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Review Article

PLANTS- THE NEXT GENERATION TREATMENT OF LEUKEMIA

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ABSTRACT
Discovery of the medicine or drug is time consuming and labour intensive process. Natural products have vast chemical diversity and it has ability to act on various biological systems. Plants and its products are the important elements in the plant medicine system. Many of the plant extracts currently used in the treatment of cancer therapy and those agents were also isolated from plants. Here the main objective of this review is to introduce the plants and its products used in the treatment of the leukemia effectively.

Key Words: *Drug, Discovery, Chemical Diversity*

INTRODUCTION

What is leukemia?

Leukemia is the type of cancer related to blood or bone marrow. It is characterized by abnormal increase of white blood cells (WBC), which is called "blasts". It is a clonal disorder, in that somatic mutation occurs in the hematopoietic cells which block the normal cell and eventually cell deaths occur. (Tenen, 2003) In the year 2000, approximately 2, 56,000 children and adults around the world developed some form of leukemia, and 2,09,000 died from it (Mathers *et al*., 2001). There are mainly two forms of leukemia: Acute and Chronic.

Table 1: Four major kinds of Leukemia

Cell Type	Acute	Chronic
Lympholytic Leukemia	Acute Lymphoblastic Leukemia(ALL)	Chronic Lymphoblastic Leukemia(CLL)
Myloid Leukemia	Acute Mylogenous Leukemia(AML)	Chronic Mylogenous Leukemia(CML)

Acute leukemia is rapid increase in the number of immature blood cells. This kind of leukemia is mostly seen in the children. Chronic leukemia is characterized by buildup of mature but abnormal white blood cells. Two types of cells are involved in that. One is lymphoid cells and another is myloid cells (Jameson *et al.,* 2005).

Plant Derived Compounds Used As Antileukemic Agents

Jasmontes exhibit number of compounds which shows anti leukemic activity, some of them are in the clinical use now-a-days. There are mainly three major types of plant derived agents which include inhibitor of carcinogen formation, blockers of carcinogen interaction and suppressor of tumor progression (Mukherjee *et al.*, 2001). Currently 60% of the anti cancer agents are derived from the natural products i.e., plants, marine organism and micro organisms. Plant derived anti cancer agents includes *Vinca* alkaloids, vincristine and vinblastin which are isolated from *Vinca rosea*. Semi synthetic analogs are vinorelbine and vindesine. These agents are used in combination with other agents to treat leukemia. Campothecin, from *Campotheca acuminata*, induces severe bladder toxicity but its derivatives, topotecan and irinotecan, are used for the treatment of various solid tumors. In addition, homoharingtonine are used in leukemias (Cragg *et al.*, 2005). Flavanoid is the phenolic compounds that are the constituents of the flowering plants. They show action against tumor cells. It also includes inhibition of growth and kinase

activity and induction of apoptosis (Kanadaswami *et al.*, 2005). Foods like wheat, beans, rice, potatoes etc contain plant lectin, which exhibit anticancer activity (De Mejia *et al*. 2005). Plant derived tyrosine kinase inhibitors are the potential anticancer agents. Given the major role these enzymes play in the regulation of cell growth, differentiation and death, their aberrant activity can lead to cancer, and could theoretically be the result of over-expression, over-activation or under-utilization of the relevant signaling pathways. It's over expression can result in the continuous stimulation of growth factor receptor system. So, inhibition of tyrosine kinase by plant derived hormones is a valid approach towards the cancer therapy (Hollosy *et al.*, 2004).

Ayurvedik Perspective

Tinospora cordifolia: The active principles from *T. cordifolia* enhance host immune system by increasing immunoglobulin and blood leukocyte levels and by the stimulation of stem cell proliferation. It has the ability to reduce solid tumor volume by 58.8%, which is comparable to cyclophosphamide, a known chemotherapeutic agent. These immune stimulating properties can be used in the prevention of tumor mediated immune suppression and hence could be a drug choice for various cancers (Sohini *et al*, 1996).

Semecarpus anacardium: In Ayurveda classics, numerous references are available on the anticancer properties of *Semecarpus anacardium* nuts (Sharma *et al.*, 1996). An extensive review describes the phytochemical and pharmacological properties of *S. anacardium* (Premalatha *et al.*, 2000). The chloroform extract of *S. anacardium* nut possess antitumor action with increased life span against leukemia (Premalatha *et al.*, 1998). The milk extract of *S. anacardium* produces regression of hepatocarcinoma by stimulating host immune system and normalizing tumors markers including alpha-fetoprotein levels (Premalatha and Sachdanandam, 1998). This preparation stabilizes the lysozomes, and normalizes glycoprotein and mineral content in the body during cancer progression (Premalatha and Sachdanandam, 1998). It also corrects hypoglycaemia (Premalatha B *et al*, 1997) and controls abnormal lipid peroxidation (Premalatha *et al*., 1997) by the maintenance of antioxidant defense status (Premalatha *et al*, 1999). *Anacartin forte,* another preparation from *S. anacardium* has been used for several decades as an anticancer drug since it is giving health improvement with alleviation or disappearance of troublesome symptoms. It provides clinical benefit with an extension of survival time in various cancers including oesophageal, chronic myeloid leukaemia (Vad, 1973).

Piper longum: Piperine, an active alkaloid extracted from this plant has been used as an ingredient of ayurvedic anticancer formulations because of its anti-oxidative potency in both in vitro and in vitro conditions (Koul and Kapil, 1993).

Figure 1: A - *Tinospora cordifolia.* B - *Semecarpus anacardium.* C - *Piper longum*

There are several common features between Ayurvedik concept and the treatment used now-a-days for cancer. Therapy currently used for cancer is aim to suppress or inactivate the cancer causing gene i.e., oncogenes. Similarly, several herbs and its extracts used in cancer therapy with the same aim (Takada and Aggraval, 2003). The use of *Vinca rosea* for the treatment of cancer is well described in ayurveda. Modern cancer therapy shows that vincristine derived from *Vinca rosea* is the standard treatment for cancer. Similarly arsenic trioxide for acute Mylogenous leukemia treatment and it was proven by the modern science (Li *et al.*, 2004).

Table 2: Herbs and their antileukemic uses

Name of herbs	Methods and uses
Barleria prionitis	The oil prepared wid whole plant is applied externally during acute stage of cysts in blood vessels (Kinjavadekara RS and Astanga S, 1998)
Boswellia serrata	Bark decocation, gum resin are given internally and oil is applied externally. It is used in the treatment of leukemia and in brain tumor also (Hostanska K *et al*, 2002)
Euphoria hirta	Powder and liquid extracts are used in the treatment of leukemia (Murthy KRS, 2001)
Phyllanthus niruri	Aqueous extracts of this herb is applied locally (Dash B and Kashyap L, 1987)
Tinospora cordifolia	The mixture of *helloborous niger, Tinospora cardigolia, Elephentopus scber* is applied locally (Dash B and Kashyap L, 1987)
Barleria prionitis	The *Barleria prionitis* oil prepared with whole plant is indicated for external application during acute stages of cyst in blood vessels (Kinjavadekara RS and Astanga S, 1998)

Medicinal Plants Safeguard against Leukemia

Allium sativum (Garlic): The effect of garlic with its possible health benefits and against the cancerous cell was noticed. More to that *A.sativum* has free radical activity and its direct cytotoxic effect on cancer cells (Abdullah *et al.*, 1988). There is promising result shown in the treatment of leukemia by the use of garlic. Garlic derive compound, Ajoene, has shown to inhibit proliferation and induce apoptosis of leukemia cells in humans Ajoene has been investigated as an anti-leukemia agent for acute myeloid leukemia therapy. The apoptosis inducing activity of ajoene is via the mitochondria-dependent caspase cascade through a significant reduction of the anti-apoptotic bcl-2 that results in release of cytochrome c and the activation of caspase-3. Since acute myeloid leukaemia (AML) is a heterogeneous malignant disease in which disease progression at the level of CD34-positive cells has a major impact on resistance to chemotherapy and relapse and the inability to undergo apoptosis is a crucial mechanism of multi-drug resistance in AML patients (Dirsch *et al.*, 1988). The aim of this present study was to investigate the effect of garlic and two garlic compounds, ajoene and allitridium, compared with commonly used chemotherapeutic drugs on apoptosis of ALL cells and normal lymphocytes in vitro from newly diagnosed ALL patients (Lamm and Riggs, 2001). Scientists have found that ajoene has many properties of interest to current medicine. It functions as an antioxidant, by inhibiting the release of superoxide. Ajoene also has antithrombotic (anti-clotting) properties, which helps prevent platelets in the blood from forming blood clots (Torres and Romero, 2012).

Withania somnifera Dunal: W. somnifera Dunal is widely used in Ayurvedic medicine, the traditional medical system of India *W. somnifera*, also known as Ashwagandha, Indian ginseng, Winter cherry, Ajagandha, Kanaje Hindi, Amukkuram in Malayalam, is a plant in the *Solanaceae* family. *W. somnifera* treatment reversed the adverse effects of urethane on total leukocyte count, lymphocyte count, body weight, and mortality (Devi *et al.*, 1995) Withaferin, A major chemical constituents of WS, primarily induces oxidative stress in human leukemia HL-60 cells and in several other cancer cell lines and the results of these studies demonstrate that withaferinA induced early ROS generation and mitochondrial dysfunction in cancer cells trigger events responsible for mitochondrial -dependent and -independent apoptosis pathways (Malik *et al.*, 2007). Another study demonstrated that Withanolide D, a pure herbal compound isolated from WS has capability to induce apoptosis in a dose and time dependant manner both in myeloid (K562) and lymphoid (MOLT-4) cells being nontoxic to normal lymphocytes and control proliferative cells and one of the Withanolides, anticancer properties of highly purified Lasparaginase from *Withania somnifera* L. against acute lymphoblastic leukemia and observed that *W. somnifera* L. proved to be an effective and a novel source of Lasparaginase (Oza *et al.*, 2010).

Vernonia amygdalina: Vernonia amygdalina, Del (Compositae) is an African medicinal plant well known for producing the anticancer agents' vernodaline and vernolide. Vernodaline and vernolide elicited antitumor activities in leukemia cells. Recently, reported that some peptides (edotides) from the aqueous extract of *V. amygdalina* showed cell growth inhibitory effects in prostate cancer cell line (PC-3) but no effect on normal human peripheral blood mononuclear cells (Izybigie, 2003). Leaves prevented proliferation of three cancer cell type, acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL) (El-Shemy *et al.*, 2007). For developing countries the use of endogenous medicinal plants as cures against leukemia and other cancers is attractive. This study was therefore designed primarily to induce normal root culture of *V. amygdalina* in vitro and to determine their antiproliferative effects on two leukemia cell types. One study shows that After 24 h incubation of the mononuclear ALL cells with plant extracts, a remarkable destruction of lymphoblasts occurred. Responses were not linear, higher doses and longer times could not kill all the leukemia cells. In addition, the extracts were incubated with normal mononuclear cells from healthy volunteer. There was no significant difference in killing healthy cells when compared to the 7% caused by the media addition control. Therefore, leukemia cells were more vulnerable to the extract than healthy cells (Mutasim *et al.*, 2009).

Vinca rosea: Approximately 10% of all cancers in the United States are hematologic in origin. This category of diseases can involve nearly any cellular component of the immune system, but the most commonly diagnosed are multiple myeloma, B-cell chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), and the broad category of non-Hodgkin lymphoma (NHL) (Neuss *et al.*, 1962). The Vinca alkaloid, vinblastin, was first isolated some 50 years ago from the Madagascar periwinkle *Catharanthus roseus* by two independent groups. Vincristine and vinblastin are structurally similar bisindole alkaloids containing a catharanthine and vindoline unit, with the latter differing only in the presence of one substituent group. Vinblastin contains a *N*-methyl group, in contrast to a *N*-formyl group in vincristine (Cutts *et al.*, 1960). *In vivo* studies using mice engrafted with L1210 and P1534 leukemia cells and Ehrlich ascites tumor cells, performed shortly after the discovery of vinblastin, demonstrated its antineoplastic activity (Chebner *et al.*, 2006). Early clinical trials with vincristine sulfate resulted in complete remission for the majority of the patients with acute leukemia. Vincristine sulfate is utilized for acute lymphoblastic leukemias and lymphomas in combination chemotherapy (Hartwell, 1976).

Plants Derived Compound Use as Antileukemic Agents

Alkaloids: They are widely distributed in the plant kingdom. It is isolated from *Helotropium indicum L,* possesses activity against leukemia. It was entered into clinical trials. Hepatotoxicity commonly associated with this class of alkaloids may not be a clinical problem with this compound. Helotropium indicum has been used against warts and it is close relative H. europaeum L., has already been well recommended for the treatment of cancer (Simanek and Venditto, 2010). Camptothecin a novel structure isolated in minute quantity from the wood of Camptotheca acuminata Decne is highly active in leukemia but causes gastrointestinal tract Toxicity (Wall and Wani, 1977). Harringtonine and homoharringtonine: These alkaloids, together with isoharringtonine, isolated from Cephalotaxus harringtonia R. Sm. var. drupacea from a type of active alkaloid which consists of complex esters of the inactive alcohol Cephalotaxine. It has shown efficacy against various myelogenous leukemias. Cryptolepine and neocryptolepine are derivatives of indoloquinoline isolated from the roots of the African plant Cryptolepis sanguinolenta. These two alkaloids have potent cytotoxic activity against P388 and HL-60 cells (Gu *et al.*, 2010).

Terpenes: This is a large and complex group of natural products. Linalool, a natural monoterpene found in *Lavendula officinalis.* Effect of linalool on various leukemia cells led to strong activation of p53, cyclin dependent kinase inhibitors. This result suggests a path of induction of apoptosis. Thus, linalool acts as lead compound for the development of new therapeutic agents for murine and human leukemia (Aoyagi *et al.*, 2006). A majority of the compounds of sesquiterpenes have cytotoxicity against KB, P388 leukemia (in vivo). Diterpenes: This subgroup has yielded two compounds of highly activity in P388 leukemia.

Triptolide is also active in L1210 leukemia. SAR study of diterpenoids from *Perovskia abrotanoides* and its semisynthetic analogues have been shown against leukemia cells (Bylka *et al*., 2004).

Table 3: Alkaloids

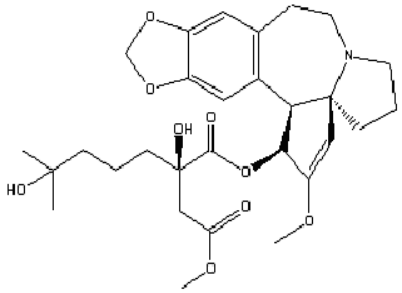
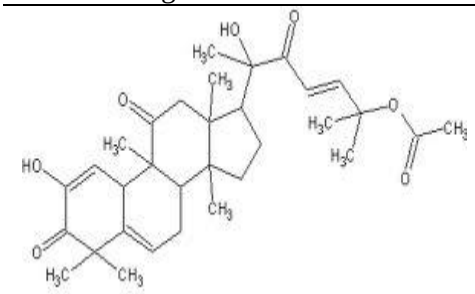
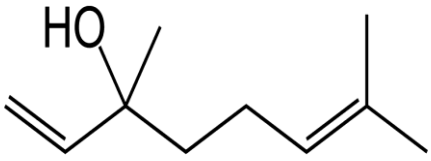
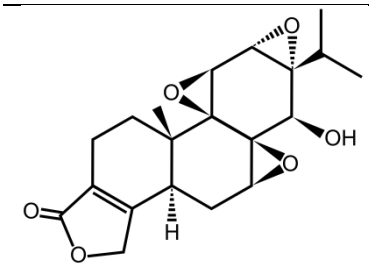
Structure & Name	Sources	Activities
 Homoharringtonine	*Cephalotaxus harringtonia drupacea*	Myelogenous Leukemias
 Cucurbitacins	*Solanum seaforthianum*	In vivo antitumor activity against P388, L1210 leukemia, B16 melanoma and Lewis lung tumor

Table 4: Terpens

Structure & Name	Sources	Activities
 Linalool	*Lavendula officinalis*	In vivo P388 leukemia
 Triptolide	*Cephaelis acuminata*	L1210 Leukemia

Flavonoids: The Flavonoids may be divided into ten types: flavones s, flavonols, flavonones, flavanone, flavanole, flavanonole, chalcones, xanthones, isoflavones and biflavones (Ishiwata *et al*., 1969). Sophoranone, extracted from a traditional Chinese medicine *Shan dou gen* (constituent of root of *Sophora subprostrata*) (Ren *et al*, 2003), inhibited cell growth and induced apoptosis in various lines of cancer cells such as human stomach cancer MKN7 cells and human leukemia U937 cells (Li-Weber, 2009).

Schinazi *et al* showed that Baicalein inhibited certain viruses in vitro, including the Rauscher marine leukemia virus and the HIV virus, as well as cellular DNA polymerases, and that the inhibition of reverse transcriptase by the flavone Baicalein is highly specific. These facts suggest that the flavone baicalein may be less toxic than the flavonols to the DNA and RNA polymerase in the host cell infected with retroviruses (Ishiwata *et al.*, 1969). Out of the three constituents of *Scutellaria baicalensis*, Baicalein possesses highest activity against murine leukemia cell.

Table 5: Flavonoids

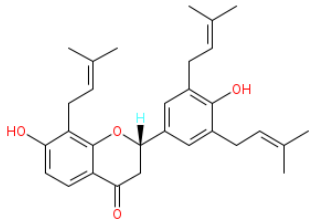
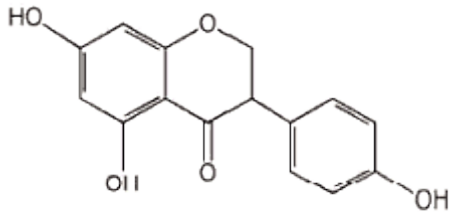
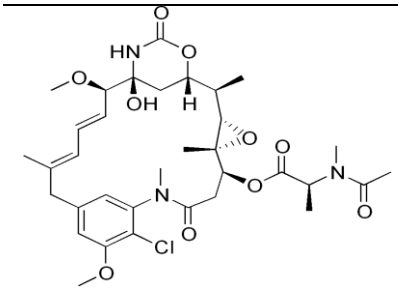
Structure & Name	Sources	Activities
 Sophoranone	*Sophora subprostrata*	Human stomach cancer MKN7 cells and human Leukemia U937 cells
 Genestein	*Lubinus perennis*	B16 melanoma cells

Table 6: Ansa Microsides

Structure & Name	Sources	Activities
 Maytansine	*Maytenus boaria*	L1210 Leukemia and B16 melanoma

Ansa Macrolides: The large macrocyclic lactone rings, frequently N-heterocyclic, incorporating within it an m or p-bridge aromatic moiety. Maytansine was isolated from several *Maytenus* species. The group is generally cytotoxic and is unusually active in P388 leukemia at remarkably low doses. Maytansine, the most readily available member of the group, is also active in L1210 leukemia and B16 melanoma is now in clinical trial (Simanek and Venditto, 2010).

CONCLUSION

The search for new pharmacologically-active compounds for drug development is an important issue, but not the only one, as the trend toward using standardized plant extracts of high quality, safety and efficacy

will continue. In India, there is an ocean of knowledge about medicinal plants and rich medicinal flora, but still only a few pearls have been searched as therapeutic agents. The therapeutic efficiency of plants and its products extensively used in Indian system of medicine has been established through modern testing and evaluation in different disease conditions. These studies place this drug as novel candidates for the drug development for the treatment of leukemia. It is hoped that the search for new medicinal compounds is likely to provide more potent antileukemic agents. The discovery of antileukemic drugs in botanicals should make important additions to leukemia therapy in the future.

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