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ROLE OF NATURAL PRODUCTS AND THEIR PHYTOCONSTITUENTS IN CANCER-TARGETING THE HALLMARKS OF CANCER

Priyanka Mishra[1] and Suresh Purohit[2]
[1]Research Scholar and [2]Professor, Department of Pharmacology, Faculty of Modern Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005, E-mail: priyanka_mishra1991@yahoo.com, suresh_purohit31@rediffmail.com Mob.: 9616378778, 7275107544, Corresponding Author: Suresh Purohit

Abstract: *Natural product has been of significant value since a long time. There are so many evidence of treatment of an ailment with the use of natural product which include from treating to simple cough, fever to much more complicated disorders such as diabetes, hypertension and cancer. Cancer is a global disorder affecting every part of the world; therefore approaches to treat it are the needs of the hour. Despite the progress in the field of cancer research, both developing and developed countries are in the grip of this deadly disease, and still there is a need to discover and develop anti-cancer therapeutic agents. It has long been recognized that natural products represent the richest source of high chemical diversity, providing the basis for identification of novel scaffold structures that serves as starting points for rational drug design. Conventional drug therapies possess serious side effects such as bone marrow depression, pancytopenia, neuropathy, and cardiomyopathy. Products derived from nature do not possess such serious side effects. Plants such as Catharanthus roseus,Taxus brevifolia, Podophyllum peltatum and Camptotheca acuminate and marine organisms (citarabine, aplidine and dolastatin) and micro-organisms (dactinomycin, bleomycin and doxorubicin)are being currently used for treating cancer. There are several other natural products that can be used to defend against cancer apart from the above stated. In this article natural products as well as their phytoconstituents targeting the six hallmarks of cancer and their mechanism of action are discussed.*
Keywords: *Cancer, toxic effects, phytoconstituents, Hallmarks of cancer.*

Introduction: Cancer is a disease characterised by uncontrolled multiplication and spread of abnormal forms of the body's own cells. 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 metastasizing. Metastases are a major cause of death from cancer [1]. Cancer is one of the leading causes of death around the world. As per WHO, in 2012, 14 million new cases were recorded and 8.8 million deaths occurred due to cancer globally in 2015, suggesting nearly 1 in 6 deaths occur globally. These numbers are further going to rise in next decades accounting for near about 24 million new cases, which also suggest that near about 60% of the world's new cancer cases will occur in Africa, Asia, and Central and South America; 70% of the world's cancer deaths also occur in these regions. The most common causes of cancer death globally are cancers of:

- Lung (1.69 million deaths)
- Liver (788 000 deaths)
- Colorectal (774 000 deaths)
- Stomach (754 000 deaths)
- Breast (571 000 deaths)
- Prostate(467300 deaths)

In men, the highest percentages of cancer types occur in the prostate, lung and bronchus, colon and rectum, and urinary bladder, respectively. In women, cancer prevalence is highest in the breast, lung and bronchus, colon and rectum, uterine corpus and thyroid, respectively. This data indicates that prostate and breast cancer constitutes a major portion of cancer in men and women,

respectively[2]. For children, the highest percentage types of cancer disease are blood cancer, and cancers related to the brain and lymph nodes, respectively [3].

There are so many ways to explain the process of carcinogenesis in which a normal cell is turned into neoplastic cells. There exist one well known theory "Hallmarks of cancer" propounded by Douglas Hanahan and Robert Weinberg in 2000 where they explain six essential traits for a normal cell to be transformed into cancer cell.

Hallmarks of Cancer: Douglas Hanahan and Robert Weinberg suggested that there are six defining hallmarks of cancer that provides a logical explanation in order to understand the remarkable diversity of neoplasm; they explained that the alteration of normal cell to neoplastic state goes through a successive step imbibing these "hallmarks" which enables incipient cancer cell to become tumorigenic and ultimately malignant[4]. These six essential alterations in cell physiology that dictate malignant growth ("hallmarks") described by the authors in the paper are: (Fig 1)

Fig 1: Hallmarks of cancer as proposed by Douglas Hannahan and Robert Weinberg

Chemoprevention focuses on the development of pharmacological, biological and nutritional interventions to prevent, reverse or delay carcinogenesis [5]. This can be accomplished through simple lifestyle changes such as smoking cessation, a diet rich in fruits and vegetables, and exercise. Exhaustive research in the field of chemoprevention has identified certain foods and drugs that ostensibly prevent the progression of specific types of cancer. Such agents should be used in a prophylactic manner by individuals who are at a high risk for these cancers. As with all medications, chemo preventive drugs are not without side effects. Various kinds of toxicities such as myelotoxicity, cardiotoxicity, bone marrow depression, pancytopenia, may occur as a result of chemotherapeutic treatments. These toxic effects of chemotherapeutic drugs sometimes create a significant problem in the treatment of cancer using allopathic or established medicine. A risk versus benefit analysis must be performed before a regimen of chemo preventive drugs is initiated, especially with asymptomatic individuals.

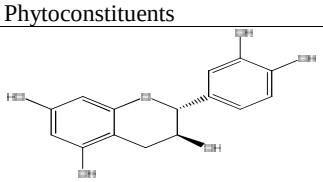
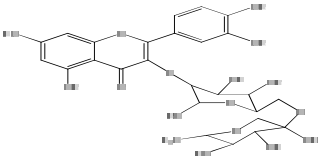
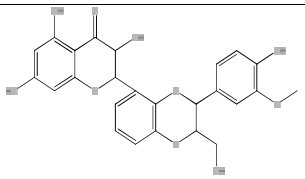
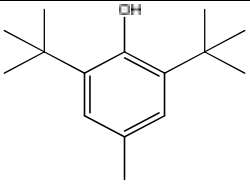
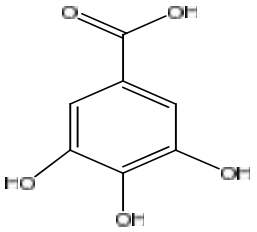
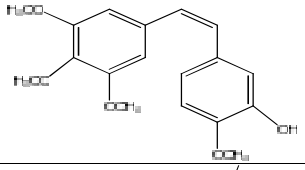
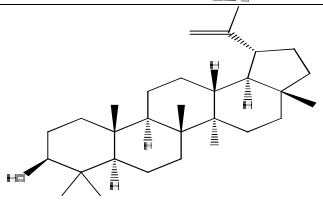
Various therapies have been advocated for the treatment of cancer, by using plant-derived products which possess less toxicity. There are four classes of plant-derived anticancer agents in the market today, the vinca alkaloids (vinblastine, vincristine and vindesine), the epipodophyllotoxins (etoposide and teniposide), the taxanes (paclitaxel and docetaxel) and the camptothecin derivatives (camptothecin and irinotecan). Plants still have enormous potential to provide newer drugs and as such are a reservoir of natural chemicals that may provide chemo protective potential against cancer.

This article focuses on the application of natural product as anticancer substance. Further this focus on the various plant derived chemical compounds that have, in recent years, shown promise as anticancer agents and will outline their potential mechanism of action.

1. Natural Product as Anti-proliferative Agent (Targeting Sustained Proliferative Growth): Normal cells require mitogenic growth signals (GS) before they can move from a quiescent state into an active proliferative state. Cancer cells, however, have the ability to grow without any external signals. There are multiple ways in

which cancer cells can do this: by producing these signals themselves, known as autocrine signalling; by permanently activating the signalling pathways that respond to these signals; or by destroying 'off switches' that prevents excessive growth from these signals (negative feedback) which finally results in sustained proliferation, following are few of the natural products and their phytoconstituents targeting sustained proliferative growth of cancer cells (Table 1).

Table 1: Natural product as anti-cancer agent targeting sustained proliferation

Natural Source	Mechanism of Action	Experimental model	Phytoconstituents
Juniperus oxycedrus , J.foetidissima , J. excels, J. communis	Anti-proliferative	In-vitro -human cervix carcinoma (HeLa) and rat brain tumour (C6) cell lines	 **CATECHIN**  **RUTIN**
Silybum marianum (standardised extract of Milk Thistle)	Anti-proliferative-loss of mitochondrial membrane potential and cell cycle arrest at sub G1phase.	In-vitro- human breast, prostate, pancreatic, and ovarian cell lines	 **SYLIBIN**
Stegnosperma halimifolium	Anti-proliferative	In-vitro human cervical cancer, human alveolar cancer, colorectal adenocarcinoma and murine connective tissue, murine macrophage, murine cell B lymphoma cell lines.	 **BHT**  **GALLIC ACID**
Combretum caffrum	Anti-proliferative-inhibition of tubulin formation,Cell cycle arrest at G_2/M phase	In-vitro -hepatocellular carcinoma HepG2 and leukaemia HL-60 cell lines.	**COMBESTRATIN A-4** 
Rhodomyrtus tomentosa (Aiton) Hassk	Anti-proliferative-increase antioxidant activity as per DPPH assay.	In-vitro-Human liver cancer cell (HepG2), breast cancer cells (MCF-7) and colon cancer cells (HT 29) lines	 **LUPEOL**

A. Junipers-Catechin and Rutin: Junipers are coniferous plants in the genus *Juniperus* of the cypress family Cupressaceae [6]. *Juniperus oxycedrus* L.subsp. *oxycedrus*, *J.foetidissima* Willd., *J. excelsa* Bieb. and *J. communis* L is a commonly used Turkish folk medicine which was evaluated for its anti-proliferative potential against against

human cervix carcinoma (HeLa) and rat brain tumour (C6) cell lines by A.Sahin, Yaglioglu and F.Eser. They made a peculiar observation that *J. foetidissima* exhibited high anti-proliferative activities with an IC_{50} value of 10.65 against C6 cell lines and for HeLa cells, the same was obtained with *J. communis* with an IC_{50} value of 32.96 [7].

B. Sylibin Analogues as Anti-proliferative Compound: Elangovan Manivanna et.al reports the synthesis and anti-proliferative activity evaluation of twelve novel silybin analogues designed using a ring disjunctive-based natural product lead (RDNPL) optimization approach against a panel of neoplastic cells (i.e. breast, prostate, pancreatic, and ovarian) and compared with normal cells. They performed preliminary mechanistic studies indicating the anti-proliferative efficacy of 15k was mediated by its induction of apoptosis, loss of mitochondrial membrane potential and cell cycle arrest at the sub-G1 phase [8].

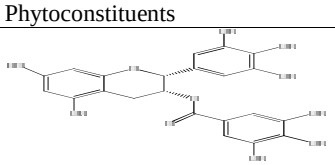
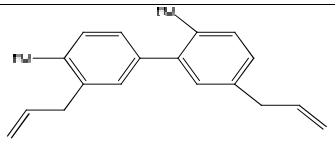
C. *Stegnosperma halimifolium*-Spinasterol: Salvador Enrique and Meneses-Sagrero et.al evaluated the anti-proliferative activity of the methanolic extracts, chemical fractions and the compound spinasterol of *Stegnosperma halimifolium* against human cervical cancer, human alveolar cancer, colorectal adenocarcinoma and murine connective tissue, murine macrophage, murine cell B lymphoma cell lines [9].

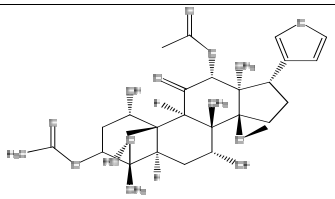
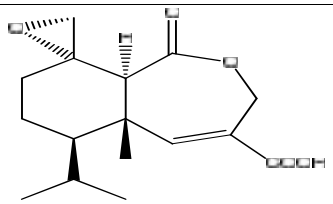
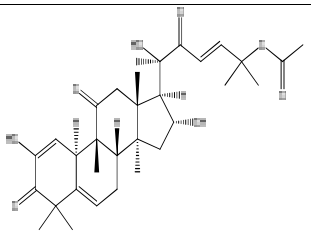
D. *Combretum caffrum*- 1, 2, 4- triazole-3-carboxamide derivative of Combestratin A-4: Muhamad Mustafa et.al reported the anti-proliferative efficacy of 1, 2, 4- triazole-3-carboxamide derivative of Combestratin A-4 obtained from African tree *Combretum caffrum.* They evaluated the derivative against hepatocellular carcinoma HepG2 and leukaemia HL-HL-60 cell lines. Their work revealed higher in-vitro tubulin polymerisation inhibition against HepG2 cell line [10].

E. *Rhodomyrtus tomentosa* (Aiton) Hassk-Lupeol: *Rhodomyrtus tomentosa* (Aiton) Hassk has been traditionally used for a wide spectrum of pharmacological effects and is effective in treating wounds, colic diarrhoea, heartburns, and abscesses and in gynaecopathy. HazrulrizawatiAbd Hamid et.al explored the anti-proliferative activity of various solvent of Rhodomytrus tomentosa against Human liver cancer cell (HepG2), breast cancer cells (MCF-7) and colon cancer cells (HT 29) lines.They observed that ethyl acetate extract of R.tomentosa was significantly effective as anti-proliferative compound against the above mention cancer cell lines, further they isolated lupeol via bioassay guided fraction which was responsible for the activity [11].

2. Natural Product Used in Suppression of Cancer Cell Growth (Targeting Oncogene): An oncogene is a gene that has the potential to cause cancer. In tumour cells, they are often mutated and /or expressed at high levels. Various transcription factors such as STATS (Signal Transducer and Activators of Transcription), NF-kB (Nuclear factor of kB), gene affecting WE (Warburg effect), EGFR (Endothelium Growth Factor Receptor) and targeting other growth factor suppresses the oncogene there by targeting growth of neoplasm. Under this category we will review the natural product that targets oncogene thereby enforcing growth suppression of tumours (Table 2).

Table 2: Natural product acting as anti-cancer agent targeting oncogene

Natural Source	Mechanism of Action	Experimental model	Phytoconstituents
Green tea-*Camellia sinensis*	a) Anti-oncogenic-activating dephosphorylation of STAT3. b)Modification of STAT3/Akt pathway leading to programmed cell death induction and autophagy	a)In-vitro study b)In-vitro cisplatin resistant oral cancer CAR cell line	 **EGCG**
Magnolia officinalis	Anti-oncogenic-down regulation of phospho-EGFR, phospho-Akt, phospho-STAT3 and cell cycle-related proteins	In-vivo-Mouse lung tumour bioassay	 **HONOKIOL**

Melia toosendan	Anti-oncogenic-effective inhibitor of STAT3, leading to the impediment of various oncogenic processes	Patient derived tumours-osteosarcoma	 **TOOSENDANIN**
Trichoderma sp (fungi)	Anti-oncogenic-selective inhibitor of GAPDH(rate limiting step for the WARBURG effect in cancer cell)	In-vitro-glycolytic tumour cell lines	 **KONINGIC ACID**
Cucurbita pepo (Styrian pumpkin)	Anti-oncogenic-inhibition of rapidly dividing cells	In-vitro- prostate, breast and colon cancer cell lines	 **CUCURBITACIN E**

A. Green tea- Epigallocatechin-3-Gallate (EGCG): Gyuman Park et.al evaluated the effect of dietary polyphenol in human cancer by targeting STAT3 which has distinct role in cancer progression and development [12]. Chien-Han Yuan, et.al investigated the ant-oncogenic potential of EGCG in cisplatin resistant oral cancer CAR cell line and found that modification of STAT3/AKT signalling pathway contributed to EGCG induced programmed cell death and autophagy in CAR cells which suggested the therapeutic potential of EGCG in oral cancer [13].

B. *Magnolia officinalis*-Honokiol: Epidermal growth factor receptor (EGFR) is commonly deregulated in pre-malignant lung epithelium; targeting EGFR may arrest the development of lung cancer. Demonstrated the effect of honokiol bioactive of *Magnolia officinalis* in concealment of lung cancer by down regulation of phospho-EGFR, phospho-Akt, phospho-STAT3 and cell cycle-related proteins as early as 6–12 h post-treatment [14].

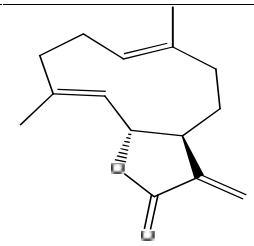
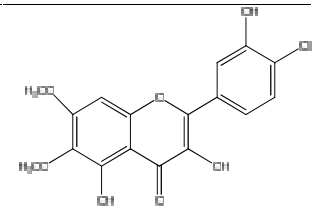
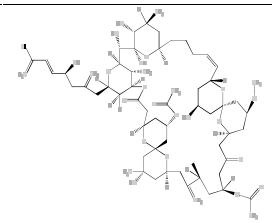
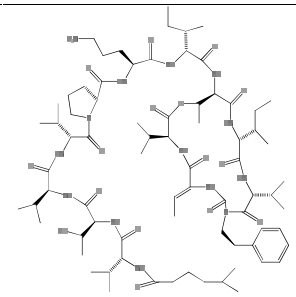
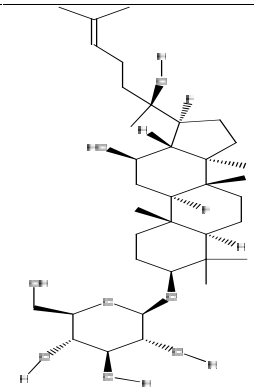
C. *Melia toosendan*-Toosendanin: T Zhang et.al identified Toosendanin as an effective inhibitor of STAT3, leading to the impediment of various oncogenic processes in osteosarcoma in their study. Toosendanin (TSN) is a triterpenoid extracted from *Melia toosendan.* Increasing evidence display that activated STAT3 contributes to tumour development and progression in the majority of cancers, including breast, prostate, ovary, lung, gastric, melanoma and blood [15].

D. *Trichoderma sp (fungi)*-Koningic Acid (Heptelidic Acid): Use metabolic control analysis and multiomics approaches to establish the role of GAPDH enzyme as a rate limiting step for the WARBURG effect in cancer cell. They determine a natural product, koningic acid (KA), as a selective inhibitor of GAPDH, an enzyme that have been characterize to have differential control properties over metabolism during the WE in cancer cell metabolism [16].

E. Cucurbita pepo (Styrian pumpkin)-Cucurbitacin E: Investigated the bioactivity of hydro ethanolic extract of pumpkin seeds obtained from Styrian pumpkin, *Cucurbita pepo* L. subsp. *pepo* var. styriaca. They observed growth inhibition in rapidly dividing cells of prostate, breast and colon cancer cell lines which validate the role of pumpkin seeds as a treatment of benign prostate hyperplasia [17].

3. Natural Product as Pro-apoptic Agent (Regulating Programmed Cell Death): Cells have the ability to 'self-destruct'; a process known as apoptosis. This is required for organisms to grow and develop properly, for maintaining tissues of the body, and is also initiated when a cell is damaged or infected. Cancer cells, however, lose this ability; even though cells may become grossly abnormal, they do not apoptose. The cancer cells may do this by altering the mechanisms that detect the damage or abnormalities. This means that proper signalling cannot occur, thus apoptosis cannot activate. Following are some of the natural product regulating apoptosis (Table 3).

Table 3: Natural product acting as anti-cancer agent inducing apoptosis

Natural Source	Mechanism of Action	Experimental model	Phytoconstituents
Saussurea lappa	a)Apoptosis inducer-the induction of apoptosis by costunolide through generation of Reactive Oxygen Species and disruption of mitochondrial membrane potential, increased expression of Bax, down-regulation of Bcl-2, survivin and significant activation of caspase-3, and its downstream target PARP (Poly (ADP-ribose) polymerase). b) stimulate the depletion of intracellular thiols and overload of nuclear Ca(2+) that cause DNA damage and p21 up-regulation	a)In-vitro-human bladder cancer T24 cells b) Human prostate cancer	 **COSTUNOLIDE**
Fructus viticis	Apoptotic activity- via mitochondrial release of cytochrome c due to the reduction of mitochondrial trans membrane potential, activation of caspase-3 and -9, and the production of reactive oxygen species.	Human cervical cancer HeLa, CasKi, SiHa cell lines and peripheral blood mononuclear cells (PBMCs).	 **CASTICIN**
Spirastrella spinispirulifera and Hyrtios (Marine sponges)	Apoptotic activity-Spongistatin 1 triggers caspase-dependent apoptosis by the release of cytochrome c, Smac /DIABLO and Omi/ HtrA2 from mitochondria into the cytosol, degradation of the anti-apoptotic X-linked inhibitor (XIAP) through spongistatin 1	Patient derived acute leukemic cell lines	 **SPONGISTATIN**
Elysia rufescens (sea slugs)	Apoptotic activity-a)efficiently inhibited the phosphatidylinositol 3-kinase (PI3K)-Akt signaling pathway b)Cytotoxic activity	a)In-vitro b)Human prostate and breast cancer cell line	 **KAHALALIDE F**
Panax quinquefolius (American ginseng)	Apoptotic activity-activation of the p53 pathway and significant rise in pro-apoptotic regulator Bax and decreased level of anti-apoptotic regulator Bcl-2	In-vitro-in HCT116 and SW480 colorectal cancer cell line	 **GINSENOSIDE Rh2**

A. *Saussurea lappa*-Costunolide: Costunolide, a member of sesquiterpene lactone family, possesses potent anticancer properties. Azhar Rasul, Rui Bao et.al, carried out a study to correlate the induction of apoptosis by costunolide through generation of Reactive Oxygen Species and disruption of mitochondrial membrane potential in human bladder cancer T24 cells [18].

Hsu JL, et.al elucidated a novel mechanism to signify the potential of costunolide chemotherapy in human prostate cancer through nuclear calcium2+ overload and DNA damage. Their findings suggest that costunolide stimulate

the depletion of intracellular thiols and overload of nuclear Ca(2+) that cause DNA damage and p21 up-regulationleading to G1 arrest of the cell cycle and subsequent apoptotic cell death in human prostate cancer cells [19].

B. *Fructus viticis*-Casticin: Casticin is one of the major components of *Fructus viticis*, which has been reported to inhibit the growth of various cancer cells, including the human cervical cancer cell line HeLa. . Dan Chen et.al performed the study to investigate the apoptotic activity of casticin and underlying molecular mechanism. Their study found out that casticin caused accumulation of the Sub-G1 cells and increased reactive oxygen species (ROS) production in HeLa, CasKi, SiHa cell lines, but not in PBMCs. They observed apoptosis of HeLa cells was induced by casticin via mitochondrial release of cytochrome c [20].

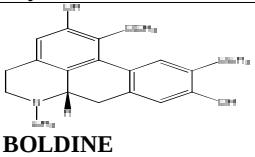
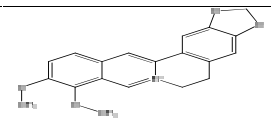
C. Spirastrella spinispirulifera and Hyrtios (Marine sponges)-Spongistatin: L Schyschka et.al show that spongistatin 1 shows interesting apoptotic feature in patient primary acute leukemic cells with higher efficiency than 8/10 clinically used cytotoxic drugs and prevents long-term survival of leukemic cell lines. In leukemic cell line, Spongistatin 1 triggers caspase-dependent apoptosis by the release of cytochrome c, Smac /DIABLO and Omi/ HtrA2 from mitochondria into the cytosol [21].

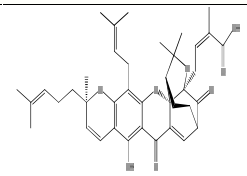
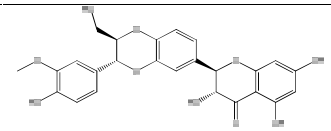
D. Elysia Rufescens (Sea Slugs)-Kahalalide F: Kahalalide F is a C75 cyclic tridecapeptide which was initially isolated from the sea slug Elysia rufescens and the green alga Bryopsis spp.Maarten L. Janmaat, et.al evaluated the cytotoxic effect of Kahalalide F in breast cancer and hepatic cancer cell line, they also explored the possible mechanism of action of the compound [22].Yajaira Suárez et.al explore the anticancer potential of Kahalalide F against Human prostate and breast cancer cell line. In their work they examined the action of KF, a novel antitumour compound derived from marine, which is under clinical investigation, in human prostate and breast cancer cells. Their study showed KF as a very potent cytotoxic drug against both tumours, that displays an unusual and interesting mode of action [23].

E. *Panax quinquefolius*-Ginsenoside Rh2: Ginsenosides are the main bioactive components in American ginseng. Showed in their study that ginsenoside Rh2 exhibited significantly more potent cell death activity than the ginsenoside Rg3 in HCT116 and SW480 colorectal cancer cell line. They observed cell deaths induced by Rh2 were mediated partly by the caspase-dependent apoptosis and partly the caspase-independent paraptosis, a type of cell death that is characterized by the accumulation of cytoplasmic vacuoles [24].

4. Natural Product Targeting Uncontrolled Replication of Cell: Non-cancer cells die after a certain number of divisions. Cancer cells escape this limit and are apparently capable of indefinite growth and division (immortality). But those immortal cells have damaged chromosomes, which can become cancerous. Cells of the body don't normally have the ability to divide indefinitely. They have a limited number of divisions before the cells become unable to divide (senescence), or die (crisis). The cause of these barriers is primarily due to the DNA at the end of chromosomes, known as telomeres. Telomeric DNA shortens with every cell division, until it becomes so short it activates senescence, so the cell stops dividing. Cancer cells bypass this barrier by manipulating enzymes that increase the length of telomeres. Thus, they can divide indefinitely, without initiating senescence. Following are some of the natural product that target uncontrolled replication of cell (Table 4).

Table 4: Natural product acting as anti-cancer agent targeting uncontrolled replication

Natural Source	Mechanism of Action	Experimental model	Phytoconstituents
Peumus boldus	Cell cycle arrest at G2/M phase, disruption of the mitochondrial membrane potential and release of cytochrome c in MDA-MB-231, activation of caspase-9 and caspase-3/7,	In-vivo-animal model of breast cancer	 **BOLDINE**
Berberis vulgaris	down-regulation of nucleophosmin/b23 and telomerase activity	In-vitro-human leukemia HL-60 cells	 **BERBERINE**

Garcinia hurburyi	The reduction in telomerase activity, hTERT activity became reduced by way of both the down-law of hTERT transcription via inhibition of the transcription activator c-Myc, and inhibition of the phosphorylation of Akt which down-regulated the hobby of hTERT in a submit-translational way.	In-vivo and In-vitro	 **GAMBOGIC ACID**
Rosa canina	Cell Cycle arrest in S-phase and repression of telomerase activity.	In-vitro-human colon cancers (WiDr) cells	 **SILIBININ**

A. *Peumus boldus*-Boldine: Boldine is an alkaloid of the aporphine class that can be found in the boldo tree (Peumus boldus). A recent study had reported anti-tumour effects of boldine by stimulation of apoptosis in vitro and its feasible application by intraperitoneal injection (50 or 100 mg/kg) in an animal model of breast cancer carried out. The anticancer mechanism is associated with disruption of the mitochondrial membrane potential and release of cytochrome c in MDA-MB-231 [25]. Another study carried out by Kazemi Noureni & Tanvar revealed that boldine has anti-proliferative effect on glioma cell lines by G2/M arrest and beneficial antitumor properties against glioma in mouse model via down-regulation of hTERT (human Telomerase Reverse Transcriptase) [26].

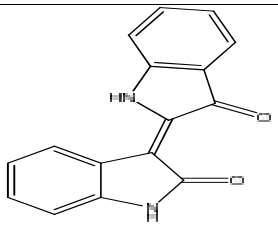
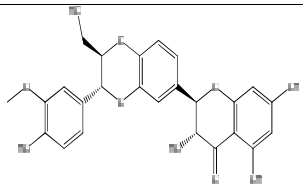
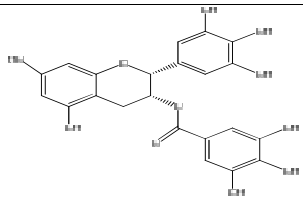
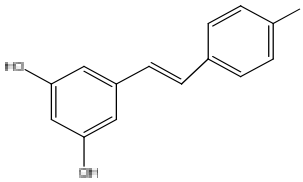
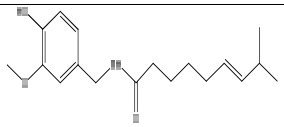
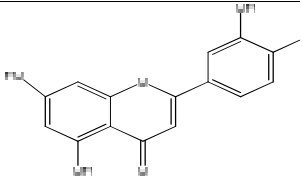
B. *Berberis vulgaris*- Berberine: Berberine is a quaternary ammonium salt from the protoberberine group of benzylisoquinoline alkaloids, isolated from the roots and stem-bark of many plants including *Berberis vulgaris* chinensis (Coptis or golden thread).In a study revealed that berberine-induced apoptosis of human leukemia HL-60 cells is associated with down-regulation of nucleophosmin/b23 and telomerase activity [27]. In a different study observed that telomerase activity was repressed to about 70% and 40% after treatment with 25µg/ml berberine for 24 and 48 h, respectively against U937 human leukemia cells[28]. Found that the anti-telomerase activity of berberine lies in its preference for binding G4 over duplex DNA to stabilize G4.[29]

C. *Garcinia hurburyi*-Gambogic Acid: Gambogic acid belongs to a circle of relatives of caged xanthones and is remoted from the gamboge resin of the *Garcinia hurburyi* tree in Southeast Asia. Studies group have shown that the induction of apoptosis via gambogic acid might also depend on the reduction in telomerase activity, hTERT activity became reduced by way of both the down-law of hTERT transcription via inhibition of the transcription activator c-Myc, and inhibition of the phosphorylation of Akt which down-regulated the hobby of hTERT in a submit-translational way.[30]

D. *Rosa canina*: *Rosa canina* is a member of the genus Rosa that has longbeen used zor scientific goals. Ibrahim Turan et.al evaluated the impact of R. canina extract on cellular viability, the cellular cycle, apoptosis, and the expression of telomerase in human colon most cancers (WiDr) cells. R. canina extract considerably repressed telomerase expressions at treatment instances of forty eight and seventy two h in WiDr cells.[31]

5. Natural Product Targeting Angiogenesis: This is an essential component of metastatic process. An expanding tumour requires new blood vessels to deliver adequate oxygen to the cancer cells, and thus exploits these normal physiological processes for its benefit. Tumours induce angiogenesis by secreting various growth factors, such as vascular endothelial growth factor (*VEGF*) and basic fibroblast growth factor (*bFGF*), which induce capillary growth into the tumour and allow it to grow by supplying nutrients and oxygen and removing waste products. In addition, the new vessels allow tumour cells to escape into the circulation and lodge in other organs (i.e. tumour metastases).Here are few natural products that act as anticancer agent by targeting angiogenesis (Table 5).

Table 5: Natural product as anti-cancer agent targeting angiogenesis

Natural Source	Mechanism of Action	Experimental model	Phytoconstituents
Indigo naturalis	Inhibition of angiogenesis-suppresses vascular endothelial growth factor (VEGF) receptor 2 mediated Janus kinase (JAK)/STAT3 signalling pathway	chick chorio allantoic membrane assay (CAM) and mouse corneal model	 **INDIRUBIN**
Glycine max (Soyabean)	Inhibition of angiogenesis-dose-dependent inhibition of expression/excretion of vascular endothelial growth factor, platelet-derived growth factor, tissue factor, urokinase plasminogen activator, and matrix metalloprotease-2 and 9	In-vitro-human bladder cancer cell lines. In-vivo-nude mice xenograft and chick chorioallantoic membrane bioassay	 **SILIBININ**
Camellia sinensis (Green tea)	the miRNA expression profile associated with angiogenesis, inhibition of expression/excretion of vascular endothelial growth factor, platelet-derived growth factor, tissue factor	In-vitro- Human Umbilical Vein Endothelial Cells	 **EGCG**
Red wine, grapes (mainly in the skin), mulberries, peanuts, vines, pines	Anti-proliferation, anti-carcinogenesis,cell cycle arrest, apoptosis, anti-angiogenesis, Inhibition of growth factor induced VEGF expression in vascular smooth muscle cells due to their antioxidant properties, by preventing the formation of intracellular reactive oxygen species and phosphorylation of p38 MAP kinase. Resveratrol treatment also leads to down-regulation of cyclin A gene expression, inhibition of MMP-2, and inhibition of p38 MAPK and PI3-kinase/Akt pathways.	In-vitro and In-vivo	 **RESVERATROL**
Capsicum annuum (Chili pepper)	Inhibition of VEGF-induced vessel formation together with VEGF-induced p38 MAPK, p125 (FAK), and AKT activation. It also inhibits chemotactic motility, and induced G1 phase arrest in endothelial cells.	Rat aortic ring assay. Mouse Matrigel plug assay	 **CAPSAICIN**
Salvia tomentosa	Inhibited vascular endothelial growth factor (VEGF)-induced *in vivo* angiogenesis. Luteolin inhibited VEGF-induced phosphatidylinositol 3′-kinase (PI3K) activity	Rabbit corneal assay. Human umbilical vein endothelial cell(HUVEC)	 **LUTEOLIN**

A. *Indigo naturalis*- Indirubin: Xiaoli Zhang et.al explored the anti angiogenic potential of indirubin an essential component of Chinese herbal medication *Banlagen,* against prostate cancer by using chick chorio allantoic membrane assay (CAM) and mouse corneal model in which they found that indirubin inhibited angiogenesis in vivo and showed in-vitro inhibition activity of indirubin in endothelial cell migration, tube formation and cell survival. They also observed that indirubin suppresses vascular endothelial growth factor (VEGF) receptor 2 mediated Janus kinase (JAK)/STAT3 signalling pathway but had minimal effect on extracellular signal-regulated kinase (ERK) activity p38 mitogen-activated protein kinase in endothelial cell [32].

B. *Glycine max* (Soyabean)-Genistin: Genistein is known as the major component of isoflavone, which is present in high-soy diets.Numerous studies have shown that genistein has antineoplastic effects against ovarian cancer. Shu-JemSu et.al designed the study to explore the novel molecular mechanism behind the antiangiogenic activity of soy isoflavone. They observed Genistein was the most compelling inhibitor of angiogenesis in vitro and in vivo among the isoflavone compounds tested. They witnessed Genistein exhibited a dose-dependent inhibition of expression/excretion of vascular endothelial growth factor, platelet-derived growth factor, tissue factor, urokinase plasminogen activator, and matrix metalloprotease-2 and 9, respectively.[33]

C. *Camellia sinensis* (Green tea)-EGCG: Green tea (from the Camellia sinensis plant) is one of the most popular beverages in the world. The polyphenolic compounds from green tea are able to change the miRNA expression profile associated with angiogenesis in various cancer types [34]. It has been revealed that the green tea catechins not only possess anti-inflammatory and anti-oxidative-stress activities but they have also shown anti-carcinogenic, anti-microbial, anti-obesity and anti-iabetic properties [35]. Green tea polyphenols inhibit cell proliferation and present a strong antiradical activity [36]. AkikoKojima-Yuasa et.al tested the ability of green tea extract (GTE) for inhibitin cell viability, cell proliferation, cell cycle dynamics, vascular endothelial growth factor (VEGF) and expression of VEGF receptors fms-like tyrosine kinase (Flt-1) and foetal liver kinase-1/ Kinase insert domain containing receptor (Flk-1/ KDR) in vitro using human umbilical vein endothelial cells (HUVECs) [37].

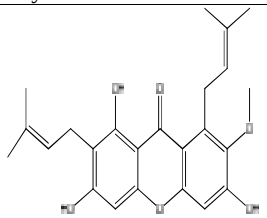
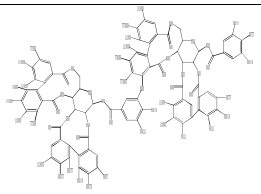
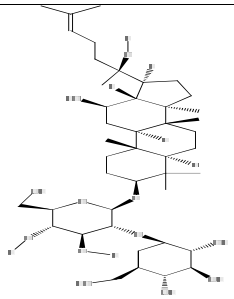
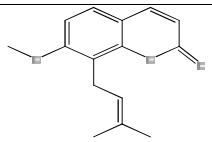
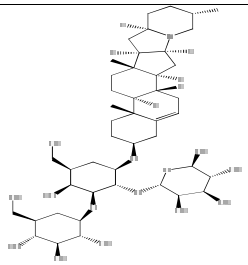
D. Resveratrol: Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) is a stilbenoid, a type of natural phenol, and a phytoalexin produced by several plants in response to injury or, when the plant is under attack by pathogens such as bacteria or fungi. RWPC (Phenolic axtract of Resveratrol) treatment also leads to down-regulation of cyclin A gene expression, inhibition of MMP-2, and inhibition of p38 MAPK and PI3-kinase/Akt pathways [38]. Yu cao et.al investigated the effect of resveratrol on angiogenesis in vitro and ex vivo, and found that resveratrol directly inhibited human umbilical vein endothelial cell growth and decreased the gelatinolytic activities of matrix metalloproteinase-2 [39]. Ming-tsan lin, and his co-workers found that upon treatment of HUVECs with 1 to 2.5 μmol/l resveratrol significantly reduced VEGF-mediated migration and tube formation but not cell proliferation [40].

E. *Capsicum annuum* (Chili pepper)-Capsaicin: Capsaicin is an alkaloid isolated from chili pepper, which belongs to the *Capsicum* genus, showed inhibitory activity against VEGF-induced proliferation, DNA synthesis, capillary-like tube formation of primary cultured human endothelial cells, VEGF-induced vessel sprouting in a rat aortic ring assay. Previous studies showed inhibition of VEGF-induced vessel formation together with VEGF-induced p38 MAPK, p125 (FAK), and AKT activation as shown in a mouse Matrigel plug assay [41]. It also inhibits chemotactic motility, and induced G1 phase arrest in endothelial cells[42]. It was reported that capsaicin inhibited carcinogenesis of the skin, colon, lung, tongue and prostate depending on signal transducers and activators of transcription (STAT) 3 inhibitions in multiple myeloma cells [43].

F. *Salvia tomentosa*-Luteolin: Eleni Bagli, et.al observed that luteolin inhibited A-431 xenograft tumour growth and angiogenesis in mice. In agreement, luteolin inhibited VEGF-induced angiogenesis in the rabbit cornea as well as survival and proliferation of HUVECs *in vitro*. Inhibition of the catalytic activity of PI3K by luteolin played an important role in both the antimitotic and apoptotic effects of the compound. Their results shed light on the mechanisms of action of phytochemicals, such as flavonoids, which might explain the protective action of plant-based diets on the incidence of cancer [44].

6. Natural Product Targeting Tumour Invasion and Metastasis: One of the most well-known properties of cancer cells is their ability to invade neighbouring tissues. It is what dictates whether the tumour is benign or malignant, and is the reason for their dissemination around the body. The cancer cells have to undergo a multitude of changes in order for them to acquire the ability to metastasize. It is a multistep process that starts with local invasion of the cells into the surrounding tissues. They then have to invade blood vessels, survive in the harsh environment of the circulatory system, exit this system and then start dividing in the new tissue. Following are some of the natural product that targets tumour invasion and metastasis (Table 6).

Table 6: Natural product as anti-cancer agent targeting tissue invasion and metastasis

Natural Source	Mechanism of Action	Experimental model	Phytoconstituents
Garcinia mangostana (mangosteen tree)	*a) α*-Mangostin suppresses Pc-3 human prostate carcinoma cell metastasis by inhibiting matrix metalloproteinase-2/9 and urokinase-plasminogen expression through the JNK signalling pathway. b) α-mangostin inhibits MDA-MB-231 cells migration and evasion through inhibit intracellular LSD1 (Lysine-specific demethylase) activity.	a) In-vitro-Human prostate cell lines. b) In-vitro- breast cancer cell lines.	 **α-MANGOSTIN**
Rubus idaeus L	Anti-metastatic activity via reduced activities of matrix metalloproteinase-2 (MMP-2) and urokinasetype plasminogen activator (u-PA)	In vivo BALB/c nude mice xenograft model	 **SANGUIIN H-6**
Panax ginseng	inhibitors of TGF-1(Transforming growth factor-beta 1)-induced EMT (Epithelial to mesenchymal transition) development	In-vitro- A549 lung cancer cell lines.	 **GINSENOSIDE RG 3**
Cnidium monnieri	Reverse IGF-1(Insulin like Growth Factor)-induced morphological changes, upregulated the expression of epithelial markers, and downregulated the expression of mesenchymal markers	In-vitro Human Brain Glioblastoma cell lines	 **OSTHOLE**
Solanum nigrum Linn	α-Solanine also significantly elevates epithelial marker E-cadherin expression, while it concomitantly decreases mesenchymal marker vimentin expression, suggesting it suppresses epithelial-mesenchymal transition (EMT).	In-vitro-human prostate cancer cell lines	 **α-SOLANINE**

A. Garcinia mangostana (Mangosteen Tree)-α-mangostin: Mangostin is a natural xanthonoid, a type of organic compound isolated from various parts of the mangosteen tree (Garcinia mangostana) [45]. Hung et. al showed α-Mangostin suppresses Pc-3 human prostate carcinoma cell metastasis by inhibiting matrix metalloproteinase-2/9 and urokinase-plasminogen expression through the JNK signalling pathway [46]. To date, almost all the developed LSD1 inhibitors are chemo-synthesized molecules, while α-mangostin is first characterized as xanthone-based natural inhibitor in the current study performed with IC50 values of 2.81±0.44 μM. Their findings provides new molecular skeleton for LSD1 inhibitor study and should encourage further modification of α-mangostin to produce more potent LSD1 inhibitors with potential anticancer activity[47].

B. *Rubus idaeus L.*-SANGUIIN H-6: Epithelial to mesenchymal transition (EMT) has been considered essential for cancer metastasis, a multistep complicated process including local invasion, intravasation, extravasation, and proliferation at distant sites. Yih-Shou Hsieh et.al provided molecular evidence associated with the antimetastatic effect of Rubus idaeus L. extracts (RIE) by showing a nearly complete inhibition on the invasion ($p < 0.001$) of highly metastatic A549 cells via reduced activities of matrix metalloproteinase-2 (MMP-2) and urokinasetype plasminogen activator (u-PA)[48].

C. *Panax ginseng*-Ginsenoside 20-Rg3: Ginseng is a perennial plant belonging to the genus Panax that exhibits a wide range of pharmacological and physiological activities. Ginsenosides 20-Rg3, which is the active component of ginseng, has various medical effects, such as anti-tumourigenic, anti-angiogenesis, and anti-fatiguing activities. In addition, ginsenosides 20(S)-Rg3 and 20(R)-Rg3 are epimers, and this epimerization is produced by steaming. However, the possible role of 20(S)-Rg3 and 20(R)-Rg3 in the EMT is unclear. Young-Joo Kima et.al investigated the effect of 20(S)-Rg3 and 20(R)-Rg3 on the EMT. Transforming growth factor-beta 1 (TGF-1) induces the EMT to promote lung adenocarcinoma migration, invasion, and anoikis resistance. To understand the repressive role of 20(S)-Rg3 and 20(R)-Rg3 in lung cancer migration, invasion, and anoikis resistance, they also investigated the potential use of 20(S)-Rg3 and 20(R)-Rg3 as inhibitors of TGF-1-induced EMT development in A549 lung cancer cells in vitro [49].

D. *Cnidium monnieri*- Osthole: Osthole (also known as osthol), 7-methoxy-8-(3-methyl-2-butenyl)-2H-1-benzopyran-2-one, is a natural O-methylated coumarin first derived from Cnidium plant. High content of osthole is found in the mature fruit of Cnidium monnieri (Fructus Cnidii), which is commonly applied in clinical practice of Traditional Chinese Medicine, while it is also widely found in other medicinal plants including *Angelica, Archangelica, Citrus, Clausena* [50]. In their study, Ying-Chao Lin et.al found that GBM8401 cells were converted to fibroblastic phenotype and the space between the cells became expanded in response to insulin-like growth factor-1 (IGF-1) treatment. Their results illustrate that osthole would reverse IGF-1-induced morphological changes, up regulated the expression of epithelial markers, and down regulated the expression of mesenchymal markers [51].

E. *Solanum nigrum* Linn-α-Solanine: α-Solanine, a naturally occurring steroidal glycoalkaloid found in nightshade (Solanum nigrum Linn.), was found to inhibit proliferation and induce apoptosis of tumour cells. Hung Shen et.al investigated the suppression mechanism of α-solanine on motility of the human prostate cancer cell PC-3. Their results show that α-solanine reduces the viability of PC-3 cells. When treated with non-toxic doses of α-solanine, cell invasion is markedly suppressed by α-solanine [52].

Conclusion: Natural products are a rich source of cancer chemotherapy drugs, and primarily target rapidly proliferating tumour cells. Chemoprevention by edible phytochemicals is of great interest and is considered to be an inexpensive, readily applicable, acceptable, and accessible approach to cancer control and management. Several phytochemicals are in preclinical or clinical trials for cancer chemoprevention. Epidemiological studies have shown that high dietary consumption of vegetables and fruits reduced the risk of cancer. Severe toxicity is the major drawback in conventional radiotherapy and chemotherapy. Both methods exert toxic side effects, such as nausea, vomiting, mucosal ulceration, alopecia, pulmonary fibrosis, cardiac, and hepatic toxicity. Use of natural compounds as an adjunct to chemotherapy and radiation may reduce treatment toxicities as well as increase the therapeutic index. Studies showed that phytochemical such as Catechin, Rutin, Silybin, Spinasterol, Combestratin-A4, Lupeol, EGCG, Honokiol, Toosendanin, Koningic acid, Cucurbitacin E, Costunolide, Casticin, Spongistatin, Kahalalide F, Ginsenoside Rh2, Boldine, Berberine, Gambogic acid, Silibinin, Indirubin, Genistin, Resveratrol, Capsaicin, Luteolin, α-mangostin, SanguinnH-6, Ginsenoside 20Rg3, Osthole and α-Solanine exert their anticancer effect by targeting at least one of the hallmarks of the cancer.

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