Leukemia Causes, Symptoms & Treatment

Chapter 1

Phytochemicals as an adjuvant in leukemia therapy

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Abstract

Aberrant production of immature white blood cells leads to the onset of leukemia. The process of leukemogenesis involves alterations in expressions of various genes and their associated signalling pathways. Existing treatment protocols for leukemia therapy may be quite effective but they pose serious adverse effects on the individual. Therefore, newer means need to be explored which may help to fight the disease. Plant derived molecules, commonly referred to as phytochemicals are stud with various disease fighting properties. They help to fight cancer as well, including leukemia. They exert their action by targeting various signalling molecules that are involved in the process of leukemia. These phytochemicals act preferentially as they target the cancer cells only, sparing the normal healthy cells. This unique property of these molecules helps to reduce the side effects of therapy. Various in vitro and in vivo studies show that when phytochemicals are used to treat cancer cells along with existing therapeutic regimens, the efficacy of the therapy is increased. Thus, if phytochemicals are used in conjunction with existing therapeutic protocols, the outcome of therapy may be improved. However intense clinical trials need to be conducted to prove the efficiency of phytochemicals as adjuvant.

Keywords: leukemia; phytochemicals; chemotherapy; side effects; adjuvant

1. Introduction

Abnormal proliferation of blood cells in the bone marrow and blood forming organs lead to a malignant condition commonly referred to as leukemia, which may be classified based on the pace of progression. The beginning of leukemia may be sudden (acute) or slow and gradual (chronic). This type of malignancy is also classified based on the type of blood cell affected. Cells belonging to both myeloid and lymphoid lineage are produced from haematopoietic stem cells during the process of haematopoiesis [1]. Malignancy involving myeloid cells, granulocytes (neutrophils, basophils, and eosinophils) and monocytes (macrophages) lead to myeloid leukemia whereas that involving T and B lymphocytes give rise to lymphocytic leukemia [2]. There are various types of leukemia. The four main types include Acute Myelogenous Leukemia (AML), Chronic Myelogenous Leukemia (CML), Acute Lymphocytic Leukemia (ALL) and Chronic Lymphocytic Leukemia (CLL) [3]. There are some other forms of leukemia which are normally infrequent; these are hairy cell leukemia, T-cell prolymphocytic leukemia, large granular lymphocytic leukemia and adult T-cell leukemia.

CML is characterized by excessive build up of relatively mature but still abnormal white blood cells. The median age for CML is 45 to 55 years [4]. CML is a common type of leukemia in the Asian countries. It affects more males than females [5]. CLL is the commonly encountered form of leukemia in the western world. The median age at which this leukemia is diagnosed is 72 years, however a small proportion of patients are diagnosed below 55 years [6, 7]. ALL is the common form of leukemia in children below 5 years of age. However, adults over 50 years of age are also susceptible to ALL. ALL is prevailing in the Caucasian population compared to the African Americans. Mortality from ALL mainly occurs in adults [8]. AML is a disease of the elderly population with a median age of 67 years at the time of diagnosis. It is more frequently seen in the US population. AML is the most common form of acute leukemia occurring in adults [9].

2. Risk Factors of Leukemia

Factors that increase the chances of having a disease are known as risk factors. Various familial, genetic, lifestyle and environmental factors are suspected to be responsible for development of leukemia. Smoking habits, though a potential cause of lung and oral cancer, can be correlated with the occurrence of leukemia. Leukemia may also develop in an individual due to exposure to chemicals like benzene and herbicides in their workplace [10]. Blood cancer often develops as secondary cancers, i.e. treatment with certain chemotherapeutic drugs and high dose radiation therapy may increase the risk of leukemia [11]. Individuals suffering from polycythemia vera, essential thrombocythemia, idiopathic myelofibrosis, and myelodysplastic syndrome are at higher risk of leukemia development [12]. Certain chronic forms of leukemia may also eventually lead to acute forms, which are aggressive. People suffering from genetic

disorders like Down syndrome, Bloom syndrome, Klinefelter syndrome, Blackfan-Diamond syndrome, Fanconi anemia, Ataxia-telangiectasia, Li-Fraumeni syndrome, Neurofibromatosis I, Kostmann Syndrome etc. are at increased risk [13]. Infection with HTLV virus may lead to a form of ALL [14]. Risks of leukemia may also depend on race or ethnicity as it is more prevalent in North America and Europe compared to that in Asia [15]. Family history may also increase the chances of having the disease. Excessive use of alcohol and drugs may be a causative factor for leukemia. Obesity also plays a vital role in development of leukemogenesis [16]. Low frequency electromagnetic field is also a probable risk factor [17].

3. Symptoms of Leukemia

Certain forms of leukemia in its initial stages may be asymptomatic. Symptoms of leukemia depend on whether the leukemia is acute or chronic. Acute forms of leukemia tend to worsen faster than the chronic forms. Acute leukemia shows flu like symptoms in its initial stages whereas the chronic leukemia hardly shows any symptoms. Chronic leukemias are often detected during routine blood tests. Some of the common signs and symptoms include fatigue, malaise, appetite loss, loss of weight, fever, shortness of breath, paleness, palpitations, easy bruising and bleeding, dizziness, susceptibility to cold, sore throat, nausea, headaches, problems in vision, night sweats, pain in joints, discomfort in abdomen, etc. Feeling of fullness in abdomen, purpura, leucocytosis, anaemia, splenomegaly and thrombocytosis are other commonly encountered symptoms [18]. When abnormal and immature blood cells accumulate under the skin or other body parts, a malignant condition called chloroma is resulted [19]. Leukemia cutis, leukocytoclastic vasculitis and Sweet's syndrome, or acute febrile neutrophilic dermatosis may also be seen in leukemic patients.

4. Genes in Leukemia

Genes play an important role in the process of leukemogenesis [20]. Chromosomal aberrations and gene mutations are characteristic features of all forms of leukemia. These changes at the genetic level affect key signal transduction pathways that lead to the disease initiation, promotion and progression. Methylation of DNA and modification of histones contribute to the development of leukemia. Mutations of transcription factors like *FLT3, KIT, NRAS, KRAS, CEBPA, NPM1, PAX5, TCF3, EBF1* etc contribute to leukemogenesis [21]. Some other genes that are implicated in leukemia are *SMAD2, CDK9, MEN1, HDAC1, LCK* etc [22]. Mutations in certain genes predispose individuals to development of leukemia; CEBPA, GATA2 and RUNX1 are few such genes. *CEBPA* plays a crucial role in myeloid differentiation. People who inherit germline mutations in this gene are likely to be susceptible to development of acute myeloid leukemia. RUNX1 gene mutations often cause autosomal dominant familial platelet disorder and may lead to myeloid malignancy. *GATA2*, a transcription factor, is involved in maintaining integrity of hematopoietic stem cell. Mutation in this gene may result in

myelodysplastic syndrome (MDS) or Acute Myeloid Leukemia (AML). Loss of a tumor suppressor gene present on chromosome 7 may contribute to initiation of MDS and AML [23].

Alterations in chromosome often lead to carcinogenesis, particularly in leukemia, where cytogenetic and genetic aberrations are very prominent. Trisomy 8 is frequently found in AML. Translocations like t (15;17)), t (8;21) and t (9;11) are commonly seen in this form of leukemia. Another chromosomal aberration that occurs in AML is inversion in chromosome 16 [24]. Of all the translocations, t (15;17) is generally found in acute promyelocytic leukemia. On the other hand, t (8;21) is a characteristic feature of acute myeloblastic leukemia with maturation [24]. Translocation between chromosome 8 and 14 is found in B-cell acute lymphoblastic leukemia [25]. Translocations t (1; 3); t (11; 14); t (4; 11); and t (9; 22) are the most frequently encountered chromosomal abnormality in ALL [26]. Chromosomal abnormalities are also seen in the chronic forms of leukemia. A majority of CLL patients show chromosomal abnormalities. Trisomy 12 and deletions in chromosomes 11q, 13q & 17p play vital role in pathogenesis of this type of leukemia [27]. Mutations in TP53 are responsible for poor prognosis of CLL. Abnormalities in NOTCH1 and SF3B1 genes also results in CLL, the most common form of leukemia seen in adults [27]. Philadelphia chromosome, a characteristic feature of CML, results due to translocation between chromosomes 9 and 22. However certain other minor genetic abnormalities are also observed like trisomy 8 and 9, inversion in chromosome 17. Sometimes an extra copy of Philadelphia chromosome is also observed in CML [28].

MicroRNAs are small non-coding molecules playing vital roles in silencing of RNA and post transcriptional gene regulation. Various microRNAs are known to contribute to pathogenesis in leukemia by regulating oncogenes and tumor suppressor genes at the transcriptional level. mir-17-92 polycistron are highly expressed in acute leukemia and contributes to development of the disease by inhibiting the normal process of haematopoiesis. The genes affected are PTEN, BIM, RASSF2, APP, E2F and so on. Other microRNAs that play pivotal role in acute leukemia are miR-155 and miR-196a & b. miR-15a/16-1has tumor suppressor properties and are expressed in low amounts in CLL [21].

Translocation between chromosomes 3 & 21 results in formation of RUNX1-EVI1. This chimeric gene contributes to transformation of myelodysplastic syndrome or chronic myelogenous leukemia to its aggressive forms. It exerts its leukemogenic effect via recruitment of histone deacetyl transferase through C-terminal binding protein [29]. Mutations in PAX5, TCF3, NOTCH1, MYB, IKZF1, CDKN2A and EBF1 lead to acute lymphoblastic leukemia [30]. NOTCH1 is vital for renewal of hematopoietic stem cells and T cell development. Mutations in this gene lead to aberration in TAL1, LYL1, LMO1, LMO2, TLX1, TLX3 and MYC pathways. The alterations in these pathways lead to elevated expression of various oncogenes and reduced expression of suppressor genes like *p16/INK4A, p14/ARF (CDKN2A), TP53, RB*. Aberrant methylation of DNA and loss of CDKN2A and CDKN2B expression are crucial in

ALL [31]. Over expression of CRLF2 and mutations in JAK STAT pathway also contributes to leukemia. Mutations in molecules involved in the MAP kinase cascade are known to be critical in the process of leukemogenesis. Chimeric proteins are formed as a result of gene translocations in AML which lead to enhanced survival of hematopoietic stem cells. Various signalling molecules deregulated in AML are CREB, Triad1, Bcl-2, Stat3, and mTOR/MEK. PI3K/AKT pathway is activated by BCR-ABL in CML and participates in development of leukemia induced by BCR-ABL. Other pathways targeted by this fusion gene are MAP kinase, JAK-STAT, Hedgehog, TGF-β and WNT/β-catenin pathways. Mutations in TET2 and ASX-L1genes lead to Ph-negative myeloproliferative neoplasms (MPNs), examples of which are polycythemia vera, essential thrombocythemia, and primary myelofibrosis. The pathogenesis of CLL may be attributed to aberrant B cell receptor signalling which leads to abnormal PI3K/AKT and NF-κB pathways [32, 33]. Pro-angiogenic factor VEGF and Fibroblast Growth Factor Receptors also contributes to survival of CLL cells. SFKs (members of Src-family kinases) consist of various members that activate PI3K/AKT, MAPK, Jak-STAT and FAK-paxillin-p130-Crk-associated substrate (Cas) cascades which lead to survival and proliferation of cancer cells [34]. Cytokines are critical regulators of the immune system and play important role in haematopoiesis and cell signalling. Aberrant cytokine signalling regulates proliferation of leukemia cells [35]. Some of the cytokines involved are TNF α, interleukins IL 2, IL 6, IL8 etc.

5. Treatment of Leukemia

There are a number of modalities used for the treatment of leukemia. The treatment options depend on several factors, i.e. the age, general health of the patient, type and stage of leukemia and whether the disease has metastasized. Chemotherapy is generally used to destroy the leukemia cells. A single drug or a number of drugs may be employed for the purpose, depending on the type of the disease. Often immunotherapy or biological therapy is given to eradicate the leukemia cells. There are certain characteristics within leukemia cells, which are often targeted by drugs. This type of therapy is called targeted therapy. High energy radiation may be used to damage the offending cells. Radiation therapy can be given to one particular position infested with leukemia cells or to the entire body. Bone marrow gets affected in leukemia and the affected bone marrow can be replaced by healthy one by stem cell transplant or bone marrow transplant.

Chemotherapy using a single drug or a combination of drugs is the acceptable treatment modality for leukemia. Therapy of AML involves an initial extensive induction chemotherapy using a combination of cytarabine and anthracyclines like daunorubicin, idarubicin etc. Other drugs like etoposide, fludarabine may also be included in therapy to improve chances of remission. The aim of this induction therapy is to reduce the number of malignant blast cells, which is followed by consolidation therapy and maintenance therapy. Consolidation therapy

comprises of chemotherapy or hematopoietic stem cell transplantation. Maintenance therapy is given to patients after complete remission; this is to ensure removal of any residual cancer cells so that relapse of the disease does not occur [24].

Treatment regimens for ALL involve use of Imatinib Mesylate (IM) for patients possessing Philadelphia chromosome. Absence of Philadelphia Chromosome may be seen in ALL, for which a combination of Imatinib Mesylate and other chemotherapy including vincristine, prednisone, and an anthracycline may be prescribed. Central nervous system (CNS) prophylaxis therapy may also be used and includes cranial radiation therapy and methotrexate. Bone marrow transplantation may be considered in case of a relapse [36]. Commonly used therapeutic protocol for CLL is high dose chemotherapy. Chlorambucil, either alone or in conjunction with rituximab or obinutuzumab may be used for patients who cannot bear the side effects of chemotherapy. Fludarabine, cyclophosphamide, bendamustine, vincristine, doxorubicin, ofatumumab, pentostatin, Alemtuzumab (Campath) etc are some of the drugs commonly used in CLL treatment [37]. Stem cell transplant is another option. There are other therapeutic options which are yet to gain much popularity, these are leukapheresis, surgery, or radiation therapy. Tyrosine kinase inhibitor Imatinib Mesylate is mainly used for CML therapy. Other drugs include dasatinib, nilotinib, ponatinib and bosutinib. Interferons or chemotherapy may also be used. Allogenic stem cell transplantation is also frequently used. Prior to advent of tyrosine kinase inhibitors, use of radiation therapy, busulphan, hydroxyurea, cytarabine were practised [38].

6. Phytochemicals as adjuvants

Phytochemicals are generally an integral part of our diet and are supposed to be free from toxicity but a few may be potential carcinogens or tumor promoters. Adjuvant therapy, employing phytochemicals is gaining importance. Certain plant molecules are known modulators of cytochrome P450 (CYP), which aids in drug metabolism. Phytochemicals display pharmacokinetic (PK) drug-drug interaction because several CYPs often share common substrates. Therefore, the biomolecules from plants may aid in drug clearance as well as carcinogen metabolism by modulation of CYPs. Modulation of CYP by phytochemicals is of enormous importance as it not only hampers carcinogen metabolism, but also drug response gets compromised. Hence, from therapeutic point of view, knowledge regarding interaction of these phytochemicals with CYP is of great importance. This is highly relevant particularly in pharmaceutical industry, in order to develop and improvise therapeutic regimens. The main points of concern are whether administration of these biomolecules hinders the efficacy of drugs or induce any toxic effects due to the reactive metabolite. Therefore, safety of these molecules along with conventionally used anticancer drugs needs to be addressed. Phytochemicals may be having conflicting effects, i.e. sometimes they act as agonist, whereas sometimes as antagonist. Some of the plant molecules like quercetin, genestein, naringenin etc may show inhibi-

tory action on CYP enzymes, diminishing the drug activity [39].

The treatment modalities followed in cancer management are generally not full proof. Besides curing the offending growth, these therapeutic strategies also show severe toxicity to the normal cells, rendering undesirable effect on the patient. There are inter-individual variations and the extent of side effect depends on the type and dose of medication or radiation and the general health of the patient. Fast dividing healthy cells are the main targets of anti neoplastic agents like hematopoietic cells, epithelial cells of the intestine and cells of the hair follicles. Chemotherapy often leads to lower resistance to infection due to suppression of the immune system. Patients frequently suffer from fatigue, hair loss, nausea, and diarrhoea, loss of appetite, sores in mouth, decreased blood cell counts, susceptibility to bleeding and bruising [40]. Radiation leads to loss of hair, dry and itchy scalp [41]. People undergoing stem cell transplantation suffer from graft versus host disorder [42]. Heart and lung problems may also develop. Nerve damage and neurological problems may also result [43]. Osteoporosis is also quite common [44]. Existing therapeutic protocols may also lead to fertility problems in men and women [45]. Children treated for childhood leukemia are at increased risk of developing second cancers like AML at their later stages. They often develop learning problems as they grow up. Their growth and development may also be affected. Children who survive leukemia may also develop psychological issues. Thus, current day cancer therapeutic procedures often lead to compromised life quality of the patient. Keeping these factors in mind, better, safer and alternative means need to be looked into. Combination of existing therapy with compounds having reduced toxicity may lead to increased therapeutic efficiency and better prognostic outcome in cancer. Dietary phytochemicals stud with anti cancer properties may be a good option in this regard. They modulate key signalling pathways involved in leukemogenesis. Not only that, they are also reported to increase the efficacy of chemotherapy and radiotherapy and reduce their side effects.

Various studies have been carried out to establish the potential of phytochemicals as an adjuvant to leukemia therapy. Generation of nitric oxide is beneficial for chemoprevention of cancer.

Flavonoids: Fisetin, a flavonoid abundantly present in strawberries, grapes, apples, onions etc is rich in anti cancer properties. It causes cancer cell death by increasing NO levels leading to breaks in DNA and activation of apoptotic pathways in acute monocytic leukemia. Thus, this phytochemical has the potential to be used as a therapeutic agent in leukemia, either alone or in conjunction with other drugs, though further trials are warranted [46]. Phytochemicals not only increases the efficacy of therapy, but it has been reported that a combination of various phytochemicals may be a better option in imparting cytotoxicity to cancer cells. Luteolin, a flavone is more effective on CLL cells in presence of either fisetin or quercetin. Binding of quercetin or fisetin to specific cellular targets contributes to increased anti-apoptotic

signalling pathways induced by luteolin [47]. Genestein, a soy isoflavone in conjunction with γ-irradiation induces death in leukemia cells by sensitizing the cells to radiation [48]. Galangin, a flavonol found in Alpina species exerts anti leukemic activity on both imatinib sensitive and imatinib resistant leukemia cells, thus suggesting its role as an adjuvant in leukemia therapy [49]. Quercetin, a flavonol found in fruits and vegetables enhances the activity of busulfan in leukemia. Increased induction of apoptosis is observed when CLL cells are treated with a combination of quercetin and fludarabine.

Polyphenols: The common drug used in CML therapy is IM. It acts by targeting BCR-ABL and its associated pathways. The indispensable part of every Indian cuisine is turmeric, whose active ingredient curcumin is responsible for its beneficial role in disease management. This phytochemical increases the efficacy of IM in CML cells and may be used as adjuvants in CML therapy [50, 51]. Curcumin activates tumor suppressor genes that have been silenced in AML by causing hypomethylation of DNA. It also causes arrest of cell cycle at G1 phase and induces apoptosis in AML cells. It also reduces tumor growth in mice implanted with the human AML MV4-11 cell line [52]. Curcumin prevents proliferation of primary leukemic cells when used in conjunction with cytarabine [53]. It also improves the activity of etoposide in leukemia cells HL-60 via histone phosphorylation, production of free radicals and induction of programmed cell death [54]. Thus, this plant product may be used singly or in combination with other drugs in AML therapy. Curcumin also serves as an adjuvant to drugs used in ALL therapy like prednisone, 6-mercaptopurine, dexamethasone, l-asparaginase, vincristine, doxorubicin, cytarabine etc by reducing oxidative stress, activating caspases and down-regulating activation of NF-κB [55]. Tea is a beverage which is widely consumed globally. Tea contains high amounts of green tea catechins, like epigallocatechin-3-gallate (EGCG). EGCG acts synergistically with conventional therapies to increase their efficacy, though proper clinical trials are required to establish their efficacy [56]. Celastrol is another phytochemical derived from the roots of Tripterygium wilfordii (Thunder god vine). Both EGCG and celastrol augments the activity of leukemic drugs in K-562 and Jurkat T human leukemia cells. The mechanism involves activation of caspase 3, cleavage of poly(ADP-ribose) polymerase cleavage and reduced levels of the oncoprotein BCR-ABL [57]. Resveratrol, a polyphenol found in abundance in grapes may be used as dietary supplement while treating leukemia patients with proteasome inhibitors. It exerts its action by inducing $p27^{Kip1}$-mediated G1/S cell cycle arrest [58]. Treatment of myeloid leukemia cells with a combination of arsenic trioxide and resveratrol potentiates the anti leukemic potential of arsenic trioxide [59].

Terpenoids: Glycyrrhetinic acid, the active compound in licorice root may serve as adjuvant to chemotherapy in leukemia [60]. Extracts from two plants used in traditional medicine namely Zingiber officinale Roscoe and Nerium oleander L. induce leukemic cell killing by causing cell cycle arrest and induction of programmed cell death. Use of these compounds in

conjunction with existing drugs may improve responses to therapy [61].

Isothiocyanates: Cruciferous vegetables owe their flavour to isothiocyanates, which possess potent cancer fighting properties. PEITC, an isothiocyanate, in combination with IM modulates various markers in CML cells, thus sensitizing the cells to imatinib [62]. B cell prolymphocytic leukemia is a rare form of leukemia with very low survival rates. Use of PEITC along with drugs like Rituximab, Cyclophosphamide, doxorubicin hydrochloride, Oncovin, Prednisone helps to sensitize B-PLL cells to these drugs, thus leading to better therapeutic outcome [63]. It has often been observed that existing drugs fail to eliminate cancer stem cells leading to relapse of the disease. Sulforaphane, another isothiocyanate when used in combination with IM helps to eliminate leukemic stem cells [64]. Indole-3-carbinol is found in cruciferous vegetables. This phytochemical in combination with anthracycline doxorubicin induces apoptosis in leukemia cells and it has been reported that indole 3 carbinol enhances the cytotoxic effects of doxorubicin in leukemia cells [65]. Combination of this phytochemical with F-ara-A shows cytotoxicity to CLL cells along with reducing the side effects of fludarabine. This combination treatment might be useful for CLL patients [66, 67].

Others: Neutraceuticals like zinc are often given to cancer patients to relieve them of the side effects of therapy. Zinc is a trace element essential for human beings, which is abundant in spinach. Supplementation of Zinc in patients suffering from acute leukemia has been reported to relieve the patients of adverse effects of chemotherapy [68]. Tumor necrosis factor α-related apoptosis-inducing ligand (TRAIL) could be a favourable option that preferentially induces cell death in cancer cells; however, one major disadvantage is development of resistance. A phytoalexin present in legumes, medicarpin is known to make leukemia cells susceptible to TRAIL induced apoptosis [69]. Saponins obtained from Panax ginseng potentiate homoharringtonin, cytarabine, adriamycin etc to leukemic stem cells [70]. Coenzyme Q10 helps to reduce the adverse effects of daunorubicin in patients suffering from leukemia [71]. Administration of vitamin E as an adjuvant to chemotherapy helps to reduce associated febrile neutropenia and bone marrow hypoplasia in ALL patients [72]. Rocaglamide and silvestrol, two flavglines differentially eliminate leukemia progenitor cells and impart sensitivity to conventional therapeutic regimens [73]. Vinblastine, a vinca alkaloid sensitizes CLL cells to drugs flavopiridol and dinaciclib [74]. Carnosic acid, an extract obtained from Rosmarinus officinalis L acts synergistically with adriamycin to prevent malignant cell growth in NOD/SCID AML mouse model inoculated with K562/A02 cells, thereby increasing their survival period [75]. Crocetin, a carotenoid and the active ingredient of Indian spice saffron may also serve as an adjuvant to conventional drugs used in leukemia cells, though intense research is warranted [76].

7. Conclusion

Phytochemicals are tumor fighting armaments, which are potential candidates for chemoprevention and therapy. However, there are certain aspects that need attention. Phytochemicals play a pivotal role in leukemia therapy. They preferentially destroy the leukemia cells, sparing the normal blood cells.

Leukemia is a hematopoietic malady involving excessive production of immature blood cells, where several genes are involved. Alterations at the genetic level perturb the signal transduction pathways involved in carcinogenesis. The conventional treatment strategies target these pathways, thereby halting the three stages of cancer namely initiation, promotion and progression. Existing therapeutic regimens pose undesirable adverse effects on an individual, as they target not only the cancer cells, but also the normal cells. Therefore, alternative means need to be explored which might help to combat the side effects of treatment. Phytochemicals are known to be rich in anti-cancer properties and they have the unique property of preferentially acting on cancer cells, sparing the normal ones. These plant-derived biomolecules help in combating leukemia by targeting various signalling pathways involved in the process. Combining phytochemicals with existing treatment modalities may prove to be effective in improving response to therapy. Laboratory based work has been conducted, proving the efficacy of plant products in this respect. However, extensive clinical trials are warranted to prove the efficacy of such combinatorial treatments.

8. Acknowledgement

Authors are indebted to Director, Chittaranjan National Cancer Institute, Kolkata, India for all help and support.

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