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Natural Products for Treatment of Chronic Myeloid Leukemia

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Abstract

Chronic myeloid leukemia (CML) is a hematological malignancy that arises due to reciprocal translocation of 3' sequences from c-Abelson (*abl*) protooncogene on chromosome 9 with 5' sequence of truncated break point cluster region (*bcr*) to chromosome 22. The fusion gene product BCR-ABL, a functional oncoprotein p210, is a constitutively activated tyrosine kinase that activates several cell proliferative signaling pathways. BCR-ABL-specific tyrosine kinase inhibitors (TKIs) such as imatinib, nilotinib and ponatinib potentially inhibit CML progression. However, drug resistance owing to BCR-ABL mutations and overexpression is still an issue. Natural products are chemical compounds or substances produced by living organisms. They are becoming an important research area for cancer drug discovery due to their low toxicity and cost-effectiveness. Several lines of evidence show that many NPs such as alkaloids, flavonoids, terpenoids, polyketides, lignans and saponins inhibit CML cell proliferation and induce apoptosis. NPs not only differentiate CML cells into monocyte/erythroid lineage but also can reverse the multi-drug resistance (MDR) in CML cells. In this chapter, we review the anti-CML activity of various NPs.

Keywords: chronic myeloid leukemia (CML), BCR-ABL, TKIs, natural products (NPs), multi-drug resistance (MDR)

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1. Chronic myeloid leukemia

Chronic myeloid leukemia (CML) is a hematoproliferative neoplasm that is marked by uncontrolled myeloid cell divisions in the bone marrow [1]. CML arises due to a reciprocal translocation between chromosome 9 and chromosome 22 [(9;22) (q34;q11)], eventually culminating in the genesis of the *bcr-abl* oncogene. Approximately 90% of CML patients have shortened chromosome called "Philadelphia chromosome" (Ph) [2].

Figure 1. Schematic representation of NPs and TKIs on BCR-ABL inhibition and downregulation of downstream signaling pathways (NP—natural products, TKI—tyrosine kinase inhibitor, CML—chronic myeloid leukemia, MDR—multi-drug resistance).

The *bcr-abl* oncogene encodes a constitutively activated tyrosine kinase, BCR-ABL. The catalytically activated kinase, in turn, activates multiple cell proliferatory signaling pathways such as RAS, a small GTPase, mitogen activated protein kinase (MAPK), signal transducers and activator of transcription (STAT), and phosphoinositide-3-kinase (PI3K) pathways [3].

Targeting Abl kinase is clearly a proven successful strategy to combat CML. First generation tyrosine kinase inhibitor (TKI), imatinib, also known as Gleevec or STI571 inhibited BCR-ABL and suppressed CML progression [4]. Second generation TKIs such as nilotinib, dasatinib & bosutinib and third generation TKIs (Ponatinib) that are more potent to inhibit BCR-ABL kinase are currently used to treat CML [5, 6]. All these TKIs were approved by the US Food and Drug Administration (FDA). TKIs have changed the clinical course of CML. However, mutations in *bcr-abl* and multi-drug resistance (MDR) due to efflux of the drug as a result of overexpression of p-glycoprotein (p-gp) make TKIs less effective. Primary or secondary resistance to TKIs therapy still exists; however, there is a constant need for alternative therapeutic strategy (Figure 1) [7].

2. Natural products

Natural products (NPs) represent a large family of diverse secondary metabolites with profound biological activities. NPs are produced in several organisms like bacteria, fungi, plants

and marine animals. NPs are inexpensive and have less (or) no side effects; hence, NPs are currently being explored as an invaluable source for treatment of cancerous and infectious diseases. As of 2013, 1453 new chemical entities (NCEs) have been approved by the US FDA, of which 40% are NPs or NP-inspired (semi-synthetic NP derivatives, synthetic compounds based on NP pharmacophores, or NP mimics) [8, 9]. A number of NPs Such as alkaloids, flavonoids, terpenoids, polyketides, lignans, saponins, peptides and plant extracts exhibited potent anti-CML activity.

2.1. Alkaloids

Alkaloids are naturally occurring organic compounds containing heterocyclic ring with nitrogen atom. Alkaloids, widely distributed in plant kingdom, are bitter secondary metabolites synthesized by plants, microbes and animals. They possess several physiological activities like anti-malarial, anti-asthmatic, anti-cancer, anti-bacterial, antiviral, anti-hyperglycemic and vasodilatory activities [10–13]. Their anti-CML activity is described below.

Berberamine (BBM) is a natural bisbenzylisoquinoline product, isolated from traditional Chinese herbal medicine *Berberis amurensis*, was tested on imatinib resistant K562 cell line (K562/IR) both *in vitro* and *in vivo*. The IC₅₀ value was found to be 17.1 and 11.1 μ M at 24 and 48 h. BBM downregulated Bcl-2, Bcl-xL, *mdr-1* mRNA, p-gp levels and enhanced Bax & cytochrome C (cyt.C) release. BALB/c or nu/nu mice were injected with K562-r subcutaneously and the tumor-bearing mice, when treated with BBM [60 mg/kg body weight (BW)] intravenously effectively suppressed the xenotransplanted tumors in these mice [14]. BBM also induced apoptosis in CML cells *via* downregulating survivin protein levels [15]. At 8 μ g/ml dose of BBM, NF κ B nuclear, IKK- α , IKB- α [16], BCR-ABL, p-BCR-ABL level were decreased [17]. Furthermore, BBM-induced differentiation of CML cells into RBC, granulocyte and megakaryocytes [18]. Interestingly, BBM is a heat shock protein 90 (Hsp90) inhibitor [19]. BBM inhibited MDR K562/adriamycin (ADR) [20] and K562/A02 cell lines consequently inducing apoptosis by reducing *mdr-1* gene expression and reversing MDR effect [21]. 4-chlorobenzoyl berberamine (BBD9), an analogue of BBM was also tested against K562/IR. BBD9 with IC₅₀ 0.5 μ g/ml was found to be more effective than BBM (IC₅₀ 8 μ g/ml), BBD9-lowered BCR-ABL, IKK α , nuclear NF- κ B. Furthermore, it increased the cleaved caspases 3,9, Poly(ADP-Ribose) polymerase (PARP) and LC3-phosphatidylethanolamine conjugate (LC3 II) expression levels. In nude mice model bearing K562 tumors, BBD9 was effective in reducing the tumor weight, promoting tumor regression [22]. E6, a derivative of BBM, was tested against MDR K562/doxorubicin (DOX) with 1, 3, 10 and 30 μ M concentrations, and it significantly reduced the IC₅₀ of DOX from 79.19 μ M to 35.18, 21.86, 6.31 and 1.97 μ M. Co-treatment of E6 with DOX arrested K562 cells at G2/M phase [23].

Camptothecin, isolated from *Camptotheca acuminata*, is documented to display anti-CML activity. Homocamptothecin (hCPT), a synthetic analogue of camptothecin, showed potent activity at IC₅₀ value of 11 nM suggesting its potential use compared to parent compound camptothecin (IC₅₀ 57 nM) [24]. BN80927, an analogue of camptothecin, effectively inhibited K562 cell proliferation with IC₅₀ of 8.4 nM [25]. NSC606985, an analogue of camptothecin, inhibited CML cell growth in a dose-dependent manner. The IC₅₀ was found to be 6.25 nM

[26]. Combination of imatinib and camptothecin increased Bax, cleavage of PARP-1, DNA-dependent protein kinase (DNA-PK) in CML cells [27].

Capsaicin, an active component of capsicum genus, is a homovanillic acid derivative experimentally is shown to exhibit anti-mutagenic activity [28]. Capsaicin treatment of K562 cells decreased microRNA (miRNA) expression such as miR-520a-5p, a putative target of STAT3. Hence, capsaicin induced apoptosis *via* reducing mRNA involved in JNK/STAT pathway [29]. Capsaicin also stimulated GATA-1 promoter in CML cells which is an essential transcriptional factor for the development of erythroid cells [30].

Homoharringtonine (HHT), isolated from *Cephalotaxus harringtona*, has been documented to inhibit CML cell proliferation in a dose-dependent manner. The IC₅₀ was found to be 43.89 ng/ml. HHT arrested K562 cells at G0/G1 phase and, in addition, downregulated Bcl-2, NF-κB, p-JAK2, p-STAT5, p-Akt, p-BCR-ABL levels [31, 32].

Sanguinarine, a benzophenanthridine alkaloid, isolated from blood root plant *Sanguinaria canadensis*, belonging to the Papaveraceae family inhibited CML cell growth in a dose-dependent manner. At 1.5 µg/ml, sanguinarine induced apoptosis in CML cells. At higher concentration (12.5 µg/ml), sanguinarine caused blister formation in CML cells [33].

Staurosporine, an alkaloid isolated from the bacterium *Streptomyces staurosporeus*, not only inhibited CML cell growth but also induced differentiation of myeloid cell lineage to megakaryocytic lineage resulting in polypoidy formation. Staurosporine treatment resulted in upregulation and activation of JAK/STAT3, p-STAT3 nuclear translocation and downregulation of c-myc [34, 35]. Staurosporine also induced differentiation of CML cells into erythroid cells *via* increased CD61 and CD42b levels [36]. 7-Hydroxy staurosporine (UCN-01), a potent PKC inhibitor is effective in inhibiting CML cell proliferation at a concentration of 3 µM for 24 h [37, 38].

Tetrandrine is a bis-benzylisoquinoline alkaloid that is isolated from Chinese herb *Stephania tetrandra*. Combination of tetrandrine and imatinib showed synergetic effect significantly inhibited CML cell growth. The combination treatment arrested CML cells at G1/S phase, enhanced caspase 3 mRNA, protein levels and decreased Bcl-2 mRNA, protein levels [39]. Combination of nilotinib and tetrandrine also effectively decreased the IC₅₀ of daunorubicin (DNR) on K562/A02 to 3.12 ± 0.13 µg/ml. This combinational effect not only increased Bax mRNA and protein levels but also decreased the survivin mRNA and protein levels [40]. Tetrandrine citrate, a novel tetrandrine salt which is highly soluble in water, Inhibited the growth of K562/IR, primary leukemic cells and primitive CD34 (+) leukemic cells with IC₅₀ ranging from 1.2 to 2.97 µg/ml. Tetrandrine citrate lowered BCR-ABL mRNA and β-catenin protein levels. Nude mice bearing CML tumors when orally administered with tetrandrine citrate (100 mg/kg BW), reduced the tumor growth [41]. Combination of 5-bromotetrandrine (analogue of tetrandrine) and DNR decreased p-JNK 1,2 and MDR/p-gp levels in ADR resistant K562 cells [42].

Alkaloids from plant and microbial source inhibited CML cell proliferation in micromole (µM)/microgram (µg) concentration (**Table 1**) (**Figure 2**) [43–66]. Alkaloids are well documented to

Alkaloid	Source of isolation	IC ₅₀ value on K562 cells	Mechanism of action	References
Berberine (bisbenzylisoquinoline alkaloid)	<i>Berberis amurensis</i>	8 µg/ml	↓Bcl-2, Bcl-xL, NFκB (nuclear), IKK-α, IKB-α, BCR-ABL, p-BCR-ABL, Hsp90	[14–17]
Camptothecin (quinoline alkaloid)	<i>Camptotheca acuminata</i>	57 nM	↑Bax, cleavage of PARP-1, DNA–PK adducts	[24]
Homoharringtonine	<i>Cephalotaxus harringtona</i>	43.89 ng/ml	↓Bcl-2, NF-κB, p-JAK2, p-STAT5, p-Akt, p-BCR-ABL and ⊥G ₀ /G ₁ phase	[31, 32]
Sanguinarine (benzophenanthridine alkaloid)	<i>Sanguinaria canadensis</i>	–	At 1.5 µg/ml induced apoptosis	[33]
Tetrandrine (bis-benzylisoquinoline alkaloid)	<i>Stephania tetrandra</i>	–	↑Caspase 3 mRNA, protein and ↓Bcl-2 mRNA, protein	[39, 40]
Ancistrocladine E (naphthylisoquinoline alkaloid)	70% EtOH extract of <i>Ancistrocladus tectorius</i>	4.18 µM	–	[43]
1,2,3-Trimethoxy-5-oxonoroporphine and ouregidion (aporphine alkaloids)	Crude HEX, EtOAc and AQE extracts of <i>Pseuduvaria rugosa</i> (Blume) Merr	*63 and 64%	–	[44]
Cathachunine	<i>Catharanthus roseus</i> (L.) G. Don	9.3 ± 1.8 µM	–	[45]
Cepharanthine	<i>Stephania</i> sp.	–	↓p-gp	[46]
Crebanine	<i>Stephania venosa</i>	13 µg/ml	↓Cyclin A, D & ↑Caspases 3,9,8 & PARP and ⊥G ₀ /G ₁ phase	[48]
Curine	<i>Chondrodendron platyphyllum</i>	17.8 ± 5.2 µM	–	[49]
Cyanogramide	<i>Actinoalloteichus cyanogriseus</i> WHI-2216-6	–	At 5 µM, reversed MDR in K562/ADR	[50]
9-Deacetoxyfumigaclavine C	<i>Aspergillus fumigatus</i>	3.1 µM	–	[51]
Evodiamine (quinazolinocarboline alkaloid)	<i>Evodia rutaecarpa</i>	34.43 µM	–	[53]
Naamidine J (imidazole containing alkaloid)	<i>Pericharax heteroraphis</i>	11.3 µM	–	[54]
Salvicine (diterpenoid alkaloid)	<i>Salvia prioniti</i>	7.82 ± 2.81 µM	⊥G ₁ phase	[56]
Solamargine (glycoalkaloid)	<i>Solanum species</i>	5.2 µM	↑Caspases and ↓Bcl-2	[57, 58]
α-Tomatine (glycoalkaloid)	<i>Solanum lycopersicum</i>	1.51 µM	Loss of MMP. ↑Bak, Mcl-1s, AIF and ↓survivin	[59]
Tylophora alkaloids (tylophorine, tylophorinine, tylophorindine)	<i>Tylophora indica</i>	–	Nuclear condensation, ↑Caspases activation, release of cyt.C	[60]
		44 and 53 µM	–	[61]

Alkaloid	Source of isolation	IC ₅₀ value on K562 cells	Mechanism of action	References
5-Chlorosclerotiamide and 10-episclerotiamide (prenylated indole alkaloids)	<i>Aspergillus westerdijkiae</i> DFFSCS013			
Eupolauramine and sampangine (azaphenanthrene alkaloids)	<i>Anaxagorea dolichocarpa</i> Sprague and sandwith	18.97 and 10.95 µg/ml	–	[62]
Arthpyrones A, B and C (4-hydroxy-2-pyridone alkaloids)	<i>Arthrimum arundinis</i> ZSDS1-F3	0.24–45 µM	–	[63]
Auranomides A, B and C	<i>Penicillium aurantiogriseum</i>	*20.48, 76.36 and 5.78%	–	[64]
Malonganenones 1–3 (tetraprenylated alkaloids)	<i>Euplexauria robusta</i>	0.35–10.82 µM	–	[65]
Virosecurinine	<i>Securinega suffruticosa</i>	32.984 µM	↑PTEN & ↓mTOR, SHIP-2 BCR-ABL, and ⊥G ₁ /S phase	[66]

↑ – upregulation, ↓ – downregulation, ⊥ – cell cycle arrest & * – Inhibition rate (IR) at 100 µg/ml.

Table 1. Anti-CML activity of alkaloids.

potently reduce tumor growth in *in vivo* models (Table 2). Besides, some alkaloids such as capasaicin, staurosporine induces differentiation of CML cells (Table 3).

2.2. Flavonoids

Flavonoids belong to polyphenolic compounds which are prevalent in plants. They contain two phenyl rings A, B and a heterocyclic ring C (commonly referred as C6-C3-C6 skeleton) and are classified into many major classes like flavones, flavonols, flavanones, flavanonols and isoflavonoids (Figure 3). They exhibit antioxidant, anti-inflammatory, anti-bacterial, antiviral and anti-cancer activities and play a significant role in human health [67–74].

Oroxylin A, an O-methylated flavone, found in the medicinal plant *Scutellaria baicalensis*, was tested against MDR K562/ADR cells. Oroxylin A specifically enhanced the sensitivity of K562/ADR to ADR by selectively inducing apoptosis. The treatment downregulated CXCR4 expression and inhibited PI3K/Akt/NF-κB pathways [75]. NOD/SCID mice-bearing K562 xenograft, treated with oroxylin A (30 mg/kg BW) alone or in combination with imatinib enhanced the sensitivity of imatinib to K562 cells through suppression of STAT3 pathway, decreasing p-gp levels thus reversing MDR in CML cells [76].

Quercetin (Q), a major flavonol, found in the kingdom Plantae, exhibits many biological effects including Antioxidant, anti-inflammatory, anti-cancer and anti-diabetic activities [77]. While evaluating the anti-proliferative effect of phytoestrogens, it was found that Q specifically inhibits K562 and MDR K562/A cell growth [78]. When K562 cells were treated with Q at a

Figure 2. List of anti-CML alkaloids as 1—Ancistrotectorine E, 2—Berbamine, 3—BBD9, 4—Camptothecin, 5—BN80927, 6—NSC606985, 7—Homocamptothecin, 8—Capsaicin, 9—Cathachunine, 10—Cephranathine, 11—Crambesidin 800, 12—Crebanine, 13—Curine, 14—Cyanogramide, 15—9-deacetoxyfumigaclavine C, 16—d-Dicentrine, 17—Evodiamine, 18—Homoharringtonine, 19—Naamidine J, 20—Piperine, 21—Salvicine, 22—Staurosporine, 23—UCN-01, 24—Tetrandrine, 25—5-bromotetrandrine, 26— α -tomatine, 27—tylophorine, 28—tylophorinine, 29—5-chlorosclerotiamide, 30—10-episclerotiamide, 31—Eupolauramine, 32—Sampangine, 33, 34, 35—Arthpyrones A, B and C, 36–38—Auranomides A, B and C and 39—Virosecurinine.

Name of NP	Type of NP	Mice strain	Type of CML cells used to induce tumors	Dosage	Mode of administration	Mechanism of action	References
BBM	Alkaloid	Balb/c	K562-r	60 mg/kg BW	Intravenously	↓ <i>mdr</i> -1 mRNA, p-gp protein	[14]
BBD9	Analogue of BBM	nu-/-	K562/IR	15 and 30 mg/kg BW	-	↓p-BCR-ABL, IKKa, NF-κBp65	[22]
Tetrandrine citrate	Alkaloid	nu-/-	K562/IR	100 mg/kg BW	Orally	↓BCR-ABL, β-catenin	[41]
d-Dicentrine	Alkaloid	SCID	K562	100 mg/kg BW	Intraperitoneal	↓tumor size	[52]
Oroxylin A	Flavonoid	SCID	K562	80 mg/kg BW	Intravenously	↓STAT3 pathway	[76]
Nobiletin	Flavonoid	Nude mice	K562	12.5, 25, 50 mg/kg BW	-	↓VEGF	[99]
dEpoF	Polyketide	Nude mice	K562	6 mg/kg	Intravenously	Complete tumor regression	[147]
HSS	Protein extract from <i>Tegillarca granosa</i>	-	K562/ADM	-	-	↓ <i>mdr</i> 1, BCR-ABL and sorcin	[177]
Gambogic acid	<i>Garcinia hanburyi</i>	Balb/c	KBM5-T315I	3 mg/kg/ 2 days	Intraperitoneal	↓Bcr-Abl, Akt, Erk1/2, and STAT5	[229]
TAF273	Fraction of <i>Eurycoma longifolia</i> MeOH extract	Balb/c	K562	50 mg/kg	Intraperitoneal	↑apoptosis and ↓blood vessel formation	[258]
NPB001-05	Piper betle extract	-	T315I	500 mg/kg	Orally	↓PI3K/AKT, MAPK pathways	[275]

Table 2. In vivo results of anti-CML NPs.

concentration of 9.2 mg/ml for 72 h, it induced apoptosis and reduced the BCR-ABL levels in CML cells [79]. Combination of Q and ADR was tested on MDR K562/ADR cells. Combined treatment enhanced activation of caspases 3,8 and loss of mitochondrial membrane potential (MMP). Furthermore, it lowered Bcl-2, Bcl-xl and enhanced the p-c-Jun-N terminal kinase and p-p38 mitogen-activated protein kinase (p-p38-MAPK). Q also significantly decreased the p-gp levels [80] and sensitized MDR K562/ADM to DNR and reversed MDR in CML cells [81]. Q inhibited K562 and MDR K562/A in the range of 5–160 μM. Q treatment of K562/ADR cells (5 μM) enhanced accumulation of ADR and, in addition, decreased the expression of MDR-causing proteins like ABC, solute carrier (SLC). Moreover, it reduced Bcl-2, TNF expression reversing MDR in CML cells [82]. Moreover, Q arrested CML cells at G2/M phase [83]. IC₅₀ of Q on K562 and K562/ADR was found to be 11 ± 2 μM and 5 ± 0.4 μM [84]. It also inhibited the

Name of NP	NP class	Differentiation of CML cells into	Mechanism of action	References
Capsaicin	Alkaloid	Erythroid cells	↑GATA-1 promoter	[28–30]
Staurosporine	Alkaloid	Megakaryocytes	↑CD61, CD42b and ↓c-myc	[34–36]
Crambescidin 800	Alkaloid	Erythroblasts, induction of hemoglobin production	↓S-phase	[47]
Piperine	Alkaloid	Macrophages/monocytes (20/40 μM)	–	[55]
Apigenin	Flavonoid	Erythroid lineage	↑ α and γ hemoglobin mRNA expression	[87]
Galangin	Flavonoid	Monocytes	↑CD61	[90]
Genistein	Flavonoid	Erythroid lineage	–	[92]
EtOH extract of <i>Olea europaea</i>	Plant extract	Monocyte lineage	↑CD14	[243]
EtOH extract of <i>Stellera chamaejasme</i>	Plant extract	Granulocytes	↑CD11b	[250]
Huangqi (Astragalus membranaceus)	Traditional Chinese medicine	Erythroid lineage	↑β-globin gene expression	[272]

Table 3. List of some NPs and its differentiation capacity.

Hsp70 levels in CML cells [85]. Q induced apoptosis *via* inhibiting the telomerase enzyme by enhancing human telomerase reverse transcriptase (hTERT) enzymes in CML cells [86].

In sum, flavonoids not only inhibit the growth of CML cells (**Table 4**) but also induce their differentiation into erythroid or monocyte lineage (**Table 3**). Flavonoid fractions of plant extracts also inhibit CML cell proliferation and induced apoptosis [87–109].

2.3. Terpenoids

Terpenoids are naturally occurring products representing the largest secondary metabolites. Approximately 60% of NPs are terpenoids. They are basically made up of five carbon isoprene units (IU). Depending upon the number of isoprene units present, terpenoids has been classified into hemiterpenoids (1 IU), monoterpenoids (2 IU), sesquiterpenoids (3 IU), diterpenoids (4 IU), sesterterpenoids (5 IU), triterpenoids (6 IU), tetraterpenoids (8 IU) and polyterpenoid (n IU). They have been documented to possess antioxidant, anti-inflammatory, anti-helminthic and anti-cancer activities [110–115].

Sesquiterpenoids, diterpenoids, sesterterpenoids and triterpenoidshas been shown to potently inhibit CML cell proliferation and induce apoptosis (**Figure 3**) (**Table 5**) [116–144]. Other diterpenoids such as scapaundulin C (from *Scapania undulate* (L.) Dum.,) [120], parvifoline Z, parvifoline AA (from *Isodon parvifolius*) [121], labdane-type diterpenes (from *Chloranthus henryi* Hemsl.) [124] and sesterterpenoid compounds 3, 11 and 12 (from *Sarcotragus* sp.) [133] and triterpenoid compounds 1, 2, 5, 7 and 9 (from *Ganoderma hainanense*) [135], (24R/S)-24-hydroxy-

FLAVONOIDS

TERPENOIDS

POLYKETIDES

LIGNANS

PEPTIDES

Figure 3. Anti-CML activity of some NPs which include – flavonoids: 1–Apigenin, 2–Baicalein, 3–Fisetin, 4–Galangin, 5–Genistein, 6–Kaempferol, 7–Myricetin, 8–Naringenin, 9–Nobiletin, 10–Oroxylin A and 11–Tamarixetin. Terpenoids: 1–Gukulenin A, 2–4–Hebeabinin A, D & E, 5–Parvifolines C, 6–3-hydrogenwadaphnin, 7–Tanshinone I, 8–EM23, 9, 10–Felixins F & G, 11–Kadlongilactone D. Polyketides: 1–Epiaspinonediol, 2–aza-EpoB, 3–dEpoF, 4–Heveadride, 5–Gilvocarin HE, 6–Rhizoxin, 7–Salarin C, 8–Tausalarin C, 9–Trineurone E. Lignans: 1–Arctigenin, 2–Cleistanthin A, 3–Honokiol, 4–6-hydroxyjusticidin C, 5–(+) –lariciresinol 9'-p-coumarate, 6–4-methoxy magnidialdehyde. Peptides: 1, 2–chujamide A, B, 3–gombamide A.

Flavonoids/flavonoid fraction	IC ₅₀ value on K562 cells	Mechanism of action	References
Oroxylin A (o-methylated flavone)	–	↓CXCR4, PI3K/Akt/NF-κB pathways	[75, 76]
Quercetin (flavonol)	11 ± 2 μM	Loss of MMP. ↑caspases 3,8 & ↓Bcl-2, Bcl-xl, Hsp70, telomerase and ↓G ₂ /M phase	[77–86]
Apigenin (flavone)	–	↓Mcl-1, Bcl-2 & ↑caspases activation and ↓G ₂ /M phase	[87, 91]
Baicalein (flavone)	–	↑ caspase 3, Fas gene and ↓ S phase	[88]
Fistein (flavonol)	–	Induced apoptosis and Altered JAK/STAT, KIT pathways and ↓S & G ₂ /M phases	[89, 97]
Galangin (flavonol)	–	↓pRb, cdk4, cdk1, cycline B & Bcl-2 levels and ↓G ₀ /G ₁ phase	[90]
Kaempferol (flavonol)	–	↑ Bax, SIRT3, caspases 3, 9 and ↓ Bcl-2	[93]
Myricetin (flavonol)	–	Myricetin pre-treatment enhanced Natural killer cells to kill K562	[96, 97]
Naringenin (flavanone)	–	↑ p21/WAF1 and ↓G ₀ /G ₁ phase	[98]
Tamarixetin (o-methylated flavonol)	–	↑ cyclin B1, Bub1, p21, caspases and ↓tubulin polymerization	[100]
3,5-Dihydroxy-6,7,3',4'-tetramethoxyflavone (DHTMF) (polymethoxyflavone)	7.85 μg/ml	↑caspases 3, 9 & PARP cleavage	[101]
2'',3''-Diidroochnaflavone (<i>Luxemburgia nobilis</i>)	89 μM	–	[102]
Isochamaejasmin (biflavonoid) (<i>Stellera chamaejasme</i> L)	24.51 ± 1.62 μM	↑caspases 3, 9 and PARP cleavage	[103]
Protoapigenone (total flavonoid fraction of <i>Macrothelypteris torresiana</i>)	0.9 μg/ml	–	[104]
Total flavonoids from <i>Lysimachia clethroides</i> Duby (ZE4)	–	↓Bcl-2 and ↑Fas, TRAIL & DR5	[105]
Total flavonoids of <i>Astragali Radix</i>	98.63 mg/L	↓ cyclin D1 mRNA levels and ↓G ₀ /G ₁ phase	[106]
Total oligomer flavonoids of <i>Rhamnus alaternus</i>	196 μg/ml	–	[107]
Flavonoid-enriched <i>Rhamnus alaternus</i> root and leaf extracts	165 and 210.73 μg/ml	–	[108]
Epigallocatechin-3-gallate (<i>Camellia sinensis</i>)	50 μM	↓CyclinD1, CDC25A and ↑TGF-β2	[109]

Table 4. Anti-CML activity of flavonoids.

3α 10α-epoxy-9-eip-cucurbita-25-ene (1a, b) (from *Fructus Viticis* Negundo) [136] are also shown to efficiently inhibit CML cell proliferation.

2.4. Polyketides

Polyketides represent a large group of natural products that are produced by microorganisms and plants. These are secondary metabolites, derived by the repetitive condensation of acetate

Terpenoid class	Name of terpenoid	Source of isolation	IC ₅₀ value on K562 cells	Mechanism of action	References
Sesquiterpenoids	EM23	<i>Elephantopus mollis</i>	10.8 μ M	$\uparrow$ caspases, PARP cleavage and $\downarrow$ NF κ B. Loss of MMP	[116]
Diterpenoids	Caesalminaxin D and H	<i>Caesalpinia minax</i>	9.9 $\pm$ 1.7 and 9.2 $\pm$ 0.9 μ M	–	[117]
	Gukulenin A and diterpenoid pseudodimers (2–5)	<i>Phorbas gukhulensis</i>	*0.26 $\pm$ 0.03, 0.12 $\pm$ 0.01, 0.44 $\pm$ 0.01, 0.32 $\pm$ 0.05 and 0.04 $\pm$ 0.09 μ M	–	[118]
	Diterpene compounds 11, 12, 13, 14 and 15	petroleum ether soluble fraction of the aerial parts of <i>Tirpitzia ovoidea</i> ethanol extract	86.4, 66.3, 91, 45.1 and 58.6 μ M	–	[119]
	7 β ,11 β ,14 β -Trihydroxy-ent-kaur-20-al-6,15-dioxo-16-ene	<i>Isodon xerophilus</i>	0.04 μ M	–	[122]
	Hebeiabinin A, D and E	<i>Isodon rubescens</i> var. <i>rubescens</i>	53.21, 5.05 and 0.91 μ M	–	[123]
	Parvifolines C	<i>Isodon parvifolius</i>	13.8 μ M	–	[125]
	3-Hydrogenwadaphnin	<i>Dendrostellera lessertii</i>	15 nM con. caused 45% apoptosis	–	[126]
	Enanderianins K–P, Rabdoetsin B and D	<i>Isodon enanderianus</i>	0.13–0.87 μ g/ml	–	[127]
	Ludongnin J	<i>Isodon rubescens</i> var. <i>lushiensis</i>	0.18 μ g/ml	–	[128]
	Tanshinone I	<i>Salvia miltiorrhiza</i> Bunge.	38 $\pm$ 5.2 μ M	$\uparrow$ Bax, caspase 3 and $\downarrow$ Survivin	[129]
Sesterterpenoids	ent-Kaurane diterpenoids 11, 16, 17 and 20	<i>Isodon nervosus</i>	2.39, 4.11, 1.05 and 1.55 μ M		[130]
	5-Episinuleptolideacetate	<i>Sinularia species</i>	4.09 μ g/ml	$\downarrow$ c-ABL, Akt, NF κ B	[144]
	Felixins F and G	<i>Ircinia felix</i>	1.27 and 19.9 μ M	–	[131]
Sesterterpenoids	Compounds 8, 9	<i>Smenospongia</i> sp.	*0.11 and 0.97 μ g/ml	–	[132]
	Two linear furanosesterterpenes	<i>Smenospongia</i> sp.	3 and 31.6 μ g/ml	–	[134]
	3 β ,21 β ,24-Trihydroxyserrat-14-en-24-(4'-hydroxybenzoate)	<i>Palhinhaea cernua</i>	56.1 μ g/ml	–	[137]
Triterpenoids	L-Arabinopyranosyloleanolic acid	<i>Garcinia hanburyi</i> resin	4.15 μ M	–	[138]

Terpenoid class	Name of terpenoid	Source of isolation	IC ₅₀ value on K562 cells	Mechanism of action	References
	Nortriterpenoids	<i>Schisandra propinqua</i> var. <i>propinqua</i>	>100 µM	–	[139]
	Kadlongilactone D	<i>Kadsura longipedunculata</i>	1.92 µM	–	[140]
	Six triterpenes	fractions of <i>Aceriphyllum rossii</i> methanolic extract	12.2–28.7 µM	–	[141]
	Argetatin B	<i>Parthenium argentatum</i>	Cytotoxic at 5–25 µM con.	–	[142]
	Celastrol (quinone methide triterpene)	<i>Tripterygium wilfordii</i> Hook F	–	↓pSTAT5, p-CRKL, pERK1/2, p-Akt, p-BCR-ABL, Bcl-xL, Mcl-1, survivin, Hsp90	[143]

*LC₅₀, lethal concentration.

Table 5. Anti-CML activity of terpenoids.

units or other short carboxylic acids catalyzed by multi-functional enzymes called polyketide synthases (PKSs) which is similar to fatty acid synthases [145]. Many polyketides suppress CML cell proliferation and induce apoptosis (**Figure 3**) (**Table 6**) [146–155].

2.5. Lignans

Lignans, natural compounds that are exclusively found in plants, are derived from amino acid phenyl alanine. They possess anti-oxidant and anti-cancer activities [156]. Various lignans effectively inhibit CML cell proliferation and induced apoptosis (**Figure 3**) (**Table 6**) [157–163].

2.6. Saponins

Saponins are a diverse group of secondary metabolites widely distributed in the plant kingdom. They produce soap-like foam when shaken in aqueous solutions. Their structure comprise of triterpene or steroid aglycone and one or more sugar chains. They exhibit anti-cancer and anti-cholesterol activities [164, 165]. Various saponins inhibited CML cell proliferation (**Table 6**) [166–174].

2.7. Peptides

Two peptides, chujamides A (1) and B (2), isolated from the marine sponge *Suberites waedoensis* inhibited K562 cell growth with LC₅₀ values of 37 and 55.6 µM [175]. Another peptide, gombamide A (1), isolated from the marine sponge *Clathria gombawuiensis* inhibited CML cell proliferation with LC₅₀ of 6.9 µM [176]. Haishengsu (HSS), a protein extract from

Type of NP	Name of compound	Source of isolation	IC ₅₀ value on K562	Mechanism of action	References
Polyketides	Epiaspinonediol	<i>Aspergillus</i> sp. 16-02-1	44.3 µg/mL	–	[146]
	Geldanamycin	<i>Streptomyces Hygroscopicus</i>	–	↓c-Raf, Akt, BCR-ABL	[148]
	Heveadride	<i>Ascomycota Dichotomyces cejpai</i>	82.7 ± 11.3 µM	↑ TNFα	[149]
	Gilvocarin HE	<i>Streptomyces</i> sp. QD01-2	45 µM	–	[150]
	Radicalol	<i>Diheterospora chlamydosporia</i> and <i>Monosporium bonorden</i>	–	↓p-Raf1, p-BCR-ABL	[151]
	Rhizoxin	<i>Burkholderia rhizoxina</i>	5×10 ⁻⁷ µg/ml	–	[152]
	Salarin C	<i>Fascaplysinopsis</i> sp.	0.1 µM	↑ caspase 3 and 9 cleavage	[153]
	Tausalarin C	<i>Fascaplysinopsis</i> sp.	1 µM	–	[154]
	Trineurone E	<i>Peperomia trineura</i>	26 µM	–	[155]
	Arctigenin	Asteraceae family	–	↑Bax and ↓ Bcl-2	[157]
Lignans	Cleistanthin A	<i>Cleistanthus collinus</i> (Rox B)	0.4 µM	–	[158]
	5,5'-Dimethoxylariciresinol-4'-O-β-D-glucoside (DMAG)	Mahonia	–	↓IC ₅₀ of DOX from 34.93 to 12.51 µM	[159]
	Honokiol	<i>Magnolia officinalis</i> Rend. Et wils.	28.4 µM	–	[160]
	6-Hydroxyjusticidin C	<i>Justica procumbens</i>	43.9 ± 2.9 µM	↑ROS levels, casapase 3	[161]
	(+)-Lariciresinol 9'-p-coumarate	<i>Larix olgensis</i> var. koreana.	2.9 µg/ml	–	[162]
	4-Methoxy magndialdehyde	<i>Magnolia officinalis</i>	3.9 µg/ml	–	[163]
	Astrgorgiosides A, B, C (19-norand aromatized B ring bearing steroid aglycone)	<i>Astrogor dumbea</i>	26.8–45.6 µM	–	[168]
Saponins	Wattoside G, H, and I (steroidal saponins)	<i>Tupistra wattii</i> Hook.F.	35.67, 76.16 and 76.96 µM	–	[169]
	Tenacissoside C (steroidal saponins)	<i>Marsdenia tenacissima</i>	31.4 µM	↓ cyclin D, Bcl-2, Bcl-xL and ↑caspases 3, 9, Bax and Bak	[170]
	Compounds 14 and 15 (C21-steroidal pregnane sapogenins)	<i>Cynanchum wilfordii</i> roots	6.72 µM	–	[171]
	Total saponin content	<i>Aralia Taibaiensis</i>	–	Loss of MMP. ↑ Bax and ↓ Bcl-2	[172]

Type of NP	Name of compound	Source of isolation	IC ₅₀ value on K562	Mechanism of action	References
	Saponin rich fraction (GSE)	<i>Gleditsia sinensis</i> Lam. fruit extract	18 ± 1.6 µg/ml	↑ Bax and ↓ Bcl-2, PCNA	[173]
	23-Hydroxybetulinic acid	Total saponin content of <i>Pulsatilla chinensis</i> (Bunge) Regel	–	↑ Bax, caspase 3 cleavage and ↓ Bcl-2, survivin	[174]
Peptides	Chujamides A and B	<i>Suberites waedoensis</i>	*37 and 55.6 µM	–	[175]
	Gombamide A	<i>Clathria gombawuiensis</i>	*6.9 µM	–	[176]

*LC₅₀—lethal concentration.

Table 6. Anti-CML activities of polyketides, lignans, saponins and peptides.

Tegillarca granosa, when administered in mice-bearing MDR K562/ADM cell tumors inhibited tumor growth and downregulated *mdr1* gene, BCR-ABL and sorcin [177]. HSS was also tested against MDR K562/ADR cells, and it induced apoptosis at 20 mg/l [178]. HSS also inhibited K562 cells at G0/G1 and S phase and lowered Bcl-2 and enhanced Bax levels (**Figure 2**) (**Table 6**) [179].

2.8. Others natural products

Other natural products such as acetylenic metabolites, betanin, bufadienolide, mamea a/ba, cryptotanshinone, bavachalcone, polyanthumin, cubebin, denbinobin, digallic acid, perforanoid A, β- and α-mangostin, parthenolide, perezone, polyphyllin D, squamocin, toxicarioside H, tripolide, woodfordin I and rhodexin A inhibited CML cell proliferation (**Table 7**) [180–230]. Moreover, many plant crude extracts enriched with NPs inhibited the CML cell proliferation and induced apoptosis (**Table 8**) [231–280].

2.9. Natural products in clinical trials

Of the several natural products, Homoharringtonine (alkaloid) (NCT00114959) is currently under phase II study sponsored by Chem Genex pharmaceuticals to reverse the Gleevac resistance in CML patients [281]. 17-AAG (analogue of glendamyacin–polyketide) (NCT00100997) is currently under phase I clinical trial sponsored by Jonsson Comprehensive Cancer Center collaborated with National Cancer Institute (NCI). Efforts are underway to determine the side effects and optimal dose of 17-AAG for treating patients with CML in chronic phase who did not respond to imatinib-mesylate [282]. Paclitaxel (diterpenoid) (NCT00003230) is currently under Phase I/II trials to study the effectiveness in treating patients with refractory or recurrent acute leukemia or CML. This work is sponsored by Swiss Group for Clinical Cancer Research [283].

Name of NP	Source of isolation	IC ₅₀ value on K562 cells	Mechanism of action	References
Acetylenic metabolites	<i>Stelletta</i> sp.	43.5, 51.3 and 62.5 µg/ml	–	[180]
Betanin (betacyanin pigment)	<i>Opuntia ficus-indica</i>	40 µM	↑ PARP cleavage, release of Cyt C and ↓ BCL-2. Loss of MMP	[182]
Bufalin 3β-acrylic ester (Bufadienolide)	“Ch’an Su”	6.83 nM	–	[183]
3-Formylcarbazole, methylcarbazole-3-carboxylate and 2-methoxy-1-(3-methyl-buten-1-yl)-9H-carbazole-3-carbaldehyde	<i>Clausena lansium</i> (Lour.) Skeels	20.48 ± 1.78, 26.5 ± 2.12 and 23.49 ± 1.85 µg/ml	–	[184]
Toxicarioside F and G	<i>Latex of Antaris toxicaria</i> (Pers.) Lasch	–	–	[185]
Pangelin and oxypeucedanin hydrate acetone	<i>Angelica dahurica</i>	8.6–14.6 µg/ml	–	[186]
Mamea A/BA	<i>Calophyllum brasiliense</i>	0.04–0.59 µM	–	[187, 188]
Cryptotanshinone (lipid soluble active compound)	<i>Salvia miltiorrhiza</i>	–	induced apoptosis ↑ PARP cleavage and ↓ BCR-ABL, STAT3, mTOR & eIF4E	[189, 190]
Bavachalcone (Chalcones)	–	2.7 µM	–	[191]
Polyanthumin (novel chalcone trimmer) and sulfuretin	<i>Memecylon polyanthum</i> H.L. Li.	45.4 and 30.5 µg/ml	–	[192]
(–)-Cubebin	<i>Piper cubeba</i>	8.66 ± 0.43 µM	–	[193]
Denbinobin	5-Hydroxy-3,7-dimethoxy-1,4-phenanthraquinone	1.84 µM	↓ BCR-ABL, CrkL and ↓ G2/M phase	[194]
Digallic acid	<i>Pistacia lentiscus</i>	–	Induced DNA fragmentation and pro-apoptotic effect in CML cells	[195]
1,4,5-Trihydroxy-7-methoxy-9H-fluoren-9-one, dendroflorin and denchrysan (fluorenones)	<i>Dendrobium chrysotoxum</i>	32.18, 26.65 and 52.28 µg/ml	–	[196]
C27-Steroidal glycoside	<i>Liriope graminifolia</i> (Linn.) Baker	18.6 µg/ml	–	[198]
9α-Acetoxyartecanin, apressin, inducumenone and centaureidin	<i>Achillea clavennae</i>	9.84 ± 2.52, 4.44 ± 0.76, 52.53 ± 8.43 and 5.37 ± 0.8 µM	–	[199]
Perforanoid A (limonoid)	–	4.24 µM	–	[200]
Linoleic acid	Methanol extracts of proso and Japanese millet	68 µM	–	[201]
β- and α-Mangostin	<i>Garcinia malaccensis</i>	–	–	[202, 203]

Name of NP	Source of isolation	IC ₅₀ value on K562 cells	Mechanism of action	References
		0.40 µM and 0.48 µM		
Nudifloside and linearoside (iridoid)	EtOH extract of the aerial parts of <i>Callicarpa nudiflora</i> Hook	20.7 and 36 µg/ml	–	[204]
Parthenolide	–	17.1, 8.67 and 9.42 for 24, 48 and 72 h	Induced apoptosis	[205]
Perezone	<i>Perezia</i> spp.	–	Cytotoxic to CML cells at 25, 50 and 100 µM and induced apoptosis	[206]
Compound 6a (phenalenone metabolite)	<i>Coniothyrium cereal</i>	8.5 µM	–	[207]
Polyphyllin D	<i>Paris polyphyllin</i>	–	↑ p21, Bax, caspase 3 & Cyt. C release and ↓ cyclin B1, cdk1, Bcl-2. Loss of MMP and ⊥ G ₂ /M phase	[208]
Polysaccharide (PSP001)	<i>Punica granatum</i>	52.8 ± 0.9 µg/ml	–	[209]
Riccardin F and Pakyonol (macrocylic bisbenzyls)	<i>Plagiochasm intermedium</i>	0–6 µg/ml	–	[210]
Highly methoxylated bibenzyls	<i>Frullania inouei</i>	11.3–49.6 µM	–	[211]
Sarcovagine and β-sitosterol 5- 8	<i>Sarcococca saligna</i>	2.5–5 µM	–	[212]
Squamocin (annonaceous acetogenins)	–	–	↑ cdk inhibitors, p21, p27 & ↓ cdk1, cdk25c and ⊥ G ₂ /M phase	[213]
Klyflaccisteroid J	<i>Klyxum flaccidum</i>	12.7 µM	–	[214]
Suvanine (N,N-dimethyl-1,3-dimethylherbipoline salt) and suvanine-lactam derivatives (4–8)	<i>Coscinoderma</i> sp. sponge	* 2.2, 1.9, 3.9, 4.6, 3.9 and 3.6 µM	–	[215]
ar-Turmerone	<i>Curcuma longa</i> L	20–50 µg/ml	Induced DNA fragmentation and apoptosis	[216]
Terpene metabolites (1–3)	<i>Clathria gombawuiensis</i>	*4.7, 3.9 and 2.1 µM	–	[217]
Toxicarioside H (nor-cardenolide)	<i>Antiaris toxicaria</i> (Pers.) Lesch	0.037 µg/ml	–	[218]
Tripolide	Chinese herbal extract	–	↓ Nrf2 and HIF-1α mRNA and protein expression	[219]
10-(Chrysophanol-7'-yl)-10-hydroxychrysophanol-9-anthrone and ramosin	Fractions of EtOH extract of <i>Asphodelus microcarpus</i> Salzm. et Vivi	0.15 ± 0.02 and 0.65 ± 0.01 µM	–	[220]

Name of NP	Source of isolation	IC ₅₀ value on K562 cells	Mechanism of action	References
Withametelins I, J, K, L and N	MeOH extract of <i>Datura metel</i> flowers	0.05, 2.5, 0.12, 0.55 and 0.46 μ M	–	[221]
Woodfordin I (macrocyclic ellagitannin dimer)	–	–	↓ Bcl-2, Bcl-xL, Bax, c-Abl & BCR-ABL and Loss of MMP	[222]
Gaudichaudic acid, isogambogenic acid and deoxygaudichaudione A (xanthenes)	<i>Garcinia hanburyi</i> resin	0.41 $\pm$ 0.03, 2.1 $\pm$ 0.14 and 1.74 $\pm$ 0.22 μ g/ml	–	[223]
Xindongnins C–D, A, B, melissoidesin G, dawoensin A and glabensin V	<i>Isodon rubescens</i> var. <i>rubescens</i>	0.3–7.3 μ g/ml	–	[224]
Hyperbeanols B and D	MeOH extract of <i>Hypericum beanie</i>	16.9 and 20.7 μ M	–	[225]
Rhodexin A	<i>Rhodea japonica</i>	19 nM	⊥G ₂ /M phase induced apoptosis	[226]
Curcumin	<i>Curcumina longa</i>	20 μ g/ml	↓BCR-ABL, Hsp90, WT1	[227, 228]
Gambogic acid	<i>Garcinia hanburyi</i>	0.62 μ M	↓p-BCR-ABL, pSTAT5, p-CRKL, pERK1/2, p-Akt	[229, 230]

*LC₅₀–lethal concentration.

Table 7. Anti-CML activity of other natural products.

Plant extract	IC ₅₀ value on K562 cells	Mechanism of action	References
Acetone extract of <i>Peucedanum nebrodense</i> (Guss.) Strohl.,	14–10.27 μ g/ml	–	[231]
AQE extract of <i>Cornus officinalis</i> Sieb. et Zuce	100 μ g/ml	–	[232]
AQE extracts of the husk fiber of the typical A and common varieties of <i>Cocos nucifera</i> (Palmae)	At 500 μ g/ml the cell viability of CML cells was found to be 60.1 $\pm$ 8.5 and 47.5 $\pm$ 11.9%	–	[233]
AQE extract of <i>Rhodiola imbricate</i>	–	↓CML cell proliferation at 100 and 200 μ g/ml for 72 hrs. induced ROS & apoptosis and ⊥G ₂ /M phase	[234]
Abnobaviscum F® (standardized AQE extract of European mistletoe from the host tree <i>Fraxinus</i>)	–	↑ caspase 9, JNK-1,2, p38 MAPK and ↓ Bcl-1, Erk-1/2 & PKB phosphorylation	[235]
Chloroform extract of <i>Polyalthia rumphii</i> stem	40–60 μ g/ml	–	[236]
Chloroform extract of <i>Tecomella undulata</i> bark	30 μ g/ml	↑ FAS, FADD, & caspase 8, 3/7. Induced DNA fragmentation & apoptosis	[237]
DCM) extract of <i>Psidium guajava</i> L.	32 μ g/ml	–	[238]

Plant extract	IC ₅₀ value on K562 cells	Mechanism of action	References
DCM extract <i>Artemisia turanica</i> Krasch	69 µg/ml	↑ caspases, PARP cleavage. Induced DNA damage and apoptosis	[239]
HEX and DCM extract of <i>Mesua beccariana</i>	*20 ± 1.5 and 43.75 ± 0.78 µg/ml	–	[240]
HEX and DCM extract of <i>Mesua ferrea</i>	*17.5 ± 1.02 and 22.91 ± 1.25 µg/ml	–	[240]
HEX extract of <i>Mesua congestiflora</i>	40.63 ± 1.45 µg/ml	–	[240]
DCM fraction of <i>Melissa officinalis</i>	At 50 µg/ml concentration, it induced 65.04 ± 0.93% apoptotic rate	↑ Fas, Bax mRNA levels and Bax/Bcl-2 ratio	[241]
DCM fraction of the crude EtOH extract of <i>Echinops grijissi</i> Hance roots	30 µg/ml	–	[242]
EtOH extract of <i>Pereskia sacharosa</i>	130 ± 0.03 µg/ml	↑ caspases, cyt. C release, p21 & p53 and ↓Akt and Bcl-2	[244]
EtOH extract of propolis (NP produced by stingless bee <i>Melipona orbignyi</i>)	At 250 and 500 µg/ml promoted cell death of CML cells by 15 ± 1 and 63 ± 2%	–	[245]
EtOH extract of <i>Isodon japonicas</i>	2.7 µg/ml	–	[246]
EtOH root extract of <i>Allamanda schottii</i>	At 800 µg/ml showed cytotoxicity	–	[247]
EtOH stem and leaf extract of <i>Physalis peruviana</i>	0.02 and 0.03 g/ml	–	[248]
Alcoholic extract of <i>Dendrostellera lessertii</i>	28 µl and 5 × 10 ⁻⁹ M	–	[249]
EtOH extract of <i>Rosmarinus officinalis</i> L	1/400 dilution	–	[251]
EtOH extract of <i>Goldfussia psilostachys</i>	0.5 µg/ml	↑ CML cells in G ₂ /M phase	[252]
Fraction from EtoAc of <i>Caesalpinia spinosa</i>	44.5 ± 4.05 µg/ml	induced chromatin condensation. Loss of MMP & ↑ caspase 3	[253]
EtoAc extract of <i>Helichrysum plicatum</i> flowers	25.9 µg/ml	–	[254]
MeOH extract of <i>Linum persicum</i>	0.1 µg/ml	–	[255]
MeOH extracts of <i>Echinophora cinerea</i> and <i>Cirsium bracteosum</i>	Less than 20 µg/ml	–	[256]
MeOH extract of <i>Galium mite</i>	39.8 µg/ml	–	[256]
MeOH extract of <i>Cyperus rotundus</i>	175 ± 1.2 µg/ml	Induced DNA damage	[257]
TAF273, F3 and F4 fractions of MeOH extract of <i>Eurycoma longifolia</i> Jack	19, 55 and 62 µg/ml	–	[258]
MeOH extract of <i>Rhaphidophora korthalsii</i>	–	Enhanced Natural killer cells to kill K562, ↑IFN-γ, TNF-α	[259]

Plant extract	IC ₅₀ value on K562 cells	Mechanism of action	References
MeOH extract of <i>Rhinella jimi</i> Stevaux (Anura: Bufonidae) skin	*235 µg/ml	–	[260]
MeOH extract of <i>Hypericum perforatum</i> L.flower extract	–	Induced apoptosis	[261]
HEX, DCM, EtoAc, butanol and MeOH extracts of <i>Helichrysum zivojinii</i> Černjavski and Soška	11.78 ± 0.94, 23.82 ± 6.54, 27.52 ± 4.96, 50.37 ± 3.28 and 74.88 ± 7.57 µg/ml (for 72 h)	–	[262]
Acetate: MeOH (95:5), acetate, chloroform and HEX fractions of <i>Erythroxylum caatingae</i> plowman	13.1 ± 0.63, 9.86 ± 0.56, 11.21 ± 0.46, 33.58 ± 1.33 µg/ml	–	[263]
DCM extract of <i>Arctium lappa</i> root	^17 µg/ml	–	[264]
<i>Alisma orientalis</i> (Sam) Juzep extract	–	Reverse of MDR	[265]
Polyphenolic extract of <i>Ichnocarpus frutescens</i> leaves	–	At 5, 10, 20 µg/ml con. ↓K562 cell proliferation	[266]
EtOH extract of <i>Orbignya speciosa</i>	33.9 ± 4.3 µg/ml	–	[267]
<i>Coptis chinensis</i> and <i>Epimedium sagittatum</i> extracts	29 and 74 µg/ml	–	[268]
Sangre de Drago is red viscous latex extract of <i>Croton lechleri</i>	2.5 ± 0.3 µg/ml	–	[269]
<i>Dionysia termeana</i> extract	20 µg/ml	–	[270]
<i>Ganoderma lucidum</i> extract	*50 µg/ml	–	[271]
Crude MeOH extracts of <i>Luehea candicans</i> Mart. et Zucc. branches and leaves	#8.1–5.4 µg/ml	–	[273]
<i>Nerium oleander</i> extract	–	↓p-gp	[274]
Ponicidin (<i>Rabdosia rubescens</i> extract)	–	↓ Bcl-2 and ↑ Bax, caspase 3 & PARP cleavage	[276]
<i>Scutellaria litwinowii</i> Bornm. and Sint. ex Bornm.	–	↑ caspase 3,8, PARP cleavage, Bax/ Bcl-2 ratio	[278]
<i>Swietenia mahagoni</i> leaf extract	–	↑ caspases 3,9, Cyt. C release and ↓G ₂ -M phase	[279]
Viscin, (lipophilic extract from <i>Viscum album</i> L)	252 ± 37 µg/ml	–	[280]

AQE, aqueous, DCM, dichloromethane, HEX, hexane, EtOH, ethanol, EtoAc, ethyl acetate, MeOH, methanol, ^TGI, tumor growth inhibition,*ED50, –effective concentration; # GI⁵⁰, growth inhibition.

Table 8. Anti-CML activity of plant extracts.

3. Conclusion

CML is a hematological malignancy that arises due to chromosomal translocation resulting in the presence of Ph chromosome. Initially, TKIs were designed to compete with the ATP binding site

of BCR-ABL. TKIs effectively inhibited wild-type BCR-ABL; however, mutations in BCR-ABL and overexpression of drug efflux proteins following treatment decreased their potency.

Since, there is a need for alternative strategy to develop new BCR-ABL inhibitors; NPs (obtaining from living organisms) offers an alternate, effective and inexpensive design for CML therapy. Moreover, they have less (or) no side effects. Studies conducted so far have revealed that many NPs inhibit CML cell proliferation and, in addition, induce cell death through apoptosis. NPs alone or in combination with other TKIs are able to reverse the MDR, thereby increasing the sensitivity of TKIs towards CML. Moreover, many NPs are able to differentiate CML cells into erythroid, monocyte or macrophage lineage. *In vivo* results have clearly shown that NPs potently suppress tumor growth. In sum, NPs serve as an inexhaustible source which renders an attractive alternate strategy to combat CML.

Conflict of interests

The authors declare that they do not have any competing interests.

Abbreviations

CML	chronic myeloid leukemia
Ph	Philadelphia chromosome
MAPK	mitogen activated protein kinase
STAT	signal transducers and activator of transcription
PI3K	phosphoinositide 3-kinase
TKIs	tyrosine kinase inhibitor
FDA	Food and Drug Administration
MDR	multi drug resistance
p-gp	p-glycoprotein
NPs	natural products
NCEs	new chemical entities
BBM	berbamine
K562/IR	imatinib resistant K562 cell line
cyt. C	cytochrome C
BW	body weight
ADR	adriamycin
Hsp90	heat shock protein 90
BBD9	4-chlorobenzoyl berbamine
PARP	Poly(ADP-Ribose) polymerase
LC3 II	LC3-phosphatidylethanolamine conjugate
DOX	doxorubicin

hCPT	homocamphothecin
DNA-PK	DNA-dependent protein kinase
miRNA	microRNA
HHT	homoharringtonine
UCN-01	7-hydroxy staurosporine
μM	micromole
μg	microgram
Q	quercetin
DNR	daunorubicin
MMP	mitochondrial membrane potential
p-p38-MAPK	p-p38 mitogen-activated protein kinase
SLC	solute carrier
hTERT	human telomerase reverse transcriptase
IU	isoprene units
PKSs	polyketide synthases
DMAG	5,5'-dimethoxylariciresinol-4'-O- β -D-glucoside
HJC	6-hydroxyjusticidin C
HSS	Haishengsu

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References

- [1] Shahrabi S, Azizidoost S, Shahjahani M, Rahim F, Ahmadzadeh A, Saki N. New insights in cellular and molecular aspects of BM niche in chronic myelogenous leukemia. *Tumour Biol.* 2014;35(11):10627–33. doi:10.1007/s13277-014-2610-9. PubMed PMID: 25234716.
- [2] Deininger MW, Goldman JM, Melo JV. The molecular biology of chronic myeloid leukemia. *Blood.* 2000;96(10):3343–56. PubMed PMID: 11071626.
- [3] Sattler M, Griffin JD. Molecular mechanisms of transformation by the BCR-ABL oncogene. *Semin Hematol.* 2003;40(2 Suppl 2):4–10. doi:10.1053/shem.2003.50034. PubMed PMID: 12783368.

- [4] Sacha T. Imatinib in chronic myeloid leukemia: an overview. *Mediterr J Hematol Infect Dis.* 2014;6(1):e2014007. doi:10.4084/MJHID.2014.007. PubMed PMID: 24455116; PubMed Central PMCID: PMC3894842.
- [5] Akard LP. Second-generation BCR-ABL kinase inhibitors in CML. *N Engl J Med.* 2010;363(17):1672–3; author reply 3–5. PubMed PMID: 20973144.
- [6] Shamroe CL, Comeau JM. Ponatinib: a new tyrosine kinase inhibitor for the treatment of chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia. *Ann Pharmacother.* 2013;47(11):1540–6. doi:10.1177/1060028013501144. PubMed PMID: 24265264.
- [7] Ali MA. Chronic myeloid leukemia in the era of tyrosine kinase inhibitors: an evolving paradigm of molecularly targeted therapy. *Mol Diagn Ther.* 2016;20(4):315–33. doi:10.1007/s40291-016-0208-1. PubMed PMID: 27220498.
- [8] Kinch MS, Haynesworth A, Kinch SL, Hoyer D. An overview of FDA-approved new molecular entities: 1827–2013. *Drug Discov Today.* 2014;19(8):1033–9. doi:10.1016/j.drudis.2014.03.018. PubMed PMID: 24680947.
- [9] Demain AL. Importance of microbial natural products and the need to revitalize their discovery. *J Ind Microbiol Biotechnol.* 2014;41(2):185–201. doi:10.1007/s10295-013-1325-z. PubMed PMID: 23990168.
- [10] Cushnie TP, Cushnie B, Lamb AJ. Alkaloids: an overview of their antibacterial, antibiotic-enhancing and antivirulence activities. *Int J Antimicrob Agents.* 2014;44(5):377–86. doi:10.1016/j.ijantimicag.2014.06.001. PubMed PMID: 25130096.
- [11] Kittakoop P, Mahidol C, Ruchirawat S. Alkaloids as important scaffolds in therapeutic drugs for the treatments of cancer, tuberculosis, and smoking cessation. *Curr Top Med Chem.* 2014;14(2):239–52. PubMed PMID: 24359196.
- [12] Qiu S, Sun H, Zhang AH, Xu HY, Yan GL, Han Y, et al. Natural alkaloids: basic aspects, biological roles, and future perspectives. *Chin J Nat Med.* 2014;12(6):401–6. doi:10.1016/S1875-5364(14)60063-7. PubMed PMID: 24969519.
- [13] Russo P, Frustaci A, Del Bufalo A, Fini M, Cesario A. Multitarget drugs of plants origin acting on Alzheimer's disease. *Curr Med Chem.* 2013;20(13):1686–93. PubMed PMID: 23410167.
- [14] Wei YL, Xu L, Liang Y, Xu XH, Zhao XY. Berbamine exhibits potent antitumor effects on imatinib-resistant CML cells in vitro and in vivo. *Acta Pharmacol Sin.* 2009;30(4):451–7. doi:10.1038/aps.2009.19. PubMed PMID: 19270722; PubMed Central PMCID: PMC3894842.
- [15] Pazhang Y, Ahmadian S, Mahmoudian M, Shafiezhadeh M. Berberine-induced apoptosis via decreasing the survivin protein in K562 cell line. *Med Oncol.* 2011;28(4):1577–83. doi:10.1007/s12032-010-9586-0. PubMed PMID: 20517657.
- [16] Wei YL, Xu L, Zhao XY. Mechanism related to inhibition of leukemia K562 cells by berbamine. *Zhejiang Da Xue Xue Bao Yi Xue Ban.* 2009;38(4):387–91. PubMed PMID: 19693977.

- [17] Wei YL, Liang Y, Xu L, Zhao XY. The anhway. *Anat Rec (Hoboken)*.tiproliferation effect of berbamine on k562 resistant cells by inhibiting NF-kappaB pat 2009;292(7):945–50. doi:10.1002/ar.20924. PubMed PMID: 19548306.
- [18] Jin L, Liao HJ, Zhang MY, Liu QY, Wang YF. Effect of berberine on the differentiation and apoptosis of K562 cell line. *Zhong Yao Cai*. 2009;32(3):384–8. PubMed PMID: 19565717.
- [19] Sun JR, Zhang XH, He ZW, Gu Y, Yu YZ, Fang YM, et al. The mechanism of apoptosis of chronic myeloid leukemia cells induced by the novel p210 bcr/abl inhibitor berbamine. *Zhonghua Yi Xue Za Zhi*. 2006;86(32):2246–51. PubMed PMID: 17064567.
- [20] Dong QH, Zheng S, Xu RZ, Lu Q, He L. Study on effect of berbamine on multidrug resistance leukemia K562/Adr cells. *Zhongguo Zhong Xi Yi Jie He Za Zhi*. 2004;24(9):820–2. PubMed PMID: 15495829.
- [21] Han YQ, Yuan JY, Shi YJ, Zhu Y, Wu SL. Reversal effect of berbamine on multidrug resistance of K562/A02 cells and its mechanism. *Zhongguo Shi Yan Xue Ye Xue Za Zhi*. 2003;11(6):604–8. PubMed PMID: 14706144.
- [22] Zhang YF, Xu GB, Gan YC, Xu XH, Xu RZ. Inhibitory effect of 4-chlorobenzoyl berbamine on imatinib-resistant K562 cells in vitro and in vivo. *Nan Fang Yi Ke Da Xue Xue Bao*. 2011;31(12):1997–2001. PubMed PMID: 22200699.
- [23] Zhu HJ, Wang JS, Guo QL, Jiang Y, Liu GQ. Reversal of P-glycoprotein mediated multidrug resistance in K562 cell line by a novel synthetic calmodulin inhibitor, E6. *Biol Pharm Bull*. 2005;28(10):1974–8. PubMed PMID: 16204958.
- [24] Lesueur-Ginot L, Demarquay D, Kiss R, Kasprzyk PG, Dassonneville L, Bailly C, et al. Homocamptothecin, an E-ring modified camptothecin with enhanced lactone stability, retains topoisomerase I-targeted activity and antitumor properties. *Cancer Res*. 1999;59(12):2939–43. PubMed PMID: 10383158.
- [25] Demarquay D, Huchet M, Coulomb H, Lesueur-Ginot L, Lavergne O, Camara J, et al. BN80927: a novel homocamptothecin that inhibits proliferation of human tumor cells in vitro and in vivo. *Cancer Res*. 2004;64(14):4942–9. doi:10.1158/0008-5472.CAN-03-3872. PubMed PMID: 15256467.
- [26] Song MG, Gao SM, Du KM, Xu M, Yu Y, Zhou YH, et al. Nanomolar concentration of NSC606985, a camptothecin analog, induces leukemic-cell apoptosis through protein kinase Cdelta-dependent mechanisms. *Blood*. 2005;105(9):3714–21. doi:10.1182/blood-2004-10-4011. PubMed PMID: 15671440.
- [27] Ju DS, Kim MJ, Bae JH, Song HS, Chung BS, Lee MK, et al. Camptothecin acts synergistically with imatinib and overcomes imatinib resistance through Bcr-Abl independence in human K562 cells. *Cancer Lett*. 2007;252(1):75–85. doi:10.1016/j.canlet.2006.12.013. PubMed PMID: 17223257.
- [28] Surh YJ, Lee E, Lee JM. Chemoprotective properties of some pungent ingredients present in red pepper and ginger. *Mutat Res*. 1998;402(1–2):259–67. PubMed PMID: 9675305.

- [29] Kaymaz BT, Cetintas VB, Aktan C, Kosova B. MicroRNA-520a-5p displays a therapeutic effect upon chronic myelogenous leukemia cells by targeting STAT3 and enhances the anticarcinogenic role of capsaicin. *Tumour Biol.* 2014;35(9):8733–42. doi:10.1007/s13277-014-2138-z. PubMed PMID: 24870597.
- [30] Lee SA, Ryu YS, Choi HI, Han IS. Capsaicin promotes the development of burst-forming units–erythroid (BFU-E) from mouse bone marrow cells. *Exp Mol Med.* 2007;39(3):278–83. doi:10.1038/emmm.2007.31. PubMed PMID: 17603282.
- [31] Ye LL, Cao WK, Shi YY, Deng ZK, Tao SD, Ji P, et al. Effect of homoharringtonine on expression of NF-kappaB and BCL-2 proteins in K562 cells. *Zhongguo Shi Yan Xue Ye Xue Za Zhi.* 2013;21(1):78–81. doi:10.7534/j.issn.1009-2137.2013.01.017. PubMed PMID: 23484696.
- [32] Tong H, Ren Y, Zhang F, Jin J. Homoharringtonine affects the JAK2-STAT5 signal pathway through alteration of protein tyrosine kinase phosphorylation in acute myeloid leukemia cells. *Eur J Haematol.* 2008;81(4):259–66. doi:10.1111/j.1600-0609.2008.01116.x. PubMed PMID: 18616510.
- [33] Hallock S, Tang SC, Buja LM, Trump BF, Liepins A, Weerasinghe P. Aurintricarboxylic acid inhibits protein synthesis independent, sanguinarine-induced apoptosis and oncosis. *Toxicol Pathol.* 2007;35(2):300–9. doi:10.1080/01926230701194211. PubMed PMID: 17366325.
- [34] Lerga A, Crespo P, Berciano M, Delgado MD, Canelles M, Cales C, et al. Regulation of c-Myc and Max in megakaryocytic and monocytic-macrophagic differentiation of K562 cells induced by protein kinase C modifiers: c-Myc is down-regulated but does not inhibit differentiation. *Cell Growth Differ.* 1999;10(9):639–54. PubMed PMID: 10511314.
- [35] Peng HY, Liao HF. Staurosporine induces megakaryocytic differentiation through the upregulation of JAK/Stat3 signaling pathway. *Ann Hematol.* 2011;90(9):1017–29. doi:10.1007/s00277-011-1186-3. PubMed PMID: 21331591.
- [36] Ogino T, Kobuchi H, Fujita H, Matsukawa A, Utsumi K. Erythroid and megakaryocytic differentiation of K562 erythroleukemic cells by monochloramine. *Free Radic Res.* 2014;48(3):292–302. doi:10.3109/10715762.2013.865840. PubMed PMID: 24237253.
- [37] Shao RG, Shimizu T, Pommier Y. 7-Hydroxystaurosporine (UCN-01) induces apoptosis in human colon carcinoma and leukemia cells independently of p53. *Exp Cell Res.* 1997;234(2):388–97. doi:10.1006/excr.1997.3650. PubMed PMID: 9260909.
- [38] Busby EC, Leistritz DF, Abraham RT, Karnitz LM, Sarkaria JN. The radiosensitizing agent 7-hydroxystaurosporine (UCN-01) inhibits the DNA damage checkpoint kinase hChk1. *Cancer Res.* 2000;60(8):2108–12. PubMed PMID: 10786669.
- [39] Shi DX, Ma LM, Lu YJ, Bai B. Apoptosis-inducing effect of tetrandrine and imatinib on K562/G01 cells and its related mechanism. *Zhongguo Shi Yan Xue Ye Xue Za Zhi.* 2014;22(3):723–8. doi:10.7534/j.issn.1009-2137.2014.03.028. PubMed PMID: 24989284.

- [40] Cui TY, Chen BA, Ding JH, Gao C, Cheng J, Bao W, et al. Inducing apoptosis and reversal effect of nilotinib in combination with tetrandrine on multidrug resistance of K562/A02 cell line. *Zhongguo Shi Yan Xue Ye Xue Za Zhi*. 2011;19(1):28–33. PubMed PMID: 21362216.
- [41] Xu XH, Gan YC, Xu GB, Chen T, Zhou H, Tang JF, et al. Tetrandrine citrate eliminates imatinib-resistant chronic myeloid leukemia cells in vitro and in vivo by inhibiting Bcr-Abl/beta-catenin axis. *J Zhejiang Univ Sci B*. 2012;13(11):867–74. doi:10.1631/jzus. B1200021. PubMed PMID: 23125079; PubMed Central PMCID: PMC3494025.
- [42] Zhang W, Chen BA, Jin JF, He YJ, Niu YQ. Involvement of c-Jun N-terminal kinase in reversal of multidrug resistance of human leukemia cells in hypoxia by 5-bromotetrandrine. *Leuk Lymphoma*. 2013;54(11):2506–16. doi:10.3109/10428194.2013. 776681. PubMed PMID: 23418897.
- [43] Jiang C, Li ZL, Gong P, Kang SL, Liu MS, Pei YH, et al. Five novel naphthylisoquinoline alkaloids with growth inhibitory activities against human leukemia cells HL-60, K562 and U937 from stems and leaves of *Ancistrocladus tectorius*. *Fitoterapia*. 2013;91:305–12. doi:10.1016/j.fitote.2013.09.010. PubMed PMID: 24076380.
- [44] Uadkla O, Yodkeeree S, Buayairaksa M, Meepowpan P, Nuntasae N, Limtrakul P, et al. Antiproliferative effect of alkaloids via cell cycle arrest from *Pseuduvaria rugosa*. *Pharm Biol*. 2013;51(3):400–4. doi:10.3109/13880209.2012.734314. PubMed PMID: 23406361.
- [45] Wang XD, Li CY, Jiang MM, Li D, Wen P, Song X, et al. Induction of apoptosis in human leukemia cells through an intrinsic pathway by cathachunine, a unique alkaloid isolated from *Catharanthus roseus*. *Phytomedicine*. 2016;23(6):641–53. doi:10.1016/j.phymed.2016. 03.003. PubMed PMID: 27161405.
- [46] Ikeda R, Che XF, Yamaguchi T, Ushiyama M, Zheng CL, Okumura H, et al. Cepharanthine potently enhances the sensitivity of anticancer agents in K562 cells. *Cancer Sci*. 2005;96(6):372–6. doi:10.1111/j.1349-7006.2005.00057.x. PubMed PMID: 15 958061.
- [47] Aoki S, Kong D, Matsui K, Kobayashi M. Erythroid differentiation in K562 chronic myelogenous cells induced by crambescidin 800, a pentacyclic guanidine alkaloid. *Anti-cancer Res*. 2004;24(4):2325–30. PubMed PMID: 15330179.
- [48] Wongsirisin P, Yodkeeree S, Pompimon W, Limtrakul P. Induction of G1 arrest and apoptosis in human cancer cells by crebanine, an alkaloid from *Stephania venosa*. *Chem Pharm Bull (Tokyo)*. 2012;60(10):1283–9. PubMed PMID: 22863844.
- [49] Dantas BB, Faheina-Martins GV, Couliadiati TH, Bomfim CC, da Silva Dias C, Barbosa-Filho JM, et al. Effects of curine in HL-60 leukemic cells: cell cycle arrest and apoptosis induction. *J Nat Med*. 2015;69(2):218–23. doi:10.1007/s11418-014-0881-5. PubMed PMID: 25616501.
- [50] Fu P, Kong F, Li X, Wang Y, Zhu W. Cyanogramide with a new spiro[indolinone-pyrroloimidazole] skeleton from *Actinoalloteichus cyanogriseus*. *Org Lett*. 2014;16(14):3708–11. doi:10.1021/ol501523d. PubMed PMID: 24968070.

- [51] Ge HM, Yu ZG, Zhang J, Wu JH, Tan RX. Bioactive alkaloids from endophytic *Aspergillus fumigatus*. J Nat Prod. 2009;72(4):753–5. doi:10.1021/np800700e. PubMed PMID: 19256529.
- [52] Huang RL, Chen CC, Huang YL, Ou JC, Hu CP, Chen CF, et al. Anti-tumor effects of d-dicentrine from the root of *Lindera megaphylla*. Planta Med. 1998;64(3):212–5. doi:10.1055/s-2006-957411. PubMed PMID: 9581516.
- [53] Pan X, Hartley JM, Hartley JA, White KN, Wang Z, Bligh SW. Evodiamine, a dual catalytic inhibitor of type I and II topoisomerases, exhibits enhanced inhibition against camptothecin resistant cells. Phytomedicine. 2012;19(7):618–24. doi:10.1016/j.phymed.2012.02.003. PubMed PMID: 22402246.
- [54] Gong KK, Tang XL, Liu YS, Li PL, Li GQ. Imidazole alkaloids from the South China Sea Sponge *Pericharax heteroraphis* and their cytotoxic and antiviral activities. Molecules. 2016;21(2):150. doi:10.3390/molecules21020150. PubMed PMID: 26821008.
- [55] Song QF, Qu YC, Zheng HB, Zhang GH, Lin HG, Yang JL. Differentiation of erythroleukemia K562 cells induced by piperine. Ai Zheng. 2008;27(6):571–4. PubMed PMID: 18570727.
- [56] Qing C, Zhang JS, Ding J. In vitro cytotoxicity of salvicine, a novel diterpenoid quinone. Zhongguo Yao Li Xue Bao. 1999;20(4):297–302. PubMed PMID: 10452112.
- [57] Wei G, Wang J, Du Y. Total synthesis of solamargine. Bioorg Med Chem Lett. 2011;21(10):2930–3. doi:10.1016/j.bmcl.2011.03.064. PubMed PMID: 21482107.
- [58] Sun L, Zhao Y, Li X, Yuan H, Cheng A, Lou H. A lysosomal-mitochondrial death pathway is induced by solamargine in human K562 leukemia cells. Toxicol In Vitro. 2010;24(6):1504–11. doi:10.1016/j.tiv.2010.07.013. PubMed PMID: 20647040.
- [59] Chao MW, Chen CH, Chang YL, Teng CM, Pan SL. alpha-Tomatine-mediated anti-cancer activity in vitro and in vivo through cell cycle- and caspase-independent pathways. PLoS One. 2012;7(9):e44093. doi:10.1371/journal.pone.0044093. PubMed PMID: 22970166; PubMed Central PMCID: PMC3435411.
- [60] Ganguly T, Khar A. Induction of apoptosis in a human erythroleukemic cell line K562 by tylophora alkaloids involves release of cytochrome c and activation of caspase 3. Phytomedicine. 2002;9(4):288–95. doi:10.1078/0944-7113-00146. PubMed PMID: 12120809.
- [61] Peng J, Zhang XY, Tu ZC, Xu XY, Qi SH. Alkaloids from the deep-sea-derived fungus *Aspergillus westerdijkiae* DFFSCS013. J Nat Prod. 2013;76(5):983–7. doi:10.1021/np400132m. PubMed PMID: 23701598.
- [62] Lucio AS, Almeida JR, Barbosa-Filho JM, Pita JC, Branco MV, Diniz Mde F, et al. Azaphenanthrene alkaloids with antitumoral activity from *Anaxagorea dolichocarpa* Sprague & Sandwith (Annonaceae). Molecules. 2011;16(8):7125–31. doi:10.3390/molecules16087125. PubMed PMID: 21860364.
- [63] Wang J, Wei X, Qin X, Lin X, Zhou X, Liao S, et al. Arthpyrones A-C, pyridone alkaloids from a sponge-derived fungus *Arthrimum arundinis* ZSDS1-F3. Org Lett. 2015;17(3):656–9. doi:10.1021/ol503646c. PubMed PMID: 25606827.

- [64] Song F, Ren B, Yu K, Chen C, Guo H, Yang N, et al. Quinazolin-4-one coupled with pyrrolidin-2-iminium alkaloids from marine-derived fungus *Penicillium aurantiogriseum*. *Mar Drugs*. 2012;10(6):1297–306. doi:10.3390/md10061297. PubMed PMID: 22822373; PubMed Central PMCID: PMC397440.
- [65] Zhang JR, Li PL, Tang XL, Qi X, Li GQ. Cytotoxic tetraprenylated alkaloids from the South China Sea gorgonian *Euplexaura robusta*. *Chem Biodivers*. 2012;9(10):2218–24. doi:10.1002/cbdv.201100374. PubMed PMID: 23081922.
- [66] Zhang G, Li M, Han S, Chen D, Wang Y, Ye W, et al. Induction of human chronic myeloid leukemia K562 cell apoptosis by virosecurinine and its molecular mechanism. *Mol Med Rep*. 2014;10(5):2365–71. doi:10.3892/mmr.2014.2531. PubMed PMID: 25189629; PubMed Central PMCID: PMC4214351.
- [67] Cushnie TP, Lamb AJ. Recent advances in understanding the antibacterial properties of flavonoids. *Int J Antimicrob Agents*. 2011;38(2):99–107. doi:10.1016/j.ijantimicag.2011.02.014. PubMed PMID: 21514796.
- [68] Gonzalez CA, Sala N, Rokkas T. Gastric cancer: epidemiologic aspects. *Helicobacter*. 2013;18 Suppl 1:34–8. doi:10.1111/hel.12082. PubMed PMID: 24011243.
- [69] Lotito SB, Frei B. Consumption of flavonoid-rich foods and increased plasma antioxidant capacity in humans: cause, consequence, or epiphenomenon? *Free Radic Biol Med*. 2006;41(12):1727–46. doi:10.1016/j.freeradbiomed.2006.04.033. PubMed PMID: 17157175.
- [70] Martinez-Micaelo N, Gonzalez-Abuin N, Ardevol A, Pinent M, Blay MT. Procyanidins and inflammation: molecular targets and health implications. *Biofactors*. 2012;38(4):257–65. doi:10.1002/biof.1019. PubMed PMID: 22505223.
- [71] Romagnolo DF, Selmin OI. Flavonoids and cancer prevention: a review of the evidence. *J Nutr Gerontol Geriatr*. 2012;31(3):206–38. doi:10.1080/21551197.2012.702534. PubMed PMID: 22888839.
- [72] Taylor PW, Hamilton-Miller JM, Stapleton PD. Antimicrobial properties of green tea catechins. *Food Sci Technol Bull*. 2005;2:71–81. PubMed PMID: 19844590; PubMed Central PMCID: PMC2763290.
- [73] Williams RJ, Spencer JP, Rice-Evans C. Flavonoids: antioxidants or signalling molecules? *Free Radic Biol Med*. 2004;36(7):838–49. doi:10.1016/j.freeradbiomed.2004.01.001. PubMed PMID: 15019969.
- [74] Woo HD, Kim J. Dietary flavonoid intake and smoking-related cancer risk: a meta-analysis. *PLoS One*. 2013;8(9):e75604. doi:10.1371/journal.pone.0075604. PubMed PMID: 24069431; PubMed Central PMCID: PMC3777962.
- [75] Wang Y, Miao H, Li W, Yao J, Sun Y, Li Z, et al. CXCL12/CXCR4 axis confers adriamycin resistance to human chronic myelogenous leukemia and oroxylin A improves the sensitivity of K562/ADM cells. *Biochem Pharmacol*. 2014;90(3):212–25. doi:10.1016/j.bcp.2014.05.007. PubMed PMID: 24858801.

- [76] Li X, Miao H, Zhang Y, Li W, Li Z, Zhou Y, et al. Bone marrow microenvironment confers imatinib resistance to chronic myelogenous leukemia and oroxylin A reverses the resistance by suppressing Stat3 pathway. *Arch Toxicol.* 2015;89(1):121–36. doi:10.1007/s00204-014-1226-6. PubMed PMID: 24671465.
- [77] Kawabata K, Mukai R, Ishisaka A. Quercetin and related polyphenols: new insights and implications for their bioactivity and bioavailability. *Food Funct.* 2015;6(5):1399–417. doi:10.1039/c4fo01178c. PubMed PMID: 25761771.
- [78] Shen J, Zhang WJ, Tai YC, Wong CH, Xie Z, Chen CS. Synergistic antileukemic effect of phytoestrogens and chemotherapeutic drugs on leukemic cell lines in vitro. *Zhongguo Shi Yan Xue Ye Xue Za Zhi.* 2008;16(2):276–81. PubMed PMID: 18426648.
- [79] Deora AB, Miranda MB, Rao SG. Down-modulation of P210bcr/abl induces apoptosis/differentiation in K562 leukemic blast cells. *Tumori.* 1997;83(4):756–61. PubMed PMID: 9349317.
- [80] Chen FY, Cao LF, Wan HX, Zhang MY, Cai JY, Shen LJ, et al. Quercetin enhances adriamycin cytotoxicity through induction of apoptosis and regulation of mitogen-activated protein kinase/extracellular signal-regulated kinase/c-Jun N-terminal kinase signaling in multidrug-resistant leukemia K562 cells. *Mol Med Rep.* 2015;11(1):341–8. doi:10.3892/mmr.2014.2734. PubMed PMID: 25339540.
- [81] Cai X, Chen FY, Han JY, Gu CH, Zhong H, Ouyang RR. Restorative effect of quercetin on subcellular distribution of daunorubicin in multidrug resistant leukemia cell lines K562/ADM and HL-60/ADM. *Ai Zheng.* 2004;23(12):1611–5. PubMed PMID: 15601547.
- [82] Han YQ, Cao LJ, Hao HJ, Shi YJ. Effects of quercetin on multidrug resistance and expression of related genes in human erythroleukemic K562/a cells. *Zhongguo Shi Yan Xue Ye Xue Za Zhi.* 2011;19(4):884–9. PubMed PMID: 21867607.
- [83] Philchenkov AA, Zavelevich MP, Mikhailenko VM, Kuyava LM. Apoptosis and content of mobile lipid domains in human leukemia K-562 cells induced to differentiate by quercetin or dimethyl sulfoxide. *Ukr Biokhim Zh (1999).* 2010;82(2):104–10. PubMed PMID: 20684251.
- [84] Kothan S, Dechsupa S, Leger G, Moretti JL, Vergote J, Mankhetkorn S. Spontaneous mitochondrial membrane potential change during apoptotic induction by quercetin in K562 and K562/adr cells. *Can J Physiol Pharmacol.* 2004;82(12):1084–90. doi:10.1139/y04-113. PubMed PMID: 15644950.
- [85] Elia G, Santoro MG. Regulation of heat shock protein synthesis by quercetin in human erythroleukaemia cells. *Biochem J.* 1994;300 (Pt 1):201–9. PubMed PMID: 8198534; PubMed Central PMCID: PMC1138143.
- [86] Avci CB, Yilmaz S, Dogan ZO, Saydam G, Dodurga Y, Ekiz HA, et al. Quercetin-induced apoptosis involves increased hTERT enzyme activity of leukemic cells. *Hematology.* 2011;16(5):303–7. doi:10.1179/102453311X13085644680104. PubMed PMID: 21902895.

- [87] Isoda H, Motojima H, Onaga S, Samet I, Villareal MO, Han J. Analysis of the erythroid differentiation effect of flavonoid apigenin on K562 human chronic leukemia cells. *Chem Biol Interact.* 2014;220:269–77. doi:10.1016/j.cbi.2014.07.006. PubMed PMID: 25058688.
- [88] Dong QH, Zheng S, Xu RZ, Lu QH. Baicalein selectively induce apoptosis in human leukemia K562 cells. *Yao Xue Xue Bao.* 2003;38(11):817–20. PubMed PMID: 14991992.
- [89] Adan A, Baran Y. Fisetin and hesperetin induced apoptosis and cell cycle arrest in chronic myeloid leukemia cells accompanied by modulation of cellular signaling. *Tumour Biol.* 2016;37(5):5781–95. doi:10.1007/s13277-015-4118-3. PubMed PMID: 26408178.
- [90] Tolomeo M, Grimaudo S, Di Cristina A, Pipitone RM, Dusonchet L, Meli M, et al. Galangin increases the cytotoxic activity of imatinib mesylate in imatinib-sensitive and imatinib-resistant Bcr-Abl expressing leukemia cells. *Cancer Lett.* 2008;265(2):289–97. doi:10.1016/j.canlet.2008.02.025. PubMed PMID: 18374481.
- [91] Budhraja A, Gao N, Zhang Z, Son YO, Cheng S, Wang X, et al. Apigenin induces apoptosis in human leukemia cells and exhibits anti-leukemic activity in vivo. *Mol Cancer Ther.* 2012;11(1):132–42. doi:10.1158/1535-7163.MCT-11-0343. PubMed PMID: 22084167; PubMed Central PMCID: PMC430727.
- [92] Honma Y, Okabe-Kado J, Kasukabe T, Hozumi M, Umezawa K. Inhibition of abl oncogene tyrosine kinase induces erythroid differentiation of human myelogenous leukemia K562 cells. *Jpn J Cancer Res.* 1990;81(11):1132–6. PubMed PMID: 2125038.
- [93] Marfe G, Tafani M, Indelicato M, Sinibaldi-Salimei P, Reali V, Pucci B, et al. Kaempferol induces apoptosis in two different cell lines via Akt inactivation, Bax and SIRT3 activation, and mitochondrial dysfunction. *J Cell Biochem.* 2009;106(4):643–50. doi:10.1002/jcb.22044. PubMed PMID: 19160423.
- [94] Ikegawa T, Ohtani H, Koyabu N, Juichi M, Iwase Y, Ito C, et al. Inhibition of P-glycoprotein by flavonoid derivatives in adriamycin-resistant human myelogenous leukemia (K562/ADM) cells. *Cancer Lett.* 2002;177(1):89–93. PubMed PMID: 11809535.
- [95] Ross JA, Kasum CM. Dietary flavonoids: bioavailability, metabolic effects, and safety. *Annu Rev Nutr.* 2002;22:19–34. doi:10.1146/annurev.nutr.22.111401.144957. PubMed PMID: 12055336.
- [96] Lindqvist C, Bobrowska-Hagerstrand M, Mrowczynska L, Engblom C, Hagerstrand H. Potentiation of natural killer cell activity with myricetin. *Anticancer Res.* 2014;34(8):3975–9. PubMed PMID: 25075019.
- [97] Lopez-Lazaro M, Willmore E, Austin CA. The dietary flavonoids myricetin and fisetin act as dual inhibitors of DNA topoisomerases I and II in cells. *Mutat Res.* 2010;696(1):41–7. doi:10.1016/j.mrgentox.2009.12.010. PubMed PMID: 20025993.
- [98] Li RF, Feng YQ, Chen JH, Ge LT, Xiao SY, Zuo XL. Naringenin suppresses K562 human leukemia cell proliferation and ameliorates Adriamycin-induced oxidative damage in polymorphonuclear leukocytes. *Exp Ther Med.* 2015;9(3):697–706. doi:10.3892/etm.2015.2185. PubMed PMID: 25667616; PubMed Central PMCID: PMC4316947.

- [99] Wang Y, Su M, Yin J, Zhang H. Effect of nobiletin on K562 cells xenograft in nude mice. *Zhongguo Zhong Yao Za Zhi*. 2009;34(11):1410–4. PubMed PMID: 19771874.
- [100] Nicolini F, Burmistrova O, Marrero MT, Torres F, Hernandez C, Quintana J, et al. Induction of G2/M phase arrest and apoptosis by the flavonoid tamarixetin on human leukemia cells. *Mol Carcinog*. 2014;53(12):939–50. doi:10.1002/mc.22055. PubMed PMID: 23765509.
- [101] Cao C, Liu B, Zeng C, Lu Y, Chen S, Yang L, et al. A polymethoxyflavone from *Laggera pterodonta* induces apoptosis in imatinib-resistant K562R cells via activation of the intrinsic apoptosis pathway. *Cancer Cell Int*. 2014;14(1):137. doi:10.1186/s12935-014-0137-1. PubMed PMID: 25530716; PubMed Central PMCID: PMC4272561.
- [102] Oliveira MC, de Carvalho MG, Grynberg NF, Brioso PS. A biflavonoid from *Luxemburgia nobilis* as inhibitor of DNA topoisomerases. *Planta Med*. 2005;71(6):561–3. doi:10.1055/s-2005-864159. PubMed PMID: 15971129.
- [103] Zhang SD, Shan L, Li W, Li HL, Zhang WD. Isochamaejasmin induces apoptosis in leukemia cells through inhibiting Bcl-2 family proteins. *Chin J Nat Med*. 2015;13(9):660–6. doi:10.1016/S1875-5364(15)30063-7. PubMed PMID: 26412425.
- [104] Huang XH, Xiong PC, Xiong CM, Cai YL, Wei AH, Wang JP, et al. In vitro and in vivo antitumor activity of *Macrothelypteris torresiana* and its acute/subacute oral toxicity. *Phytomedicine*. 2010;17(12):930–4. doi:10.1016/j.phymed.2010.03.006. PubMed PMID: 20381325.
- [105] Liu YL, Tang LH, Liang ZQ, You BG, Yang SL. Growth inhibitory and apoptosis inducing by effects of total flavonoids from *Lysimachia clethroides* Duby in human chronic myeloid leukemia K562 cells. *J Ethnopharmacol*. 2010;131(1):1–9. doi:10.1016/j.jep.2010.04.008. PubMed PMID: 20420897.
- [106] Zhang D, Wang D, Yu Y. Effects and mechanisms of total flavonoids of astragali radix and calycosin on inhibiting human erythroleukemia cell line K562. *Zhongguo Zhong Yao Za Zhi*. 2011;36(24):3502–5. PubMed PMID: 22368866.
- [107] Ammar RB, Neffati A, Skandrani I, Sghaier MB, Bhouiri W, Ghedira K, et al. Anti-lipid peroxidation and induction of apoptosis in the erythroleukaemic cell line K562 by extracts from (Tunisian) *Rhamnus alaternus* L. (Rhamnaceae). *Nat Prod Res*. 2011;25(11):1047–58. doi:10.1080/14786419.2010.490783. PubMed PMID: 21726127.
- [108] Ammar RB, Kilani S, Bouhlel I, Ezzi L, Skandrani I, Boubaker J, et al. Antiproliferative, antioxidant, and antimutagenic activities of flavonoid-enriched extracts from (Tunisian) *Rhamnus alaternus* L.: combination with the phytochemical composition. *Drug Chem Toxicol*. 2008;31(1):61–80. doi:10.1080/01480540701688725. PubMed PMID: 18161508.
- [109] Goker B, Caliskan C, Onur Caglar H, Kayabasi C, Balci T, Erbaykent Tepedelen B, et al. Synergistic effect of ponatinib and epigallocatechin-3-gallate induces apoptosis in chronic myeloid leukemia cells through altering expressions of cell cycle regulatory genes. *J BUON*. 2014;19(4):992–8. PubMed PMID: 25536607.

- [110] Aziz M, Karboune S. Natural antimicrobial/antioxidant agents in meat and poultry products as well as fruits and vegetables: a review. *Crit Rev Food Sci Nutr*. 2016. doi:10.1080/10408398.2016.1194256. PubMed PMID: 27437876.
- [111] da Silva e Sa Rde C, Andrade LN, de Sousa DP. Sesquiterpenes from essential oils and anti-inflammatory activity. *Nat Prod Commun*. 2015;10(10):1767–74. PubMed PMID: 26669122.
- [112] Evidente A, Kornienko A, Lefranc F, Cimmino A, Dasari R, Evidente M, et al. Sesterterpenoids with anticancer activity. *Curr Med Chem*. 2015;22(30):3502–22. PubMed PMID: 26295461; PubMed Central PMCID: PMC4955362.
- [113] Grassmann J. Terpenoids as plant antioxidants. *Vitam Horm*. 2005;72:505–35. doi:10.1016/S0083-6729(05)72015-X. PubMed PMID: 16492481.
- [114] Mukherjee N, Mukherjee S, Saini P, Roy P, Babu SP. Phenolics and terpenoids; the promising new search for anthelmintics: a critical review. *Mini Rev Med Chem*. 2015. PubMed PMID: 26586122.
- [115] Tholl D. Biosynthesis and biological functions of terpenoids in plants. *Adv Biochem Eng Biotechnol*. 2015;148:63–106. doi:10.1007/10_2014_295. PubMed PMID: 25583224.
- [116] Li H, Li M, Wang G, Shao F, Chen W, Xia C, et al. EM23, a natural sesquiterpene lactone from *Elephantopus mollis*, induces apoptosis in human myeloid leukemia cells through thioredoxin- and reactive oxygen species-mediated signaling pathways. *Front Pharmacol*. 2016;7:77. doi:10.3389/fphar.2016.00077. PubMed PMID: 27064563; PubMed Central PMCID: PMC4809879.
- [117] Zheng Y, Zhang SW, Cong HJ, Huang YJ, Xuan LJ. Caesalminaxins A-L, cassane diterpenoids from the seeds of *Caesalpinia minax*. *J Nat Prod*. 2013;76(12):2210–8. doi:10.1021/np400545v. PubMed PMID: 24303808.
- [118] Jeon JE, Liao L, Kim H, Sim CJ, Oh DC, Oh KB, et al. Cytotoxic diterpenoid pseudodimers from the Korean sponge *Phorbas gukhulensis*. *J Nat Prod*. 2013;76(9):1679–85. doi:10.1021/np400389c. PubMed PMID: 24025124.
- [119] Su D, Yang XY, Feng X, Shang MY, Cai SQ. The diterpenes ovoideal A-G from *Tirpitzia ovoidea*. *Molecules*. 2014;19(11):18966–79. doi:10.3390/molecules191118966. PubMed PMID: 25412043.
- [120] Kang YQ, Zhou JC, Fan PH, Wang SQ, Lou HX. Scapaundulin C, a novel labdane diterpenoid isolated from Chinese liverwort *Scapania undulate*, inhibits acetylcholinesterase activity. *Chin J Nat Med*. 2015;13(12):933–6. doi:10.1016/S1875-5364(15)30100-X. PubMed PMID: 26721712.
- [121] Li LM, Li GY, Li SH, Weng ZY, Xiao WL, Han QB, et al. Cytotoxic ent-kauranoids from *Isodon parvifolius*. *Chem Biodivers*. 2006;3(9):1031–8. doi:10.1002/cbdv.200690101. PubMed PMID: 17193336.

- [122] Li LM, Weng ZY, Huang SX, Pu JX, Li SH, Huang H, et al. Cytotoxic ent-kauranoids from the medicinal plant *Isodon xerophilus*. J Nat Prod. 2007;70(8):1295–301. doi:10.1021/np070205m. PubMed PMID: 17665952.
- [123] Huang SX, Pu JX, Xiao WL, Li LM, Weng ZY, Zhou Y, et al. ent-Abietane diterpenoids from *Isodon rubescens* var. *rubescens*. Phytochemistry. 2007;68(5):616–22. doi:10.1016/j.phytochem.2006.11.007. PubMed PMID: 17173940.
- [124] Wu B, He S, Wu XD, Pan YJ. Bioactive terpenes from the roots of *Chloranthus henryi*. Planta Med. 2006;72(14):1334–8. doi:10.1055/s-2006-947256. PubMed PMID: 17022005.
- [125] Li LM, Li GY, Huang SX, Li SH, Zhou Y, Xiao WL, et al. 7 α ,20-epoxy-ent-kauranoids from *Isodon parvifolius*. J Nat Prod. 2006;69(4):645–9. doi:10.1021/np0600200. PubMed PMID: 16643043.
- [126] Moosavi MA, Yazdanparast R, Sanati MH. The cytotoxic and anti-proliferative effects of 3-hydrogenkwadaphnin in K562 and jurkat cells is reduced by guanosine. J Biochem Mol Biol. 2005;38(4):391–8. PubMed PMID: 16053705.
- [127] Xiang W, Na Z, Li SH, Li ML, Li RT, Tian QE, et al. Cytotoxic diterpenoids from *Isodon enanderianus*. Planta Med. 2003;69(11):1031–5. doi:10.1055/s-2003-45151. PubMed PMID: 14735442.
- [128] Han QB, Zhao AH, Zhang JX, Lu Y, Zhang LL, Zheng QT, et al. Cytotoxic constituents of *Isodon rubescens* var. *lushiensis*. J Nat Prod. 2003;66(10):1391–4. doi:10.1021/np030165w. PubMed PMID: 14575445.
- [129] Liu JJ, Liu WD, Yang HZ, Zhang Y, Fang ZG, Liu PQ, et al. Inactivation of PI3k/Akt signaling pathway and activation of caspase-3 are involved in tanshinone I-induced apoptosis in myeloid leukemia cells in vitro. Ann Hematol. 2010;89(11):1089–97. doi:10.1007/s00277-010-0996-z. PubMed PMID: 20512574.
- [130] Li LM, Li GY, Ding LS, Yang LB, Zhao Y, Pu JX, et al. ent-Kaurane Diterpenoids from *Isodon nervosus*. J Nat Prod. 2008;71(4):684–8. doi:10.1021/np800027a. PubMed PMID: 18345641.
- [131] Lai YY, Chen LC, Wu CF, Lu MC, Wen ZH, Wu TY, et al. New cytotoxic 24-homoscalarane sesterterpenoids from the sponge *Ircinia felix*. Int J Mol Sci. 2015;16(9):21950–8. doi:10.3390/ijms160921950. PubMed PMID: 26378524; PubMed Central PMCID: PMC4613290.
- [132] Song J, Jeong W, Wang N, Lee HS, Sim CJ, Oh KB, et al. Scalarane sesterterpenes from the sponge *Smenospongia* sp. J Nat Prod. 2008;71(11):1866–71. doi:10.1021/np8003694. PubMed PMID: 18973387.
- [133] Wang N, Song J, Jang KH, Lee HS, Li X, Oh KB, et al. Sesterterpenoids from the sponge *Sarcotragus* sp. J Nat Prod. 2008;71(4):551–7. doi:10.1021/np0780147. PubMed PMID: 18341287.

- [134] Rho JR, Lee HS, Shin HJ, Ahn JW, Kim JY, Sim CJ, et al. New sesterterpenes from the sponge *Smenospongia* sp. J Nat Prod. 2004;67(10):1748–51. doi:10.1021/np040103l. PubMed PMID: 15497955.
- [135] Ma QY, Luo Y, Huang SZ, Guo ZK, Dai HF, Zhao YX. Lanostane triterpenoids with cytotoxic activities from the fruiting bodies of *Ganoderma hainanense*. J Asian Nat Prod Res. 2013;15(11):1214–9. doi:10.1080/10286020.2013.820712. PubMed PMID: 23909866.
- [136] Huang D, Qing S, Zeng G, Wang Y, Guo H, Tan J, et al. Lipophilic components from Fructus Vitis Negundo and their anti-tumor activities. Fitoterapia. 2013;86:144–8. doi:10.1016/j.fitote.2013.02.009. PubMed PMID: 23454672.
- [137] Yan J, Zhou ZY, Zhang M, Wang J, Dai HF, Tan JW. New serratene triterpenoids from *Palhinhaea cernua* and their cytotoxic activity. Planta Med. 2012;78(12):1387–91. doi:10.1055/s-0032-1314999. PubMed PMID: 22753038.
- [138] Wang LL, Li ZL, Song DD, Sun L, Pei YH, Jing YK, et al. Two novel triterpenoids with antiproliferative and apoptotic activities in human leukemia cells isolated from the resin of *Garcinia hanburyi*. Planta Med. 2008;74(14):1735–40. doi:10.1055/s-2008-1081355. PubMed PMID: 18781544.
- [139] Lei C, Huang SX, Chen JJ, Yang LB, Xiao WL, Chang Y, et al. Propindilactones E-J, schiartane nortriterpenoids from *Schisandra propinqua* var. *propinqua*. J Nat Prod. 2008;71(7):1228–32. doi:10.1021/np8001699. PubMed PMID: 18578539.
- [140] Pu JX, Huang SX, Ren J, Xiao WL, Li LM, Li RT, et al. Isolation and structure elucidation of kadlongilactones C-F from *Kadsura longipedunculata* by NMR spectroscopy and DFT computational methods. J Nat Prod. 2007;70(11):1706–11. doi:10.1021/np070247a. PubMed PMID: 17970593.
- [141] Lee I, Yoo JK, Na M, Min BS, Lee J, Yun BS, et al. Cytotoxicity of triterpenes isolated from *Aceriphyllum rossii*. Chem Pharm Bull (Tokyo). 2007;55(9):1376–8. PubMed PMID: 17827765.
- [142] Parra-Delgado H, Garcia-Pillado F, Sordo M, Ramirez-Apan T, Martinez-Vazquez M, Ostrosky-Wegman P. Evaluation of the cytotoxicity, cytostaticity and genotoxicity of argentatins A and B from *Parthenium argentatum* (Gray). Life Sci. 2005;77(22):2855–65. doi:10.1016/j.lfs.2005.05.024. PubMed PMID: 15979099.
- [143] Lu Z, Jin Y, Qiu L, Lai Y, Pan J. Celastrol, a novel HSP90 inhibitor, depletes Bcr-Abl and induces apoptosis in imatinib-resistant chronic myelogenous leukemia cells harboring T315I mutation. Cancer Lett. 2010;290(2):182–91. doi:10.1016/j.canlet.2009.09.006. PubMed PMID: 19819619.
- [144] Huang KJ, Chen YC, El-Shazly M, Du YC, Su JH, Tsao CW, et al. 5-Episinuleptolide acetate, a norcembranoidal diterpene from the formosan soft coral *Sinularia* sp., induces leukemia cell apoptosis through Hsp90 inhibition. Molecules. 2013;18(3):2924–33. doi:10.3390/molecules18032924. PubMed PMID: 23459302.

- [145] Huffman J, Gerber R, Du L. Recent advancements in the biosynthetic mechanisms for polyketide-derived mycotoxins. *Biopolymers*. 2010;93(9):764–76. doi:10.1002/bip.21483. PubMed PMID: 20578001; PubMed Central PMCID: PMCPMC2894268.
- [146] Chen XW, Li CW, Cui CB, Hua W, Zhu TJ, Gu QQ. Nine new and five known polyketides derived from a deep sea-sourced *Aspergillus* sp. 16–02–1. *Mar Drugs*. 2014;12(6):3116–37. doi:10.3390/md12063116. PubMed PMID: 24871461; PubMed Central PMCID: PMCPMC4071568.
- [147] Stachel SJ, Lee CB, Spassova M, Chappell MD, Bornmann WG, Danishefsky SJ, et al. On the interactivity of complex synthesis and tumor pharmacology in the drug discovery process: total synthesis and comparative in vivo evaluations of the 15-aza epothilones. *J Org Chem*. 2001;66(12):4369–78. PubMed PMID: 11397179.
- [148] Nimmanapalli R, O'Bryan E, Bhalla K. Geldanamycin and its analogue 17-allylamino-17-demethoxygeldanamycin lowers Bcr-Abl levels and induces apoptosis and differentiation of Bcr-Abl-positive human leukemic blasts. *Cancer Res*. 2001;61(5):1799–804. PubMed PMID: 11280726.
- [149] Harms H, Orlikova B, Ji S, Nesaei-Mosaferan D, Konig GM, Diederich M. Epipolythiodiketopiperazines from the marine derived Fungus *Dichotomomyces cejpui* with NF-kappaB inhibitory potential. *Mar Drugs*. 2015;13(8):4949–66. doi:10.3390/md13084949. PubMed PMID: 26258781; PubMed Central PMCID: PMCPMC4557009.
- [150] Hou J, Liu P, Qu H, Fu P, Wang Y, Wang Z, et al. Gilvocarcin HE: a new polyketide glycoside from *Streptomyces* sp. *J Antibiot (Tokyo)*. 2012;65(10):523–6. doi:10.1038/ja.2012.61. PubMed PMID: 22854339.
- [151] Morceau F, Buck I, Dicato M, Diederich M. Radicicol-mediated inhibition of Bcr-Abl in K562 cells induced p38-MAPK dependent erythroid differentiation and PU.1 down-regulation. *Biofactors*. 2008;34(4):313–29. doi:10.3233/BIO-2009-1085. PubMed PMID: 19850986.
- [152] Scherlach K, Partida-Martinez LP, Dahse HM, Hertweck C. Antimitotic rhizoxin derivatives from a cultured bacterial endosymbiont of the rice pathogenic fungus *Rhizopus microsporus*. *J Am Chem Soc*. 2006;128(35):11529–36. doi:10.1021/ja062953o. PubMed PMID: 16939276.
- [153] Ben-Califa N, Bishara A, Kashman Y, Neumann D, Salarin C, a member of the salarin superfamily of marine compounds, is a potent inducer of apoptosis. *Invest New Drugs*. 2012;30(1):98–104. doi:10.1007/s10637-010-9521-4. PubMed PMID: 20734109.
- [154] Bishara A, Rudi A, Goldberg I, Akinin M, Neumann D, Ben-Califa N, et al. Tausalarin C: a new bioactive marine sponge-derived nitrogenous bismacrolide. *Org Lett*. 2009;11(16):3538–41. doi:10.1021/ol9011019. PubMed PMID: 19627102.
- [155] Ferreira EA, Reigada JB, Correia MV, Young MC, Guimaraes EF, Franchi GC, Jr., et al. Antifungal and cytotoxic 2-acylcyclohexane-1,3-diones from *Peperomia alata* and *P. trineura*. *J Nat Prod*. 2014;77(6):1377–82. doi:10.1021/np500130x. PubMed PMID: 24905499.

- [156] Adlercreutz H. Lignans and human health. *Crit Rev Clin Lab Sci.* 2007;44(5–6):483–525. doi:10.1080/10408360701612942. PubMed PMID: 17943494.
- [157] Wang L, Zhao F, Liu K. Induction of apoptosis of the human leukemia cells by arctigenin and its mechanism of action. *Yao Xue Xue Bao.* 2008;43(5):542–7. PubMed PMID: 18717345.
- [158] Pradheepkumar CP, Panneerselvam N, Shanmugam G. Cleistanthin A causes DNA strand breaks and induces apoptosis in cultured cells. *Mutat Res.* 2000;464(2):185–93. PubMed PMID: 10648905.
- [159] Wang TX, Shi XY, Cong Y, Wang SG, Wang YY, Zhang ZQ. Reversal of multidrug resistance by 5,5'-dimethoxylariciresinol-4-O-beta-D-glucoside in doxorubicin-resistant human leukemia K562/DOX. *Indian J Pharmacol.* 2013;45(6):597–602. doi:10.4103/0253-7613.121371. PubMed PMID: 24347768; PubMed Central PMCID: PMC3847250.
- [160] Luo Y, Xu Y, Chen L, Luo H, Peng C, Fu J, et al. Preparative purification of anti-tumor derivatives of honokiol by high-speed counter-current chromatography. *J Chromatogr A.* 2008;1178(1–2):160–5. doi:10.1016/j.chroma.2007.11.072. PubMed PMID: 18082756.
- [161] Luo J, Kong W, Yang M. HJC, a new aryl-naphthalene lignan isolated from *Justicia procumbens*, causes apoptosis and caspase activation in K562 leukemia cells. *J Pharmacol Sci.* 2014;125(4):355–63. PubMed PMID: 25141923.
- [162] Yang BH, Zhang WD, Liu RH, Li TZ, Zhang C, Zhou Y, et al. Lignans from bark of *Larix olgensis* var. *koreana*. *J Nat Prod.* 2005;68(8):1175–9. doi:10.1021/np058022s. PubMed PMID: 16124756.
- [163] Youn UJ, Chen QC, Jin WY, Lee IS, Kim HJ, Lee JP, et al. Cytotoxic lignans from the stem bark of *Magnolia officinalis*. *J Nat Prod.* 2007;70(10):1687–9. doi:10.1021/np070388c. PubMed PMID: 17918910.
- [164] Guclu-Ustundag O, Mazza G. Saponins: properties, applications and processing. *Crit Rev Food Sci Nutr.* 2007;47(3):231–58. doi:10.1080/10408390600698197. PubMed PMID: 17453922.
- [165] Podolak I, Galanty A, Sobolewska D. Saponins as cytotoxic agents: a review. *Phytochem Rev.* 2010;9(3):425–74. doi:10.1007/s11101-010-9183-z. PubMed PMID: 20835386; PubMed Central PMCID: PMC2928447.
- [166] Nguyen VT, Darbour N, Bayet C, Doreau A, Raad I, Phung BH, et al. Selective modulation of P-glycoprotein activity by steroidal saponins from *Paris polyphylla*. *Fitoterapia.* 2009;80(1):39–42. doi:10.1016/j.fitote.2008.09.010. PubMed PMID: 18940238.
- [167] Zhou Y, Yang J, Peng L, Li Y, Chen W. Two novel saponins of 20, 26-epoxy derivatives of pseudojujubogenin from the seeds of *Hovenia trichocarpa*. *Fitoterapia.* 2013;87:65–8. doi:10.1016/j.fitote.2013.03.014. PubMed PMID: 23529014.
- [168] Lu YN, Cui P, Tian XQ, Lou LG, Fan CQ. Unusual cytotoxic steroidal saponins from the gorgonian *Astrogorgia dumbea*. *Planta Med.* 2016;82(9–10):882–7. doi:10.1055/s-0042-106168. PubMed PMID: 27352300.

- [169] Shen P, Wang SL, Liu XK, Yang CR, Cai B, Yao XS. Steroidal saponins from rhizomes of *Tupistra wattii* Hook. f. Chem Pharm Bull (Tokyo). 2003;51(3):305–8. PubMed PMID: 12612416.
- [170] Ye B, Yang J, Li J, Niu T, Wang S. In vitro and in vivo antitumor activities of tenacissoside C from *Marsdenia tenacissima*. Planta Med. 2014;80(1):29–38. doi:10.1055/s-0033-1360128. PubMed PMID: 24338554.
- [171] Huang LJ, Wang B, Zhang JX, Yan C, Mu SZ, Hao XJ. Studies on cytotoxic pregnane sapogenins from *Cynanchum wilfordii*. Fitoterapia. 2015;101:107–16. doi:10.1016/j.fitote.2014.10.014. PubMed PMID: 25451793.
- [172] Fan Y, Guo DY, Song Q, Li T. Effect of total saponin of aralia taibaiensis on proliferation of leukemia cells. Zhong Yao Cai. 2013;36(4):604–7. PubMed PMID: 24134011.
- [173] Chow LM, Chui CH, Tang JC, Teo IT, Lau FY, Cheng GY, et al. *Gleditsia sinensis* fruit extract is a potential chemotherapeutic agent in chronic and acute myelogenous leukemia. Oncol Rep. 2003;10(5):1601–7. PubMed PMID: 12883747.
- [174] Liu M, Zhao X, Xiao L, Liu G, Liu H, Wang X, et al. Cytotoxicity of the compounds isolated from *Pulsatilla chinensis* saponins and apoptosis induced by 23-hydroxybetulinic acid. Pharm Biol. 2015;53(1):1–9. doi:10.3109/13880209.2014.907323. PubMed PMID: 25026337.
- [175] Song J, Jeon JE, Won TH, Sim CJ, Oh DC, Oh KB, et al. New cyclic cystine bridged peptides from the sponge *Suberites waedoensis*. Mar Drugs. 2014;12(5):2760–70. doi:10.3390/md12052760. PubMed PMID: 24824023; PubMed Central PMCID: PMC4052314.
- [176] Woo JK, Jeon JE, Kim CK, Sim CJ, Oh DC, Oh KB, et al. Gombamide A, a cyclic thiopeptide from the sponge *Clathria gombawuiensis*. J Nat Prod. 2013;76(7):1380–3. doi:10.1021/np4003367. PubMed PMID: 23799303.
- [177] Li GY, Liu JZ, Zhang B, Yang M, Chen SG, Hou M, et al. Tegillarca granosa extract Haishengsu (HSS) suppresses expression of mdr1, BCR/ABL and sorcin in drug-resistant K562/ADM tumors in mice. Adv Med Sci. 2013;58(1):112–7. doi:10.2478/v10039-012-0069-8. PubMed PMID: 23729583.
- [178] Li GY, Liu JZ, Chen SG, Zhang B, Wang CB, Wang LX. Tegillarca granosa extract Haishengsu inhibits the expression of P-glycoprotein and induces apoptosis in drug-resistant K562/ADM cells. Pharm Biol. 2010;48(5):529–33. doi:10.3109/13880200903176620. PubMed PMID: 20645795.
- [179] Li GY, Liu JZ, Yu XM, Chen SF, Zhang B, Zhang WF, et al. Effect of a seashell protein Haishengsu on cell growth and expression of apoptosis genes in leukemia K562 cells. Clin Invest Med. 2008;31(4):E218–21. PubMed PMID: 18682046.
- [180] Lee HS, Rho JR, Sim CJ, Shin J. New acetylenic acids from a sponge of the genus Stelletta. J Nat Prod. 2003;66(4):566–8. doi:10.1021/np020345q. PubMed PMID: 12713419.

- [181] Peng K, Mei WL, Zhao YX, Tan LH, Wang QH, Dai HF. A novel degraded sesquiterpene from the fresh stem of *Aquilaria sinensis*. J Asian Nat Prod Res. 2011;13(10):951–5. doi:10.1080/10286020.2011.598860. PubMed PMID: 21972811.
- [182] Sreekanth D, Arunasree MK, Roy KR, Chandramohan Reddy T, Reddy GV, Reddanna P. Betanin a betacyanin pigment purified from fruits of *Opuntia ficus-indica* induces apoptosis in human chronic myeloid leukemia Cell line-K562. Phytomedicine. 2007;14(11):739–46. doi:10.1016/j.phymed.2007.03.017. PubMed PMID: 17482444.
- [183] Xu R, Xie HQ, Deng LL, Zhang JX, Yang FM, Liu JH, et al. A new bufadienolide with cytotoxic activity from the Chinese traditional drug Ch'an Su. Chin J Nat Med. 2014;12(8):623–7. doi:10.1016/S1875-5364(14)60095-9. PubMed PMID: 25156289.
- [184] Jiang HY, Wang CF, Fan L, Yang K, Feng JB, Geng ZF, et al. Cytotoxic constituents from the stems of *Clausena lansium* (Lour.) Skeels. Molecules. 2013;18(9):10768–75. doi:10.3390/molecules180910768. PubMed PMID: 24005969.
- [185] Dai HF, Gan YJ, Que DM, Wu J, Wen ZC, Mei WL. Two new cytotoxic cardenolides from the latex of *Antiaris toxicaria*. J Asian Nat Prod Res. 2009;11(9):832–7. doi:10.1080/10286020903164285. PubMed PMID: 20183332.
- [186] Thanh PN, Jin W, Song G, Bae K, Kang SS. Cytotoxic coumarins from the root of *Angelica dahurica*. Arch Pharm Res. 2004;27(12):1211–5. PubMed PMID: 15646793.
- [187] Reyes-Chilpa R, Estrada-Muniz E, Apan TR, Amekraz B, Aumelas A, Jankowski CK, et al. Cytotoxic effects of mammea type coumarins from *Calophyllum brasiliense*. Life Sci. 2004;75(13):1635–47. doi:10.1016/j.lfs.2004.03.017. PubMed PMID: 15261767.
- [188] Gomez-Verjan JC, Estrella-Parra EA, Gonzalez-Sanchez I, Vazquez-Martinez ER, Vergara-Castaneda E, Cerbon MA, et al. Molecular mechanisms involved in the cytotoxicity induced by coumarins from *Calophyllum brasiliense* in K562 leukaemia cells. J Pharm Pharmacol. 2014;66(8):1189–95. doi:10.1111/jphp.12245. PubMed PMID: 24673519.
- [189] Ge YQ, Cheng RB, Yang B, Huang Z, Chen Z. Effect of cryptotanshinone on imatinib sensitivity and P-glycoprotein expression of chronic myeloid leukemia cells. Zhongguo Zhong Yao Za Zhi. 2015;40(12):2389–95. PubMed PMID: 26591531.
- [190] Ge Y, Yang B, Xu X, Dai Q, Chen Z, Cheng R. Cryptotanshinone acts synergistically with imatinib to induce apoptosis of human chronic myeloid leukemia cells. Leuk Lymphoma. 2015;56(3):730–8. doi:10.3109/10428194.2014.928934. PubMed PMID: 24884318.
- [191] Wang HM, Zhang L, Liu J, Yang ZL, Zhao HY, Yang Y, et al. Synthesis and anti-cancer activity evaluation of novel prenylated and geranylated chalcone natural products and their analogs. Eur J Med Chem. 2015;92:439–48. doi:10.1016/j.ejmech.2015.01.007. PubMed PMID: 25590864.
- [192] Chen G, Cui CB, Qi AD, Li CW, Tao ZW, Ren R. Polyanthumin, a novel cyclobutane chalcone trimmer from *Memecylon polyanthum*. J Asian Nat Prod Res. 2015;17(2):170–7. doi:10.1080/10286020.2014.945439. PubMed PMID: 25434469.

- [193] Rajalekshmi DS, Kabeer FA, Madhusoodhanan AR, Bahulayan AK, Prathapan R, Prakasan N, et al. Anticancer activity studies of cubebin isolated from *Piper cubeba* and its synthetic derivatives. *Bioorg Med Chem Lett*. 2016;26(7):1767–71. doi:10.1016/j.bmcl.2016.02.041. PubMed PMID: 26916436.
- [194] Huang YC, Guh JH, Teng CM. Denbinobin-mediated anticancer effect in human K562 leukemia cells: role in tubulin polymerization and Bcr-Abl activity. *J Biomed Sci*. 2005;12(1):113–21. doi:10.1007/s11373-004-8171-y. PubMed PMID: 15864744.
- [195] Bhouri W, Skandrani I, Sghair MB, Franca MG, Ghedira K, Ghedira LC. Digallic acid from *Pistascia lentiscus* fruits induces apoptosis and enhances antioxidant activities. *Phytother Res*. 2012;26(3):387–91. doi:10.1002/ptr.3540. PubMed PMID: 21780210.
- [196] Chen Y, Li Y, Qing C, Zhang Y, Wang L, Liu Y. 1,4,5-Trihydroxy-7-methoxy-9H-fluoren-9-one, a new cytotoxic compound from *Dendrobium chrysotoxum*. *Food Chem*. 2008;108(3):973–6. doi:10.1016/j.foodchem.2007.12.007. PubMed PMID: 26065760.
- [197] Liao B, Ge RY, Chen X, Huangfu ZP, Qi Y, Song YP, et al. Synergistic reversal effect of Chinese medicine compound FFJZ combined with cyclosporine A on multidrug resistance of leukemia K562/VCR cell line. *Zhongguo Shi Yan Xue Ye Xue Za Zhi*. 2007;15(4):752–5. PubMed PMID: 17708797.
- [198] Wang KW, Ju XY, Zhang L, Wang W, Shen LQ. A novel C27-steroidal glycoside sulfate from *Liriope graminifolia*. *Yao Xue Xue Bao*. 2012;47(5):619–23. PubMed PMID: 22812006.
- [199] Trifunovic S, Vajs V, Juranic Z, Zizak Z, Tesevic V, Macura S, et al. Cytotoxic constituents of *Achillea clavennae* from Montenegro. *Phytochemistry*. 2006;67(9):887–93. doi:10.1016/j.phytochem.2006.02.026. PubMed PMID: 16616262.
- [200] Lv C, Yan X, Tu Q, Di Y, Yuan C, Fang X, et al. Isolation and asymmetric total synthesis of perforanoid A. *Angew Chem Int Ed Engl*. 2016;55(26):7539–43. doi:10.1002/anie.201602783. PubMed PMID: 27167098.
- [201] Aburai N, Esumi Y, Koshino H, Nishizawa N, Kimura K. Inhibitory activity of linoleic acid isolated from proso and Japanese millet toward histone deacetylase. *Biosci Biotechnol Biochem*. 2007;71(8):2061–4. doi:10.1271/bbb.70068. PubMed PMID: 17690455.
- [202] Taher M, Susanti D, Rezali MF, Zohri FS, Ichwan SJ, Alkhamaiseh SI, et al. Apoptosis, antimicrobial and antioxidant activities of phytochemicals from *Garcinia malaccensis* Hk. f. *Asian Pac J Trop Med*. 2012;5(2):136–41. doi:10.1016/S1995-7645(12)60012-1. PubMed PMID: 22221758.
- [203] Chen JJ, Long ZJ, Xu DF, Xiao RZ, Liu LL, Xu ZF, et al. Inhibition of autophagy augments the anticancer activity of alpha-mangostin in chronic myeloid leukemia cells. *Leuk Lymphoma*. 2014;55(3):628–38. doi:10.3109/10428194.2013.802312. PubMed PMID: 23734655.
- [204] Mei WL, Han Z, Cui HB, Zhao YX, Deng YY, Dai HF. A new cytotoxic iridoid from *Callicarpa nudiflora*. *Nat Prod Res*. 2010;24(10):899–904. doi:10.1080/14786410802267544. PubMed PMID: 19753502.

- [205] Yi J, Chen J, Sun J, Wei H, Shi J. Effect of parthenolide on leukemia K562 cells and its leukemia stem cells. *Zhongguo Zhong Yao Za Zhi*. 2010;35(2):219–22. PubMed PMID: 20394299.
- [206] Sanchez-Torres LE, Torres-Martinez JA, Godinez-Victoria M, Omar JM, Velasco-Bejarano B. Perezzone and its isomer isoperezzone induce caspase-dependent and caspase-independent cell death. *Phytomedicine*. 2010;17(8–9):614–20. doi:10.1016/j.phymed.2009.12.011. PubMed PMID: 20089388.
- [207] Elsebai MF, Ghabbour HA, Mehiri M. Unusual nitrogenous phenalenone derivatives from the marine-derived fungus *Coniothyrium cereale*. *Molecules*. 2016;21(2):178. doi:10.3390/molecules21020178. PubMed PMID: 26840293.
- [208] Wu L, Li Q, Liu Y. Polyphyllin D induces apoptosis in K562/A02 cells through G2/M phase arrest. *J Pharm Pharmacol*. 2014;66(5):713–21. doi:10.1111/jphp.12188. PubMed PMID: 24325805.
- [209] Joseph MM, Aravind SR, Varghese S, Mini S, Sreelekha TT. Evaluation of antioxidant, antitumor and immunomodulatory properties of polysaccharide isolated from fruit rind of *Punica granatum*. *Mol Med Rep*. 2012;5(2):489–96. doi:10.3892/mmr.2011.638. PubMed PMID: 22012001.
- [210] Ji M, Shi Y, Lou H. Overcoming of P-glycoprotein-mediated multidrug resistance in K562/A02 cells using riccardin F and pakyonol, bisbibenzyl derivatives from liverworts. *Biosci Trends*. 2011;5(5):192–7. PubMed PMID: 22101374.
- [211] Guo DX, Xiang F, Wang XN, Yuan HQ, Xi GM, Wang YY, et al. Labdane diterpenoids and highly methoxylated bibenzyls from the liverwort *Frullania inouei*. *Phytochemistry*. 2010;71(13):1573–8. doi:10.1016/j.phytochem.2010.05.023. PubMed PMID: 20561654.
- [212] Yan YX, Sun Y, Chen JC, Wang YY, Li Y, Qiu MH. Cytotoxic steroids from *Sarcococca saligna*. *Planta Med*. 2011;77(15):1725–9. doi:10.1055/s-0030-1271101. PubMed PMID: 21590651.
- [213] Lu MC, Yang SH, Hwang SL, Lu YJ, Lin YH, Wang SR, et al. Induction of G2/M phase arrest by squamocin in chronic myeloid leukemia (K562) cells. *Life Sci*. 2006;78(20):2378–83. doi:10.1016/j.lfs.2005.09.048. PubMed PMID: 16310807.
- [214] Tseng WR, Huang CY, Tsai YY, Lin YS, Hwang TL, Su JH, et al. New cytotoxic and anti-inflammatory steroids from the soft coral *Klyxum flaccidum*. *Bioorg Med Chem Lett*. 2016;26(14):3253–7. doi:10.1016/j.bmcl.2016.05.060. PubMed PMID: 27256910.
- [215] Kim CK, Song IH, Park HY, Lee YJ, Lee HS, Sim CJ, et al. Suvanine sesterterpenes and deacyl irciniasulfonic acids from a tropical *Coscinoderma* sp. sponge. *J Nat Prod*. 2014;77(6):1396–403. doi:10.1021/np500156n. PubMed PMID: 24828374.
- [216] Ji M, Choi J, Lee J, Lee Y. Induction of apoptosis by ar-turmerone on various cell lines. *Int J Mol Med*. 2004;14(2):253–6. PubMed PMID: 15254774.

- [217] Woo JK, Kim CK, Ahn CH, Oh DC, Oh KB, Shin J. Additional sesterterpenes and a nortriterpene saponin from the sponge *Clathria gombawuiensis*. J Nat Prod. 2015;78(2):218–24. doi:10.1021/np500753q. PubMed PMID: 25634623.
- [218] Dai HF, Gan YJ, Que DM, Wu J, Wen ZC, Mei WL. A new cytotoxic 19-nor-cardenolide from the latex of *Antiaris toxicaria*. Molecules. 2009;14(9):3694–9. doi:10.3390/molecules14093694. PubMed PMID: 19783952.
- [219] Chen F, Liu Y, Wang S, Guo X, Shi P, Wang W, et al. Triptolide, a Chinese herbal extract, enhances drug sensitivity of resistant myeloid leukemia cell lines through downregulation of HIF-1 α and Nrf2. Pharmacogenomics. 2013;14(11):1305–17. doi:10.2217/pgs.13.122. PubMed PMID: 23930677.
- [220] Ghoneim MM, Ma G, El-Hela AA, Mohammad AE, Kottob S, El-Ghaly S, et al. Biologically active secondary metabolites from *Asphodelus microcarpus*. Nat Prod Commun. 2013;8(8):1117–9. PubMed PMID: 24079182.
- [221] Pan Y, Wang X, Hu X. Cytotoxic withanolides from the flowers of *Datura metel*. J Nat Prod. 2007;70(7):1127–32. doi:10.1021/np070096b. PubMed PMID: 17583953.
- [222] Liu MJ, Wang Z, Li HX, Wu RC, Liu YZ, Wu QY. Mitochondrial dysfunction as an early event in the process of apoptosis induced by woodfordin I in human leukemia K562 cells. Toxicol Appl Pharmacol. 2004;194(2):141–55. PubMed PMID: 14736495.
- [223] Han QB, Wang YL, Yang L, Tso TF, Qiao CF, Song JZ, et al. Cytotoxic polyprenylated xanthenes from the resin of *Garcinia hanburyi*. Chem Pharm Bull (Tokyo). 2006;54(2):265–7. PubMed PMID: 16462081.
- [224] Han QB, Xiang W, Li RT, Li ML, Li SW, Sun HD. Cytotoxic ent-kaurane diterpenoids from *Isodon rubescens* var. *rubescens*. Planta Med. 2004;70(3):269–72. doi:10.1055/s-2004-818922. PubMed PMID: 15114509.
- [225] Chen XQ, Li Y, Li KZ, Peng LY, He J, Wang K, et al. Spirocyclic acylphloroglucinol derivatives from *Hypericum bearii*. Chem Pharm Bull (Tokyo). 2011;59(10):1250–3. PubMed PMID: 21963634.
- [226] Umebayashi C, Yamamoto N, Nakao H, Toi Y, Chikahisa-Muramatsu L, Kanemaru K, et al. Flow cytometric estimation of cytotoxic activity of rhodexin A isolated from *Rhodea japonica* in human leukemia K562 cells. Biol Pharm Bull. 2003;26(5):627–30. PubMed PMID: 12736502.
- [227] Anuchapreeda S, Thanarattanakorn P, Sittipreechacharn S, Chanarat P, Limtrakul P. Curcumin inhibits WT1 gene expression in human leukemic K562 cells. Acta Pharmacol Sin. 2006;27(3):360–6. doi:10.1111/j.1745-7254.2006.00291.x. PubMed PMID: 16490174.
- [228] Giommarelli C, Zuco V, Favini E, Pisano C, Dal Piaz F, De Tommasi N, et al. The enhancement of antiproliferative and proapoptotic activity of HDAC inhibitors by curcumin is mediated by Hsp90 inhibition. Cell Mol Life Sci. 2010;67(6):995–1004. doi:10.1007/s00018-009-0233-x. PubMed PMID: 20039095.

- [229] Shi X, Chen X, Li X, Lan X, Zhao C, Liu S, et al. Gambogic acid induces apoptosis in imatinib-resistant chronic myeloid leukemia cells via inducing proteasome inhibition and caspase-dependent Bcr-Abl downregulation. *Clin Cancer Res.* 2014;20(1):151–63. doi:10.1158/1078-0432.CCR-13-1063. PubMed PMID: 24334603; PubMed Central PMCID: PMC3938960.
- [230] Zhang L, Yi Y, Chen J, Sun Y, Guo Q, Zheng Z, et al. Gambogic acid inhibits Hsp90 and deregulates TNF- α /NF- κ B in HeLa cells. *Biochem Biophys Res Commun.* 2010;403(3–4):282–7. doi:10.1016/j.bbrc.2010.11.018. PubMed PMID: 21074517.
- [231] Schillaci D, Venturella F, Venuti F, Plescia F. Antimicrobial and antiproliferative activity of *Peucedanum nebrodense* (Guss.) Strohl. *J Ethnopharmacol.* 2003;87(1):99–101. PubMed PMID: 12787961.
- [232] Chang JS, Chiang LC, Hsu FF, Lin CC. Chemoprevention against hepatocellular carcinoma of *Cornus officinalis* in vitro. *Am J Chin Med.* 2004;32(5):717–25. doi:10.1142/S0192415X04002296. PubMed PMID: 15633807.
- [233] Koschek PR, Alviano DS, Alviano CS, Gattass CR. The husk fiber of *Cocos nucifera* L. (Palmae) is a source of anti-neoplastic activity. *Braz J Med Biol Res.* 2007;40(10):1339–43. PubMed PMID: 17713650.
- [234] Mishra KP, Padwad YS, Dutta A, Ganju L, Sairam M, Banerjee PK, et al. Aqueous extract of *Rhodiola imbricata* rhizome inhibits proliferation of an erythroleukemic cell line K-562 by inducing apoptosis and cell cycle arrest at G2/M phase. *Immunobiology.* 2008;213(2):125–31. doi:10.1016/j.imbio.2007.07.003. PubMed PMID: 18241696.
- [235] Park YK, Do YR, Jang BC. Apoptosis of K562 leukemia cells by *Abnobia viscum* F(R), a European mistletoe extract. *Oncol Rep.* 2012;28(6):2227–32. doi:10.3892/or.2012.2026. PubMed PMID: 22972372.
- [236] Wang T, Yuan Y, Wang J, Han C, Chen G. Anticancer activities of constituents from the stem of *Polyalthia rumphii*. *Pak J Pharm Sci.* 2012;25(2):353–6. PubMed PMID: 22459461.
- [237] Ravi A, Mallika A, Sama V, Begum AS, Khan RS, Reddy BM. Antiproliferative activity and standardization of *Tecomella undulata* bark extract on K562 cells. *J Ethnopharmacol.* 2011;137(3):1353–9. doi:10.1016/j.jep.2011.07.067. PubMed PMID: 21843623.
- [238] Rizzo LY, Longato GB, Ruiz AL, Tinti SV, Possenti A, Vendramini-Costa DB, et al. In vitro, in vivo and in silico analysis of the anticancer and estrogen-like activity of guava leaf extracts. *Curr Med Chem.* 2014;21(20):2322–30. PubMed PMID: 24438525.
- [239] Tayarani-Najaran Z, Sareban M, Gholami A, Emami SA, Mojarreb M. Cytotoxic and apoptotic effects of different extracts of *Artemisia turanica* Krasch. on K562 and HL-60 cell lines. *Sci World J.* 2013;2013:628073. doi:10.1155/2013/628073. PubMed PMID: 24288497; PubMed Central PMCID: PMC3830890.
- [240] Teh SS, Ee GC, Mah SH, Yong YK, Lim YM, Rahmani M, et al. In vitro cytotoxic, antioxidant, and antimicrobial activities of *Mesua beccariana* (Baill.) Kosterm., *Mesua*

- ferrea* Linn., and *Mesua congestiflora* extracts. Biomed Res Int. 2013;2013:517072. doi:10.1155/2013/517072. PubMed PMID: 24089682; PubMed Central PMCID: PMCPMC3780478.
- [241] Ebrahimnezhad Darzi S, Amirghofran Z. Dichloromethane fraction of *Melissa officinalis* induces apoptosis by activation of intrinsic and extrinsic pathways in human leukemia cell lines. Immunopharmacol Immunotoxicol. 2013;35(3):313–20. doi:10.3109/08923973.2013.768268. PubMed PMID: 23432355.
- [242] Jin W, Shi Q, Hong C, Cheng Y, Ma Z, Qu H. Cytotoxic properties of thiophenes from *Echinops grijissi* Hance. Phytomedicine. 2008;15(9):768–74. doi:10.1016/j.phymed.2007.10.007. PubMed PMID: 18068965.
- [243] Samet I, Han J, Jlaiel L, Sayadi S, Isoda H. Olive (*Olea europaea*) leaf extract induces apoptosis and monocyte/macrophage differentiation in human chronic myelogenous leukemia K562 cells: insight into the underlying mechanism. Oxid Med Cell Longev. 2014;2014:927619. doi:10.1155/2014/927619. PubMed PMID: 24803988; PubMed Central PMCID: PMCPMC3997986.
- [244] Asmaa MJ, Al-Jamal HA, Ang CY, Asan JM, Seeni A, Johan MF. Apoptosis induction in MV4–11 and K562 human leukemic cells by *Pereskia sacharosa* (Cactaceae) leaf crude extract. Asian Pac J Cancer Prev. 2014;15(1):475–81. PubMed PMID: 24528077.
- [245] Campos JF, dos Santos UP, Macorini LF, de Melo AM, Balestieri JB, Paredes-Gamero EJ, et al. Antimicrobial, antioxidant and cytotoxic activities of propolis from *Melipona orbignyi* (Hymenoptera, Apidae). Food Chem Toxicol. 2014;65:374–80. doi:10.1016/j.fct.2014.01.008. PubMed PMID: 24412556.
- [246] Hwang YJ, Kim J, Park DS, Hwang KA. Study on the immunomodulation effect of *Isodon japonicus* extract via splenocyte function and NK anti-tumor activity. Int J Mol Sci. 2012;13(4):4880–8. doi:10.3390/ijms13044880. PubMed PMID: 22606016; PubMed Central PMCID: PMCPMC3344252.
- [247] de FNSD, Yunes RA, Schaab EH, Malheiros A, Cechinel Filho V, Franchi GC, Jr., et al. Evaluation of the anti-proliferative effect the extracts of *Allamanda blanchetti* and *A. schottii* on the growth of leukemic and endothelial cells. J Pharm Pharm Sci. 2006;9(2):200–8. PubMed PMID: 16959189.
- [248] Quispe-Mauricio A, Callacondo D, Rojas J, Zavala D, Posso M, Vaisberg A. Cytotoxic effect of *Physalis peruviana* in cell culture of colorectal and prostate cancer and chronic myeloid leukemia. Rev Gastroenterol Peru. 2009;29(3):239–46. PubMed PMID: 19898596.
- [249] Sadeghi H, Yazdanparast R. Effect of *Dendrostellera lessertii* on the intracellular alkaline phosphatase activity of four human cancer cell lines. J Ethnopharmacol. 2003;86(1):11–4. PubMed PMID: 12686435.
- [250] Tsolmon S, Han J, Isoda H. Inhibition of cell growth by *Stellera chamaejasme* extract is associated with induction of autophagy and differentiation in chronic leukemia K562

- cells. *J Biosci Bioeng.* 2010;110(2):262–8. doi:10.1016/j.jbiosc.2010.02.006. PubMed PMID: 20547324.
- [251] Cheung S, Tai J. Anti-proliferative and antioxidant properties of rosemary *Rosmarinus officinalis*. *Oncol Rep.* 2007;17(6):1525–31. PubMed PMID: 17487414.
- [252] Gao X, Zhang G, Zhou M, Luo D, Li B. Antiproliferative activity of *Goldfussia psilostachys* ethanolic extract on K562 leukemia cells. *Fitoterapia.* 2004;75(7–8):639–44. doi:10.1016/j.fitote.2004.06.008. PubMed PMID: 15567238.
- [253] Castaneda DM, Pombo LM, Uruena CP, Hernandez JF, Fiorentino S. A gallotannin-rich fraction from *Caesalpinia spinosa* (Molina) Kuntze displays cytotoxic activity and raises sensitivity to doxorubicin in a leukemia cell line. *BMC Complement Altern Med.* 2012;12:38. doi:10.1186/1472-6882-12-38. PubMed PMID: 22490328; PubMed Central PMCID: PMC3353181.
- [254] Bigovic D, Savikin K, Jankovic T, Menkovic N, Zdunic G, Stanojkovic T, et al. Antiradical and cytotoxic activity of different *Helichrysum plicatum* flower extracts. *Nat Prod Commun.* 2011;6(6):819–22. PubMed PMID: 21815418.
- [255] Amirghofran Z, Bahmani M, Azadmehr A, Javidnia K. Induction of apoptosis in leukemia cell lines by *Linum persicum* and *Euphorbia cheiradenia*. *J Cancer Res Clin Oncol.* 2006;132(7):427–32. doi:10.1007/s00432-006-0084-x. PubMed PMID: 16477442.
- [256] Amirghofran Z, Bahmani M, Azadmehr A, Javidnia K. Anticancer effects of various Iranian native medicinal plants on human tumor cell lines. *Neoplasma.* 2006;53(5):428–33. PubMed PMID: 17013538.
- [257] Soumaya KJ, Zied G, Nouha N, Mounira K, Kamel G, Genvieve FD, et al. Evaluation of in vitro antioxidant and apoptotic activities of *Cyperus rotundus*. *Asian Pac J Trop Med.* 2014;7(2):105–12. doi:10.1016/S1995-7645(14)60004-3. PubMed PMID: 24461522.
- [258] Al-Salahi OS, Ji D, Majid AM, Kit-Lam C, Abdullah WZ, Zaki A, et al. Anti-tumor activity of *Eurycoma longifolia* root extracts against K-562 cell line: in vitro and in vivo study. *PLoS One.* 2014;9(1):e83818. doi:10.1371/journal.pone.0083818. PubMed PMID: 24409284; PubMed Central PMCID: PMC3883656.
- [259] Yeap SK, Omar AR, Ho WY, Beh BK, Ali AM, Alitheen NB. *Rhaphidophora korthalsii* modulates peripheral blood natural killer cell proliferation, cytokine secretion and cytotoxicity. *BMC Complement Altern Med.* 2013;13:145. doi:10.1186/1472-6882-13-145. PubMed PMID: 23800124; PubMed Central PMCID: PMC3701493.
- [260] Brito SV, Sales DL, Costa JG, Rodrigues FF, Ferreira FS, Angelico EC, et al. Investigation of the cytotoxic potential of *Rhinella jimi* skin methanol extracts. *Pharm Biol.* 2012;50(8):1026–30. doi:10.3109/13880209.2012.655858. PubMed PMID: 22775420.
- [261] Roscetti G, Franzese O, Comandini A, Bonmassar E. Cytotoxic activity of *Hypericum perforatum* L. on K562 erythroleukemic cells: differential effects between methanolic

- extract and hypericin. *Phytother Res.* 2004;18(1):66–72. doi:10.1002/ptr.1369. PubMed PMID: 14750204.
- [262] Matic IZ, Aljancic I, Zizak Z, Vajs V, Jadranin M, Milosavljevic S, et al. In vitro antitumor actions of extracts from endemic plant *Helichrysum zivojinii*. *BMC Complement Altern Med.* 2013;13:36. doi:10.1186/1472-6882-13-36. PubMed PMID: 23414290; PubMed Central PMCID: PMC3585823.
- [263] Aguiar JS, Araujo RO, Rodrigues Mdo D, Sena KX, Batista AM, Guerra MM, et al. Antimicrobial, antiproliferative and proapoptotic activities of extract, fractions and isolated compounds from the stem of *Erythroxylum caatingae* plowman. *Int J Mol Sci.* 2012;13(4):4124–40. doi:10.3390/ijms13044124. PubMed PMID: 22605969; PubMed Central PMCID: PMC3344205.
- [264] Predes FS, Ruiz AL, Carvalho JE, Foglio MA, Dolder H. Antioxidative and in vitro antiproliferative activity of *Arctium lappa* root extracts. *BMC Complement Altern Med.* 2011;11:25. doi:10.1186/1472-6882-11-25. PubMed PMID: 21429215; PubMed Central PMCID: PMC3073957.
- [265] Fong WF, Wang C, Zhu GY, Leung CH, Yang MS, Cheung HY. Reversal of multidrug resistance in cancer cells by *Rhizoma Alismatis* extract. *Phytomedicine.* 2007;14(2–3):160–5. doi:10.1016/j.phymed.2006.03.004. PubMed PMID: 16713217.
- [266] Kumarappan CT, Mandal SC. Antitumor activity of polyphenolic extract of *Ichnocarpus frutescens*. *Exp Oncol.* 2007;29(2):94–101. PubMed PMID: 17704739.
- [267] Renno MN, Barbosa GM, Zancan P, Veiga VF, Alviano CS, Sola-Penna M, et al. Crude ethanol extract from babassu (*Orbignya speciosa*): cytotoxicity on tumoral and non-tumoral cell lines. *An Acad Bras Cienc.* 2008;80(3):467–76. PubMed PMID: 18797799.
- [268] Lin CC, Ng LT, Hsu FF, Shieh DE, Chiang LC. Cytotoxic effects of *Coptis chinensis* and *Epimedium sagittatum* extracts and their major constituents (berberine, coptisine and icariin) on hepatoma and leukaemia cell growth. *Clin Exp Pharmacol Physiol.* 2004;31(1–2):65–9. PubMed PMID: 14756686.
- [269] Rossi D, Bruni R, Bianchi N, Chiarabelli C, Gambari R, Medici A, et al. Evaluation of the mutagenic, antimutagenic and antiproliferative potential of *Croton lechleri* (Muell. Arg.) latex. *Phytomedicine.* 2003;10(2–3):139–44. doi:10.1078/094471103321659843. PubMed PMID: 12725567.
- [270] Amirghofran Z, Bahmani M, Azadmehr A, Ashouri E, Javidnia K. Antitumor activity and apoptosis induction in human cancer cell lines by *Dionysia termeana*. *Cancer Invest.* 2007;25(7):550–4. doi:10.1080/07357900701518487. PubMed PMID: 18027150.
- [271] Muller CI, Kumagai T, O’Kelly J, Seeram NP, Heber D, Koeffler HP. *Ganoderma lucidum* causes apoptosis in leukemia, lymphoma and multiple myeloma cells. *Leuk Res.* 2006;30(7):841–8. doi:10.1016/j.leukres.2005.12.004. PubMed PMID: 16423392.

- [272] Cheng XD, Hou CH, Zhang XJ, Xie HY, Zhou WY, Yang L, et al. Effects of Huangqi (Hex) on inducing cell differentiation and cell death in K562 and HEL cells. *Acta Biochim Biophys Sin (Shanghai)*. 2004;36(3):211–7. PubMed PMID: 15202506.
- [273] da Silva DA, Alves VG, Franco DM, Ribeiro LC, de Souza MC, Kato L, et al. Antiproliferative activity of *Luehea candicans* Mart. et Zucc. (Tiliaceae). *Nat Prod Res*. 2012;26(4):364–9. doi:10.1080/14786411003752102. PubMed PMID: 21432719.
- [274] Turan N, Akgun-Dar K, Kuruca SE, Kilicaslan-Ayna T, Seyhan VG, Atasever B, et al. Cytotoxic effects of leaf, stem and root extracts of *Nerium oleander* on leukemia cell lines and role of the p-glycoprotein in this effect. *J Exp Ther Oncol*. 2006;6(1):31–8. PubMed PMID: 17228522.
- [275] Wagh V, Mishra P, Thakkar A, Shinde V, Sharma S, Padigaru M, et al. Antitumor activity of NPB001–05, an orally active inhibitor of Bcr-Abl tyrosine kinase. *Front Biosci (Elite Ed)*. 2011;3:1349–64. PubMed PMID: 21622141.
- [276] Liu JJ, Huang RW, Lin DJ, Wu XY, Lin Q, Peng J, et al. Antiproliferation effects of ponocidin on human myeloid leukemia cells in vitro. *Oncol Rep*. 2005;13(4):653–7. PubMed PMID: 15756438.
- [277] Zhang XJ, Xu XF, Gao RL, Xu JF. *Rubus parvifolius* L. inhibited the growth of leukemia K562 cells in vitro and in vivo. *Chin J Integr Med*. 2014;20(1):36–42. doi:10.1007/s11655-013-1537-0. PubMed PMID: 24242132.
- [278] Tayarani-Najaran Z, Mousavi SH, Vahdati-Mashhadian N, Emami SA, Parsaee H. *Scutellaria litwinowii* induces apoptosis through both extrinsic and intrinsic apoptotic pathways in human promyelocytic leukemia cells. *Nutr Cancer*. 2012;64(1):80–8. doi:10.1080/01635581.2012.630162. PubMed PMID: 22098153.
- [279] Roy S, Banerjee B, Vedasiromoni JR. Cytotoxic and apoptogenic effect of *Swietenia mahagoni* (L.) Jacq. leaf extract in human leukemic cell lines U937, K562 and HL-60. *Environ Toxicol Pharmacol*. 2014;37(1):234–47. doi:10.1016/j.etap.2013.11.008. PubMed PMID: 24366058.
- [280] Urech K, Scher JM, Hostanska K, Becker H. Apoptosis inducing activity of viscin, a lipophilic extract from *Viscum album* L. *J Pharm Pharmacol*. 2005;57(1):101–9. doi:10.1211/0022357055083. PubMed PMID: 15638998.
- [281] <https://clinicaltrials.gov/ct2/show/NCT00114959?term=chronic+myeloid+leukemia&rank=5>.
- [282] <https://clinicaltrials.gov/ct2/results?term=NCT00100997&cond=%22Chronic+Myeloid+Leukemia%22>.
- [283] <https://clinicaltrials.gov/ct2/show/NCT00003230?term=NCT00003230&rank=1>.