Targets and Mechanism of Action of Chemical constituents from Plants with Potential Anti-leukemic Activity

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INTRODUCTION

In leukaemia, normal white blood cells (WBCs) are replaced by a large number of immature cells, thus leaving the body highly susceptible to infections (Bennett et al., 1976). Based on cell lineage and evolution of the disease, leukaemia is classified into lymphoid or myeloid and acute or chronic, respectively (Javed et al., 2012). The most effective method of leukaemia treatment involves chemotherapy, but the side effects associated with chemotherapy and drug resistance of leukemic cells makes it an unhealthy treatment method.

Further, most leukemic children and adults die despite the significances in chemotherapy. Significant attention is paid to cytotoxic agents due to the significant health and economic impact of leukaemia. Scientific investigations in the direction of modifying treatment options or treatment modalities are being carried out to avoid the side effects of cytotoxic agents which are currently used in the treatment of leukaemia (Shaked et al., 2005). Cancer preventive agents with higher efficacy as well as reduced side effects are need of the hour, which

The plant kingdom has been the most significant source of anticancer drugs. These include alkaloids, diterpenes, tannins, phenolics, lignans, glycosides which have exhibited lesser toxicity than conventional drugs. In leukaemia, the human body is susceptible to infections due to the replacement of normal leucocytes replaced by a large number of immature cells. Chemotherapy for leukaemia is associated with side effects and drug resistance by the leukemic cells. Cytotoxic agents with higher efficacy and lesser side effects are good candidates in cancer therapy, and plant metabolites serve as potential bioactive agents in anticancer drug formulations. This review article discusses the anti-leukemic properties of compounds obtained from plants and the mechanism of anti-leukemic activity induced by each of these plants. Effect of plants and their metabolites on different leukemic cell lines such as HL60, Kasumi-1, CCRF-CEM, K-562, U-937, THP-1 and MOLT-3 was compared. The findings showed anti-leukemic activity through cell cycle arrest, DNA damage, destruction of mitochondrial function, suppression of tumour genes, apoptosis-inducing enzymes and cytotoxic activities of plants and their derivatives. Based on extensive research findings from this review, phytochemicals and their derived analogues possess the most promising option for the better and less toxic anti-leukemic treatment. Identification of the mechanism of action by the plant bioactive compounds helps in developing standard herbal medicines for effective leukaemia treatment.

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could be used as cytotoxic agents in cancer therapy. Identifying new agents for treatment leukemia lead to intensified efforts from the scientific community globally. Among the novel agents, natural products from plant origin have been used as alternative drugs for malignant tumours due to their wide range of biological activities and lack of toxicity in animal models. Anticancer agents from natural origin with mild to moderate side effects makes them as good candidates during drug identification. Phytochemicals, due to their complex nature and interaction with cancer cell receptors, influences various biochemical and molecular cascades thus serve as potential bioactive agents in anticancer drug formulations. Hence treatment of cancer involving using bioactive compounds from plants has attracted considerable attention worldwide, and plant-derived drugs against leukemic cell types were reported earlier by Aboulf-Soud et al. (2016).

Plants due to their bioactive compounds play an essential role in drug development, thus hold key promises for cancer prevention and treatment as explored by many scientists throughout the world. Both in vitro and in vivo anticancer activities of several plants were reported by many researchers using various cell lines and animal models. Based on the anticancer properties of plants, this review focuses on various plants that exhibited potential anti-leukemic activity.

SOURCES AND METHODOLOGY

Detailed search using the keywords such as anti-leukemic potential, cytotoxicity and medicinal plants were done in PubMed, Scopus, ScienceDirect, Web of Science and Google Scholar to retrieve the published information between 1976 and 2019. The inclusion was based on anti-leukemic activities of plants and their parts along with the mechanism of action. The obtained data were extracted in the form of Table 1, and further explained under subheadings.

Plants and their Anti-leukemic Activity

Cell Cycle Arrest

Wattakaka Volubilis leaves were investigated for the in vitro anti-leukemic activities using U-937, HL-60 and K-562 cell-lines (Nandi et al., 2012). The experiments reported the IC_{50} values of 13.5, 10.8, and 13.2 (μg/ml) in U-937, K-562, and HL-60 cell lines by kaempferol-3-O-[α-l-rhamnopyranosyl-(1→4)-O-α-l-rhamnopyranosyl-(1→6)-O]-β-d-glucopyranoside present in the leaf extract. Inhibition of cell proliferation was associated with cell cycle arrest at G1 phase in U-937 and K-562, whereas it was G2/M phase in HL60 cell lines. Caxito et al. (2015) reported the inhibitory effect of Xanthosoma sagittifolium on leukemia cell proliferation by decreasing the cell number at the G2/M phase. Further, DNA fragmentation led to the higher leukaemia cell numbers in the sub-G1 phase in the presence of leaf extract.

Induction of apoptosis by Bidens pilosa in HTLV-1-infected T-cell lines was associated with a cell cycle arrest in G1 phase (Nakama et al., 2011). Water extracts of B. pilosa inhibited the phosphorylation of inhibitor of nuclear factor κB (IκB) kinase β and α, DNA binding of NF-κB and protein expression reduction during G1/S cell cycle transition. Reactive oxygen species-mediated suppression of NF-κB activity and AP-1-DNA binding suppression was through inhibition of expression of JunN and JunD. Vitek et al. (2017) investigated the biological activities of phytocompounds from leaves and stem bark of Eugenia dysenterica. The presence of quercetin-3-O-(6′-O-galloyl)-β-d-glucopyranoside in E. dysenterica promoted cell cycle arrest and exerted cytotoxic effects on Kasumi-1 and CCRF-CEM cells.

Eurycomanone from Eurycoma longifolia exhibited anti-proliferative and apoptotic potentials in K-562 leukemic cell lines both in vitro and in vivo (Al-Salahi et al., 2014). Does dependent cytotoxic effects were confirmed by observing chromatin fragmentation, uniform condensation and forming clusters against the nuclear periphery. Cell cycle arrest in both G1 and S phases was reported in a dose and time-dependent manner. In a study by Zhamanbayeva et al. (2016), different combinations of Hippophae rhamnoides, Rosa canina, Salvia officinalis and Origanum vulgare extracts had reduced viable cell counts on HL60 cells. A marked decrease in G1/S ratios indicated that HL-60 cells were more prone to cell cycle changes after treatment with combined plant extracts. Reduction in G0/G1-phase populations and relatively enlarged S-phase populations resulted in anti-proliferative effects in HL-60 cells as induced by the plant extracts.

Rosa cymosa fruit extract prepared from ethanol displayed reactive oxygen species and endoplasmic reticulum stress-mediated apoptosis (Wang et al., 2019). This led to overexpression of PTEN and the dysregulation of PI3K/Akt and Jak/Stat 3 signalling pathways which ultimately resulted in Molt-4 cell death. Besides, suppression of protein expressions involved in signalling pathways by the R. cymosa extra was observed. The anti-leukemic activity of Pseuduvaria rugosa alkaloids in human promyelocytic (HL-60) cells resulted in cell cycle
<table>
<thead>
<tr>
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<th>Part used</th>
<th>Phytochemicals</th>
<th>Mode of action</th>
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<tr>
<td><em>Acacia salicina</em></td>
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<td>Flavonoids</td>
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<td>(Chatti et al., 2009)</td>
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<tr>
<td><em>Arctium lappa</em></td>
<td>Root</td>
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<td>Increase S1PR1 expression</td>
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<td>(Nakama et al., 2011)</td>
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<td>Aerial parts</td>
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<td><em>Ceratonia siliqua</em></td>
<td>Leaves</td>
<td>Oligomer flavonoids</td>
<td>Cytotoxicity, Cell proliferation inhibition</td>
<td>(Sassi et al., 2016)</td>
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<td><em>Cinnamomum parthenoxylon</em></td>
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<td>Hinokinin and cubebin</td>
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<td><em>Corchorus acutangulus</em></td>
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<td><em>Cyperus rotundus</em></td>
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<td><em>Eugenia dysenterica</em></td>
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<td><em>Euphorbia Terracina</em></td>
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<td>Phenolic compounds and terpenoids</td>
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<td><em>Glycine max</em></td>
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<td>Genistein</td>
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<td>Scientific name</td>
<td>Part used</td>
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<td>Mode of action</td>
<td>Reference</td>
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<tr>
<td>Hypericum perforatum</td>
<td>Hyperforin</td>
<td>Inhibition of kinase activity downregulates the expression of P-glycoprotein</td>
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<td>Polyalthia longifolia</td>
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<td>Raphanus sativus</td>
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<td>Teucrum ramosissimum</td>
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<td>Vernonia amygdalina</td>
<td>Root</td>
<td>Phenolic compounds</td>
<td>DNA damage</td>
<td>(Khalafalla et al., 2009)</td>
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<td>Wattakaka Volubilis</td>
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<td>Xanthosoma sagittifolium</td>
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<td>Zingiber officinale</td>
<td>Rhizomes</td>
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<td>Apoptosis and inhibition of DNA synthesis</td>
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</table>
arrest in G2/M and G1 phase by 1,2,3-trimethoxy-5-oxonoraphthone and ouregidione, respectively. In the case of U937 cells, both the alkaloids induced cell arrest at the S phase.

Anti-proliferative activity of *Pseudoaria rugosa* in K-562, U-937 and HL-60 human leukemic cell lines was performed by Uadkla et al. (2013). Human promyelocytic (HL-60) cells treated with 1,2,3-trimethoxy-5-oxonoraphthone and ouregidione were arrested in the G2/M and G1 phase, respectively. On the other hand, both alkaloids induced U937 arrest in S phase.

Aerial parts of *Corchorus acutangulus* were investigated for their anti-leukemic activity by Mallick et al. (2010). Solvent fractions of the aerial parts were prepared in methanol and butanol with the identification of corchorusin-D. A triterpene saponin, corchorusin-D in the solvent fraction was found to release apoptosis-inducing factors from mitochondria, thereby producing mitochondrial dysfunction and cell death. Activation of caspase-3 and PARP cleavage due to translocation of Bax from the cytosol to mitochondria by corchorusin-D resulted in DNA fragmentation in U-937 and HL-60 cell lines.

**Cytotoxicity**

Ayesh et al. (2014) studied a concentration-dependent cell viability reduction of THP-1 cells by *Origanum syriacum* and *Thymus vulgaris* with an IC₅₀ value of 2.13 and 0.16 mg/ml, respectively. Lethal concentration (LC₅₀) value of 9.65 mg/ml demonstrated the significant cytotoxic effect against THP-1 cells by *O. syriacum* extract. Natural products with reported anti-leukemic activity were tested against clinically isolated primary leukaemia cell lines (Aboul-Soud et al., 2016). By performing the trypan blue assay the order of cytotoxicity percentage exhibited by cerulenin, retinyl palmitate, honokiol, mevinolin, L-ascorbic acid 6-palmitate, cholecalciferol, chrysin, salicin and (S)-(--)-limonene were 34.9%, 30.9%, 22.9%, 22.6%, 20.0%, 18.3%, 15.6%, 14.9% and 14.7% respectively.

Chang et al. (2001) evaluated Anti-leukemic activity by *Bidens pilosa* L. var. minor (Blume) Sherf using XTT-based colourimetric assay. *B. pilosa* extract prepared in hot water exhibited a various degree of cytotoxicity in L1210, P3HR1, Raji cells and K-562 cells at 100 µg/ml concentration. Inhibition percentage ranged between 15.9 % and 39.2% by the extract at 100 µg/ml however, 6.8% inhibition on U-937 at 250 µg/ml concentration. Furanodiene isolated from *Curcuma cf. viridiflora* exerted cytotoxic, anti-leukemic and anti-proliferative effects and the anti-leukemic potential could be due to suppression of Wilms tumour 1 (WT1) protein expression (Anuchapreeda et al., 2018). In leukaemia, WT1 is a well-known biomarker and is shown to promote the proliferation of leukemic cells. Treatment of Molt4 cells with furanodiene had significantly lowered the WT1 expression. Papiez et al. (2016) investigated the action of curcumin in myeloid leukemia cells. They found that modulation of etoposide action was intensified through free radical production, which led to higher apoptosis levels.

Jamaican boll moss was examined against various leukemic cell lines, and the highest inhibition with an IC₅₀ value of 1.83 µM was observed against K562 cell lines (Lowe et al., 2014). In another study, root extracts of *Vernonia amygdalina* had completely destructed the lymphoblastic leukaemia cells, whereas 70% cytotoxicity was observed in myeloid leukaemia cells (Khalafalla et al., 2009).

Chiang et al. (2003) demonstrated the cytotoxic potential of linalool, oleanolic acid, ursolic acid and luteolin against human leukaemia and lymphoma cell lines. Linalool exhibited the strongest activity against U-937, P3HR1 cell lines with IC₅₀ values of 3.51 and 4.21 µg/ml, respectively. Cell proliferation of P3HR1 and K-562 was inhibited by ursolic acid with IC₅₀ of 2.5 and 17.8 µg/ml. Afolabi et al. (2017) isolated a tetranorditerpene from *Polyalthia longifolia* to treat human leukemic-60 cells after methyl esterification of the compound. After treatment, changes in the cellular morphology as indicated by cell shrinkage, blebbing and formation of apoptotic bodies were observed. Morphological changes were due to the synergistic relationship between native tetranorditerpene and methyl esterification reaction in the process of discovering novel cytotoxic and chemopreventive agents.

**Apoptosis**

Curcumin was also known to induce apoptosis by an increase of phosphatase and tensin homolog (PTEN) in a dose-dependent manner (Taverna et al., 2015). Further, it also decreased protein kinase B and vascular endothelial growth factor expression and release. Derivatives of curcumin are more active than natural curcumin. For example, 4-(4-Pyridinyl methylene) curcumin, inhibited the heat shock protein 90 (Fan et al., 2018) in K-562 cells by induced apoptosis through a stimulated mitochondrial pathway.

Induced apoptosis and inhibition of cell proliferation in human leukaemia HL-60 cells by a member of Meliaceae family, *Toona Sinensis* is reported by Kakumu et al. (2014). Nuclei fragmentation, chromatin condensation and membrane blebbing were due to the activity of loropetalin D isolated.
from *T. Sinensis*. Similarly, *T. Sinensis* extract, along with gallic acid had induced apoptosis through the release of cytochrome *c*, caspase 3 activation and specific proteolytic cleavage of poly (ADP-ribose) polymerase (PARP). Besides, the apoptosis was associated with reduced levels of cell death inhibitor (Bcl-2) and increase of Bax protein (*Yang et al., 2006*).

Kabeel *et al.* (2018) investigated the effect of *Arctium lappa* on leukaemia in vivo. The plant contains antagonists for sphingosine-1-phosphate receptor-1 that regulates its expression in dimethyl Benz(a)anthracene treated rats. It was also reported that caspase-mediated apoptotic cell death in MH 60 cells by *A. lappa* (*Matsumoto et al., 2006*). Pardede *et al.* (2016) isolated 4-methoxylanceoletin from methanolic extract of *Coreopsis lanceolata* and claimed its apoptotic potential in human leukaemia HL-60 cells.

**Mitochondrial function destruction**

The potent anti-leukemic activity of *Zingiber officinale* Roscoe and *Nerium oleander* L characterized by apoptosis resulted through destruction of mitochondrial function of both K562 and MOLT-4 cells is reported by Bhargava *et al.* (2015). Cell viability assays revealed the IC50 values up to 11.2 and 27.8 μg/ml for *N. oleander* and *Z. officinale*, respectively.

**Kinase activity inhibition**

Hyperforin from *Hypericum perforatum* activates pro-apoptotic proteins, targets matrix metalloproteinase-2 and vascular endothelial growth factor in leukemic cells (*Zaher et al., 2012; Billard et al., 2012*). This is, in turn, inhibits the kinase activity and resulted in cell death of acute myeloid and chronic lymphoid leukaemia cells. Adfa *et al.* (2016) studied the utility of *Cinnamomum parthenoxylon* to treat leukaemia. Hinokinin and cubebin from *C. parthenoxylon* woods displayed strong cell proliferation inhibition and induced apoptotic morphology in leukemic cell lines.

**Tumour suppressor genes**

Soybean isoflavone, genistein was effective against leukemic cell lines as reported by Raynal *et al.* (2008). Anti-proliferative assays revealed MOLT-3 lymphoid cells as the most sensitive cell lines, followed by HL-60 and Raji cell lines. The anti-leukemic potential of genistein is also associated with reactivation of tumour suppressor genes and its reduced effect on promoter demethylation.

**CONCLUSION**

This review summarizes the anti-leukemic potential of various plants, their bioactive compounds and mode of action against leukemic cell lines. The collective information presented in this review helps to identify new, effective therapeutics from plant origin to treat leukaemia by understanding the mode of action of each bioactive compound.

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**Conflict of Interest**

The authors declare that they have no conflict of interest for this study.

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