



HERBAL ANTI-NEOPLASTIC DRUGS: A RECENT TREND IN CANCER THERAPY

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ABSTRACT

Cancer is a severe metabolite syndrome and is one of the leading causes of death regardless of developments in the tools of disease diagnosis, treatment and prevention measures. Cancer is one of the principal causes of mortality and morbidity around the globe and the number of cases are constantly increasing estimated to be 21 million by 2030. This has driven researchers to develop synthetic drugs that can inhibit the growth of rapidly dividing cells, but these also lead to side effects which minimize the drug's overall efficacy. Many cancer treatments exist. Depending on your particular situation, you may receive one treatment or you may receive a combination of treatments. Scientific and research interest is drawing its attention towards naturally-derived compounds as they are considered to have less toxic side effects compared to current treatments such as chemotherapy. The plant kingdom produces naturally occurring secondary metabolites which are being investigated for their anticancer activities leading to the development of new clinical drugs. New technologies include nanoparticles for nano-medicines which aim to enhance anticancer activities of plant-derived drugs by controlling the release of the compound and investigating new methods for administration. The various herbal drugs like Aloe Vera, Burdock Root, Grapes, Clove, Licorice Sticks, Turmeric Root, Red Clover etc are known for their Anti-neoplastic activity. The review discusses the demand for naturally-derived compounds from medicinal plants and their properties which make them targets for potential anticancer treatments.

KEYWORDS: Cancer, Herbal Drugs, Anti-Cancer Properties.

INTRODUCTION^[1,2]

Cancer is a generic term for a large group of diseases that can affect any part of the body. Other terms used are malignant tumours and neoplasms. One defining feature of cancer is the rapid creation of abnormal cells that grow beyond their usual boundaries, and which can then invade adjoining parts of the body and spread to other organs; the latter process is referred to as metastasis. Metastases are the primary cause of death from cancer. Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body. Cancer can start almost anywhere in the human body, which is made up of trillions of cells. Normally, human cells grow and multiply through a process called cell division to form new cells as the body needs them. When cells grow old or become damaged, they die, and new cells take their place.

Cell cycle, the ordered sequence of events that occur in a cell in preparation for cell division. These events include the duplication of its DNA (DNA replication) and some of its organelles, and subsequently the partitioning of its cytoplasm and other components into two daughter cells in a process called cell division.

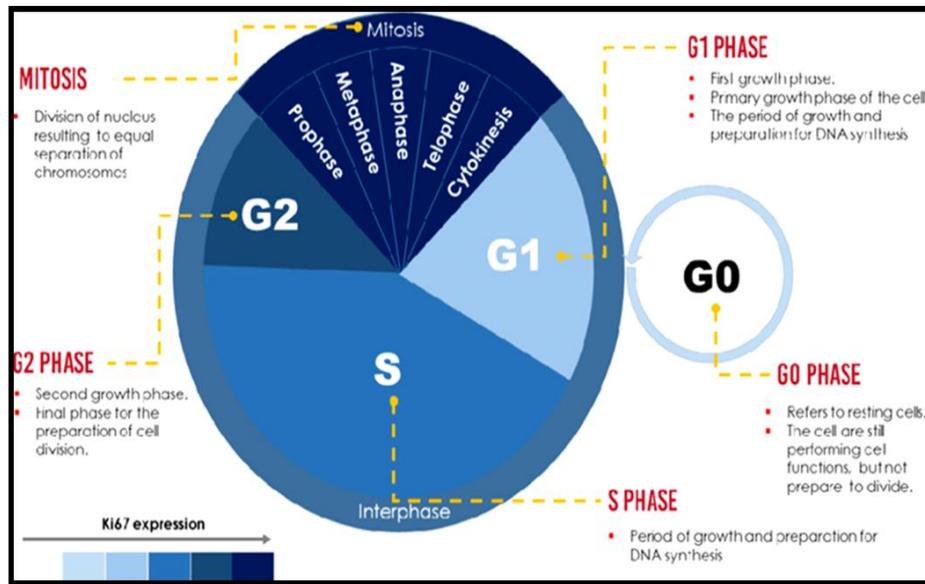


Fig no. 01: Cell cycle.

Sometimes this orderly process breaks down, and abnormal or damaged cells grow and multiply when they shouldn't. These cells may form tumors, which are

lumps of tissue. Tumors can be cancerous or not cancerous (benign).

Differences between Cancer Cells and Normal Cells

Normal cell	Cancer cell
Small, uniformly shaped nuclei	Large, variable shaped nuclei
Relatively large cytoplasmic volume.	Relatively small cytoplasmic volume.
Conformity in cell size and shape.	Variation in cell size and shape.
Cells arranged into discrete tissues.	Disorganized arrangement of cells.
May possess differentiated cell structures.	Loss of normal specialized features.
Normal presentation of cell surface markers.	Elevated expression of certain cell markers.
Lower levels of dividing cells.	Large number of dividing cells.

Causes

1. Smoking
2. Infections
3. Diet
4. Obesity
5. Alcohol
6. Virus
7. UV radiation
8. Genetic mutations
9. Lack of exercise
10. Occupational
11. Obesity
12. Pollution

Types of Genes that Cause Cancer

The genetic changes that contribute to cancer tend to affect three main types of genes—proto-

oncogenes, tumor suppressor genes, and DNA repair genes. These changes are sometimes called “drivers” of cancer. Proto-oncogenes are involved in normal cell growth and division. However, when these genes are altered in certain ways or are more active than normal, they may become cancer-causing genes (or oncogenes), allowing cells to grow and survive when they should not. Tumor suppressor genes are also involved in controlling cell growth and division. Cells with certain alterations in tumor suppressor genes may divide in an uncontrolled manner. DNA repair genes are involved in fixing damaged DNA. Cells with mutations in these genes tend to develop additional mutations in other genes and changes in their chromosomes, such as duplications and deletions of chromosome parts. Together, these mutations may cause the cells to become cancerous.

Types Of Cancer

1. Breast Cancer	2. Uterine Cancer	3. Melanoma	4. Leukemia
5. Childhood Cancer	6. Prostate Cancer	7. Ovarian Cancer	8. Kidney Cancer
9. Colon Cancer	10. Liver Cancer	11. Head & Neck Cancer	12. Cervical Cancer
13. Lung Cancer	14. Thyroid Cancer	15. Multiple Myeloma	16. Esophageal
17. Lymphoma	18. Bone Cancer	19. Pancreatic Cancer	20. Skin Cancer

History^[1,2,3]

The origin of the word cancer is credited to the Greek physician Hippocrates (460-370 BC), who is considered the “Father of Medicine.” Hippocrates used the terms *carcinos* and *carcinoma* to describe non-ulcer forming and ulcer-forming tumors. In Greek, these words refer to a crab, most likely applied to the disease because the finger-like spreading projections from a cancer called to mind the shape of a crab. The Roman physician, Celsus (28-50 BC), later translated the Greek term into *cancer*, the Latin word for crab. Galen (130-200 AD), another Greek physician, used the word *oncos* (Greek for swelling) to describe tumors. Although the crab analogy of Hippocrates and Celsus is still used to describe malignant tumors, Galen’s term is now used as a part of the name for cancer specialists – oncologists.

In 1915, Katsusaburo Yamagiwa and Koichi Ichikawa at Tokyo University, induced cancer in lab animals for the first time by applying coal tar to rabbit skin. More than 150 years had passed since clinician John Hill of London recognized tobacco as a *carcinogen* (a substance known or believed to cause cancer in humans). Many more years passed before tobacco was “rediscovered” as the most destructive source of chemical carcinogens known to man. In 1911, Peyton Rous, at the Rockefeller Institute in New York, described a type of cancer (sarcoma) in chickens caused by what later became known as the Rous sarcoma virus. As of 2014, the World Health Organization’s International Agency for Research on Cancer (IARC) has identified more than 100 chemical, physical, and biological carcinogens. Many of these associations were recognized long before scientists understood much about how cancer develops. By the middle of the 20th century, scientists had the instruments

they needed to work on some of the complex problems of chemistry and biology that remained unsolved. The growth in our knowledge of cancer biology has led to remarkable progress in cancer prevention, early detection, and treatment. Scientists have learned more about cancer in the last 2 decades than had been learned in all the centuries preceding.

Cancer was once a word that people were afraid to speak in public, and people rarely admitted to being a cancer survivor. Now, many celebrities and national leaders very openly discuss and share their cancer experiences. The view that cancer cannot be cured and the fears that have historically been attached to the disease are slowly changing.

Herbal Anti-Cancer Drugs**PHYTOCHEMICAL SCREENING AND THEIR MECHANISM OF ACTION^[4-17]****1] Aloe Vera^[4,5]**

Plants are a natural source of bioactive molecules. *Aloe vera* (AV) is a succulent plant species used in traditional herbal medicine to treat burns. *Aloe Vera* ethanolic leaves extract is effective in treatment of cancer by inhibiting the tumor growth with highest cytotoxic activity. Isolation of active compounds responsible for such action is therefore essential to treat cancer. Recently, it was reported that AV also possesses anticancer activity. AV components, such as the emodin or aloemodin, reportedly suppress proliferation of human breast cancer cells, gastric cancer cells, human hepatoma cells and glioma cells *in vitro* and *in vivo*.

Aloe Vera with longstanding history of safe use, has anti-neoplastic and anti-proliferative effects on multiple cancer types and cell lines.

Effect on human cancer cell lines of non-protein components of Aloe Vera extracts**Table no. 01 Effect on human cancer cell lines of non-protein components of Aloe Vera extracts.**

Cancer type	Cell type	Aloe
Leukemia	K562, HL-60, KG-1a, U937	Aloe-emodin
	K562, HL-60, U937	<i>Aloe Vera</i> (DEHP)
	K562, HL-60, U937, THP-1	<i>Aloe Vera</i> (DEHP)
Neuroblastoma	SJ-N-KP, SK-N-BE(2c)	Aloe-emodin
Breast	MCF-7	Aloe dawei
	MCF-7	Emodin, Aloe-emodin
Prostate	PC-3	Aloe-emodin
Lung	H460	Aloe-emodin
	H460	Aloe-emodin
Tongue	SCC-4	Aloe-emodin
	SCC-4	Aloe-emodin
Liver	Hep G2, Hep 3B	Aloe-emodin
	Huh-7	Aloe-emodin

2] Burdock Root^[4,5]

Arctium lappa is a traditional medicine in China and other parts of the world. Its roots is used in Europe for the management of dermatological and blood disorders, its leaves are used as an anti-inflammatory agent in traditional medicine to treat gastrointestinal disorders in

Brazil. Both fruits and roots are used to treat diabetes mellitus in Asian countries. The European Medicines Agency (EMA) recommends the roots of *Arctium tomentosum* and of *Arctium lappa* as adjunct therapy for seborrheic skin conditions and urinary tract infections. The *Arctium* genus comprised of 200 non-volatile

compounds including lactones, lignans, flavonoids, quinic acids, phenolics, polyacetylenes, terpenoids and polysaccharides. Arctigenin is widely used in traditional medicine and numerous studies have reported the therapeutic potential of this compound as an immune modulator, anti-inflammatory and antitumor agent. There has been significant interest in the antitumor activity of arctigenin, particularly in *in vitro* studies using several human cancer cell lines such as the lung, stomach, intestine, ovaries and breast. Furthermore, as Burdock is widely growing and could also be easily cultivated, it could provide a cost effective and viable alternative to costly drugs.

3] Grapes^[7]

A number of studies suggest that the high consumption of grape components could be associated with the reduced risk of certain cancers such as breast cancer and colon cancer. The anticancer effects of grape antioxidants have been demonstrated in *in vitro* and *in vivo* models. Grape antioxidants have been shown to induce cell cycle arrest and apoptosis in cancer cells.

Considering the diversity of grape antioxidants, it is very likely that these compounds are to exert potential anticancer activity by acting on multiple cellular events associated with tumor initiation, promotion, and progression.

Essential components in grapes:

- Flavonols(antioxidants)
- Phenolic Acids
- Resveratrol(antioxidants)
- Flavan-3-ols
- Anthocyanins (in red and purple grapes)
- Tannins (especially proanthocyanidins)

Proposed mechanisms of potential anticancer effects of grape antioxidants include antioxidant, anti-inflammatory, and ant proliferative activities grape antioxidants exert an antitumor activity partially related to their immunopotentiating activities through the enhancements of lymphocyte proliferation, NK cell cytotoxicity, CD4+/CD8+ ratio, IL-2, and IFN- γ productions.

The effects of grape antioxidants on cell cycle arrest are reported to be involved in promoting the expression of p21(Cip1)/p27(Kip1) protein G1-phase arrest. Grape antioxidants can also target the transcription factor nuclear factor kappa B (NF- κ B) by inhibiting its DNA-binding capacity to inhibit cancer cell invasion.

4-hydroxytamoxifen, the receptor antagonist, can block the anthocyanidins-induced cell proliferation and combination treatments of anthocyanidins with estradiol-reduced proliferative activity of estradiol strongly suggest that the estrogenic activity of certain grape is relevant to its beneficial activity against estrogen-dependent cancers.

4] Clove^[8]

Clove is actually the dried flower buds from trees native to India, Pakistan, Zanzibar, and Madagascar. Clove oil from cloves has been studied for their ability to improve immune function, which means it offers cancer protection or prevention. The *in vitro* and *in vivo* antitumor effects and biological mechanisms of ethyl acetate extract of cloves (EAEC) and the potential bioactive components responsible for its antitumor activity. The molecular changes associated with the effects of EAEC were analyzed by Western blot and (qRT)-PCR analysis. It is identified that oleanolic acid (OA) is one of the components of EAEC responsible for its antitumor activity. EAEC promoted G₀/G₁ cell cycle arrest and induced apoptosis in a dose-dependent manner. Treatment with EAEC and OA selectively increased protein expression of p21^{WAF1/Cip1} and γ -H2AX and down regulated expression of cell cycle-regulated proteins. The clove extract may represent a novel therapeutic herb for the treatment of colorectal cancer, and OA appears to be one of the bioactive components.

Cloves possess antiseptic, antibacterial, antifungal, and antiviral properties, but their potential anticancer activity remains unknown.

5] Licorice Sticks

In the United States, licorice products are most often used as flavoring and sweetening agents in food products. Licorice root has been used by Ancient Chinese medicine as an anti-virus, anti-inflammatory, and anti-ulcer agent. Constituents of licorice include triterpenoids, such as glycyrrhizin and its aglycone glycyrrhizic acid, various polyphenols, and polysaccharides. A number of pharmaceutical effects of licorice are known or suspected (anti-inflammatory, antiviral, antiulcer, anticarcinogenesis, and others). Licorice and its derivatives may protect against carcinogen-induced DNA damage and may be suppressive agents as well. Glycyrrhizic acid is an inhibitor of lipoxygenase and cyclooxygenase, inhibits protein kinase C, and down regulates the epidermal growth factor receptor. Licorice polyphenols induce apoptosis in cancer cells.

Licorice regulates the production of hormones from your adrenal glands, and it reduces stress chemicals. Chronic stress often triggers the growth of cancer cells. Licorice root stops the proliferation of breast cancer cells in humans, according to a study done in South Korea.

6] Red Clover

The University Of Maryland Medical Center found that red clover help to prevent certain types of cancer. These same scientists mention in their article that they believe red clover should not be consumed by women with breast cancer or women with a history of breast cancer in their family It is unclear whether red clover is safe for consumption by women with a history of estrogen-receptor (ER) positive cancer. Although it may have

competitive binding effects with stronger endogenous estrogens, and thus may actually reduce risks associated with elevated estrogen levels, an *in vitro* study demonstrated that red clover was equipotent to estradiol in its ability to stimulate cell proliferation in estrogen receptor-positive breast cancer cells. Studies on Jurkat T-leukemia cells and prostate cancer cell lines (PC-3 and LNCaP) suggested that genistein (an isoflavone, found in red clove 5-10 µg/mL) could suppress tumor cell growth through arresting the cell-cycle (G2/M) and inducing apoptosis.

7] Turmeric Root^[9]

Curcumin is a diferuloylmethane derived from the Indian spice, turmeric (popularly called "curry powder") that has been shown to interfere with multiple cell signaling pathways, including cell cycle (cyclin D1 and cyclin E), apoptosis (activation of caspases and down-regulation of antiapoptotic gene products), proliferation (HER-2, EGFR, and AP-1), survival (PI3K/AKT pathway), invasion (MMP-9 and adhesion molecules), angiogenesis (VEGF), metastasis (CXCR-4) and inflammation (NF-kappaB, TNF, IL-6, IL-1, COX-2, and 5-LOX). The activity of curcumin reported against leukemia and lymphoma, gastrointestinal cancers, genitourinary cancers, breast cancer, ovarian cancer, head and neck squamous cell carcinoma, lung cancer, melanoma, neurological cancers, and sarcoma reflects its ability to affect multiple targets. A SAR study of curcumin derivatives demonstrates that the presence of a coplanar hydrogen donor group and a β-diketone moiety is essential for the antiandrogenic activity for the treatment of prostate cancer. Dimethylcurcumin or ASC-J9 (5-hydroxy-1, 7-bis (3, 4-dimethoxyphenyl)-1, 4, 6-heptatrien-3-one) is a newly developed curcumin analogue which enhances androgen receptor degradation and has been used for treatment of prostate cancer. Moreover, it has also shown a significant antiproliferative effect against estrogen-dependent breast cancer cells.

8] Onion

Onion (*Allium cepa* L.) is widely cultivated and consumed around the world (1). The common onion varieties with three different colors, including red, yellow, and white, are normally available in the food market. Onion is a good source of natural antioxidants. The content of phenolics in the onion bulb and its antioxidant property were increased with the application of mycorrhizal inocula, humic acids, and elevated atmospheric CO₂. Thiosulfinate compounds, phenolic compounds, polysaccharides, and essential oils, have been reported to possess potent antibacterial properties, antifungal activities, and antiviral effects. Onion also exhibited anti-inflammatory property, showing protective effects against inflammation-related diseases. The consumption of *Allium* vegetables was found to be negatively associated with the risk of diverse cancers, including breast cancer, gastric cancer, colorectal cancer, and upper aero digestive tract cancers.

Bioactive compounds in onion: sulfur compounds, flavonoids, saponins, onionin.

The major bioactive compounds of onion are sulfur-containing compounds, such as onionin. Onion extract or its major bioactive compounds showed potent anticancer activities, including cytotoxic, antiproliferative, antimigratory, and apoptosis-inducing activities, in different cancer cells. Onion A, a sulfur compound from onion, exhibited antitumor effects by inhibiting the activation of suppressing signal transducer. Besides, a wild edible onion showed a synergistic anticancer effect with doxorubicin against human hepatoma (HepG2) and lung carcinoma (A549) cells. Moreover, the intake of fresh onion was reported to reduce fasting blood glucose and improve insulin sensitivity in doxorubicin-treated breast cancer patients.

9] Ginger root

Ginger has long been used in traditional medicine as a cure for some diseases including inflammatory diseases. Ginger contains active phenolic compounds such as gingerol, paradol and shogaol that have antioxidant, anti-cancer, anti-inflammatory, anti-angiogenesis and anti-atherosclerotic properties. It has also been shown to down-regulate NF-κB-regulated gene products involved in cellular proliferation and angiogenesis, including IL-8, VEGF and ovarian cancer cells.

With respect to anticancer activity, ginger and its constituents have been shown to inhibit the proliferation of and induce apoptosis of a variety of cancer cell types *in vitro*. In addition, the use of ginger for the chemoprevention of colorectal cancer has attracted attention. However, the anticancer activity of ginger extract and its constituents against pancreatic cancer has been poorly investigated.

Ginger extract inhibited the production of ROS, DNA strand breaks, and cytotoxicity caused by the incubation of HepG2 hepatocarcinoma cells with aflatoxin. Additionally, ginger extract up-regulated the Nrf2/HO-1 pathway. Regarding pancreatic cancer cells, Akimoto et al. reported that ginger extract suppressed cell cycle progression and consequently, induced death. The extract markedly up-regulated 5'AMP-activated protein kinase (AMPK). The extract also suppressed tumor growth in an orthotopic model of pancreatic cancer without adverse effects on the host animal.

10] vinca^[10]

In vinca plant constitute of vinblastin and vincristine, on the chemotherapy medication it is used for several types of cancers. They inhibit the growth of human tumors. Vinblastine is used experimental or treatment of neoplasmas and for Hodakins disease, choric carcinoma. Vincristine and another active ingredients are used for leukemia in children. Vinca is popular for anticancer

property but as well as it have memory enhancement, anti helmentic, antioxidant properties.

Vinblastin:- Vinblastin, under the marketed brand name Velban amongst others, is chemotherapy. These are treat various type of cancer includes non-small cell lung cancer, hodgkin's lymphoma, bladder cancer, brain cancer, testicular cancer and melanoma.

Vincristin:- Vincristin is also called *leurocristine* and under marketed brand name is Oncovin among other, in a chemotherapy. It is used to treat acute lymphocytic leukemia, acute myeloid leukemia, hodgkin's disease, neuroblastoma, and small cell lung cancer amongst other.

Vindesine:- Vindesine is the anti – mitotic Vinca alkaloid. It should be used in the treatment of various type of cancer including or under the leukemia, multiple melanoma, Lymphoma, breast cancer and lung cancer.

Tabersonine:- Tabersonine is the terpenes of indole alkaloid which are found in the medicinal plant of vinca rosea. It is first intermediate leading to form the vindoline one of the two precursors are required for vinblastine biosynthesis.

Vinpocetine:- These are the chemical synthetic derivative of the vinca alkaloid vincamine. These are the extracted from the leaves of vinca minor (lesser periwinkle) or the seeds of voacangan africona.

11] Green Tea^[11]




Green tea is obtained from the leaves of the plant *Camellia sinensis*, and it is one of the most popular beverages worldwide, particularly in Asia. Its antioxidant, anti-inflammatory, and antibacterial properties have been reported to provide various benefits to its consumers. Most of the anti-cancer effects of tea are catechin-mediated, of which EGCG has the most prominent effect. Among tea catechins, EGCG has the










strongest inhibitory potency, followed by ECG, EGC, and EC, and mixtures of catechins was observed to have better anti-tumor activity than pure EGCG owing to synergistic effect. GTCs exhibit numerous anti-carcinogenic and anti-mutagenic potentials in human cancers including breast, esophagus, prostate, stomach, small intestine, colon, liver and lung, it is believed that green tea extracts, tea catching mixtures or pure EGCG are capable of affecting the carcinogenesis process in the tumor initiation, -promotion and -progression phases through diverse mechanisms. A multitude of studies have been exploring the mechanism of tea catechins in suppressing breast cancer. *In vitro* studies on hepatic cancer cell lines conducted so far have demonstrated that EGCG suppressed the growth of human HCC cells. More recently, green tea has been used as a sensitizer to improve the radiotherapy effect of prostate cancer.

12] Goldenseal Root

Goldenseal (*Hydrastis canadensis*) is a perennial plant native to eastern North America. Its roots and leaves have been used in traditional medicine to treat a variety of ailments, especially those involving infections or inflammation. The herb is naturally rich in a class of alkaloid compounds, with berberine, hydrastine, and canadine being found in the highest concentrations. The powerful compound in goldenseal, berberine, has antibiotic compounds. These alkaloids are linked to antibacterial and anti-inflammatory properties and believed to be the main reason behind goldenseal's purported health benefits. Care should be taken with goldenseal and it is best used under the supervision of a doctor or herbalist as high doses can become toxic. Since Goldenseal was able to decrease P-gp protein (paraglycoprotein) function in colon cancer cell lines, if the same effect translates to in vivo clinical colon cancers leading to a decrease in P-gp function, this could lead to an increase in the availability of orally administered drugs with the added benefit of goldenseal conferring anti-intestinal pathogen effects as well.

Herbal Anti-Cancer Drugs

<p>1. Aloe Vera Family : Asphodelaceae Biological Name: <i>Aloe Vera(L.)Burm.f.</i></p> 	<p>2. Burdock Root Family : Asteraceae Biological Name : <i>Arctium lappa</i></p> 	<p>3. Grapes Family : Vitaceae Biological Name : <i>Vitis vinifera L.</i></p> 
<p>4. Clove Family : Myrtaceae Biological Name: <i>Syzygium aromaticum</i></p>	<p>5. Licorice Sticks Family : Asteraceae Biological Name : <i>Glycyrrhiza glabra</i></p>	<p>6. Red Clover Family : Fabaceae Biological Name : <i>Glycyrrhiza glabra</i></p>

		
7. Turmeric Root Family : zingiberaceae Biological Name : <i>Curcuma longa</i>	8. Onion Family : Amaryllidaceae Biological Name : <i>Allium cepa</i>	9. Ginger Root Family : Zingiberaceae Biological Name : <i>Zingiber officinale</i>
		
10. Vinca Family : Apocynaceae Biological Name : <i>Vinca Rosea</i> (<i>Catharanthus Roseus</i>)	11. Green Tea Family : Theaceae Biological Name : <i>Camellia sinensis</i>	12. Goldenseal Root Family : Ranunculaceae Biological Name : <i>Hydrastis Canadensis</i>
		

CONCLUSION

Cancer is one of the world wide spreaded disease. Millions of people are suffering from cancer. Several synthetic drugs and therapies like surgery, chemotherapy, radiation therapy, hormonal therapy, immunotherapy are used for cancer treatment. These synthetic drugs show various side effects which may be harmful for human body. Chemotherapy can cure cancer because it kills cancer cells but along with cancer cells normal cells are also kill during this therapy. All these therapy shows severe side effects. Theses side effects can be minimize by using naturally derived compound and nanotechnology. They enhance anticancer activities of plant-derived drugs by controlling the release of the compound and investigating new methods for administration.

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