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Medicinal plants, a gold mine of anticancer compounds

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***Abstract**: Cancer is one of the leading causes of adult deaths worldwide. Chemotherapy, radiation therapy and surgical removal of tumors are the most common clinical approaches being used for the treatment of cancer. Today, there are more than 100 FDA approved drugs in the markets for cancer therapy. Unfortunately, the chemotherapy treatment is almost always accompanied by a varied range of short and long term adverse effects. Also the cancerous cells evolve and develop resistance against these drugs during the course of treatment to escape the process of cell death and sustain their survival. Hence, the need arises to explicate the various molecular mechanisms which get altered and support the survival of transformed cells. This would help us find novel targets highly specific to tumor cells and design drugs against them. Since natural compounds offer a potentially infinite source of chemical diversity which cannot be matched by any synthetic chemical collection or combinatorial chemistry approach, we have here discussed various possible molecular mechanisms underlying the cause of cancer and the role of various medicinal plants with anti-proliferative and chemopreventive activity.*

***Keywords**: Natural compound, cancer, anticancer, antiproliferative, chemopreventive, molecular target*

I. Introduction

Cancer is an umbrella term used to describe a variety of diseases in which cells start dividing abnormally. These cells then spread through blood and lymph system to invade other tissues of the body. There exist more than 100 different types of cancer. Depending upon the site of origin, cancer can be grouped as carcinoma (starting in the skin or tissue lining of internal organs), sarcoma (cancer of connective and supportive tissue), leukemia (staring in the blood forming tissue), lymphoma or myeloma (beginning in the immune cells) and central nervous system cancer (originating in brain or spinal cord) [1].

Cancer is one of the leading causes of adult deaths worldwide. One in every four deaths in United States is due to cancer. American Cancer Society projected an estimate of about 1,638,910 new cancer cases and 577,190 deaths from cancer in US for the year 2012. Prostate cancer is the most prevalent one among the males whereas in females breast cancer tops the chart [2]. In India the most common fatal cancers include oral, stomach and lung cancer in males and cervical, stomach and breast cancer in females [3].

The effective therapies for completely removing the cause of cancer are not yet available but efficient measures can be taken to control the growth of cancer. The traditional treatment options available for controlling cancer include chemotherapy, radiation therapy, childhood hematopoietic cell transplantation, bone marrow transplantation, surgical procedures and biological therapies for cancer. The newer technologies include hyperthermia, photodynamic therapy, gene therapy and targeted cancer therapies [1].

Chemotherapy (also described by the terms antineoplastic or cytotoxitic therapy) is a treatment that involves the use of drugs for destroying the transformed cells or slowing the growth of rapidly dividing cancerous cells. Unlike radiation and surgery, which are considered to be local treatments, chemotherapy has a systemic effect as the drug enters the circulation to encounter the cancer cells wherever they are present. More than 100 FDA approved drugs are available today to be used for the treatment of cancer. But most of the drugs have some side effects associated with their long term administration which limits their use. For example, alkylating agents used to treat various cancers including leukemia, sarcoma, multiple myloma, lymphoma, breast cancer, etc. can cause long term damage to bone marrow eventually leading to acute leukemia. Alkyl sulfonates, Triazines, Ethylenimines and Nitrosoureas are some families of drugs which belong to this category. The use of high dosages of antitumor antibiotics, another group of drugs that interfere with the enzymes essential for the process of DNA replication may cause permanent damage to the heart. Daunorubicin, Doxorubicin (Adriamycin®), Actinomycin-D and Mitomycin-C are some of the prominent antitumor antibiotics being used. Specific topoisomerase inhibitors including topotecan, irinotecan (CPT-11), etoposide (VP-16) and teniposide are also being used for the treatment of certain leukemias along with many other cancers like lung, gastrointestinal and

ovarian. Administration of inhibitors targeting topoisomerase II increases the chances of acute myelogenous leukemia (AML). This secondary leukemia may arise within 2-3 years from the time of administration. Antimitotic agents targeting the cell cycle may lead to peripheral nerve damage. Examples include Taxanes, Epothilones and vinorelbine (Navelbine®) [4].

Along with the drug specific side effect, chemotherapy is almost always accompanied by a varied range of adverse effects. Normal cells of the body which divide more rapidly like bone marrow/blood cells, cells comprising the hair follicles and the ones lining the reproductive tract and digestive tract are most likely to get damaged. The other common side effects include low RBC, WBC and platelet count, nausea and vomiting, appetite loss, constipation, diarrhea, mouth or throat sores, fatigue, heart damage, reproductive and sexual problems, damage to liver, kidney, urinary system, and much more. Permanent damage to organs, delay in development of children, nervous damage, elevated risk of secondary cancer are some of the long term adverse effects associated with the administration of these drugs [4].

Owing to the severe side effects associated with the use of these chemotherapeutic agents, the focus of the ongoing research is shifting from the drugs which have a systemic effect on the body to the therapies targeting molecules which either over express or differentially express in specific tumor or cancer cells and hence use the therapies which differentiate cancerous cells from normal cells of healthy tissues. Since these are more target specific, they often have lesser side effects as compared to the conventional chemotherapy drugs. Examples of targeted therapies include gefitinib (Iressa®), sunitinib (Sutent®), imatinib (Gleevec®) and bortezomib (Velcade®). Estrogen receptor became the first molecule of interest for molecular targeted therapy. Selective estrogen modulators (SEMs) including tamoxifen and toremifene (Fareston®) interfere with the binding of estrogen to its receptor (in ER-positive breast cancer cells) thus making it an effective approach to retard cancerous growth and proliferation. Other potential biomolecules for targeted therapies include aromatases, tyrosine kinases, serine/threonine kinases, growth factor receptors and many more enzymes which are specific for cancer cells or tissues [4].

Hormonal and immunotherapy are two more options available for cancer treatment. Hormonal therapy is generally used for the treatment of breast, prostate, and endometrial (uterine) cancers, which show growth in response to hormones found in the body. Hormonal therapy makes use of sex hormones or hormone like drugs to either prevents the body from producing the hormone or prevents the cancer cells from using the synthesized hormone. Leuprolide (Lupron®), bicalutamide (Casodex®), megestrol acetate (Megace®) and exemestane (Aromasin®) are some of the drugs which best fall in this category. Immunotherapy uses drugs which stimulate the natural immune system of a patient to recognize and attack the transformed cells. It uses two approaches: potentiating the body's own immune system (Active Immunotherapy) or using *ex vivo* created immune system components to be inserted into the patient's body to strengthen its defense mechanism (Passive Immunotherapy). Monoclonal antibody therapy such as rituximab (Rituxan®) and alemtuzumab (Campath®), Immunomodulatory drugs like thalidomide and lenalidomide (Revlimid®), the first FDA approved cancer vaccine, the Provenge® (in 2010), for instance are the examples for this group of drugs [4].

Cancer is a very active area of research. Since most of the proposed synthetic inhibitors fail to clear preclinical or clinical trial because of the drug related or drug induced toxicities, the need arises for finding natural products or their derivatives having the potential to act as inhibitors against the cancer molecular targets. Most of the natural products follow the lipinski's rule of five. Even the exceptions with high molecular weight, rotatable bonds and more stereogenic centers retain relatively low log P values. Thus, these have a higher tendency to get absorbed as compared to the conventional synthetic drugs. With the availability of more number of chiral centers [5] along with a wider distribution of molecular attributes like octanol-water partition coefficient, molecular mass and diversity of ring system, make natural products more suitable to be used as drugs [6]. Thus this review summarizes the experimental evidences of plant products being helpful in the treatment of cancer.

II. Plant Products Affecting the Molecular Basis for Cancer, the Key to New Age Cancer Therapy

The knowledge about molecular mechanism of cancer initiation, progression andmetastasis is increasing rapidly. Different signaling pathways, transcription and translationregulating factors and post-translational modification state of proteins can be developed intotherapeutic targets to treat cancer. Here we will explore various processes involved intumorogenesis and discuss about the plants with antitumor and anticancer activity.

A. Enhancement of persistent oxidative stress in cancer cells

Reactive oxygen species can be used to understand the biology of malignant neoplasia. A free radical contains unpaired electrons which either donate their electrons or accept electrons from other biological molecules of the cell in order to pair and attain a more stabilized state. This results in the initiation of a chain reaction which causes severe damage to the adjacent biological structures. Cell uses the mechanism of antioxidation to protect itself from this oxidative stress [7]. The transformed cells experience a persistent and slightly higher oxidative stress as compared to the neighboring healthy cells. There are evidences to support both the facts, firstly, that the cancer cells produce large amounts of ROS resulting in excessive oxidative stress [8] and secondly, that the natural antioxidant system of the cell gets suppressed [9, 10].

Despite the fact that the cancer cells experience more oxidative stress than the non-neoplastic cells, the stress is not sufficient to cause the cell death. These cells develop other mechanisms to combat this stress. This importunate oxidative stress provides advantage to the cancerous cells for their survival and to escape the apoptosis mechanism. It allows the constitutive activation of certain transcription factors like NF-κB and induces expression of proto-oncogenes like *c-jun, c-foc* and *c-myc*. It also causes DNA damage with modification in the base, further leading to mutations and chromosomal aberrations resulting in genome instability. Activation of cancer specific antioxidant system makes the cancer cells resistant to many chemotherapeutic agents being used for the treatment. Enhanced activity of the proteases due to the inactivation of their inhibitors, also facilitate tumor invasion and metastasis [11].

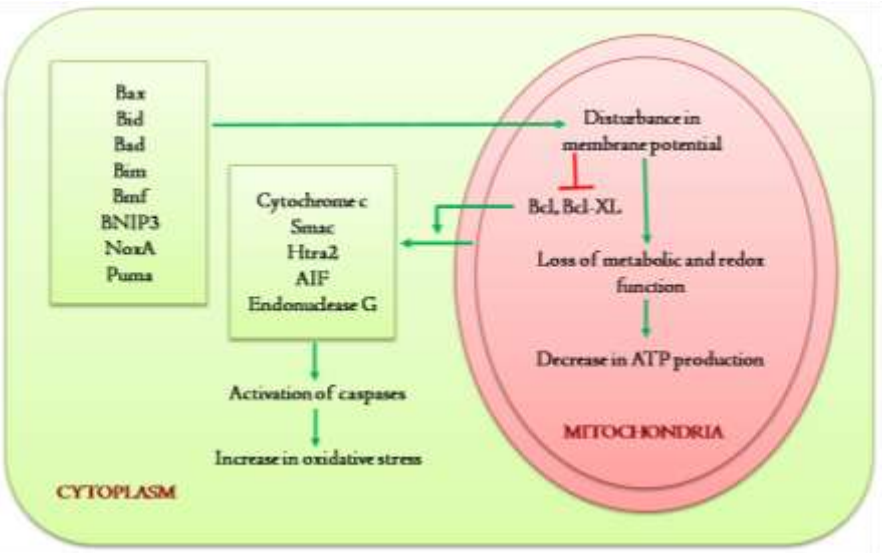
In a study conducted by Jahangir T. and Sultana S. in 2007, rats with induced renal carcinogenesis were orally administered with *Adhatoda vasica*. A significant decrease was observed in lipid peroxidation, H_2O_2 generation, xanthine oxidase (XO), blood urea nitrogen, serum creatinine, renal ODC activity and DNA synthesis leading to reduced incidence of tumors. Thus it was shown that *A. vasica* can be used as a chemopreventive agent as it reduces hyperproliferative response and carcinogenic activity induced because of Fe-NTA [12]. Many different studies report that extracts from *Aegle marmelos* ameliorate the chemical induced carcinogenesis by enhancing the antioxidant defense system. Oral administration of *A. maemelos* significantly elevates the amount of superoxide dismutase, catalase, glutathione, and vitamin C in AME-treated groups in comparison to the carcinogen-treated control [13-17]. *Aloe vera* is another promising source for chemopreventive drugs of plant origin. Saini M et al. showed that oral administration of *Aloe vera* protects the mice against skin papilloma due to the presence of various antioxidant enzymes, vitamins, minerals and polysaccharides in high concentration [18, 19]. The prophylactic effect of Aloctin I, the main lectin present in *Aloe vera* was also assayed by another group of scientists. They showed that pretreatment with the lectin regressed the tumor size probably because of its immunomodulatory activity [20]. *Alstonia scholaris*, commonly called sapthaparna was also investigated for its chemopreventive and anti-oxidant properties. On treatment with the bark extract of the plant, there was an increase in the level of reduced glutathione, superoxide dismutase and catalase along with significant decrease in lipid peroxidation. This resulted in reduced tumors with decrease in cumulative number of papillomas in carcinogen treated mice [21-23]. Inhibiting the generation of H_2O_2 in tumor cells is another way of controlling the adverse effects of oxidative stress in the transformed cells. According to a report, experiments with diacetylenic spiroketal enol ether epoxide AL-1 from *Artemisia lactiflora* in mouse with TPA-induced intracellular peroxide formation shows considerable dwindling in the tumor incidences and tumor induced biological responses. This antioxidant property of *A. lactiflora* might be attributable to the inhibition of O^{2-} generation [24]. Several *in vitro* experiments and studies on animal model suggest the efficacy of tea (*Camellia sinensis*) in the chemoprevention of cancer [25-28]. Consumption of black tea has been shown to notably decrease the micronuclei frequency and chromosomal aberrations in patients suffering from oral precancerous lesions [29]. Hossain E et al. in 2012 used the methanol extract of *Dregea volubilis* leaves to treat tumors in EAC cell lines and EAC tumor-bearing mice. They showed a decrease in tumor volume with an increase in the non-viable cell count in the infected animal model. Thus it exhibited both in vitro and in vivo antitumor activity through augmentation of antioxidant defense system of the body [30]. The seeds of *Glycine max* also emcompass some chemomodulatary potential against skin and cervical papillomas. The preventive action against the cancer is due to alteration in the levels of detoxifying and antioxidative enzymes [31]. Oral administration of ethanol extract from *Indigofera aspalathoides* in tumor bearing rats revealed a significant decrease in the levels of different enzymes- glutamate pyruvate transaminase, glutamate oxaloacetate transaminase, alkaline phosphatase, total bilirubin, gamma glutamate transpeptidase, lipid peroxidase, glutathione peroxidase and glutathione S-transferase with a simultaneous increase in superoxide dismutase and catalase levels [32, 33]. The affect of methanolic extract of *Operculina turpethum* stems on 7,12-dimethylbenz(a)anthracene induced breast cancer was investigated by Anbuselvam C et al. in female Sprague-Dawley rats. Reduce tumor weight as a consequence of low lipid peroxidation activity and increased levels of antioxidant enzymes was observed, thereby indicating its role in the protection against breast cancer [34]. *Picrorhiza kurroa*, a well known traditional herb possess a diverse set of therapeutic potentials including antioxidant and anti-neoplastic activity [35].

B. Targeting the mitochondrial stress pathway or intrinsic cell death

Many chemotherapeutic agents destroy the cancerous cells by inducing the process of apoptosis in them. The different apoptotic signaling pathways ultimately lead to mitochondrial membrane permeabilization (MMP). Involving many direct and indirect mechanisms, the intrinsic cell death or stress pathway to a maximum extent is regulated by the proteins of Bcl-2 protein family. The pro-apoptotic members of this family which include Bax, Bid, Bad, Bim, Bmf, BNIP3, NoxA, Puma translocate from the cytosol of the cell to the mitochondria and dissipate the membrane potential. In response to this change in membrane potential a number of soluble apoptogenic proteins from the intermembrane space of the mitochondria get released into the cytosol. These lethal proteins include cytochrome c, Smac/DIABLO, Htra2/Omi, AIF and endonuclease G. These in turn activate the maturation process or proteolytic cleavage of zymogens (pro-caspases) for the activation of caspases cascade. Because of this membrane permeabilization, mitochondrion loses its important metabolic and redox functions,

inner transmembrane potential and its capacity to act as Ca^{2+} storage organelle. As a consequence, the oxidative stress progressively increases and the ATP production decreases, eventually leading to the death of the cell. To keep a check on the pro-apoptotic signal transduction, a number of different proteins called anti-apoptotic proteins and metabolites are employed to locally protect the mitochondria from apoptotic events. Bcl and Bcl-X_L, the two MMP inhibitors have been reported to block the Voltage-dependent anion channels which are the prime source for release of cytochrome c from the intermembrane space into the cytosol. Figure 1 illustrates the mitochondrial cell death pathway. Thus, impairment in the balance between pro-apoptotic and anti-apoptotic proteins may result in cells with potential to divide infinitely, giving rise to a cancerous state [36].

Figure 1: Schematic representation of mitochondrial cell death pathway.



There are many medicinal plants which alter the changes that occur in the cancerous cells thereby inducing apoptosis to kill them. *Dianthus chinensis L.* is being used to treat many diseases including cancer. Nho et al. in 2012 investigated the molecular mechanism by which the ethanolic extract of this plant inhibit cell growth. He found that it selectively downregulates the anti-apoptotic proteins without altering the expression of Bax protein. Increase in the ratio of bax:bcl-2 and bax:bcl-xl leads to the activation of caspases [37]. *Panax ginseng*, another medicinal plant shows similar kind of activity. Increase in the expression of anti-apoptotic genes as a result of carcinogenic exposure got suppressed; initiating the process of apoptosis [38]. Maslinic acid is a triterpene present in high amounts in *Olea europea*. It has the potential to be used as a tumor suppressant as it was shown to induce apoptosis in the HT29 and Caco-2 colon-cancer cell lines via disturbance in the mitochondrial membrane potential with increase in the expression of Bid and Bax and decrease in the level of Bcl-2. Release of cytochrome c was characterized by the increased activity of caspases-3 [39-41]. *Betula platyphylla* is another potential anticancer plant. It shows significant radical scavenging activity and increase in cell viability against H_2O_2 along with increase in the expression of pro-apoptotic protein, Bax, thereby activating caspases-3 [42]. Some polysaccharides from *Patrinia heterophylla* could also inhibit tumor growth and induce tumor cell apoptosis by increasing the expression of p53, Bax and down regulating the expression of Bcl-2 [43].

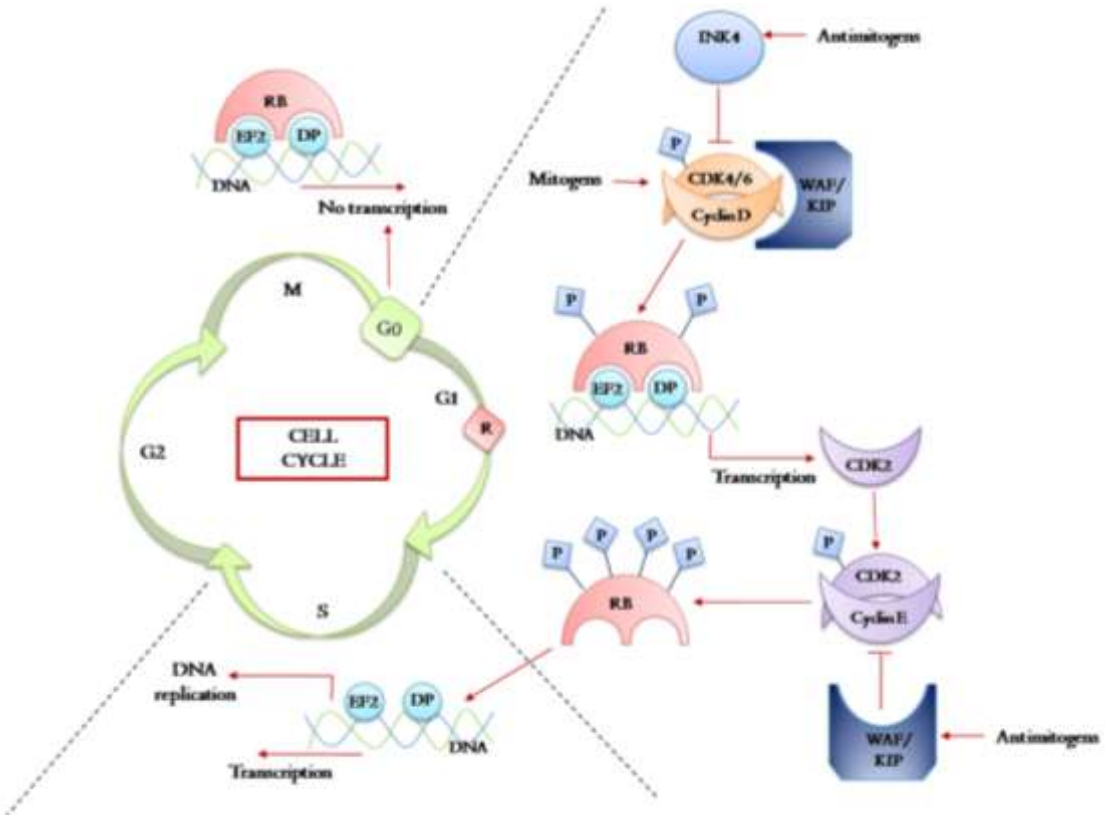
C. Modulation of cell cycle regulators for cancer therapy

Cancer is often considered to be a disorder of impaired cell cycle. Mammalian cell cycle consists of four phases. In S phase, the cell forms a copy of its own genetic material and in M phase, the cellular components are partitioned into two daughter cells. During G1 and G2 phase the cell prepares itself and synthesises the components required for the successful completion of S and M phase respectively. In the absence of adequate mitogenic stimuli or if the cell has reached the state of terminal differentiation, it enters a non-dividing state known as G0. As soon as a cell encounters mitogenic signals, it progresses towards the G1 phase. There is a specific event in G1 phase, called Restriction Point (R), after which the cell proliferates independently of the mitogenic signals. R prevents the cell from getting through the other phases of cell cycle until it has accumulated a certain threshold of mitogen induced events. It represents a point of no return that commits cell to enter a new round of cell division. Thus there are several checkpoints which ensure that the cell does not progress to a new phase until it has completed the previous one [44].

Cyclin Dependent Kinases (CDKs), a group of serine/threonine kinases are the important factors which control the early events of the cell cycle. They form active heterodimeric complexes with their regulatory subunits, the cyclins. CDK4 and CDK6 are believed to drive cell through early G1 phase whereas CDK2 is required for the completion of G1 phase and intiation of S phase. CDK4 and CDK6 bind with D type cyclins to form active complexes while CDK2 get activated by E type cyclins in G1/S transition and A type cyclins during the

succession of S phase. CDK3 is also important in cell cycle regulation but its role is still ambiguous. These activated heterodimeric complexes act on the members of retinoblastoma protein family (including RB, p107, p130). These serve as docking sites for a variety of proteins whose function needs to be regulated tightly throughout the process of cell proliferation. RB proteins remain in bound state with E2F family of transcription factors to ensure that they remain in inactive state during M and G0 phase. The activated CDK4/6-cyclin-D complexes partially phosphorylate the RB of RB-E2F-DP complex. It enables the transcription of some genes like cyclin E. Cyclin E then pairs with CDK2 and completely phosphorylates the RB protein. This process induces the expression of E2F responsive genes that help the cell to enter S phase and initiate DNA replication. The level of CDK activity is negatively controlled by CDK kinase inhibitors. These are of two types. The INK4 family including INK4A (p16), INK4B (p15), INK4C (p18) and INK4D (p19) prevent the association of CDK4 and CDK6 to D-type cyclins thus inhibiting their activity. The three CDK inhibitors of WAF/KIP family- WAF1 (p21), KIP1 (p27) and KIP2 (p57) form heterotimeric complexes with various CDKs, mainly CDK2-cyclin-E thereby inhibiting their kinase activity [44]. Figure 2 shows the schematic representation of these important checkpoints of cell cycle that may serve as potential targets for controlling the dysregulated cell division in cancerous state.

Figure 2: Schematic representation of the cell cycle along with its important regulators



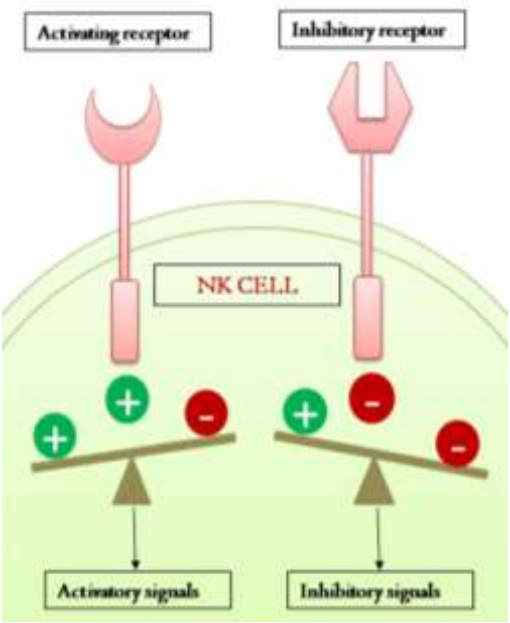
Cheng et al. in 2004 reported that the acetone extract of *Angelica sinensis* inhibits the proliferation of human cancer cells by inducing G1/S arrest and decreasing the levels of CDK4 protein, thereby activating the mechanism of apoptosis [45]. Chemopreventive and anti-cancer properties of the aqueous extract of flowers of *Butea monosperma* were investigated by G. Mathan and his colleagues. They found that treatment with this aqueous extract stimulated apoptotic cell death by accumulating cells in G1 phase which was then accompanied by decrease in the level of activated Erk1/2 and SAPK/JNK [46]. Salograviolide A, a bioactive molecule isolated from *Centaurea ainetensis* reduces the growth of colon cancer by increasing the preG1 phase which causes apoptosis, increases the Bax/Bcl-2 ratio, p53 and p21 protein levels and reduces cyclin B1 proteins [47, 48]. A family of natural products, Flavaglines from the genus *Aglaia* exhibit anti-cancer activity *by* inhibiting translation initiation. Silvestrol, one of the flavaglines, was shown to modulate the activity of eIF4A, a subunit of the eukaryotic initiation factor (eIF) 4F complex that stimulates recruitment of ribosome during translation initiation [49]. Two new bibenzyls, designated as combretastatins B-3 and B-4 where isolated from *Combretum caffrum*. It was observed that these bibenzyls possess activity against the protein tubulin which is the major component of the mitotic spindles [50]. Another chemical constituent of *Nothapodytes foetida*, 9-Methoxycamptothecin was found to have antitumour activity through topoisomerase inhibition [51]. Cell cycle analysis after treating a tumor bearing mice with a polysaccharide isolated from *Patrinia heterophylla* showed that G2/M phase specific tumor cells were accumulating and there was a relative decrease in the number of tumor cells in S phase. It was inferred

that this polysaccharide could inhibit tumor growth by inducing apoptosis [43]. Elevating the levels of CDK inhibitors is another effective approach to arrest cell cycle. *Curcuma longa Linn* was found to have beneficial effects on the early and late stages of pathogenesis by upregulating the p21 and p57 protein level, thus preventing and delaying carcinogenesis [52, 53]. A protein from *Nidus vespae* could also arrest the cell cycle at stage G1 and inhibit the mRNA expression of cyclin B, cyclin D1 and cyclin E. It suppressed cdk2 expression, but increased p27 and p21 protein expression, thus promoting apoptosis and hence has been identified as a potential drug for cancer treatment [54].

D. Activation of body's own immune system against transformed cells

NK cells are a part of the innate immune system which play a vital role in defense against pathogen infected or transformed cells. It was shown that NK cells effectively eliminate tumor cells from the circulation in mice and rats and also spontaneously kill MHC-I deficient tumor cells. Tumor cells are believed to evade T-cell response by downregulating the expression of MHC-I molecules on their surface. NK cells possess two types of receptors-activating and inhibitory. The activity of these immune cells is regulated by a balance between activating and inhibitory signals (figure 3). The ligand for inhibitory receptors are MHC-I molecules. Lack of MHC-I expression, which is very frequently observed in cancerous cells, makes them sensitive to NK cells mediated cytotoxicity. In the absence of these inhibitory signals, activating receptors of NK cells recognize stress induced ligands being expressed on the cell surface of tumors. Thus, finding ways to stimulate these cells of innate immune system have proved to be effective means of cancer therapy [55].

Figure 3: A balance between the activity of activating and Inhibitory receptors regulate the function of NK cells



Agrimoniin, tannin contained in *Agrimonia pilosa* has the potential to augment the activity of NK cell in tumor cells. Increase in cytostatic activity and induction of antibody-dependent cell lysis were observed [56]. The sympathetic nerve of spleen has a suppressive effect on local natural killer (NK) cytotoxicity. Extract from *Lentinus edodes* was found to inhibit tumor proliferation by affecting the splenic sympathetic nerve activity [57].

E. Fatty acid synthase, a potential therapeutic target in cancer

Fatty acid synthase (FASN) is an important enzyme that performs lipogenesis in neoplastic tissues. Cancer or tumor cells require more energy for the rapid proliferation of cells. The glucose uptake increases leading to higher production of pyruvate via glycolytic pathway. This pyruvate is utilized to generate more ATP using Krebs cycle. The intermediate product, acetyl-CoA acts as a substrate for FASN enzyme. Lipogenesis leads to the production of long-chain fatty acids from acetyl-CoA and malonyl-CoA. Most of the normal cells have a low expression of FASN, which is tightly regulated by diet, hormones and growth factors. To meet the energy and lipid demands of highly proliferating cells for membrane synthesis, β-oxidation and lipid modification of proteins, they start *de novo* synthesis of fatty acids, thereof showing high expression of FASN. Many studies report an important role of FASN in tumor growth and survival. Knockdown or inhibition of this enzyme results in apoptosis of cancerous cells. It is believed that the selective anti tumor activity of FASN inhibitors might be due to the accumulation of toxic intermediate metabolites leading to cytostatic and cytotoxic effects. It has also been proposed that the over expression of FASN makes cells resistant to many chemotherapeutic agents. Thus, FASN blockage represents an attractive strategy for cancer treatment [58].

A series of compounds consisting of cylphloroglucinol derivatives, extracted from the rhizomes of *Dryopteris crassirhizoma*, has been reported to possess fatty acid synthase inhibitory activity [59].

F. Inhibiting overexpressed tyrosine kinases for cancer treatment

Tyrosine kinases (TKs) are key players involved in the modulation of growth factor signals. These enzymes transfer ϒ phosphate group from adenosine triphosphate to the target proteins and regulate a variety of cellular processes. Hyperactivation of these enzymes can cause increased cell growth and proliferation, induce antiapoptotic effect and promote angiogenesis and metastasis. Overexpression TKs like BCR-ABL, epidermal growth factor receptor (ErbB/HER) family members (EGFR), vascular endothelial growth factor receptors (VEGF), and platelet-derived growth factor (PDGF) receptors has been observed in various forms of cancer [60]. BCR-ABL, a fusion protein, is found to be constitutively expressed in many cases of chronic mylegenous leukemia and acute lymphoblastic leukemia. It dysregulates intracellular signaling with enhancement in proliferative capability and induction of resistance to apoptosis of hematopoietic stem or progenitor cells, which ultimately leads to a immense increase in number of myeloid cells [60, 61]. The transmembrane EGFR activates various downstream signaling pathways like Ras/Raf mitogen-activated protein kinase pathway and the phosphoinositol 3'-kinase/Akt pathway. Various neoplastic processes like cell cycle progression, inhibition of apoptosis, tumor cell motility, invasion and metastasis are under the control of these proteins. It also further activates vascular endothelial growth factor, a primary inducer of angiogenesis[60]. Angiogenesis is a process that remodels the existing network of blood vessels. VEGF is secreted by almost all the solid tumors [60]. Interaction of PDGF with their respective tyrosine kinase receptors: PDGFR α and β, induces cell proliferation, cell growth and differentiation. Hyperactivation of these kinases generate excess mitotic signals, transforming the normal cells to transformed cells which results in solid tumors [60].

Anti tumor activity conferred by the extract of flesh fruit of *Phaleria macrocarpa* was attributed to downregulation of a number of proteins at mRNA level which also included Vascular Endothelial Growth Factor Tyrosine Kinase, the primary angiogenesis inducer. It also significantly reduced phosphoinositide-3 (PI3)-kinase/protein kinase B (AKT) signalling with control at PI3K transcript level followed by reduction in phosphorylation of AKT. [62]. The Akt pathway/insulin like growth factor 1 receptor downstream to the activation of Epidermal Growth Factor Receptor Tyrosine Kinase was found to be downregulated byGinsenoside Rp1 from *Panax ginseng*, thus exhibiting anti-cancer activity [63].

G. Targeting mTOR having an expanding role in the pathogenesis of cancer

The mammalian target for rapamycin (mTOR) is a serine-threonine kinase that controls both cell growth and cell cycle progression. It helps the cell to respond to its changing environment and adjust accordingly. It helps the cell to grow by directly acting on the cell cycle regulators, maintaining the supply of nutrients into the cell by overproduction of nutrient transporters and promotion of angiogenesis. It primarily controls the synthesis of cyclin D1. It also increases the expression of hypoxia-inducible factor-1(HIF1) which further helps in transcription of hypoxia stress responsive genes, including various angiogenesis growth factors. The increase in nutrient transporter proteins as a consequence of mTOR activation results in greater uptake of amino acids, glucose and other nutrients which support the abnormal growth of the cells. It also helps the rapidly dividing cells to survive by activating the anti-apoptotic proteins. There are many evidences that show deregulated mTOR pathway in a number of cancers, anticipating it to be a potential target of high therapeutic value for cancer therapy [64].

Gallic acid, a natural antioxidant isolated from the fruits of *Phaleria macrocarpa* was shown to have the potential to induce apoptosis selectively in esophageal cancer cells. It resulted in downregulation of mTOR pathway, with decrease in anti-apoptosis proteins such as Bcl-2 and Xiap, increase in pro-apoptosis protein Bax, and stimulation of caspase-cascade activity in cancer cells, suggesting it to be a powerful anticancer agent [65].

H. Upregulation of p53 for controlling some specific cancers

p53 is a transcription factor which regulates the expression of many genes and microRNAs in response to cellular stress. It performs a variety of biological functions like regulation of the cell cycle, cellular differentiation, the immune response, apoptosis, senescence, DNA metabolism and angiogenesis. The main function of p53 is to act as a tumor suppressor by blocking the cell cycle progression and inducing apoptosis in stressed cells (such as in response to DNA damage). It has been observed that almost all cancers show altered p53 activity. Impairment in the p53 activity is associated with accumulation of DNA damage in the cells leading to genomic instability, a phenotype particular to cancer. Thus the concept of restoring the lost activity of p53 is an attractive approach for cancer therapy. Efficient tumor regression was observed in experimental animal models upon reactivation and modulation of wild type p53 [66].

Oldenlandia diffusa is a well-known medicinal plant being used to prevent and treat many disorders. Ursolic and oleanolic acids are the two bioactive components responsible for its antiproliferative property. These were shown to upregulate the expression of p53 protein by increased the binding of ERα/Sp1 complex to the p53 promoter region and selectively inhibiting cellular growth in ERα-positive breast cancer cells [67]. Another study reveals the proapoptotic effects of Eupatilin, an active flavones derived from *Artemisia asiatica*on human gastric cancer cells. It was found that eupatilin treatment resulted in elevated expression of p53, followed by inactivation of ERK1/2 and Akt [68]. Elevated p53 expression levels were also observed in colon-derived cancer cells upon treatment with the extracts *Centaurea ainetensis*, containing salograviolide A as the bioactive molecule [47].

Ginkgo biloba and *Patrinia heterophylla* are other examples of plants believed to have similar kind of properties with clinical significance [43, 69].

III. Conclusion

Cancer being a major global health problem has become an important and highly activearea of research. Because of overlapping nature of the underlying molecular mechanisms there isan urgent need for more work to untangle the signaling networks and focus on their tightlycontrolled regulation process by which they regulate cellular growth and proliferation. Thisknowledge would further facilitate the development of new approach towards treatment ofcancer. The new age therapy focuses on a high specificity towards tumors or cancerous cells,thus providing a broader therapeutic window with less toxicity to healthy bystander cells. Thenew targeted therapies in combination with traditional treatment methods can produce additive orsynergistic cancer therapy. We have seen that plant derived products play an important role intreatment of cancer, but only a small part of fauna has been explored for its therapeutic value.Many plant products or naturally occurring compounds are effective as targeted therapy orimmune potentiation that has the inherent capability to distinguish between tumor cells andhealthy cells. Thus, plants are expected to provide a potential gold mine of bioactive compoundsfor the development of new drugs to combat cancer.

IV. References

[1] J. Wu, K. Kandavelou, and S. Chandrasegaran, "Custom-designed zinc finger nucleases: what is next?," Cell Mol Life Sci, vol. 64, pp. 2933-44, Nov 2007.

[2] R. Siegel, D. Naishadham, and A. Jemal, "Cancer statistics, 2012," CA Cancer J Clin, vol. 62, pp. 10-29, Jan-Feb 2012.

[3] R. Dikshit, P. C. Gupta, C. Ramasundarahettige, V. Gajalakshmi, L. Aleksandrowicz, R. Badwe, R. Kumar, S. Roy, W. Suraweera, F. Bray, M. Mallath, P. K. Singh, D. N. Sinha, A. S. Shet, H. Gelband, and P. Jha, "Cancer mortality in India: a nationally representative survey," Lancet, vol. 379, pp. 1807-16, May 12 2012.

[4] American_Cancer_Society, "Chemotherapy Principles: An Indepth Discussion of the Techniques and Its Role in Cancer Treatment," American Cancer Society2011.

[5] M. Feher and J. M. Schmidt, "Property distributions: differences between drugs, natural products, and molecules from combinatorial chemistry," J Chem Inf Comput Sci, vol. 43, pp. 218-27, Jan-Feb 2003.

[6] M. L. Lee and G. Schneider, "Scaffold architecture and pharmacophoric properties of natural products and trade drugs: application in the design of natural product-based combinatorial libraries," J Comb Chem, vol. 3, pp. 284-9, May-Jun 2001.

[7] G. Bounous and J. H. Molson, "The antioxidant system," Anticancer Res, vol. 23, pp. 1411-5, Mar-Apr 2003.

[8] T. P. Szatrowski and C. F. Nathan, "Production of large amounts of hydrogen peroxide by human tumor cells," Cancer Res, vol. 51, pp. 794-8, Feb 1 1991.

[9] K. Sato, K. Ito, H. Kohara, Y. Yamaguchi, K. Adachi, and H. Endo, "Negative regulation of catalase gene expression in hepatoma cells," Mol Cell Biol, vol. 12, pp. 2525-33, Jun 1992.

[10] Y. Sun, "Free radicals, antioxidant enzymes, and carcinogenesis," Free Radic Biol Med, vol. 8, pp. 583-99, 1990.

[11] S. Toyokuni, K. Okamoto, J. Yodoi, and H. Hiai, "Persistent oxidative stress in cancer," FEBS Lett, vol. 358, pp. 1-3, Jan 16 1995.

[12] T. Jahangir and S. Sultana, "Tumor Promotion and Oxidative Stress in Ferric Nitrilotriacetate-Mediated Renal Carcinogenesis: Protection by Adhatoda vasica," Toxicol Mech Methods, vol. 17, pp. 421-30, 2007.

[13] A. Agrawal, S. Jahan, D. Soyal, E. Goyal, and P. K. Goyal, "Amelioration of chemical-induced skin carcinogenesis by Aegle marmelos, an Indian medicinal plant, fruit extract," Integr Cancer Ther, vol. 11, pp. 257-66, Sep 2012.

[14] T. H. Khan and S. Sultana, "Effect of Aegle marmelos on DEN initiated and 2-AAF promoted hepatocarcinogenesis: a chemopreventive study," Toxicol Mech Methods, vol. 21, pp. 453-62, Jul 2011.

[15] A. Agrawal, P. Verma, and P. K. Goyal, "Chemomodulatory effects of Aegle marmelos against DMBA-induced skin tumorigenesis in Swiss albino mice," Asian Pac J Cancer Prev, vol. 11, pp. 1311-4, 2010.

[16] G. C. Jagetia, P. Venkatesh, and M. S. Baliga, "Aegle marmelos (L.) Correa inhibits the proliferation of transplanted Ehrlich ascites carcinoma in mice," Biol Pharm Bull, vol. 28, pp. 58-64, Jan 2005.

[17] V. Chockalingam, S. S. Kadali, and P. Gnanasambantham, "Antiproliferative and antioxidant activity of Aegle marmelos (Linn.) leaves in Dalton's Lymphoma Ascites transplanted mice," Indian J Pharmacol, vol. 44, pp. 225-9, Mar 2012.

[18] M. Saini, P. K. Goyal, and G. Chaudhary, "Anti-tumor activity of Aloe vera against DMBA/croton oil-induced skin papillomagenesis in Swiss albino mice," J Environ Pathol Toxicol Oncol, vol. 29, pp. 127-35, 2010.

[19] G. Chaudhary, M. R. Saini, and P. K. Goyal, "Chemopreventive potential of Aloe vera against 7,12-dimethylbenz(a)anthracene induced skin papillomagenesis in mice," Integr Cancer Ther, vol. 6, pp. 405-12, Dec 2007.

[20] N. Akev, G. Turkay, A. Can, A. Gurel, F. Yildiz, H. Yardibi, E. E. Ekiz, and H. Uzun, "Tumour preventive effect of Aloe vera leaf pulp lectin (Aloctin I) on Ehrlich ascites tumours in mice," Phytother Res, vol. 21, pp. 1070-5, Nov 2007.

[21] S. Jahan, R. Chaudhary, and P. K. Goyal, "Anticancer activity of an Indian medicinal plant, Alstonia scholaris, on skin carcinogenesis in mice," Integr Cancer Ther, vol. 8, pp. 273-9, Sep 2009.

[22] B. Manjeshwar Shrinath, "Alstonia scholaris Linn R Br in the treatment and prevention of cancer: past, present, and future," Integr Cancer Ther, vol. 9, pp. 261-9, Sep 2010.

[23] G. C. Jagetia and M. S. Baliga, "Evaluation of anticancer activity of the alkaloid fraction of Alstonia scholaris (Sapthaparna) in vitro and in vivo," Phytother Res, vol. 20, pp. 103-9, Feb 2006.

[24] Y. Nakamura, N. Kawamoto, Y. Ohto, K. Torikai, A. Murakami, and H. Ohigashi, "A diacetylenic spiroketal enol ether epoxide, AL-1, from Artemisia lactiflora inhibits 12-O-tetradecanoylphorbol-13-acetate-induced tumor promotion possibly by suppression of oxidative stress," Cancer Lett, vol. 140, pp. 37-45, Jun 1 1999.

[25] J. Liu, J. Xing, and Y. Fei, "Green tea (Camellia sinensis) and cancer prevention: a systematic review of randomized trials and epidemiological studies," Chin Med, vol. 3, p. 12, 2008.

[26] K. Boehm, F. Borrelli, E. Ernst, G. Habacher, S. K. Hung, S. Milazzo, and M. Horneber, "Green tea (Camellia sinensis) for the prevention of cancer," Cochrane Database Syst Rev, p. CD005004, 2009.

[27] P. Ghosh, S. E. Besra, G. Tripathi, S. Mitra, and J. R. Vedasiromoni, "Cytotoxic and apoptogenic effect of tea (Camellia sinensis var. assamica) root extract (TRE) and two of its steroidal saponins TS1 and TS2 on human leukemic cell lines K562 and U937 and on cells of CML and ALL patients," Leuk Res, vol. 30, pp. 459-68, Apr 2006.

[28] R. Xu, H. Ye, Y. Sun, Y. Tu, and X. Zeng, "Preparation, preliminary characterization, antioxidant, hepatoprotective and antitumor activities of polysaccharides from the flower of tea plant (Camellia sinensis)," Food Chem Toxicol, vol. 50, pp. 2473-80, Jul 2012.
[29] A. Halder, R. Raychowdhury, A. Ghosh, and M. De, "Black tea (Camellia sinensis) as a chemopreventive agent in oral precancerous lesions," J Environ Pathol Toxicol Oncol, vol. 24, pp. 141-4, 2005.
[30] E. Hossain, S. Chakroborty, A. Milan, P. Chattopadhyay, S. C. Mandal, and J. K. Gupta, "In vitro and in vivo antitumor activity of a methanol extract of Dregea volubilis leaves with its antioxidant effect," Pharm Biol, vol. 50, pp. 338-43, Mar 2012.
[31] M. Singh, E. Mendez, A. R. Rao, and R. K. Kale, "Chemomodulatory potential of Glycine max against murine skin and cervical papillomagenesis," Indian J Exp Biol, vol. 49, pp. 864-70, Nov 2011.
[32] B. Rajkapoor, N. Murugesh, D. Chodon, and D. Sakthisekaran, "Chemoprevention of N-nitrosodiethylamine induced phenobarbitol promoted liver tumors in rat by extract of Indigofera aspalathoides," Biol Pharm Bull, vol. 28, pp. 364-6, Feb 2005.
[33] A. J. Christina, M. Alwin Jose, S. J. Heison Robert, R. Kothai, N. Chidambaranathan, and P. Muthumani, "Effect of Indigofera aspalathoides against Dalton's ascitic lymphoma," Fitoterapia, vol. 74, pp. 280-3, Apr 2003.
[34] C. Anbuselvam, K. Vijayavel, and M. P. Balasubramanian, "Protective effect of Operculina turpethum against 7,12-dimethyl benz(a)anthracene induced oxidative stress with reference to breast cancer in experimental rats," Chem Biol Interact, vol. 168, pp. 229-36, Jul 20 2007.
[35] V. Rajkumar, G. Guha, and R. A. Kumar, "Antioxidant and anti-neoplastic activities of Picrorhiza kurroa extracts," Food Chem Toxicol, vol. 49, pp. 363-9, Feb 2011.
[36] K. M. Debatin, D. Poncet, and G. Kroemer, "Chemotherapy: targeting the mitochondrial cell death pathway," Oncogene, vol. 21, pp. 8786-803, Dec 12 2002.
[37] K. J. Nho, J. M. Chun, and H. K. Kim, "Ethanol Extract of Dianthus chinensis L. Induces Apoptosis in Human Hepatocellular Carcinoma HepG2 Cells In Vitro," Evid Based Complement Alternat Med, vol. 2012, p. 573527, 2012.
[38] T. Varjas, G. Nowrasteh, F. Budan, E. Nadasi, G. Horvath, S. Makai, T. Gracza, J. Cseh, and I. Ember, "Chemopreventive effect of Panax ginseng," Phytother Res, vol. 23, pp. 1399-403, Oct 2009.
[39] F. J. Reyes, J. J. Centelles, J. A. Lupianez, and M. Cascante, "(2Alpha,3beta)-2,3-dihydroxyolean-12-en-28-oic acid, a new natural triterpene from Olea europea, induces caspase dependent apoptosis selectively in colon adenocarcinoma cells," FEBS Lett, vol. 580, pp. 6302-10, Nov 27 2006.
[40] F. J. Reyes-Zurita, E. E. Rufino-Palomares, J. A. Lupianez, and M. Cascante, "Maslinic acid, a natural triterpene from Olea europaea L., induces apoptosis in HT29 human colon-cancer cells via the mitochondrial apoptotic pathway," Cancer Lett, vol. 273, pp. 44-54, Jan 8 2009.
[41] F. J. Reyes-Zurita, G. Pachon-Pena, D. Lizarraga, E. E. Rufino-Palomares, M. Cascante, and J. A. Lupianez, "The natural triterpene maslinic acid induces apoptosis in HT29 colon cancer cells by a JNK-p53-dependent mechanism," BMC Cancer, vol. 11, p. 154, 2011.
[42] E. M. Ju, S. E. Lee, H. J. Hwang, and J. H. Kim, "Antioxidant and anticancer activity of extract from Betula platyphylla var. japonica," Life Sci, vol. 74, pp. 1013-26, Jan 9 2004.
[43] W. Z. Lu, G. X. Geng, Q. W. Li, J. Li, F. Z. Liu, and Z. S. Han, "Antitumor activity of polysaccharides isolated from Patrinia heterophylla," Pharm Biol, vol. 48, pp. 1012-7, Sep 2010.
[44] M. Malumbres and M. Barbacid, "To cycle or not to cycle: a critical decision in cancer," Nat Rev Cancer, vol. 1, pp. 222-31, Dec 2001.
[45] Y. L. Cheng, W. L. Chang, S. C. Lee, Y. G. Liu, C. J. Chen, S. Z. Lin, N. M. Tsai, D. S. Yu, C. Y. Yen, and H. J. Harn, "Acetone extract of Angelica sinensis inhibits proliferation of human cancer cells via inducing cell cycle arrest and apoptosis," Life Sci, vol. 75, pp. 1579-94, Aug 13 2004.
[46] G. Mathan, G. Fatima, A. K. Saxena, B. K. Chandan, B. S. Jaggi, B. D. Gupta, G. N. Qazi, C. Balasundaram, K. D. Anand Rajan, V. L. Kumar, and V. Kumar, "Chemoprevention with aqueous extract of Butea monosperma flowers results in normalization of nuclear morphometry and inhibition of a proliferation marker in liver tumors," Phytother Res, vol. 25, pp. 324-8, Mar 2011.
[47] N. El-Najjar, S. Dakdouki, N. Darwiche, M. El-Sabban, N. A. Saliba, and H. Gali-Muhtasib, "Anti-colon cancer effects of Salograviolide A isolated from Centaurea ainetensis," Oncol Rep, vol. 19, pp. 897-904, Apr 2008.
[48] A. Ghantous, A. A. Tayyoun, G. A. Lteif, N. A. Saliba, H. Gali-Muhtasib, M. El-Sabban, and N. Darwiche, "Purified salograviolide A isolated from centaurea ainetensis causes growth inhibition and apoptosis in neoplastic epidermal cells," Int J Oncol, vol. 32, pp. 841-9, Apr 2008.
[49] R. Cencic, M. Carrier, G. Galicia-Vazquez, M. E. Bordeleau, R. Sukarieh, A. Bourdeau, B. Brem, J. G. Teodoro, H. Greger, M. L. Tremblay, J. A. Porco, Jr., and J. Pelletier, "Antitumor activity and mechanism of action of the cyclopenta[b]benzofuran, silvestrol," PLoS One, vol. 4, p. e5223, 2009.
[50] G. R. Pettit, S. B. Singh, J. M. Schmidt, M. L. Niven, E. Hamel, and C. M. Lin, "Isolation, structure, synthesis, and antimitotic properties of combretastatins B-3 and B-4 from Combretum caffrum," J Nat Prod, vol. 51, pp. 517-27, May-Jun 1988.
[51] N. Liao, P. Zhang, M. Ao, J. Wang, Y. Shi, and L. Yu, "9-methoxycamptothecin from Nothapodytes foetida induces apoptosis in murine sarcoma S180 cells," Z Naturforsch C, vol. 66, pp. 471-6, Sep-Oct 2011.
[52] K. V. Rao, T. Samikkannu, K. B. Dakshayani, X. Zhang, S. S. Sathaye, M. A. Indap, and M. P. Nair, "Chemopreventive potential of an ethyl acetate fraction from Curcuma longa is associated with upregulation of p57(kip2) and Rad9 in the PC-3M prostate cancer cell line," Asian Pac J Cancer Prev, vol. 13, pp. 1031-8, 2012.
[53] J. Kim, H. L. Ha, H. B. Moon, Y. W. Lee, C. K. Cho, H. S. Yoo, and D. Y. Yu, "Chemopreventive effect of Curcuma longa Linn on liver pathology in HBx transgenic mice," Integr Cancer Ther, vol. 10, pp. 168-77, Jun 2011.
[54] C. Wang, P. Chen, H. Jin, X. Yan, L. Gan, Y. Li, S. Zhou, J. Chang, Y. Wang, G. Yang, and G. He, "Nidus vespae protein inhibiting proliferation of HepG2 hepatoma cells through extracellular signal-regulated kinase signaling pathways and inducing G1 cell cycle arrest," Acta Biochim Biophys Sin (Shanghai), vol. 40, pp. 970-8, Nov 2008.
[55] M. J. Smyth, Y. Hayakawa, K. Takeda, and H. Yagita, "New aspects of natural-killer-cell surveillance and therapy of cancer," Nat Rev Cancer, vol. 2, pp. 850-61, Nov 2002.
[56] K. Miyamoto, N. Kishi, T. Murayama, T. Furukawa, and R. Koshiura, "Induction of cytotoxicity of peritoneal exudate cells by agrimoniin, a novel immunomodulatory tannin of Agrimonia pilosa Ledeb," Cancer Immunol Immunother, vol. 27, pp. 59-62, 1988.
[57] J. Shen, M. Tanida, Y. Fujisaki, Y. Horii, K. Hashimoto, and K. Nagai, "Effect of the culture extract of Lentinus edodes mycelia on splenic sympathetic activity and cancer cell proliferation," Auton Neurosci, vol. 145, pp. 50-4, Jan 28 2009.
[58] R. Flavin, S. Peluso, P. L. Nguyen, and M. Loda, "Fatty acid synthase as a potential therapeutic target in cancer," Future Oncol, vol. 6, pp. 551-62, Apr 2010.
[59] M. Na, J. Jang, B. S. Min, S. J. Lee, M. S. Lee, B. Y. Kim, W. K. Oh, and J. S. Ahn, "Fatty acid synthase inhibitory activity of acylphloroglucinols isolated from Dryopteris crassirhizoma," Bioorg Med Chem Lett, vol. 16, pp. 4738-42, Sep 15 2006.

[60] A. Arora and E. M. Scholar, "Role of tyrosine kinase inhibitors in cancer therapy," J Pharmacol Exp Ther, vol. 315, pp. 971-9, Dec 2005.
[61] G. Vlahovic and J. Crawford, "Activation of tyrosine kinases in cancer," Oncologist, vol. 8, pp. 531-8, 2003.
[62] R. R. Tjandrawinata, P. F. Arifin, O. M. Tandrasasmita, D. Rahmi, and A. Aripin, "DLBS1425, a Phaleria macrocarpa (Scheff.) Boerl. extract confers anti proliferative and proapoptosis effects via eicosanoid pathway," J Exp Ther Oncol, vol. 8, pp. 187-201, 2010.
[63] J. H. Kang, K. H. Song, J. K. Woo, M. H. Park, M. H. Rhee, C. Choi, and S. H. Oh, "Ginsenoside Rp1 from Panax ginseng exhibits anti-cancer activity by down-regulation of the IGF-1R/Akt pathway in breast cancer cells," Plant Foods Hum Nutr, vol. 66, pp. 298-305, Sep 2011.
[64] S. H. Advani, "Targeting mTOR pathway: A new concept in cancer therapy," Indian J Med Paediatr Oncol, vol. 31, pp. 132-6, Oct 2010.
[65] A. Faried, D. Kurnia, L. S. Faried, N. Usman, T. Miyazaki, H. Kato, and H. Kuwano, "Anticancer effects of gallic acid isolated from Indonesian herbal medicine, Phaleria macrocarpa (Scheff.) Boerl, on human cancer cell lines," Int J Oncol, vol. 30, pp. 605-13, Mar 2007.
[66] K. Suzuki and H. Matsubara, "Recent advances in p53 research and cancer treatment," J Biomed Biotechnol, vol. 2011, p. 978312, 2011.
[67] G. Gu, I. Barone, L. Gelsomino, C. Giordano, D. Bonofiglio, G. Statti, F. Menichini, S. Catalano, and S. Ando, "Oldenlandia diffusa extracts exert antiproliferative and apoptotic effects on human breast cancer cells through ERalpha/Sp1-mediated p53 activation," J Cell Physiol, vol. 227, pp. 3363-72, Oct 2012.
[68] M. J. Kim, D. H. Kim, H. K. Na, T. Y. Oh, C. Y. Shin, and D. P. Y. J. Surh Ph, "Eupatilin, a pharmacologically active flavone derived from Artemisia plants, induces apoptosis in human gastric cancer (AGS) cells," J Environ Pathol Toxicol Oncol, vol. 24, pp. 261-9, 2005.
[69] J. C. Chao and C. C. Chu, "Effects of Ginkgo biloba extract on cell proliferation and cytotoxicity in human hepatocellular carcinoma cells," World J Gastroenterol, vol. 10, pp. 37-41, Jan 2004.