

Review

Bioactive Compounds from Herbal Medicine Targeting Multiple Myeloma

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Abstract: Multiple myeloma (MM) is one of the most widespread hematological cancers. It is characterized by a clonal proliferation of malignant plasma cells in the bone marrow and by the overproduction of monoclonal proteins. In recent years, the survival rate of patients with multiple myeloma has increased significantly due to the use of transplanted stem cells and of the new therapeutic agents that have significantly increased the survival rate, but it still cannot be completely cured and therefore the development of new therapeutic products is needed. Moreover, many patients have various side effects and face the development of drug resistance to current therapies. The purpose of this review is to highlight the bioactive active compounds (flavonoids) and herbal extracts which target dysregulated signaling pathway in MM, assessed by in vitro and in vivo experiments or clinical studies, in order to explore their healing potential targeting multiple myeloma. Mechanistically, they demonstrated the ability to promote cell cycle blockage and apoptosis or autophagy in cancer cells, as well as inhibition of proliferation/migration/tumor progression, inhibition of angiogenesis in the tumor vascular network. Current research provides valuable new information about the ability of flavonoids to enhance the apoptotic effects of antineoplastic drugs, thus providing viable therapeutic options based on combining conventional and non-conventional therapies in MM therapeutic protocols.

Keywords: multiple myeloma; flavonoids; plant extracts

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1. Introduction

Multiple myeloma (MM) is one of the most widespread hematological cancers. It is characterized by a clonal proliferation of malignant plasma cells in the bone marrow and by the increased production of M monoclonal protein [1]. MM represents approximately 1% of all cancers [2] and 10% of all hematological tumors [2,3]. Its incidence depends on different factors, such as age, sex, and country [2] and is estimated to 6.2 in 1 × 10⁵ individuals [4]. Moreover, MM affects people over 65 years [5], especially males, from the industrialized regions of Europe, North America, and Australia [6].

Multiple myeloma is heterogeneous cytogenetically and shows numerous genetic and epigenetic changes, in which numerous signaling pathways are involved [7]. It is characterized by chromosomal instability and frequent genetic mutations, including RB1, DIS3, KRAS, MYC, TP53, NRAS, TP53, FAM46C, BRAF, and p18 (CDKN2c) [8,9]. Due to its increased heterogeneity, MM has numerous refractory/recurrent cases. Because the bone marrow is the ideal site for homing and malignant cells progression [10], 70% of

patients have bone metastases at the diagnosis, and their percentage increases to 90% during the progression of the malignancy. These patients experience bone lysis caused by inhibition of osteoblast differentiation [11]. Additionally, this condition is associated with hypercalcemia, renal failure, and anemia, which affect the quality of life as well [7,12].

In the recent years, the survival rate of MM patients has increased significantly due to the use of transplanted stem cells or new therapeutic agents, and significantly increased survival rate [13].

The main therapies used in MM are:

Glucocorticoids as dexamethasone and prednisone are steroids used in the treatment of MM [14]. Glucocorticoids indirectly inhibit target genes through inhibitory interactions of glucocorticoid (GC)-glucocorticoid receptor (GR) monomers with NF- κ B and activator protein-1 (AP-1) [15], the latter being important factors in the pathogenesis of multiple myeloma [16–18].

- Proteasome inhibitors [19–21]. The proteasome is a multicatalytic target responsible for the degradation of the proteins. To date, there are only three proteasome inhibitors approved for clinical: ixazomib [22], bortezomib [23], and carfilzomib [24]. These drugs can stimulate osteogenesis in MM patients [25]. Proteasome modulation can also be achieved by binding lenalidomide to thalidomide and acting as E3-Ligase inhibitors [26].
- DNA damaging agents. This category includes alkylating drugs, such as melphalan, or other agents, as doxorubicin, as well as histone deacetylase inhibitors such as panobinostat [27].
- Immunomodulatory drugs, such as pomalidomide and lenalidomide [28–30]. MM was one of the first tumors in which the therapeutic efficacy based on immune receptors inhibition, especially of the PD-1 axis, was evaluated in preclinical models [6].
- Monoclonal antibodies [31–33]. There are two monoclonal-based therapy approved for the treatment of MM: daratumumab (CD38 pathway) [34], and elotuzumab (targetSLAMF7 pathway) [35]. The efficacy of monoclonal antibodies is the highest, but this therapy has a high cost [6]. In 2020, the FDA approved a third monoclonal antibody for MM therapy, Sarclisa (isatuximab—irfc) in combination with pomalidomide and dexamethasone [36]. Isatuximab is a monoclonal antibody that targets the transmembrane receptor and the ectoenzyme CD38, a protein overexpressed by malignant hematological cells [37]. Isatuximab is a new MM treatment for patient's refractory to lenalidomide and proteasome inhibitor [38].

Although various pharmacological strategies for the MM clinical treatments have been developed, in most patients it eventually recurred [39]. Patients have various side effects and face the development of drug resistance [39–41]. One of the harmful side effects of MM therapy is neurotoxicity. It is often associated with chemotherapy-induced peripheral neuropathy and has symptoms such as hypersensitivity, dysaesthesia, and paresthesia [42,43]. More than 50% of bortezomib-treated patients experienced this side effect, leading to dose reduction or treatment discontinuation [6]. All these problems highlight the need to research new therapeutic targets to improve the treatment [44,45].

In recent years, there has been a growing interest in the development of drugs to alleviate the side effects of antineoplastic therapy and the emergence of drug resistance, through the use of biologically active compounds with low side effects and that are effective in the treatment of several cancers [46]. Bioactive compounds such as alkaloids, flavonoids, terpenoids or saponins have the ability to prevent the side effects of chemotherapeutic drugs, prolong survival and improve the quality of life of cancer patients [47–50]. It is estimated that about 70% of cancer drugs are natural products or derived from natural products [51]. However, there are limitations when using non-conventional therapies in oncohematological diseases, because *in vitro* or *in vivo* studies predominate, clinical trials are missing, or the results provide non-uniformity in their mechanism of action.

Interest in the study of phenolic compounds has increased over the last decade due to promising biological activities and potential medical applications [52–54]. These effects are mainly related to their antioxidant activity. Polyphenols have the ability to eliminate free radicals and chelated metal ions [55]. They can indirectly decrease the production of reactive oxygen species (ROS), either by improving the activity of antioxidant enzymes or by inhibition of pro-oxidant enzymes [56]. Phenolic compounds can induce reversal of carcinogenesis by modulating molecules involved in intracellular signaling and by blocking cancer progression [57]. The property of it to neutralize free radicals (free radical-scavenging properties) helps to prevent chronic pathologies, such as cancer, cardiovascular or neurodegenerative diseases [53]. The anticancer and pro-apoptotic properties of polyphenols have been highlighted in numerous studies [58,59], properties that qualify them to be analyzed as therapeutic options in MM. Currently, there are just a few clinical trials provided by Database ClinicalTrials.Gov. regarding synergic anti-tumor activity of herbal compounds and MM drugs (curcumin and Bioperine or Lenalidomide, EGCG and monoclonal gamopathy) and therefore it is necessary to focus on other flavonoids or plant extracts as possible options in the therapeutic management of MM.

The aim of this review is to highlight bioactive active compounds (flavonoids) and herbal extracts that target dysregulated signaling pathway in MM, assessed by in vitro and in vivo experiments or clinical studies, in order to explore their therapeutic potential in the treatment of multiple myeloma.

2. Molecular Pathways Involved in Multiple Myeloma Progression

Numerous signaling pathways (WNT, RANK/RANKL/OPG, RAS/MAPK, PI3K/Akt/mTOR, JAK/STAT3, NF- κ B) are involved in MM, as well as extracellular mediators (TNF α , IL8, TGF β 1, IL6, FGF-2, PDGF, IGF, VEGF) [60].

Mitochondrial-mediated apoptosis is an important apoptotic pathway, influenced by pro-apoptotic factors, such as cleaved-caspase-3 and -9, and Bcl-2 family [61]. Bcl-2 family proteins (Bax, Bad, and Bcl-2) are the major regulators of apoptotic processes and play a key role in mitochondrial-mediated apoptosis [62,63].

Activation of Bcl-2 pathways may regulate mitochondrial-mediated apoptosis. Interactions between Bcl-2 proteins can regulate permeabilization of the outer mitochondrial membrane by cytoplasmic releasing of cytochrome C, and plays a critical role in activation of the apoptosis-inherited pathway [64,65]. Moreover, Bax, Bad and Bcl-xs, may facilitate the releasing of cytochrome C or may inhibit anti-apoptotic proteins [66].

Inhibition of the PI3K/Akt/mTOR signaling pathway is crucial for the antiproliferative effect on MM cells [67,68]. Akt is the main downstream target of PI3K [69]. Inhibition of PI3K/Akt/mTOR is beneficial for improving the life quality of MM patients [70]. Phosphorylated Akt binds to PI3K-activated products, and inhibit the pro-apoptotic factors of caspase-3, -9, and Bad [71]. Moreover, MTOR is a significant downstream target of Akt [72].

STAT3 is a transcription factor that may be overexpressed in multiple myeloma. It correlates with enhanced proliferation and apoptosis resistance to therapy. STAT3 activation negatively regulated the T cell-mediated immune response [60]. Aberrant signal transducer activation and transcriptional activator 3 (STAT3) is a key event of the cancerogenesis by inducing anti-apoptosis, angiogenesis, invasion, and metastasis [73–76]. STAT3 has been shown to be constitutively active in approximately 40 to 60% of MM tumors [77–81].

Decreased expression of different IL6/JAK/STAT signaling pathways by epigenetic silencing may sensitize MM cells to IL-6-regulated proliferation and survival [77,78,82].

Activated STAT3 induced transcription of target genes leads to increased survival, proliferation and drug resistance of MM cells: Src homology containing protein 1 (SHP-1), suppressor of cytokine signaling 1 (SOCS1), estrogen receptor (ER), Janus Associated kinase (JAK), phosphatase of regenerating liver 3 (PRL3), and peroxisome proliferator activated receptors (PPAR) [83].

Abnormal activation of the Wnt signaling mediate MM cells proliferation, survival, and drug resistance [84–86]. β -catenin is an essential component of the canonical Wnt pathway regulation [87,88]. B-catenin activity is strictly controlled by several processes, such as ligand-receptor interactions, protein stability, nuclear translocation, protein stability, and transcriptional activity [89–91].

Nuclear factor kappa B (NF- κ B) is an important transcription factor involved in the proliferation and MM cells survival. NF- κ B regulates the activation of various molecules involved in apoptosis, as anti-apoptotic proteins or X-linked inhibitor of apoptosis protein). XIAP is the most studied protein that inhibits apoptosis and negatively regulates caspases in MM [92].

Mitogen-activated protein kinase (MAPK) is a cell survival regulator, and Jun N-terminal kinase (JNK) signaling is a component of this pathway. PARP14 is overexpressed in over 80% of MM cells and is regulated by JNK2 [93].

The best strategy for the treatment of MM is a single agent or combination of molecules targeting several dysregulated signaling pathways.

3. Flavonoids in Multiple Myeloma

Flavonoids are ubiquitous in plants and in human nutrition and bring a number of health benefits [94]. Flavonoids are classified into flavonols, flavanones, aurones, flavones, isoflavones, flavan-3-ols, proanthocyanidins, anthocyanidins, and chalcones [95].

They represent a large group of water-soluble antioxidant compounds, which frequently occur in plants as glycosides and consist of two aromatic rings linked by a carbon bond and form a heterocyclic ring [96].

Flavonoids have been extensively studied due to their antitumor activity [97–99]. Due to various bioactive activities, flavonoids are considered to be multi-targeting and have multifunctional molecules. They have the ability to kill resistant cancer cells and re-sensitize conventional anticancer drugs to induce multidrug resistance reversal, which highlights their role in resistant cancer treatment [100].

Flavonoids target membrane lipids and modify their physicochemical properties to exert their bioactive activities [101–104], most likely due to a membrane bilayer-mediated mechanism [105]. Therefore, it is considered that they act neither as specific regulators of target proteins, but rather as multifunctional agents that negatively regulate key factors involved in multidrug resistance [100].

Moreover, many flavonoids may function as ROS modulators (scavengers or inducers), because they affect the ROS level in cancer cells [106,107]. In order to overcome multidrug resistance, they act as inducers for ROS production, enreaching the toxic threshold for cancer cell apoptosis [106].

Flavonoids involved in management of MM are part of a different class (Table 1).

Table 1. Flavonoids involved in the management of multiple myeloma.

Class of Flavonoids	Bioactive Compounds
Flavones	Apigenin, Baicalein, Crysoeriol, Luteolin, Scutellarin, Wogonin
Flavonols	Fisetin, Myricetin, Quercetin
Flavanols	Epigallocatechin-3-gallate
Isoflavonones	Daidzin, Genistein
Chalcones	Butein, Cardamonin, Isobavachalcone, Isoliquiritigenin, Xanthohumol
Prenylated flavonoids	Bavachin, Icaritin, Icaritin, Icariside II

3.1. Apigenin

Apigenin is a non-mutagenic yellow crystalline solid flavonoid [108]. This is a flavonoid found in oranges, grapefruit, grapefruit, celery, parsley, onions, wheat germ, and chamomile (Figure 1) [109–111].

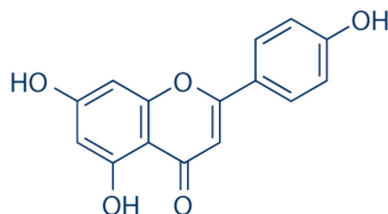


Figure 1. The chemical structure of apigenin.

The anti-cancer activity of apigenin was first reported in 1986 by Birt et al. [112].

Apigenin can be used in cancer prevention due to its antioxidant, anti-inflammatory, antigenotoxic effects and its ability to neutralize free radicals [113,114]. Apigenin inhibited prostate, gastrointestinal, bladder, ovarian, colon, and neck cancers, as well as other forms of tumors by inhibiting cancer cell proliferation [115–118]. Apigenin had a cytotoxic effect on cancer cells [119] and showed proteasome inhibitory activities [120].

Adham et al. [121] evaluated the cytotoxic activity of apigenin in several human MM cell lines, such as MOLP-8, NCI-H929, RPMI-8226, KMS-11, KMS-12 BM, OPM-2, 1-363, AMO-I, and JJN-3. Apigenin inhibited cell growth of MM cell lines in a dose-dependent manner, while NCIH-929 cells showed increased sensitivity to apigenin compared to other MM cells. Apigenin induced apoptosis, blocked cell cycle in G2/M phase, increased intracellular ROS, and promoted autophagy in NCI-H929 cells. Induction of autophagy by apigenin was demonstrated by upregulation of the expression of Beclin1 and LC3B-II markers.

Zhao et al. [122] reported cytotoxic effects of apigenin on both MM cell lines and primary MM cells, but not on normal blood mononuclear cells (PBMCs). Apigenin inhibited casein kinase 2 (CK2) activity and blocked the cell cycle in G2/M phase in U266 and RPMI 8226 cells. Additionally, it induced apoptosis and downregulated the expression of anti-apoptotic proteins in MM cells, respectively, such as Mcl-1, XIAP, Bcl-xL, Bcl-2, and survivin. Apigenin inhibited the activation of STAT3, ERK, AKT and NF-κB. Apigenin decreased Cdc37 phosphorylation, disassociated Hsp90/Cdc37/kinase complexes and degraded Hsp90/Cdc37 client proteins. Apigenin induced degradation of multiple kinases, including Src, RIP1, Raf-1, AKT and cyclin dependent kinase 4 (CDK4). In CD138+ primary MM cells, apigenin inhibited CK2 activity, and depleted Cdc37 client kinases.

3.2. Baicalein

Baicalein is one of the main biologically active compounds present in the root of *Scutellariae radix* [123]. The molecular formula of baicaleine is C₁₅H₁₀O₅, as can be seen in Figure 2. The particular structure is the di-orthohydroxyl functional group, located on ring A of its molecular structure [124].

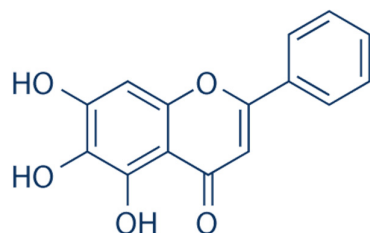


Figure 2. The chemical structure of baicalein.

Baicalein has a wide range of biological activities, such as antioxidant activity [125], anti-inflammatory [126], antiviral [127], antitumor activity and lower toxicity [123].

Baicalein has inhibited many types of cancer, for example, gastric cancer, hepatocellular carcinoma, lung cancer, pancreatic cancer, bladder cancer, colorectal cancer, prostate cancer, ovarian and cervical cancer, breast cancer, multiple myeloma, melanoma and osteosarcoma [123].

The antitumor activity of baicalein is due to cell cycle regulation by inhibition of several cyclins/cyclin-dependent kinases [128], attenuating MAPK, Akt and mTOR activities or neutralizing free radicals [129], inducing apoptosis by activating caspase -9, -3 [130] and tumor invasion and metastases inhibition by decreasing MMP-2, -9 expression [131].

Baicalein inhibited the U266 cells proliferation and stimulated their apoptosis. Baicalein also increased cereblon (CRBN) mRNA level and downregulated IKZF1 and IKZF3 transcription factors by proteasomal degradation. MM patients had a lower expression of IKZF3 and IKZF1, providing a better survival rate than those with a higher expression of IKZF1 and IKZF3 [132].

Gu et al. [133] reported inhibitory effects of baicalein inhibited in RPMI 8226 cells and significantly reduced ATP-binding cassette protein expression, G subfamily, ABC -transporter proteins family [133], which is thought to be involved in drug resistance in cancer [134]. Previously, Lin et al. [135] showed that baicalein significantly reduced the RPMI8226 cells by decreasing ABCG2 expression.

Baicalein treatment inhibited the proliferation and migration of MM cells by down-regulating the expression of β -catenin, cyclin D1, c-myc, and β 7 integrin [136].

Liu et al. [137] demonstrated that baicalein inhibited STAT1 phosphorylation, as well as IL-6-mediated phosphorylation of Jak, MAPK, STAT3, and Akt. Baicalein increased the U266 cell sensitivity to dexamethasone and inhibited IL-6-induced bcl-xl gene expression. Baicalein also showed a strong inhibitory effect on Erk1/2 phosphorylation. Thus, baicalein could be considered an active inhibitor of IL-6-induced protein phosphorylation, and a potential agent in the treatment of MM.

Co-administration of baicalein with dexamethasone inhibited MPC-1-immature myeloma cells by activation of peroxisome proliferator-activated (PPARs) and glucocorticoid receptors, having a synergistic inhibitory effect on NF- κ B [138].

Previously, Ma et al. [139] showed in vitro baicalein inhibition of the MM cells, especially MPC-1-immature MM cells. Baicalein inhibited I κ B- α phosphorylation, followed by reduced IL-6 and XIAP gene expression and activation of caspase-9 and -3.

3.3. Chrysoeriol

Chrysoeriol (Figure 3) is a methoxy flavone [140–143], extracted from Rooibos tea (*Aspalathus linearis*) [144].

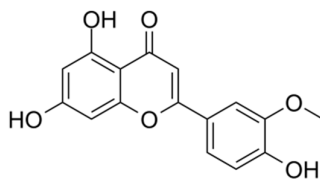


Figure 3. The chemical structure of chryseoriol.

This bioactive compound has been shown to have antioxidant, anti-mutagenic, anti-inflammatory, anti-obesity properties [141,143,145–148], a cytotoxic effect in human lung carcinoma [149], and antitumor activity on breast cancer [150].

Yang et al. [151] studied the anti-myeloma activity of chryseoriol in vitro. Chryseoriol has been shown to be a selective inhibitor of PI3K-AKT-mTOR pathway. It inhibited the proliferation of KM3 and RPMI 8226 cells, but did not affect the proliferation of the normal peripheral blood mononuclear cells. Chryseoriol blocked the cell cycle of MM cells in the G2/M phase and inhibited the phosphorylation of the AKT protein in MM cells. Chryseoriol significantly decreased p-AKT expression and increased Cyclin B1 and p21 protein expression.

3.4. Luteolin

Luteolin is a flavone found in carrots, peppers, cabbage, broccoli, onion leaves, thyme, parsley, mint, basil, celery, and artichokes [152].

Structurally luteolin has a hydroxyl (-OH) group attached to the 5-, 7-, 3', and 4'-positions of the flavone backbone structure. The chemical structure of luteolin is shown in Figure 4 [152]. The antioxidant activity of luteolin is ensured by the ortho-dihydroxy structure in the B-ring and the 2,3-double bond in conjugation with the 4-oxo function of the C ring [153].

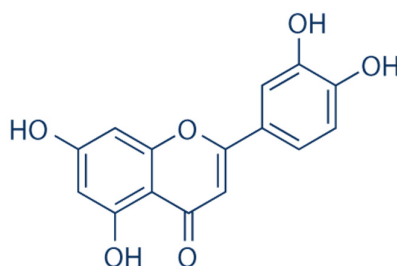


Figure 4. The chemical structure of luteolin.

Luteolin has shown antioxidant, antimicrobial, anti-inflammatory, chemopreventive, chemotherapeutic, cardioprotective, antidiabetic, neuroprotective and anti-allergic activity [152].

Luteolin has shown anticancer activity in many cancers, such as breast [154–157], colon [158], prostate [159,160], cervical [161] cancers, as well as glioblastoma [162], oral squamous cell carcinoma [163,164], adenocarcinoma [165], renal carcinoma [166], gastric cancer [167–169], hepatocellular carcinoma [170], and pancreatic cancer [171].

Luteolin inhibited the carcinogenesis progression through various pathways, such as kinase inhibition, induction of apoptotic cell death, cell cycle regulation, and decreased

the transcription factors [153]. Apoptosis induction involves DNA damage, regulation of redox and protein kinases in inhibiting cancer cell proliferation [172].

Regarding the anti-myeloma activity of luteolin, it has been shown to inhibit RPMI-8226 cell proliferation by apoptosis or autophagy, being interactive or promoting each other [173].

3.5. Scutellarin

Scutellarin (Figure 5), a bioactive flavone isolated from *Scutellaria baicalensis* [174] is a proteasome inhibitor [175].

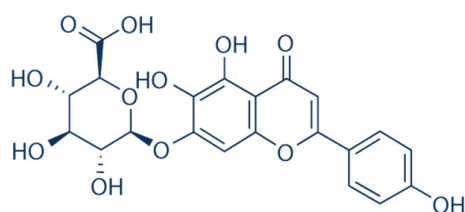


Figure 5. The chemical structure of scutellarin.

Scutellarin showed antioxidant [176], anti-inflammatory [177], and neuroprotective [178] activity. Its anti-cancer activity has been highlighted in various types of tumors, including hepatocellular carcinoma [179], colorectal cancer [180], and squamous cell carcinoma [181].

Scutellarin induced antitumor immunity and attenuated chemoresistance in neoplastic diseases by various signal transduction pathways: ERK/p53, c-met/AKT, AKT/mTOR/4EBP1, and STAT3 [174,175]. Misso et al. [182] highlight the role of the miR-125b/IL-6R/STAT3 feedback loop in modulating miR-34a in MM.

Scutellarin amplified the anti-tumoral effects of bortezomib in a xenograft mouse model. It downregulated the epigenetic modulators HDAC1/3 and amplified the expression of miR-34a. Scutellarin induced a decreased expression of c-Met, p-Akt, mTOR, NF- κ B, and XIAP. Co-administration of scutellarin and bortezomib inhibited MM tumor progression. Scutellarin inhibited tumor resistance to bortezomib and induced apoptotic cell death [92].

3.6. Wogonin

Wogonin is one of the active mono-flavones extracted from the root of the *Scutellaria baicalensis* (Figure 6) [124,183].

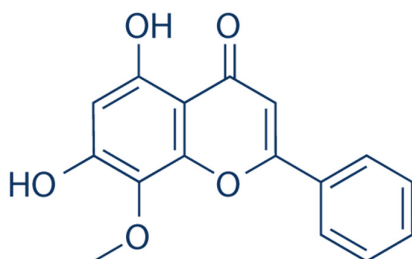


Figure 6. The chemical structure of wogonin.

It has neuroprotective [184,185], anti-inflammatory, and anti-cancer activity [186–192]. Wogonin has been shown to induce cytotoxicity to cancer cells in vitro and inhibited tumoral growth in vivo [124,183].

Wogonin targets several signaling pathways to prevent and inhibit the development of cancer both in vitro and in vivo [193,194]. Wogonin is involved in several anti-proliferative processes mediated by ER stress, MAPK, ROS, inhibition of transcription factors, such as NF- κ B or activator protein-1 (AP-1), and intracellular suppression Ca^{2+} signaling [124,194]. Due to its therapeutic potential and a lower toxicity to normal cells [183], this bioactive compound is an adjuvant in chemotherapy by increasing the therapeutic effects and reducing the side effects of conventional drugs [195].

Because MM-induced angiogenesis is an essential process for cancer progression and metastasis, methods of inhibiting angiogenesis have been studied as a new anti-multiple myeloma treatment [196,197]. Fu et al. [198] showed that wogonin inhibited MM-induced angiogenesis in both normoxic and hypoxic conditions by reducing the secretion of proangiogenic factors (VEGF, PDGF and bFGF) in U266 and RPMI 8226 cells and in co-cultures of MM and stromal cells. The antiangiogenic effect of wogonin was previously reported by Song et al. [199] in MCF-7 breast cancer cells.

The c-Myc/HIF-1 α plays an essential role in activation of different pro-angiogenic factors (e.g., PDGF, VEGF, and bFGF) [200]. Wogonin induced c-Myc inhibition and stimulated HIF-1 α degradation in vitro. This biologically active compound has the ability to inhibit in vivo tumor angiogenesis and growth in an experimental model of BALB/c-nude mice. Wogonin showed synergistic action against MM-dependent angiogenesis in combination with lenalidomide and bortezomib and inhibited expression of c-Myc and HIF-1 α in primary MM cells [198].

Zhang et al. [201] reported a cytotoxic effect of wogonin in vitro, as demonstrated by the induction of apoptosis on RPMI8226 cells. Wogonin blocked the cells in the sub-G1 phase. Poly ADP ribose polymerase (PARP) has an important role in mediating the normal cellular response to DNA damage, and enzymatic cleavage is considered to be a marker of apoptosis. Wogonin inhibited PARP in a dose-dependent manner and induced PARP cleavage. Moreover, wogonin increased Bax expression in MM cells, suggesting its ability to stimulate apoptosis via Bax-regulating pathway. Besides, Bcl-2 expression was reduced following wogonin treatment. Wogonin inhibited Akt phosphorylation (Ser 473) in MM cells, the latter being a key event in tumorigenesis and apoptosis. Wogonin treatment did not alter the total Akt protein level. This study suggests that wogonin-induced MM cell apoptosis could be modulated by the Akt pathway, because residual phosphorylation at Ser 473 is required for Akt activation [202].

3.7. Fisetin

Fisetin is a bioactive flavonol that has a diphenylpropane structure [203] containing two aromatic rings bounded by a three carbons and supplemented with four hydroxyl group substitutions and one oxo group [204,205] (Figure 7).

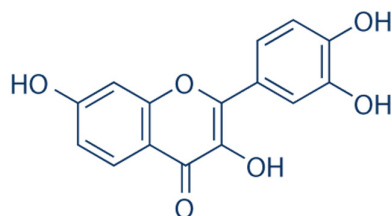


Figure 7. The chemical structure of fisetin.

Fisetin is synthesized in strawberries, apples, cucumbers, and onions [206] or plants such as *Acacia berlandieri*, *Acacia greggii*, *Gleditschia triacanthow*, and *Rhus cotinus* [207]. The average daily intake of fisetin is estimated to be about 0.4 mg in humans [208]. This potent bioactive phytoconstituent acts as a coloring agent in plants [206].

Fisetin has low water solubility and poor intestinal absorption and therefore has low bioavailability [209,210]. Its solubility and bioavailability can be improved by complexing it with cyclodextrins, encapsulating with nanoparticles [211–213] and cocrystallization with caffeine, isonicotinamide and nicotinamide [214,215]. These changes aim to improve stability, solubility and biological effects of fisetin. The biological activity of fisetin depends on the presence of hydroxyl and oxo groups. Hydroxyl groups at C-7 and the double bond C2–C3 are essential for its antioxidant activity [216,217].

Fisetin showed antioxidant [218], anti-angiogenic [219–221], anti-proliferative [222,223], anti-inflammatory [208,224], anti-aging [225], and antitumor properties [226,227].

Fisetin induced apoptosis, cell cycle blocking and inhibition of CDK activity in various human cancer cell lines. It has also modulated lipid kinase and protein kinase pathways [228–230]. The anticancer activity of fisetin has been highlighted by its involvement in various signaling pathways, as blocking the mammalian target of rapamycin (PI3K/Akt/mTOR)/phosphatidylinositol-3-kinase/protein kinase B, mitogen-activated protein kinases)-dependent nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and p38 [231,232].

Jang et al. [207] reported that fisetin showed cytotoxic effect and induced apoptosis in U266 cells and blocked the cell cycle in sub-G1 phase. Additionally, it improved the PARP cleavage. Fisetin inhibited the expression of anti-apoptotic Bcl-2 and Mcl-1L, but not Bcl-xL, and increased the expression of pro-apoptotic Bax, Bim and Bad.

AMP-activated protein kinase (AMPK) plays an important role in inducing apoptosis [233–235]. Fisetin induced an increase in phosphorylated AMPK and phosphorylated acetyl-CoA carboxylase, as a major substrate of AMPK. Fisetin treatment inhibited mTOR phosphorylation and reduced phosphorylated AKT, the upstream protein of mTOR. ROS have the role of mediating apoptosis in cancers [236,237]. Thus, fisetin induced ROS growth in U266 cells [207].

3.8. Myricetin

Myricetin is a phenolic compound found in berries, grapes, wine, nuts, etc. Myricetin is also known as hydroxy quercetin due to the presence of additional -OH group and exists in two forms: a free form and a glycosidically bound form (Figure 8) [238].

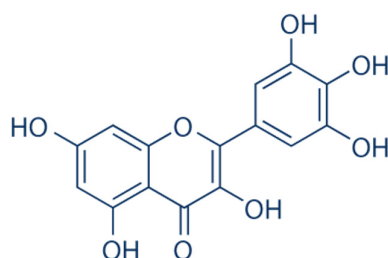


Figure 8. The chemical structure of myricetin.

Myricetin has various pharmacological activities, such as antioxidant, anti-inflammatory, analgesic, antitumor, hepatoprotective, and antidiabetic activity [238].

The anti-cancer activity of myricetin was confirmed by a number of in vitro and in vivo cytotoxicity studies. Myricetin acted as an antioxidant, antimetastatic, immunomodulatory agent, apoptosis inducer, inhibitor of angiogenesis, and proliferation and growth promoter [238].

Myricetin induced apoptosis in different cell lines, including colon, pancreatic, esophageal, ovarian, or hepatoma carcinoma cells [239–242].

Akhtar et al. [243] showed that bulk and nano forms of myricetin showed an insignificant genotoxicity level in the lymphocytes of MM patients compared to those of healthy ones. This effect was induced by altering the Bcl-2 expressions. The Bcl-2/Bax ratio decreased and the level of P53 protein increased in the lymphocytes of MM patients. Myricetin bulk and nano-treatment induced an increase in intracellular ROS levels, suggesting that modulation of apoptotic proteins triggered by myricetin occurs through P53 and oxidative stress-dependent pathways.

3.9. Quercetin

Quercetin is one of the most important bioflavonoids found in over 20 plants [244], such as berries (blueberries and cranberries), apples, green leafy vegetables, onions, broccoli, cauliflower, cabbage, as well as nuts and seeds [244,245]. It contains two benzene rings joined through a 3-carbon heterocyclic pyrone one (Figure 9). Due to the presence in the structure of quercetin of two antioxidant pharmacophores, it has the ability to easily neutralize free radicals and can bind to metal ions. Catechol with OH group present in the C3 position is an ideal structure that favors the free radical neutralization [246].

The quercetin name derives from the Latin word “Quercetum”, which means oak forest [247]. The name of the International Union of Pure and Applied Chemistry (IUPAC) of quercetin is 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one [245].

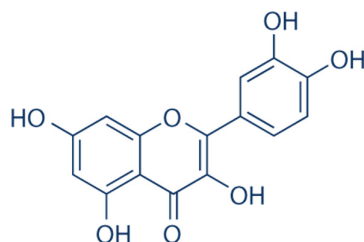


Figure 9. The chemical structure of quercetin.

Quercetin belongs to the flavonols and is not being produced by the body [247]. It is soluble in lipids and alcohol, insoluble in cold water and has a lower solubility in hot water [244,245].

Quercetin is available as a supplement and can be safely orally administrated at a dose of 1 g/ day and absorbed up to 60% [248].

Quercetin exhibits many pharmacological activities, such as antioxidant, anti-inflammatory, anti-diabetic, and anti-proliferative activity [246,249]. The anticancer properties of quercetin have been highlighted in numerous studies [250–252], as evidenced by the antioxidant, antiproliferative and growth factor inhibition effect deletion [253]. This flavonol has had the ability to inhibit various cancers, such as breast cancer [254], lung [255], pancreatic [256], colorectal [257], prostate [258], ovarian cancer [259], nasopharyngeal [260], and kidney [261].

Quercetin increased the sensitivity of tumor cells to doxorubicin [246,262], vincristine [263], and 5-fluorouracil [264].

Xu et al. [265] studied the effect of quercetin on multiple myeloma cell line NCI-H929. Quercetin inhibited cell proliferation, stimulated apoptosis and induced cell cycle

blockade in G2/M phase. Quercetin activated caspase-3, -8, -9, and PARP apoptosis-associated proteins and inhibited BCL-2 expression. It also stimulated P21, P53, and P27 expression and inhibited CDK4 expression in NCI-H929 cells. Quercetin decreased the p-ERK and p-AKT phosphorylation in NCI-H929 cells.

He et al. [266] demonstrated that quercetin inhibited proliferation in ARP-1, RPMI8226, and MM.1R cell lines by inducing apoptosis and blocking the cell cycle in the G2/M phase. Quercetin upregulated caspase-3, -9, PARP, p21 and downregulated c-myc. The combination of quercetin with dexamethasone showed in vitro and in vivo synergistic inhibitory effect, stimulated apoptosis of MM cells and induced caspase-3 activation. Quercetin also inhibited in vivo tumor growth in vivo (ARP-1 cells in NOD-SCID mouse model).

Quercetin inhibited MM cell proliferation by downregulating the expression of IQ motif-containing GTPase activating protein 1 (IQGAP1) and the activation of extracellular signal-regulated kinase 1/2 (ERK1/2). Quercetin also inhibited activation of MAPK and the interaction between IQGAP1 and ERK1/2 in MM cells [267].

3.10. Epigallocatechin-Gallate

Epigallocatechin-gallate (EGCG) is the common catechin in green tea (Figure 10) [268,269], representing at least 50% of the total catechins in the leaves [269] and is responsible for most biological activities, including angiogenesis [270].

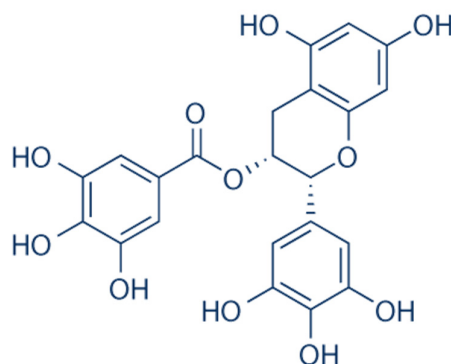


Figure 10. The chemical structure of epigallocatechin-3-gallate.

The anti-proliferative, pro-apoptotic, anti-invasive and anti-angiogenic properties of EGCG have been highlighted in numerous studies [271].

EGCG inhibited tumorigenesis by inhibiting carcinogenic activity [272,273]. EGCG decreased tumor proliferation by acting against angiogenesis [274–277]. EGCG inhibited tumor migration [278–281] and induced tumor cell death by several mechanisms, such as lysosomal membrane permeabilization, mediated cell death, autophagy, caspase-dependent apoptosis, and caspase-independent apoptosis [268].

EGCG targeted tumor microenvironment components (e.g., fibroblasts, macrophages, fibroblasts, and microvasculature) and reduced oxidative stress, inflammation, oxidative stress, and hypoxia [282].

EGCG has acted synergistically with other natural compounds both in vitro and in vivo in various cancers (e.g., quercetin, curcumin, genistein, and caffeine) [271,283].

EGCG has been tested in combination with currently used chemotherapeutic drugs (e.g., doxorubicin, sunitinib, and cisplatin) [284–287].

In order to improve the stability and bioavailability of EGCG, new formulations were developed [288–291].

Apoptosis is the main mechanisms by which EGCG exerts anticancer activity, along with cell proliferation and migration inhibition [292,293]. EGCG affected the expression of anti-apoptotic factors (e.g., Bcl-xl, Bcl-2) and up-regulated pro-apoptotic molecules (e.g., caspase-3, Bax) in several experiments [285,294–296].

EGCG inhibited cell growth by inducing apoptosis in MM cell lines or primary MM cells from patients [297,298], by caspase 3 activation and Bcl-2 and Mcl-1 reduction. Additionally, it induced loss of mitochondrial transmembrane potential and intracellular H_2O_2 and superoxide increasing [298].

EGCG-mediated apoptosis was the result of a direct interaction with 67LR laminin receptor and lipid-shelf clustering, which correlated with increased activation of sphingomyelinase acid (ASM) via protein kinase C delta (PKC δ). This has been demonstrated both in vitro in U266 cells and in cells harvested from patients with MM [299,300] and in vivo [297,300].

EGCG inhibited proliferation and induced apoptosis in U266 cells, a phenomena that was accompanied by the inhibition of the expression enhancer of homologous zest 2 (EZH2) [301], EGCG activated caspase-3, -8, cleaved caspase-9, and PARP and subsequent apoptosis [302].

EGCG has been used in MM clinical practice in combination with phosphodiesterase 5 inhibitor vardenafil [299] or in vitro, together with L-Threo-dihydrosphingosine in vitro [303], and hydrogen sulphide donors [304]. Thus, an attempt was made to reduce the dose of EGCG and hepatic adverse effects [305–308] and to improve the anti-hepatic effects. MM ale EGCG [299,303,304].

Bae et al. [309] reported that cyclic guanosine monophosphate (cGMP) induced by EGCG activated the PKC δ /ASM singling axis in MM cells. Induction of cGMP was sufficient to induce phosphorylation of PKC δ at Ser664, the major kinase for the induction of ASM activation by EGCG. The inhibitors of the negative regulators of diacylglycerol (DAG) increased the effect of EGCG. EGCG treatment increased phospholipase C (PLC) activity. EGCG-induced ASM activation was completely suppressed by PLC inhibition. Thus, EGCG-induced cGMP activated the cGMP/PLC/PKC δ /ASM signaling axis in MM cells.

The limitations related to the use of this flavonoid in the treatment of patients with MM are represented by the fact that EGCG is active in killing the proliferation of clonal/aberrant plasma cells (aPCs) at concentrations higher than those that can be achieved by drinking tea, and MM cells present a different sensitivity [298–300].

3.11. Daidzin

Daidzin (Figure 11) is a phytoestrogen that can be isolated from *Pueraria lobate* (Fabaceae) [310,311].

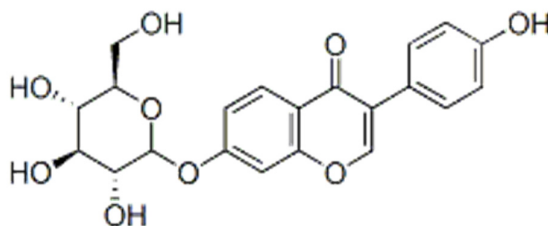


Figure 11. The chemical structure of daidzin.

Daidzin presented a large variety of pharmacological effects, such as anti-cancer properties [312,313], anti-cholesterol [314], anti-osteoporosis [315], anti-angiocardopathy [316] and stimulated osteoblast differentiation [317].

Daidzin has shown preventive activities against breast and prostate cancer. This bio-active compound showed anti-proliferative activity against MCF cells by affecting the

invasive potential [318,319]. Daidzin has been shown to have an anti-cancer effect in the early stages of prostate carcinogenesis [313].

Daidzin inhibited the viability of U266 and MM1.S cells, downregulated STAT3 in U266 cells, modulated activation of upstream kinases, inhibited MM cell proliferation, stimulated apoptotic cell death, potentiated anti-inflammatory and anti-cancer properties of bortezomib [320].

3.12. Formononetin

Formononetin (Figure 12), is an isoflavone, isolated from the roots of *Trifolium pratense*, *Astragalus membranaceus*, *Glycyrrhiza glabra*, or *Pueraria lobate* [321].

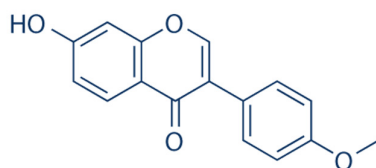


Figure 12. The chemical structure of formononetin.

It has the ability to influence a number of carcinogenesis pathways in different malignant cells through various molecular mechanisms [322–326]. Formononetin has various pharmacological activities, such as anti-inflammatory, antiviral, antioxidant, neuroprotective activity, and wound healing [325,327–330].

Formononetin inhibited NF- κ B and activated AP-1 in MM cells, attenuated activation of PI3K/AKT and MAPK pathways, decreased tumorigenic protein levels, induced apoptosis, potentiated the antitumor properties of bortezomib, and enhanced its apoptotic effects [321].

Formononetin affected MM growth through the negative regulation of (STAT) 3/5 cascades mediated via oxidative stress. Formononetin inhibited STAT activation in MM cells, reduced the ability to bind STAT3 and STAT5 to DNA, as well as the nuclear pool of p-STAT3 and p-STAT5 in U266 cells. Formononetin inhibited the activation of upstream kinases involved in the STAT3 signaling cascade in MM cells, inhibited IL-6-induced STAT3-dependent reporter gene expression, decreased the expression of proteins involved in anti-apoptosis, angiogenesis, and proliferation (CDK2, CDK4 and Cyclin E), activated caspase-3 and induced cleavage PARP in U266 cells, negatively affected the cell cycle in MM cells, reduced the expression of cyclin D1 and cyclin B1 associated with cell cycle regulation, inhibited cell viability in MM cells, inhibited glutathione reductase expression in U266 cells, induced antitumor effects in the MM model xenograft, inhibited the growth of MM in vivo and inhibited the activation of STAT3 / 5 in tumor tissues, activated caspase-3 and induced cleavage of MM tissular PARP and reduced the expression of apoptotic proteins in tumor tissues [331].

It is also thought to be involved in various signaling pathways, such as NF- κ B, phosphatidylinositol 3—kinase/protein kinase B (PI3K/AKT), and AP-1 [332,333].

3.13. Genistein

Genistein belongs to the aglycone subgroup of isoflavones (Figure 13) [334].

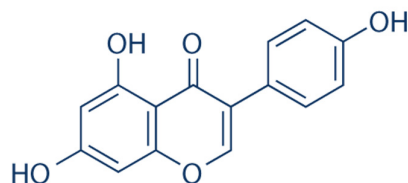


Figure 13. The chemical structure of genistein.

Genistein has shown anticancer activity in many cancers, such as prostate cancer [335,336], ovarian cancer [337–339], gastric cancer [340], colon cancer [341], hepatocellular carcinoma [342], and neuroblastoma [343].

Genistein decreased cell mitosis, induced apoptosis and increased caspase-3 activity and inhibited NF- κ B expression in U266 cells. Genistein treatment inhibited human MM cell proliferation by miR-29b upregulation [344].

Genistein inhibited NF- κ B expressed by MM cells, inhibited Akt phosphorylation, decreased the expression of NF- κ B-regulated genes, inhibited MM cell proliferation, and induced apoptosis in MM cells [345].

3.14. Chalcones

Chalcones are polyphenolic compounds that belong to flavonoids [346]. They are considered to be precursors of flavonoids and isoflavonoids [347,348].

Chalcone is an α , β -unsaturated ketone [349]. Chemically, chalcones are formed by openchain flavonoids in which the two aromatic rings bind three carbons in an α , β -unsaturated system [350]. Chalcones have a diverse structure due to the number and position of different substituents, such as hydroxy or methoxy groups on rings A or B. Chalcones are also C-prenylated and, less frequently, O-prenylated. The most common type of prenylation is the substitution of 3,3-dimethylallyl (prenyl group). In addition, chalcones also have isopentenyl, dimethylchromano, furano, geranyl, and farnesyl groups [351].

Chalcones shows various pharmacological activities such as anticancer [352], cytotoxic, antitumor [350], antimicrobial [353], antituberculosis [354], anti-inflammatory [355], antioxidant [356,357], antidiabetic [358], and antihypertensive [359].

Chalcones act as chemopreventive agents of cancer. They have been shown to have antioxidant properties and an anticancer effect [360]. Compounds containing chalcone moiety have the ability to induce apoptosis and are blocked in the G2/M phase by triggering mitochondrial apoptotic pathway through activation of caspases and bcl-2 family [361].

Zhu et al. [61] noted the ability of 2,4-dihydroxy-30-methoxy-40-ethoxychalcone (DMEC) to inhibit cell proliferation and induce apoptosis in MM via the PI3K/Akt/mTOR pathway. The inhibitory effect of DMEC on MM cells was correlated with mitochondria-mediated apoptosis via upregulation of the cleaved-caspase-3, -9, and cytochrome C, Bcl-2 and PARP downregulation. DMEC showed a pro-apoptotic effect on U266 cells and decreased PI3K expression, p-mammalian target of rapamycin (p-mTOR) and phosphorylated-protein kinase B (Akt). Pretreatment with IGF-1 attenuated DMEC-induced apoptosis in U266 cells.

3.15. Butein

Butein is a chalcone isolated from *Toxicodendron vernicifluum*, *Semecarpus anacardium* *Butea monosperma*, or *Dalbergia odorifera* [362], with a central core structure that has been shown to give it anti-cancer properties [363]. The IUPAC name of this compound is (E)-1-(2,4-dihydroxyphenyl)-3-(3,4-dihydroxyphenyl) prop-2-en-1-one (Figure 14) [362].

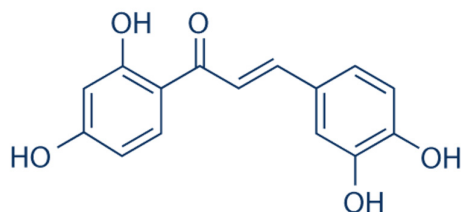


Figure 14. The chemical structure of butein.

Butein prevented cancer metastasis via MMP-9 and urokinase plasminogen activator (uPA) repression [364]. Butein has been shown to inhibit survival, angiogenesis, proliferation, invasion and metastasis, chemoresistance in different types of cancer, such as breast cancer, leukemia, colorectal cancer, prostate cancer, pancreatic cancer, etc., by modulating several signaling pathways. These studies highlighted that butein acts as a multitargeted agent for both cancer prevention and treatment [362].

Butein inhibited constitutive and interleukin-6-inducible STAT3 activation in MM cells. This was mediated by inhibition of the activation of the upstream kinases c-Src, Janus-like kinase (JAK) 1, and JAK2. Butein induced SHP-1 protein expression and reversed inhibition of STAT3 activation in U266 cells [365].

STAT3 activation regulates the gene expression involved in cell survival and proliferation, as antiapoptotic proteins Bcl-2, Bcl-xL, and Mcl-1 and cyclin D1 [366]. Butein down-regulated the expression of these proteins and led to the suppression of proliferation and induction of apoptosis. Overexpression of STAT3 significantly reduced buteine-induced apoptosis. Butein potentiated the apoptotic effects of thalidomide and Velcade in MM cells [366], which are two drugs used in the clinical therapy of MM [367].

3.16. Cardamonin

Cardamonin, a chalcone, has been isolated from *Zingiberaceae* species (Figure 15) [368]. It is also found in cardamom and other species, such as *Boesenbergia pandurata*, *Syzygium samarangense*, *Catimbium speciosum*, *Alpinia sp.*, and *Elettaria cardamomum* [369–371].

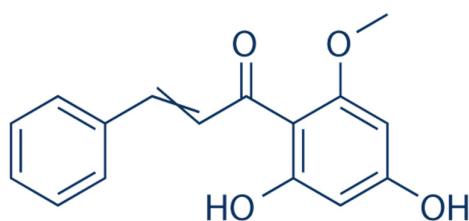


Figure 15. The chemical structure of cardamonin.

Cardamonin has shown antioxidant [372], anti-inflammatory [373,374], antineoplastic [375], and hypoglycemic [376,377] activities.

The anticancer properties have been highlighted in different cancers, such as gastric cancer [378,379], nasopharyngeal cancer [380], ovarian cancer [381], breast cancer [382],

lung cancer [383], colon cancer [384], prostate cancer [385], colorectal cancer [386,387], and leukemia [388].

The chemotherapeutic properties are mediated by inhibition of oncogenic molecules (c-MYC), transcription factors (NF- κ B, Wnt/ β -catenin, STAT-3), Bcl-2 anti-apoptotic proteins, plasma proteins (P glycoprotein) and cell cycle drivers (cyclin D1). It induced the activation of pro-apoptotic proteins (Bax) and the release of cytochrome c, autophagy inducers (LC3-II), cysteine proteases (caspase 3, 8, 9), tumor suppressor genes (p53), and thus suppressed carcinogenesis, metastasis and drug resistance to conventional therapy [368].

Cardamonin inhibited the growth and proliferation of U266, RPMI 8226 and ARH-77 cells. This calcone induced apoptosis in these cell lines and induced the activation of caspase-3 and PARP. Cardamonin down-regulated the expression of anti-apoptotic gene products in MM cells, inhibited constitutively active NF- κ B in MM cells, repressed the expression of IKKs and inhibited phosphorylation of I κ B α in MM cells, and down-regulated NF- κ B-regulated gene product expression in MM cells [375].

3.17. Isobavachalcone

Isobavachalcone is a prenylated chalcone of the flavonoids (Figure 16). The compound was first isolated in 1968 from *Psoralea corylifolia* L. [389] (Kuethe et Sandjo, 2012). It is found in medicinal plants, such as *Broussonetia papyrifera*, *Angelica keiskei*, *Psoralea corylifolia*, and *Maclura tinctoria* [390,391].

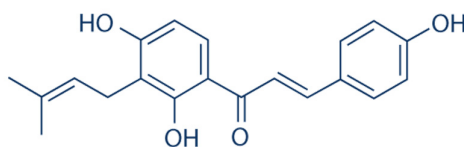


Figure 16. The chemical structure of isobavachalcone.

This naturally occurring chalcone compound has been used in traditional Chinese medicine as an anthelmintic, antibacterial, aphrodisiac, astringent and antiplatelet agent [347,392,393]. Isobavachalcone showed antioxidant, antifungal, antibacterial, and anti-cancer activity [347].

Isobavachalcone has been shown to have anticancer activity [394,395]. It inhibited skin tumors in vivo [396], induced apoptosis in multiple myeloma, neuroblastoma, prostate cancer, breast cancer, ovarian cancer, and lung cancer [394,395,397,398].

Isobavachalcone showed reduced toxicity to normal cells. Isobavachalcone inhibited the proliferation of MM H929 cells by inducing apoptosis and autophagy. Mitochondrial cell death pathway was involved in its anti-proliferative activity. Proteolytic activation of PKC δ was involved in chloroquine plus isobavachalcone-induced cell death. The combination of chloroquine with isobavachalcone showed low toxicity for normal PBMCs [397].

3.18. Isoliquiritigenin

Isoliquiritigenin (20,40,4-trihydroxychalcone), a bioactive compound with a chalcone structure, was isolated from licorice root (Figure 17) [399].

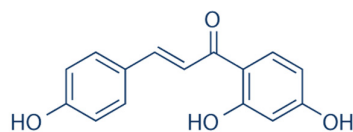


Figure 17. The chemical structure of isoliquiritigenin.

Isoliquiritigenin has various biological activities, such as antioxidant, antiviral, anti-inflammatory, neuroprotective, antidiabetic, chemopreventive and antitumor activity [399].

Isoliquiritigenin has been shown to have anticarcinogenic activity in different cancers, such as breast cancer [400], colon cancer [401], ovarian cancer [402], acute myeloid leukemia [403], and melanoma [404].

Chen et al. [405] studied the effect of isoliquiritigenin on MM cells, both in vitro and in vivo. Isoliquiritigenin inhibited the growth of MM cells and induced their apoptosis. In MM xenograft models, isoliquiritigenin showed significant antitumor activity and potentiated the anti-MM activity of adriamycin. Isoliquiritigenin downregulated IL-6 expression and reduced levels of phosphorylated ERK and STAT3. Isoliquiritigenin inhibited phosphorylation levels of ERK and STAT3 induced by recombinant human IL-6, which are critical signaling proteins in IL-6 signaling regulation networks.

3.19. Xanthohumol

Xanthohumol is a prenylated chalcone found in *Humulus lupulus* (Figure 18) [406,407].

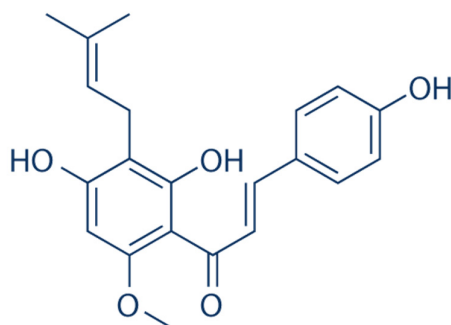


Figure 18. The chemical structure of xanthohumol.

Xanthohumol has a number of pharmacological activities [408]. It has shown anti-cancer activity in various cancers, such as breast cancer [409], colorectal cancer [410], cervical cancer [411], non-small cell lung cancer [412], and leukemia [413].

Xanthohumol showed cytostatic and cytotoxic effects in MM cells and slightly affected the viability of PBMCs. Xanthohumol treatment induced cell cycle blockade in the G1 phase, induced cell death in RPMI8226 cells by the apoptotic mechanism, affected the expression of apoptosis-related and cell cycle-associated, induced ROS generation in RPMI8226 cells, and modulated MAP phosphorylation kinases. Xanthohumol-induced apoptosis in RPMI8226 cells involved in the production of ROS and the activation of ERK1/2 and JNK1/2. Xanthohumol decreased sIL6R and VEGF production in RPMI8226 cells [414].

3.20. Bavachin

Bavachin is a prenylated flavonoid [415] isolated from *Psoralea corylifolia* [416] (Figure 19).

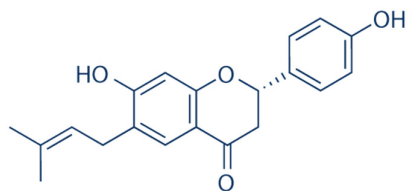


Figure 19. The chemical structure of bavachin.

Bavachin has had beneficial effects in cancer [417], inflammation [416], and diabetes [418].

Bavachin reduced the MM cells viability, inhibited NF- κ B and STAT3 phosphorylation, increased p53 and NOXA expression, decreased XIAP, survivin, Bcl-xL and Bcl-2 expression, induced apoptosis by activating caspase-3 and -9 and decreased mitochondrial membrane potential [417].

3.21. Icariin

Icariin is a prenylated flavonol glycoside (Figure 20) [419].

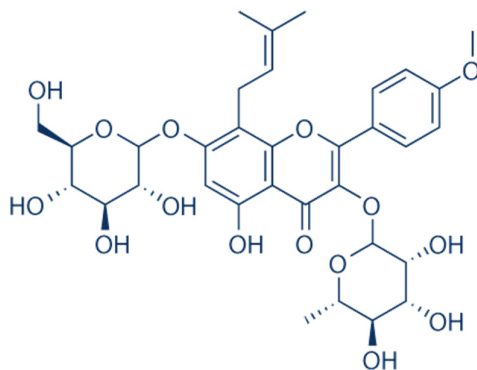


Figure 20. The chemical structure of icariin.

Icariin has shown antitumor activity in various cancers, such as gastric cancer [420], liver cancer [421,422], colon cancer [423], breast [424], ovarian [425], or esophageal [426,427].

Jung et al. [428] demonstrated that icariin had the ability to potentiate the anti-proliferative effects of bortezomib by inhibiting STAT3 activation in MM cells. Icariin inhibited STAT3 phosphorylation in U266 and MM.1S cells. Icariin inhibited STAT3 DNA binding activity and nuclear translocation in MM cells, inhibited JAK1, JAK2 and Src, inhibited inducible activation of STAT3 and upstream kinases in MM.1S cells, inhibited the IL-6-induced STAT3-dependent reporter gene, inhibited anti-apoptosis, proliferation, angiogenesis, and metastasis related proteins. Icariin activated caspase-3 and induced PARP cleavage, blocked the cell cycle and stimulated apoptosis in U266 cells, and inhibited the viability of MM cells. This bioactive compound enhanced the cytotoxic effect of bortezomib. Combination treatment of icariin with bortezomib inhibited the activation of

STAT3 and its upstream kinases, facilitated the blockade of cell cycle growth in the G0/G1 phase and cellular apoptosis. Icaritin showed a synergistic effect with bortezomib in inhibiting the expression of various oncogenic proteins. Inhibition of STAT3 by siRNA reversed the pro-apoptotic effects of icariin.

3.22. Icaritin

Icaritin, a prenylflavonoid, is a hydrolytic product of icariin, extras din *Herba Epimedii* [429]. Icaritin is a monoprenylated flavonol with 4'-methoxyl (Figure 21) [419].

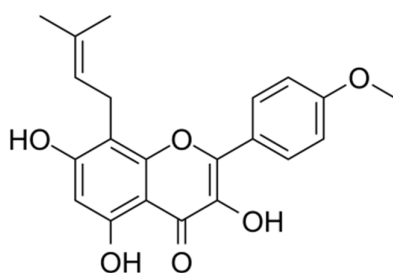


Figure 21. The chemical structure of icaritin.

Icaritin has been able to inhibit different tumors, including breast cancer [430–435], hepatocellular carcinoma [436–438], lung cancer [439], squamous cell carcinomas [440,441], esophageal cancer [442], ovarian cancer [443], endometrial cancer [444,445], colorectal cancer [446,447], glioblastoma [448,449], and osteosarcoma [449].

Icaritin showed cytotoxic effects and limited tumor progression. It induced inhibition of tumor cell migration, and stem/progenitor cell growth [434,442,450,451]. It also showed a significant inhibitory effect in acute myeloid leukemia (AML), multiple myeloma and lymphoma, and chronic myeloid leukemia (CML) [451–455].

Li et al. [456] showed that icaritin inhibited cell proliferation, induced apoptosis of MM cell line KM3/BTZ and induced the reverse multidrug resistance. The mechanisms involved are thought to be related to down-regulation of heat shock protein 27 (HSP27), P-glycoprotein (P-gp) expression, and up-regulation of Par-4 expression.

Previously, Zhu et al. [452] showed the effect of icaritin on MM cell line (U266) and primary MM cells inhibition, due to S-phase cell cycle blockade by targeting cyclin-related proteins and CDK2 and apoptosis by IL-6/JAK2/STAT3 signaling inhibition. The effects of icaritin on the inhibition of proliferation and induction of apoptosis in MM cells were independent of estrogen receptor blockade. Icaritin showed anti-myeloma activity in vivo, underlined by inhibition of tumor growth, downregulation of p-JAK2, p-STAT3 and VEGF expression and decreased serum levels of IL-6 and IgE. The antimyeloma effect of icaritin in vivo is thought to be mediated by inhibition of the p-JAK2/p-STAT3/VEGF-mediated signaling pathway.

3.23. Icariside II

Icariside II is a flavonoid glycoside isolated from *Herba Epimedii* (Figure 22) [457].

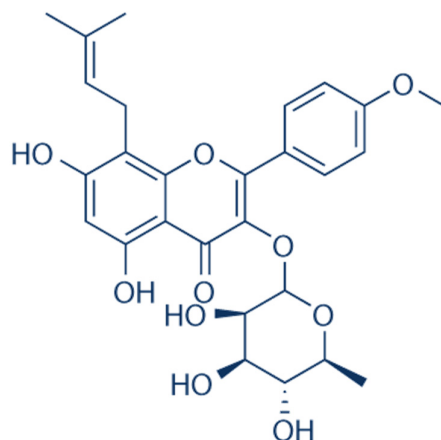


Figure 22. The chemical structure of icariside II.

Icariside II showed anti-cancer activity, including osteosarcoma, prostate and breast tumors [458,459].

Icariside II inhibited the STAT3 signaling pathway in U266 cells, inhibited proliferation, induced apoptosis, and suppressed STAT3-related gene products in U266 cells. Icariside II amplified the effect of bortezomib and thalidomide on the induction of apoptosis in U266 cells [460].

The main molecular mechanisms of flavonoids against multiple myeloma (MM) from in vitro and in vivo experiments, clinical studies, and modulation of proteins and signaling pathways are summarized in Figure 23.



Figure 23. Molecular functions of flavonoids against multiple myeloma (MM) from in vitro and in vivo experiments and clinical studies. ↑ increased/upregulated; ↓ decreased/downregulated; PI3K, phosphatidylinositol 3-kinase/protein kinase B; Akt, protein kinase B; mTOR, mechanistic target of rapamycin; STAT3/5, signal transducer and activator of transcription 3/5; CDK2, cyclin-dependent kinase 2; CDK4, cyclin-dependent kinase 4; NF- κ B, nuclear factor- κ B; p-JAK2, phosphorylated janus kinase 2; STAT3, signal transducer and activator of transcription 3; p-STAT3, phosphorylated signal transducer and activator of transcription 3; EGCG, epigallocatechin-gallate; CDKc, cyclin-dependent kinases; VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; bFGF, basic fibroblast growth factor; HIF-1- α , hypoxia-inducible factor 1- α ; Bcl-2, B-cell lymphoma-2; Mcl-1L, myeloid cell leukemia-1 long; Bax, Bcl-2-associated X protein; Bad, Bcl-2-associated death promoter; MMP-2, matrix metalloproteinase 2; MMP-9, matrix metalloproteinase 9; ER stress, endoplasmic reticulum stress; MAPK, mitogen-activated kinase; ROS, reactive oxygen species; PARP, poly(ADP-ribose) polymerase; AMPK, AMP, activated protein kinase.

4. Plant Extracts in Multiple Myeloma

In recent years, research has focused on the discovery of new plant extract metabolites that act as antitumor agents in various cancers, including hematological cancers [461]. Plant extracts target different signaling pathways in cancer cells, such as proliferation, differentiation, and apoptosis [462], acting through synergistic and/or additive effects [463–465].

Concomitant administration of plant extracts and anti-cancer drugs has increased the therapeutic efficacy of treatment by increasing the sensitivity of cancer cells to drugs and overcoming drug-induced resistance to cancer [466]. Currently in clinical practice a significant number of plant-isolated compounds are used in the treatment of cancer in combination with other drugs [467], against hematological malignancies [468–472].

The main pharmacological effects exerted by herbal extracts are summarized in Table 2.

Table 2. Pharmacological effects of different plant extracts in multiple myeloma.

Herbal Extracts	In Vitro/In Vivo	Cancer Cell Line and Animal Model	Bioactive Effect	References
<i>Azorella cglabra</i>	In vitro	SKMM1, RPMI-8226, and MM1S cells PBMCs	↑ antioxidant activity ↓ cell viability, induced apoptosis, and cell cycle arrest	[461]
<i>Corchorus olitorius</i> leaf extracts (LE) and seed extracts (SE)	In vitro	ARH-77 cells	- cytotoxic effects on cells (LE and SE) - SE had higher cytotoxicity on cells - genotoxicity effects in dose-dependent manner (LE and SE)	[473]
Frankincense and myrrh extracts	In vitro	U266 cells	- inhibited cell proliferation - ameliorated the secretion of cytokines ↓ expression of JAK/STAT signaling pathway - 3-O-acetyl- α -boswellic acid, 11-keto-boswellic acid and 3-acetyl-11 keto-boswellic acid had the most significant anti-multiple myeloma activities	[474]
<i>Fumaria officinalis</i> extracts	In vitro	MOLP-8, NCI-H929, KMS-12BM, RPMI-8226, KMS-11, AMO-I, L-363, OPM-2, JJN-3 cells	- CF induced viability of NCI-H929 cell line - EF induced cytotoxicity on OPM-2 cells - CF and EF induced apoptosis in NCI-H929 cells by loss of MMP, generation of ROS - EF induced autophagic cell death, while CF stimulated iron-dependent cell death	[475]
<i>Hibiscus sabdariffa</i> extracts	In vitro	RPMI-8226 cells	- antiproliferative effects (Hib-ester and Hib-carbaldehyde compounds) ↓ cell migration and invasion, events involved in the process of metastasis	[6]
<i>Hibiscus sabdariffa</i> extract (HSE)	In vitro	RPMI-8226 cells	↓ cell growth, motility and invasiveness by ERK1/2 modulation ↑ cytostatic effects dependent on p38 activation	[476]
<i>Patrinia scabiosaefolia</i> ethanol extract (EEEEPS)	In vitro	U266 cells	- inhibited the activation of STAT3 - inhibited the proliferation - induced apoptosis ↓ the expression of Bcl-2 and cyclin D1	[477]
<i>Punica granatum</i> leaves, flowers and stem extracts	In vitro	U266 cells	- inhibited proliferation - apoptotic effect - caused cell cycle arrest in G2/M and S phases	[462]
<i>Salvia miltiorrhiza</i> (SM) extract	In vitro	U266 and U937 cells	- suppressed the growth of U266 and U937 cells ↑ ROS generation and cytotoxic effect was dependent on ROS - induced ER stress mediated apoptosis ↑ expression of miR-216b and ↓ its target, c-Jun, in U266 and U937 Cells	[478]

<i>Scutellaria baicalensis</i> extract	In vitro	RPMI-8226 cells	- Scutellaria extract riched in baicalin, wogonoside, baicalein and wogonin - inhibited the proliferation ↓ the expression level of ABCG2 protein	[135]
<i>Serenoa repens</i>	In vitro	U266, RPMI 8226 multiple myeloma cells	- induced growth arrest - induced apoptosis ↑ the expression of cleaved-PARP or p27 protein ↓ basal level of phosphorylated form of STAT 3 ↓ IL-6 induced level of phosphorylated form of STAT 3 and ERK - inhibition of STAT 3 signaling	[479]
<i>Strychnos nux-vomica</i> root extract	In vitro	U266B1 cells	- anti-proliferative effect - accumulation of the sub-G0/G1 cell population with consequent decline in other phases of cell cycle ↓ IL-6 and CD-138	[480]
<i>Strychnos nux-vomica</i> root extract	In vitro	RPMI 8226	- anti-proliferative activity -the SN-treated cells exhibited significant features associated with apoptosis: cell shrinkage, condensed chromatin, nuclear fragmentation and membrane blebbing ↑ the accumulation of cells at sub-G0/G1 phase - induced disruption of mitochondrial membrane potential and subsequent leakage of mitochondrial cytochrome c	[481]
<i>Thymus vulgaris</i> and <i>Arctium lappa</i> extracts	In vitro	MOLP-8, KMS-11, NCI-H929, RPMI-8226, KMS-12BM, JJN-3, L-363, AMO-I, and OPM-2 cells	- cytotoxicity in CCRF-CEM and CEM/ADR 5000 cell lines - TCF induced apoptosis in NCI-H929 cells with a higher ratio, compared to ACF - ACF demonstrated more potent autophagy activity than TCF - TCF and ACF induced cell cycle arrest and ferroptosis	[482]
<i>Viscum album</i> QuFrF (VAQuFrF) extract	In vitro	Molp-8, LP-1, OPM-2, Colo-677, RPMI-8226, and KMS-12-BM cells	- VAQuFrF + vincristine inhibited cell proliferation, arrested the cell cycle phases, and increased the number of apoptotic/necrotic cells. - VAQuFrF inhibited the proliferation of the cells more effectively than vincristine in Molp-8, LP-1, and RPMI-8226 cells at a dose of 10 µg/105 cells - VAQuFrF affected the tumour cells mainly via cytostatic effect	[483]
Bioactive compounds from <i>Abelmoschus manihot</i> L.	In vitro In vivo	ARP1 and H929 human MM cell lines and murine MM cell line, 5TMM3VT C57BL/KaLwRij mice	- HKC improved survival rate of MM-prone mice - promoted osteoblastogenesis and suppressed osteoclastogenesis in murine cell lines - HK-11 inhibited MM cells proliferation and ↓ β-catenin signaling	[484]

Legend: ↑ increased/upregulated; ↓ decreased/downregulated; ACF—*Arctium lappa* chloroform fractions; CDKs—cyclin-dependent kinases; CF—chloroform fractions; CRBN—cereblon; EF—ethyl acetate fractions; ERK—extracellular signal-related kinase; HK-11—3-O-kaempferol-3-O-acetyl-6-O-(p-coumaroyl)-β-D-glucopyranoside; HKC—*Abelmoschus manihot* (L.) Medik. derived Huangkui capsules; HSE—*Hibiscus sabdariffa* extract; IL-6—interleukin-6; KEGG—Kyoto Encyclopedia of Genes and Genomes; LE—*Corchorus olitorius* leaf extracts; MYC—myrrh ethanol extracts; PARP—poly (ADP-ribose) polymerase; PBMCs—peripheral blood mononuclear cells; RXC—frankincense ethanol extracts; SE—*Corchorus olitorius* seed extracts; SM—ethanol extract of *Salvia miltiorrhiza*; SN—*Strychnos nux-vomica* L.; SP—side population; STAT 3—signal transducer and activator of transcription 3; TCF—*Thymus vulgaris* chloroform fractions; VAQuFrF—*Viscum album* QuFrF; YDC—frankincense-myrrh ethanol extracts; YDS—frankincense-myrrh water extracts.

5. Conclusions and Therapeutic Perspectives

In this review, we presented 21 flavonoids and 16 plant extracts that have shown an antitumor potential in the experimental studies on MM cell lines, preclinical and clinical studies on MM patients, results that could propose them in subsequent therapeutic

protocols of MM. Mechanistically, they demonstrated the ability to induce cell cycle blockage and apoptosis or autophagy in cancer cells, as well as the inhibition of proliferation/migration and tumor progression, and inhibition of angiogenesis in the tumor vascular network. However, there are currently ongoing clinical trials only for curcumin and EGCG in combination with conventional drugs. Meanwhile, current research provides valuable new information about the ability of flavonoids to enhance apoptotic effects of antineoplastic drugs (baicalein/quercetin/dexamethasone; EGCG/doxorubicin, cisplatin, sunitinib, phosphodiesterase 5 inhibitor vardenafil, safinol; Butein/thalidomide and Velcade; Icaritin/bortezomib), thus providing viable therapeutic options based on combining conventional and non-conventional therapies in MM therapeutic protocols.

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