Anticancer and multidrug-resistance reversing potential of traditional medicinal plants and their bioactive compounds in leukemia cell lines

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[ABSTRACT] Multidrug resistance remains a serious clinical problem in the successful therapy of malignant diseases. It occurs in cultured tumor cell lines, as well as in human cancers. Therefore, it is critical to develop novel anticancer drugs with multidrug-resistance modulating potential to increase the survival rate of leukemia patients. Plant-derived natural products have been used for the treatment of various diseases for thousands of years. This review summarizes the anticancer and multidrug-resistance reversing properties of the extracts and bioactive compounds from traditional medicinal plants in different leukemia cell lines. Further mechanistic studies will pave the road to establish the anticancer potential of plant-derived natural compounds.

[KEY WORDS] Traditional medicinal plants; Leukemia; Multidrug resistance (MDR); Reversal multidrug resistance; Apoptosis

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Introduction

Cancer is one of the leading causes of human deaths worldwide, accounting for 7.6 million deaths in 2008. The World Health Organization (WHO) has estimated that deaths from cancer worldwide are projected to continue rising, with an estimated 13.1 million casualties in 2030 [1]. By 2050, 27 million new cancer cases and 17.5 million cancer deaths are projected to occur in the world [2]. It is also estimated that 48,610 people (27,880 men and 20,730 women) will be diagnosed with leukemia in 2013 [3]. Leukemia is a cancer of leukocytes, characterized by the presence of a large number of immature white blood cells in the bone marrow, thymus, lymph node, spleen, and circulating blood. Leukemias are divided into acute and chronic types. When immature white blood cells or blasts proliferate, presentation is usually acute, whereas leukemias arising from mature cells tend to be chronic. Leukocytes are usually of lymphoid origin (T and B cells) or myeloid origin (neutrophils, basophils, eosinophils, and monocytes). There are four main types of leukemia: chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), and acute myeloid leukemia (AML) [4]. Accordingly, much effort has been made to develop various approaches to reduce the threat posed by cancer [5], especially leukemia.

Chemotherapy is an important option in modern cancer treatment, and many, clinically available, anticancer drugs, of synthetic or natural origin, are currently used to treat some types of leukemias, lymphomas, and solid tumors [6]. Most natural products used to treat cancer for centuries are known to have multiple targets and thus are preferred over mono-targeting...
drugs \[^7\]. Chemoprevention involving the use of plant metabolites to suppress, block, or reverse the process of carcinogenesis has received considerable attention over several decades \[^8\]. Several types of phytochemicals in vegetables and fruits, such as carotenoids, flavonoids, and vitamins have been studied as potential chemopreventive agents \[^9-10\]. Conventional therapies cause serious side effects, and at best, merely extend the patient’s life span by a few years \[^11\]. Hence, there is an urgent need to utilize medicinally important, plant-derived compounds for the treatment of cancer.

The antiproliferative agents appear to act primarily by impairing cell reproductive integrity. The affected cells may remain alive and may continue to carry out many of their functions, but are unable to reproduce successfully. Synthesis of DNA, RNA, and other cell constituents may continue at the normal rate, but the cells are unable to divide and this eventually leads to cell death \[^12-13\]. In tumor cell lines, multidrug resistance is often associated with an ATP-dependent decrease in cellular drug accumulation which is attributed to the overexpression of certain ATP-binding cassette (ABC) transporter proteins \[^14\]. P-Glycoprotein belongs to the ABC transporter superfamily of membrane transport proteins \[^15\]. P-glycoprotein mediates resistance to various classes of anticancer drugs including vinblastine, daunorubicin, and paclitaxel, by actively extruding the drugs from the cells \[^16\]. The search for inhibitors of anticancer drug efflux transporters has uncovered natural compounds as promising candidates \[^17\]. Anticancer drugs which circumvent the ABC transporters might be a solution for drug resistance. Compounds that reverse the resistance against anticancer drugs are called multi-drug resistance (MDR) inhibitors, MDR modulators, MDR reversal agents, or chemosensitizers \[^18\]. Currently, there is increased interest globally to identify multidrug resistance reversal compounds from medicinal plants having low or no side effects for use in cancer treatment \[^19-21\].

Medicinal plants are the oldest friends of mankind. They have provided food and shelter and served to treat many ailments. Traditional or natural medicine, has always existed in one form or other in different cultures and civilizations, including traditional Chinese medicine (TCM, China), Ayurvedic (India), Egyptian, Native American, Kampo (Japan), and Greco-Arab or Unani-Tibb (South Asia) systems. Traditional medicine all over the world is currently being re-evaluated through extensive research on various medicinal plant species and their therapeutic properties \[^22\]. Here the antiproliferative and multidrug resistance reversing potential of active compounds present in traditional medicinal plants on different leukemia cell lines are reviewed. In this study, the medicinal plants and bioactive compounds have been chosen with respect to in vitro anti-leukemic properties and MDR reversing activity.

**Anti-Leukemic Activities of Traditional Medicinal Plants on Different Cell Lines**

*Alisma orientale*  
*Alisma orientale* (Sam.) Juz. (Alismataceae) is widely used in traditional Chinese medicine (TCM). Rhizoma alismatis (RA) is a stem tuber derived from this plant used to treat hyperlipidemia \[^23\]. It is one of the main constituents of the Chinese herbal remedy formulation Long Dan Xie Gan Wan (LD), and showed cytotoxicity against HL60 human promyelocytic leukaemia cell lines \[^24\]. Investigations of TCM formulae also established that *A. orientale* has anti-diabetic and diabetic foot ulcer healing properties \[^25-26\]. Alisol B 23-acetate (ABA), an active compound isolated from *A. orientale* exhibited P-gp reversing activity in the MDR leukemia cell line (K562-DR). ABA (1–10 µmol-L\(^{-1}\)) could sensitize and reverse the resistance of K562-DR cells to vinblastine by arresting the cell cycle at the G2/M phase. Further, a combination index study revealed that ABA had synergism with anticancer drugs, but not with non-P-gp substrates, such as cis-platin and fluorouracil (5-FU) \[^27-28\].

**Annona glabra**

*Annona glabra* L. (Annonaceae), also known as pond apple tree, grows in tropical North, Central, South America, West Africa, and Asia \[^29\]. The stem bark of *A. glabra* possesses a high degree of antibacterial, antifungal, anti-helminthic, insecticidal, sporicidal, and cytotoxic activities \[^30\]. Diterpenoid compounds, such as cunabid acid and ent-kauran-19-α-l-ol-β-acid, from this plant inhibited the proliferation of the human liver cancer cell line SMMC-7721 \[^31\]. Cochran et al. investigated the anticancer potential of alcoholic extracts prepared from *A. glabra* leaves, pulp, and seed against human leukemia cell lines. The alcoholic extract of the seeds of *A. glabra* was highly cytotoxic to drug sensitive (CEM) and vinblastine-resistant leukemia (CEM/VELB) cell lines in a concentration-dependant manner. The extract was not cytotoxic to normal human lymphocytes. Treatment of CEM and CEM/VELB cells with the seed extract induced the apoptosis, increased the accumulation of daunorubicin and up-regulated the expression of cyclin kinase inhibitor. The results of this study revealed the competitive P-glycoprotein binding ability, cell cycle arrest and MDR reversing effect of the seed extract \[^32\]. Further isolation, identification, and characterization of active principles from *A. glabra* are required to discern the possible anticancer compounds.

**Aronia melanocarpa**

*Aronia melanocarpa* (Michx.) Elliott (Rosaceae), known as black chokeberry, is a shrub native to North America \[^33\]. The juice of *A. melanocarpa* is a rich source of natural polyphenols and possesses numerous health benefits, including cardioprotective, hepatoprotective, and anti-diabetic activities \[^34-35\]. The reconstituted, commercially available, polyphenol-rich *A. melanocarpa* juice inhibited acute lymphoblastic leukemia Jurkat cell proliferation, which was associated with cell cycle arrest in the G2/M phase, up-regulation of the expression of tumor suppressor p73, and active caspase 3, and a down-regulation of the expression of cyclin B1. It also induced apoptosis in different human lymphoblastic leukemia cells (HSB-2, Molt-4, and CCRF-CEM) \[^36\]. These results suggest that *A. melanocarpa* has chemotherapeutic properties against acute lymphoblastic leukemia by specifically targeting lymphoblast-
derived tumor cells.

*Coptis chinensis*

*Coptis chinensis* Franch. is a well-known, traditional Chinese medicine, which belongs to the family Ranunculaceae. The main active ingredient is berberine, an isoquinoline alkaloid, which plays an important role in treating visceral leishmaniasis [37–38]. Berberine alkaloids, such as berberine, coptisine, and palmatine have strong antibacterial activity on *Escherichia coli*, and protect against ethanol-induced gastric lesions by inhibiting gastric acid secretions [39–40]. Lin et al. observed the cytotoxic effect in various leukemia cell lines K562 (IC_{50} 29 µg⋅mL^{-1}), U937 (IC_{50} 29 µg⋅mL^{-1}), P3H1 (IC_{50} 31 µg⋅mL^{-1}) and Raji (IC_{50} 4 µg⋅mL^{-1}) of crude extracts of *C. chinensis*. Interestingly, the isolates berberine (IC_{50} 0.6 to 14.1 µg⋅mL^{-1}) and coptisine (IC_{50} 0.6 to 7.2 µg⋅mL^{-1}) showed moderate inhibitory activity in leukemia cell lines [41]. Berberine suppresses the growth of human promyelocytic leukemia HL-60 and murine myelomonocytic leukemia WEHI-3 cell lines by activating caspase-3. The increased production of ROS and Ca^{2+} led to cell death, DNA damage, and genomic instability [42]. These findings reflect that berberine isolated from *C. chinensis* inhibits the growth of leukemia cell lines through a caspase-dependent apoptotic pathway.

*Evodia rutaecarpa*

*Evodiae fructus* is the fruit of *Evodia rutaecarpa* (Juss.) Benth. (Rutaceae). In Chinese, the fruit is known as wu zhuyu. It has been used in the traditional Chinese medicine (TCM) for more than 2000 years for treating digestive problems, and is officially listed in the Chinese Pharmacopoeia [43]. Evodiamine is an indole alkaloid, and one of the bioactive compounds extracted from this plant. It (10 µmol⋅L^{-1}) inhibits the proliferation of human acute T-lymphocytic leukemia CCRF-CEM cells (IC_{50} 0.57 ± 0.05 µmol⋅L^{-1}), and also induces apoptosis by arresting at the G2/M phase and enhancing polymerized tubulin levels [44]. Lee et al. tested evodiamine for its apoptotic mechanism in U937 human leukemia cell line. Flow cytometry analysis revealed that evodiamine markedly increased the accumulation of sub-G1 phase cells. Further, it activated the mitochondrial caspase-dependent apoptotic pathway, which was partly prevented by pretreatment with a pancaspase inhibitor z-VD-FMK (benzoylloxycarbonyl-Val-Ala-Asp-fluoromethyl ketone). This result suggested that evodiamine-induced apoptosis was mediated by the caspase-independent, as well as the caspase-dependent, apoptotic pathways. At the same time, evodiamine did not cause cytotoxicity to human normal peripheral blood mononuclear cells (PBMC) *in vitro* [45]. These encouraging results highlight the importance of further research on evodiamine in plant-derived anticancer drug development.

*Garcinia hanburyi*

*Garcinia hanburyi* Hook. f. a small to medium-sized tree belonging to the family Clusiaceae, is widely distributed in Southeast Asia. In China and Thailand gamboges, a yellow gum-resin secreted in stembark, has been used in traditional medicine as a potent purgative and for infected wounds [46–47]. In addition, xanthones derived from the resin of *G. hanburyi* have been shown to induce apoptosis in human gastric carcinoma cells and cholangiocarcinoma cells [38–40]. Han et al. [50] collected this plant from Shaxi province China, isolated thirteen xanthones and analyzed the resin by HPLC and NMR. Ten xanthones (gaudichaudiacid, isogambogenic acid, deoxygaudichaudione A, gambogenic acid A, gambogenic acid, desoxygambogenin, isomorellic acid, morellic acid, desoymorellin, and isomorellin) exhibited considerable cytotoxic activity against both a drug-sensitive leukemia K562 (K562/S) cell line and a doxorubicin-resistant leukemia cell subline (K562/ADR). The range of IC_{50} values of xanthones (0.6 to 3 µg⋅mL^{-1}) in drug resistant K562/ADR was much lower than that of doxorubicin (1.79 µg⋅mL^{-1}). All of the compounds need to be evaluated for their cell signaling and apoptotic mechanism of action to study the MDR-reversing effect of xanthones.

*Gardenia obtusifolia*

There are 80 species in the genus *Gardenia* (Rubiaceae), and widely distributed in the tropical forests in various parts of the world. *Gardenia obtusifolia* Roxb. ex Hook. f. is a shrub traditionally used in Thailand for a variety of ailments including bacterial disease, pyrexia, pain, and diuresis [51–53]. *G. obtusifolia* (DH-PMF) was isolated from the leaves of *G. obtusifolia* [54]. Phromnoi et al. tested DH-PMF against chronic myelogenous leukemia (KBM-5), human lymphoblastic leukemia (Jurkat), promyelocytic leukemia (HL-60), and chronic myelogenous leukemia (K562) cell lines. DH-PMF inhibited the proliferation of all leukemia cell lines through the modulation of anti-apoptotic gene products, cell cycle proteins, activation of caspases, and the inhibition of cell signaling PI3K/ AKT/GSK3β (phosphatidylinositol 3 kinase-activation-glycogen synthase kinase 3-beta) pathway [55]. This study shows that DH-PMF has the potential to induce apoptosis in cancer cells.

*Ichnocarpus frutescens*

*Ichnocarpus frutescens* (L.) W.T.Aiton, is a large, climbing, multi-branched shrub belonging to the family Apocynaceae. It is typically found in rural areas of India, and grows up to an altitude of 4,000 ft [56]. *In vitro* cytotoxicity of a polyphenolic extract derived from the leaves was performed against the monocytoid leukemia (U-937) and erythroleukemia (K-562) cell lines. MTT assay results revealed that the polyphenolic extract, at 20 µg⋅mL^{-1}, effectively inhibited the proliferation of the U-937 (70%) and K-562 (60%) cell lines [57]. Further phytochemical investigation of *I. frutescens* extracts would give an idea on anti-leukemic bioactive compounds.

*Picrolemma sprucei*

Silva et al. isolated the quassinoids (polyoxygenated and degraded triterpenes) isobrucin B and neoergeolide from the
Amazonian medicinal plant *Picrolemma sprucei* Hook.f. (Simaroubaceae). Isobrucine B and neosergeolide exhibited cytotoxicity against HL-60 leukemia cell line [58]. Cavalcanti *et al.* observed that neosergeolide strongly inhibited the human promyelocytic leukemia cell (HL-60) proliferation (IC50 0.1 µmol·L−1). Interestingly, it had no antiproliferative effect on human peripheral blood mononuclear cells (PBMC). In addition, biochemical and molecular analysis revealed that submicromolar concentrations (0.05, 0.1, and 0.2 µmol·L−1) of neosergeolide could induce apoptosis in HL-60 cells [59].

Since natural quassinoids have cytotoxic properties it can be further investigated to find out the mechanism of action.

*Piper methysticum*

*Piper methysticum* G. Forst. belongs to the Piperaceae family, and is also known as kava or kava-kava. Kava drink, a traditional health beverage from the extract of its rhizome is commonly used and lowers the cancer incidence in South Pacific countries due to its chemopreventive efficacy [60].

Kava acts as a cognitive enhancing agent which relieves stress, anxiety, and sleeplessness [61-62]. Compounds such as kavalactone and the chalcone flavokawavin B have the ability to induce apoptosis in lung, prostate, colon, squamous carcinoma, synovial sarcoma, uterine leiomyosarcoma, and human osteosarcoma cells [63-69]. Weiss *et al.* prepared aqueous methanol extract from kava-kava root powder. They studied the P-gp-inhibitory activity in the murine monocytic leukemia cell line P388 and the doxorubicin resistant cell line P388/dx overexpressing mdr1a/1b. Calcein assay and f2 (concentration needed to double baseline fluorescence) values was obtained to determine the P-gp inhibitory potency. The results revealed that the crude extract (f2 170 µg·mL−1) and the kavalactones (f2 17 to 90 µmol·L−1) showed moderate to potent P-gp inhibitory activity [70]. Therefore, further investigation on kavalactone and flavokawavin B may be of interest in developing MDR reversing agents.

*Premna herbacea*

*Premna herbacea* Roxb., belonging to the family Lamiaceae, is used in Siddha, the traditional system of medicine practiced in South India [71]. The plant is a small bushy tree, and has been used for the treatment of various human diseases [72].

Gupta *et al.* [73] isolated a novel compound bharangin, a diterpenoid quinonemethide from the acetone extract of the root nodules of *P. herbacea*, and studied its cytotoxic properties on human cell lines U937 (leukemic monocyte lymphoma), HL-60 (promyelocytic leukemia), Jurkat (T-cell leukemia), and KBM-5, K-562 (chronic myeloid leukemia). The results of this study showed that 5 µmol·L−1 bharangin suppressed the TNFα induced nuclear factor (NF)-κB activation in different leukemia cell lines by downregulating the expression of proteins involved in tumor cell survival, proliferation, invasion, angiogenesis and apoptosis. Further *in vivo* studies may support the traditional medicinal use of this plant.

*Psoralea corylifolia*

*Psoralea corylifolia* L. (Fabaceae) is a widely-used medicinal plant in China for the treatment of skin diseases [74]. Cytotoxic properties of the methanol extract fractions isolated from *P. corylifolia* seeds were carried out in the K562 and K562/ADM leukemia cell lines. Fractions IV and V (psoralen and isopsoralen) inhibited the growth of cancer cells in a dose-dependent manner and induced apoptosis significantly in tumor cells. These results suggested that psoralen and isopsoralen contribute to the anticancer effect of *P. corylifolia* [75].

*Amaryllidaceae Plants*

The Amaryllidaceae plant family contains several important alkaloids used for the treatment of Alzheimer’s disease [76]. Zupko *et al.* tested five alkaloids, 2-O-acetyllycorine, homolycorine (*Leucojum vernum* L.), pretazettine (*Sprekelia formosissima* L.), and trisphaeridine and ismine (*Hymenocallis festalis* Hort.) for their inhibitory effect on P-glycoprotein (P-gp), and their apoptosis-inducing capacity. Human MDR1-gene, transfected L5178 mouse lymphoma cells resistant towards colchicine, vinblastine, and doxorubicin were used to evaluate the multidrug reversing activity of alkaloids. Among the five alkaloids, trisphaeridine, pretazettine, and 2-O-acetyllycorine showed excellent antiproliferative effect on both the human and the mouse cell lines. In addition, trisphaeridine significantly inhibited the activity of P-glycoprotein [77]. This study provides an important clue to execute further research in developing natural MDR-reversing agents from Amaryllidaceae species.

*Berry plants*

Skupien *et al.* studied the *in vitro* antileukemic activity of extracts obtained from selected berry plant leaves against sensitive and multidrug resistant leukemia cell lines. They found that the blueberry (*Vaccinium corymbosum* L. cv Bluecrop, Ericaceae) leaf extract was the most efficient against a sensitive HL60 cell line, but presented less activity towards resistant cell lines HL60/VINC (overexpressing P-glycoprotein) and HL60/DOX (overexpressing MRP1 protein). In contrast, strawberry (*Fragaria ananassa* Duch. cv Elsanta, Rosaceae) and raspberry (*Rubus idaeus* L. cv Polana, Rosaceae) extracts exhibited high cytotoxic activity against sensitive leukemia HL60 cell line (IC50: 0.414 ± 0.095; 0.380 ± 0.074) as well as its MDR sublines, HL60/VINC (IC50: 0.133 ± 0.090; 0.130 ± 0.010) and HL60/DOX (IC50: 0.609 ± 0.032; 0.772 ± 0.065). This result suggests that compounds present in the leaves of strawberry and raspberry plants could be responsible for its cytotoxic activity [78].

*Cameroonian plants*

Medicinal plants and spices have been used traditionally to treat cancers in Cameroon. Methanol extracts from *Xylopia aethiopica* (Dunal) A.Rich. (Annonaceae) seeds, *Echinops giganteus* var. *ileyi* (C.D.Adams) C.D. Adams. (Asteraceae) rhizomes, *Imperata cylindrica* (L.) P. Beauv. (Poaceae) roots, *Dorstenia psilirus* Welw. (Moraceae) roots, and *Piper capense* L. f. (Piperaceae) seeds inhibited the proliferation of the leukemia cell line CCRF-CEM and the multidrug resistant (MDR) subline CEM/ADR5000. Among the tested plants, *X. aethiopica* exhibited the lowest IC50 value of 3.91 µg·mL−1 against CCRF-CEM, and *P. capense* showed IC50 6.56
Rhodiola rosea extracts of gastrointestinal ailments [84]. Majewska et al. found that the rhizome of Rhodiola rosea (225 and 450 µg·mL⁻¹) significantly decreased the proliferation of the human erythroleukemic cell line K-562. This extract was also found to induce intracellular reactive oxygen species (ROS) in K-562, cells and arrested cell cycle progression in G2/M phase in early and late period of exposure [83].

R. imbricata rhizome has been used extensively for its medicinal properties in traditional medicine in India, China, Tibet, Mongolia, and the former Soviet Republics, to increase physical endurance, work productivity, longevity, and medicinal properties in traditional medicine in India, China, Tibet, Mongolia, and the former Soviet Republics, to increase physical endurance, work productivity, longevity, and to treat fatigue, asthma, hemorrhage, impotence, and gastrointestinal ailments [84]. Majewska et al. found that the rhizome extract of Rhodiola rosea (225 and 450 µg·mL⁻¹) greatly reduces the survival of promielotic HL-60 leukemia cells, and inhibits cell division at the prophase stage. This leads to induction of apoptosis and necrosis in HL-60 cells, and the cells enter apoptosis from the G2/M phase of the cell cycle [85]. These observations suggest that Rhodiola species have potent anti-proliferative activity against leukemia cell lines, and provide encouraging results for future research.

Other materials

Effert et al. tested the purified compounds derived from traditional Chinese medicine (TCM) for their antileukemic activity toward CCRF-CEM cell lines. Flow cytometry analysis revealed that artesunate (60 µg·mL⁻¹ from Artemisia annua L. of the Asteraceae family) significantly increased daunorubicin accumulation in CEM/E1000 cells. Bufalin (60 µg·mL⁻¹ from Bufo marinus and B. viridis) caused a significant increase of daunorubicin accumulation in CEM/VLB100 and CEM/E1000 cells. This study showed that artesunate and bufalin possess potent anticancer activity and, after further testing, might be considered as a suitable combination treatment strategy to combat leukemia [86].

The Athapaskans are a large language group of Native Americans living in Alaska and Canada, as well as in the southwest and the West coast of the USA. Medicinal plants have a long tradition among the tribes of Native Americans to treat various human ailments [87]. Deeg et al. [88] tested twenty-nine medicinal plants of the West-Canadian Gwich’in Native American for cytotoxic activity against human acute lymphoblastic CCRF-CEM leukemia cells. Hexane extracts of three plants, Cladina mitis (Sandst.) W.L. Culb., Picea mariana (Mill.) Britton, Sterns and Poggenb. (Pinaceae), and

<table>
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<td>Alisma orientalis</td>
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<td>P-gp-inhibitory activity</td>
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</tr>
<tr>
<td>Annona glabra</td>
<td>CEMCEM/VLB</td>
<td>Multidrug-resistance reversal effect and induction of apoptosis</td>
<td>Cochrane et al. [12]</td>
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<tr>
<td>Aronia melanocarpa</td>
<td>Jurkat</td>
<td>Induction of apoptosis</td>
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</tr>
<tr>
<td>Artemisia annua</td>
<td>CEM/VLB100, CEM/E1000</td>
<td>Increases daunorubicin accumulation</td>
<td>Effert [86]</td>
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<tr>
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<td>Cytotoxicity</td>
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<tr>
<td>Eudenia Ritaearcara</td>
<td>U937</td>
<td>Caspase-dependent and caspase independent apoptotic pathways</td>
<td>Lee et al. [45]</td>
</tr>
<tr>
<td>Garcinia hanburyi</td>
<td>K562, K562/ADR</td>
<td>Cytotoxicity</td>
<td>Han et al. [58]</td>
</tr>
<tr>
<td>Gardenia obtusifolia</td>
<td>KMB-5, Jurkat, HL-60/K562</td>
<td>Modulation of antiapoptotic gene products</td>
<td>Phromnoi et al. [55]</td>
</tr>
<tr>
<td>Ichnocarpus frutescens</td>
<td>U937, K-562</td>
<td>Antiproliferation</td>
<td>Kumarappan and Mandal [37]</td>
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<td>Picrolemma sprucei</td>
<td>HL-60</td>
<td>Cytotoxicity</td>
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<td>Piper methysticum</td>
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<tr>
<td>Premna herbacea</td>
<td>U937, HL-60, Jurkat, KMB-5, K-562</td>
<td>Suppression of (NF)-κB activation</td>
<td>Gupta et al. [73]</td>
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<tr>
<td>Psoralea corylicolia</td>
<td>K562, K562/ADM</td>
<td>Induction of apoptosis</td>
<td>Wang et al. [79]</td>
</tr>
<tr>
<td>Rhodiola imbricata</td>
<td>K-562</td>
<td>Induce intracellular ROS and cell cycle arrest</td>
<td>Mishra et al. [83]</td>
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</tbody>
</table>
Table 2  List of plant-derived individual compounds showing cytotoxic and MDR-reversing activity in various leukemia cell lines

<table>
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<th>Individual compounds</th>
<th>Leukemia cell lines</th>
<th>Mechanism of action</th>
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<td>Alkaloids</td>
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<td>MDR modulator</td>
<td>Effert et al. [89]</td>
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<td>CEM/ADR5000</td>
<td>Synergistic inhibition</td>
<td>Gillet et al. [90]</td>
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<td>CEM/ADR5000</td>
<td>Induction of apoptosis</td>
<td>Eid et al. [91]</td>
</tr>
<tr>
<td></td>
<td>K562, K562/A02U-937</td>
<td>MDR reversing effect</td>
<td>Wang et al. [93]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Induction of apoptosis</td>
<td>Vázquez et al. [96]</td>
</tr>
<tr>
<td>Curcumin</td>
<td>L1210/Adr</td>
<td>Down regulation of P-gp expression</td>
<td>Choi et al. [90]</td>
</tr>
<tr>
<td>Diallyltrisulfide (DATS)</td>
<td>K562, K562/A02</td>
<td>Downregulation of NF-κB</td>
<td>Xia et al. [102]</td>
</tr>
<tr>
<td>Dihydroptchantol A</td>
<td>K562/A02</td>
<td>P-gp-inhibitory activity</td>
<td>Li et al. [103]</td>
</tr>
<tr>
<td>Guggulsterone</td>
<td>K-562, K562/DOX</td>
<td>Induction of apoptosis</td>
<td>Xu et al. [106-107]</td>
</tr>
<tr>
<td>Hyperforin</td>
<td>U937, K562</td>
<td>Caspase-3 activation</td>
<td>Quiney et al. [109]</td>
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<td>Hyperforin B1</td>
<td>U937, OCI-AML3, NB4, HL-60, K562</td>
<td>DNA fragmentation</td>
<td>Liu et al. [110], Zaher et al. [111], Merhi et al. [112], Bignon et al. [113]</td>
</tr>
<tr>
<td>Isothiocyanates</td>
<td>HL60, HL60/ADR, HL60/VCR</td>
<td>Mitotic inhibitors and apoptosis inducers</td>
<td>Jakubikova et al. [115]</td>
</tr>
<tr>
<td>Lycorine</td>
<td>K562, U937, HL-60, K562/G01</td>
<td>Induction of cell-cycle arrest</td>
<td>Liu et al. [117]</td>
</tr>
<tr>
<td>Phenolic diterpenes</td>
<td>K562, K562/R</td>
<td>Cytotoxicity</td>
<td>Valdes et al. [122]</td>
</tr>
<tr>
<td></td>
<td>K562/A02</td>
<td>P-gp-inhibitory activity</td>
<td>Yu et al. [124]</td>
</tr>
<tr>
<td>Quercetin</td>
<td>HL-60</td>
<td>Downregulation of anti-apoptotic proteins</td>
<td>Niu et al. [126]</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>K562</td>
<td>Induction of apoptosis</td>
<td>Puissant et al. [140]</td>
</tr>
<tr>
<td>Shikonin</td>
<td>U937, CCRF-CEM, CEM/ADR5000, HL-60, HL60/AR</td>
<td>Cell-cycle arrest and induction of apoptosis</td>
<td>Wieneh et al. [129]</td>
</tr>
<tr>
<td>Tetranderine</td>
<td>K562/A02</td>
<td>MDR modulator</td>
<td>Xu et al. [134]</td>
</tr>
<tr>
<td>Triterpenoids</td>
<td>K562, Lucena 1, KBM-5, U937, Jurkat</td>
<td>Induction of apoptosis</td>
<td>Fernandes et al. [136]</td>
</tr>
<tr>
<td>Vincristine</td>
<td>K562, K562/ADM</td>
<td>P-gp-inhibitory activity</td>
<td>Ikegawa et al. [138]</td>
</tr>
<tr>
<td>Withaferin A</td>
<td>K562, K562/Adr</td>
<td>NFκB inhibitors</td>
<td>Suttana et al. [142]</td>
</tr>
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</table>

Artemisia frigida Willd. (Asteraceae) revealed considerable growth inhibition on CCRF-CEM cells.

Anti-Leukemic Activities of Individual Compounds on Different Cell Lines

Alkaloids

Doxorubicin-resistant MDR subline CEM/ADR5000 is also known to overexpress MDR1, thus these cells represent an excellent model for screening the modulatory effects of active compounds on P-gp [88-90]. Eid et al. studied the effect of combinations of phytochemicals and their potential synergistic interactions against multidrug resistant cell lines. Phytochemicals including alkaloids, phenolics, and terpenoids alone, or in combination with the saponin digitoxin, were tested against the Caco-2 human colorectal adenocarcinoma cell line and the CEM/ADR 5000 adriamycin-resistant leukemia cell line. Eventually, it was found that the combination of the benzophenanthidine alkaloid sanguinarine (1 µmol·L⁻¹) and digitoxin (5 µmol·L⁻¹) with doxorubicin (0.001–100 µmol·L⁻¹) was powerful and synergistically inhibited the proliferation of both Caco-2 and CEM/ADR 5000 cells with IC₅₀ values of 0.12 and 13.19 µg·mL⁻¹, respectively. Thus, synergistic drug combinations can sensitize doxorubicin efficacy in MDR cancer cell lines [91]. Caco-2 cells are an ideal model for studying multidrug resistance since they highly express ABC transporter proteins, including P-gp (MDR1), MRPI, and BCRP [92]. The alkaloid chelidonine from Chelidonium majus L. (Papaveraceae) inhibited Pgp/MDR1 activity in a concentration-dependent manner in Caco-2 and CEM/ADR 5000 cells. cDNA expression analysis identified that treatment of Caco-2 cells with 50 µg·mL⁻¹ alkaloid extract and 50 µmol·L⁻¹ chelidonine, resulted in a sig-
significant decrease in mRNA levels of Pgp/MDR1, MRP1, BCRP, CYP3A4, GST, and hPXR. In addition, a notable increase in caspase-3 and caspase-8 mRNA was found [92]. Since the alkaloid inhibited P-gp expression and the proliferation of leukemia cells, it is suggested to further explore the use of chelidonine as a potential multidrug resistance reversal agent, alone, or in combination with other phytochemicals.

**Coumarins**

Wang et al. [93] isolated ten known coumarins from the aerial parts of *Cicuta virosa* L. (Apiaceae) roots. The coumarins were tested on the human myelogenous leukemia cell line K562 and its multidrug-resistant counterpart K562/A02. Among the isolated coumarins, 20 µmol L⁻¹ of archangelicin A and B (a methylbutenoic acid) showed a remarkable MDR reversing effect. The non-cytotoxic concentration (20 µmol L⁻¹) of the compounds A and B reversed the resistance of K562/A02 cells by 7.25 and 6.20 RF (reversal fold), respectively.

*Toddalia asiatica* (L.) Lam. (Rutaceae) is widely distributed in Southeast Asia, South Africa, and tropical Africa, including Madagascar [94]. The genus *Toddalia* is known to produce prenylated coumarins and benzophenanthridine alkaloids and derivatives [95]. Vázquez et al. evaluated the anti-leukemic potential of the prenylated coumarins isolated from the stem bark of *T. asiatica*. Toddaculin (6-(3-methyl-2-butenyl)-5,7-dimethoxycoumarin) exhibited notable anti-leukemic potential of the prenylated coumarins isolated from the root bark of *T. asiatica*. Toddaculin (6-(3-methyl-2-butenyl)-5,7-dimethoxycoumarin) exhibited notable anti-proliferative (IC₅₀ 51.38 ± 4.39 µmol L⁻¹) and cytotoxic (CC₅₀ 138.90 ± 3.50 µmol L⁻¹) effects in U-937 cells. In addition, toddaculin was induced apoptosis in U-937 cells by decreasing the phosphorylation levels of ERK and Akt [96].

These findings suggest that toddaculin displays a dual effect as a cell differentiating agent and apoptosis inducer in leukemia cells.

**Curcumin**

Curcumin is derived from turmeric (*Curcuma longa* L., Zingiberales), and has been used for thousands of years for a variety of illnesses. Research over the last few decades has shown that curcumin is a potent chemopreventive agent and has therapeutic potential against a variety of cancers [97]. Choi et al. [98] demonstrated that curcumin contributes to the reversal of resistance to adriamycin in mouse leukemia L1210/Adr cell lines. Curcumin (15–45 µmol L⁻¹) has the ability to suppress P-glycoprotein expression in multidrug-resistant L1210/Adr cells by 45 to 73% after 48 h incubation. PI3K inhibitor, LY294002 (10 µmol L⁻¹) was used alone, and also combined with curcumin (20 µmol L⁻¹) to decrease P-gp expression. It was decreased by 51.6%, 62.8%, and 12.1% by LY294002, curcumin, and their combination, respectively. Hence, it was suggested that curcumin down-regulates P-gp expression in multidrug-resistant cells by inhibiting the PI3K/Akt/NF-κB signaling pathway and NF-κB-mediated mdr1b gene promoter activation [98].

*Diallyltrisulfide (DATS)*

Garlic (*Allium sativum* L., Aliiaceae) is widely used in culinary preparations and as a traditional medicine [99]. Epidemiologic studies in China and Italy indicate that frequent consumption of garlic may be associated with decreased gastric cancer incidence [100-101]. Diallyltrisulfide (DATS) is the major sulfur compound in garlic. Xia et al. [102] demonstrated that DATS could overcome P-glycoprotein (P-gp)-mediated MDR in K562/A02 cells. The MTT assay revealed that co-treatment with DATS increased the response of K562/A02 cells to adriamycin without side effects. DATS (2 µmol L⁻¹) could enhance the intracellular concentration of adriamycin by inhibiting the function and expression of P-gp. The down-regulation of NF-κB/p65 was significantly linked to the drug-resistance mechanism of DATS, whereas the expression of IκBα was not affected by DATS. The result suggested that DATS would be a novel, non-toxic modulator of MDR, and can reverse the MDR of K562/A02 cells in vitro by increasing intracellular adriamycin concentration and inducing apoptosis [102].

**Dihydroptychantol A**

Dihydroptychantol A (DHA) is a macrocyclic bishibenzyl from the liverwort *Asterella angusta* (Stephani) Pande, K.P. Srivast. and Sultan Khan (Aytioniaceae) having diverse biological properties. DHA displayed good potency to reverse adriamycin-resistant K562/A02 cells by MTT the assay. Adriamycin with 20 µmol L⁻¹ of DHA treatment showed 8.18 reversal folds (RF). Different concentrations of DHA (5, 10 and 20 µmol L⁻¹) decreased the expression of P-glycoprotein in K562/A02 cells in a dose-dependent manner (32.4%, 46.5% and 54.0% respectively). This study explains the DHA potential in reversing multidrug resistance by inhibiting the P-gp function and expression pathway [103].

**Guggulsterone**

The gum resin of *Commiphora mukul* (Hook. ex Stocks) Engl., (syn. *Commiphora wightii*) (Burseraceae), commonly referred to as the Guggul tree, has been used in traditional Hindu Ayurvedic medicine for nearly 3,000 years [100]. Guggulsterone, 4,17(20)-pregnadiene-3,16-dione, the active component of gugulipid, is derived from the gum resin [101]. Xu et al. reported that 100 µmol L⁻¹ of guggulsterone could reverse multidrug resistance in K562/ DOX cells effectively by inhibiting the expression and drug-transport function of P-glycoprotein [106]. Guggulsterone (2.5 to 80 µmol L⁻¹) significantly promoted the activity of P-gp ATPase in a dose-dependent manner. The intracellular pH of the K562/ DOX cells was found to be higher than the K562 cells. Guggulsterone treatment (1 to 100 µmol L⁻¹) decreased the intracellular pH of K562/DOX cells in a dose-and time-dependent manner [107]. This observation suggests that guggulsterone should be further investigated as a MDR reversal agent.

**Hyperforin**

Hyperforin (HF) is a bioactive compound found in St John’s Wort (SJW), *Hyperforin perforatum* L. (Hypericaceae). Alcoholic extracts of SJW induced dose-dependent growth...
arrest of the human leukemia cell lines K562 (GI\(_{50}\) 248.3-621.3 \(\mu\)g mL\(^{-1}\)) and U937 (GI\(_{50}\) 378.2-911.7 \(\mu\)g mL\(^{-1}\)) [108]. HF was found to promote apoptosis in B-cell chronic lymphocytic leukemia (B-CLL) by disruption of the mitochondrial transmembrane potential, caspase-3 activation and cleavage of the caspase substrate PARP-1 [109]. Liu et al. [110] investigated the cytotoxic effects of the dicyclohexyl ammonium salt of hyperforin (DCHA-HF) on the chronic myeloid leukemia K562 cell line. DCHA-HF inhibited K562 cell growth (8.6 and 3.2 \(\mu\)mol L\(^{-1}\) for 48 and 72 h, respectively) by inducing the caspase-dependent apoptosis pathway and arresting the cell cycle at the G1 phase. Zaher et al. [111] observed that hyperforin induced the mitochondrial pathway of caspase-dependent apoptosis in chronic lymphocytic leukemia (CLL) cells, and that this effect was associated with the up-regulation of Noxa, a BH3-only protein of the Bcl-2 family. HF inhibited the growth of AML cell lines (U937, OCI-AML3, NB4, and HL-60) in a time- and concentration-dependent (IC\(_{50}\) 1.4 \(\mu\)g mL\(^{-1}\) at 72 h) manner by inducing apoptosis, as evidenced by the accumulation of sub-G1 population, phosphatidylserine externalization, and DNA fragmentation. The apoptotic process in U937 cells was accompanied by down-regulation of antiapoptotic Bcl-2, up-regulation of pro-apoptotic Noxa, mitochondrial membrane depolarization, activation of procaspases and cleavage of the caspase substrate PARP-1 [112].

Hyperforin B1 is a limonoid isolated from leaves of *Harrisionia perforata* (Blanco) Merr. (Simaroubaceae). Bignon et al. synthesized hyperforin B1 in the course of which they found an intermediate product E-5-iodomethylene-6,6-dimethyl-5, 6-dihydropyrans-2-one (IDDP), which is more toxic to K562 leukemia cells (IC\(_{50}\) 0.15 \(\mu\)mol L\(^{-1}\)). Cancer cells were arrested in the G2/M phase in a time-dependent manner before cell death occurred through apoptosis [113]. This study shows that hyperforin possesses notable cytotoxicity against leukemia cells, and might be a promising compound for future research.

### Isothiocyanates

Cruciferous or *Brassica* vegetables belong to the family Brassicaceae (formerly Cruciferae). Commonly consumed cruciferous vegetables include broccoli, cabbage, cauliflower, collard greens, kale, kohlrabi, mustard, horseradish, radish, turnips, Chinese cabbage, etc. Isothiocyanates (ITCs) from cruciferous vegetables have been identified as potent anticancer agents in animal and human studies [114]. Jakubikova et al. studied six dietary allyl isothiocyanates (AITC), benzyl-ITC (BITC), phenethyl-ITC (PEITC), sulforaphane (SFN), erucin (ERN), and iberin (IBN), in sensitive HL60 cell line and two multidrug-resistant HL60/ADR (MRP-1-positive) and HL60/VCR (Pgp-1-positive) cell lines. Multidrug-resistant cells were less sensitive (IC\(_{50}\) values from 2.1 to 10.5 \(\mu\)mol L\(^{-1}\)) than the parental HL60 cells to all of the six tested ITCs, and induced G2/M arrest in cell cycle. The results of this study demonstrated that dietary isothiocyanates could be used as chemopreventive agents in cells with multidrug resistance phenotypes [115].

### Lycorine

Lycorine is an alkaloid isolated from several Amaryllidaceae plants [116]. Lycorine suppressed the growth of HL-60 leukemia cells and reduced cell survival through cell cycle arrest and apoptosis [117]. Treatment with lycorine inhibited the growth of human leukemia cell lines K562, U937, HL-60 and imatinib-resistant K562/G01 cell line (IC\(_{50}\) values ranging from 1.5 to 5.5 \(\mu\)mol L\(^{-1}\)). It induced apoptosis through the intrinsic mitochondria pathway, and caused down regulation of Mcl-1 [118]. Liu et al. [119] treated HL-60 cells with different concentrations of lycorine (1.5 to 5 \(\mu\)mol L\(^{-1}\)) and found that expression of p21 and TNF-\(\alpha\) was up-regulated in a concentration-dependent manner. Li et al. [120] observed the inhibition of histone deacetylase activity and the induction of cell-cycle arrest in the G0/G1 phase by the action of lycorine (5 \(\mu\)mol L\(^{-1}\)) on the K562 leukemia cell line. These investigations provide a new insight of lycorine to carry out further preclinical studies.

### Phenolic diterpenes

Rosemary (*Rosmarinus officinalis* L.), belonging to the family Lamiaceae, has been recognized as a plant with many pharmacological properties [121]. It contains phenolic diterpenes (carnosol, rosmanol, carnosic acid, and methyl carnosate) and phenolic acids (rosmarinic and caffeic acids). Valdes et al. [122] demonstrated the antiproliferative properties of the bioactive compounds from rosemary leaves in two human leukemia lines, a drug-sensitive phenotype (K562) and a drug-resistant phenotype (K562/R). The results revealed that the rosemary polyphenols (10 \(\mu\)mol L\(^{-1}\)) are cytotoxic to the sensitive leukemia cell line. K562/R cells were less sensitive to the cytotoxic effect of rosemary polyphenols. This greater resistance was due to overexpression of the *ABCB1* gen product, which is responsible for the active (drug) efflux of many chemotherapeutic drugs [123].

Yu et al. [124] evaluated the P-gp modulating potential of carnosic acid in multidrug-resistant K562/AO2 cells. The effect of carnosic acid on the reversal of multidrug resistance was evaluated by various molecular techniques. These findings showed that carnosic acid (25 \(\mu\)mol L\(^{-1}\)) served as a novel, non-toxic modulator of multidrug resistance in K562/AO2 cells by increasing the intracellular adriamycin concentration, down-regulating the expression of MDR1, and inhibiting the function of P-gp.

### Quercetin

Quercetin is present abundantly in plants, and has chemopreventive and anticancer effects [125]. Niu et al. examined the activity of quercetin against the acute leukemia cell line, HL-60. The results showed that quercetin inhibited cell proliferation (IC\(_{50}\) 61.11 \(\mu\)mol L\(^{-1}\) at 48 h) and down-regulated the expression of the anti-apoptosis protein Bcl-2, and up-regulated the expression of pro-apoptosis protein Bax [126]. Further, these findings suggested that quercetin induces apoptosis in a caspase-3-dependent pathway by inhibiting...
Cox-2 expression.

Shikonin

The pigment shikonin is a naphthoquinone, and is a pharmacologically active substance derived from the dried root of Lithospermum erythrorhizon Siebold & Zucc. (Boraginaceae). In traditional Chinese medicine, root extracts of L. erythrorhizon have been used to treat various diseases, such as macular eruption, measles, sore throat, carbuncles, and burns [127]. The anticancer potential of shikonin was first evidenced by its activity against murine sarcoma-180 cells [128]. Shikonin possesses strong cytotoxic effects on a wide variety of cancer cell lines, especially different types of sensitive and MDR leukemia cell lines U937 (IC₅₀ 0.19 µmol L⁻¹ at 48 h), CCRF-CEM (IC₅₀ 0.24 µmol L⁻¹ at 48 h), CEM/ADR5000 (IC₅₀ 0.36 µmol L⁻¹ at 24 h), HL-60 (IC₅₀ 0.39 µmol L⁻¹ at 24 h), and HL60/AR (IC₅₀ 0.47 µmol L⁻¹ at 48 h) cells. Transcriptome-wide mRNA expression studies showed that shikonin induced genetic pathways regulating cell cycle, mitochondrial function, levels of reactive oxygen species, and cytoskeletal formation. Shikonin was specifically accumulated in the mitochondria, which was associated with a shikonin-dependent deregulation of cellular Ca²⁺ and ROS levels. This deregulation led to a breakdown of the mitochondrial membrane potential, dysfunction of microtubules, cell-cycle arrest, and the induction of apoptosis [129]. Since shikonin reveals pronounced cytotoxic effects by inducing various genetic pathways, it is suggested that in vivo studies would provide more clues to the design of an antileukemic agent for further development.

Tetrandrine

In traditional Chinese medicine, tetrandrine (Tet), is the main component of the alkaloids extracted from the tubers of Stephania tetrandra S. Moore (Menispermaceae). It is considered to have a number of major biological activities [130] and is a potent inhibitor of the MDR-1 efflux pump [131-133]. Xu et al. used tetrandrine combined with daunorubicin (DNR), etoposide, and cytarabine (TET-DEC) for the treatment of acute myeloid leukemia (AML). Daunorubicin retention by P-gp-overexpressing K562/A02 cells was evaluated and compared with patient plasma after 6 hours of TET administration. This study reveals that tetrandrine reverses multidrug resistance in leukemia cell lines [134].

Triterpenoids

Triterpenoids are metabolites of isopentenyl pyrophosphate oligomers, and are widely distributed in plants. It has been estimated that more than 20,000 triterpenoids exist in nature [135]. The triterpenoids betulinic, oleanolic, and pomolic acids were isolated from the dichloromethane extract of the root of L. erythrorhizon. In traditional Chinese medicine, root extracts of L. erythrorhizon are distinctly employed for the treatment of arthritis and menstrual disorders [141]. Withaferin A

Withaferin A

The medicinal plant Withania somnifera (L.) Dunal (Solanaceae) has been thoroughly researched for its anti-inflammatory, cardioactive, and central nervous system effects. In Ayurveda, the major traditional Indian medicine system, extracts from W. somnifera are distinctively employed for the treatment of arthritis and menstrual disorders [141]. Withaferin A
A is a triterpenoid isolated from *W. somnifera* which showed inhibition of NFκB target genes in doxorubicin-sensitive K562 and resistant K562/Adr cells (IC50 values from 0.5 to 1 μmol·L⁻¹). Withaferin A (10 μmol·L⁻¹) could overcome attenuated caspase activation and apoptosis in K562/Adr cells and decreased protein levels of cytoskeletal tubulin, PARP cleavage, caspase 3 activation. This demonstrates that natural NFκB inhibitors can show different chemosensitizing effects in P-gp overexpressing cancer cells with impaired caspase activation and attenuated apoptosis [142].

**Perspectives**

Over the past few decades, researchers have proposed many strategies to combat multidrug resistance in cancer [143]. Drugs or substances which inhibit the over-expression of ATP-binding cassette (ABC) transporters have been classified as first, second, third, and fourth generation inhibitors [144].

First generation inhibitors (e.g., verapamil) possessed biological properties, but had no specificity to modulate P-gp expression. On the other hand, the second (e.g., dexamethasone) and third generation (e.g., tariquidar) were specifically designed with high affinity towards P-gp [145]. These generations of drugs inhibit P-gp expression effectively *in vitro*, but have failed to prove activity as MDR reversers in pre-clinical and clinical trials. The P-gp inhibitors or modulators derived from natural sources are referred as “Fourth Generation Inhibitors” [146]. The prime reasons for failure in clinical trials are due to the complexity of drug accumulation, drug uptake, uncertain pharmacokinetics, cellular toxicity, poor bioavailability, and limitations in specificity. These daunting challenges reinforce the scientific community to design novel drugs with high potency and specificity. Therefore, great effort should be invested to identify natural compounds that inhibit ABC transporters (P-gp expression) and sensitize cancer cells to conventional chemotherapeutic agents without causing side effects [147].

**Conclusions**

The complete cure for cancer is still elusive in conventional therapeutic strategies. Modern drug therapy causes serious side effects in already ailing cancer patients. The search for new therapies should aim at minimizing the side effects in the cancer patients by combining modern drug therapy with medicinal plant-based therapy. Medicinal plants, being used for therapeutic purposes in many ailments for thousands of years, are known for their reduced or no side effects. This review focused on the studies conducted on traditionally used medicinal plants and their active compounds for their cytotoxic and reversal of multi-drug resistance potential on various leukemia cell lines, and the mechanism of their activity. In-depth studies on these medicinal plants and their active principles for the treatment of leukemia are needed. Further studies should explore the effectiveness of these medicinal plant-based compounds, along with the conventional drugs, for their synergistic potential in designing new therapies for saving cancer patients.

**References**


[53] Hussain MM, Sokomba EN, Shok M. Pharmacological effects...


[115] Jakubikova J, Bao Y, Sedlak J. Isothiocyanates induce cell cycle arrest, apoptosis and mitochondrial potential depolarization in HL-60 and multidrug-resistant cell lines [J]. Anticancer Res,
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