JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

POTENTIAL ANTICANCER PHYTOCONSTITUENTS FROM NATURAL PRODUCTS-A REVIEW

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Abstract: Cancer is a crucial disease amongst others that cause death of millions people in worldwide. Due to abnormal growth of normal cells internally and underwent by repeating division of cells with growing unwanted tissue in translation and transcription processes cause cancer. According to GLOBOCAN 2018 database, 18.1 million cases have arisen and 9.6 million death in 2018. Every 5th man and 6th women cause of cancer in worldwide. It is expected to rise 21 million by 2030, both developing and developed countries are unlikely underwent as crab's paw hold on this deadly disease. Its incidence is expected to rise by about 70% over the next two decades.It is life-threatening disease and produces various side effects in the different parts of the body due to toxicity of chemotherapeutic processes (surgery and radiations) therefore increasing demand of people, researcher and scientists have been keeping its attention towards natural product originated from fauna and flora that use in the treatment of cancer and enhance immunity from long time period.

Various bioactive phyto-constituents isolated and identified for its treatment which based on their mechanism of actions and design synthetic derivatives to cure and control this disease. Natural anticancer drugs have been discovered as therapeutic agents and composed of diverse functional groups contained various skeleton like indole, diketo conjugated with aromatic rings, triterpenes, flavonoids, saponins, lycopenes, carotenoids, quinones and lactones etc from traditional medicinal plants. They are natural antioxidants and prevent abnormal growth of cells in the body and stop the faster breakdown the cells.

Hence on the basis of literature study, this review compiled all information have been made from naturally originated drugs and challenges based on cancer that will be more pronounced and effective throughout the disease.

Index Terms- Cancer, Cause and Mechanism, Anticancer Natural Products.

I. INTRODUCTION

Plants are rich source of primary and secondary metabolites assimilate in different parts: root, stem, fruit, leaves etc. Primary metabolites carbohydrates, proteins, fats and nucleic acids are present essentially in all living organisms. Plants act as reservoir for bioactive constituents to synthesize and derivetise thus worked as natural factory results to give secondary metabolites with chemical diversity. They have different pharmacological actions due to repository of chemically different functionality present in it.

Cancer is unknowingly cause of abnormal growth of human cells due to may change our life style, irregular routine-work and intake of food, tension, low sleepiness and low immunity power. It is major recognized global health problem and according to GLOBOCAN 2018 database, 18.1 million cases have arisen and 9.6 million death in 2018.Every 5th man and 6th women cause of cancer in worldwide. It is expected to rise 21 million by 2030, both developing and developed countries are unlikely underwent as crab's paw hold on this deadly disease. Its incidence is expected to rise by about 70% over the next two decades[1].

Cancer cells can initiate and spread in different tissues and organs throughout the body and extent to pandemic mainly lungs, prostate, colorectal, stomach, and liver except breast and uterus in women. Lung cancer (14.5%), prostate cancer (13.5 %) and colorectal cancer (10.9%), liver (10.2%) and stomach cancer(9.5%) in men world- wide mortality and breast cancer(15.0 %) in women. Chemotherapeutic processes are not completely killed cells and main disadvantages that may recurrence cancer again with adverse side effects of use of chemicals[2].

Despite this, From ancient to now a day various natural anticancer drugs have been discovered as therapeutic agents and composed of basic skeleton of indole, diketo conjugated with aromatic rings, triterpenes, flavonoids, saponins, lycopenes, carotenoids, quinones and lactones etc from traditional medicinal plant source(Table:1). . Some chemo preventive agents have anti-angiogenesis activities including curcumins from *Curcuma longa*, epicatechin gallate from tea leaves, thymoquinne from seeds of *Nigella sativa*, genistein from soybean and resvertrol from grapes and red wine. A number of herbs can be prevent cancer and already know every people present in daily routine like: Amla, Garlic, Turmeric, Ashvagandha, Holy Basil, Ginger, Kalongi, Lemon. Vitamin C, containing herbs are very important for gaining healthy life.

II. DEVELOPMENT OF CANCER

Cancer arises as a result of a series of genetic changes in the cell, the main genetic lesions being- Inactivation of tumor suppressor genes and the activation of oncogenes (normal genes controlling cell division).

Normal cells changed to abnormal one can cause this disease and it can be characterized as-

1. **Uncontrolled proliferation**- Irregular cell division and tissue growth.
2. **Loss of function**- Loss of normal function, faster the growth.
3. **Invasiveness**- They are grown and found outside the cell/tissue.
4. **The ability of metastasis**- It may change to secondary tumor from release the signal of primary.

Normal cell division follows G0, G1, S, G2, M then it may return to G0 and G1 cycle but when irregular cell division takes place then G0 phase has to be faster and abnormal cell division and lead to cancerous cell. During this DNA is damaged and internal cellular structures are successively dismantled, shrink and destroyed by immune cells.

The cells are exposed to oxidative stress, oxidation and free radicals are involved to develop various kinds of irregulation in cell growth and cause cancer. COX-1 and COX-2 enzymes are also responsible triggers inflammation. Number of key genes, proteins and enzymes are responsible to regulate the cycle and can be identified apoptosis. Two factors either inhibit cell proliferation through TP53 gene, produce P53 together with PB1 gene or the group of proteins (cyclins-dependant kinase CDKs) stimulate the cell to progress over the cell cycle have been identified[3].

These key factors may be disturbed from:

Carcinogenic sources: Pesticides, organic and inorganic chemicals, alkylating agents.

Radiation energy: UV rays, gamma rays, nuclear fission, x-rays and other chemical weapons.

Viruses: Oncogenic viruses that possess DNA or RNA genome.

Environmental factors and Daily routine life -It includes variation in temperature, harm-full irradiation of rays, breathing and smoking, intake alcohol, crispy food etc

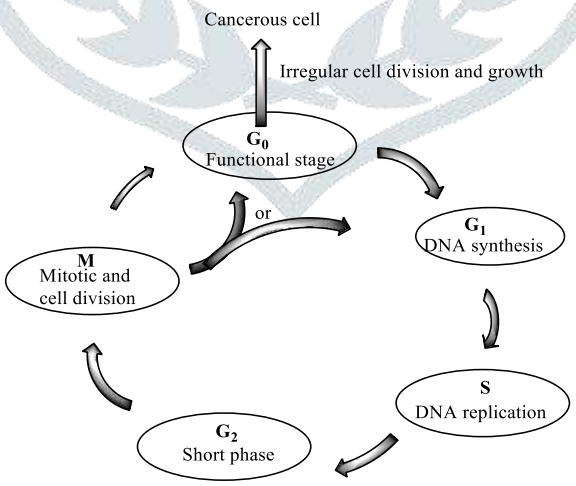

Figure:1 Cell cycle

2.1 MECHANISM OF DRUG ACTION: Cancer develops as a result of concurrent change of genetic material in a cell, the main genetic lesions being- inactivated tumor suppressor genes and the activated oncogenes (normal genes controlling cell division).

The drug interacts with cancerous cell where cell cycles underwent abnormal, proliferated the cell, dna replication taken fast. It interact in a way that either decreased the synthesis of dna/rna or attack on protein/enzymes which responsible for replication and transcription, alkylated the DNA, hence inhibited the synthesis of DNA at target cells.

If growth of blood vessel is inhibited, than the growth of tumor can be controlled. But most dangerous tumors secrete signals that tell the body to grow new blood vessels toward them. Hence angiogenesis inhibitors were designed to stop these signals from being received, and come in various forms.
Natural product embraces a main source of small molecular weight called angiogenesis inhibitor and they have been derived from a number of sources, including fractions of proteins and monoclonal antibodies.

Due to variety of functionalities identified in molecules from plant source have been studied to prevent the development of malignancies from some plants. They are natural antioxidant to prevent abnormal growth of cells in the body and stop the faster breakdown the cells. Naturally isolated phytoconstituents from different plant sources like Curcumin, Barberin, Beta-elemene, Paclitaxel, Nigellidine and its derivatives, Catechin and its derivatives, Vincristine, Vinblastine and Lycopene etc play a major role to prevent abnormal cell growth and cause antiangigenesis actitvity(Figure:2-4).

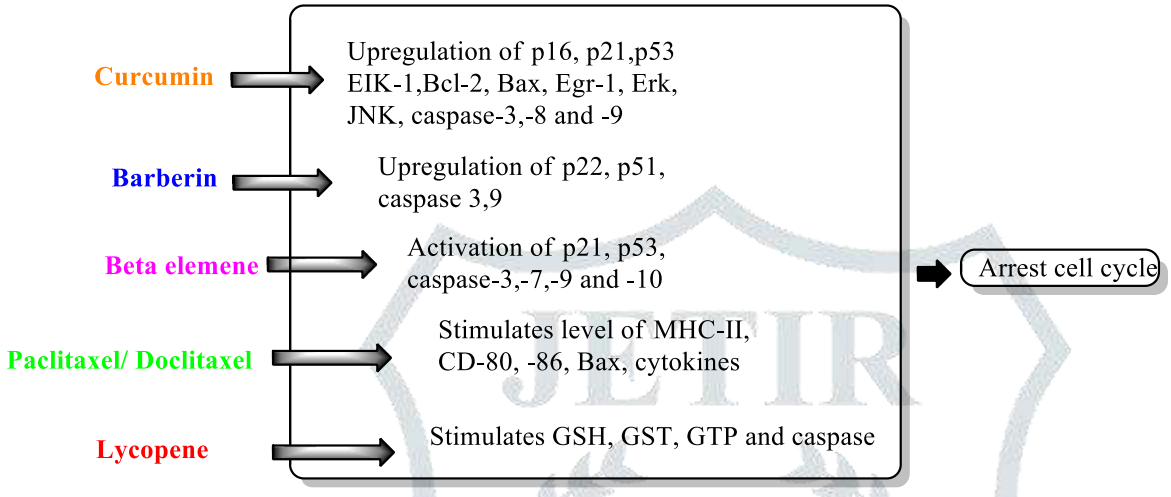

Figure: 2 The antiangiogenesis acitivity of phytoconstituents

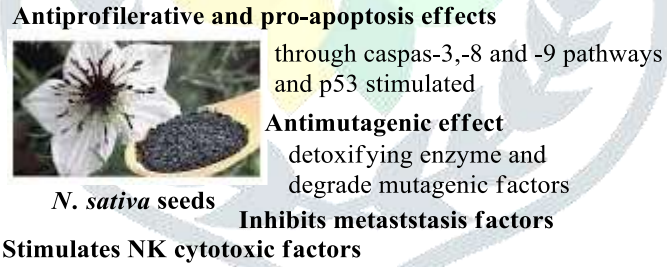

Figure:3 Anticancer activity of seeds of *N. sativa*(http://www.ncbi.nlm.nih.gov)

Conclusion

Cancer is highly precautionary disease in developed and developing countries. Naturally originated drugs are most useful and beneficial to our health since they cause very less tolerable side effects. Chemotherapy and radiations cause high risk of side effects. Hence each and every citizen take care in daily routine life, eat fresh food, pay attention on Yoga and meditation, take proper sleep and keep peace in surrounding us we can prevent disease like cancer at limit.

Table:1 Medicinal plants with phyochemicals and biological action

	Medicinal plants/ sources	Chemical constituents	Mechanism and Biological activity
1	Emblica officinalis (Indian gooseberries)/ Amla Fruits	Flavonoids, tannins, Gallic acid, ellagic acid, pyrgallol and terpenoids	It Reduces genotoxic effects of heavy metals, carcinogenic hydrocarbons and shows free radical scavenging activities(antioxidant), reduces the levels of cytochrome enzymes in the liver cells and shows anti-inflammatory and potent antitumor activities[5].
2	Allium cepa Peel	Flavonoids and organo-sulphur compounds	Its extract prompts apoptosis process with stimulation of p53 and modulating Bcl-2 proteins that inhibit PI3K/Akt signals in human cancer cells (AGS)[6].
3	Allium sativum tuber	s-allylcysteine, s-allylmercaptol, allicin, diallyltrisulfide and reduction in danger of intestinal cancer. methyl allyltrisulfide	Minimize the intestinal and stomach cancers, skin, colon, breast, liver and other types of cancers. The OSC-enhanced changes in the propagation of cancer cells are often linked with interruption sequences of c.c. and detain G2/M phase. It has also been verified to prompt apoptosis through altering the ratio of proteins family Bcl-2, both in vivo models and cell cultures.19 Radical scavenging activities are shown by cysteine derivatives; S-allylmercapto-L-cysteine and S-allylcysteine Moreover, a number of organosulfur compounds including S-allylcysteine also shown reverse the development of transplantable and chemically induced tumors[7].
4	Aloe vera/ Aloe arborescence Leaf	Aloin, aloe-emodin, aloesin(antiproliferative), Acemannan(immunostimulatory -mucopolysaccharide), Polyphenols (radical scavenging activity).	Shows anticancer activity through three basic mechanism; antiproliferative, immunostimulatory and antioxidant effects[8].
5	Nigella sativa Seed	Thymoquinone, dithymouinone	TQ initiates apoptotic cell death in human colorectal c.c. and interrupted G1 phase hence arrest the cycle. It prompts apoptosis with an increase in mRNA expression of the p53 target gene, p21WAF1, and a noteworthy inhibition of anti-apoptotic Bcl-2 protein[9-10].
6	Curcuma longa Rhizome	Polyphenols, curcumins	Powerful anti-invasive action in estrogen negative MCF-7 cell line against breast cancer. Down regulation of MMP-2 (matrix metalloproteinase) and the up regulation of TIMP-1 lung cancer, lymphoma, leukemia, multiple myeloma. Lung cancer- NF- factor suppress apoptosis, induce cellular proliferation, incursion metastasis and inflammation which activates by carcinogens. Curcumin may suppress this NF-. It also prevent prostatic cancer and shows significant toxic effect against cancerous cells on the CRPC by testing (PC3 and DU145) cells. Study reported that both analogs induced apoptosis and inhibited the role of nuclear factor (NF)-(49)[11].
7	Withaniasomnifera/Ashwagandha	Withaferin A, withanolides	Cancers (breast, colon, prostate, colon, ovarian, lung, brain) Breast- ROS, p53(+),inhibit mitochondrial res[12]
8	Ginger Rhizome	[6]-shogaol and [6]-gingerol	Autosis, LC3-II/LC3-I ratio increased and SQSTM1/p62 protein decreased and increased vacuole concentration of the cytoplasm in Panc-1 cells. Its constituents are useful to prevent pancreatic cancer[13]
9	Holy Basil Leaf	eugenol, rosmarinic acid, apigenin, and carnosic acid are also shown to prevent radiation-	Study reported Sarcoma-180 cells inoculated in the hind limb of mice grew well and from ethanolic extract treatment (E3 group) tumor volume was reduced potently, due to

		induced DNA damage.	intracellular GSH depletion. The proliferation, migration and invasion of PC cells are promoted by activated ERK-1/2, FAK, and p65 (subunit of NF-κB), but after administration of leaves extract, the process was downregulated in PC cells, means extract inhibit the proliferation, migration, incursion, and stimulate apoptosis of PC cells *in vitro*[14-15].
10	Lemon Fruit Peel	Flavonoids; hesperidin and naringin, and O-methylated aglycones of flavones such as nobiletin and tangeretin,	Polymethoxy flavones in citrus peel inhibits carcinogenesis by spoiling the metastasis cascade, inhibited mobility of cancer cell in circulatory systems and enhances pro-apoptosis and antiangiogenesis[16].
11	Annonamuricata Leaf	Annonacin, annomuricin E, muricoreacin, murihexocin C	Leaves extract stimulated apoptosis through diminish early phase cancer cells and give immunogenic response against tumor cells. Front pharmacol[17].
12	Astragalusmembranaceous Extract	isoflavones, campanulin, ononin, calycosin and formononetin	Swainsonine (prevent metastases) Inhibited cells proliferation of MCF-7, SK-BR-3 and MDA-MB-231 and induced cell apoptosos via PI3K/AKT/mTOR pathway and inhibit breast cancer[18].
13	Azadirechtaindica Leaves, flower and seed	Nimbin,nimbanine, nimbandiol, nimbolide, ascorbic acid, azadirachtin, nimbiol, gedunin, quercetin	Nimbolide and azadirachtin treated against human cervical cell line HeLa and shows cytotoxic effect through down the level (cyclin B and cyclin D1) with induced CKI p21 results arrest the cell cycle G0/G1. They increased the production of reactive oxygen species by decreasing mitochondrial trans membrane potential and liberating cytochrome c. Apoptotic signal is transduced via the mitochondrial pathway[19].
14	Barberisaristata/ Daruhaldi Stem	Alkaloid, quercetin, triterpenoid glycoside	Methanolic ext. Showed activity against human breast cancer cell line and inhibit MCF-7 cancer cell[20].
15	Cameliasinensis	Alkaloids, polyphenols, amino acids, polysaccharides, volatile acids EC, ECGC	Extract shows antiproliferative effects on stomach and colon cancer, lung, ovarian and breast cancers on different types of carcinoma cell lines (HT-29, MCF-7, A 549). The cell lines HT-29 (colon cancer) and MCF-7 (breast cancer) were more sensitive to the extract than A549 (lung cancer) after 72 h of cultivation[21] may slow the progression of atherogenesis by reducing oxidation of lipoproteins and preservation of paraoxonase/arylesterase activities streptozocin-induced diabetic in rats[93].
16	Cannabis sativa/marijuana .	Δ^9-tetrahydrocannabinol (THC)	The cannabinoid-inhibit AKT therefore cycle arrest against breast cancer and melanoma cells. Simultaneous stimulated apoptosis through decreased phosphorylation of the pro-apoptotic protein BCL2 and activated cyclin-dependent kinase inhibitory proteins p21 and p27[22].
17	Catharanthusroseous/periwinkle Apocynaceae	Vincristine, vinflunine,vindesine	(breast, lung, uterine, colon, melonamasetc)its alkaloids arrests proliferation by binding to tubulin in the mitotic spindle andalso induce apoptosis (Programmed cell death). Vincristine binds to tubulin dimer, which is a structural protein, inhibiting assembly of micro-tubule structures. Disruption of the microtubules and captures mitosis in metaphase stage of the cell cycle[23].
18	Glycine max Seeds	Peptide: Leu/Ile-Val-Pro-Lys (L/I-VPK)	A peptide fraction was isolated and found to be antioxidant and anticancer activity from black soybeanHepG2, MCF-7

			and Hela cells and it effectively bound with four apoptosis with key proteins (XIAP, caspas-3, caspas-7, Bcl-2). Extract of seed inhibited breast cancer against cell lines MCF-7 and MDA-MB-231 probable through ameliorate cancer by affecting the expression of JMJD5[24-25].
19	Linumusitatissimum	Podophyllotoxin	Anticancer activity of compound is shown against lung, colon and breast cancer with conjugated Au-NPs-POT and without Au-Nps using MTT test[26].
20	Podophyllum hexeandrum	Podophyllotoxin, semisyntheic-etoposide, teniposide, etopophos.	PTOX prevented the polymerization of microtubule resulting in mitotic detention as shown by accumulation of mitosis-related proteins, BIRC5 and aurora B(Chen et al, 2013). Semisynthetic products also inhibited on DNA topoisomerase II and prevent the re-ligation of DNA[27-28]. (Choi et al, 2015)
21	Punicagranatum Peel and Extract	Ellagitannins,ellagicacid,gallic acid, Punicalagin, hydroxyl benzoic acids,anthocyanindins, flavonoids	Breast, and liver prostate, lung, colon, skin cancers. Punicalagin inhibited beta catenin signaling pathway in cervical cancer of human. The anticancer potential of pomegranate extract in breast cancer cells is due to targeting microRNAs155 and 27a partly Pomegranate leaves extract affected H1299 cell survival by arresting cell cycle progression in G2/M phase It suppress pro survival pathways in human A549 lung carcinoma cells and tumor growth in the nude mice[29-31].
22	Oroxylumindicum/ Arlu/ Bignoniaceae Bark/leaves	Polyphenols, flavonoids	Different extracts showed free radical scavenging activity through DPPH assay and std taken L-ascorbic acid. Activity was shown L-ascorbic acid (97.4 %)>Ethyl acetate (I) 61.4 %>Methanol 40.8 % (II) > Water (III) 29.2 % [32].
23	Rubiacordifolia/Indian Maddar/ Asteraceae Leaves/bark		Root extract showed anticancer activity against humanlarynx carcinoma and Human cervical cancer using HEK 293, HeLa and HEp-2 cell lines[33-34].
24	Silybummarianum/Milk thistle Seed/fruit	Flavonolignans (flavonoids + Fatty acids + polyphenols) silibinins,	Seed extract (silymarin) showed anti-inflammatory effect and anticancer by regulate cell cycle through apoptosis induction, inhibition of angiogenesis, inhibition of invasion and metastasis and growth inhibition of cancerous cells[35].
25	Teraxacumofficinale Leaves	Butyrolactones, butanotes, taraxoside A-F	On a pediatric cancer cell line (neuroblastoma cell lines SH-SY5Y and Kelly), It caused apoptosis and loss of mitochondrial integrity as well as an inhibition of invasion and migration[36].
26	Vernoniaamygdalina Asteraceae	Sesquiterpene lactones (vernodalinol, vernolepin, vernomygdin, hydroxyvernolide, vernolide and vernodalol	Antiproliferative against Breast cancer MCF-7 cell line. Growth arrest was associated with p53 and p21 increased, and a concomitant decreased cyclinD1(-) and cyclin E(-). And stimulated specific G1/S phase cell cycle arrest[37-38].
27	VismiaLaurentii Root	Laurentixanthone A, laurentixanthone B, Xanthone V1 euxanthone, 6-deoxyisojacareubin, vismiaquinone A, vismiaquinone B, bivismiaquinone, 1,8-dihydroxy-3-geranyloxy-6-methylanthraquinone	Anticancer activity against MiaPaCa-2 pancreatic and CCRF-CEM leukemia cells and their multidrug-resistant subline, CEM/ADR5000. Caspase 3/7 was activated by xanthone V_1 The most sensitive cell lines (IC_{50}<1 µg/ml) were breast MCF-7 cervix HeLa and Caski leukemia PF-382 and melanoma colo-38 to xanthone V1[39].
28	Capcicum annum Red pepper Fruit	Capsaicin	Anticancer effects on pancreatic, prostatic, liver, skin, leukemia, lung, bladder, colon and endothelial cancerous cells. Inducing apoptosis with increasing intracellular calcium and ROS, disruption of microtublule and activated NF-KB and STATS[40].
29	Guduchi (Tinospora*cordifolia*)	Ethanolic extract/ aqueous extract/Polysaccharide(effective against lymphoma[42])	Inhibited Glioblastomas (brain tumor) against C6 glioma cells and shows anti-proliferative and apoptosis activity by specific proteins cyclin D1 and Bcl-xLrespectiviely and

	heavenly elixir		suppressed G1/S phase[41].
30	Yashtimadhu (Glycyrrhizaglabra)	glycyrrhizin	Der Pharmacia Lettre, 2016, 8 (19):417-420
31	Opium (*Papaversomniferum*)poppy Seeds	Noscapine	Antiproliferative properties; microtubule interfering; inhibits tumour growth and progressionPhase[43]
32	*Dysoxylumbinectariferum* Hook. f. (*Meliaceae*)	(Flavopiridol Synthetic flavonoid derivative; rohitukine based structure)	Anti-inflammatory, immunamodulatory activity; inhibitor of several cyclin-dependant kinases (CDKs), growth inhibitory effects against ovarian and breast cancer[44]
33	*Raphanussativus* L., radish (*Brassicaceae*) Cotyledons, sprout	Roscovitine Derived from olomucine	Inhibition of cyclin dependent kinases; reduction of cell cycle progression Phase. Chemically modified it's a new more potent inhibitor is roscovitine[45]
34	*Maclurapomifera; DereeisMalaccensis Fruit*	Prenylatedisoflavones, osajin and pomiferin	Potential inhibitory activity against HDAC enzyme. Inhibited the growth of cancer lines of lung, breast, kidney, colon, prostate and melanoma. Shows Pro-apoptotic effects, DNA fragmented and inhibits oxidative damage of DNA and histone deacetylases[46].
35	*Combretumcaffrum*	Combretastatin A-4 phosphate Water-soluble analogue of combretastatin	Anti-angiogenic, vasuclar shut-down of tumors; tumor necrosis[47]
36	*Eugenia jambolana, Java Plum* *Fruit extract*	Anthocyanins;glucosides of delphinidin, cyanidin, petunidin, peonidin and malvidin.	anti-cancer properties shows against human cancer colon cancer in the early stage HCT-116 and trigger apoptosis and repressed self-renewal ability in colon CSCs also[48].
37	*Magnolia cones Bark*	Honokiol (neolignanbiphenols)	**Honokiol** is potent cytotoxic against B-CLL cells and shows anti-proliferative effects. It induced caspase-3, -8 and-9 and cell apoptosis[49].
38	*Nothapodytes foetida*, Ghanera/ Icacenaceae Bark	Camptothecin and 9-methoxycamptothecin containeddry wt. % Immature seeds (0.27/0.11) Mature seeds (0.32/0.16) Zyg. Embryo immat. seeds (0.11/0.01) Cotyledons of immature seeds (0.42/0.18)	These alkaloids bind tightly to tubulin in cells and interfere with its normal function in spindle formation and make the tubulin less stable. The net result is metaphase arrest of cell division[50].
39	*Taxus sp./ Taxuscuspidata*Taxaceae Callus culture	Paclitaxel and other compounds	various cancers as well as HIV- associated Kaposi's sarcoma. Taxusin showed strong MDR-reversing activity than verapamil toward 2780 AD tumor cells[51]

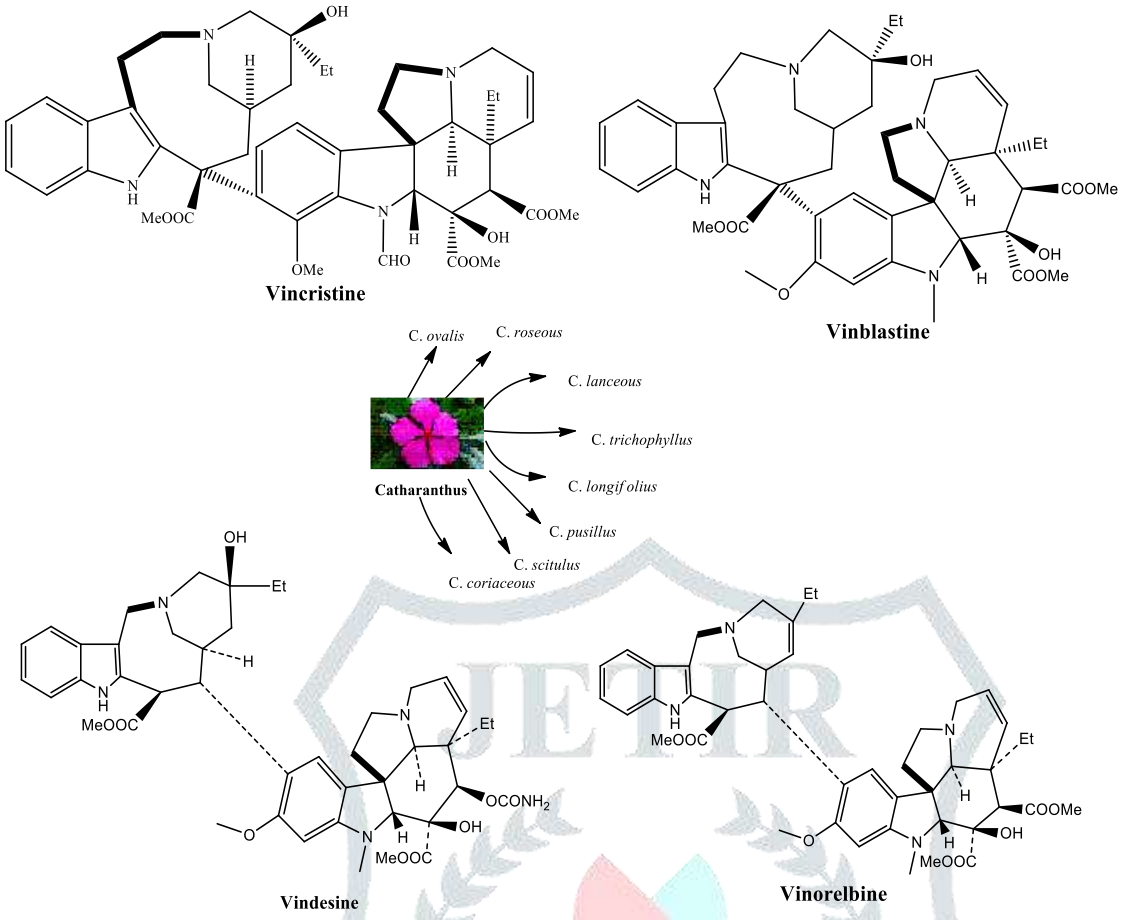

Figure:3 Structures of Vinca/Catharanthus alkaloids

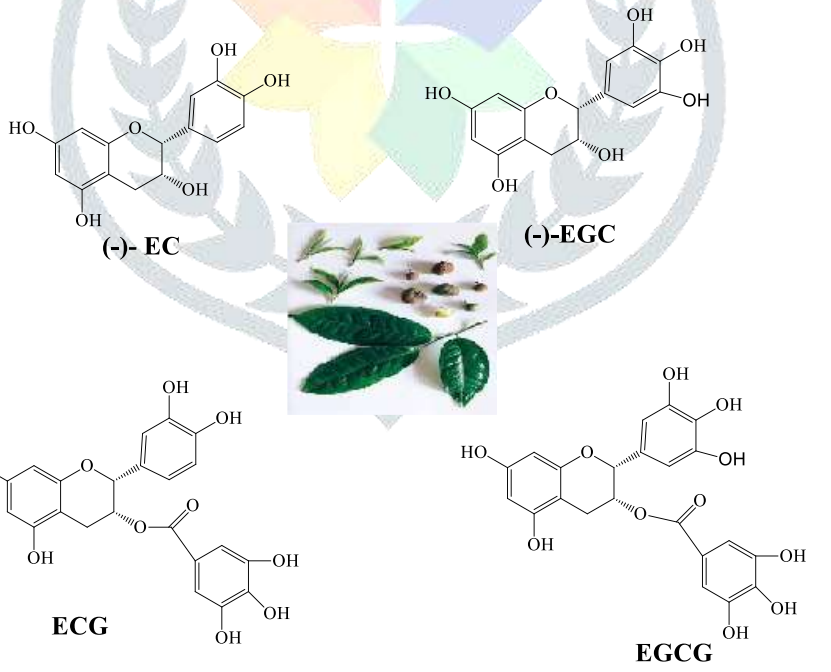

Figure:4 Phytoconstituents from *Cameilia sinensis(http://www.istockphoto.com)*

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