Chapter 1

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 potently 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)

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].

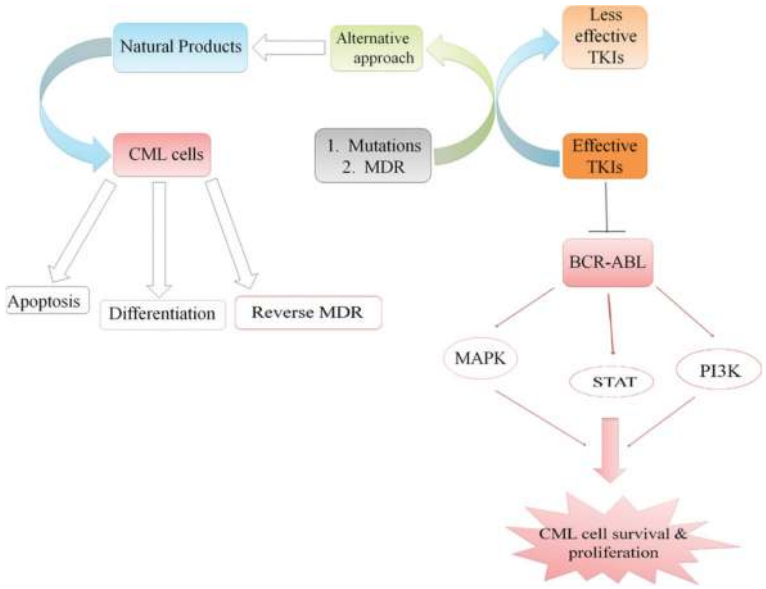

Figure 1. Schematic representation of NPs and TKIs on BCR-ABL inhibition and downregulation of downstream signaling pathways (NP—natural products, TKI—tyrosine kinase inhibitor, CML—chronic myeloid leukemia, MDR—multidrug resistance).

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 Gleevac 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.

Berbamine (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 IC_{50} value was found to be 17.1 and 11.1 μM 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 xenotransplated tumors in these mice [14]. BBM also induced apoptosis in CML cells *via* downregulating survivin protein levels [15]. At 8 μg/ml dose of BBM, NFκB 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 berbamine (BBD9), an analogue of BBM was also tested against K562/IR. BBD9 with IC_{50} 0.5 μg/ml was found to be more effective than BBM (IC_{50} 8 μg/ml), BBD9-lowered BCR-ABL, IKK a, nuclear NF-κB. 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 μM concentrations, and it significantly reduced the IC_{50} of DOX from 79.19 μM to 35.18, 21.86, 6.31 and 1.97 μM. Co-treatment of E6 with DOX arrested K562 cells at G2/M phase [23].

Camptothecin, isolated from *Camptotheca acuminate,* is documented to display anti-CML activity. Homocampthothecin (hCPT), a synthetic analogue of camptothecin, showed potent activity at IC_{50} value of 11 nM suggesting its potential use compared to parent compound camptothecin (IC_{50} 57 nM) [24]. BN80927, an analogue of camptothecin, effectively inhibited K562 cell proliferation with IC_{50} of 8.4 nM [25]. NSC606985, an analogue of camptothecin, inhibited CML cell growth in a dose-dependent manner. The IC_{50} 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 IC_{50} 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 tetrandine and imatinib showed syngerisitic 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 IC_{50} 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 IC_{50} 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 11,2 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
Berbamine (bisbenzylisoquinoline alkaloid)	*Berberis amurensis*	8 μg/ml	↓Bcl-2, Bcl-xL, NFκB (nuclear), IKK-α, IKB-α, BCR-ABL, p-BCR-ABL, Hsp90	[14–17]
Camptothecin (quinoline alkaloid)	*Camptotheca acuminate*	57 nM	↑Bax, cleavage of PARP-1, DNA—PK adducts	[24]
Homoharringtonine	*Cephalotaxus harringtona*	43.89 ng/ml	↓Bcl-2, NF-κB, p-JAK2, p-STAT5, p-Akt, p-BCR-ABL and $\perp G_0/G_1$ phase	[31, 32]
Sanguinarine (benzophenanthridine alkaloid)	*Sanguinaria canadensis*	–	At 1.5 μg/ml induced apoptosis	[33]
Tetrandrine (bis-benzylisoquinoline alkaloid)	*Stephania tetrandra*	–	↑Caspase 3 mRNA, protein and ↓Bcl-2 mRNA, protein	[39, 40]
Ancistrotectorine E (napthylisoqunoline alkaloid)	70% EtOH extract of *Ancistrocladus tectorius*	4.18 μM	–	[43]
1,2,3-Trimethoxy-5-oxonoraporphine and ouregidion (aporphine alkaloids)	Crude HEX, EtOAc and AQE extracts of *Pseuduvaria rugosa* (Blume) Merr	*63 and 64%	–	[44]
Cathachunine	*Catharanthus roseus* (L.) G. Don	9.3 ± 1.8 μM	–	[45]
Cepharanthine	*Stephania* sp.	–	↓p-gp	[46]
Crebanine	*Stephania venosa*	13 μg/ml	↓Cyclin A, D & ↑Caspases 3,9,8 & PARP and $\perp G_0/G_1$ phase	[48]
Curine	*Chondrodendron platyphyllum*	17.8 ± 5.2 μM	–	[49]
Cyanogramide	*Actinoalloteichus cyanogriseus* WHI-2216-6	–	At 5 μM, reversed MDR in K562/ADR	[50]
9-Deacetoxyfumigaclavine C	*Aspergillus fumigatus*	3.1 μM	–	[51]
Evodiamine (quinazolinocarboline alkaloid)	*Evodia rutaecarpa*	34.43 μM	–	[53]
Naamidine J (imidazole containing alkaloid)	*Pericharax heteroraphis*	11.3 μM	–	[54]
Salvicine (diterpenoid alkaloid)	*Salvia prioniti*	7.82 ± 2.81 μM	$\perp G_1$ phase	[56]
Solamargine (glycoalkaloid)	*Solanum species*	5.2 μM	↑Caspases and ↓Bcl-2	[57, 58]
α-Tomatine (glycoalkaloid)	*Solanum lycopersicum*	1.51 μM	Loss of MMP. ↑Bak, Mcl-1s, AIF and ↓survivin	[59]
Tylophora alkaloids (tylophorine, tylophorinine, tylophorindine)	*Tylophora indica*	–	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)	*Aspergillus westerdijkiae* DFFSCS013			
Eupolauramine and sampangine (azaphenanthrene alkaloids)	*Anaxagorea dolichocarpa* Sprague and sandwith	18.97 and 10.95 μg/ml	–	[62]
Arthpyrones A, B and C (4-hydroxy-2-pyridone alkaloids)	*Arthrinium arundinis* ZSDS1-F3	0.24—45 μM	–	[63]
Auranomides A, B and C	*Penicillium aurantiogriseum*	*20.48, 76.36 and 5.78%	–	[64]
Malonganenones 1–3 (tetraprenylated alkaloids)	*Euplexauria robusta*	0.35—10.82 μM	–	[65]
Virosecurinine	*Securinega suffruticosa*	32.984 μM	↑PTEN & ↓mTOR, SHIP-2 BCR-ABL, and $\perp G_1$/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 pytoestrogens, it was found that Q specifically inhibits K562 and MDR K562/A cell growth [78]. When K562 cells were treated with Q at a

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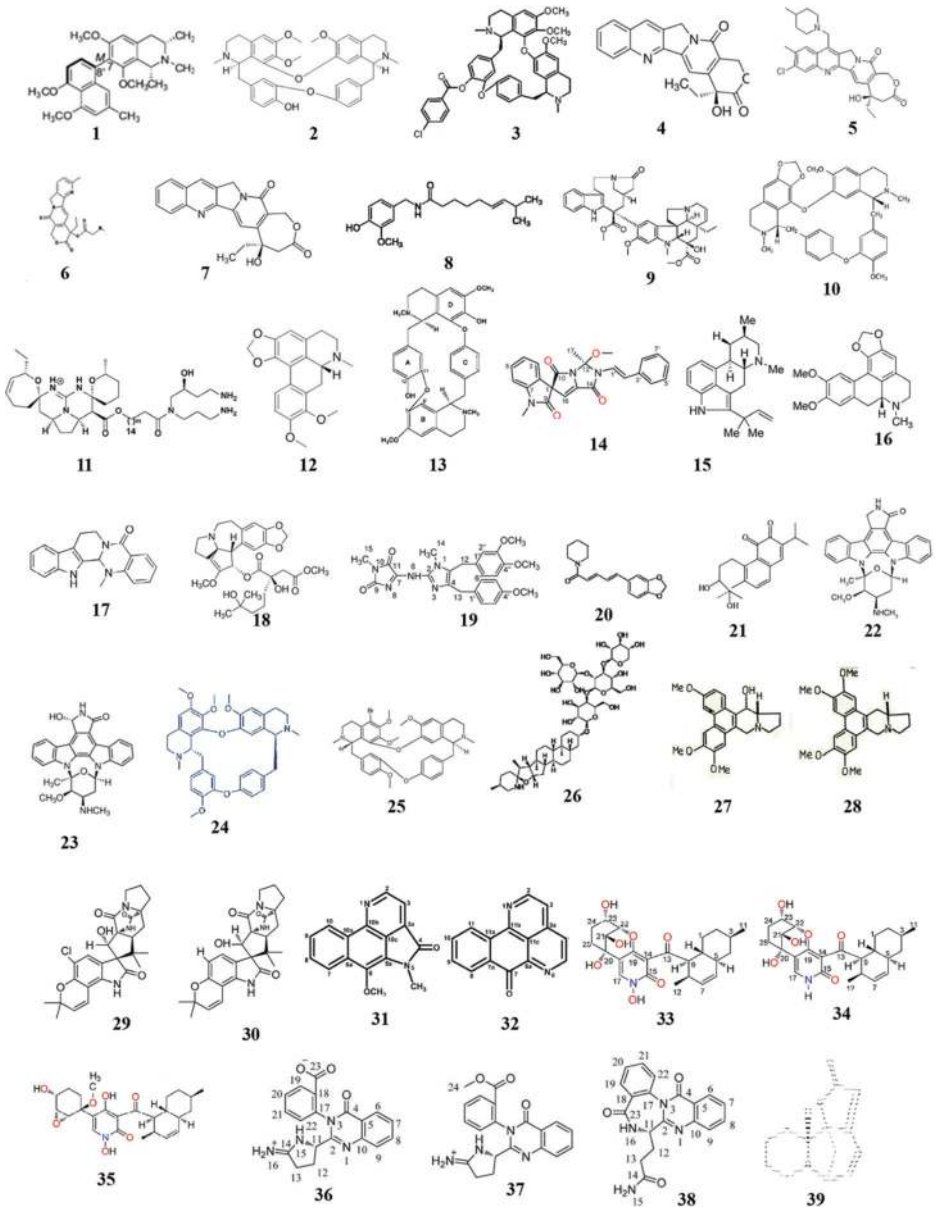

Figure 2. List of anti-CML alkaloids as 1—Ancistrotectorine E, 2—Berbamine, 3—BBD9, 4—Camptothecin, 5—BN80927, 6—NSC606985, 7—Homocamptothecin, 8—Capsaicin, 9—Cathachunine, 10—Cephranathine, 11—Crambescidin 800, 12—Crebanine, 13—Curine, 14—Cyanogramide, 15—9-deacetoxyfumigaclavine C, 16—d-Dicentrine, 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	↓*mdr*-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 *Tegillarca granosa*	–	K562/ADM	–	–	↓mdr1, BCR-ABL and sorcin	[177]
Gambogic acid	*Garcinia hanburyi*	Balb/c	KBM5-T315I	3 mg/kg/2 days	Intraperitoneal	↓Bcr-Abl, Akt, Erk1/2, and STAT5	[229]
TAF273	Fraction of *Eurycoma longifolia 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]. IC_{50} 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 ϒ hemoglobin mRNA expression	[87]
Galangin	Flavonoid	Monocytes	↑CD61	[90]
Genistein	Flavonoid	Erythroid lineage	–	[92]
EtOH extract of *Olea europaea*	Plant extract	Monocyte lineage	↑CD14	[243]
EtOH extract of *Stellera chamaejasme*	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-helminitic 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-

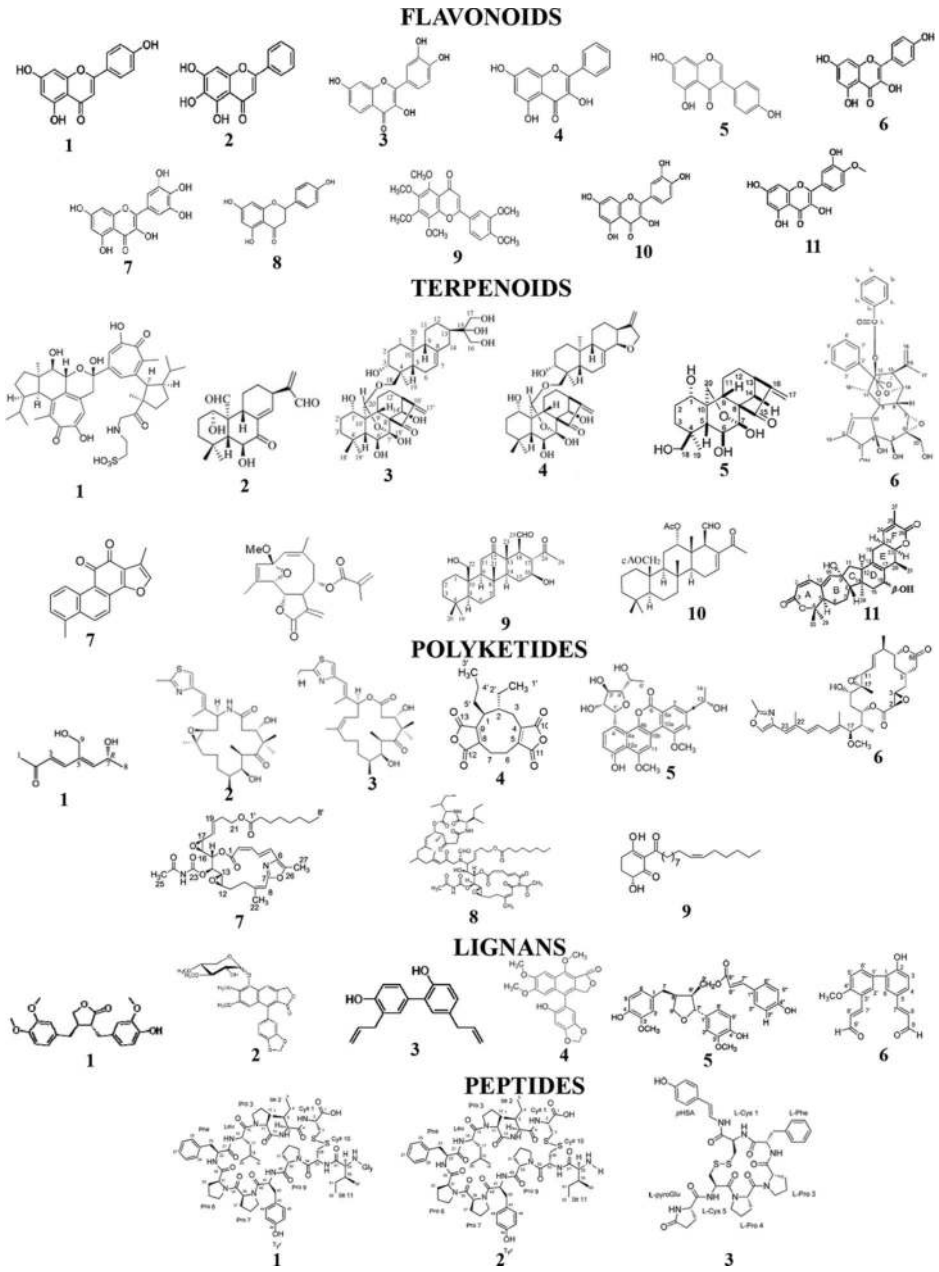

Figure 3. Anti-CML activity of some NPs which include – flavonoids: 1—Apigenin, 2—Baicalein, 3—Fistein, 4—Galangin, 5—Genistein, 6—Kaempferol, 7—Myricetin, 8—Naringenin, 9—Nobiletin, 10—Oroxylin A and 11—Tamarixetin. Terpenoids: 1—Gukulenin A, 2–4—Hebeiabinin A, D & E, 5—Parvifolines C, 6—3-hydrogenwadaphnin, 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 magndialdehyde. 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 $\perp G_2$/M phase	[77–86]
Apigenin (flavone)	–	↓Mcl-1, Bcl-2 & ↑caspases activation and $\perp G_2$/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 $\perp G_0/G_1$ 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 $\perp G_0/G_1$ phase	[98]
Tamarixetin (o-methylated flavonol)	–	↟ cyclin B1, Bub1, p21, caspases and ↓tublin 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 (*Luxemburgia nobilis*)	89 μM	–	[102]
Isochamaejasmin (biflavonoid) (*Stellera chamaejasme* L)	24.51 ± 1.62 μM	↟caspases 3, 9 and PARP cleavage	[103]
Protoapigenone (total flavonoid fraction of *Macrothelypteris torresiana*)	0.9 μg/ml	–	[104]
Total flavonoids from *Lysimachia clethroides* Duby (ZE4)	–	↓Bcl-2 and ↑Fas, TRAIL & DR5	[105]
Total flavonoids of *Astragali Radix*	98.63 mg/L	↓ cyclin D1 mRNA levels and $\perp G_0/G_1$ phase	[106]
Total oligomer flavonoids of *Rhamnus alaternus*	196 μg/ml	–	[107]
Flavonoid-enriched *Rhamnus alaternus* root and leaf extracts	165 and 210.73 μg/ml	–	[108]
Epigallocatechin-3-gallate (*Camellia sinensis*)	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	*Elephantopus mollis*	10.8 μM	↟ caspases, PARP cleavage and ↓ NFκB. Loss of MMP	[116]
Diterpenoids	Caesalminaxin D and H	*Caesalpinia minax*	9.9 ± 1.7 and 9.2 ± 0.9 μM	–	[117]
	Gukulenin A and diterpenoid pseudodimers (2–5)	*Phorbas gukhulensis*	*0.26 ± 0.03, 0.12 ± 0.01, 0.44 ± 0.01, 0.32 ± 0.05 and 0.04 ± 0.09 μM	–	[118]
	Diterpene compounds 11, 12, 13, 14 and 15	petroleum ether soluble fraction of the aerial parts of *Tirpitzia ovoidea* ethanol extract	86.4, 66.3, 91, 45.1 and 58.6 μM	–	[119]
	7β,11β,14β-Trihydroxy-ent-kaur-20-al-6,15-dioxo-16-ene	*Isodon xerophilus*	0.04 μM	–	[122]
	Hebeiabinin A, D and E	*Isodon rubescens* var. rubescens	53.21, 5.05 and 0.91 μM	–	[123]
	Parvifolines C	*Isodon parvifolius*	13.8 μM	–	[125]
	3-Hydrogenwadaphnin	*Dendrostellera lessertii*	15 nM con. caused 45% apoptosis	–	[126]
	Enanderianins K—P, Rabdocoetsin B and D	*Isodon enanderianus*	0.13–0.87 μg/ml	–	[127]
	Ludongnin J	*Isodon rubescens* var. lushiensis	0.18 μg/ml	–	[128]
	Tanshinone I	*Salvia miltiorrhiza* Bunge.	38 ± 5.2 μM	↟ Bax, caspase 3 and ↓Survivin	[129]
	ent-Kaurane diterpenoids 11, 16, 17 and 20	*Isodon nervosus*	2.39, 4.11, 1.05 and 1.55 μM		[130]
	5-Episinuleptolideacetate	*Sinularia species*	4.09 μg/ml	↓c-ABL, Akt, NFκB	[144]
Sesterterpenoids	Felixins F and G	*Ircinia felix*	1.27 and 19.9 μM	–	[131]
	Compounds 8, 9	*Smenospongia* sp.	*0.11 and 0.97μ/ml	–	[132]
	Two linear furanosesterterpenes	*Smenospongia* sp.	3 and 31.6 μg/ml	–	[134]
Triterpenoids	3β,21β,24-Trihydroxyserrat-14-en-24-(4′-hydroxybenzoate)	*Palhinhaea cernua*	56.1 μg/ml	–	[137]
	L-Arabinopyranosyloleanolic acid	*Garcinia hanburyi* resin	4.15 μM	–	[138]

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

*LC_{50}, lethal concentation.

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 LC_{50} 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 LC_{50} 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	*Aspergillus* sp. 16–02–1	44.3 μg/mL	–	[146]
	Geldanamycin	*Streptomyces Hygroscopicus*	–	↓c-Raf, Akt, BCR-ABL	[148]
	Heveadride	*Ascomycota Dichotomyces cejpii*	82.7 ± 11.3 μM	↟ TNFα	[149]
	Gilvocarin HE	Streptomyces sp. QD01–2	45 μM	–	[150]
	Radicicol	*Diheterospora chlamydosporia* and *Monosporium bonorden*	–	↓p-Raf1, p-BCR-ABL	[151]
	Rhizoxin	*Burkholderia rhizoxina*	5×10^{-7} μg/ml	–	[152]
	Salarin C	*Fascaplysinopis* sp.	0.1 μM	↟ caspase 3 and 9 cleavage	[153]
	Tausalarin C	*Fascaplysinopis* sp.	1 μM	–	[154]
	Trineurone E	*Peperomia trineura*	26 μM	–	[155]
Lignans	Arctigenin	Asteraceae family	–	↑Bax and ↓ Bcl-2	[157]
	Cleistanthin A	*Cleistanthus collinus* (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	*Magnolia officinalis* Rend. Et wils.	28.4 μM	–	[160]
	6-Hydroxyjusticidin C	*Justica procumbens*	43.9 ± 2.9 μM	↟ROS levels, casapase 3	[161]
	(+)-Lariciresinol 9′-p-coumarate	*Larix olgensis* var. koreana.	2.9 μg/ml	–	[162]
	4-Methoxy magndialdehyde	*Magnolia officinalis*	3.9 μg/ml	–	[163]
Saponins	Astrgorgiosides A, B, C (19-norand aromatized B ring bearing steroid aglycone)	*Astrogor dumbea*	26.8—45.6 μM	–	[168]
	Wattoside G, H, and I (steroidal saponins)	*Tupistra wattii* Hook.F.	35.67, 76.16 and 76.96 μM	–	[169]
	Tenacissoside C (steroidal saponins)	*Marsdenia tenacissima*	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)	*Cynanchum wilfordii* roots	6.72 μM	–	[171]
	Total saponin content	*Aralia Taibaiensis*	–	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)	*Gleditsia sinensis* Lam. fruit extract	18 ± 1.6 μg/ml	↑ Bax and ↓ Bcl-2, PCNA	[173]
	23-Hydroxybetulinic acid	Total saponin content of *Pulsatilla chinensis* (Bunge) Regel	–	↟ Bax, caspase 3 cleavage and ↓ Bcl-2, survivin	[174]
Peptides	Chujamides A and B	*Suberites waedoensis*	*37 and 55.6 μM	–	[175]
	Gombamide A	*Clathria gombawuiensis*	*6.9 μM	–	[176]

*LC_{50}—lethal concentation.

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 glendamycin–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	*Stelletta* sp.	43.5, 51.3 and 62.5 μg/ml	–	[180]
Betanin (betacyanin pigment)	*Opuntia ficus-indica*	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	*Clausena lansium* (Lour.) Skeels	20.48 ± 1.78, 26.5 ± 2.12 and 23.49 ± 1.85 μg/ml	–	[184]
Toxicarioside F and G	*Latex of Antaris toxicaria (Pers.) Lasch*	–	–	[185]
Pangelin and oxypeucedanin hydrate acetonide	*Angelica dahurica*	8.6–14.6 μg/ml	–	[186]
Mamea A/BA	*Calophyllum brasiliense*	0.04–0.59 μM	–	[187, 188]
Cryptotanshinone (lipid soluble active compound)	*Salvia miltiorrhiza*	–	induced apoptosis ↑ PARP cleavage and ↓BCR-ABL, STAT3, mTOR & eIF4E	[189, 190]
Bavachalcone (Chalcones)	–	2.7 μM	–	[191]
Polyanthumin (novel chalcone trimmer) and sulfuretin	*Memecylon polyanthum H.L. Li.*	45.4 and 30.5 μg/ml	–	[192]
(−)-Cubebin	*Piper cubeba*	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	*Pistascia lentiscus*	–	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)	*Dendrobium chrysotoxum*	32.18, 26.65 and 52.28 μg/ml	–	[196]
C27-Steroidal glycoside	*Liriope graminifolia* (Linn.) Baker	18.6 μg/ml	–	[198]
9α-Acetoxyartecanin, apressin, inducumenone and centaureidin	*Achillea clavennae*	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	*Garcinia malaccensis*		–	[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 *Callicarpa nudiflora* 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	*Perezia* spp.	–	Cytotoxic to CML cells at 25, 50 and 100 μM and induced apoptosis	[206]
Compound 6a (phenalenone metabolite)	*Coniothyrium cereal*	8.5 μM	–	[207]
Polyphyllin D	*Paris polyphyllin*	–	↑ p21, Bax, caspase 3 & Cyt. C release and ↓ cyclin B1, cdk1, Bcl-2. Loss of MMP and ⊥ G_2/M phase	[208]
Polysaccharide (PSP001)	*Punica granatum*	52.8 ± 0.9 μg/ml	–	[209]
Riccardin F and Pakyonol (macrocyclic bisbenzyls)	*Plagiochasm intermedium*	0–6 μg/ml	–	[210]
Highly methoxylated bibenzyls	*Frullania inouei*	11.3–49.6 μM	–	[211]
Sarcovagine and β-sitosterol 5- 8	*Sarcococca saligna*	2.5–5 μM	–	[212]
Squamocin (annonaceous acetogenins)	–	–	↑ cdk inhibitors, p21, p27 & ↓ cdk1, cdk25c and ⊥G_2/M phase	[213]
Klyflaccisteroid J	*Klyxum flaccidum*	12.7 μM	–	[214]
Suvanine (N,N-dimethyl-1,3-dimethylherbipoline salt) and suvanine-lactam derivatives (4–8)	*Coscinoderma* sp. sponge	* 2.2, 1.9, 3.9, 4.6, 3.9 and 3.6 μM	–	[215]
ar-Turmerone	*Curcuma longa* L	20–50 μg/ml	Induced DNA fragmentation and apoptosis	[216]
Terpene metabolites (1–3)	*Clathria gombawuiensis*	*4.7, 3.9 and 2.1 μM	–	[217]
Toxicarioside H (nor-cardenolide)	*Antiaris toxicaria* (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 *Asphodelus microcarpus* 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 *Datura metel* flowers	0.05, 2.5, 0.12, 0.55 and 0.46 μM	–	[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 (xanthones)	*Garcinia hanburyi* resin	0.41 ± 0.03, 2.1 ± 0.14 and 1.74 ± 0.22 μg/ml	–	[223]
Xindongnins C–D, A, B, melissoidesin G, dawoensin A and glabcensin V	*Isodon rubescens var. rubescens*	0.3–7.3 μg/ml	–	[224]
Hyperbeanols B and D	MeOH extract of *Hypericum beanie*	16.9 and 20.7 μM	–	[225]
Rhodexin A	*Rhodea japonica*	19 nM	⊥G_2/M phase induced apoptosis	[226]
Curcumin	*Curcumina longa*	20 μg/ml	↓BCR-ABL, Hsp90, WT1	[227, 228]
Gambogic acid	*Garcinia hanburyi*	0.62 μM	↓p-BCR-ABL, pSTAT5, p-CRKL, pERK1/2, p-Akt	[229, 230]

*LC_{50}–lethal concentation.

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

Plant extract	IC_{50} value on K562 cells	Mechanism of action	References
Acetone extract of *Peucedanum nebrodense* (Guss.) Strohl.,	14–10.27 μg/ml	–	[231]
AQE extract of *Cornus officinalis* Sieb. et Zuce	100 μg/ml	–	[232]
AQE extracts of the husk fiber of the typical A and common varieties of *Cocos nucifera* (Palmae)	At 500 μg/ml the cell viability of CML cells was found to be 60.1 ± 8.5 and 47.5 ± 11.9%	–	[233]
AQE extract of *Rhodiola imbricate*	–	↓CML cell proliferation at 100 and 200 μg/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 *Fraxinus)*	–	↟ caspase 9, JNK-1,2, p38 MAPK and ↓ Bcl-1, Erk-1/2 & PKB phosphorylation	[235]
Chloroform extract of *Polyalthia rumphii* stem	40–60μ/ml	–	[236]
Chloroform extract of *Tecomella undulata* bark	30 μg/ml	↟ FAS, FADD, & caspase 8, 3/7. Induced DNA fragmentation & apoptosis	[237]
DCM) extract of *Psidium guajava* L.	32 μg/ml	–	[238]

Plant extract	IC_{50} value on K562 cells	Mechanism of action	References
DCM extract *Artemisia turanica Krasch*	69 μg/ml	↟ caspases, PARP cleavage. Induced DNA damage and apoptosis	[239]
HEX and DCM extract of *Mesua beccariana*	*20 ± 1.5 and 43.75 ± 0.78 μg/ml	–	[240]
HEX and DCM extract of *Mesua ferrea*	*17.5 ± 1.02 and 22.91 ± 1.25 μg/ml	–	[240]
HEX extract of *Mesua congestiflora*	40.63 ± 1.45 μg/ml	–	[240]
DCM fraction of *Melissa officinalis*	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 *Echinops grijissi* Hance roots	30 μg/ml	–	[242]
EtOH extract of *Pereskia sacharosa*	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 *Melipona orbignyi*)	At 250 and 500 μg/ml promoted cell death of CML cells by 15 ± 1 and 63 ± 2%	–	[245]
EtOH extract of *Isodon japonicas*	2.7 μg/ml	–	[246]
EtOH root extract of *Allamanda schottii*	At 800 μg/ml showed cytotoxicity	–	[247]
EtOH stem and leaf extract of *Physalis peruviana*	0.02 and 0.03 g/ml	–	[248]
Alcoholic extract of *Dendrostellera lessertii*	28 μl and 5×10^{-9}M	–	[249]
EtOH extract of *Rosmarinus officinalis* L	1/400 dilution	–	[251]
EtOH extract of *Goldfussia psilostachys*	0.5 μg/ml	↟ CML cells in G_2/M phase	[252]
Fraction from EtoAc of *Caesalpinia spinosa*	44.5 ± 4.05 μg/ml	induced chromatin condensation. Loss of MMP & ↑ caspase 3	[253]
EtoAc extract of *Helichrysum plicatum* flowers	25.9 μg/ml	–	[254]
MeOH extract of *Linum persicum*	0.1 μg/ml	–	[255]
MeOH extracts of *Echinophora cinerea* and *Cirsium bracteosum*	Less than 20 μg/ml	–	[256]
MeOH extract of *Galium mite*	39.8 μg/ml	–	[256]
MeOH extract *of Cyperus rotundus*	175 ± 1.2 μg/ml	Induced DNA damage	[257]
TAF273, F3 and F4 fractions of MeOH extract of *Eurycoma longifolia* Jack	19, 55 and 62 μg/ml	–	[258]
MeOH extract of *Rhaphidophora korthalsii*	–	Enhanced Natural killer cells to kill K562, ↟IFN-ϒ, TNF-α	[259]

Plant extract	IC_{50} value on K562 cells	Mechanism of action	References
MeOH extract of *Rhinella jimi* Stevaux (Anura: Bufonidae) skin	*235 μg/ml	–	[260]
MeOH extract of *Hypericum perforatum L.*flower extract	–	Induced apoptosis	[261]
HEX, DCM, EtoAc, butanol and MeOH extracts of *Helichrysum zivojinii* 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 *Erythroxylum caatingae* plowman	13.1 ± 0.63, 9.86 ± 0.56, 11.21 ± 0.46, 33.58 ± 1.33 μg/ml	–	[263]
DCM extract of *Arctium lappa* root	^17 μg/ml	–	[264]
Alisma orientalis (Sam) Juzep extract	–	Reverse of MDR	[265]
Polyphenolic extract of *Ichnocarpus fructescens* leaves	–	At 5, 10, 20 μg/ml con. ↓K562 cell proliferation	[266]
EtOH extract of *Orbignya speciosa*	33.9 ± 4.3 μg/ml	–	[267]
Coptis chinensis and Epimedium sagittatum extracts	29 and74 μg/ml	–	[268]
Sangre de Drago is red viscous latex extract of *Croton lechleri*	2.5 ± 0.3 μg/ml	–	[269]
Dionysia termeana extract	20 μg/ml	–	[270]
Ganoderma lucidum extract	*50 μg/ml	–	[271]
Crude MeOH extracts of *Luehea candicans* Mart. et Zucc. branches and leaves	#8.1–5.4 μg/ml	–	[273]
Nerium oleander extract	–	↓p-gp	[274]
Ponicidin (*Rabdosia rubescens* extract)	–	↓ Bcl-2 and ↑ Bax, caspase 3 & PARP cleavage	[276]
Scutellaria litwinowii Bornm. and Sint. ex Bornm.	–	↟ caspase 3,8, PARP cleavage, Bax/Bcl-2 ratio	[278]
Swietenia mahagoni leaf extract	–	↟ caspases 3,9, Cyt. C release and ⊥G_2-M phase	[279]
Viscin, (lipophilic extract from *Viscum album* 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; # GI^{50}, 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	homocampthothecin
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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