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Chapter 1

Natural Products for Treatment of Chronic Myeloid Leukemia

Kalubai Vari Khajapeer and Rajasekaran Baskaran

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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].
The \textit{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 \textit{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 (\textbf{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

![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).](image)
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 xenotransplanted 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, IκB-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 α, nuclear NFκB. 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 acuminata, is documented to display anti-CML activity. Homocamptothecin (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.
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 harringtoniana*, 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 polypody 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 synergistic 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
<table>
<thead>
<tr>
<th>Alkaloid</th>
<th>Source of isolation</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; value on K562 cells</th>
<th>Mechanism of action</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berbamine (bisbenzylisoquinoline alkaloid)</td>
<td>Berberis amurensis</td>
<td>8 μg/ml</td>
<td>↓Bcl-2, Bcl-xL, NFκB (nuclear), IKK-α, IKK-α, BCR-ABL, p-BCR-ABL, Hsp90</td>
<td>[14–17]</td>
</tr>
<tr>
<td>Camptothecin (quinoline alkaloid)</td>
<td>Camptotheca acuminata</td>
<td>57 nM</td>
<td>↓Bax, cleavage of PARP-1, DNA–PK adducts</td>
<td>[24]</td>
</tr>
<tr>
<td>Homoharringtonine</td>
<td>Cephaletaxus harringtonia</td>
<td>43.89 ng/ml</td>
<td>↓Bcl-2, NFκB, p-JAK2, p-STAT5, p-Akt, p-BCR-ABL and LC50/G1 phase</td>
<td>[31, 32]</td>
</tr>
<tr>
<td>Sanguinarine (benzophenanthridine alkaloid)</td>
<td>Sanguinaria canadensis</td>
<td>–</td>
<td>At 1.5 μg/ml induced apoptosis</td>
<td>[33]</td>
</tr>
<tr>
<td>Tetrandrine (bisbenzylisoquinoline alkaloid)</td>
<td>Stephania tetrandra</td>
<td>–</td>
<td>↑Caspase 3 mRNA, protein and ↓Bcl-2 mRNA, protein</td>
<td>[39, 40]</td>
</tr>
<tr>
<td>Ancistrotectorine E (naphthylisoquinoline alkaloid)</td>
<td>70% ETOH extract of Ancistrocladus tectorius</td>
<td>4.18 μM</td>
<td>–</td>
<td>[43]</td>
</tr>
<tr>
<td>1,2,3-Trimethoxy-5-oxonoraporphine and ouregidion (aporphine alkaloids)</td>
<td>Crude HEX, EtOAc and AQE extracts of Pseuduvaria rugosa (Blume) Merr</td>
<td>*63 and 64%</td>
<td>–</td>
<td>[44]</td>
</tr>
<tr>
<td>Cathachunine</td>
<td>Catharanthus roseus (L.) G. Don</td>
<td>9.3 ± 1.8 μM</td>
<td>–</td>
<td>[45]</td>
</tr>
<tr>
<td>Cepharanthine</td>
<td>Stephania sp.</td>
<td>–</td>
<td>↓p-gp</td>
<td>[46]</td>
</tr>
<tr>
<td>Crebanine</td>
<td>Stephania venosa</td>
<td>13 μg/ml</td>
<td>↓Cyclin A, D &amp; ↑Caspases 3,9,8 &amp; PARP and ⊥G0/G1 phase</td>
<td>[48]</td>
</tr>
<tr>
<td>Curine</td>
<td>Chondrodendron platyphyllum</td>
<td>17.8 ± 5.2 μM</td>
<td>–</td>
<td>[49]</td>
</tr>
<tr>
<td>Cyanogramide</td>
<td>Actinalloteichus cyanogriseus WHI-2216-6</td>
<td>–</td>
<td>At 5 μM, reversed MDR in K562/ADR</td>
<td>[50]</td>
</tr>
<tr>
<td>9-Deacetoxyfumigaclavine C</td>
<td>Aspergillus fumigatus</td>
<td>3.1 μM</td>
<td>–</td>
<td>[51]</td>
</tr>
<tr>
<td>Evodiamine (quinazolinocarboline alkaloid)</td>
<td>Evodia rutaecarpa</td>
<td>34.43 μM</td>
<td>–</td>
<td>[53]</td>
</tr>
<tr>
<td>Naamidine J (imidazole containing alkaloid)</td>
<td>Pericharax heterophylus</td>
<td>11.3 μM</td>
<td>–</td>
<td>[54]</td>
</tr>
<tr>
<td>Salvicine (diterpenoid alkaloid)</td>
<td>Salsea prioiniti</td>
<td>7.82 ± 2.81 μM</td>
<td>LC50 phase</td>
<td>[56]</td>
</tr>
<tr>
<td>Solamargine (glycoalkaloid)</td>
<td>Solanum species</td>
<td>5.2 μM</td>
<td>↑Caspases and ↓Bcl-2</td>
<td>[57, 58]</td>
</tr>
<tr>
<td>α-Tomatine (glycoalkaloid)</td>
<td>Solanum lycopersicum</td>
<td>1.51 μM</td>
<td>Loss of MMP, ↑Bak, Mcl-1s, AIF and ↓survivin</td>
<td>[59]</td>
</tr>
<tr>
<td>Tylophora alkaloids (tylophorine, tylophorinine, tylophoridine)</td>
<td>Tylophora indica</td>
<td>–</td>
<td>Nuclear condensation, ↑Caspases activation, release of cyt.C</td>
<td>[60]</td>
</tr>
</tbody>
</table>

44 and 53 μM – [61]
potently reduce tumor growth in in vivo models (Table 2). Besides, some alkaloids such as capsaicin, 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

<table>
<thead>
<tr>
<th>Alkaloid</th>
<th>Source of isolation</th>
<th>IC₅₀ value on K562 cells</th>
<th>Mechanism of action</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Chlorosclerotiamide and 10-episclerotiamide (prenylated indole alkaloids)</td>
<td><em>Aspergillus westerdijkiae</em> DFFSCS013</td>
<td>18.97 and 10.95 μg/ml</td>
<td>–</td>
<td>[62]</td>
</tr>
<tr>
<td>Eupolauramine and sampangine (azaphenanthrene alkaloids)</td>
<td><em>Anastragaea dolichocarpa</em> Sprague and sandwith</td>
<td>0.24–45 μM</td>
<td>–</td>
<td>[63]</td>
</tr>
<tr>
<td>Arthpyrones A, B and C (4-hydroxy-2-pyridone alkaloids)</td>
<td><em>Arthrinium arundinis</em> ZSDS1-F3</td>
<td>20.48, 76.36 and 5.78%</td>
<td>–</td>
<td>[64]</td>
</tr>
<tr>
<td>Auronomides A, B and C</td>
<td><em>Penicillum aurantisongeen</em></td>
<td>0.35–10.82 μM</td>
<td>–</td>
<td>[65]</td>
</tr>
<tr>
<td>Malonganenones 1–3 (tetraprenylated alkaloids)</td>
<td><em>Euplexauria robusta</em></td>
<td>32.984 μM</td>
<td>↑PTEN &amp; ↓mTOR, SHIP-2, BCR-ABL, and ↓G₁/S phase</td>
<td>[66]</td>
</tr>
<tr>
<td>Virosecurinine</td>
<td><em>Securinega suffruticosa</em></td>
<td>32.984 μM</td>
<td>↑PTEN &amp; ↓mTOR, SHIP-2, BCR-ABL, and ↓G₁/S phase</td>
<td>[66]</td>
</tr>
</tbody>
</table>

Table 1. Anti-CML activity of alkaloids.
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

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

<table>
<thead>
<tr>
<th>Name of NP</th>
<th>Type of NP</th>
<th>Mice strain</th>
<th>Type of CML cells used to induce tumors</th>
<th>Dosage</th>
<th>Mode of administration</th>
<th>Mechanism of action</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>BBM</td>
<td>Alkaloid</td>
<td>Balb/c</td>
<td>K562-r</td>
<td>60 mg/ kg BW</td>
<td>Intravenously</td>
<td>↓ mdr-1 mRNA, p-gp protein</td>
<td>[14]</td>
</tr>
<tr>
<td>BBD9</td>
<td>Analogue of BBM</td>
<td>nu−/−</td>
<td>K562/IR</td>
<td>15 and 30 mg/ kg BW</td>
<td>–</td>
<td>↓ p-BCR-ABL, IKKα, NF-xBp65</td>
<td>[22]</td>
</tr>
<tr>
<td>Tetrandrine citrate</td>
<td>Alkaloid</td>
<td>nu−/−</td>
<td>K562/IR</td>
<td>100 mg/ kg BW</td>
<td>Orally</td>
<td>↓ BCR-ABL, β-catenin</td>
<td>[41]</td>
</tr>
<tr>
<td>d-Dicentrine</td>
<td>Alkaloid</td>
<td>SCID</td>
<td>K562</td>
<td>100 mg/ kg BW</td>
<td>Intraperitoneal</td>
<td>↑ tumor size</td>
<td>[52]</td>
</tr>
<tr>
<td>Oroxylin A</td>
<td>Flavonoid</td>
<td>SCID</td>
<td>K562</td>
<td>80 mg/ kg BW</td>
<td>Intravenously</td>
<td>↓ STAT3 pathway</td>
<td>[76]</td>
</tr>
<tr>
<td>Nobiletin</td>
<td>Flavonoid</td>
<td>Nude mice</td>
<td>K562</td>
<td>12.5, 25, 50 mg/ kg BW</td>
<td>–</td>
<td>↓ VEGF</td>
<td>[99]</td>
</tr>
<tr>
<td>dEpoF</td>
<td>Polyketide</td>
<td>Nude mice</td>
<td>K562</td>
<td>6 mg/kg</td>
<td>Intravenously</td>
<td>Complete tumor regression</td>
<td>[147]</td>
</tr>
<tr>
<td>HSS</td>
<td>Protein extract from Tegillarca granosa</td>
<td>–</td>
<td>K562/ADM</td>
<td>–</td>
<td>–</td>
<td>↓ mdr1, BCR-ABL and sorcin</td>
<td>[177]</td>
</tr>
<tr>
<td>Gambogic acid</td>
<td>Garcinia hanburyi</td>
<td>Balb/c</td>
<td>KBM5-T315I</td>
<td>3 mg/kg/ 2 days</td>
<td>Intraperitoneal</td>
<td>↓ Bcr-Abl, Akt, Erk1/2, and STAT5</td>
<td>[229]</td>
</tr>
<tr>
<td>TAF273</td>
<td>Fraction of Eurycoma longifolia MeOH extract</td>
<td>Balb/c</td>
<td>K562</td>
<td>50 mg/ kg</td>
<td>Intraperitoneal</td>
<td>↓ apoptosis and ↓ blood vessel formation</td>
<td>[258]</td>
</tr>
<tr>
<td>NPB001–05</td>
<td>Piper betle extract</td>
<td>–</td>
<td>T315I</td>
<td>500 mg/ kg</td>
<td>Orally</td>
<td>↓ PI3K/AKT, MAPK pathways</td>
<td>[275]</td>
</tr>
</tbody>
</table>
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-

### Table 3.

List of some NPs and its differentiation capacity.

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

Table 3. List of some NPs and its differentiation capacity.
Flavonoids/flavonoid fraction | IC_{50} value on K562 cells | Mechanism of action | References
--- | --- | --- | ---
Oroxylin A (o-methylated flavone) | – | ↓CXCR4, PKC, P38, 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) | – | ↑cycrin 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 Macrohelypteris 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 | ↓cycrin D1 mRNA levels and ↓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...
<table>
<thead>
<tr>
<th>Terpenoid class</th>
<th>Name of terpenoid</th>
<th>Source of isolation</th>
<th>IC_{50} value on K562 cells</th>
<th>Mechanism of action</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sesquiterpenoids</td>
<td>EM23</td>
<td>Elephantopus mollis</td>
<td>10.8 μM</td>
<td>† caspases, PARP cleavage and ↓ NFκB. Loss of MMP</td>
<td>[116]</td>
</tr>
<tr>
<td>Diterpenoids</td>
<td>Caesalminaxin D and H</td>
<td>Caesalpinia minax</td>
<td>9.9 ± 1.7 and 9.2 ± 0.9 μM</td>
<td>–</td>
<td>[117]</td>
</tr>
<tr>
<td></td>
<td>Gukulenin A and diterpenoid pseudodimers (2–5)</td>
<td>Phorbas gikhalensis</td>
<td>*0.26 ± 0.03, 0.12 ± 0.01, 0.44 ± 0.01, 0.32 ± 0.05 and 0.04 ± 0.09 μM</td>
<td>–</td>
<td>[118]</td>
</tr>
<tr>
<td></td>
<td>Diterpene compounds 11, 12, 13, 14 and 15</td>
<td>petroleum ether soluble fraction of the aerial parts of T. ovoida ethanol extract</td>
<td>86.4, 66.3, 91, 45.1 and 58.6 μM</td>
<td>–</td>
<td>[119]</td>
</tr>
<tr>
<td></td>
<td>7β,11β,14β-Trihydroxy-ent-kaur-20-α,6,15-dioxo-16-ene</td>
<td>Isodon xerophilus</td>
<td>0.04 μM</td>
<td>–</td>
<td>[122]</td>
</tr>
<tr>
<td></td>
<td>Hebebinin A, D and E</td>
<td>Isodon rubescens var. rubescens</td>
<td>53.2, 5.05 and 0.91 μM</td>
<td>–</td>
<td>[123]</td>
</tr>
<tr>
<td></td>
<td>Parvifolines C</td>
<td>Isodon parvifolius</td>
<td>13.8 μM</td>
<td>–</td>
<td>[125]</td>
</tr>
<tr>
<td></td>
<td>3-Hydrogenwadaphnin</td>
<td>Dendrostella lesserti</td>
<td>15 nM con. caused 45%</td>
<td>–</td>
<td>[126]</td>
</tr>
<tr>
<td></td>
<td>Enanderianins K–P, Rabdocoetsin B and D</td>
<td>Isodon enanderianus</td>
<td>0.13–0.87 μg/ml</td>
<td>–</td>
<td>[127]</td>
</tr>
<tr>
<td></td>
<td>Ludongnin J</td>
<td>Isodon rubescens var. lushiensis</td>
<td>0.18 μg/ml</td>
<td>–</td>
<td>[128]</td>
</tr>
<tr>
<td></td>
<td>Tanshinone I</td>
<td>Salvia miltiorrhiza Bunge.</td>
<td>38 ± 5.2 μM</td>
<td>† Bax, caspase 3 and ↓ Survivin</td>
<td>[129]</td>
</tr>
<tr>
<td></td>
<td>ent-Kaurane diterpenoids 11, 16, 17 and 20</td>
<td>Isodon nervosus</td>
<td>2.39, 4.11, 1.05 and 1.35 μM</td>
<td>–</td>
<td>[130]</td>
</tr>
<tr>
<td>Sesterterpenoids</td>
<td>Felixins F and G</td>
<td>Ircinia flexi</td>
<td>1.27 and 19.9 μM</td>
<td>–</td>
<td>[131]</td>
</tr>
<tr>
<td></td>
<td>Compounds 8, 9</td>
<td>Smenospongia sp.</td>
<td>*0.11 and 0.97 μM</td>
<td>–</td>
<td>[132]</td>
</tr>
<tr>
<td></td>
<td>Two linear furanosesterterpenes</td>
<td>Smenospongia sp.</td>
<td>3 and 31.6 μg/ml</td>
<td>–</td>
<td>[134]</td>
</tr>
<tr>
<td>Triterpenoids</td>
<td>3β,21β,24-Trihydroxyserat-14-en-24-(4′-hydroxybenzoate)</td>
<td>Palinthaea cernua</td>
<td>56.1 μg/ml</td>
<td>–</td>
<td>[137]</td>
</tr>
<tr>
<td></td>
<td>L-Arabinopyranosyleanolic acid</td>
<td>Garcinia hanburyi resin</td>
<td>4.15 μM</td>
<td>–</td>
<td>[138]</td>
</tr>
</tbody>
</table>
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 wuedoensis 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

<table>
<thead>
<tr>
<th>Terpenoid class</th>
<th>Name of terpenoid</th>
<th>Source of isolation</th>
<th>IC$_{50}$ value on K562 cells</th>
<th>Mechanism of action</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nortriterpenoids</td>
<td>Schisandra propinqua var. propinqua</td>
<td>&gt;100 μM</td>
<td>–</td>
<td>[139]</td>
<td></td>
</tr>
<tr>
<td>Kadlongilactone D</td>
<td>Kadsura longipedunculata</td>
<td>1.92 μM</td>
<td>–</td>
<td>[140]</td>
<td></td>
</tr>
<tr>
<td>Six triterpenes</td>
<td>fractions of Acriphyllum rossii methanolic extract</td>
<td>12.2–28.7 μM</td>
<td>–</td>
<td>[141]</td>
<td></td>
</tr>
<tr>
<td>Argetatin B</td>
<td>Parthenium argentatum</td>
<td>Cytotoxic at 5–25 μM con.</td>
<td>–</td>
<td>[142]</td>
<td></td>
</tr>
<tr>
<td>Celastrol (quinone methide triterpene)</td>
<td>Tripterygium wilfordii Hook F</td>
<td>–</td>
<td>ipSTAT5, p-CRKL, pERK1/2, p-Akt, p-BCR-ABL, Bcl-xl, Mcl-1, survivin, Hsp90</td>
<td>[143]</td>
<td></td>
</tr>
</tbody>
</table>

*LC$_{50}$, lethal concentration.

Table 5. Anti-CML activity of terpenoids.
<table>
<thead>
<tr>
<th>Polyketides</th>
<th>Name of compound</th>
<th>Source of isolation</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; value on K562</th>
<th>Mechanism of action</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epiaspinonediol</td>
<td>Aspergillus sp. 16–02–1</td>
<td>44.3 μg/mL</td>
<td>–</td>
<td>–</td>
<td>[146]</td>
</tr>
<tr>
<td>Geldanamycin</td>
<td>Streptomyces sp.</td>
<td>–</td>
<td>16 – 02 – 144.3 μg/mL</td>
<td>↓c-Raf, Akt, BCR-ABL</td>
<td>[148]</td>
</tr>
<tr>
<td>Heveadride</td>
<td>Ascomyces sp.</td>
<td>82.7 ± 11.3 μM</td>
<td>↑TNFα</td>
<td>[149]</td>
<td></td>
</tr>
<tr>
<td>Gilvocarin HE</td>
<td>Streptomyces sp.</td>
<td>45 μM</td>
<td>–</td>
<td>[130]</td>
<td></td>
</tr>
<tr>
<td>Radicicol</td>
<td>Dithesxovora sp.</td>
<td>–</td>
<td>↓p-Raf1, p-BCR-ABL</td>
<td>[151]</td>
<td></td>
</tr>
<tr>
<td>Rhizoxin</td>
<td>Burkholderia rhizoxina</td>
<td>5×10&lt;sup&gt;−7&lt;/sup&gt; μg/mL</td>
<td>–</td>
<td>[152]</td>
<td></td>
</tr>
<tr>
<td>Salarin C</td>
<td>Fascaplysinopis sp.</td>
<td>0.1 μM</td>
<td>↑ caspase 3 and 9 cleavage</td>
<td>[153]</td>
<td></td>
</tr>
<tr>
<td>Tausalarin C</td>
<td>Fascaplysinopis sp.</td>
<td>1 μM</td>
<td>–</td>
<td>[154]</td>
<td></td>
</tr>
<tr>
<td>Trineurone E</td>
<td>Pseudomonas trineura</td>
<td>26 μM</td>
<td>–</td>
<td>[155]</td>
<td></td>
</tr>
<tr>
<td>Lignans</td>
<td>Arctigenin</td>
<td>–</td>
<td>↑Bax and ↓Bcl-2</td>
<td>[157]</td>
<td></td>
</tr>
<tr>
<td>Cleistanthin A</td>
<td>Cleistanthus collitus (Rox B)</td>
<td>0.4 μM</td>
<td>–</td>
<td>[158]</td>
<td></td>
</tr>
<tr>
<td>5,5′-Dimethoxylaricresinol-4′-O-β-D-glucoside (DMAG)</td>
<td>Mahonia</td>
<td>–</td>
<td>↓IC&lt;sub&gt;50&lt;/sub&gt; of DOX from 34.93 to 12.51 μM</td>
<td>[159]</td>
<td></td>
</tr>
<tr>
<td>Honokiol</td>
<td>Magnolia officinalis</td>
<td>28.4 μM</td>
<td>–</td>
<td>[160]</td>
<td></td>
</tr>
<tr>
<td>6-Hydroxyjusticidin C</td>
<td>Justica procumbens</td>
<td>43.9 ± 2.9 μM</td>
<td>↑ROS levels, caspase 3</td>
<td>[161]</td>
<td></td>
</tr>
<tr>
<td>(+)-Laricresinol 9′-p-coumarate</td>
<td>Larix olgensis var. koreana.</td>
<td>2.9 μg/ml</td>
<td>–</td>
<td>[162]</td>
<td></td>
</tr>
<tr>
<td>4-Methoxy magndaldehyde</td>
<td>Magnolia officinalis</td>
<td>3.9 μg/ml</td>
<td>–</td>
<td>[163]</td>
<td></td>
</tr>
<tr>
<td>Saponins</td>
<td>Astragagiosides A, B, C (19-norand aromatic B ring bearing steroid aglycone)</td>
<td>Astegor dumbea</td>
<td>26.8–45.6 μM</td>
<td>[168]</td>
<td></td>
</tr>
<tr>
<td>Wattoside G, H, and I (steroidal saponins)</td>
<td>Tapistra watti Hook.F.</td>
<td>35.67, 76.16 and 76.96 μM</td>
<td>–</td>
<td>[169]</td>
<td></td>
</tr>
<tr>
<td>Tenacissoside C (steroidal saponins)</td>
<td>Marsdenia tenacissima</td>
<td>31.4 μM</td>
<td>↓ cyclin D, Bel-2, Bel-xl, and ↑ caspases 3, 9, Bax and Bak</td>
<td>[170]</td>
<td></td>
</tr>
<tr>
<td>Compounds 14 and 15 (C21-steroidal pregnane sapogenins)</td>
<td>Cynanchum wilfordii roots</td>
<td>6.72 μM</td>
<td>–</td>
<td>[171]</td>
<td></td>
</tr>
<tr>
<td>Total saponin content</td>
<td>Aralia Taibaiensis</td>
<td>–</td>
<td>Loss of MMP, ↑ Bax and ↓ Bcl-2</td>
<td>[172]</td>
<td></td>
</tr>
</tbody>
</table>
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 Gleevec 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].

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

*LC<sub>50</sub>—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].
<table>
<thead>
<tr>
<th>Name of NP</th>
<th>Source of isolation</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; value on K562 cells</th>
<th>Mechanism of action</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylenic metabolites</td>
<td>Stelletta sp.</td>
<td>43.5, 51.3 and 62.5 μg/ml</td>
<td>–</td>
<td>[180]</td>
</tr>
<tr>
<td>Betanin (betacyanin pigment)</td>
<td>Opuntia ficus-indica</td>
<td>40 μM</td>
<td>↓ PARP cleavage, release of Cyt C and ↓ BCI-2. Loss of MMP</td>
<td>[182]</td>
</tr>
<tr>
<td>Bufalin 3β-acrylic ester (Bufadienolide)</td>
<td>“Ch’an Su”</td>
<td>6.83 nM</td>
<td>–</td>
<td>[183]</td>
</tr>
<tr>
<td>3-Formylcarbazole, methylcarbazole-3-carboxylate and 2-methoxy-1-(3-methyl-buten-1-yl)-9H-carbazole-3-carbaldehyde</td>
<td>Clausena lanisum (Lour.) Skeels</td>
<td>20.48 ± 1.78, 26.5 ± 2.12 and 23.49 ± 1.85 μg/ml</td>
<td>–</td>
<td>[184]</td>
</tr>
<tr>
<td>Toxicarioside F and G</td>
<td>Latex of Antaris toxicaria (Pers.) Lasch</td>
<td>–</td>
<td>–</td>
<td>[185]</td>
</tr>
<tr>
<td>Pangelin and oxypropycajan hydrate acetamide</td>
<td>Angelica dakteha</td>
<td>8.6–14.6 μg/ml</td>
<td>–</td>
<td>[186]</td>
</tr>
<tr>
<td>Mamea A/BA</td>
<td>Calophyllum brasiliense</td>
<td>0.04–0.59 μM</td>
<td>–</td>
<td>[187, 188]</td>
</tr>
<tr>
<td>Cryptotanshinone (lipid soluble active compound)</td>
<td>Salvia miltiorrhiza</td>
<td>–</td>
<td>induced apoptosis ↑ PARP cleavage and ↓ BCR-ABL, STAT3, mTOR &amp; eIF4E</td>
<td>[189, 190]</td>
</tr>
<tr>
<td>Bavaracoline (Chalcones)</td>
<td>–</td>
<td>2.7 μM</td>
<td>–</td>
<td>[191]</td>
</tr>
<tr>
<td>Polyanthumin (novel chalcone trimmer) and sulforetin</td>
<td>Menecylon polyanthum H.L. Li.</td>
<td>45.4 and 30.5 μg/ml</td>
<td>–</td>
<td>[192]</td>
</tr>
<tr>
<td>(−)-Cubebin</td>
<td>Piper cubeba</td>
<td>8.66 ± 0.43 μM</td>
<td>–</td>
<td>[193]</td>
</tr>
<tr>
<td>Denbinobin</td>
<td>5-Hydroxy-3,7-dimethoxy-1,4-phenanthraquinone</td>
<td>1.84 μM</td>
<td>↓ BCR-ABL, CrkL and G2/M phase</td>
<td>[194]</td>
</tr>
<tr>
<td>Digallic acid</td>
<td>Pistacia lentiscus</td>
<td>–</td>
<td>Induced DNA fragmentation and pro-apoptotic effect in CML cells</td>
<td>[195]</td>
</tr>
<tr>
<td>1,4,5-Trihydroxy-7-methoxy-9H-fluoren-9-one, dendorfolin and denchrysan (fluorenones)</td>
<td>Dendrobiun chrysotrichum</td>
<td>32.18, 26.65 and 52.28 μg/ml</td>
<td>–</td>
<td>[196]</td>
</tr>
<tr>
<td>C27-Steroidal glycoside</td>
<td>Liriope graminifolia (Linn.) Baker</td>
<td>18.6 μg/ml</td>
<td>–</td>
<td>[198]</td>
</tr>
<tr>
<td>9α-Acetoxyartecanin, apressin, inducumenone and centaureidin</td>
<td>Achillea clavennae</td>
<td>9.84 ± 2.52, 4.44 ± 0.76, 92.53 ± 8.43 and 5.37 ± 0.8 μM</td>
<td>–</td>
<td>[199]</td>
</tr>
<tr>
<td>Perforanoid A (limonoid)</td>
<td>–</td>
<td>4.24 μM</td>
<td>–</td>
<td>[200]</td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>Methanol extracts of pros and Japanese millet</td>
<td>68 μM</td>
<td>–</td>
<td>[201]</td>
</tr>
<tr>
<td>β- and α-Mangostin</td>
<td>Garcinia malacens</td>
<td>–</td>
<td>–</td>
<td>[202, 203]</td>
</tr>
<tr>
<td>Name of NP</td>
<td>Source of isolation</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt; value on K562 cells</td>
<td>Mechanism of action</td>
<td>References</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>------------------------------------------------------</td>
<td>--------------------------------------</td>
<td>--------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Nudifloside and linearside (iridoid)</td>
<td>EtOH extract of the aerial parts of Callicarpa nudiflora Hook</td>
<td>0.40 μM and 0.48 μM</td>
<td>–</td>
<td>[204]</td>
</tr>
<tr>
<td>Parthenolide</td>
<td>–</td>
<td>0.40 μM, 0.48 μM and 0.05 μM</td>
<td>Induced apoptosis</td>
<td>[205]</td>
</tr>
<tr>
<td>Perezone</td>
<td>Perzia spp.</td>
<td>–</td>
<td>Cytotoxic to CML cells at 25, 50 and 100 μM and induced apoptosis</td>
<td>[206]</td>
</tr>
<tr>
<td>Compound 6a (phenalenone metabolite)</td>
<td>Coniothyrium cereal</td>
<td>8.5 μM</td>
<td>–</td>
<td>[207]</td>
</tr>
<tr>
<td>Polysaccharide (PSP001)</td>
<td>Punica granatum</td>
<td>52.8 ± 0.9 μg/ml</td>
<td>–</td>
<td>[209]</td>
</tr>
<tr>
<td>Riccardin F and Pakyonol (macrocyclic bisbenzyls)</td>
<td>Plagiochasma intermedium</td>
<td>0–6 μg/ml</td>
<td>–</td>
<td>[210]</td>
</tr>
<tr>
<td>Highly methoxylated bibenzyls</td>
<td>Frullania inouei</td>
<td>11.3–49.6 μM</td>
<td>–</td>
<td>[211]</td>
</tr>
<tr>
<td>Sarcovagine and β-sitosterol 5-8</td>
<td>Sarcoceca saligna</td>
<td>2.5–5 μM</td>
<td>–</td>
<td>[212]</td>
</tr>
<tr>
<td>Squamocin (ammonaceous acetylglucins)</td>
<td>–</td>
<td>–</td>
<td>¥ p21, Bax, caspase 3 &amp; Cyt. C release and ↑ cyclin B1, cdk1, Bcl-2. Loss of MMP and ↓ G2/M phase</td>
<td>[213]</td>
</tr>
<tr>
<td>Klyflaccisteroid J</td>
<td>Klyxum flaccidum</td>
<td>12.7 μM</td>
<td>–</td>
<td>[214]</td>
</tr>
<tr>
<td>Suvanine (N,N-dimethyl-1,3-dimethyl/herbitopine salt) and suvanine-tetram derivatives (4–8)</td>
<td>Coscinoderma sp. sponge</td>
<td>2.2, 1.9, 3.9, 4.6, 3.9 and 3.6 μM</td>
<td>–</td>
<td>[215]</td>
</tr>
<tr>
<td>ar-Turmerone</td>
<td>Curcuma longa L</td>
<td>20–50 μg/ml</td>
<td>Induced DNA fragmentation and apoptosis</td>
<td>[216]</td>
</tr>
<tr>
<td>Terpene metabolites (1–3)</td>
<td>Clathria gombauensis</td>
<td>4.7, 3.9 and 2.1 μM</td>
<td>–</td>
<td>[217]</td>
</tr>
<tr>
<td>Toxicarioside H (nor-cardenolide)</td>
<td>Antiaris toxicaria (Pers.) Lesch</td>
<td>0.037 μg/ml</td>
<td>–</td>
<td>[218]</td>
</tr>
<tr>
<td>Tripolide</td>
<td>Chinese herbal extract</td>
<td>–</td>
<td>↓ Nrf2 and HIF-1α mRNA and protein expression</td>
<td>[219]</td>
</tr>
<tr>
<td>10-(Chrysophanol-7′-yl)-10-hydroxychrysophanol-9-anthrone and ramosin</td>
<td>Fractons of EtOH extract of Asphodelus microcarpus Salzm. et Vivi</td>
<td>0.15 ± 0.02 and 0.65 ± 0.01 μM</td>
<td>–</td>
<td>[220]</td>
</tr>
</tbody>
</table>
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

Woodfordini I (macrocyclic ellagitannin dimer)
–
– ↓ Bcl-2, Bcl-xL, Bax, c-Abl & BCR-ABL and Loss of MMP

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

Xindongnins C–D, A, B, melissoidesin G, dawoensin A and glabcensin V
Isodon rubescens var. rubescens
0.3–7.3 μg/ml

Hyperbeanols B and D
MeOH extract of Hypericum beanie
16.9 and 20.7 μM

Rhodexin A
Rhodea japonica
19 nM ↓ G2/M phase induced apoptosis

Curcumin
Curcumina longa
20 μg/ml ↓ BCR-ABL, Hsp90, WT1

Gambogic acid
Garcinia hanburyi
0.62 μM ↓ p-BCR-ABL, pSTAT5, p-CRKL, pERK1/2, p-Akt

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

Chloroform extract of Polyalthia rumphi stem
40–60μg/ml
–

Chloroform extract of Tecomella undulata bark
30 μg/ml ↑ FAS, FADD, & caspase 8, 3/7. Induced DNA fragmentation & apoptosis

DCM) extract of Psidium guajava L.
32 μg/ml
–

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

<table>
<thead>
<tr>
<th>Name of NP</th>
<th>Source of isolation</th>
<th>IC50 value on K562 cells</th>
<th>Mechanism of action</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withametelins I, J, K, L and N</td>
<td>MeOH extract of Datura metel flowers</td>
<td>0.05, 2.5, 0.12, 0.55 and 0.46 μM</td>
<td>–</td>
<td>[221]</td>
</tr>
<tr>
<td>Woodfordini I (macrocyclic ellagitannin dimer)</td>
<td>–</td>
<td>–</td>
<td>↓ Bcl-2, Bcl-xL, Bax, c-Abl &amp; BCR-ABL and Loss of MMP</td>
<td>[222]</td>
</tr>
<tr>
<td>Gaudichaudic acid, isogambogenic acid and deoxygaudichaudione A (xanthones)</td>
<td>Garcinia hanburyi resin</td>
<td>0.41 ± 0.03, 2.1 ± 0.14 and 1.74 ± 0.22 μg/ml</td>
<td>–</td>
<td>[223]</td>
</tr>
<tr>
<td>Xindongnins C–D, A, B, melissoidesin G, dawoensin A and glabcensin V</td>
<td>Isodon rubescens var. rubescens</td>
<td>0.3–7.3 μg/ml</td>
<td>–</td>
<td>[224]</td>
</tr>
<tr>
<td>Hyperbeanols B and D</td>
<td>MeOH extract of Hypericum beanie</td>
<td>16.9 and 20.7 μM</td>
<td>–</td>
<td>[225]</td>
</tr>
<tr>
<td>Rhodesin A</td>
<td>Rhodesa japonica</td>
<td>19 nM ↓ G2/M phase induced apoptosis</td>
<td></td>
<td>[226]</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Curcumina longa</td>
<td>20 μg/ml ↓ BCR-ABL, Hsp90, WT1</td>
<td></td>
<td>[227, 228]</td>
</tr>
<tr>
<td>Gambogic acid</td>
<td>Garcinia hanburyi</td>
<td>0.62 μM ↓ p-BCR-ABL, pSTAT5, p-CRKL, pERK1/2, p-Akt</td>
<td></td>
<td>[229, 230]</td>
</tr>
</tbody>
</table>

*IC50-lethal concentation.
<table>
<thead>
<tr>
<th>Plant extract</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; value on K562 cells</th>
<th>Mechanism of action</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCM extract</td>
<td>69 µg/ml</td>
<td>↑ caspases, PARP cleavage. Induced DNA damage and apoptosis</td>
<td>[239]</td>
</tr>
<tr>
<td>Artemisia turanica Krasch</td>
<td>*20 ± 1.5 and 43.75 ± 0.78 µg/ml</td>
<td>–</td>
<td>[240]</td>
</tr>
<tr>
<td>HEX and DCM extract of Mesua beccariana</td>
<td>*17.5 ± 1.02 and 22.91 ± 1.25 µg/ml</td>
<td>–</td>
<td>[240]</td>
</tr>
<tr>
<td>HEX extract of Mesua congestiflora</td>
<td>40.63 ± 1.45 µg/ml</td>
<td>–</td>
<td>[240]</td>
</tr>
<tr>
<td>DCM fraction of Melissa officinalis</td>
<td>At 50 µg/ml concentration, it induced 65.04 ± 0.93% apoptotic rate</td>
<td>↑ Fas, Bax mRNA levels and Bax/Bcl-2 ratio</td>
<td>[241]</td>
</tr>
<tr>
<td>DCM fraction of the crude EtOH extract of Echinops grijissi Hance roots</td>
<td>30 µg/ml</td>
<td>–</td>
<td>[242]</td>
</tr>
<tr>
<td>EtOH extract of Peresokia sacharosa</td>
<td>130 ± 0.03 µg/ml</td>
<td>↑ caspases, cyt. C release, p21 &amp; p53 and ↓ Akt and Bcl-2</td>
<td>[244]</td>
</tr>
<tr>
<td>EtOH extract of propolis (NP produced by stingless bee Melipona orbignyi)</td>
<td>At 250 and 500 µg/ml promoted cell death of CML cells by 15 ± 1 and 63 ± 2%</td>
<td>–</td>
<td>[245]</td>
</tr>
<tr>
<td>EtOH extract of Isodon japonicas</td>
<td>2.7 µg/ml</td>
<td>–</td>
<td>[246]</td>
</tr>
<tr>
<td>EtOH root extract of Allamanda schottii</td>
<td>At 800 µg/ml showed cytotoxicity</td>
<td>–</td>
<td>[247]</td>
</tr>
<tr>
<td>EtOH stem and leaf extract of Physalis peruviana</td>
<td>0.02 and 0.03 g/ml</td>
<td>–</td>
<td>[248]</td>
</tr>
<tr>
<td>Alcoholic extract of Dendrostrella lesserti</td>
<td>28 µl and 5 × 10&lt;sup&gt;−9&lt;/sup&gt;M</td>
<td>–</td>
<td>[249]</td>
</tr>
<tr>
<td>EtOH extract of Rosmarinus officinalis L</td>
<td>1/400 dilution</td>
<td>–</td>
<td>[251]</td>
</tr>
<tr>
<td>EtOH extract of Goldfussia psilostachys</td>
<td>0.5 µg/ml</td>
<td>↑ CML cells in G&lt;sub&gt;2&lt;/sub&gt;/M phase</td>
<td>[252]</td>
</tr>
<tr>
<td>Fraction from EtoAc of Caesalpinia spinosa</td>
<td>44.5 ± 4.05 µg/ml</td>
<td>induced chromatin condensation. Loss of MMP &amp; ↑ caspase 3</td>
<td>[253]</td>
</tr>
<tr>
<td>EtoAc extract of Helichrysum plicatilis flowers</td>
<td>25.9 µg/ml</td>
<td>–</td>
<td>[254]</td>
</tr>
<tr>
<td>MeOH extract of Linum persicum</td>
<td>0.1 µg/ml</td>
<td>–</td>
<td>[255]</td>
</tr>
<tr>
<td>MeOH extracts of Echinophora cinerea and Cirsium bracteosum</td>
<td>Less than 20 µg/ml</td>
<td>–</td>
<td>[256]</td>
</tr>
<tr>
<td>MeOH extract of Galium mite</td>
<td>39.8 µg/ml</td>
<td>–</td>
<td>[256]</td>
</tr>
<tr>
<td>MeOH extract of Cyperus rotundus</td>
<td>175 ± 1.2 µg/ml</td>
<td>Induced DNA damage</td>
<td>[257]</td>
</tr>
<tr>
<td>TAF273, F3 and F4 fractions of MeOH extract of Eurycoma longifolia Jack</td>
<td>19, 55 and 62 µg/ml</td>
<td>–</td>
<td>[258]</td>
</tr>
<tr>
<td>MeOH extract of Rhaphidophora korthalsii</td>
<td>–</td>
<td>Enhanced Natural killer cells to kill K562, ↑IFN-Υ, TNF-α</td>
<td>[259]</td>
</tr>
</tbody>
</table>
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  
ew 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
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