



## Review Article

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## Nutraceuticals in leukemia

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### ABSTRACT

The term Leukemia signifies cancer of the blood, bone marrow and lymphoid system and is resulted due to abnormal proliferation of immature white blood cells. Conventional therapeutic modalities for leukemia act by targeting various signalling pathways that contribute to leukemogenesis. These treatment strategies may be effective in tackling the disease but they often pose severe side effects as they harm the normal healthy cells along with the cancer cells. Thus alternative means of leukemia therapy need to be explored. Ayurveda, one of the ancient forms of medicine practised in the Indian subcontinent, may be a good option. Ayurveda aims to cure diseases by harnessing the power of natural herbs and other plant resources or phytochemicals. It has been documented that ayurveda is effective in the treatment of various types of cancer, including leukemia. These ayurvedic formulations may find their use as an adjuvant therapy in conjunction with existing treatment protocols. Ayurveda is unique in the way that it helps to control the disease in a non-toxic way by preventing growth of abnormal blood cells vis a vis sparing the normal cells. They also aid to relieve the leukemic patient of pain and anxiety in the later stages of the disease. Thus intense research is warranted to establish the potential of ayurveda or natural medicine in the therapy of leukemia.

**Keywords:** Leukemia, Ayurveda, Nutraceuticals, Leukemogenesis.

### INTRODUCTION

Leukemia, coined as Vatolvana Sannipataja Pandu Roga in ayurveda, is a cancer of white blood cells termed blasts or leukemia cells, which are not fully developed. Cancer of blood, bone marrow and lymphoid system are collectively called leukemia where the white blood cells grow in number. These white blood cells are not fully matured and are called blasts. In Ayurveda good health is a balance between three doshas (bio-elements) namely Vata (space and air), Pitta (fire and water) and Kapha (earth and water), and any imbalance culminates in a disease process.<sup>[1]</sup> Leukemia, according to Ayurveda is perturbation of all these three doshas. Leukemia can be broadly categorised into 'acute', characterized by increase in the number of immature blood cells and 'chronic', resulting due to over accumulation of comparatively mature, yet abnormal white cells. Further sub-classification is based on the types of blood cell involved. Often marrow cells that are destined to form lymphocytes are affected, thereby hampering infection-fighting immune system. A subtype of lymphocyte called the B cell are responsible for development of leukemia. The other sub-classification is myelogenous leukemia, where bone marrow cells that are supposed to form red blood cells and some other types of white cells and platelets start malfunctioning. Based on these classifications, leukemia may be of four main categories, which are again divided into several subcategories.<sup>[2]</sup> Apart from these, there are some other types, which remain outside these classifications. Thus leukemia can be broadly classified as:

1. Acute lymphoblastic leukemia (ALL): though the commonest type of leukemia in young children, it also affects adults, especially the elderly persons. Subtypes include precursor B acute lymphoblastic leukemia, precursor T acute lymphoblastic leukemia, Burkitt's leukemia, and acute biphenotypic leukemia.
2. Chronic lymphocytic leukemia (CLL): mainly seen in adults over the age of 55, but may affect younger adults. Incidence is more in male population. B-cell prolymphocytic leukemia, which is a very aggressive disease is a subtype of CLL.
3. Acute myelogenous leukemia (AML): Like CLL, this type is common in men and in adults, though children may get affected. Subtypes of AML are acute promyelocytic leukemia, acute myeloblastic leukemia, and acute megakaryoblastic leukemia.

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4. Chronic myelogenous leukemia (CML): Common in adults, children may get affected, though frequency is low. Chronic myelomonocytic leukemia is a subtype.<sup>[3]</sup>
5. Hairy cell leukemia (HCL): This is an uncommon hematological malignancy where abnormal B lymphocytes are accumulated. This type is often mistaken as a subset of CLL.<sup>[4]</sup>
6. T-cell prolymphocytic leukemia (T-PLL): Though rare, this type is very aggressive. Adults are affected and this is common in men than women. This form of leukemia affects T cells.<sup>[5]</sup>
7. Large granular lymphocytic leukemia: T-cells or NK cells are involved and this is a rare and non-aggressive type of leukemia.<sup>[6]</sup>
8. Adult T-cell leukemia: Human T-lymphotropic virus (HTLV) infects CD4+ T-cells and replicates within them without destroying them. Therefore, HTLV imparts immortality to the infected T-cells, giving them the ability to proliferate abnormally.<sup>[7]</sup>
9. Juvenile myelomonocytic leukemia (JMML): This is a childhood leukemia, which is neither chronic nor acute. JMML originates from myeloid cells, but is not as fast-growing as AML or as slow as CML.<sup>[8]</sup>

### Signs and Symptoms of leukemia

There are certain signals that are not in the right mode in the body. It is always important to be aware of the signs and symptoms as both give an indication of injury, illness, disease. The common symptoms of leukemia are feelings of fatigue, repetitive infections (both viral or bacterial), bone and joint pain, loss of appetite followed by abdominal pain, weight loss, swollen and palpable lymph nodes under the arms, in the groin, chest and neck, bleeding or bruising, vomiting, rashes, gum problem etc. With these knowledge, a person should see a competent doctor to rule out the possibility of cancer. There are some diagnostic procedures that help detect the disease. Diagnostics include bone-marrow aspiration and biopsy (where marrow may be removed by aspiration or a needle biopsy), a complete blood count (to get an estimate of measurement of size, number, and maturity of different cells in blood), blood tests (blood chemistry, liver and kidney function test and genetic studies), a lymph-node biopsy (lymph node tissue is surgically removed for microscopic examination to look for malignant cells), a spinal tap (to collect cerebral spinal fluid for diagnosis).

### Causes of Leukemia

Exact causes of leukemia are not known till date, however it appears that a combination of genetic and environmental factors may lead to cancer of blood. Mutation may arise due to error in DNA of some blood cells leading to derailment of cell's machinery, which fails to instruct the cells for its proper functioning. There may be other factors. Some of the suspected causes are ionizing radiation, Viruses - HTLV-1 (human T-lymphotropic virus) and HIV (human immunodeficiency virus), some petrochemicals, benzene, hair dyes etc.<sup>[9]</sup> Some chemotherapeutic drugs used to treat cancer themselves are potential cause of leukemia. People with Down syndrome are susceptible of developing leukemia.<sup>[10]</sup> Therefore, some chromosomal abnormalities may be associated with leukemogenesis. Exposure to electromagnetic fields might be a cause of leukemia.<sup>[11]</sup> Genetic predisposition cannot be ignored, first degree relatives of CLL patients, or having an identical twin who has or had AML or ALL, may increase the risk for developing the disease in the other. Smoking increases the chances of development of leukemia. Males are more likely to develop CML, CLL and AML than females. Certain abnormalities cause the cell to grow and divide more rapidly and to continue living when normal cells would die. With the passage of time, these abnormal cells can crowd out healthy blood cells in the bone marrow, leading to fewer healthy white

blood cells, red blood cells and platelets, causing the signs and symptoms of leukemia.

### Treatment modalities

A plethora of treatment modalities are available for leukemia. Pharmaceutical intervention, often in combination with multi-drug chemotherapy regimen may be effective. Radiation therapy and sometimes a bone marrow transplant may be helpful. ALL cases are aimed to control bone marrow, which is done by induction chemotherapy. Prednisone, vincristine, anthracycline drugs, L-asparaginase, cyclophosphamide are used. Prednisone, L-asparaginase, and vincristine are generally chosen for paediatric patients. Patients with ALL are given methotrexate and 6-mercaptopurine, both being antimetabolite drugs. Dose of drugs is chosen depending on the extent of risk.<sup>[12]</sup> For high risk, in addition to antimetabolites, other drugs are given. To arrest the spread of the disease to brain and nervous system in high risk ALLs, CNS (Central Nervous System) prophylaxis is common as a preventive measure. Radiation is a good prophylactic measure. Often chemotherapeutic drugs are used to prevent come back of cancer. These are maintenance strategy, which are used in low dosages for a period of three years. For high risk or relapsed patients, bone marrow transplantation may be the choice. For CLL, the scenario is slightly different. Majority of CLL patients have a low grade disease, which are not benefitted from treatment. CLL, being an incurable disease, the target is to suppress the disease for many years. Combination chemotherapy is followed using chlorambucil or cyclophosphamide in conjunction with corticosteroid prednisone or prednisolone. The corticosteroid does an additional function by tackling autoimmune diseases namely immunohemolytic anemia or immune-mediated thrombocytopenia. When drug resistance occurs, nucleoside drugs like fludarabine, pentostatin, or cladribine may yield better outcome. For CLL, bone marrow transplant may be an option for better outcome.<sup>[13]</sup> AML patients are treated with the target to control bone marrow, vis a vis rendering treatment for central nervous system (CNS). Combination chemotherapy for AML may be good for early remission and lower risk of development of resistance to the drug.<sup>[14]</sup> Proper measures are taken to prevent recurrence of disease. Maintenance doses are much lower than those prescribed for induction phase. Imatinib mesylate (Gleevec) is the standard treatment regimen for CML patients. Imatinib has a few advantages that it is an orally administrable drug having less side effects and can control the disease for at least 5 years.<sup>[15]</sup> But, tolerance of drugs has individual variation, therefore, in such cases imatinib usage may be replaced by allogenic bone marrow transplant where chemotherapy and radiation followed by subsequent bone marrow transplant is performed. However, the success rate of this allogenic bone marrow transplant is not good. For HCL, the treatment is given when obvious signs are noticed. Generally daily application of cladribine for a week, or intravenous infusion of pentostatin for six months may lead to prolonged remission. Rituximab or interferon-alpha may also be helpful for HCL.<sup>[16]</sup> Splenectomy is also done, but outcome of cladribine or pentostatin is much better. The rare, but aggressive leukemia called TPLL normally is unresponsive to chemotherapeutic drugs. Pentostatin, fludarabine, cladribine, chlorambucil, and various forms of combination chemotherapy [cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP), cyclophosphamide, vincristine, prednisone (COP), vincristine, doxorubicin, prednisone, etoposide, cyclophosphamide, bleomycin VAPEC-B) have been used, but with not very promising results. A monoclonal antibody Alemtuzumab (Campath) works better for this type of leukemia. For better response stem cell transplantation may be practiced. For JMML line of treatment involves splenectomy, chemotherapy and bone marrow transplant.<sup>[17]</sup>

The goal of any treatment regimen is to achieve better prognosis. The prognosis of leukemia depends upon the type of leukemia that is present and the age and health status of the patient. Mortality rate is

less in children and young adults than in elderly patients. 5-year survival rates for CML and CLL are 89% <sup>[18]</sup> and 75 % <sup>[19]</sup> respectively. For acute leukemia overall survival rates are 40 % for AML <sup>[20]</sup> and 50% for ALL <sup>[21]</sup> in case of adults. For children, the survival rate is as high as 70% in case of AML <sup>[22]</sup> and more than 85% for ALL <sup>[21]</sup>.

When cancer cells are destroyed, often a condition sets in, called tumour lysis syndrome, which is a group of metabolic abnormalities and this can be fatal.<sup>[23]</sup> This complication is quite common after treatment in case of leukemia or lymphoma and is marked by increased levels of blood potassium (hyperkalemia), blood phosphorus (hyperphosphatemia), blood uric acid (hyperuricemia), and higher than normal levels of blood urea nitrogen (BUN) and other nitrogen containing compounds, or low level of blood calcium (hypocalcemia). When leukemic cells are smashed rapidly due to treatment, large number of phosphate is released. All these abnormalities culminate in nausea and vomiting, acute uric acid nephropathy, acute kidney failure, seizures, cardiac arrhythmias, and death. Children receiving therapy encounter adverse effects at a later stage. These include impairment of central nervous system (CNS), growth retardation, infertility, cataracts. Risk of development of other cancers is also increased.

### Pitfalls of conventional therapy

Like all other cancers, therapy of leukemia has their own side effects, but that depends on the treatment they receive. Also, individual variation on extent and type of side effects are there. Apart from killing the cancer cells, these drugs damage the healthy cells to a great extent. Immune status of an individual receiving treatment is impaired. Often fatigue sets in, followed by bleeding and bruising. Alopecia, nausea, vomiting, sore in the mouth are other common side effects.<sup>[24]</sup> Infertility may arise and for women menstrual cycle is disrupted and often typical symptoms of menopause may occur. Some of these complications goes off gradually after completion of the treatment. Radiation therapy is also given to patients. Radiation exposure makes the skin of exposed area red, dry, tender and itchy. Radiation may also cause hair loss, nausea, vomiting and anorexia.<sup>[25]</sup> Stem cell transplantation is another treatment modality for leukemia, which has its adversities. They encounter higher risk of infection, bleeding, and other associated side effects due to high doses of chemotherapy and radiation given to them. Another common problem associated with stem cell transplantation is graft versus host disease (GVHD), which may arise when an individual is given stem cells from a donor's bone marrow.<sup>[26]</sup> The stem cells from donor may react with patient's tissues, affecting liver, skin or digestive tract. This effect may not always be immediate, but may occur much later. Steroids may be given as a treatment of GVHD. With much development of medical science, diagnostic tools and treatment strategies have become much advanced. In spite of modern interventions, prognosis is not up to the mark. Therefore, the search for newer solution is warranted. Anticancer agents with high efficacy and minimum side effects may come to rescue. Plant derived molecules may pave a way as remedy in this regard. Plants, since ages are used as a curative measure in Ayurveda. A group of botanicals named medicinal plants elicit anticancer effects. Some of the chemotherapeutic drugs conventionally used to treat cancer are also derived from plants. The bioactive components exert their beneficial effects on human health, as preventive, as well as curative agents.

### Nutraceuticals may be a better option

Since ages Ayurveda has gained in importance, utilising the richness and power of herbs. Herbal medicine utilises plants, plant extracts as remedy of many diseases. Inherent power of natural herbs often works miraculously on human body as they target to restore body's ability to protect, regulate and heal itself. These nutraceuticals are often termed phytomedicine, phytotherapy or botanical medicine. These herbs are

natural and have no toxicity. In leukemia, certain herbal formulation restricts the abnormal growth of cells and at the same time regenerate normal healthy body cells. Pain and anxiety can be well controlled with the aid of these drugs. Many modern medicines are derived from plants and some chemotherapy drugs have a plant origin. Herbal medicines are used in complementary and alternative therapies (CAM). Side by side the conventional treatment regimen, these form of treatment is given to the cancer patients. To diagnose leukemia in Ayurveda, trividhpariksha consisting of inspection (darshan), palpation (sparshan) and questioning (parshan) is followed.<sup>[2]</sup> Physician diagnose leukemia by observing some obvious signs like anemia, bleeding tendency etc. Some other signs of leukemia are Splenomegaly, Hepatomegaly, fever, sternal tenderness among others, which can be observed by examining the patient by palpation. Some other associated problems are seen in a patient suffering from leukemia. Fatigue, weight loss, pain in bones, night sweats are some of these problem. An Ayurveda practitioner confirms the diagnosis by questioning the patient.

Several herbs find their use in cancer. Some of these are quite effective in case of leukemia. *Withania Somnifera* (Ashwagandha), *Giloy* (Guduchi), *Curcuma Longa* (Curcumin), *Ocimum Tenuiflorum* (Tulsi), *Embllica Officinalis* (Amalaki), *Terminalia Chebula* (Haritaki), *Terminalia Belerica* (Vibhitaki) are some of the plants that are helpful in leukemia. The versatile herb Ashwagandha is very advantageous to tackle impotency, stress, constipation, rheumatism and other chronic ailments. Stress in any form leads to poor health condition, including cancer. Ashwagandha, being a good antioxidant help promoting overall well-being and boosts stamina, strength and immunity.<sup>[27,28]</sup> Another important plant product is Giloy. It aids in maintaining homeostasis, overcomes calcium deficiency and thereby prevent diseases.<sup>[29]</sup> Curcumin, also called Indian saffron is the active ingredient of an age old Indian spice, isolated from the rhizome of the turmeric plant. Curcumin targets various key molecules involved in the disease process. It has established its role as an anticancer agent. It is stud with anti-oxidants and therefore can counter the free radicals, which is a pillar in the development of carcinogenesis. Curcumin is anti-inflammatory, anti-diabetic, anti-bacterial, anti-viral, anti-fungal and anti-protozoal. Curcumin is efficient in inhibiting polycyclic aromatic hydrocarbons (PAHs) and prevents chromosomal damage. It often relieves gastric and liver problems. Besides acting as an anticancer agent curcumin may be used in Alzheimer's disease, malaria etc. Curcumin aids in retarding the growth of leukemia cells, therefore preventing their spreading. Curcumin prevents production of the growth factor of cancer cells – basic fibroblast growth factor (bFGF), a member of the fibroblast growth factor family, overproduction of which is one of the causes of leukemia. The guardian of genome p53 is upregulated by curcumin. TNF-alpha, the inflammatory cytokine, which is highly implicated in development of leukemia gets inhibited by curcumin. Curcumin inhibited the expression of pro-survival proteins like STAT3, Akt, and NF-kB etc; some of the proteins that aid in apoptosis like BIM, Mcl-1 and XIAP are upregulated.<sup>[30,31]</sup> The Hindus consider Tulsi to be a sacred plant. *Ocimum Tenuiflorum* or Tulsi has a characteristic aroma and is beneficial to the throat and chest and thereby works against common cold, flu and headaches. It is a stress reliever <sup>[32]</sup> and controls emotions. Many of the cough syrups contains Tulsi. Amalaki or Amla is also a powerful antioxidant and enhances vitality and immunity. Anemia and other blood related disorders are also cured by Amalaki.<sup>[33]</sup> It is good for the hair, as it prevents premature greying of hair, hair loss and helps to grow new hair. It is also good for vision, acts as a mouth freshner, nourishes nail, bones and teeth. Triphala is a known name in India and Haritaki is one of the ingredients of Triphala. Haritaki is good for splenomegaly, hepatomegaly <sup>[34]</sup>, tumors, ascites, anemias; it boosts appetite and improves digestion. Another important part of Triphala is Vibhitaki or *Terminalia Belerica*. It is a very good heart tonic, purifies blood by removing toxins.<sup>[35]</sup>

Not only these, there are other herbal medicines to control vata, pitta and kapha, which, according to Ayurveda are responsible for leukemogenesis. For acute forms of leukemia, a formulation of Muktapisht, Bajra Bhasma, Pandupanchanan Rasa may be used. For chronic form of leukemia similar formulation may be used, but Muktapisht is replaced by Yakritaplihodarariloaha Rasa. Some other drugs used for treatment of leukemia are Davyardileha, Trailokyasundar, Chandrasuryatmak Rasa and Vishadi Churna.

Malvidin, an anthocyanin and its glycosides are responsible for the red or blue color of many foodies like red grapes, cranberries, blueberries and black rice. The anthocyanin metabolites of malvidin and other polyphenols present in red wine may be responsible for the observed antioxidant effects. An *in vitro* study shows the cytotoxicity of malvidin to human leukemia cells. In addition, it retards cell cycle in G2-M transition and induce apoptosis.<sup>[36,37]</sup> Euphorbia hirta has been reported to be effective in Freund virus leukemia.<sup>[24]</sup> Andrographolide is cytotoxic towards a number of cancer cells, including lymphocytic leukemia cells. The tropical tree Mappia foetida/ Nothapodytes foetida has gained importance. Camptothecin, an acceptable chemotherapeutic drug, isolated from this tree is used as a therapeutic agent in leukemia. Camptothecin has also been isolated from a fungus that grows on this plant. This compound inhibits the nuclear enzyme DNA topoisomerase. Several clinical trials have been initiated using some semi-synthetic derivative of camptothecin.<sup>[38]</sup> Cedrus deodara is another tree of enormous importance, its bark has multifaceted uses. It works well with fever, rheumatoid arthritis, ulcers, diarrhea and dysentery, inflammation and cancer. Cedarwood oil is a good expectorant and pain reliever. A lignin composition has been found to increase the activity of cysteine proteases in human leukemic cell HL60; caspase 8 and caspase 9 get activated facilitating apoptosis. The lignin mixture not only activate caspases, but also responsible for peroxide generation and mitochondrial depolarization, triggering mitochondrial-dependent and mitochondrial-independent apoptotic pathways.<sup>[39]</sup> Certain herbs that are a part and parcel of gourmets are good anticancer agents. The fragrant herb Rosemary garnished over chicken roast can kill cells of childhood leukemia.<sup>[40]</sup> Active biomolecules in grapes, strawberries kill ALL cells. How do they do that? The powerhouse in a cell is the mitochondria, the phytochemicals disrupt mitochondrial function and facilitates cell killing.<sup>[41]</sup> Tea is the most popular beverage throughout the world. Among various components of tea, the root extract and steroidal saponins induce apoptosis in leukemia cells in *in vitro*. EGCG, the key polyphenol in green tea, leads to induction of apoptosis in B-CLL cells by partial inhibition of VEGFR1 and VEGFR2 phosphorylation, by activation of caspase-3 and as a consequence cleavage of PARP. Bcl-2 is down-regulated by EGCG, as is Mcl-1 and XIAP. A combinatorial treatment of EGCG and curcumin increased leukemia cell death.<sup>[41]</sup> Saponins are found to activate caspases. Some anti-apoptotic proteins are down-regulated. The isoflavone Genistein, found in abundance in soybeans, function as a tyrosine kinase inhibitors by inhibiting DNA topoisomerase II. It has been found to be effective against leukemia cells as evident from *in vivo* and *in vitro* studies. Another important component of soy namely beta-conglycinin imparts cytotoxicity to leukemia cells.<sup>[41]</sup> Gingerol from ginger is an antioxidant, anti-inflammatory and show antitumor properties; decreases iNOS and TNF-alpha expression via suppression of IκBα phosphorylation and NF-κB nuclear translocation. Gingerol has been found to induce programmed cell death by mitochondrial pathway in leukemia cells K-562. Resveratrol is an active ingredient of red grapes, peanuts etc. Resveratrol aids in cancer prevention. By induction of phase II metabolizing enzymes, it acts as a cancer preventive agent. It can retard the promotional step of human promyelocytic leukemia. In leukemia cell line U937, another herbal product rosmarinic acid has been found to sensitize TNF-α induced apoptosis via suppression of NF-

κB and reactive oxygen species (ROS).<sup>[41]</sup> Sulfur-containing glycosides called Glucosinolates (GL) are found in several cruciferous vegetables that we consume frequently. These vegetables possess a characteristic flavour, which is due to the presence of isothiocyanates (ITCs). During cooking, food preparation and chewing thiocyanates and nitriles are formed, which are breakdown products upon exposure of GLs to myrosinase. Phenethyl isothiocyanate (PEITC) and sulforaphane, two main isothiocyanates are reported to inhibit development of carcinogenesis and tumorigenesis. They do so by inhibiting cytochrome P450 enzymes, which oxidize compounds such as benzo[a]pyrene and other polycyclic aromatic hydrocarbons (PAHs) into ultimate carcinogenic form i.e. polar epoxy-diols. This leads to mutation and finally cancer. PEITC is a potent inducer of apoptosis, even in drug resistant leukemia cells, where level of anti-apoptotic protein Bcl-2 is very high. PEITC activates c-Jun N-terminal kinase (JNK) and tyrosine phosphorylation and thereby induce apoptosis. Caspase8 plays a critical role in PEITC induced apoptosis in leukemia.<sup>[42]</sup> Natural products belonging to flavagline class of molecules namely rocaglamide and silvestrol are unique in showing preferential effect on leukemia stem cells, being not prudent to normal stem and progenitor cells. In addition to efficacy as single agents, flavaglines sensitize leukemia cells to several anticancer compounds, including front-line chemotherapeutic drugs used to treat leukemia patients. Rocaglamide and silvestrol are distinct from clinically available translational inhibitors and represent promising candidates for the treatment of leukemia.<sup>[43]</sup> Another important molecule is berberine, which is a natural isoquinoline alkaloid isolated from Berberis species. Berberine has been shown to induce caspase activation, thereby induce apoptosis. It shows anti-proliferative, cytotoxic, and pro-apoptotic activities in leukemia, which lack p53 expression.<sup>[44]</sup> Some herbal medicines of Chinese origin also contribute to leukemia therapy. One such herbal formulation is Tanshinone IIA (Tan IIA), which is a diterpene quinone isolated from Salvia miltiorrhiza root. It has been observed that TanIIA is capable of imparting prolonged survival in *in vivo* (acute promyelocytic leukemia (APL)-bearing mice) and also in *in vitro* model of leukemia.<sup>[45,46]</sup> Another Chinese medicine glycyrrhetic acid (GA), derived from licorice root shows its efficacy on human leukemic HL60 cells. GA does so by induction of apoptosis via CD95 and CD178 signaling pathway.<sup>[47]</sup> Celastrol, a triterpenoid isolated from the Chinese medicine *Tripterygium wilfordii* Hook F. has been found to potentiate TRAIL-induced apoptosis through down-modulation of cell survival gene products and up-regulation of death receptors. This triterpenoid inhibited cell proliferation and induced apoptosis, probably due to the regulation of Notch or NF-kappaB.<sup>[48,49]</sup>

Some anti-leukemia formulations are there in Ayurveda. Sandpuspa (*Lochnera rosea*), Bhallatak (*Semecarpus anacardium*), Vanpalandu (*Urginea indica*), Vantrapush (*Podophyllum hexeandrum*), Guggulu (*Commiphora mukul*) are some of the herbs used in Ayurveda for treatment of leukemia.

There are certain polyherbal compounds which may show their efficacy in leukemia. A list of such compounds along with the constituents are given in Table 1.

## DISCUSSION

Cancer is a deadly disease worldwide in terms of morbidity and mortality. Extensive research is in progress, but the exact cause is yet to be elucidated. It is interesting to know in detail the development of cancer and its progression. Carcinogenesis is a multistep process involving several genes and proteins. There are a number of treatment modalities in medical science which are beyond the reach of common people. The treatment regimens are also not free from side effects; and may also alter the normal functioning of genes. Thus, a safe and

**Table 1:** Polyherbal compounds effective in leukemia

Compound	Constituents	Application
Rodra Ras	Suta(mercury), Gandhak (sulphur), Nagavalli ( <i>Piper betal</i> ), Meghanada ( <i>Amaranthus spinosus</i> ), Punarnava ( <i>Boerhaavia diffusa</i> ) Pippali ( <i>Piper longum</i> ) and Gomutra (cow's urine).	with honey orally
Vradhdaru churn	Vradhdaru ( <i>Argyrea speciosa</i> ), Haritki ( <i>Terminalia Chebula</i> ), Amalaki ( <i>Emblica officinalis</i> ), Shunthi ( <i>Zinziber officenalis</i> ), Marich ( <i>Piper nigrum</i> ), Pipali ( <i>Piper longum</i> ), Daruhaldi ( <i>Berberis aristata</i> ), Chavya ( <i>Piper retrofractum</i> ), Varun (Crataevanurvala), Gokshur ( <i>Tribulus terrestris</i> ), Chopchini ( <i>Smilex china</i> ), Sudha, Mundi ( <i>Sphaeranthus indicus</i> )	with kanji or gomutra
Vradhdaru yoga	Vradhdaru ( <i>Argyrea speciosa</i> ), Haridra ( <i>Curcuma longa</i> ), Shunthi ( <i>Zinziber officenalis</i> ), Marich ( <i>Piper nigrum</i> ), Pipali ( <i>Piper longum</i> ), Haritki ( <i>Terminalia Chebula</i> ), Amalaki ( <i>Emblica officinalis</i> ), Vibhitaki ( <i>Terminalia bellerica</i> ), Shigru ( <i>Moringa oleifera</i> ), Kampillak ( <i>Mallotus philippinensis</i> ) Ajnayan ( <i>Trachysprmu mammi</i> ), puranaguda and Gomutra (cow's urine)	Orally
Nityan and Ras	Suta (mercury), Gandhak (sulphur), Tamra Bhasma, Kansya Bhasma, Vang Bhasma, Tuth, Sankh Bhasma, Varatica Bhasma, Shunthi ( <i>Zinziber officenalis</i> ), Marich ( <i>Piper nigrum</i> ), Pipali ( <i>Piper longum</i> ), Haritki ( <i>Terminalia Chebula</i> ), Amalaki ( <i>Emblica officinalis</i> ), Vibhitaki ( <i>Terminalia bellerica</i> ), Loha Bhasma, Vidang (Embeliaribes), Sandhav lavana, Samudhra lavana, Sauvarchal lavana, Vidlavana, Audhbhidha lavana, Chavya ( <i>Piper retrofractum</i> ), Karchura ( <i>Curcuma zedoria</i> ), Padha ( <i>Cissampelo spareira</i> ), Devdaru (Cedrusdeodara), Ela ( <i>Elettaria cardamomum</i> ), Vradhdaru ( <i>Argyrea speciosa</i> ), Nishoth ( <i>Operculina turpethum</i> ), Chitrka ( <i>Plumbago zeylanica</i> ), Danti ( <i>Baliospermum montanum</i> )	With water orally
Kachnargugulu	Kachnar ( <i>Bauhinia variegata</i> ), Shunthi ( <i>Zinziber officenalis</i> ), Marich ( <i>Piper nigrum</i> ), Pipali ( <i>Piper longum</i> ), Haritki( <i>Terminalia Chebula</i> ), Amalaki ( <i>Emblica officinalis</i> ), Vibhitaki ( <i>Terminalia bellerica</i> ), Varun ( <i>Crataevanur valaa</i> ), Tezpatra ( <i>Cinnamom nmtamala</i> ), Dalchini ( <i>Cinnamomnm zeylanicum</i> ), Guggalu ( <i>Commiphera mukul</i> ), Ela ( <i>Elettaria cardamomum</i> )	orally
Hargauriras	Raskar poor (Hgcl2), Hartal (AS2S3), Somal (AS2O3), Bhojpatra (Betulautillis),	with Dhrat
Herbo mineral Navjeevan Ras	Rajat Bhasma (Silver Bhasma), Jahar Mohara (Serpentine Stone), Nirvisha ( <i>Delphinum denudatum</i> ), Taruni, Gulab ( <i>Rosea centifolia</i> ), Chandan ( <i>Santalum album</i> ), Gojihva ( <i>Onosma bracteatum</i> ), Latakasturi ( <i>Hibiscus abelmoschus</i> ). Navjeevan Ras	Daily as a tablet
Kamdudha Ras	Maukticpishti ( <i>Mytilusmar gartiferus</i> ), Pravalapishti ( <i>Corallium rubrum</i> ), Muktasuktishti ( <i>Mytilusmar gartiferus</i> ), Kapardikabhasma (Calcinated and purified Cypraeamoneta shells), Sankha bhasma (Calcinated and purified Turbinellarapa shells), Amratasatva ( <i>Tinospora cordifolia</i> ).	
Keharubapisti	Trinakantamanichurn, Gulab ark (for mardan), Kamdudhar and Kaharubapisti	

effective mode of treatment is needed to control the cancer development and progression. Some medicinal plants provide a safe, effective and affordable remedy to control the progression of malignant cells. The importance of medicinal plants and their constituents has been documented in Ayurveda, Unani medicine, and various religious books. In this review, we summarize the understanding of chemopreventive effects of nutraceuticals in the prevention of cancer via the regulation of various cell signaling and genetic pathways.

Cancer is a deadly disease for both men and women and also a major health problem worldwide. The present mode of treatment based on chemotherapy and radiotherapy is very expensive and also exhibits serious side effects in human beings. Keeping in view the significance of herbs, this review is written to show the role of plant molecules in the prevention of various types of cancer through the activation or inactivation of various genetic pathways. Due to safety, low cost, easy access and others, phytochemicals may prove to be an effective therapeutic strategy in the management of cancers.

Leukaemia which is characterised by abnormal growth of the WBC are primarily of two types Myeloid and Lymphoid, which are further divided into Acute and Chronic. Genetic factors, radiation and chemical carcinogens some infection RNA virus and the addiction of tobacco may be regarded as the causative factors responsible for leukemia. Vitiatio of Doshas with in blood sources compress the blood cells and resulted the Rakta Arbuda or leukemia. The typical symptoms of leukemia in Ayurveda are Anaemia, Splenomegaly, Hepatomegaly and Bleeding tendency which are in agreement with the distinct cytogenetics, clinical features, and biologic characteristics described in modern medicine. In allopathy there are several drugs to treat leukemia, which have their own adverse effects. The toxicity and associated side effects of these chemotherapeutic drugs often pose a significant problem during treatment of cancer. Plant derived molecules are safer, cheaper and quite effective and therefore may be considered as an alternative to the toxic therapeutics. There are other plant molecules with enormous potential. Therefore, it is time to explore and dig out more and more of these molecules from a garden of nutraceuticals, so that a new treatment regimen can be established in future, where a patient will be cured with minimal adverse effects.

## CONCLUSION

Nutraceuticals have found their place in cancer research for their chemopreventive potential. These plant molecules are efficient inducers of programmed cell death or apoptosis, a process by which defective cells leading to carcinogenesis are destroyed. Many of these molecules also retard the uncontrolled growth of cancer cells. The importance of nutraceuticals emerges, where conventional chemotherapeutics fail to act. The drugs commonly used for curing leukemia show adverse effect on an individual, often leading to failure of treatment. The holistic approach is very scientific, as the mode of action of all these molecules are no longer unknown. Therefore, nutraceuticals have gained enormous recognition in the scientific world.

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