the active secondary metabolites in Epimedium (family Berberidaceae), used in Chinese medicine.[41,42] Zhu and co-workers reported that icariin inhibits proliferation and induces apoptosis via inhibition of IL-6 driven-JAK2/STAT3 signalling pathway in MM cells (Figure 2) without any toxicity on the normal bone marrow cells.[43] Sinomenine is an alkaloid extracted from the Chinese herb *Sinomenium acutum*.[44] A derivative of sinomenine, YL064, selectively induces apoptosis in primary MM cells and MM cell lines due to inhibiting the IL-6-induced activation of STAT3 (Figure 2). Moreover, in the same study, it has been observed that YL064 decreases tumour weight in MM tumour-bearing mice in a xenograft MM mouse model.[45]

CAPE (caffeic acid phenethyl ester) synergism with bortezomib exhibits growth inhibitor and cytotoxicity on RPMI 8226, 0H929, U266, and ARH77 cell lines through the diminished NF-κB binding activity and IL-6 levels (Figure 2).[46]

Baicalein inhibits the phosphorylation of IκB-α and induces suppression of the NF-κB target genes such as IL-6, which inhibits the nucleic translocation of NF-κB in U266 cells (Figure 2).[47] Baicalein forbids the phosphorylation of IκB-α and reduces the protein level of the two transcription factors- Ikaros family zinc finger transcription factors IKZF1 and IKZF3 by degradation of proteasome which may link with the suppression of the NF-κB activation in the MM cell (Figure 2).[48]

He and co-workers have demonstrated that genistein inhibits the activation of apoptosis-related genes in the RPMI8226 and XG-1 cell lines, both untreated and treated with doxorubicin by regulating NF-κB.[49] Further, they have reported that genistein downregulates the expression of the NF-κB-regulated gene products, including Bcl-2, Bcl-xl, cyclin D1, and intercellular adhesion molecule-01 (ICAM-1) (Figure 2) and this prevents the translocation of NF-κB to the nucleus by inhibiting the phosphorylation of Akt (Figure 2). [49]

Chrysoeriol acts as a protein kinase p-Akt inhibitor (Figure 2) and reduces the proliferation of cells in RPMI 8226 and KM3 cells, arresting the cell cycle in G2/M.[50] Fu and co-workers found that wogonin suppresses the main pro-angiogenic factors (VEGF, PDGF, bFGF) in MM cells (Figure 2).[36] Further, they demonstrated down-regulation of the c-Myc/HIF-1α/c VEGF axis, consequently inhibiting angiogenesis and preventing MM cell proliferation *in vivo* and *in vitro* by wogonin. Moreover, wogonin degrades the HIF-1α through the proteasome/ubiquitination pathway.[36] In addition to other mechanisms, wogonin induces apoptosis in the MM cell line by direct binding to Akt and reduces its phosphorylation.[51]

Lin and co-workers have found two major active flavonoids, baicalein and wogonin of Scutellaria extract, strongly inhibit side population (SP) cells and diminish the ATP binding cassette subfamily G membrane 2 (ABCG2) expression in myeloma cells *in vitro*.[52]

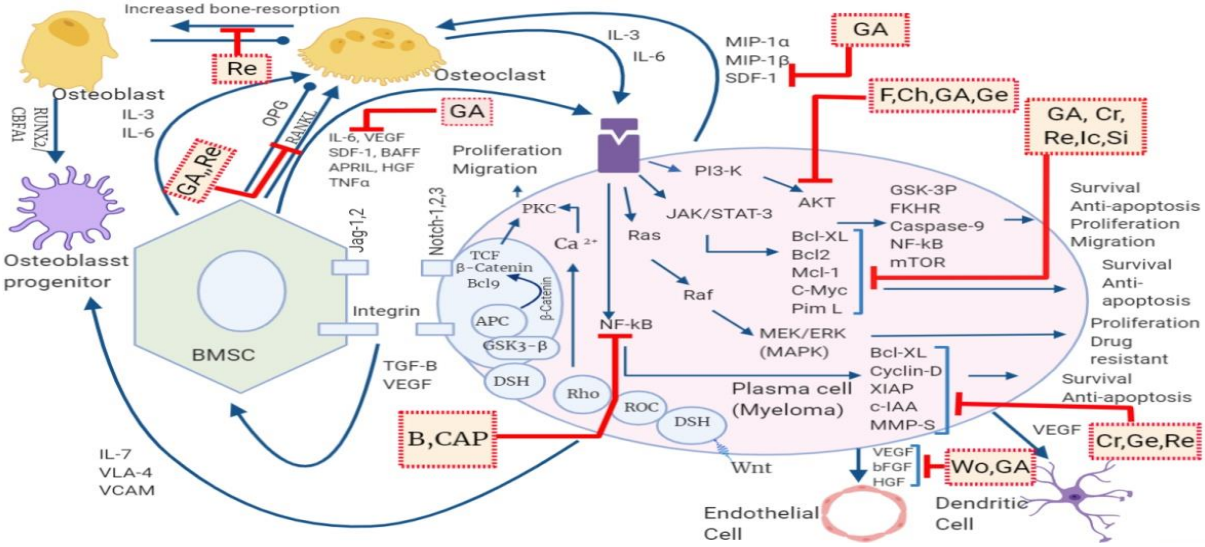

Figure 2: Signalling interactions between myeloma cells, other bone marrow cells, microenvironment and therapeutic targets of some active compounds. (OPG–osteoprotegerin; TGF–transforming growth factor; CAMDR–cytokine adhesion-mediated drug resistance, GA–Gambogic acid, Wo–Wogonin, Ch–Chryseoriol, Cr–Curcumin, Re–Resveratrol, Ge–Genistein, Ca–Cardamonin, Qu–Quercetin, A–Apigenin, B– Baicalein, F–Fisetin).

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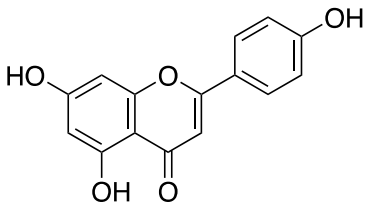
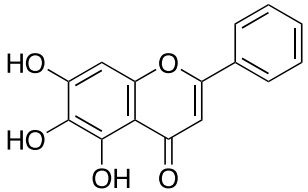
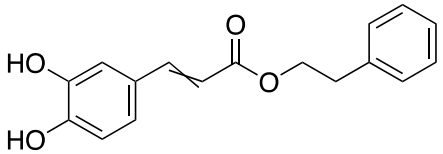
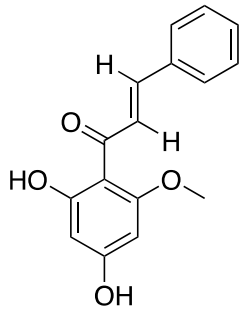
Table 1: Natural products derived from terrestrial plants with antimyeloma activity

Natural Product	Chemical Structure	Mechanism of Action
Apigenin		Inhibits CK2. Disassociates Hsp90/Cdc37/client complex. Degrades kinase clients RIP1, Src, Raf-1, Cdk4 and Akt. Reduces Mcl-1, Bcl-2, Bcl-xL, XIAP and Survivin levels. Reduces the levels of downstream mediators ERK, Akt, and IκBα as well as phosphorylated versions of STAT3, PDK, MEK, and IKK in both constitutive and induced states.[69,30]
Baicalein		Inhibits phosphorylation of IκBα, nuclear translocation of p65 NF-κB. Inhibits expression of IL6 and XIAP. Up-regulates cereblon at a transcriptional level. Reduces in the protein level of IKZF1 and IKZF3 by proteasomal degradation. Inhibits IL-6-induced STAT3, STAT1, Akt, JAK1 and TYK2 and ERK1/2 phosphorylation.[70,48,30]
CAPE (Caffeic acid phenethyl ester		Suppresses cell proliferation. Reduces NF-κB binding activity and IL6 levels. Activates apoptosis.[46,30,71]
Cardamonin		Cardamonin pre-treatment boosted the activation of caspase-3 and PARP while suppressing the expression of many anti-apoptotic proteins, triggering cell death and lowering the viability of human myeloma cells. Through an increase in IKK and IkBα phosphorylation, the NF-κB pathway activation was decreased. Decreases ICAM-1, COX-2, and VEFG levels. Reduces cell growth and induce apoptosis.[72,73]

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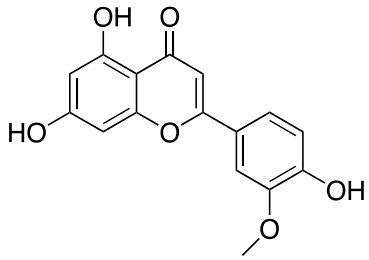
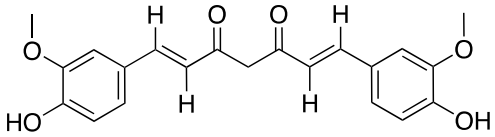
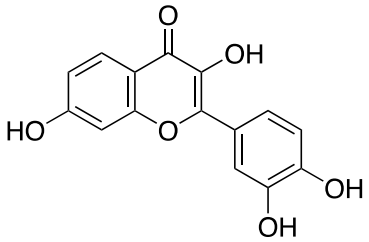
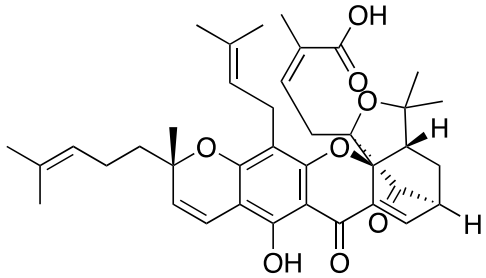
Chrysoeriol		Inhibits phosphorylation Akt. Reduces phosphorylated 4eBP1. Increases cyclin B1 and p21 levels. Reduces cell growth in RPMI8226 and KM3 cells. Cell cycle arrest in G2/M phase. Reduces phosphorylated 4eBP1 (eukaryotic initiation factor 4E (eIF4E)-binding protein 1).[30]
Curcumin		Suppresses the activity of NF-κB pathway. Down-regulates expression of IL-6, cyclin D1, Bcl-xL. Suppresses constitutive phosphorylation of STAT3.[74,75,30]
Fisetin		Reduces Bcl-2 and Mcl-1. Increases levels of Bax, Bim and Bad. Produces ROS. Reduces phosphorylation of AMPK (5' Adenosine monophosphate-activated protein kinase) and acetyl-CoA carboxylase (ACC) Reduces of phosphorylation of Akt and mTOR.[76,77,30]
Gambogic acid		Inhibits mTOR) signalling pathway. Induces apoptosis in RPMI-8226 cells via ROS accumulation followed by caspase-3 activation, PARP cleavage and SIRT1 down-regulation.[78]

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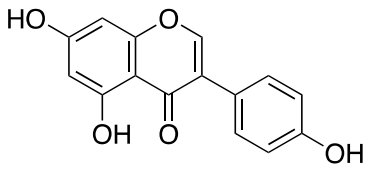
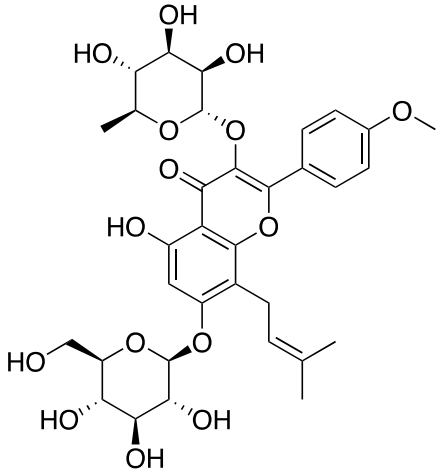
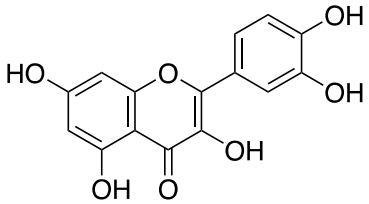
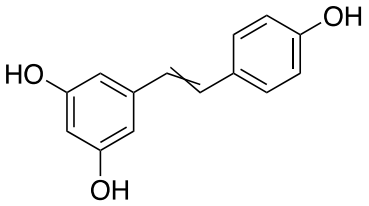
Genistein		Suppresses constitutional activity of NF-κB. Reduces p65 protein level. Increases miR-29b expression. Reduces phosphorylated Akt levels. Reduces expression of NF-κB regulated genes Bcl-2, Bcl-x, cyclin D1, ICAM-1.[79,30]
Icariin		Inhibits proliferation and induces apoptosis via inhibition of IL-6 driven-JAK2/STAT3 signalling pathway in MM cells.[80,42]
Quercetin		Cells cycle arrest in the G2/M phase. Activates caspase 3 and caspase 9. Up-regulation of p21. Down-regulation of c-Myc. Down-regulation of IQGAP1. Reduction of ERK1/2 activation.[81,77,30]
Resveratrol		Modulation of the p53 and FOXO. Activates apoptosis through inducing oxidative stress.[82,30,78]

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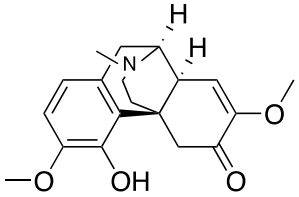
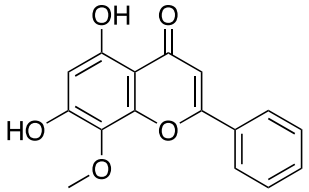
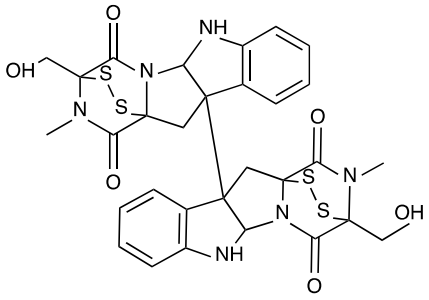
Sinomenine		Selectively induces apoptosis in primary MM cells and MM cell lines due to inhibiting the IL-6-induced activation of STAT3.[45,83]
Wogonin		Reduces Akt phosphorylation. Inhibits angiogenesis. Reduces the amount of VEGF, PDGF and bFGF.[36,30,84]

Table 2: Natural products derived from animal toxins with antimyeloma activity

Natural Product	Chemical Structure	Mechanism of Action
Melittin		Inhibits constitutive phosphorylation of Akt and mTOR in MM cells (MMS1), suppressing Akt / mTOR driven signalling pathway. Various gene product expressions necessary in cell longevity, proliferation, and invasions, such as cyclin D1, COX-2, and antiapoptotic gene products.[59]

Table 3: Natural products derived from macro-fungi with antimyeloma activity

Natural Product	Chemical Structure	Mechanism of Action
Chaetocin		Induces apoptosis via accumulating oxidative stress.[85,86]

Furthermore, they found that baicalein and wogonin exert lower toxicity on the normal plasma cells or corresponding dormant. [52] Gu et al. showed that baicalein dock into all five TM domain binding sites of ABCG2 and resulted in the declined of SP in RPMI 8226.[53]

Animal toxins with antimyeloma activity

Animal venom is one of the potential natural toxins in drug development. The venom is composed of a mixture of toxins, enzymes, growth factors, activators inhibitors, carbohydrates and minerals, providing new insight into medical research and therapy.[54] Studies on drug development using poisonous terrestrial animals such as reptiles, insects, spiders and scorpions, as well as marine animals such as jellyfish, anemones and cone snails, are well documented.[55,56] Melittin is the major active component in honeybee venom.[57] Kim and colleagues showed that melittin inhibits constitutive phosphorylation of Akt and mTOR in MM cells (MMS1), suppressing Akt / mTOR driven signalling pathway.[58] Furthermore, they found various gene product expressions necessary in cell longevity, proliferation, and invasions, such as cyclin D1, COX-2, and antiapoptotic gene products.[58] (Table 2) A study carried out with *Walterinnesia aegyptia* venom using an MM-bearing nude mouse model, treated with venom in combination with silica nanoparticles, demonstrated that the cell cycle has been deregulated by decreased expression of cyclin D1 and increased expression of cyclin B.[59] Moreover, inhibition of insulin-like growth factor 1 (IGF-1) and IL-6, decrease in the secretion of Bcl-2 and phosphorylation of Akt, altered mitochondrial membrane potential, caspase-3, -8 and -9 activation, sensitize the MM cells to induce apoptosis. In addition, when venom is treated alongside nanoparticles, the results are more noticeable. These findings confirm the efficacy of the nanoparticles to treat multiple myeloma and the sustained administration of snake venom to combat multiple myeloma.[59] Very few studies have been reported with animal-derived secondary metabolites in MM therapy and are yet to be discovered.

Macro-fungi with antimyeloma activity

Medicinal macro-fungi (mushrooms) have been consumed as food due to their abundant nutrients and possess a wide range of pharmacological effects, including anticancer activity.[60,61] Chaetocin, a fungal secondary metabolite, belongs to the group thiodioxopiperazines exist in the *Chaetomium* species (Table 3). *In vitro, ex vivo,* and *in vivo* studies demonstrate that chaetocin has potent antimyeloma activity and induces apoptosis via accumulating oxidative stress.[62] *Ganoderma lucidum,* a Chinese medicinal fungus, possesses many pharmacological properties, including anticancer, antidiabetic, and hepatoprotective activity.[63] *G. lucidum* induces apoptosis in multiple myeloma cells (RPMI8226, ARH77, U266, NCI-H929).[63] Water extract of *Agaricus blazei* Murill inhibits myeloma growth *in-vivo,* and the inhibition is more prominent with the encapsulation of marine phospholipid with the extract.[64] AndoSan™, a commercially available product, contains *Agaricus blazei* Murill (82.4%) with another two macro-fungi, *Grifola frondosa* (2.9%) and *Hericium erinaceus* (14.7%).[65] AndoSan™ shows *in-vitro* anti-proliferative activity on rat myeloma cells (MOPC315.BM) and demonstrates immunomodulatory effects in MM patients.[66] Furthermore, Tangen et al. reveal that AndoSan™ has *in-vitro* anticancer activity on primary MM cells of humans and myeloma cell lines (RPMI-8226 and U226).[65] AndoSan™ stimulates the expression of type Interleukin 12 (IL-12) in type 1 T helper cells (Th1) and NF-κB.[65] *Agaricus blazei* Murill is rich in *β*-glucans, a polysaccharide with immunomodulatory properties.[67] Interaction of *β*-glucan with the Lactosylceramide (LacCer) receptor activates the myocardial ischemic preconditioning upregulated protein 2 (MIP2) signalling mechanism, which further stimulates the protein kinase-C (PKC) cascade. Beyond that, the interaction of *β*-glucan to scavenger receptors (SRs) activates the mitogen-activated protein kinase (MAPK) signalling pathway with the involvement of PI3K and Akt.[68]

Conclusion

Many cutting-edge treatments for myeloma, such as IMiDs, PIs, MoAbs, steroids and bisphosphonates, act by targeting one or more antigens expressed on or signalling pathways in plasma cells, BMSCs, osteoclasts or bone marrow microenvironment. This review has attempted to summarize the plethora of available information on natural products and their bioactive compounds in the treatment of MM by categorizing them according to the product type and its potential target/s. This information should be of value for a better understanding of current trends and future research perspectives

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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