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Review article

A NATURAL WAY TO CANCER PREVENTION AND THERAPY

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ABSTRACT: In economically developing countries, the global burden of cancer persists to increase chiefly because of the aging and growth of the world population along with an increasing implementation of cancer-causing behaviors, particularly smoking, physical inactivity and fast food. Cancer group accounts approximately 13% of all deaths each year with the most common being: lung cancer (1.3 million deaths), stomach cancer (803,000 deaths), colorectal cancer (639,000 deaths), liver cancer (610,000 deaths), and breast cancer (519,000 deaths). In India, the rate of oral, oesophagus and cervical cancers are some highest in the world according to 2011 Statistics. Various treatments are used to cure some cancers, but the battle against this disease is ongoing. The source of biologically active compounds originally isolated from plants. These natural compounds can acts as anti cancerous agents. Hence, the current study focuses on the use of 15 different natural products in the treatment of cancer.

Keywords- Cancer prevention and therapy, Natural products, Herbs.

INTRODUCTION

Natural products are the organic molecules which are obscured by living tissues derived from higher plants, fungi, microbes, marine organisms and animals. It exhibits a remarkably wide range of chemical diversity that are a multiplicity of biological properties. For thousands of years natural resources have been in use for combating human ailments. Over the last fifteen years interest in drugs of plant origin has been reviving and growing steadily, and the drug researchers are exploring the potential of natural products for cure the cancer. Alteration in the ratio between differentiation, proliferation and death of cells cause cancer (Ramirez, et. al., 2001) since cancer cells can spread to other parts of the body through the blood and lymph pathways; there are many sites in the body for cancer metastasis. Global cancer rates have been increasing due to an aging population and lifestyle changes in the developing world. It is possible for cancer to strike at any age; in Europe and Asia up to 36% of people have harmless thyroid cancer at time of their deaths. The most common childhood cancers are leukemia, brain tumors (23%), and lymphomas (12%) (Kaatsch, 2010). Cancer represents a combination of diseases which provides a dreadful threat to human population. An actual mechanism by which cancer is generated still leaves a gap for the researchers. Also, there are so many treatment strategies which are time to time suggested by investigators. Many of these strategies are not adequate and applicable to every type of cancer. Many other methods of treatment are quite expensive and need a skillful technique as treatment by culturing the cells *in vitro*. Present review deals with the natural products which are helpful in cancer therapy. Our aim is to focus the protective action of some natural products in cancer which may be useful for researchers to target their study in the relevant field.

Natural products are organic molecules isolated from animals, plants, or microbes that can be used to treat human disease (Li and Vederas, 2009). A natural product is a chemical compound or substance produced by a living organism. It is found in nature that usually has a pharmacological or biological activity for use in pharmaceutical drug discovery and drug design (Cutler, et. al., 2000). Natural Products have long been a fertile source of cure for cancer, which is projected to become the major causes of death in this century (Park, 2012). However, there is a continuing need for development of new anticancer drugs, drug combinations and chemotherapy strategies, by methodical and scientific exploration of enormous pool of synthetic, biological and natural products.

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Mechanism of action of natural products:

Natural products stimulates the immune system of the body and inhibits cancer initiation and growth by improving insulin sensitivity, blood lipid levels, lean body mass to fat ratios. Some of the natural products directly inhibit the enzymatic reaction used in cancer growth cycle. The anti tumor activity of natural products has been associated their ability to trigger cell death pathways including apoptosis in cancer cells. Apoptosis or programmed cell death is the cell's intrinsic death program that plays a pivotal role in maintaining tissue homeostasis and that is highly conserved among different species. Apoptosis is a programmed cell death and a highly organized physiological mechanism to destroy injured or abnormal cells.

Apoptotic cells exhibit remarkable morphological features and characteristic molecular expression. Apart from physiological stimuli there are exogenous factors which can contribute to induce apoptosis. The induction of apoptosis in tumor cells is considered very useful in the management and therapy as well as in the prevention of cancer. These substances are compounds with different chemical entities and many of these are present in plants with medicinal value and in various fruits and vegetables commonly consumed by humans. Mode of action in the apoptotic pathway of some of these compounds has been delineated.

The present reviews emphasizes many such structures and their related chemistry along with the recent advances in understanding mechanism of action and structure function relationships of nature derived anti-cancer agents at the molecular, cellular and physiological levels. Various natural products are now known which have antitumor property and attract the attention of scientific community. Some of them are summarized in list as following:

Table 1: List of natural products which are used in cancer treatment

S.No	Drug/Chemical	Action/Clinical Use	Plant Source
1	Aescin	Anti-inflammatory	*Aesculus hippocastanum*
2	Andrographolide	Antioxidant	*Andrographis paniculata*
3	Hyoscyamine	Anticancer, antitumor agent	*Hyoscyamus niger*
4	Menthol	Immunostimulatory	*Mentha species*
5	Taxol	Antitumor agent	*Taxus brevifolia*
6	Paclitaxel	Antitumor agent	*Taxus brevifolia*
7	Vinblastine	Antitumor, Antileukemic agent	*Catharanthus roseus*
8	Vincristine	Antileukemic agent	*Catharanthus roseus*
9	Bromelain	Anticancerous	*Ananas comosus*
10	Camptothecin	Antitumor agent, anti-gout	*Camptotheca acuminata*
11	Etoposide	Anticholinergic	*Podophyllum peltatum*
12	Lapachol	Smoking and respiratory stimulant	*Tabebuia sp.*
13	Betulinic acid	Anticancerous	*Betula alba*
14	Tetrandrine	Antitumor, anticancer agent	*Stephania tetrandra*
15	Lycopene	Antioxidant, anticancer	*Lycopersicon esculentum*
16	Phytosterols	Breast, colon, stomach, rectum and lung cancers	*Glycine javanica*

Cancer medicine utilizes small molecules as therapeutics. Many compounds in use today are derivatives of plant alkaloids. Among the most widely used drugs derived from plant alkaloids are the taxanes, vinca alkaloids and topoisomerase inhibitors. Antibiotic anti-tumor agents including anthracyclines, bleomycin and mitomycin-C have been isolated from streptomyces bacterial cultures. Several anti metabolites also have their origins in natural products. Some natural products which are potential anticancer compounds are mentioned as following:

4.5.2.1. Aescin

Origin of the compound: Aescin is produced from horse chestnut seeds. This tree mainly found in Asia. Aescin is the main active compound in horse chestnut, and is well-liked for its medicinal properties (Table 1).

Structure: It is the mixture of triterpene glycosides (Fig 1). The polysulphate sodium salt form of aescin is used in the preparation of therapeutic agents used for topical therapy.

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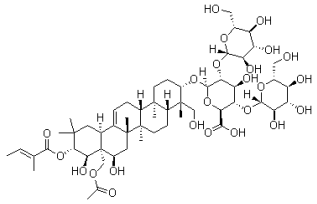

Figure 1: Chemical structure of Aescin

Pharmacological activity: Pharmacological studies of Aescin showed that β-Aescin is very slightly absorbed from the gastro-intestinal tract, whereas amorphous α-Aescin is constantly absorbed. Water-soluble α-Aescin is therefore used in the preparation of therapeutic agents required for oral administration. The lattice structure of crystalline β –Aescin destructed and undergoes a transformation and converted into an amorphous form. Now, this form can be used for preparation of therapeutic agents (Khan and Mahmood, 2006).

Anticancerogenic compound and its mechanism: Aescin or escin is a mixture of saponins with anti-inflammatory, vasoconstrictor and vasoprotective effects found in *Aesculus hippocastanum* (the horse chestnut). High-quality evidence suggests aescin is a safe and effective treatment for chronic venous insufficiency (Sirtori, 2001; Pittler and Ernst, 2006). The molecular mechanism of β-escin includes the improved entry of ions into channels, thus raising venous tension (Pearson and Vanhoutte, 1993), release of prostaglandin-$F_2\alpha$ from veins antagonism to 5-HT and histamine (Matsuda and Yoshikawa, 200), and its property to decrease the activity of tissue hyaluronidase (Facino, et. al., 1990). Some of these properties plausibly make β-Aescin a prime candidate for a potential cancer chemo preventive agent. For instance, prostaglandin-$F_2\alpha$ strongly inhibited cell proliferation in dimethylhydrazine-induced rat colon adenocarcinoma (Tutton and Barkla, 1980), and compounds with anti-hyaluronidase activity are associated with an increased resistance to tumors. Aescin appears to produce effects through a wide range of mechanisms. Previous reports concluded that aescin induces endothelial nitric oxide synthesis by making endothelial cells more permeable to calcium ions, and also induces release of prostaglandin F2α, serotonin and histamine antagonism and reduced catabolism of tissue muco polysaccharides (Carrasco and Vidrio, 2007; Sirtori, 2001).

4.5.2.2. Andrographolide

Origin of the compound: Andrographolide, the active constituent isolated from the plant *Andrographis paniculata*. *Andrographis paniculata* plant extract is known to possess a variety of pharmacological activities (Jarukamjorn and Nemaoto, 2008) (Table 1).

Structure: It is a labdane diterpenoid (Fig 2). Two forms of lactones rings are present, two are present in the methylene dioxy group, while the fifth is present as an alcoholic group of tertiary character.

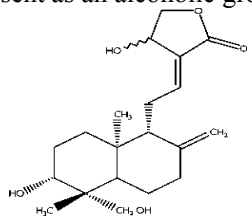

Figure 2: Chemical structure of Andrographolide

Pharmacological activity: Andrographolide shows various pharmacological activities such as Anti-Infective, Antiparasitic, Antiprotozoal, Antirheumatic, Antiviral, Hematologic, Non-Narcotic Analgesic, Non-Steroidal Anti-Inflammatory, Peripheral Nervous System, and Platelet aggregation inhibitor (Wiart, 2005).

Anticancerogenic compound and its mechanism: A study has been conducted on the cellular processes and target.s modulated by andrographolide treatment in human cancer and immune cells. Andrographolide treatment inhibited the *in vitro* proliferation of different tumor cell lines, representing various types of cancers. The *Andrographis paniculata* exerts direct anticancer activity on cancer cells by cell cycle arrest at G0/G1 phase through induction of cell cycle inhibitory protein p27 and decreased expression of cyclin dependent kinase 4. Immunostimulatory activity of andrographolide is evidenced by increased proliferation of lymphocytes and production of interleukin 2. Andrographolide also enhanced the tumor necrosis factor α production and CD marker expression, resulting in increased cytotoxic activity of lymphocytes against cancer cells, which may contribute for its indirect anticancer activity.

The *in vivo* anticancer activity of the compound is further substantiated against B16F0 melanoma syngenic and HT 29 xenograft models. These results suggest that andrographolide is an interesting pharmacophore with anticancer and immunomodulatory activities. Hence, it has the potential for being developed as a cancer therapeutic agent (Gunn, et. al., 2011).

4.5.2.3. Hyoscyamine

Origin of the compound: Hyoscyamine is a tropane alkaloid. It is a secondary met.abolite found in certain plants of the Solanaceae family, including henbane (*Hyoscyamus niger*), mandrake (*Mandragora officinarum*), jimsonweed (*Datura stramonium*), tomato (*Solanum lycopersicum*) and deadly nightshade (*Atropa belladonna*). Hyoscyamine should not be confused with hyoscine, an older alternate name for the related nightshade-derived (Ziegler and Facchini, 2008) (Table 1).

Structure: It is the levorotary isomer of atropine (Fig 3) (third of the three major nightshade alkaloids) and thus sometimes known as levo-atropine (Ziegler and Facchini, 2008).

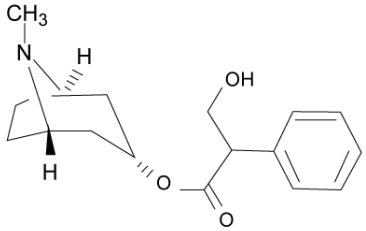

Figure 3: Chemical structure of Hyoscyamine

Pharmacological activity: Hyoscyamine is used along with opioids or other anti-peristaltic agents, measures to prevent constipation are especially important given the risk of paralysis and anticholinergic scopolamine (Shaheen, 1990).

Anticarcinogenic and its mechanism: Hyoscyamine is an anticholinergic, specifically an antimuscarinic, working by blocking the action of acetylcholine at parasympathetic sites in smooth muscle, secretory glands and the CNS. It also increases cardiac output, dries secretions, and antagonizes serotonin. At comparable doses, hyoscyamine has 98 percent of the anti cholinergic power of atropine. The other major belladonna-derived drug scopolamine has 92 percent of the anti muscarinic potency of atropine.

4.5.2.4. Menthol

Origin of compound: Mentha is a genus of flowering plants in the family Lamiaceae (mint family). It is fast growing, extending their reach along surfaces through a network of runners (Table 1). Due to their speedy growth, one plant of each desired mint, along with a little care, will provide more than enough mint for home use. Some mint species are more invasive than others. Even with the less invasive mints, care should be taken when mixing any mint with any other plants, lest the mint take over. To control mints in an open environment, mints should be planted in deep, bottomless containers sunk in the ground, or planted above ground in tubs and barrels (Carrasco and Vidrio, 2007).

Structure: In natural conditions, menthol occurred in steroisomeric form. 8 different forms of menthol were found. It is a monocyclic terpene alcohol (Moreno, et. al., 2002)] (Fig 4).

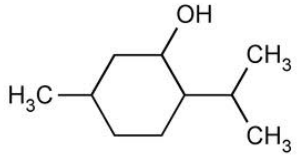

Figure 4: Chemical structure of Menthol

Pharmacological activity: It is an antipriritics, antiinflammtory, anti-odema activity, choleret.ic activity. It has anti microbial (Mahady, et. al., 2005), antifungal (Oumzil, et. al., 2002; Sartoratto, et. al., 2004; Tampieri, et..al., 2005 ; Lee, et. al., 2007 ; Soković, et. al., 2009). The essential oil from *Mentha* spp. may be considered a safe ingredient for the development of antibiofilm agents that could find a role in the pharmaceutical industry (Rasooli, et. al., 2008).

Anticarcinogenic activity and its mechanism: To investigate the cytotoxic activities, three human tumor cell lines, A-549, PC- 3 and MCF-7, were exposed to increasing concentrations of essential oils. Cell viability was det.ermined by the MTT assay (Bradley, 1992). The essential oils of menthe revealed different cytotoxic activities towards the three human cancer cell lines investigated. In general, a dose-dependent decrease in the survival of the three tumor cell lines was observed. However, mint essential oil exhibited no effect onA549 cell over a concentration range of 0.002% to 0.2% (v/v) (Gören, et. al., 2002). At a concentration of 0.002% (v/v), the essential oils did not considerably affect the viability of the three human tumor cell lines compared with untreated control cells. The cell survival after treatment with essential oils was more than 80%.At a concentration of 0.200% (v/v) however all essential oils exhibited strong cytotoxicity towards PC-3 and A549 cells. Cell viability was lower than 4%.However, cells treated with mint essential oil still grew well, and the number of survival cells was comparable to that of untreated control cells. For MCF-7 cell, the cytotoxicties of cinnamon, thyme, chamomile, and jasmine essential oils were significantly stronger than that of the other six essential oils. The fractions of viable cells were reduced to 5.31%, 3.47%, 6.93% and 4.34%, respectively. Essential oils from grapefruit and ginger exhibited the lowest cytotoxicities towards MCF-7 cells. The percentages of cells viability were 75.03% and 81.85%, respectively. Of all essential oils investigated, thyme essential oil exhibited the strongest cytotoxicities towards cancer cells. The IC50 values for thyme essential oil against PC-3, A549 and MCF-7 cells were 0.010%, 0.011% and 0.030% (v/v), respectively. Moreover, cinnamon and jasmine essential oils possessed stronger cytotoxic activities towards PC-3 and A549 cell lines.

4.5.2.5. Taxol

Origin of the compound: Taxol (Fig 5) is a natural product derived from the bark of the Pacific yew *Taxus brevifolia* that increases the polymerization of tubulin to stabilize the cellular microtubule net.work (Table 2). These microtubules form the mitotic spindle in cells and are therefore an important cellular element (Hata, et. al., 2003). *Taxus brevifolia* is a conifer native to the Pacific Northwest of North America. It is small plant in family Taxaceae.

Structure:

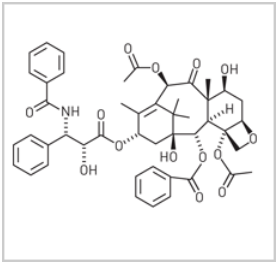

Figure 5: Chemical structure of Taxol

Pharmacological activity: It has an antimicrobial activity.

Anticarcinogenic activity and its mechanism: Taxol is one of the most outstanding agents that have been found beneficial in treatment of refractory ovarian, breast and other cancers (Ait Mbarek, et. al., 2007). Among the many drugs tested for chemotherapy of epithelial ovarian cancer in the last few years. Taxol has been reported to have antiangiogenic activity in xenografts at concentrations that translate to treatment doses at or below those that are administered therapeutically in patients (McGuire and Ozols, 1998). The mechanism of this antiangiogenic effect is considered to be inhibition of proliferation, motility and cord formation of endothelial cells, the angiogenic response *in vivo* (Belotti, et.al., 1996) and neo vascularization induced by vascular endothelial growth factor (VEGF) (Klauber, et.al., 1997).

4.5.2.6. Paclitaxel

Origin of the compound: Almost all paclitaxel produced was derived from bark from the Pacific yew, the harvesting of which kills the tree in the process (Fig 6). It was not until the early 1990s, at a time of increased sensitivity to the ecology of the forests of the Pacific Northwest, that taxol was successfully extracted on a clinically useful scale from these sources (Dordunoo, et.al., 1995) (Table 1).

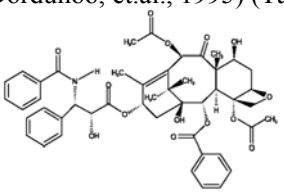

Figure 6: Chemical structure of Paclitaxel

Pharmacological activity: It has an antineoplastic activity.
Anticarcinogenic activity and its mechanism: It is a mitotic inhibitor used in cancer chemotherapy. Paclitaxel-treated cells have defects in mitotic spindle assembly, chromosome segregation, and cell division. Unlike other tubulin-targeting drugs such as colchicine that inhibit microtubule assembly, paclitaxel stabilizes the microtubule polymer and protects it from disassembly. Chromosomes are thus unable to achieve a metaphase spindle configuration. This blocks progression of mitosis and prolonged activation of the mitotic checkpoint triggers apoptosis or reversion to the G-phase of the cell cycle without cell division (Myoung, et.al., 2001).
4.5.2.7. Vinblastine
Origin of the compound: It is isolated from the rosy periwinkle used especially in the form of its sulfate to treat human neoplastic diseases (Table 1).
Structure: It is an alkaloid (Fig 7).

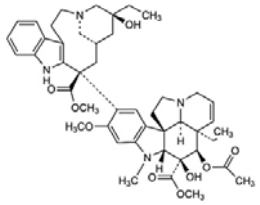

Figure 7: Chemical structure of Vinblastine

Pharmacological activity: It is an antimicrotubule agent.
Anticarcinogenic activity and its mechanism: Previous reports showed the efficacy and toxicity of combined met.hotrexate, vinblastine, 4'-epirubicin and cisplatin (M-VEC) for the treatment of advanced urothelial tract tumors in 58 evaluable patients. M-VEC proved to be equally effective in treating advanced urinary tract cancer, with toxic effects that were milder than those previously reported for other, comparable chemotherapeutic. The extremely low incidence of mucositis obtained with M-VEC was probably due to consequent urine alkalinization, preventing tubular reabsorption of methotrexate. First investigations into the use of M-VEC as adjuvant or neoadjuvant therapy have been done, with promising results, but its efficacy remains to be defined (Bhardwaj and Yu, 2004).
4.5.2.8. Vincristine
Origin of the compound: Vincristine (brand name, Oncovin), formally known as leurocristine (Fig 10), somet.imes abbreviated "VCR", is a vinca alkaloid from the *Catharanthus roseus* (Madagascar periwinkle), formerly *Vinca rosea* and hence its name (Table 1).
Structure:

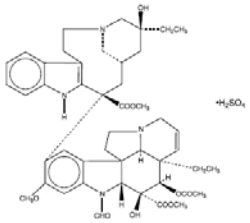

Figure 8: Chemical structure of Vincristine

Pharmacological activity: Vincristine used as an immunosuppressant.
Anticarcinogenic activity and its mechanism: It is a mitotic inhibitor, and is used in cancer chemotherapy. The Southeastern Cancer Study Group, in a prospectively randomized study involving patients with advanced breast cancer, has compared a low dose intermittently administered five-drug regimen including cyclophosphamide, met.hotrexate, 5-fluorouracil, vincristine, and prednisone (CMFVP) with an aggressively administered Three drug regimen including cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF). CAF induced more responses and more complete responses and a longer duration of disease control (Ottaggio, et.al., 2008). Tubulin is a structural protein that polymerizes to microtubules. The cell cytoskeleton and mitotic spindle, among other things, are made of microtubules. Vincristine binds to tubulin dimers, inhibiting assembly of microtubule structures. Disruption of the microtubules arrests mitosis in metaphase. Therefore, the vinca alkaloids affect all rapidly dividing cell types including cancer cells, but also those of intestinal epithelium and bone marrow.

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4.5.2.9. Bromelain

Origin of the compound: Bromelain is a crude extract from the pineapple that contains, among other components, various closely related proteinases (Fig 9) (Table 1).

Structure:

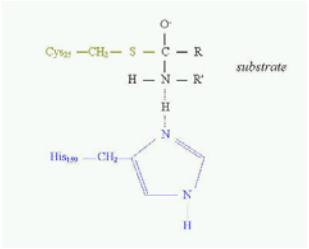

Figure 9: Chemical Structure of Bromelain

Pharmacological activity: Bromelain has *in vitro* and *in vivo*, anti edematous, antiinflammatory, antithrombotic and fibrinolytic activities (Scher, et.al., 1988). A wide range of therapeutic benefits has been claimed for bromelain, such as reversible inhibition of platelet. aggregation, angina pectoris, bronchitis, sinusitis, surgical traumas, thrombophlebitis, pyelonephritis and enhanced absorption of drugs, particularly of antibiotics.

Anticarcinogenic activity and its mechanism: Gerard in 1972 and Nieper in 1976 reported on beneficial effects following oral administration of bromelain to cancer patients (Maurer, 2001). After treatments with relatively high doses for several weeks and months, respectively, they noted remarkable remissions of malignant tumors with negligible side effects. Bromelain inhibits the proliferation of different tumor cells *in vitro*. The inhibitory activity can be traced neither to the proteolytic nor to the peroxidase activity or to the platelet aggregation-inhibitory activity. As well as confirmed the concentration-dependent inhibitory activity of bromelain crude extract and bromelain fractions on various tumor cells *in vitro* (Vellini, et.al., 1986).

It was found that bromelain may induce differentiation of leukemic cells *in vitro* and proposed this phenomenon as a possible mechanism of action. Apoptosis of tumor cells may result from induction of differentiation, a process by which many cytostatic drugs may eliminate tumor cells.

4.5.2.10. Camptothecin

Origin of the compound: Camptothecin (CPT) was first isolated from the Chinese deciduous tree, *Camptotheca acuminate* (Garbin, et.al., 1994) (Table 1). The other plant species from which CPT is isolated are *Merriliodendron megacarpum* (Grabowska, et.al., 1997) and *Nothapodytes nimmoniana* Graham both belonging to the family Icacinaceae, Ophirrohiza mugos and *O. pumila* from the family Rubiaceae, Eravatamia heyneana (Uma, et.al., 2008) belonging to Apocynaceae, and Mostuea brunonis, belonging to the family. CPT showed remarkable anticancer activity in preliminary clinical trials but also low solubility and (high) adverse drug reaction. The tree commonly referred to as "stinking tree" is native to warmer regions of South India.

Structure: CPT, a pyrrolo quinoline alkaloid, is one of the most promising anticancer drugs of the 21st century. It is the penta cyclic structure (Fig 10).

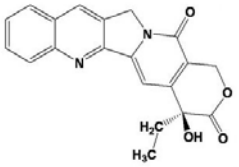

Figure 10: Chemical structure of Camptothecin

Pharmacological activity: It has been used for psoriasis, leukemia and diseases of liver, gall bladder, spleen, and stomach. Anticarcinogenic activity and its mechanism: It is developed for more useful chemotheraptic agent used in treatment of gastric, rectal, colon and blander cancer. CPT exhibits a broad spectrum of antitumor activity both under *in vitro* and *in vivo* conditions. Irinotecan (CPT11) and Topotecan (TPT), two water-soluble derivatives of CPT, have been approved by the United States Food and Drug Administration for treating colorectal and ovarian cancers as well as against several types of brain tumor in children. CPT has been reported to exist in several species; the highest concentration (about 0.3 %) to date has been realized from *Nothapodytes nimmoniana*.

CPT binds to the topo I and DNA complex (the covalent complex) resulting in a ternary complex, and thereby stabilizing it. This prevents DNA re-ligation and therefore causes DNA damage which results in apoptosis. CPT binds both to the enzyme and DNA with hydrogen bonds. The most important part of the structure is the E-ring which interacts from three different positions with the enzyme. The hydroxyl group in position 20 forms hydrogen bond to the side chain on aspartic acid number 533 (Asp533) in the enzyme. It's critical that the configuration of the chiral carbon is (S) because (R) is inactive. The lactone is bonded with two hydrogen bonds to the amino groups on arginine 364 (Arg364). The D-ring interacts with the +1 cytosine on non-cleaved strand and stabilizes the topo I-DNA covalent complex by forming hydrogen bond. This hydrogen bond is bet.ween carbonyl group in position 17 on the D-ring and amino group on the pyrimidine ring of +1 cytosine. Toxicity of CPT is primarily a result of conversion of single-strand breaks into double-strand breaks during the S-phase when the replication fork collides with the cleavage complexes formed by DNA and CPT (Gunasekera, et.al., 1979). Because of these disadvantages synthetic and medicinal chemists have developed numerous syntheses of CPT and various derivatives to increase the benefits of the chemical, with good results. Two CPT analogues have been approved and are used in cancer chemotherapy (topotecan and irinotecan).

4.5.2.11. Etoposide

Origin of the compound: Etoposide was firstly synthesized from podophyllotoxin (Fig 11), it is the toxin found in the *American Mayapple* (Table 2).

Structure:

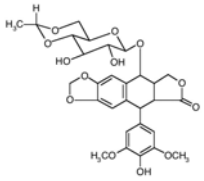

Figure 11: Chemical structure of Etoposide

Pharmacological activity: It is an antineoplastic activity.

Anticarcinogenic activity and its mechanism: Etoposide, known to be effective for small cell cancers of the lungs and testes (Mukherjee, et. al., 2001). Etoposide is an anti-cancer agent. It is known in the laboratory as a topoisomerase poison. Etoposide is often incorrectly referred to as a topoisomerase inhibitor in order to avoid using the term "poison" in a clinical setting. Unlike enzyme inhibitors, it exploits the normal mechanism of action of the enzyme topoisomerase II, which aids in DNA unwinding and by doing so causes DNA strands to break. Cancer cells rely on this enzyme more than healthy cells, since they divide more rapidly. It is used as a form of chemotherapy for cancers such as Ewing's sarcoma, lung cancer, testicular cancer, lymphoma, non-lymphocytic leukemia, and glioblastoma multiforme. It is often given in combination with other drugs. It is also sometimes used in a conditioning regimen prior to a bone marrow or blood stem cell transplant. Its chemical make-up derives from podophyllotoxin, a toxin found in the American *Podophyllum peltatum* commonly called *American Mayapple*. It is an herbaceous perennial plant in the family Berberidaceae, native to wooded areas of eastern North America. Etoposide forms a ternary complex with DNA and the topoisomerase II enzyme, preventing re-ligation of the DNA strands. This causes errors in DNA synthesis and promotes apoptosis of the cancer cell (Takimoto and Calvo, 2008).

4.5.2.12. Lapachol

Origin of the compound: Lapachol is a naphthoquinone (Fig 12) that was first isolated by E. Paterno from *Tabebuia avellanedae* (Bignoniaceae) in 1882 (Table 1).

Structure:

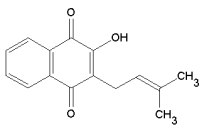

Figure 12: Chemical Structure of Lapachol

Pharmacological activity: A wide spectrum of therapeutic activities have been attributed to lapachol or its derivatives viz., anti-abscess, anti-ulcer, antileishmanial, anticarcinomic, antiedemic, anti-inflammatory, antimalarial, antiseptic, antitumor, antiviral, bactericidal, fungicidal, insecticidal, pesticidal, protisticidal, respiradepressant, schistosomicidal, termiticidal, and viricidal (Pommier, et.al., 2005).

Anticarcinogenic activity and its structure: Lapachol demonstrated highly significant activity against cancerous tumors in rats then in 1974, the NCI reported that phase I clinical trials failed to produce a therapeutic effect with lapachol without side effects and discontinued further cancer research. In a small study in 1980 with nine patients with various cancers (liver, kidney, breast, prostate and cervix), Pure lapachol demonstrated an ability to shrink tumors and reduce feeling of pain caused by these tumors and achieved complete remissions in three of the patients. It is believed that the antitumor activity of lapachol may be due to its interaction with nucleic acids. Additionally it has been proposed that interaction of the naphthoquinone moiety between base pairs of the DNA helix occurs with subsequent inhibition of DNA replication and RNA synthesis (Murray and Pizzorno, 1998).

4.5.2.13. Betulinic acid

Origin of the compound: Betulinic acid (BA) is a pentacyclic triterpene natural product, isolated from various plants (Table 1). It can be isolated from the methanolic extract of *Quisqualis fructus* which was discovered in National Cancer Institute drug screening program natural plant extracts, and has been recognized to possess potent pharmacological properties (Kessler, et.al., 2007).

Structure: It is a pentacyclic triterpene (Fig 13).

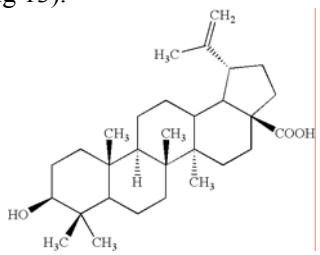

Figure 13: Chemical Structure of Betulinic acid

Pharmacological activity: It has recently been shown to possess antitumor properties in many different cancer cells and exhibit low toxicity in animal models (Selzer, et.al., 2000). It induces apoptosis and antiangiogenic responses in tumors derived from multiple tissues

Anticarcinogenic activity and its mechanism: The present study aims at studying the effects of BA on VEGF expression and tumor growth of colorectal cancer cells *in vivo*. Then compounds of this class which includes betulin and betulinic acid were found to show significant antitumor activity on a broad panel of cancers (Zuco, et.al., 2002). Betulinic acid was found to cause cancer cell death by induction of apoptosis involving caspases. Moreover it was demonstrated that betulinic acid was well tolerated in mice up to 500 mg/kg with no toxic effects. The induction of apoptosis is through the induction of changes in mitochondrial membrane potential, production of reactive oxygen species, and permeability of transition pore openings these processes lead to the release of mitochondrial apoptogenic factors, activation of caspases, and DNA fragmentation (Fulda and Debatin, 2000). It was observed that betulinic acid inhibited the *in vitro* activity of amino peptidase. An endogenous angiogenic factor, but could not inhibit the enzyme *in vivo* even though it inhibits mitochondrial function in endothelial cells. Betulinic acid killed melanoma, leukemia, lung, colon, breast, prostate and ovarian cancer cells via induction of apoptosis (Liu and Luo, 2012)

Betulinic acid, by an antioxidant mechanism tends to protect congenital melanocyte naevi cells from UV-C-induced DNA strand breakage independent of p53 and p21. Betulinic acid induces weak inhibitory effects against topoisomerase I and IIa, but does not stabilize the topoisomerase IIa–DNA complex. Betulinic acid is active *in vivo* against TPA-induced tumors. The *in vitro* cytotoxic activity of the derivatives of betulinic acid and betulin was studied on five different tumor cell lines, 518A2 (melanoma), A549 (lung tumor), FaDu (head and neck), HT-29 (colon), and MCF-7 (breast cancer) by sulforhodmine B colorimetric assay method. The compounds showed dose dependent antitumoral activity against investigated cell lines.

4.5.2.14. Tetrandrine

Origin of the compound: Tetrandrine (Tet), a bis-benzylisoquinoline alkaloid (Fig 14) that was isolated from the dried root of Hang- Fang-Chi (*Stephania tetrandra S. Moore*), is well known as processing a marked antitumor eVect *in vitro* and *in vivo* (Table 1).

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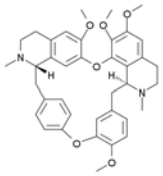

Figure 14: Chemical Structure of Tetrandrine

Pharmacological activity: The aim of this study was to assess the interaction between Tet and chemotherapeutic agents widely used in gastric cancer treatment and to investigate the influence of Tet on chemotherapeutic agent-associated gene expression and apoptosis (Jia, et.al., 2007).

Anticarcinogenic activity and its mechanism: Tet is one member of bis-benzylisoquinoline alkaloid which was accepted as cytotoxic agent and certain structural requirements for antitumor activity. Synergistic interaction on human gastric cancer BGC-823 and MKN-28 cells was evaluated using the combination index (CI) method. The double staining with both Annexin-V-FITC and PI was employed to distinguish the apoptotic cells from living cells. Expression of chemotherapeutic agent-associated genes, i.e., excision repair cross-complementing 1 (ERCC1), thymidylate synthase (TS) and tau, of BGC-823 cells with or without Tet treatment were measured by real time quantitative PCR. Tet had a synergistic effect on the cytotoxicity of chemotherapeutic agents in both two gastric cancer cell lines. The combination of Tet and chemotherapeutic agents could also induce apoptosis in a synergistic manner. Tet could suppress the mRNA expression of ERCC1, TS, tubulin II and tau. Most prominently, ERCC1, TS and tubulin III mRNA levels were markedly suppressed at 0.29-, 0.12- and 0.60-fold, respectively by the presentation of Tet (Grant, 1999).

4.5.2.15. Lycopene

Origin of the compound: Lycopene is a chemical in some fruits and vegetables that has demonstrated some potential in the prevention of prostate cancer. Lycopene is being thoroughly studied in a number of on going trials. Lycopene is found primarily in nature in tomatoes and tomato products but is also found in carrots, green peppers, apricots, watermelon, and pink grape fruit (Table 1).

Structure:

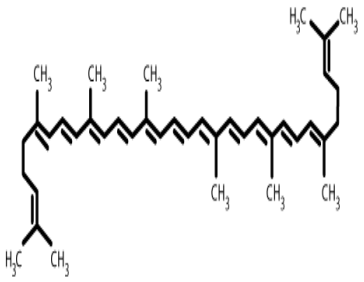

Figure 15: Chemical Structure of Lycopene

Pharmacological activity: Lycopene is a carotenoid present in blood that has proven antioxidant active [86]. It has a cardioprotective role. Lycopene are a valuable source carotenoids, polyphenols, potassium, folate, ascorbic acid and α-tocopherol (Fig 15). Most of these nutrients in tomatoes can interact with the host to confer a preventive benefit against oxidative stress-associated diseases, through various mechanisms including antioxidant action (Rao and Agarwal, 2000).

Anticarcinogenic activity and its mechanism: *In vitro* and *in vivo* studies have shown that lycopene has protective effects against some types of cancers. Lycopene ingestion has been shown to reduce some types of digestive system cancers but has been primarily studied in association with prostate cancer (Canene-Adams, et.al., 2005). A case-control study that analyzed plasma levels of lycopene in men with prostate cancer and in healthy men found that men with the highest levels of lycopene in plasma were less likely to develop prostate cancer. An additional study of 12 prostate cancer patients and 12 ages matched healthy subjects found significantly lower lycopene serum and tissue levels in cancer patients than in controls (Putnam, 2000). A study of mortality from prostate cancer in 41 countries found that men who ingest more than 6 Kcal per day of tomatoes and tomato products have a significantly reduced risk of developing prostate cancer.

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4.5.2.16. Phytosterols

Origin of the compound: Phytosterols, which encompass plant sterols and stanols (Fig 16), are steroid compounds similar to cholesterol which occur in plants and vary only in carbon side chains and/or presence or absence of a double bond (Table 2). Stanols are saturated sterols, having no double bonds in the sterol ring structure. Free phytosterols extracted from oils are insoluble in water, relatively insoluble in oil, and soluble in alcohols. Phytosterols are widely recognized as a food additive with proven cholesterol-lowering efficacy (Moghadasian, 2004).

Structure:

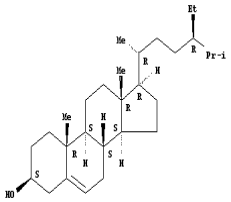

Figure 16: Chemical structure of Phytosterols

Pharmacological activity: It has property to intestinal absorption and metabolic fate. It helps in bile acid synthesis, oxidation and uptake of lipoprotein, cholesterol acyltransferase activity and anti-atherogenic activities. It also regulates the level of LDL-lipoprotien. It also acts immuno modulators (Ostlund, 2004).

Anticarcinogenic activity and its mechanism: Phytosterols can acts as an anticarcinogen to cure cancer. It seem to act through multiple mechanisms of action, including inhibition of carcinogen production, cancer-cell growth, angiogenesis, invasion and metastasis, and through the promotion of apoptosis of cancerous cells. Its consumption may also increase the activity of antioxidant enzymes and thereby reduce oxidative stress. In addition to altering cell-membrane structure and function, phytosterols probably promote apoptosis by lowering blood cholesterol levels.

Conclusion:

Cancer is the abnormal growth of cells in our bodies that can lead to death. Cancer cells usually invade and destroy normal cells. These cells are born due to imbalance in the body and by correcting this imbalance, the cancer may be treated. The imbalance is actually between antioxidant and free radicals generated in the body. Billions of dollars have been spent on cancer research and yet we do not understand exactly what cancer is. According to the American Cancer Society, deaths arising from cancer constitute 2–3% of the annual deaths recorded worldwide. Thus cancer kills about 3500 million people annually all over the world. Cancer therapies cause serious side effects and, at best, merely extend the patient's lifespan by a few years. Therefore Plants have been used for treating various diseases of human beings and animals without any side effect. They maintain the health and vitality of individuals, and also cure diseases, including cancer without causing toxicity. More than 50% of all modern drugs in clinical use are of natural products, many of which have the ability to control cancer cells. Natural products mentioned in present review are used against various types of tumors/cancers such as lymphoma, carcinoma and leukemia. Many of these natural products have found effective in experimental and clinical cases of cancers.

The medicinal plants possess good immune modulatory and antioxidant properties, leading to anticancer activity. Thus, consuming a diet rich in antioxidant plant food (e.g. fruits and vegetables) will provide health-protective effects. Natural antioxidants are having side effects like synthetic drugs, so attempts should be made to treat cancer causing such remedies. Present review deals with 15 plant products which are supplemented with antioxidant property as a gift of nature. Study is important because their mechanism of action and treatment strategies about cancer still leaves a research gap for scholars and one challenging parameter to be worked out.

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REFERENCES

A.A. Ramirez De Molin, A. Rodriguez-Gonzalez and J.C. Lacal (2001). Targeting new anticancer drugs within signaling pathways regulated by the Ras GTPase superfamily. Int J Oncol: Vol.19 5-17.

A. Gören, G. Topçu, G. Bilsel, M. Bilsel, Z. Aydoğmuş and J.M. Pezzuto (2002). The chemicalconstituents and biological activity of essential oil of Lavandula stoechas ssp. Z Naturforsch C: Vol. 57 797–800.

A.K. Mukherjee, S. Basu, N. Sarkar and A.C. Ghosh (2001). Advances in cancer therapy with plant based natural products. Curr Med Chem: Vol.12 1467-1486.

A. Sartoratto, A.L.M. Machado, C. Delarmelina, G.M. Figueira, M.C.T. Duarte and V.L.G. Rehder (2004). Composition and antimicrobial activity of essential oils from aromatic plants used in Brazil. Braz J Microbiol: Vol. 35 275-280.

A.V. Rao and S. Agarwal (2000) Role of antioxidant lycopene in cancer and heart disease. J Am Coll Nutr.: Vol. 19 563–569.

Bradley and Fern (1992). Rodal e's All-new Encyclopedia of Organic Gardening. Emmaus, Pennsylvania, USA: Rodale Press: Vol. 390.

C.H. Takimoto and E. Calvo. Principles of Oncoligc Pharmacotherapy In Pazdur R, Wagman LD, Camphausen KA, Hoskins WJ. Cancer Management: A multidisciplinary approach: 11.

C.R. Sirtori (2001). Aescin: pharmacology, pharmacokinetics and therapeutic profile. Pharmacol Res: Vol. 44 183-193.

C. Wiart, K. Kumar, M.Y. Yusof, H. Hamimah, Z.M. Fauzi and M. Sulaiman (2005). Antiviral properties of ent-labdene diterpenes of Andrographolide paniculata. Phytother Res: Vol.19 1069-1070.

Cutler, J.Stephen and G.Horace (2000). Biologically active natural products: pharmaceuticals. C.R.C Press: Vol. 5.

D. Belotti, V. Vergani, T.Drudis, P. Borsotti, M.R.Pitelli and G.Viale (1996). The microtubule-affecting drug paclitaxel has anti angiogenic activity. Clin Cancer Res: Vol. 2 1843.

E. Grabowska, K. Eckert, I. Fichtner, K. Schulze-Forster and H.R. Maurer (1997). Bromelain proteases suppresses growth, invasion and lung metastasis of B16F10 mouse melanoma cells. Int J Oncol: Vol. 11 243–248.

E. Selzer, E. Pimentel E and V. Wacheck V (2000). Effects of betulinic acid alone and in combination with irradiation in human melanoma cells. J Invest Dermatol: Vol. 114 935–940.

E.J. Gunn, J.T. Williams, D.T. Huynh, M.J. Iannotti, C.Han and F.J. Barrios (2011). The natural products parthenolide and andrographolide exhibit anti-cancer stem cell activity in multiple myeloma. Leuk Lymphoma: Vol. 52(6) 1085-1097.

F. Garbin, T. Harrach, K. Eckert and H.R. Maurer (1994). Bromelain proteinase F9 augments human lymphocyte-mediated growth inhibition of various tumor cells *in vitro*. Int J Oncol: Vol. 5 197–203.

G. Gerard. (1972). Therapeutique anti-cance use of bromelaine. Agressologie: Vol.13 261–274.

G.B. Mahady, S.L.Pendland, A.Stoia, F.A.Hamill, D.Fabricant and B.M. Dietz (2005). In vitro susceptibility of Helicobacter pylori to botanical extracts used traditionally for the treatment of gastrointestinal disorders. Phytother Res: Vol.19 988-991.

H.A. Nieper (1976). Bromelain in der Kontrolle malignenWachstums. Krebsgeschehen: Vol.1 9–15.

H.I. Scher, A. Yagoda, H.W. Herr, C.N. Sternberg, G. Bosl and M.J. Morse et al. (1988). Neoadjuvant M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) effect on the primary bladder lesion. J Urol: Vol. 139 470-47.

H.Li.Y. Matsuda and M. Yoshikawa (2000). Possible involvement of 5-HT and 5-HT2 receptors in acceleration of gastrointestinal transit by escin Ib in mice. Life Sci: Vol. 66 2233-2238.

H. Myoung, S.D.Hong, Y.Y. Kim, S.P. Hong and M.J. Kim (2001). Evaluation of the anti-tumor and anti-angiogenic effect of paclitaxel and thalidomide on the xenotransplanted oral squamous cell carcinoma. Cancer Lett: Vol.163 191-200.

H. Oumzil, S. Ghoulami, M. Rhajaoui, A. Ilidrissi, F, Tetouani and M. Faid (2002). Antibacterial and antifungal activity of essential oils of Mentha suaveolens. Phytother Res: Vol.167 27-731.

H.R. Maurer (2001) Bromelain: biochemistry pharmacology and medical use. Cellular and Molecular Life Sciences: Vol. 58 1234–1245.

I. Rasooli, S. Shayegh, M. Taghizadeh and S.D. Astaneh (2008). Phytotherapeutic prevention of dental biofilm formation. Phytother Res: Vol. 22(9) 1162-7.

J.H. Kessler, F.B. Mullauer and J.P. Medema (2007). Broad *in vitro* efficacy of plant-derived betulinic acid against cell lines derived from the most prevalent human cancer types. Cancer Lett: Vol. 251 132–145.

J.W.H. Li and J.C.Vederas (2009). Drug discovery and natural products: end of an era or an endless frontier. S Science: Vol.325 161-165.

J. Ziegler and P.J. Facchini (2008). Alkaloid biosynthesis: metabolism and trafficking. Annual review of plant biology: Vol. 59 735–769.

K. Canene-Adams, J.K. Campbell, S. Zaripheh, E. Heffery and J.W. Erdman (2005). The Tomato As a Functional Food. J. Nutr*:* Vol. 135 (5) 1226-1230.

K. Jarukamjorn and Nemaoto (2008). Pharmacological apects of Andrographis paniculata on Health and Its major diterpenoid constituent Andrographolide. Journal of Health Science: Vol. 54 (4) 370-381.

L. Ottaggio, F. Bestoso, A. Armirotti, A. Balbi, G. Damonte and M. Mazzei, et al. (2008). "Taxanes from Shells and Leaves of Corylus avellana". Journal of natural products: Vol. 71 58–60.

L. Ait Mbarek, H. Ait Mouse, N. Elabbadi, M. Bensalah, R. Aboufatima and A. Gamouh (2007). Anti-tumor effect of blackseed (Nigella sativa L) extracts. Braz J Med and Biol Res: Vol. 40 839-847.

L. Khan and T. Mahmood (2006). Drugs of natural origin. Tech. monitor: 53-56.

L. Moreno, R.Bello, E.Primo-Yúfera and J.Esplugues (2002). Pharmacological properties of the methanol extract from Mentha suaveolens Ehrh. Phytother Res: Vol.16 (1) 10-3.

M. Vellini, D. Desideri, A. Milanese, C. Omini, L. Daffonchio and A. Hernandez (1986). Possible involvement of eicosanoids in the pharmacological action of bromelain. Arzneim.-Forsch./ Drug Res.: Vol. 36 110–112.

M.D. Soković, J. Vukojević, P.D. Marin, D.D. Brkić, V. Vajs and L.J. Griensven (2009). Chemical composition of essential oils of Thymus and Mentha species and their antifungal activities. Molecules: Vol. 14(1) 238-249.

M.H. Moghadasian (2004). Pharmacological properties of plant sterols: In vivo and in vitro observations. Life Sci: Vol. 67(6) 605-15.

M.H. Pittler and E. Ernst (2006). Horse chestnut seed extract for chronic venous insufficiency. Cochrane Database Syst Rev: Vol.1.

M.P.Tampieri, R.Galuppi, F.Macchioni, M.S.Carelle, L.Falcioni and P.L.Cioni (2005). The inhibition of Candida albicans by selected essential oils and their major components. Mycopathologia: Vol. 159 339-345.

M.T. Murray and J.E. Pizzorno (1998). Encyclopedia of natural medicine 2nd ed. PA4 Rocklin, CA. Prima Pub: 967-972.

N.J. Shaheen, D.J. Robertson, M.A. Crosby, S.J. Furs, D.T. May and W.R. Harlan (1999). Hyoscyamine as a pharmacological adjunct in colonoscopy: a randomized, double blinded, placebo-controlled trial. Am J Gastroenterol: Vol. 94 (10) 2905-2908.

N. Klauber, S. Parangi, E. Flynn, E.D. Hamel and R.J. Amato (1997). Inhibition of angiogenesis and breast cancer in mice by theb microtubule inhibitors 2-methoxyestradiol and Taxol. Cancer Res: Vol.57 81.

O.F.Carrasco and H. Vidrio (2007). Endothelium protectant and contractile effects of the antivaricose principle escin in rat aorta. Vascul Pharmacol: Vol.47 (1) 68-73.

P. Kaatsch (2010). Epidemiology of childhood cancer. Cancer treatment reviews: Vol.36 277-285

P.J.M. Tutton and D.H. Barkla (1980). Influence of prostaglandin analogues on epithelial cell proliferation and xenograft growth. Br J Cancer: Vol.41 47-51.

P.J. Pearson and P.M. Vanhoutte (1993). Vasodilator and vasoconstrictor substances produced by the endothelium. Rev Physiol Biochem Pharmacol: Vol.122 1-67.

R. Bhardwaj and H. Yu (2004). The spindle checkpoint, aneuploidy, and cancer. Oncogene: Vol.11 2016–2027.

R. Uma, B.T. Shanker, G. Ramesha, R.P. Ravikanth, R. Gunaga, K.N. Vasudeva and K.G. Ramawat, et al. (2008). Bioactive Molecules and Medicinal: Vol. 3 540-603.

R.E. Ostlund RE Jr. (2004). Phytosterols and cholesterol metabolism. Curr. Opin. Lipidol: Vol.15 37–41.

R.M. Facino, M.Carini, R. Stefani, G.Aldini and L. Saibene (1990). Anti-elastase and anti-hyaluronidase activities of saponins and sapogenins from Hedera helix, Aesculus hippocastanum, and Ruscus aculeatus: factors contributing to their efficacy in the treatment of venous insufficiency. Arch Pharm (Weinheim): Vol. 328 20-24.

S. Fulda and Debatin KM (2000). Betulinic acid induces apoptosis through a direct effect on mitochondria in neuroectodermal tumors. Med Pediatr Oncol: Vol. 35 616–618.

S.B. Lee, K.H. Cha, S.N. Kim, S. Altantsetseg, S. Shatar, O. Sarangerel and C.W. Nho (2007). The antimicrobial activity of essential oil from Dracocephalum foetidum against pathogenic microorganisms. J Microbiol: Vol.45 (1) 53-57.

S.D. Putnam (2000). Lifestyle and anthropometric risk factors for prostate cancer in a cohort of Iowa men. Ann Epidemiol: Vol. 10 361-9.

S.K. Dordunoo, J.K. Jackson, L.A. Arsenault, A.M. Oktaba, W.L. Hunter and H.M. Burt (1995). Taxol encapsulation in poly (epsilon-caprolactone) microspheres. Cancer Chemother Pharmacol: Vol. 36 279.

S.P. Gunasekera, M.M. Badawi, G.A. Cordell, N.R. Farnsworth and M. Chitnis (1979). Plant anticancer agents X. Isolation of camptothecin and 9-methoxycamptothecin from Ervatamia heyneana.. J Nat Prod.: Vol. 42 475-477.

S.U. Park (2012). Anticancer compounds from plants. EXCLI Journal: Vol. 11 386-389.

T. Hata, I. Sakaguchi, M. Mori, N. Keda, Y. Kato and M. Minamino (2003). Induction of apoptosis by Citrus paradisi essential oil in human leukemic (HL-60) cells: Vol. 17 553–559.

V. Zuco, R. Supino, S.C. Righetti, K. Cleris, E. Marchesi, C. Gambacorti- Passerini and F. Formelli (2002). Selective cytotoxicity of betulinic acid on tumor cell lines, but not normal cells. Cancer Lett: Vol. 175 17.

W. Jia, B. Liu, L. Wang, X. Qian, Y. Ding and L. Yu (2007). Synergistic interaction between tetrandrine and chemotherapeutic agents and influence of tetrandrine on chemotherapeutic agent-associated genes in human gastric cancer cell lines. Cancer. Chemother. Pharmacol: Vol. 60 703–711.

W.B. Grant (1999). An ecologic study of dietary links to prostate cancer. Altern Med Rev: Vol.4 162-169.

W.P. McGuire and R.F. Ozols (1998). Chemotherapy of advanced ovarian cancer. Semin Oncol: Vol.25 340.

Y. Liu and W. Luo. Betulinic acid induces Bax/ Bak-independent cytochrome c release in human nasopharyngeal carcinoma cells.Mol Cells: Vol. 33 517-24.

Y. Pommier, O. Sordet, A. Rao, H. Zhang and K.W. Kohn (2005). Targeting Chk2 kinase: Molecular interaction maps and therapeutic rationale. Curr Pharm Design: Vol. 11 2355-2872.