Review Article

Targeting Multiple Myeloma with natural polyphenols

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Abstract

Multiple myeloma (MM) is still an incurable hematologic malignancy. Although new therapeutic strategies have been developed to target different pathways in malignant cells, such as proliferation, differentiation, and apoptosis, better survival rates have also been achieved by the introduction of autologous stem cell transplantation (ASCT). Hematopoietic stem cell transplantation and novel targeted agents, such as proteasome inhibitors, monoclonal antibodies, immunomodulatory drugs, check-point inhibitors and epigenetic modulators, have significantly achieved long remission time and increased survival rates. However, most patients relapse, develop resistance, and eventually die because of refractory disease. All these issues highlight the need to investigate newer therapeutic targets to improve patient outcomes. Natural products play an important role in anti-tumor drug discovery, for this reason, in the investigation of novel natural anti-MM agents, we focused on natural polyphenols. Moreover, plant extracts have a favorable pharmacokinetic profile and show no or low toxicity towards normal cells. The biological activities of plant extracts are mainly due to their content in polyphenols, flavonoids, and terpenoids. Numerous studies showed that polyphenols, generally recognized as antioxidants, possess anticancer and pro-apoptosis properties. Other studies reported the potential clinical applications of flavonoids for their well-known protective and therapeutic effects against cancer, cardiovascular, and neurodegenerative diseases. The combination of plant extracts with anti-cancer drugs may offer a relevant advantage for therapeutic efficacy by sensitizing malignant cells to drugs and overcoming drug-induced resistance in cancer. For all these reasons, a significant number of polyphenolic compounds isolated from plants are still used nowadays in cancer clinical practice in combination with other drugs, also against hematologic malignancies.

Keywords: natural polyphenols; multiple myeloma; anticancer drug.

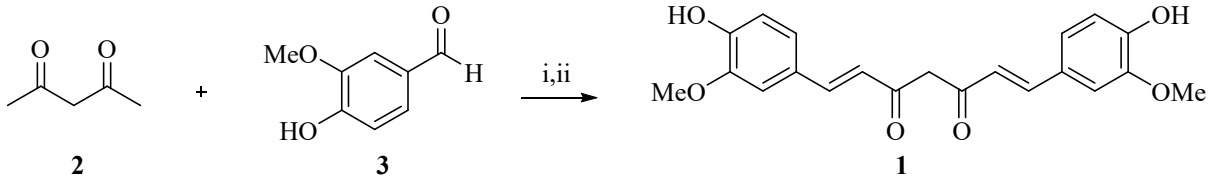
1. Introduction

The search of a definitive cure for multiple myeloma (MM) has demonstrated a long difficult pathway since the first description of the disease in 1844 [1-3]. With the improvement of the general understanding of this pathological entity, it became evident that two asymptomatic conditions, named monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) are associated with a risk of progression towards MM, which has been estimated as 1 % per year for MGUS and 10 % per year for SMM. A complex interplay among proliferation of clonal/aberrant plasma cells (aPCs), immune system failure and support from bone marrow microenvironment cells leads to the fracture of the equilibrium in bone marrow niches and to the development of treatment required for MM [4, 5]. Up to date, treatment of MGUS and SMM is not uniformly recommended out of clinical trials, thus these patients are periodically monitored to detect signs of end organ damage and increases in aPC proliferation [6, 7]. Therapeutic intervention is started only at the exordium of MM and made notable progresses in the last 20 years. Through multiple attempts, better survival rates have been achieved by the introduction of autologous stem cell transplantation (ASCT) and the implementation of therapeutic protocols ranging from immunomodulatory drugs and proteasome inhibitors to monoclonal antibodies and checkpoint inhibition [2, 6, 8 - 12, 13]. However, the course of the disease implies continue monitoring to assess the burden of minimal residual disease and to allow an early detection of relapses [2 - 4, 9, 10]. A wide debate is still going on about the possibility that MGUS and SMM patients may benefit from an early intervention [14], and MM patients still lack a definitive therapy bringing together the need of debulking/eradicating the tumor with acceptable tolerability [10-12]. In the context of global efforts directed to finding improved treatment options in plasma cell malignancies, phytochemicals especially natural polyphenols (Figure 1) reveal some interesting applications as both single agents and combination therapy [15]. Natural polyphenols have been largely studied in MGUS and MM, but the complexity and lack of uniformity in their mechanism of action have left the space to some speculations about their safe employment together with classical anti-MM drugs, especially proteasome inhibitors. In this review, we want to summarize the most recent discoveries in the field (Table 1), taking some time to critical evaluation of the best strategy to consider the use of natural polyphenols in treatment of MGUS and MM.

2. Curcumin

Polyphenol (1E, 6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione **1**, familiarly known as curcumin, is extracted by various members of the genus *Curcuma*, including *Curcuma longa*, a spice widely used all around the world [16 -17].

Curcumin was recently synthetized [18] according to a slight modification of Pedersen method [19] as reported in the Scheme **1**.



Scheme 1. Reagents and conditions: (i) EtOAc, B_2O_3; (ii) $B(n\text{-}BuO)_3$, $n\text{-}BuNH_2$, HCl.

A boric acetylacetone anhydride complex was prepared refluxing 2,4-pentanedione with boric anhydride in order to avoid the unwanted Knoevenagel reaction at C-3 of acetylacetone. Subsequent aldol condensation with 4-hydroxy-3-methoxybenzaldehyde **3** allowed the isolation of curcumin in 51% yield.

Curcumin exhibits anti-inflammatory, anti-cancer and immunomodulatory properties, in a large variety of pathological settings, ranging from osteoarthritis to solid tumors and hematological malignancies like chronic lymphocytic leukemia [15-17, 20, 21]. The panel of beneficial effects associated with curcumin administration together with its highly safe profile [16, 20 - 22] make it an excellent perfect candidate as a therapeutic option in both MGUS and SMM, as well as in MM.

Curcumin exerts inhibitory functions on MM survival molecular pathways reducing *in vitro* levels of p-Akt with a time dependent pattern [23]. Additionally, treatment with curcumin produced a full suppression of constitutive activation of NF-κB (RelA/NF-κB1) with cell line specific kinetics. This effect was reached through a curcumin mediated superior retention of RelA subunit in the cytoplasm and dose dependent direct inhibition of IKK kinase activity, which in turn produced a reduced phosphorylation of IκBα. Suppression of NF-κB transcriptional activation activity by curcumin affected depletion of NF-κB regulated gene products, including Bcl-2, Bcl-x_L, cyclin-D1, TRAF1, XIAP and VEGF [23, 24]. Treatment with curcumin for 1 hour completely abolished constitutive STAT3 phosphorylation and nuclear STAT3 translocation, and INFα inducible STAT1 phosphorylation with a 4 hours pretreatment, with no effect on STAT5, as demonstrated *in vitro*. Similar results were obtained in the case of IL-6 induced STAT3 phosphorylation treating cell lines for 4 hours. The measured effects on STAT3 activation were completely reversible in 24 hours after curcumin removal [25]. In MM patient derived cells, treatment with 50 μM curcumin precluded

nuclear localization of NF- κB and STAT3, reduced the level of phosphorylation of STAT3 and IκBα, and suppressed constitutive expression of NF- κB and STAT3 regulated products Bcl-2 and Bcl-x_L [26]. Curcumin also exerts an influence on activation of p53 network. In RPMI 8226 an increase in *p53* and *BAX* expression and a downregulation of *MDM2* was caused by curcumin in a dose and time dependent fashion [27].

These effects on molecular pathways have a measurable impact on cell survival. Curcumin alone at 1 μM dose was sufficient to hamper cell proliferation in U266, RPMI 8226, MM.1S, and MM.1R cells, with a full suppression of cell growth with a 10 μM dose. A dose dependent induction of apoptosis and a time dependent induction of caspase 9 and caspase 7 was evidenced after treatment with curcumin in U266 cells [24]. In the same cell line, increasing doses of curcumin (10-50 μM) produced activation of caspase 3, cleavage of PARP, reduction of cyclin D1 and CDK4, and accumulation of p21 at protein level [28]. As low as 5 μM curcumin for 24 hours induced the activation of caspase 3 and a G0/G1 cell cycle arrest in U266 cell line [29]. A dose of 10 μM curcumin for 48 hours caused a stop in IL6 induced proliferation of U266, MM.1R and MM.1S cells [25]. Also, in MM patient derived cells a dose dependent inhibition of cell proliferation was recorded, and this effect was higher than that elicited by dexamethasone [26].

MM cells exhibit different sensitivity to curcumin as a function of their genetic background. Analyzing 29 MM cell lines it became evident that cells harboring t(11;14) tend to be less sensitive to curcumin then other cell lines devoid of this translocation, exhibiting a higher median lethal dose 50 (LD_{50}= 32.9 μM) than the non-t(11;14) subgroup (LD_{50}= 17.9 μM). The non-t(11;14) subgroup also included cells carrying cytogenetic alteration indicative of poor prognosis, namely t(4;14) and t(14;16). These results were reproduced also in aPCs from MM patients. Sensitivity to curcumin also influences the mechanism by which this polyphenol triggers apoptosis. Treatment with 15 μM curcumin induced activation of caspase 3 and reduction in Mcl-1 in L363 cells (highly sensitive to curcumin), whereas no alterations in cell survival and caspase activation were recorded in XG5 cell line (poorly sensitive to curcumin). [30].

The activity of curcumin can be described also in terms of aPC interaction with the BM microenvironment. Curcumin reduced TNF-induced adhesion of U266 cells to BM stromal cells and diminished constitutive and U266 induced secretion of IL6 by BM stromal cells [26]. Curcumin can offer the space to prevent appearance of osteolytic bone lesions in MM patients. In fact, in murine monocytic cell line RAW 264.7, suppression of both RANKL-induced activation of NF-κB and RANKL-induced IκBα phosphorylation and degradation, together with a loss of IKK activity was demonstrated. As a final result, a dose dependent inhibition of osteoclastogenesis from RAW 264.7 and mouse derived macrophages was recorded [31]. Curcumin can overcome the protective effect

exerted by the BM microenvironment causing a reduction in cellular proliferation of U266 and RPMI8226 cell lines, both alone and in co-culture conditions with bone marrow stromal cells (BMSCs). Curcumin inhibited phosphorylation of STAT3 and Erk induced by exposure to cell culture supernatant of BMSCs and by pretreatment with IL-6 and IL-6/sIL-6. Release of IL-6 and sIL-6R by U266 cells and secretion of IL-6 and VEGF by BMSCs were efficiently inhibited by increasing doses of curcumin [28].

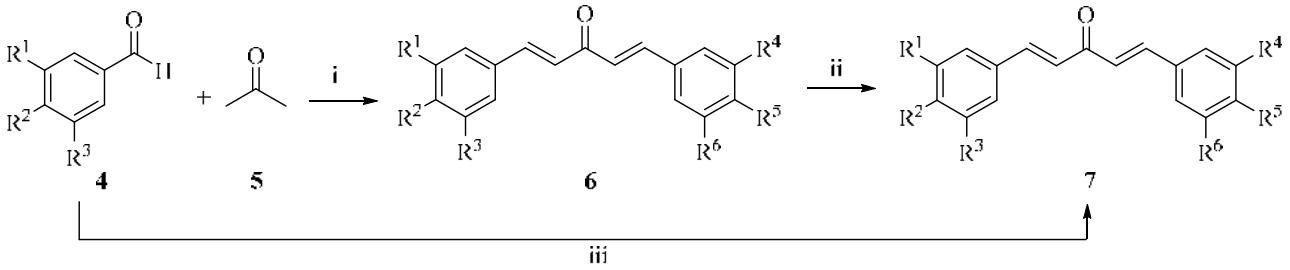
Curcumin demonstrated the abilities to circumvents drug resistance and to increase the effect of chemotherapeutic drugs *in vitro*. Curcumin efficiently suppress cell proliferation of MM cell lines independently of drug resistance, as assessed in MM.1R cells [25, 23], and in MM.1S, U266, RPMI 8226, RPMI-8226-Dox-6 (doxorubicin resistant) and RPMI-8226-LR-5 (melphalan resistant) [23]. Curcumin augmented the cytotoxic effect of vincristine and melphalan *in vitro*, as measured on U266, RPMI 8226, MM.1S, and MM.1R cells [24]. Experiments on melphalan resistant MOLP-2/R cell line put some light on the improved pro-apoptotic action of curcumin in combination with melphalan. Treatment with curcumin diminished levels of FANCD2 monoubiquitination in a dose dependent manner, thus suggesting the involvement of the FA/BRCA pathway. In addition, curcumin can increase melphalan intracellular concentration [32]. Curcumin can enhance the effects of bortezomib through multiple molecular mechanisms. In H929 cells, combining bortezomib with curcumin produced a marked cytotoxicity, which was related to a reduction in nuclear content of p65 subunit of NF-κB, stabilization IκB and increase in the amount of intracellular phospho-JNK. The use of JNK specific inhibitor SP600125 in H929 cells reduced the inhibitor effect on NF-κB improving cell survival, thus revealing that the combined treatment bortezomib+curcumin acts through a JNK dependent mechanism [33]. In U266 cells, combinatory pretreatment with bortezomib and 5 μM curcumin was superior than bortezomib alone in reducing levels of p-STAT3 and p-ERK induced by IL-6/sIL-6R. Moreover, as low as 4 and 8 μM doses of curcumin synergistically contributed to bortezomib blockage of cell proliferation [28]. Curcumin potentiated the apoptotic effect of bortezomib and thalidomide in U266 cell line, and it was able to abolish constitutive NF-κB activation in combination with bortezomib or thalidomide, even when all the three compounds were used at suboptimal concentration. In murine xenografts of U266 cells, curcumin ameliorated the antiproliferative and anti-angiogenetic effects of bortezomib through NF-κB inhibition and VEGF downregulation [23]. Curcumin increased carfilzomib elicited cytotoxicity in U266 cell line through a proteasome independent mechanism. Also, both curcumin and carfilzomib caused dose-independent increase in reactive oxygen species (ROS), but when used in combination, the final effect was neither additive nor synergic. Instead, combination of curcumin and carfilzomib affected nuclear accumulation of p65 (RelA) subunit of NF-κB and increased the protein level of p53 and p21. The

combined effect of carfilzomib and curcumin produced and arrest in the G0/G1 phase, a reduction in the fraction of cells in S phase and an increment in caspase 3 activation [29].

Another poorly investigated aspect that can contribute to curcumin anti-myeloma activity is its interaction with drug transporters and drug metabolizing enzymes. Despite documented ability of curcumin to inhibit P-glycoprotein, multidrug resistance protein 1, cytochrome P450 monooxygenases, uridine dinucleotide phosphate glucuronosyltransferases and glutathione-s-transferase may rise some concerns about curcumin safety in combination with multiple drug regimens. Pharmacokinetic effects exerted by curcumin can produce a reduction in conventional drug doses to obtain measurable therapeutic effects, reducing the entity of side effects and adverse events [22, 34]

One of the most frustrating inconvenience related to curcumin administration depends on its modest absorption, its rapid metabolism/elimination and thus its poor availability after ingestion [16, 21, 22, 35, 36]. An extended panel of solution have been described to overcome the problem of curcumin low bioavailability, ranging from incorporation of curcumin in micelles to the synthesis of analogues with improved bioavailability and superior growth suppressive abilities against aPCs [35 - 40].

In particular Kudo et al. [37] have recently synthesized 69 diarylpentanoid curcumin analogs, which were investigated both for their antitumor activity and for their in silico ADME (absorption, distribution, metabolism and elimination) properties. Structurally, the new analogues were either symmetrical and asymmetrical 1,5-diarylpentadienone whose aromatic rings were decorated with an alkoxy group at each of the positions 3 and 5. The synthetic pathway leading to the symmetric derivatives is reported in the Scheme 2. [41]



Scheme 2. Reagents and conditions: for symmetric compounds (R^1=R^4, R^2=R^5, R^3=R^6) (i) **4**, acetyltrimethylammoniumbromide (CTABr), 10% aq. NaOH, EtOH; (ii) HCl, EtOH; for asymmetric compounds (iii) 3,4,5-trimethoxybenzaldehyde, DADC, DCM; then 10% aq. NaOH, EtOH.

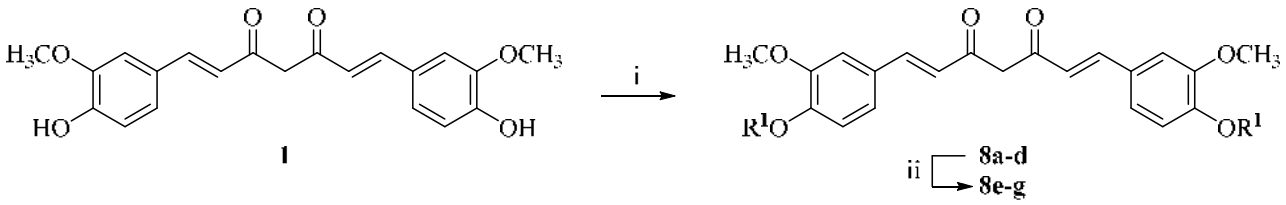
Symmetric derivatives were synthetized starting from hydroxybenzaldehydes properly protected with methoxylmethyl (MOM) or ethoxyethyl groups prior to aldol condensation. The protecting groups

were then removed by hydrolysis under acidic conditions.

Asymmetric bis(arylmethylidene)acetones [42] were synthesized in a two-step sequence in which trimethoxybenzaldehyde was initially reacted with acetone under Strauss's conditions using dimethylammonium dimethyl carbamate (DADC) [43]. Subsequent reaction with the suitable aryl aldehydes **4** allowed the isolation of the desired analogs **7** (Scheme 2).

Among the analogs thus obtained GO-Y030 (**6**, R^1=R^3=R^4=R^6=OMOM, R^2=R^5=H) and GO-Y078 (**7**, R^1=R^2=R^3=R^4=R^6=OMe, R^5=OH) were 7 to 12-fold more potent growth suppressors for myeloma cells, and 6- to 15-fold stronger inhibitors of NF-κB, PI3K/AKT, JAK/STAT3, and IRF4 pathways than curcumin. Moreover GO-Y78 14-fold more potently inhibited IL-6 production. Although the efficacy and safety of GO-Y030 and GO-Y078 *in vivo* remain to be elucidated, the new curcumin analogs can offer potential leads for the development of therapeutic agents against MM.

With the aim of improving curcumin water solubility, curcumin amino acid cojugates **8a-g** were synthesized by Wan et al. and Mujtaba et al. as reported in Scheme 3 [36, 40].



Scheme 3. Reagents and conditions: (i) N-Boc-aminoacid/EDCI/DMAP; (ii) TFA/CH_2Cl_2.

CPD	R^1
8a	N-Bocglycinoyl
8b	N-Boc-L-alaninoyl
8c	N-Boc-L-valinoyl
8d	N-Boc-L-glutamoyl, 5-tert-butylester
8e	glycinoyl
8f	L-alaninoyl
8g	L-valinoyl

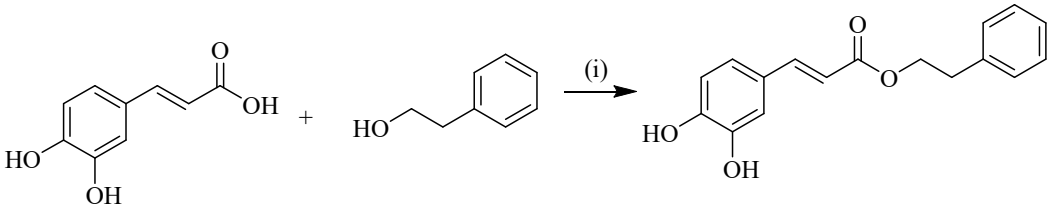
Another possible reason of concerning about the use of curcumin in MM patients is represented by curcumin ability to act as an iron chelator in culture and to inhibit the synthesis of hepcidin, reducing systemic level of hemoglobin, blood free iron and circulating iron in form of saturated transferrin, and thus exacerbating anemia which is a hallmark of MM subjects [21].

Curcumin efficacy and tolerability as a therapeutic option in plasma cell dyskrasia patients was tested in clinical trials. In MGUS and SMM subjects, curcuminoids administered at a dose of 4 g daily for three months caused a persistent reduction in free light chain ratio, in involved (monoclonal) free light chain, and in difference between involved and uninvolved free light chains, which continued after patient cross over to placebo. After a doubleblind placebo controlled cross-over study, administration of curcuminoids 8g daily for three months produced a significant reduction of free light chain ratio, total protein and random urinary protein vs baseline in both groups of patients of the 4 g-arm. Another positive effect was measured at bone turnover level, with a reduction in serum parathyroid hormone vs baseline, which in turn led to a reduction in urinary deoxypyridinoline [44]. In one phase I/II study, treatment of 29 MM patients in various phases of the disease (asymptomatic, refractory/relapsed or plateau) with curcumin alone and in combination with bioperine was associated with good tolerability. In MM patients a downregulation of NF- κB, STAT3 and COX-2 was recorded in the absence of objective responses [45, 46]. Outside of clinical trials, administration of curcumin was considered an option in multiple relapsing patients. More studies with improved patient stratification strategies would be highly recommendable to assess the full contribution of curcumin to the prevention of MGUS and SMM progression and to overcoming drug resistance in MM patients. Moreover, the possibility to use curcumin as a debulk agent in combination with standard first line treatments could be considered in future. Versatility and tolerability of curcumin have been opening the space to preliminary clinical studies combining this polyphenol with other natural compounds as an approach to achieve a better health status and quality of life in MGUS and SMM subjects [47].

3. Phenolic acids

3.1 Caffeic Acid Phenethyl Ester

Caffeic acid (3,4-dihydroxycinnamic acid) phenethyl ester (**9**, **CAPE**) chemical synthesis was described by different authors [48 - 51], but a very versatile method was reported by Nakamura et al. [52]. CAPE was obtained in high yield (95%) through a convenient conversion of caffeic acid into the corresponding ester using iBocCl in one-pot reaction (Scheme 4).



10 **11** **9**
CAPE

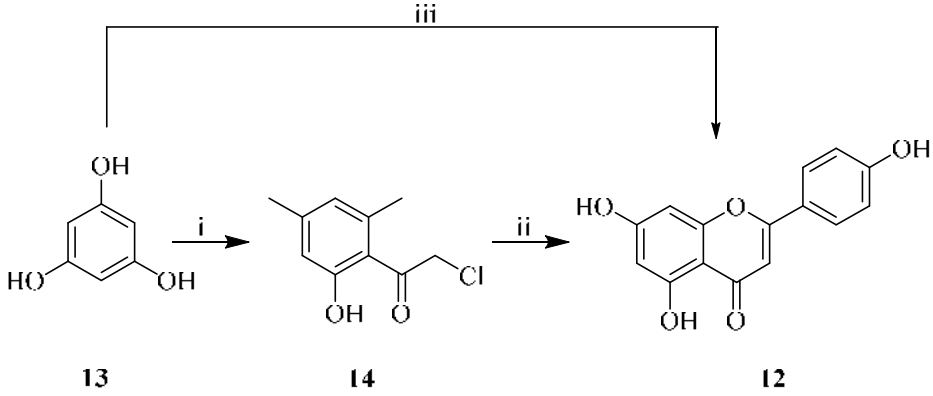
Scheme 4. Reagents and conditions: (i) DMAP, TEA, iBocCl.

CAPE has a documented cytotoxic and growth inhibitor effect on RPMI 8226, H929, U266 and ARH77 cell lines [53, 54], showing a high degree of synergism with bortezomib in suppressing cell proliferation and reducing NF-κB binding activity and IL6 levels [53]. The mechanism elicited by caffeic acid phenethyl ester involve glutathione depletion, triggering of oxidative stress response and apoptosis induction through activation of caspase 3 [54]. Caffeic acid phenethyl ester resulted non-toxic to normal human blood B cells up to a 50 μM dose [54].

4. Flavones

4.1 Apigenin

4′,5,7-Trihydroxyflavone, or apigenin (**12**) can be synthetized through a two-step synthetic pathway as reported in scheme 5 [55].



Scheme 5. Reagents and conditions: (i) $ClCH_2CN$, $ZnCl_2$; (ii) p-hydroxytolualdehyde, NaOH, then HCl; (iii) Microwave irradiation, ethyl p-hydroxybenzoyl acetate.

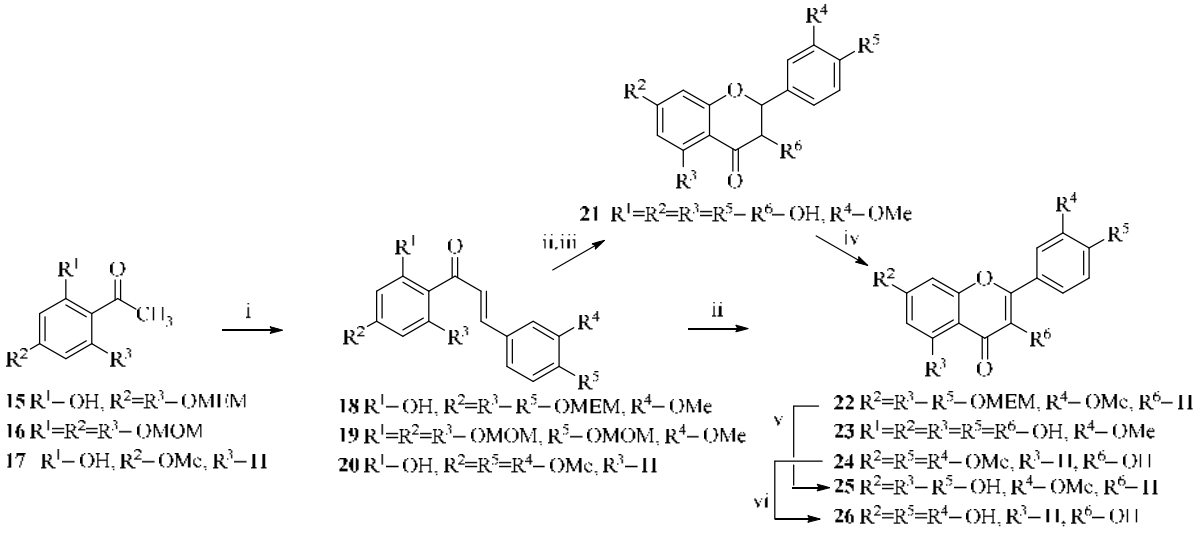
Condensation of phloroglucinol (**13**) with chloroacetonitrile catalyzed by $ZnCl_2$ followed by hydrolysis reaction, provided ketone **14** which was in turn treated with *p*-hydroxytolualdehyde in basic media, followed by acidification with aqueous HCl. Desired compound **12** was isolated in 92% yield.

Synthesis of apigenin was also described by Seijas et al. [56] who developed an efficient solvent-free method under microwave irradiation, reacting ethyl p-hydroxybenzoyl acetate and phloroglucinol giving **12** in 66% yields (Scheme 5**)**.

The interest in apigenin, arises from evidences demonstrating its proteasome inhibitor activities [57]. In U266 and RPMI8226 cells, apigenin produced cell cycle arrest in G2/M and accumulation of cells in sub-G1 flanked by inhibition of CK2 (Casein kinase 2) activity and downregulation of expression of the alpha subunit. By reducing CK2 mediated phosphorylation of Cdc37, apigenin can disassociate the Hsp90/Cdc37/client complex thus producing proteasome dependent degradation of kinase clients RIP1, Src, Raf-1, Cdk4 and AKT. The depletion of Hsp90/Cdc37/client complex was enhanced by addition of HDAC inhibitor SAHA or Hsp90 inhibitor geldanamycin. Apoptosis induced by apigenin was accompanied by reduction in Mcl-1, Bcl-2, Bcl-x_L, XIAP and Survivin. Apigenin in high dose (90 μM) was effective in reducing constitutive and inducible levels of phosphorylated forms of STAT3, kinases PDK, MEK and IKK and downstream mediators ERK, Akt and IκBα [58].

4.2 Chryseoriol

4',5,7-Trihydroxy-3'-methoxyflavone or chryseoriol **25** was explored as an anti-myeloma drug only by *in vitro* studies. It acted as a p-Akt inhibitor and reduced cell growth in RPMI8226 and KM3 cells, arresting cell cycle in G2/M. Chrysoeriol reduced phosphorylated 4eBP1 (eukaryotic initiation factor 4E (eIF4E)-binding protein 1) and increased levels of cyclin B1 and p21 [59].



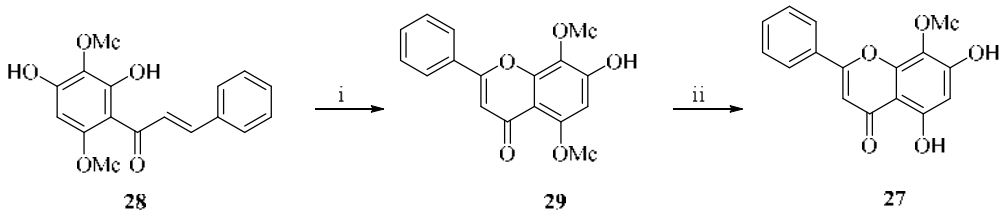
Scheme 6. Reagents and conditions: (i) 3,4-disubstituted benzaldehyde, NaOH or KOH, MeOH, EtOH or DMF; (ii) for **18** $NaIO_4$, DMSO, for **19,20** H_2O_2, NaOH, MeOH; (iii) HCl, MeOH; (iv) $K_2S_2O_5$ soln; (v) HCl, THF; (vi) Me_3SiI, MeOH.

Chryseoriol **25** can be obtained by a conventional synthetic route (Scheme 6) involving the base-catalysed aldol condensation of 4',6'-MEM-2'-hydroxyacetophenone **15** with MEM protected 4-hydroxy-3-methoxybenzaldehyde leading to chalcone derivative **18**. This latter can be converted into

flavone **22** with sodium periodate. The final synthetic step involved the selective cleavage of the protecting groups of flavone **22** affording the expected chryseoriol **25** in 90% yields. [60]

4.3 Wogonin

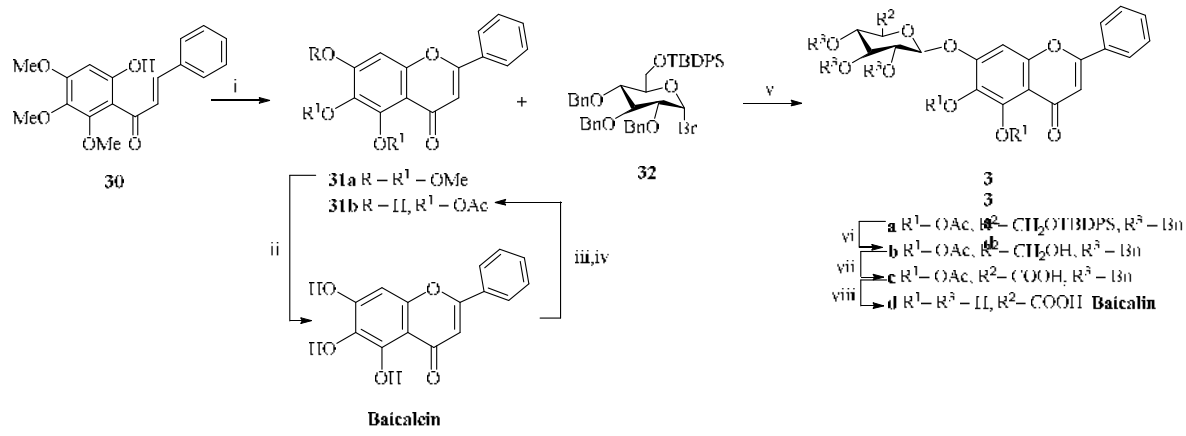
5,7-Dihydroxy-8-methoxyflavone, commonly named wogonin, is cytotoxic for MM cells, as demonstrated by apoptosis induced in RPMI8226. By direct binding to Akt, wogonin reduced its phosphorylation [61]. Moreover, wogonin attracted researchers' interest for its applications in targeting the bone marrow microenvironment. *In vitro*, at non-cytotoxic dose (80 μM) it inhibited angiogenesis in both normoxic and hypoxic conditions through a reduction in the amount of VEGF, PDGF and bFGF secreted by MM cell lines. This result was reached by downregulation of c-myc and alteration in VHL complex stability and turnover, leading to increased degradation of HIF1α. Moreover, wogonin displayed a synergistic action against MM-dependent angiogenesis when combined with bortezomib or lenalidomide [62].



Scheme 7. Reagents and conditions: (i) I_2, DMSO; (ii) $AlCl_3$, CH_3CN.

Recently Bian et al. have reported a multistep synthesis to obtain wogonin **27** (Scheme 7)[63]. Intermediate **28**, properly prepared, was cyclized to the corresponding flavone **29**, which was demethylated to afford compound **27**.

4.4 Baicalein



Scheme 8. Reagents and conditions: (i) I_2, DMSO; (ii) 47% HBr, AcOH ; (iii) Ac_2O, AcONa,; (iv) first BnBr, KI, K_2CO_3, acetone, then $Pd(OH)_2/C$, H_2, THF; (v) Ag_2O, quinoline; (vi) TBAF, AcOH, THF; (vii) TEMPO, BAIB, DCM/H_2O; (viii) $Mg(OMe)_2$, MeOH [64].

Baicalin, that is baicalein 7-O-β-D-glucuronic acid (Scheme 8), is the major component of *S. baicalensis*. The synthesis of its aglycon baicalein was described by Huang et al. [65] and more recently by Chen [66].

However, the former synthetic route has the advantage to represent a strategy to obtain not only baicalein but also other flavonoids. In literature, there have been no appropriate approaches available for a facile synthesis of those chemical entities, since the traditional procedures based on conventional Baker–Venkataraman approach [67] or the Wittig strategy [68] proved to be impractical because of multistep synthetic route giving too low overall yields and encountering considerable challenges due to irreproducible workout.

Therefore, Huang et al. [65] performed synthesis of baicalein *via* chalcone **30**, properly prepared, which was subjected to intramolecular oxidative cyclization using I_2 and dimethyl sulfoxide (DMSO). Demethylation of **31a** with a solution 47% HBr/AcOH afforded to baicalein in excellent yield (89%) (Scheme 8).

Baicalein, suppresses proliferation of U266, ILKM2 and AMO1 cells as wells as MPC-1-immature myeloma cells from patients and side population cells in a dose and time dependent manner, without affecting survival of normal myeloid and peripheral blood cells [69 – 72] . When tested on U266 cells, baicalein caused release of mitochondrial cytochrome c and inhibited phosphorylation of IkBα, nuclear traslocation of p65 NF-κB and expression of IL-6 and XIAP [69]. In the same cell line, baicalein upregulated cereblon at a transcriptional level, and reduced the protein level of IKZF1 and IKZF3 by proteasomal degradation in a dose dependent manner [72]. As detected through multiple experiments involving various cell lines (U266, NOP2, ILKM2 and AMO1) baicalein inhibited IL-6-induced STAT3, STAT1, Akt, JAK1 and TYK2 and ERK1/2 phosphorylation in a dose dependent manner [73]. In addition, baicalein reduced both constitutive and IL6 induced Bcl-XL levels [73]. Baicalein may also be considered to sensitize cells to other treatments, given that it reduced the protein level of ABCG2 in RPMI8226 cells through a mechanism that might involve direct interaction [70, 71]. Differently from apigenin, baicalein showed no proteasome inhibitor activity or a direct role in the increase of ubiquitinated proteins [74].

Baicalein can be used in combined regimens. Baicalein stimulates PPAR-β activity, and in U266 and ILKM2 cell lines cooperates with dexamethasone to upregulate PPAR response element (PPRE)-mediated target products ILK and PPARγ1. The cooperative effect of baicalein with dexamethasone

also produces growth suppression, as recorded for U266, NOP2 and ILKM2 cells and for MPC-1- immature myeloma from patients, with a less frequent inhibitor effect on primary MPC-1+ mature myeloma cells [75]. Stimulation of U266 with IL1α in the presence of dexamethasone and baicalein enhanced the physical interaction of p65 NF-κB with PPAR-β, reducing the expression of NF-κB target genes [75].

Despite its versatile pharmaceutical applications, only one total synthesis of baicalin **33d** was reported by Mazey-Vandor in low yield (44%) [76] A more efficient synthesis of baicalin and its analogs was described by Li et al. from cheap commercially available starting materials [64].

Baicalein was treated with Ac_2O and AcONa to give fully acetylated baicalein, in which the most reactive 7-OAc was selectively substituted with a benzyl group providing an intermediate further subjected to hydrogenolysis to afford compound **31b**. The glycosydic linkage between 2,3,4-tri-O-benzoyl-6-O-tert-butyldipenylsilyl-α-D-glucopyranosyl bromide **32** and 5,6-diacetylbaicalein **31b** was formed by the Koenigs–Knorr protocol and was fully stereoselective, since the only the β-isomer was detected. Widlanski oxidation (TEMPO/BAIB) of intermediate **33b** allowed the isolation of the carboxylic acid **33c** (87% yield) [77, 78]. Finally, through treatment with a mild base as $Mg(OMe)_2$ **33d** was obtained in a high 85% yield (Scheme 8).

Baicalin was mainly studied for its less powerful anti-myeloma effects in comparison with baicalein, despite some exceptions were occasionally reported [79]. However, both of the cited compounds are able to suppress the proliferation of primary MPC-1- immature myeloma cells and to reduce the expression of ABCG2 [69, 70, 73]. Baicalin showed no effect on IL-6-induced STAT3, STAT1 and ERK1/2 phosphorylation in vitro [73], and its anti-proliferative mechanism requires further investigation.

5. Flavonols

5.1 Quercetin

In literature only few methods for the synthesis of flavone-3-ols are reported. Among them, Allan-Robinson synthesis can be considered a method of choice but it employs very harsh experimental conditions and requires selective protection and deprotection of the free hydroxyl groups with benzyl and/or benzoyl groups [80]. An alternative method is Algar–Flynn–Oyamada (AFO) reaction which suffers of variable yields and side products formation [81, 82].

Recently Pandurangan et al. [83] have reported the synthesis of quercetin (3,5,7,3′,4′-pentahydroxyflavon) and other flavone-3-ols by modified Algar–Flynn–Oyamada method, using methoxymethyl (MOM) ethers as protecting group, which can be easily removed [84]. Condensation of 2,4,6-tri-MOM phloracetophenone **16** with MOM protected 4-hydroxy-3-methoxybenzaldehyde

[85] allowed the isolation of chalcone **19** subsequently converted into dihydroflavonol **21** using alkaline H_2O_2 followed by treatment with methanolic HCl; finally treatment with potassium metabisulfite solution gave quercetin **23** by Scheme 6.

Quercetin, has documented anticancer activity challenged in various tumor scenarios, including MM [86, 87]. Quercetin suppressed cell growth as documented in RPMI8226, ARP-1, MM.1R and primary MM cells in a dose and time dependent fashion, producing G2/M cell cycle arrest and induction of apoptosis via activation of caspase 3 and caspase 9, upregulation of p21 and downregulation of c-myc [86]. Moreover, quercetin downregulates IQGAP1 (IQ motif-containing GTPase activating protein 1), reducing ERK1/2 activation [88]. Both *in vitro* and *in vivo*, quercetin showed a synergistic inhibitor effect when combined with dexamethasone [86]. However, the consequences of dose selection and cell specific susceptibility to quercetin may play an important role in setting combinatory treatments with bortezomib. 40 μM Quercetin abrogated the pro-apoptotic effect of bortezomib in U266 and RPMI8226 cell lines, despite the fact that at high doses quercetin was able to promote cell death [89].

5.2 Fisetin

7,3′,4′-Flavon-3-ol **26**, known as fisetin, can be synthesised using the Algar–Flynn–Oyamada reaction. The synthetic pathway starts from reaction of compound **17** with 3,4-dimethoxybenzaldehyde in the presence of 50% NaOH to afford methoxychalcone **20**, which was converted to the corresponding methoxyflavanol **24** by treatment with H_2O_2 in the presence of a base. Demethylation of compound **24** using Me_3SiI/MeOH afforded the desired flavonol **26** (Scheme 6)[90].

Data available for fisetin, are largely insufficient. In U266 cells, fisetin induced apoptosis by activation of caspase 3, reduction in Bcl-2 and Mcl-1, and increase in levels of Bax, Bim and Bad. Production of ROS elicited by fisetin led to increased phosphorylation of AMPK (5’ Adenosine monophosphate-activated protein kinase) and acetyl-CoA carboxylase (ACC), and a decreased phosphorylation of Akt and mTOR [91].

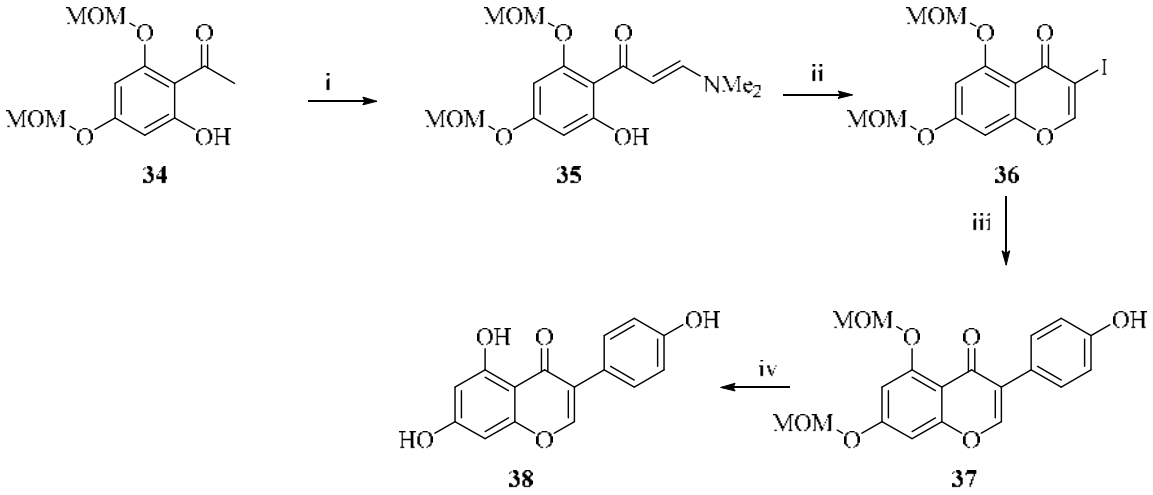
6. Isoflavones

6.1 Genistein

Genistein is an isoflavone found in Leguminosae, with documented anticancer activity [92].

In 2010, genistein was efficiently synthesized by Denis et al. starting from the MOM protected (2,4,6-trihydroxyphenyl)ethanone through a multi-step procedure involving the formation of an enamino ketone of type **35**, followed by ring closure and a Suzuki coupling reaction using palladium acetate and poly(ethyleneglycol) [93].

The MOM protected acetophenone **34** was treated with (dimethoxymethyl)dimethylamine to form the enamino ketone **35**, which underwent tandem cyclization and iodination through treatment with an excess of iodine, to afford 3-iodo-5,7-bis(methoxymethoxy)-4*H*-1-benzopyran-4-one **36**, followed by a Suzuki coupling reaction to attach the final ring of the isoflavone (Scheme 9).



Scheme 9. Reagents and conditions: (i) $Me_2NCH(OMe)_2$, DMF; (ii) I_2, MeOH; (iii) $Pd(OAc)_2$, Na_2CO_3, PEG100000, (4-hydroxyphenyl)boronic acid, MeOH; (iv) HCl, $CHCl_3$-MeOH.

The use of a green approach to this kind of reaction involving poly(ethylene glycol) (PEG 10000), methanol, sodium carbonate, and palladium diacetate as a source of palladium at a mild temperature of 50 °C, allowed the isolation of the 5,7-bis(methoxymethoxy)-3-[4-(methoxymethoxy)phenyl]-4*H*-1-benzopyran-4-one **37** with good yield. This latter one was then deprotected to give the desired genistein **38** (Scheme 9).

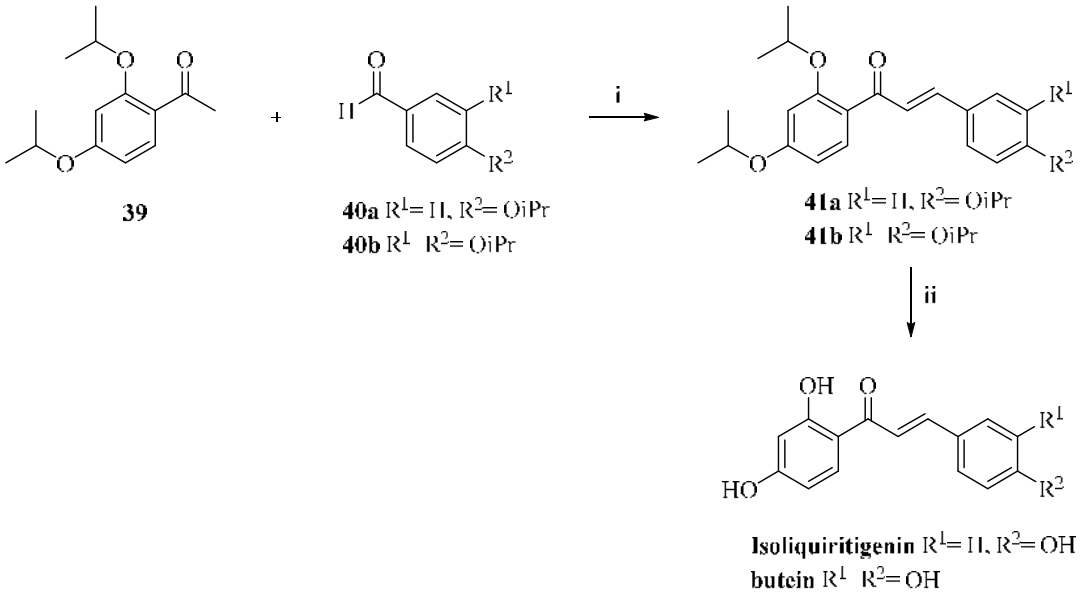
In vitro, genistein inhibit MM cell line growth and induces apoptosis with a dose dependent pattern [92 - 95]. Genistein was able to suppress the constitutional activity of NF-κB in both untreated and doxorubicin treated RPMI8226 and XG-1 cell lines [he], and to reduce the protein level of p65 by increasing the expression of miR‐29b in U266 cells [92]. Also, genistein reduced levels of phosphorylated Akt and expression of NF-κB regulated genes Bcl-2, Bcl-x_L, cyclin D1, and ICAM-1 in a dose dependent fashion [94].

7. Chalcones

Chalcones can be synthesized by the base catalyzed Claisen Schmidt condensation of an aldehyde and ketone in a polar solvent like ethanol or methanol [96 - 99]. They can also be synthesized by acid-catalyzed aldol condensations [100, 101] and Suzuki coupling. [102].

Isoliquiritigenin, or (E)-1-(2,4-dihydroxyphenyl)-3-(4-hydroxyphenyl)-2-propen-1-one,4,2′,4′-trihydroxychalcone, is extracted from plants belonging to licorice, including *Glycyrrhiza uralensis* and *Dianthus chinensis* [103].

Isoliquiritigenin can be obtained through a classical Claisen–Schmidt condensations of isopropyl protected acetophenone **39** and benzaldehyde **40a** using $Ba(OH)_2$, as base, followed from deprotection of the isopropoxy ether **41a** with BCl_3 (Scheme 10) [104].



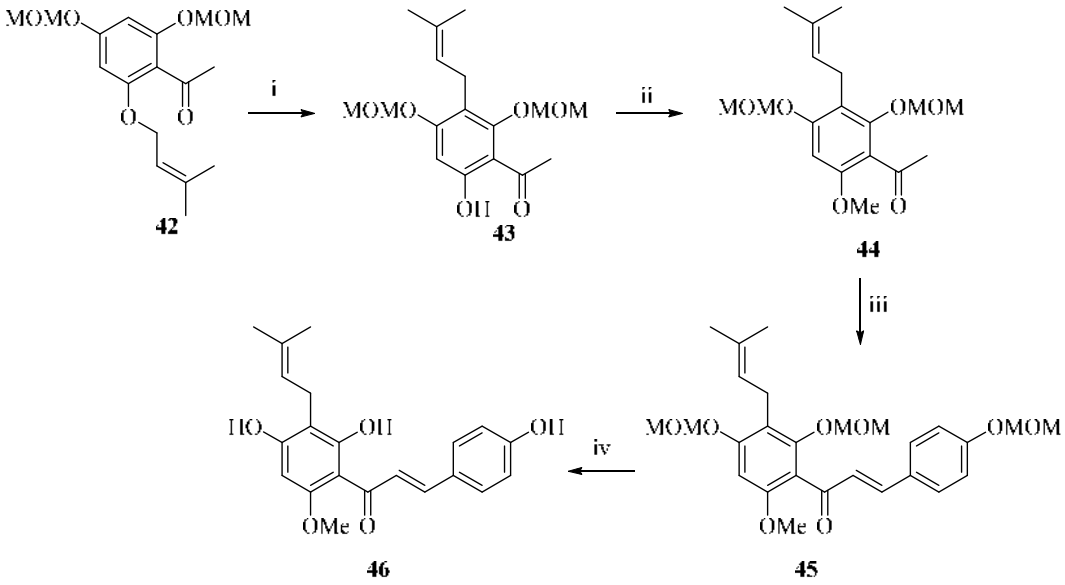
Scheme 10. (i) $Ba(OH)_2$ 8 H_2O, MeOH; (ii) BCl_3, CH_2Cl_2.

It hampers cell growth, produces G2 or G1 cell cycle arrest and induces apoptosis in a dose dependent manner as demonstrated in both human (ARH-77, U266, RPMI8226) and murine (MPC-11, SP2/0) cell lines, with cell line specific dose susceptibility to growth suppression. 4 μg/ml isoliquiritigenin were able to vigorously reduce protein levels of Bcl-2 and Bcl-x_L and to activate caspase 3 in U266 cells. Moreover, isoliquiritigenin is able to downregulate production of IL6, and to diminish both constitutive and IL6 induced phosphorylation of ERK and STAT3 [105]. *In vivo*, isoliquiritigenin reduced subcutaneous tumour masses by decreasing the amount of circulating IL6 and levels of phosphorylated ERK and STAT3 [105].

Chalcone 2’,4’,6’,4-tetrahydroxy-3’-prenylchalcone, better known as xanthohumol, is a prenylated chalcone isolated from *Humulus lupulus* L. [106]. 50 μM xanthohumol potentiated TNF induced apoptosis suppressing constitutive NF-κB activation in U266 cells [106].

Xanthohumol synthetic pathway, shown in Scheme 11, starts from prenyl ether precursor **42**, which was subjected to Claisen rearrangement in *N,N*-dimethylaniline to obtain the MOM protected and prenylated acetophenone **43**. This latter was treated with dimethylsulfate to give the intermediate

44, which was reacted with MOM protected 4-hydroxybenzaldehyde leading to derivative **45**in turn deprotected by refluxing in MeOH in presence of HCl to give xanthohumol **46** [107].



Scheme 11 Reagents and conditions: (i) *N,N*-dimethylaniline; (ii) dimethylsulfate, NaOH, DCM/H_2O 3:2, tetrabutylammonium iodide; (iii) 4-MOM-benzaldehyde, KOH, EtOH/H_2O; (iv) HCl, MeOH.

3,4,2',4'-tetrahydroxychalcone, familiarly called butein, can be found in numerous plants: *Semecarpus anacardium*, *Dalbergia odorifera*, *Caragana jubata* and *Rhus verniciflua* [108].

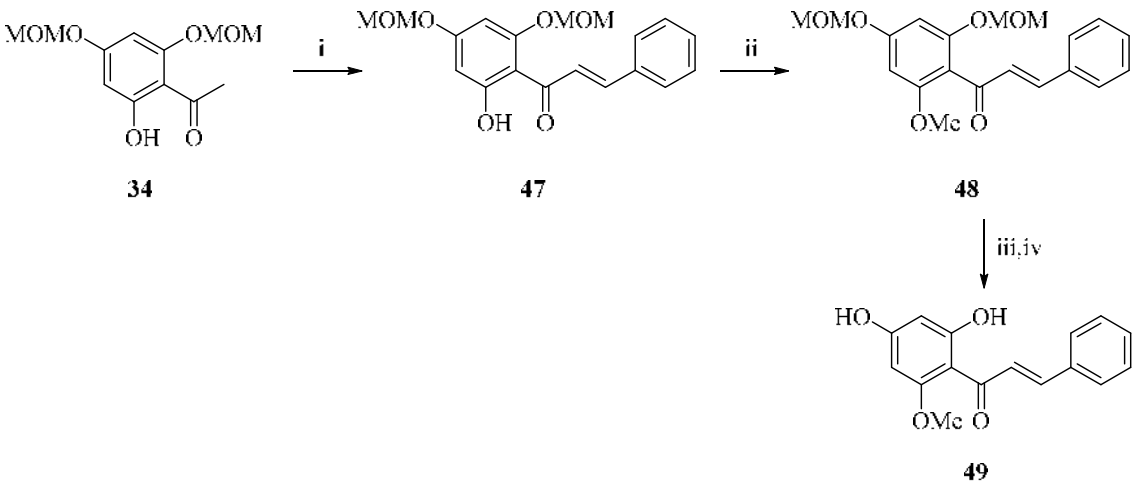
As for isoliquiritigenin, butein can be obtained through a Claisen–Schmidt condensations of isopropyl protected acetophenone **39** and benzaldehyde **40b** (Scheme 10) [104].

Butein inhibited constitutive phosphorylation of STAT3 in a dose and time dependent fashion, reducing its nuclear localization and binding activity, by upregulating the expression of SHP-1 *in vitro*. This led to a time-dependent diminution in both mRNA and protein level of Bcl-x_L, Bcl-2, Mcl-1 and cyclin D1, and induction of apoptosis. Also, butein diminished IL6 induced phosphorylation of STAT3 and Akt, and constitutive activity of JAK1, JAK2 and c-Src. In addition, butein revealed to be able to enhance the effects of bortezomin and thalidomide [108]. Butein can have applications in preventing and treatment of bone lesions. Treatment with butein can prevent MM (MM.1S and U266) and RANKL induced differentiation of macrophages to osteoclasts. Butein downregulated the expression of RANKL *in vitro*, and affected RANKL signaling producing a suppression of RANKL induced NF-κB activation, IKKs activity and IκBα degradation in macrophages [109].

2',4'-dihydroxy-6'-methoxychalcone or cardamonin, extracted from *Alpinia katsumadai* exerted anti-MM activity by induction of apoptosis as recorded in RPMI 8226, U266 and ARH-77 cells. The

mechanism elicited by cardamonin involved increase in cleaved caspase 3 and PARP, and reduction in anti-apoptotic proteins Bcl-2, Bcl-x_L, survivin, XIAP, cIAP-1 and cIAP-2. As observed in vitro, cardamonin was able to suppress constitutive activation of NF-κB reducing p65 phosphorylation and levels of IKKα, IKKβ and phosphor-IκBα [110]. Similarly to butein, cardamonin blocks osteoclastogenesis induced by both RANKL and MM cells in vitro. In fact, cardamonin inhibits RANKL dependent activation of NF-κB in a dose dependent manner via reduction of phosphorylation and degradation of IκBα, and diminished RANKL dependent phosphorylation of ERK and p38 [111].

Cardamonin was synthetized starting from condensation of MOM protected 2,4,6-trihydroxyacetophenone **34** with benzaldehyde, which gave compound **47**, further methylated with dimethylsulfate to give intermediate **48**. Deprotection in two step gave cardamonin **49** (Scheme 12) [112].



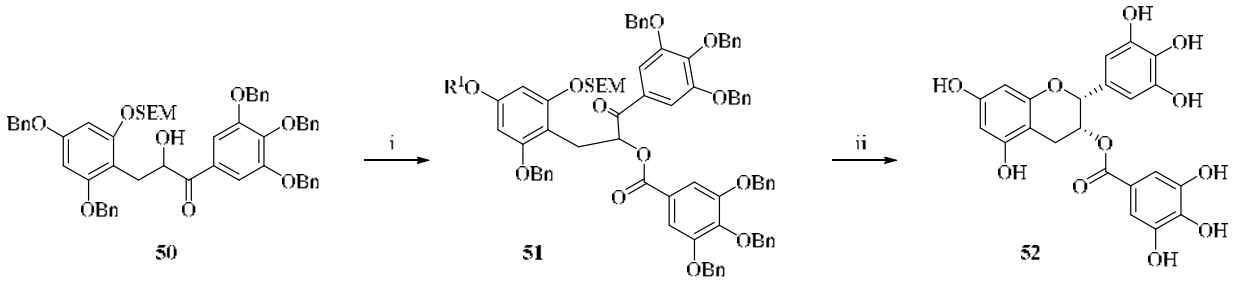
Scheme 12. (i) KOH, MeOH; (ii) NaH, $(CH_3)_2SO_4$, THF; (iii) *cat.* I_2, MeOH; (iv) *cat.* TsOH, MeOH.

8. Flavanols

8.1 Epigallocatechin-3-gallate

(-)-epigallocatechin-3-gallate (EGCG) is one of the polyphenolic compounds that can be extracted by green tea obtained from *Camellia sinensis* [15].

Different syntheses of epicatechins are based on epimerization of the C3 hydroxyl group on the catechin skeleton with 2,3-*trans*-stereochemistry [113 - 116]. In 2006, Kitade et al. reported the total synthesis of EGCG using a direct reductive cyclization of α-acyloxy ketone to give *cis*-benzopyran[117]. A multi-step sequence was used to synthetize α-hydroxyketone **50**, which was acylated to afford ester **51**. Reductive cyclization of compound **51** followed by deprotection of the benzyl groups led to EGCG **52** (Scheme 13).



Scheme 13. Reagents and conditions: (i) 3,4,5-triphenoxybenzoic acid, EDCI, DMAP, CH_2Cl_2; (ii) first TFA, Et_3SiH, CH_2Cl_2 then H_2, $Pd(OH)_2$

EGCG is generally considered as an antioxidant, despite it exhibit pro-oxidant properties in a number of conditions [15, 118 - 120]. EGCG hampers proliferation and causes apoptosis inhibiting diverse signaling pathways as documented in various types of cancers [15, 118].

In vitro, treatment of myeloma cell lines and MM cells isolated from patients with EGCG inhibited cell growth through apoptosis induction as a function of time of exposure [118, 121], by activation of caspase 3 and reduction in levels of Bcl-2 and Mcl-1 in a dose dependent manner; also, exposure to 100 μM EGCG caused loss of mitochondrial transmembrane potential and increase in intracellular H_2O_2 and superoxide [118]. EGCG mediated apoptosis is the result of direct interaction of EGCG with 67LR (67 kDa laminin receptor) and lipid-raft clustering, which in turn are related to EGCG dose-dependent increase in membrane localization and activation of ASM (acid sphingomyelinase) via PKCδ, as demonstrated in vitro (on patients' MM cells and U266 cells) [122, 123] and *in vivo* through both oral and intraperitoneal administration [121, 123]. EGCG also reduces levels of phosphorylated IκBα, p65 and its phosphorylated form, while increasing IκBα protein expression, in a dose dependent manner as described in KM3 cells [124]. Another possible mechanism of action for EGCG involve inhibition of expression of EZH2 (Enhancer of zeste homolog 2), which in turn acts as an inhibitor of mitochondrial apoptosis in U266 cells [125]. Cell lines exhibit different susceptibility to EGCG effects on cell viability [118], making the choice of experimental concentration a critical factor. A study performed by Golden et al. failed to detect any increase in cell death in RPMI8226 cells when treated with EGCG doses as high as 10 μM and 20 μM; on the contrary, the EGCG dependent reduction in basal apoptosis level led the viability of cell culture to more than 100% [126]. The importance of the choice of the right dose was verified in other experimental models and was fundamental in demonstrating that action of EGCG has cGMP as a rate determining mediator. 5 μM EGCG was able to rise NO production in U266 cells via augmented eNOS phosphorylation mediated by increased Akt activity. Elevated NO levels were able to activate soluble guanylate cyclase, with an increase in cGMP in U266, which increased following a dose dependent pattern with

EGCG 5-50 μM. Given that in U266 cells IC50 for EGCG was measured as 23.2 μM, and that phosphodiesterase 5 is overexpressed in MM patients and cell lines, at physiologically achievable concentrations EGCG was able to increment NO production but not cGMP at a level sufficient to trigger cell death [122].

The use of insufficient quantities of EGCG may have detrimental effects on bortezomib efficacy. In case of treatment of RPMI8226 with increasing amounts of bortezomib, the cytoprotective effect of 10 μM EGCG completely prevented cell death. Despite some cell cycle inhibitor effect was recorded in U266 and MM1 cells for 20 μM EGCG, when RPMI8226, U266, MM1 and patients' MM cells were treated with increasing doses of bortezomib the presence of EGCG (ranging from 2.5 μM to 20 μM) blocked or reduced bortezomib cytotoxicity. The same neutralizing effect of EGCG on bortezomib was observed in vivo. However, this EGCG protective effect was limited to co-treatment with proteasome inhibitors harboring a boronic acid moiety (like bortezomib); it was mediated by EGCG related prevention of accumulation of ubiquitinated proteins and reduction of ER stress, together with direct ECGC chemical interaction with bortezomib. Instead addition of EGCG was irrelevant to the action of proteasome inhibitors devoid of a boronic acid moiety [126]. Completely different results were obtained by Wang et al. who recorded the synergistic effect of treatment combining bortezomib with 25 or 50 μM EGCG in terms of inhibition of cell growth, induction of apoptosis, reduction in *p65* expression, increase in IκBα, caspase 3, caspase 8 and cleaved caspase 9 and PARP, and decrease in p65 [124].

EGCG has documented transcriptional effects on both mRNA and miRNA. In INA6 cells, exposure to 10 μM EGCG triggered the up-regulation of cell cycle and apoptosis modulating genes, including DAPK2 (death-associated protein kinase 2), Fas, Fas ligand, caspase 4, p63, p16, p18, and caspase recruitment domain proteins CARD10 and CARD14 [121]. Treatment of MM1.S cells with 1 μM EGCG is sufficient to inhibit p53 targeting miRNAs miR-25, miR-92, miR-141, and miR-200a, and 5 μM EGCG inhibited benzo[a]pyrene and 2,3,7,8-tetrachlorodibenzo-ρ-dioxin induced miR-25 expression [127].

EGCG administration may be helpful in treating metastatic MM. Treatment of both 5T2MM and 5T33MM murine cell lines with 40 μM EGCG had a quantifiable impact on metalloprotease activity, reducing invasion in Matrigel invasion assay [128]. Therapy with EGCG may be considered to reduce the number of bone lesions and to support the effect of radiation therapy, given that EGCG enhanced apoptosis elicited by X-irradiation on IM-9 cell line [129].

The main limitations about the employment of this flavonoid in routine treatment of MM are that EGCG is active in killing aPCs at concentrations higher than those reachable through normal tea ingestion, and that MM cells exhibit different sensitivity to EGCG [118, 122, 123], making the choice

of the highest tolerable concentration the ideal approach, in order to avoid the expansion of less sensible subclones favored by EGCG anti-oxidant properties. More studies are thus necessary in order to detect genetic background dependent factors determining susceptibility to EGCG action.

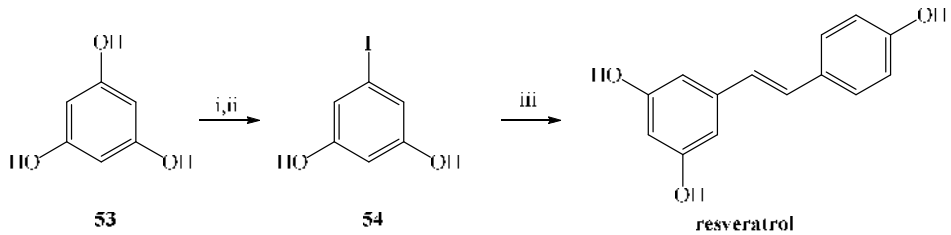
Potential application of EGCG in MM have recently been explored as part of combination treatment with phosphodiesterase 5 inhibitor vardenafil [122] and L-Threo-dihydrosphingosine (safingol) *in vitro* [130], and hydrogen sulphide donors *in vitro* and *in vivo* [131]. These results represent a valid attempt to reduce EGCG dose (and associated adverse effects especially at hepatic level) [132 - 135], while enhancing EGCG associated anti-MM effects [122, 130, 131].

9. Stilbenes

9.1 Resveratrol

In the synthesis of (*Z*)- and (*E*)-stilbenes the key step is represented by carbon–carbon double bond formation [136]. Principal methods involve the Wittig reaction [137 - 141] for the Z-isomer and the Wittig–Horner reaction [142 – 146] for the E-isomer. Other strategies involve palladium-catalyzed Heck[147, 148] and Suzuki [149] coupling reactions, the Perkin reaction,[150, 151] Diels–Alder/Wittig reaction [152].

The synthesis of resveratrol was reported by many authors. Among these, in 2012, Morales-Serna and his research group were be able to synthesize resveratrol in three steps using a cross-coupling reaction catalysed by an air-stable phosphinito complex of palladium(II), which allowed to obtain the desired product with full regioselectivity, without the use of protecting groups in the aryl halide.[153] In brief, the treatment of commercial phloroglucinol **53** with ammonia and ammonium hydroxide, followed by a Sandmeyer reaction afforded iododiphenol **54**. The cross-coupling reaction, performed between aryl halide **54** and methoxystyrene in presence of the palladium catalyst, potassium carbonate in acetonitrile under microvawe irradiation, was then followed by demethylation with boron trichloride and tetrabutylammonium iodide to give resveratrol with a good overall yield (63%) (Scheme 14).



53 54 resveratrol

Scheme 14. Reagents and conditions: (i) first NH_3, NH_4OH then HCl; (ii) first $NaNO_2$, H_2SO_4 then KI; (iii) first 4-methoxystyrene, MeCN, K_2CO_3 then BCl_3, TBAI

Resveratrol (trans-3, 4', 5-trihydroxystilbene) is probably the most renowned among stilbenes for its ability to inhibit cell proliferation in solid cancers and hematological malignancies, with experimental data available also for MM [154 - 156]. *In vitro*, a concentration as low as 50 μM resveratrol suppressed proliferation of drug sensitive (U266, MM1.S) and drug resistant (MM.1R, RPMI 8226–Dox6, RPMI 8226–LR5) cells [157]. These effects were reached through cell cycle arrest (which varies according to the considered cell line: in sub-G1 phase for U266 and MM.1S cells, in G1 and S phases for RPMI8226 and IM9 cells, respectively), accumulation of Bax, reduction in phosphorylated Akt, inhibition of IKK activity, suppression of constitutive NF-κB activation, downregulation of constitutive and IL6 induced p-STAT3 levels, suppression of the expression of anti-apoptotic proteins and activation of caspases in a time dependent fashion, as shown by multiple cell lines treated with resveratrol in diverse studies [156 - 159]. In addition, a dose dependent increase in apoptosis induced by resveratrol was detected in CD138+ cells from MM patients [157]. In IM9 cells, 30 μM resveratrol induces an increase in phorylation of p38 MAPK, and this event is essential for its pro-apoptotic effect [158]. Resveratrol can reduce cellular proliferation through downregulation of NEAT1, thus suppressing its effect on the Wnt/ β-catenin pathway, and accounts for a superior cytoplasmic retention of β-catenin and a reduction in c-Myc, MMP-7, survivin and nuclear β-catenin in a dose dependent manner, as detected in U266 and LP1 cells. Resveratrol exerts also inhibitory effects on the unfolded protein response, being responsible for a reduction in DNA damage-inducible transcript 3 protein (CHOP), Xbox binding protein 1 (XBP1) and endoplasmic reticulum to nucleus signaling 1 protein (IRE1α) levels when used at a concentration of 50 μM in U266 and LP1 cell lines [160]. However, these mechanisms may be dose dependent or vary according to the evaluated cell line. In ANBL-6 cells treatment with 100 μM resveratrol led to apoptosis and produced phosphorylation of IRE1α, with phosphorylation of JNK, increase in CHOP level and increase in XBP1s (spliced) protein levels; similar findings were obtained for OPM2 and MM1.S cells. Analysis of mRNA levels revealed an enhancement of non- IRE1α ER stress pathways, and the inhibition of the XBP1s pathway through SIRT1 mediated suppression of XBP1s transcriptional activity [161]. Another study evidenced that clustering of Fas/CD95 death receptor, TRAIL receptors DR4 and DR5, FADD, procaspase 8, procaspase 10, Bid, JNK and part of the cellular pool of active caspase 8 and caspase 10 into lipid rafts, followed by disruption of mitochondrial transmembrane potential (Δψm), are the key steps to resveratrol induced apoptosis of MM144 and MM1.S and primary MM cells [162]. A recent work suggests that resveratrol can hamper proliferation through mTOR pathways, in a time dependent fashion [163].

The use of resveratrol should be considered to interrupt progression of MM through blocking of migration, angiogenesis and osteolytic lesion formation. In U266 and LP1 cell lines, 30 μM

resveratrol repressed constitutive NEAT1 expression, and 50 μM resveratrol counteracted the effect of NEAT1 overexpression on proliferation, migration and invasiveness [160]; in addition, resveratrol inhibits the release of MMP-2 and MMP-9 from KM3 cells in a dose dependent fashion, and hampers VEGF induced migration of RPMI 8226, U266, and KM3 cells [164]. In an in vitro angiogenesis model involving RPMI8226 and HUVEC, resveratrol inhibited HUVEC proliferation, migration and tube formation induced by co-culture with MM cells, by reducing the levels of expression of MMP-2, MMP-9, VEGF and b-FGF [165]. Increasing doses of resveratrol inhibit RANKL induced osteoclast formation from monocytes, by suppression of RANKL induced NFATc1 upregulation, with full inhibition of both events reached with 100 μM resveratrol. Also, the same amount of resveratrol reduced RANK mRNA level and RANKL induced NF-κB nuclear translocation, while upregulating c-fms, CD14 and CD11a, that are all monocyte markers. In hMSC-TERT cell line, resveratrol upregulated the expression of osteoblastic markers osteocalcin and osteopontin and the expression of vitamin D receptor in a dose dependent manner, exhibiting synergism with 1,25(OH)2D3 [166].

Resveratrol can be used in combined regimens to improve the performance of routinely and non-routinely employed drugs. Rapamycin with resveratrol affected MM1.S cell viability by inhibiting the mTORC1 and mTORC2 signaling, with a consistent reduction in cyclin D1 and pRb levels and an high level of activated caspase 3 and PARP [163]. Pretreatment with INFγ sensitizes MM1.S cells to apoptosis elicited by resveratrol [162]. 25 μM resveratrol increased the cytotoxic effect exerted by dexamethasone on RPMI 8226, U266, and KM3 cells [156]. In LP-1, U266, MM1.S, and MM1.R cells, 50 μM resveratrol showed a synergistic effect with carfilzomib in inducing apoptosis and reducing levels of cyclin D1 and p-CdK4, although the two compounds alone arrest the cell cycle at different phases (resveratrol alone at G0/G1 phase and carfilzomib at G2/M phase). The mechanism elicited by resveratrol and carfilzomib combination involved ROS production resistant to N-Acetylcysteine (NAC) scavenger activity, HMOX1 upregulation, downregulation of sirtuin 1 (SIRT1) deacetylase and survivin, increased Bcl-2 expression, augmented phosphorylation of p38, and upregulation of Smac, the latter effect mediated by resveratrol alone. The combined treatment can also trigger a protective autophagy, whose inhibition leads to an increase in the oxidative stress [159]. 25 μM and 30 μM resveratrol in combination with bortezomib or thalidomide exhibited an exacerbation of the apoptotic rate induced in U266 cells, reducing the levels of NF-κB and p-STAT3; the same evidences were detected in CD138+ cells from MM patients [157]. On the basis of these and other encouraging results, a micronized oral formulation of resveratrol was used with or without bortezomib to treat patients with relapsed and refractory MM, but an unacceptable safety profile and minimal efficacy emerged as main consequences of the therapy. The critical aspects raised by the

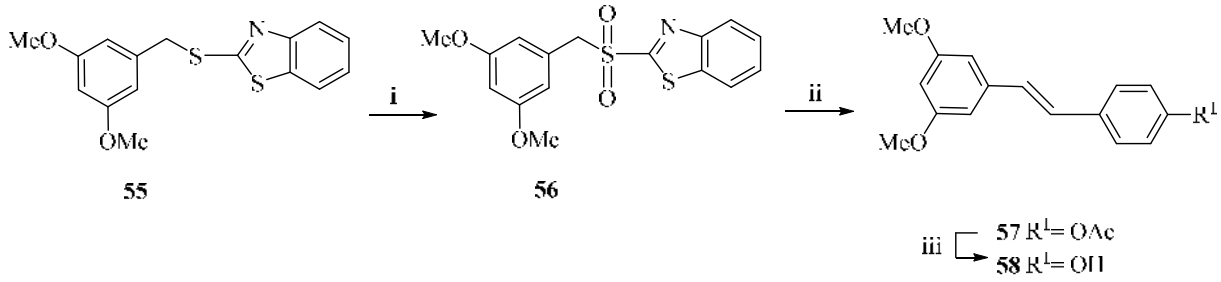
clinical study trace a putative connection between increased susceptibility to renal failure in MM patients and augmented renal toxicity related to the use of resveratrol [167]. Further studies are necessary to assess safety and efficacy of resveratrol in treating MM patients.

Progresses have been made in the look for synthetic derivatives with potential anti-MM activity. (E)-2-(2-chlorostyryl)-3,5,6-trimethylpyrazine (CSTMP), a novel tetramethylpyrazine (TMP) and resveratrol derivative, is able to induce apoptosis in RPMI8226 cells flanked by dose dependent activation of caspase 3, 8 and 9, increase at both protein and mRNA level of Bax levels, and reduction in Bcl-2 and Bcl-XL mRNAs and proteins. Treatment with CSTMP also augmented the levels of CHOP, GRP78, GRP94, p-PERK, p-eIF2a, IRE1a, ATF6 and cleaved caspase 12, that are all signs of ER stress [168]. Larger confirmations are expected in this direction.

9.2 Pterostilbene

The classical methods used for the synthesis of biologically active stilbenes are Wittig-type olefinations, but harsh reaction conditions, expensive starting materials, multistep synthetic pathway and geometrical isomers formation lead to the development of alternative methods. Thus, the Julia [169] or modified Julia olefination reaction is a versatile synthetic approach that, allowing an excellent control of geometrical isomerism, represents an economical alternative method for the gram-scale preparation of pterostilbene.

Thus Peddikotla et al. [170] have reported the synthesis of pterostilbene as described in the Scheme 15.



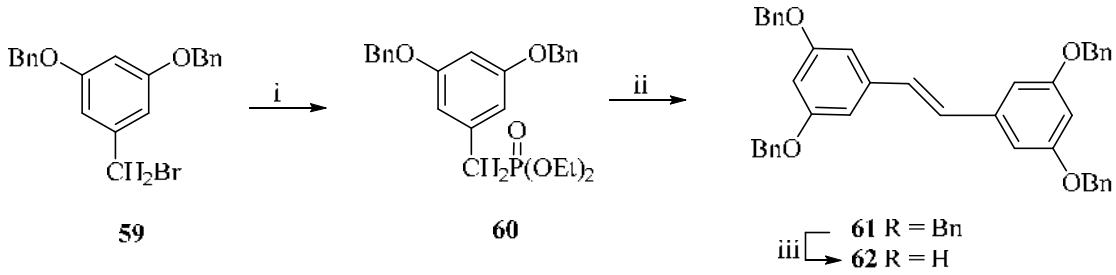
Scheme 15. Reagents and conditions: (i) $(NH_4)_6Mo7O_{24}$, H_2O_2, AcONa; (ii) substituted aldehydes, LiHMDS, THF; (iii) substituted aldehydes, LiHMDS, THF; (iv) K_2CO_3, MeOH.

Sulfide intermediate **55** was oxidized with ammonium heptamolybdate to sulfone **56** in high yield (95%). Derivative **56** was reacted with 4-acetoxybenzaldehyde in a modified Julia olefination, allowing the isolation of the expected product, E-4-acetylpterostilbene **57**, in turn deprotected to pterostilbene **58** with K_2CO_3 in methanol.

Pterostilbene (trans-3,5-dimethoxy-4'-hydroxystilbene) is a naturally occurring dimethoxy analog of resveratrol found in blueberries. Pterostilbene exhibits anti-myeloma properties as demonstrated *in vitro*, and its action is mainly exerted at metabolic and translational level [171, 172]. In H929, ARP-1, ARH77, RPMI8226 and OCI-MY5 cell lines pterostilbene reduces cell viability in a dose dependent fashion [171, 173]. A detailed analysis performed on H929 showed that as low as 10 μM pterostilbene produces G0/G1 cell cycle arrest dependent on DNA damage, ROS generation, the increase in p-CHK1, p-CHK2 and p21 and the decrease in CDK4, CDK6 and cyclin D1; in addition, pterostilbene induces apoptosis mediated by caspase 3, caspase 8, and caspase 9 activation [173]. Treatment with 20 μM pterostilbene caused loss of mitochondrial potential, and an increase in pERK1/2 and pJNK was detected after administration of pterostilbene with a dose dependent pattern [173]. In RPMI8226 and ARH77 pterostilbene induces apoptosis mediated by the increased phosphorylation of AMP‐activated protein kinase (AMPK), producing a reduction in fatty acid synthase (FASN) protein levels and an increase in phosphorylation of acetyl‐CoA carboxylase (ACC) [171]. Also, pterostilbene inhibits mTOR and 4E‐BP1 phosphorylation while increasing eIF2α phosphorylation. This hypo nutrient state leads to autophagy, which was revealed to be a protective mechanism that can be inhibited to improve the anti-myeloma effects of pterostilbene [171]. Properties of pterostilbene were further demonstrated in mouse models, confirming results obtained in vitro together with the show of a safe toxicity profile [171, 173]. Also, the toxic effect of pterostilbene seems to be limited to MM cells, with no sign of toxicity on peripheral blood mononuclear cells [173]. The use of pterostilbene could be considered to overcome bortezomib resistance, as demonstrated in vitro on H929R cells. In this bortezomib resistance cell line, treatment with pterostilbene produced DNA damage and cell cycle arrest in S phase, that led to apoptosis mediated by activation of Akt and p38 MAPK [172]. In addition, pterostilbene exhibit a synergistic inhibitor effect on cellular proliferation with histone deacetylase inhibitors panobinostat and vorinostat [172].

9.3 Piceatannol

Piceatannol, also known as 3,3′,4,5′-tetrahydroxy-trans-stilbene, can be synthesized through a Wittig–Horner reaction starting from 5-(hydroxymethyl)benzene-1,3-diol, which was appropriately converted to the corresponding bromine derivative **59**, which was transformed into phosphorus ylide **60** using triethyl phosphite. Ylide **60** was reacted with 3,4-bis(benzyloxy)benzaldehyde to give benzyl protected piceatannol **61**. Finally piceatannol **62** was obtained by deprotection with boron tribromide (Scheme 16) [174].



Scheme 16. Reagents and conditions (i) $PO(OEt)_3$, rt; (ii) 3,4-bis(benzyloxy)benzaldehyde, EtONa; (iii) BBr_3, CH_2Cl_2

Piceatannol affected cell viability and induced apoptosis in OPM2, RPMI8226, and U266 cell lines in a dose dependent manner [175, 176]. *In vitro*, piceatannol acts as a downregulator of spleen tyrosine kinase (Syk) and a migration inhibitor, reducing phosphorylation of ERK1/2 and p38 MAPK as well as nuclear traslocation of NF-κB in AMO1, RPMI8226, and U266 [176]. In the same cell lines, induction of apoptosis was flanked by caspase 3 activation and PARP1 cleavage [176]. Piceatannol in OPM2, RPMI8226 and U266 cells caused a reduction in β catenin levels, and in OPM2 and U266 cells only also a reduction of TCF4 [175]. Also, piceatannol can be combined with ethacrynic acid (EA), or with ciclopirox olamine (CIC), or with dual PI3 kinase/mTor inhibitor NVP-BEZ235, or with MAP2K inhibitors U0126 and PD98059 to synergistically increase its therapeutic activity [176, 177].

10. Future perspectives and conclusion

Given the high complexity of MM clones both at a genetic and immunophenotypic point of view, associated with the true risk of insurgence of drug resistance at any point of the therapeutic process, the use of drug combination therapies is widely adopted in MM. The main purpose of these strategies is to attack the pool of aPCs in diverse ways, targeting multiple molecular pathways while carefully minimizing size and undesired effect. The use of combinatory regimens associating standard treatment with highly tolerated natural compounds may produce a number of potential advantages: the possibility to assume the natural compound orally at home, reducing the psychological impact on patients and facilitating therapy management; a reduction in the requested doses for standardly used drugs thanks to one or both of additive/synergistic cytotoxic effect elicited by the natural compound itself and pharmacokinetic interference of the natural compound with standard therapy; increase the number of therapeutic options to prolong the time to next treatment and to prevent the insurgence of multidrug resistant disease.

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Active Molecule	Biological effects	Natural sources	References

Curcumin	• reduction of pAkt levels • full suppression of constitutive activation of NF-κB (RelA/NF-κB1) • depletion of NF-κB regulated gene products Bcl-2, Bcl-x_L, cyclin-D1, TRAF1, XIAP and VEGF • inhibition of constitutive STAT3 phosphorylation and nuclear STAT3 translocation • inhibition of INFα inducible STAT1 phosphorylation • increase in *p53* and *BAX* expression and a downregulation of *MDM2* • activation of caspase 3 • cleavage of PARP • reduction in cyclin D1 and CdK4 • accumulation of p21 at protein level • reduction in TNF-induced adhesion MM cells to BM stromal cells • suppression of both RANKL-induced activation of NF-κB and RANKL-induced IκBα phosphorylation and degradation, together with a loss of IKK activity in a murine monocytic cell line • inhibition of phosphorylation of STAT3 and Erk induced by exposure to cell culture supernatant of BMSCs and by pretreatment with IL-6 and IL-6/sIL-6R • inhibition of release of IL-6 and sIL-6R by MM cells • inhibition of secretion of IL-6 and VEGF by BMSCs • Overcoming on drug resistance when used in combination with other drugs (see text for details)	*Curcuma spp.*	[23 – 33]
Caffeic acid phenethyl ester	• glutathione depletion	Honey bee propolis	[53 - 54]

	• triggering of oxidative stress response • activation of caspase 3 • synergism with bortezomib (see text for details)	extract	
Apigenin	• inhibition of CK2 • disassociation of the Hsp90/Cdc37/client complex • degradation of kinase clients RIP1, Src, Raf-1, Cdk4 and AKT • reduction in Mcl-1, Bcl-2, Bcl-x_L, XIAP and Survivin levels • reduction in constitutive and inducible levels of phosphorylated forms of STAT3, kinases PDK, MEK and IKK and downstream mediators ERK, Akt and IκBα • synergism with HDAC inhibitor SAHA or Hsp90 inhibitor geldanamycin (see text for details)	fruits and vegetables	[57 – 58]
Chryseoriol	• inhibition of Akt • reduction in phosphorylated 4eBP1 • increase in levels of cyclin B1 and p21	*Aspalathus linearis*	[59]
Wogonin	• reduction in Akt phosphorylation • reduction in the amount of secreted VEGF, PDGF and bFGF • downregulation of c-myc • alteration in VHL complex stability and turnover • increased degradation of HIF1α • synergistic effect with bortezomib and lenalidomide (see text for details)	*Scutellaria baicalensis*	[61 – 62]
Baicalein	• release of mitochondrial cytochrome c • inhibition of phosphorylation of IkBα, nuclear traslocation of	*Scutellaria* radix	[69 – 75]

	p65 NF-κB and expression of *IL-6* and *XIAP* • upregulation of cereblon at a transcriptional level • reduction in the protein level of IKZF1 and IKZF3 by proteasomal degradation • inhibition of IL-6-induced STAT3, STAT1, Akt, JAK1 and TYK2 and ERK1/2 phosphorylation • reduction in both constitutive and IL6 induced Bcl-X_L levels • reduction in the protein level of ABCG2 • cooperative effects with dexamethasone (see text for details)		
Baicalin	• reduction in the expression of ABCG2	*Scutellaria* radix	[69, 70, 73, 79]
Quercetin	• activation of caspase 3 and caspase 9 • upregulation of p21 • downregulation of c-myc and IQGAP1 • synergistic effect with dexamethasone (see text for details) • abrogation of pro-apoptotic bortezomib effects (see text for details)	apples, red grapes, onions, raspberries, honey, cherries, citrus fruits and green leafy vegetables	[86 – 89]
Fisetin	• activation of caspase 3 • reduction in Bcl-2 and Mcl-1 • increase in levels of Bax, Bim and Bad • production of ROS • increased phosphorylation of AMPK and acetyl-CoA carboxylase (ACC) • decreased phosphorylation of Akt and mTOR	*Acacia greggii, Acacia berlandieri, Rhus cotinus, Gleditschia triacanthow*	[91]
Genistein	• suppression of the constitutional activity of NF-κB • reduction in the protein level of p65	*Genista tinctorial,* Leguminosae	[92 - 95]

	• increase in the expression of miR‑29b • reduction in the levels of phosphorylated Akt and expression of NF-κB regulated genes Bcl-2, Bcl-x_L, cyclin D1, and ICAM-1		
Isoliquiritigenin	• reduction in protein levels of Bcl-2 and Bcl-x_L • activation of caspase 3 • downregulation of production of IL6 • reduction in both constitutive and IL6 induced phosphorylation of ERK and STAT	*Glycyrrhiza uralensis, Dianthus chinensis*	[103, 105]
Xanthohumol	• suppression of constitutive NF-κB activation	*Humulus lupulus* L.	[106]
Butein	• inhibition of constitutive phosphorylation of STAT3 • upregulation of the expression of SHP-1 • reduction in both mRNA and protein level of Bcl-x_L, Bcl-2, Mcl-1 and cyclin D1 • reduction in IL6 induced phosphorylation of STAT3 and Akt, and constitutive activity of JAK1, JAK2 and c-Src • downregulation of the expression of RANKL • suppression of RANKL induced NF-κB activation, IKKs activity and IκBα degradation in macrophages • synergistic effects with bortezomib and thalidomide (see text for details)	*Semecarpus anacardium*, *Dalbergia odorifera*, *Caragana jubata, Rhus verniciflua*	[108, 109]
Cardamonin	• increase in cleaved caspase 3 and PARP • reduction in anti-apoptotic proteins Bcl-2, Bcl-x_L, survivin, XIAP, cIAP-1 and cIAP-2 • suppression of constitutive activation of NF-κB	*Alpinia katsumadai*	[110, 111]

	• reduction in p65 phosphorylation and levels of IKKα, IKKβ and p-IκBα • inhibition of RANKL dependent activation of NF-κB via reduction of phosphorylation and degradation of IκBα • reduction in RANKL dependent phosphorylation of ERK and p38		
Epigallocatechin-3-gallate	• activation of caspase 3 • reduction in levels of Bcl-2 and Mcl-1 • loss of mitochondrial transmembrane potential • increase in intracellular H_2O_2 and superoxide • lipid-raft clustering • increase in membrane localization and activation of ASM via PKCδ • reduction in levels of phosphorylated IκBα, and p65 and its phosphorylated form • increase in IκBα protein expression • inhibition of expression of EZH2 • increase in NO levels • augmented eNOS phosphorylation mediated by increased Akt activity • increase in cGMP • up-regulation of cell cycle and apoptosis modulating genes, including DAPK2 ,Fas, Fas ligand, caspase 4, p63, p16, p18, and caspase recruitment domain proteins CARD10 and CARD14 • inhibition of p53 targeting miRNAs miR-25, miR-92, miR-141, and miR-200a, • inhibition of benzo[a]pyrene and 2,3,7,8-	*Camellia sinensis*	[15, 129 - 135]

	tetrachlorodibenzo-ρ-dioxin induced miR-25 expression • reduction in invasiveness capacity • dose dependent inhibitor effects on bortezomib induced cell death (see text for details) • dose dependent synergistic effects with bortezomib (see text for details) • synergistic effects with other drugs (see text for details)		
Resveratrol	• accumulation of Bax • reduction in phosphorylated Akt • inhibition of IKK activity • suppression of constitutive NF-κB activation • downregulation of constitutive and IL6 induced p-STAT3 levels • suppression of the expression of anti-apoptotic proteins • activation of caspases • increase in phosphorylation of p38 MAPK • downregulation of NEAT1 and suppression of its effect on the Wnt/ β-catenin pathway • superior cytoplasmic retention of β-catenin • reduction in c-Myc, MMP-7, survivin and nuclear β-catenin • reduction in CHOP, XBP1 and IRE1α levels • enhancement of non-IRE1α ER stress pathways • clustering of Fas/CD95 death receptor, TRAIL receptors DR4 and DR5, FADD, procaspase 8, procaspase 10, Bid, JNK and part of the cellular	grapes, root extracts of the weed *Polygonum cuspidatum*	[157 - 168]

	pool of active caspase 8 and caspase 10 into lipid rafts, followed by disruption of mitochondrial transmembrane potential • reduction in the levels of p-mTOR • repression of constitutive NEAT1 expression • inhibition of the release of MMP-2 and MMP-9 • inhibition of VEGF induced migration • inhibition of HUVEC proliferation, migration and tube formation • inhibition of RANKL induced osteoclast formation from monocytes, by suppression of RANKL induced NFATc1 upregulation • synergistic effects with other drugs (see text for details)		
Pterostillbene	• production of DNA damage • ROS generation • increase in p-CHK1, p-CHK2 and p21 • decrease in CDK4, CDK6 and cyclin D1 • caspase 3, caspase 8, and caspase 9 activation • loss of mitochondrial potential • increase in pERK1/2 and pJNK • increased phosphorylation of AMPK • reduction FASN protein levels • increase in phosphorylation of ACC • inhibition of mTOR and 4E‐BP1 phosphorylation • increase in eIF2α phosphorylation • autophagy	Blueberries	[171 - 173]

	• synergistic effects with other drugs (see text for details)		
Piceatannol	• downregulation of Syk • reduction in phosphorylation of ERK1/2 and p38 MAPK as well as nuclear traslocation of NF-κB • caspase 3 activation • PARP1 cleavage • reduction in β catenin levels • reduction in TCF4 • synergistic effects with other drugs (see text for details)	grapes, berries, red wine, *Rheum undulatum*	[175 - 177]

Table 1. List of sources and molecular mechanisms elicited by natural polyphenols leading to apoptosis in MM cells and affecting other cellular components of the bone marrow microenvironment.