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Prevention and Treatment of Cancer with Alternative Anticancer Approach: Current Scenario

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CANCER is a serious concern right away which severely affects the mankind. Recently, the centre of interest of pharmaceutical industry is to develop newer drug molecules with very less or no toxicity to prevent and cure this life-threatening disease. Nature is the origin of remedies for human. Natural therapeutic agents brought a great change in recent drug market, as these are simple, safer, eco-friendly, low-cost, and less toxic in respect to commonly using drugs. Natural anticancer agents are selective in their functions and targetfully act on tumor cells without having any effect on normal cells. Cancer is a complex phenomenon which requires many signaling pathways. Natural therapeutic agents are the appropriate candidates to develop anticancer drug on account of their pleiotropic actions on target events with diverse manners. In this review we have collected a basket, flooded with latest information (2010-2020) on prevention and treatment of cancer with several products from nature, such as phytohemical (artemisinin, parthenolide, thapsigargin, curcumin, resveratrol, quercetin, coumarin, calcitriol, capsaicin, fisetin, evodiamine, boswellic acid, betulinic acid, deoxyelephantopin), plant (*Rosmarinus officinalis L.*, *Aloe vera, Olea europaea*), functional foods (pomegranate, mango, amla, garlic, ginger, broccoli, mushroom, green tea, coffee, honey), textile and marine product based on their mechanism of action.

Keywords: Cancer, Anticancer agent, Phytochemical, Plant, Functional food, Textile, Marine product

Introduction:

A severe metabolic syndrome is the leading cause of uncontrolled proliferation and adaptation of a normal cell, called cancer. It is the foremost cause of mortality and morbidity; after cardiovascular disease it is in the second risk factor to death in the world. The number of cases was assessed 9.6 million deaths, or one in six deaths, in 2018 and the cases are repeatedly growing approximated to be 21 million by 2030 [1-5]. Some of the cancers that most often affect men are lung, prostate, colorectal, stomach and liver cancer, while in case of women that are breast, colorectal, lung, cervical and thyroid cancer. Among these, specifically, lung cancer in men and breast cancer in women is reported to be the most common [5,6]. A lot of external and internal factors such as radiation, smoking, pollutants, food, chemicals, certain metals, infectious agents, genetic mutations, hormones and immune conditions can generate this severe disease [7]. Cancer cells have potential of invasion and angiogenesis and also to overcome the apoptosis [8]. Cancer stem cells (CSCs), a small subset of tumor are capable for inducing tumorigenesis. These CSCs exhibit high resistance to the therapy and even grow after treatment [9].

Chemotherapy, radiotherapy, immunotherapy cancer vaccinations, photodynamic therapy, stem cell transformation and chemically derived epigenetic drugs are the gold standard approaches for the treatment of cancer worldwide [10, 11]. But, patients associated with these types of treatment undergo several side effects such as alopecia, nausea, vomiting, limited bioavailability, diarrhoea, constipation, anemia, a weakened immune system, neutropenia, weakness etc [12,13].

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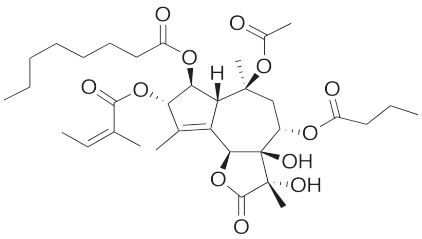
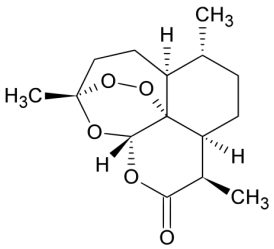
Due to these side effects of standard therapies which are in practice for the treatment of various cancers, an alternative green approaches are the centre of interest nowadays for the prevention and treatment of cancer by utilizing several natural products from plant source, food and marine source [14-16]. Sesquiterene lactone triterpenoid, polyphenol, flavonoid, bioflavonoid, coumarin, indole, quinolone and many more obtained from natural sources are the most important nucleus for the prevention and treatment of cancer. A lot of natural therapeutic compounds bearing these nucleuses have been examined in searching of novel anticancer agents with less or no toxicity and few of them are in clinical trial also.

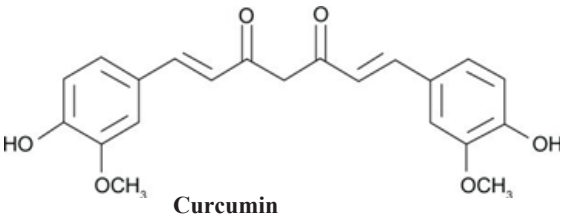
Phytochemicals that fight cancer:



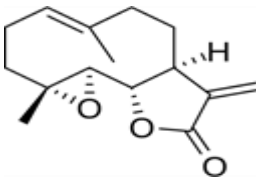
Thapsigargin



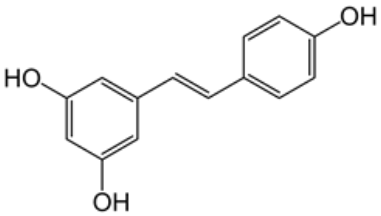
Artemisinin



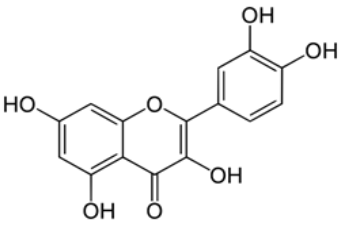
Curcumin



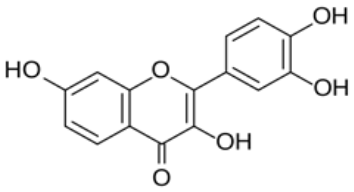
Parthenolide



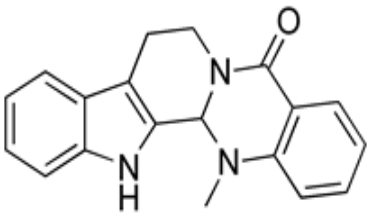
Resveratrol



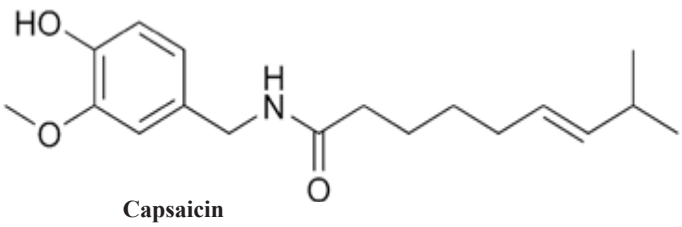
Quercetin



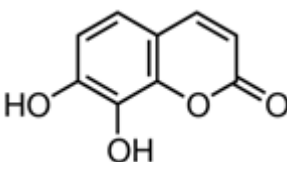
Fisetin



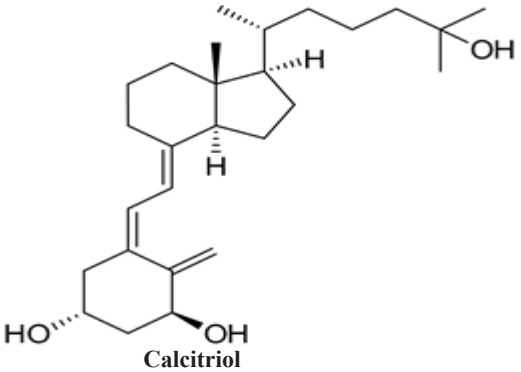
Evodiamine



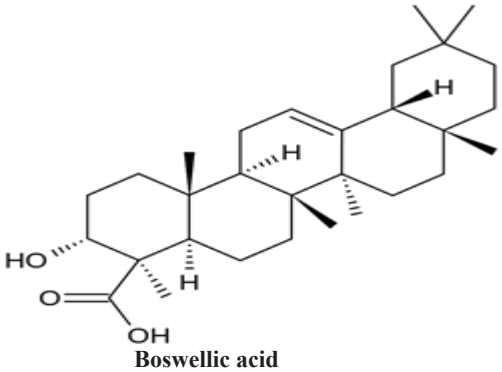
Capsaicin



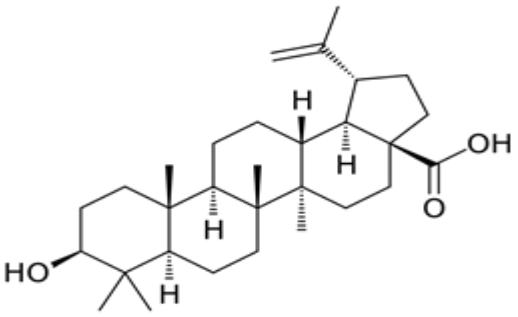
Daphnetin



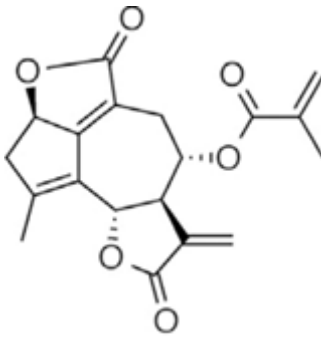
Calcitriol



Boswellic acid



Betulinic acid



Deoxyelephantopin

Fig.1: Phytochemicals used in cancer therapy

(i) Artemisinin: Artemisinin, an antimalarial drug, wined Nobel Prize for its anticancer activity in 2015. It is a sesquiterpene lactone derived from a Chinese herb, sweet wormwood (*Artemisia annua* L. belonging to the family Asteraceae). Artemisinin and its semisynthetic derivatives including artesunate, artemether and dihydroartemisinin exihibit highly selective and potent cytotoxic activity against wide range of cancer cell type both *in-vitro* and *in-vivo* (17). Artesunate **(**Succinyl dihydroartemisinin**)** shown great restraining response against leukemia, colon, melanoma, breast, ovarian, prostate, central nervous system, and renal cancer cells and Dihydroartemisinin has also satisfactory antineoplastic activity against pancreatic, leukemic, osteosarcoma, and lung cancer cells according to National Cancer Institute (18). Artemisinin induced apoptosis through the mitochondrial pathway, with intracellular heme (Fe^{2+} protoporphyrin IX) as the molecular target and prohibited the DU 145 and PC-3 human prostate carcinoma cell growth (19,20). The structure-activity relationship (SAR) study indicated that the endoperoxide group of Artemisinin is important for its cytotoxic action (21). Recently, Artesunate has entered in phase II trials against non-small cell lung cancer, colorectal cancer, metastatic uveal melanoma, and laryngeal squamous cell carcinoma (22)

(ii) Parthenolide: The plant-derived multifunctional sesquiterpene lactone, parthenolide is the active component of *Tanacetum parthenium* L. belonging to the family Asteraceae, repressed proliferation and eliminated several cancer cells by inducing apoptosis (23). The underlying molecular mechanisms were proposed for the anti-cytotoxic effect of parthenolide including suppression of NFκB activation, inhibition of STAT3, reduction of MAPK activity and sustained activation of JNK, activation of p53, inhibition of nucleic acid synthesis, induction of oxidative stress, induction of mitochondrial dysfunction etc (24). Proliferation, invasion and tumor induced angiogenesis of glioblastoma cells repressed by this natural molecule. Parthenolide reduced Akt phosphorylation and mitochondrial apoptotic signaling by inhibiting NF-κB

(25). Some parthenolide analogues with high cytotoxicity against T cell leukemia, mantle cell lymphoma, adenocarcinoma cells,and neuroblastoma cells were reported (26). Dimethylamino-parthenolide was used in phase I trial for the treatment of leukemia and other blood cancers (27)

(iii) Thapsigargin: The plant *Thapsia garganica* L. is the source of thapsigargin, a sesquiterpene lactone. Thapsigargin and its analogues were exhibited anticancer activity by inhibiting sarcoplasmic reticulum Ca(2+)-ATPase via of apoptotic pathways (28). Mipsagargin [8-O-(12-dodecanyl)-8-O-debutanoylthapsigargin], a prodrug of thapsigargin has completed phase II clinical trial against the treatment of liver cancer and glioblastoma or, brain tumors (27,29).

(iv) Curcumin: A nutritious and medicative agent, curcumin (diferuloylmethane), a polyphenol, derived from the rhizomes of *Curcuma longa* Linn. belonging to the family Zingiberaceae, which frequently known as turmeric. Curcumin possessed tremendous anti-tumorigenic effect and inhibited the cancer cell migration and invasion by manipulating several signaling pathways. During epigenetic modifications curcumin inhibited the acetylation of histone proteins and DNA methylation process by altering DNA methyltransferase activity (30). At 10μM dose curcumin supressed the migration and invasion of 801D lung cancer cells, this was induced by epidermal growth factor. The inhibition of Rac1/PAK1 signaling pathway and the reduced MMP-2 (matrix metalloproteinase-2) and MMP-9 (matrix metalloproteinase-9) expression was responsible for anti-metastatic effect on these cells (32). Curcumin shown the anti-vasculogenic mimicry ability in liver cancer cell by down-regulating the Akt (or Protein Kinase B) and STAT3 (Signal transducer and activator of transcription-3) pathways (33). It played important role to suppress several cancer cells such as colorectal, breast, prostate, bone, nasopharyngeal, brain and nervous system. Curcumin manifested its numerous anti-cancer properties *in-vitro*, *ex-vivo* and *in-vivo* as well as in clinical trials by regulating a variety of biological pathways involved in tumor invasion, metastasis and angiogenesis.

(v) Resveratrol: A natural polyphenolic phyloalexin, resveratrol (3,5,4'-trihydroxy-trans-stilbene) particularly found in the skin or peel of grapes (*Vitis vinifera*), peanuts, berries and red wine. In a study, resveratrol was extracted from the roots of *Polygonum cuspidatum* and shown its activity as a chemopreventive agent (33). It was found that resveratrol prevent the conversion of procarcinogen to carcinogen (34). Via different signaling molecules resveratrol and its two derivatives (acetyl-resveratrol and polydatin) shown the antigrowth activity against 3D cell aggregates of the EGF-R/Her-2-positive and -negative ovarian cancer cell lines (35). Resveratrol inhibited tumorogenesis by hindering KRAS (a proto-oncogene) expression in a KRAS-activated sporadic colorectal cancer mouse model (36). It also serves its chemopreventive action in A549 lung cancer cell by prohibiting the induction of cell attachment, invasion and migration, mediated by TGF-β1 (37). Resveratrol and quercetin (RQ) in combination (1:1 ratio) decreased the generation of reactive oxygen species (ROS) induced caspase-3-cleavage (2-fold), increased PARP cleavage, reduced the expression of Sp1, Sp3, and Sp4 mRNA in HT-29 colon cancer cells. RQ obstructed growth of Human leukemia cells (38).

(vi) Quercetin: The most abundant bioflavonoids, quercetin (3,3′,4′,5,7- pentahydroxy-flavone), present in various nutritive vegetables, fruits and beverages like broccoli, red onions (*Allium cepa*), citrus, peppers, kale, spinach, berries, apples, grapes, black tea, green tea, red wine. Quercetin inhibited neoplastic cell growth by decreasing the oncogene expression, induction of malignant cells apoptosis and restraining angiogenesis (39,40). Quercetin suppressed the maturation of HepG2 cells and generated apoptosis by taking part in cyclin D1 regulation (41). It has been reported that quercetin inhibitd the cytochrome P450, which can activate numerous suspected human carcinogens (42). It shown remarkable inhibitory activities on the growth of cancerous cells in breast, hepatic, ovarian, gastric, colorectal, endometrial cancers and in leukemia (43).

(vii) Coumarin: Coumarins belonging to benzo-α-pyrone chemical class and found in higher plants, essential oils (e.g. cinnamon bark oil, cassia leaf oil, lavender oil etc) possesses anti-tumor activity (44). 5-geranyloxy-7-methoxycoumarin derived from *Citrus aurantifolia* L. (*Rutaceae*) induced apoptosis via stimulation of tumor repressor gene p53,

caspase 8/3 and prohibition of p38 MAPK phosphorylation for blocking the proliferation of SW-480 cell (human colon cancer cell) (45). Osthole, a coumarin derivative, isolated from the fruit of *Cnidium monieri* (*L) Cuss* and *Angelica pubescens* shown its anticancer activity by inhibiting Akt/NF-κ B signaling pathway, which promotes G2/M arrest and apoptosis in HCC tumor cells (46). Daphnetin, a coumarin derivative, exhibited anti-neoplastic activity by depressing the Akt/ NF-κ B signaling pathway leads to induction of apoptosis to inhibit the proliferation of A549 human lung adenocarcinoma cells (47).

(viii) Calcitriol: The biologically active metabolite of vitamin-D, commonly named as calcitriol, a steroid like molecule, found in oily fish and egg yolk, possessed various biological phenomenon like induction of apoptosis, modulation of the immune system, inhibition of inflammation and prevention of cell proliferation by binding to the nuclear receptor and modulating gene expression (48,49). The elementary non-genomic mechanism of action of calcitriol include activation of signalling systems such as the phospholipase C, the phosphatidylinositol-3 kinase (PI3K) and the mitogen-activated protein kinases (MAPK) pathways, rapid generation of second messenger molecules such as Ca^{2+} and cyclic AMP and modulating Ca^{2+} channels are responsible for giving the anticancer activity (50). Inecalcitol is an epi-analogue of calcitriol, shown to be more potent than calcitriol in reducing tumor cell growth and inducing apoptosis in different models of breast cancer, prostate cancer and squamous cell cancer. In the squamous cancer model, inecalcitol exhibited effect via caspase 3 and 8/10-induced apoptosis (51,52).

(ix) Capsaicin: Capsaicin is the major spicy component in chili peppers that are consumed as a spice. Capsaicin (*trans*-8-methyl-*N*-vanillyl-6-nonenamide) is a homovanillic acid derivative as well as a alkaloid, exihibited anticancer, analgesic, antioxidant, anti-inflammatory, anti-obesity activities widely (53). Via down-regulation of the phosphoinositide 3-kinase (PI3K) signaling pathway along with reduction in RAS related c3 botulinum toxin substrate 1 (RAC1), capsaicin significantly suppressed the migration of melanoma cells (54). In prostatic cancer, capsaicin inhibited NF*κ*B signaling route as a radio-sensitizing agent and promoted the secretion of TNF-*α*-stimulated IL-6 in PC-3 cells and via TRPV1, ERK, PKC-a, PI3K/Akt activation it induced the expression of IL-6 (55,56). It is active over several types of cancer such as lung, colorectal and gastric cancer.

(x) Fisetin: A naturally occurring flavonoid, fisetin (3,7,3′,4′-tetrahydroxyflavone) is a polyphenol and abundantly found in fruits and vegetables such as apple, strawberry, grape, kiwi, cucumber and onion that has an interesting chemopreventive property (57). Recently sereval clinical and preclinical studies shown that fisetin inhibited cell proliferation, migration and invasion, and induced apoptosis in various cancers such as colon cancer, lung cancer, nasopharyngeal carcinoma, prostate cancer, bladder cancer and cervical carcinoma. It also inhibited micro-ophthalmia associated transcription factor (MITF) in melanoma cells. Via modulation of the MAPK and NF-κB pathways, fisetin restrained invasion of melanoma cells (58). Fisetin induced apoptosis in HCT-116 cancer cells via downregulation of HSP70/BAG3 followed by significant reduction of the amounts of Bcl-2, Bcl-xL and Mcl-1 proteins (59).

(xi) Evodiamine: A natural quinolone alkaloid, evodiamine is the active constituent of the fruit of *Evodia rutaecarpa* Bentham, a herb belonging to the family Rutaceae, traditionally used in China. This bioactive compound exhibited good anti-tumor property (60). Evodiamine showed the most tenacious cytotoxic effect againest human hepatoblastoma and colon cancer cell lines. Recently, it played a great role in prevention of human papillary thyroid cancer, breast cancer and leukemia (61,62). It has been reported that evodiamine decreased thyroid tumorigenesis via suppressing PI3K/AKT (Phosphoinositide-3-kinase/Protein kinase B) pathway (63). Evodiamine decreased metastatic growth in MDA-MB-231 (triple negative breast cancer cell line) breast cancer cell (64). By suppression of JAK2/ STAT3 pathway evodiamine reduced the MMP3's (matrix metalloproteinase-3) expression in HCT-116 human colorectal cells (65).

(xii) Boswellic acid: A pentacyclic triterpenoid, boswellic acid is the chief constituents of *Boswellia serrata* belonging to the family Burseraceae, shown its activity against cancer cells via numerous mechanisms that include apoptosis and cell cycle arrest. By inhibition of PI3K/AKT signalling pathway and G2/M cell cycle arrest in a concentration-dependent manner boswellic acid exerted its cytotoxic activity in HCT-116 colon cancer cells (66). It also reported that boswellic acid nanoparticles formulation caused apoptosis and DNA fragmentation and given promising anti-cancer effect (67). Via suppression of cyclin D1 cdk4 expression and activation of Akt and Erkl1/2 boswellic acid shown its anti-proliferative and pro-apoptotic activities against pancreatic tumours (68).

(xiii) Betulinic acid: A pentacyclic lupane-type triterpenoid, betulinic acid, occurred in animal, fungi and plant. Betulinic acid and its derivatives shown antiproliferative activity by inducing apoptosis via affecting the mitochondrial membrane permeability and enhancing the release of cytochrome c [69,70]. As seen from various investigations that the treatment of 5-flurouracil (5-FU) with BA induced apoptosis in ovariancancer cells OVACAR 432 by mitochondrial pathway [71]. Betulinic acid arrested tumour growth and decreased the tumour size by reducing the expression of mRNA of Sp transcription factors in nude mice with xenografted MDA-MB-231 brest cancer cells [72]. In another study, it was reported that BA in combination with vincristine suppressed lung metastasis of murine melanoma B16F10 cells in C57BL/6 mice (73)

(xiv) Deoxyelephantopin: One of the major sesquiterpene lactone of *Elephantopus scaber*, deoxyelephantopin (DET), exhibted cytotoxic activity against varuous cancer cell lines and malignant tumors in different *in vitro* and *in vivo* studies. It also demondtrated cytotoxicity against human breast cancer cell lines (74). In nasopharyngeal carcinoma cells, DET triggred Akt and Mitogen-activated protein kinase (MAPK) signalling pathways (75). Via inducing apoptosis through multiple signaling pathways, DET inhibited HCT116 human colorectal carcinoma cell growth (76).

Plants that fight cancer

(i) *Rosmarinus officinalis* L.: It has been observed that *Rosmarinus officinalis* L. (rosemary) extract and its polyphenols carnosic acid and rosmarinic acid found to have potent anticancer effects (77,78). Via upregulation of PARP cleavage and modulation of TYMS and TK1, rosemary extract exhibited its immense activity against colon cancer by decreasing the cell proliferation and inducing apoptosis. Rosemary extract has shown a synergistic effect with 5-fluorouracil, a chemotherapeutic drug (79). It has been reported that rosemary extract dissolved in olive oil interestingly reduced the tumor size in HCT116 colon cancer in mice through increasing the Nrf2 and sestrin-2 expression (80).

(ii) *Aloe vera:* *Aloe vera* has been used as a traditional herbal remedies for its curative properties for various biological activities including anti-tumor, purgative, anti-microbial, anti-inflammatory and anti-diabetic activities (81). Aloesin, an active constituent of aloe caused downregulation of cyclin A, CDK2 and cyclin D1 and suppression of MAPK signaling pathway, hence induced apoptosis in ovarian cancer (82). Another bioactive component of aloe vera, aloe-emodin, inhibited proliferation of human monoblastic leukemia (U937) cells through increased ROS and NO (Nitric oxide) production 8(3). It was found that aloe vera gives synergistic effect in combination with chemopreventive drug named cisplastin by inducing apoptosis in human breast and cervical cancer cells (84).

(iii) *Olea europaea*: Extra virgin olive oil from *Olea europaea* was found to have anticancer effect in human colon cancer by inducing apoptosis through metastasis and cell death (85). An olive flavanoid named apigenin prohibited the proliferation by downregulation of GLUT1 expression in prostate cancer (86). Several evidence has demonstrated that the bioactive constituent of olive i.e. oleuropein suppressed the oestrogen activated ERK1/2 signaling pathway in MCF-7 breast cancer cell lines and restrained cell proliferation via modulation of NF-□B (87). Another olive component, luteolin was found to have anti tumor activity in prostate cancer of mice (88).

Functional foods that fight cancer:

(i) Pomegranate (Punica granatum): A nutritious fruit, pomegranate belonging to the family Lythraceae, is grown in various parts of the world, including Iran, India and America, was effective in treatment of cancer, diabetes,


Rosmarinus officinalis L.


Aloe vera


Olea europaea


Elephantopus scaber


Artemisia annua L.


Boswellia serrata


Tanacetum parthenium L.


Thapsia garganica L.


Vitis vinifera


Evodia rutaecarp


Allium cepa


Curcuma longa L.


Punica granatum


Mangifera indica


Allium sativum


Zingiber officinale


Phyllanthus emblica


Brassica oleracea


Pleurotus ostreatus


Camellia sinensis

Fig. 2: Plants and plant sources with anticancer activity

ulcer and anemia. Pomegranate potentially shown cytotoxic activity by promoting apoptosis in breast cancer cells (89). Several studies reported that pomegranate fruit extract inhibited proliferation via reduction of STAT3 phosphorylation and downstream regulation of NF□B signaling pathway (90,91). In both, A549 and H1299 lung cancer cell lines, punicalagin, an active constituent of pomegranate peel, reduced DNA adduct formation hence proliferation prohibited (92).

(ii) Mango (*Mangifera indica*)**:** The most exotic and juicy fruit mango abundantly found in worldwide contains bioactive compound mangiferin which shown its promising activity against cancer (93). Recently, it was found that mango kernel extract accelerated the ROS production hence promoted apoptosis and cell growth inhibition via modulation of p53 tumor suppressor protein in MCF-7 breast cancer cell lines (94). It also reported that mangiferin, the chief constituent of mango, inhibited tumor necrosis factor (TNF) and shown its cytotoxic effect in cervical cancer. Mango exhibited synergistic effect with the chemopreventive drugs such as paclitaxel and cisplastin (95).

(iii) Amla (*Phyllanthus emblica*)**:** Amla, a traditionally used Ayurvedic wonder berry, reported to possess various pharmacologicl activities such as antipyretic, analgesic, gastroprotective, antianemia, cardioprotective, hepatoprotective, neuroprotective and specifically acted as radiomodulator, chemomodulator and immunomodulator that are advantageous in the prevention of cancer (96). Several studies found the potent anti-tumorigenic effect of amla extracts against numerous cancer both *in-vitro* and *in-vivo* (97). Recently, flowcytometric results demonstrated the underlaying mechanism of amla fruit extract, which could possibly arrest the cell cycle at the G0/G1, S or G2/M phase and promoted cell apoptosis in human colorectal cancer (HCT-116) and neuroblastoma cell lines (98). Via downregulation of HPV (human papillomavirus) gene expression and repression of AP-1(activator protein-1), amla fruit extract strongly exhibited the anti cancer activity over cervical cancer cells (99).

(iv) Garlic (*Allium sativum*)**:** For thousands of years garlic used as spice and has been shown its medicative properties and used globally in various kinds of diseases together with cancer as a natural remedy, the beneficial effects include antifungal, antimicrobial, anti-diabetic, anti-thrombic, immunomodulator (100). Garlic contains many bioactive compounds such as allicin, alliin, ajoene, diallyldisulfide, diallyltrisulfide. Among wich allicin exhibited chemopreventive effect to gastric cancer by decreasing the growth of cancer cells at G2/M phase via the caspase-dependent/-independent pathway (101). Alliin was found to suppress VEGF (vascular endothelial growth factor) and fibroblast growth factor 2- (FGF-2) induced tube formation and angiogenesis in HUVEC (human umbilical vein endothelial cell) (102). Diallyltrisulphide, the most bioactive constituent of garlic inhibited the cell growth via increasing the levels of intracellular ROS (Reactive Oxygen Species) and damaging the DNA and also induced endoplasmic reticulum stress as well as mitochondria-mediated apoptosis in human melanoma A375 cells and basal cell carcinoma (103). Via stimulation of peroxide production, activation of caspase-3 and caspase-8, ajoene (secondary metabolite of garlic) induced apoptosis in human leukemic cells (104).

(v) Ginger (*Zingiber officinale*)**:** The major constituents of ginger, a spice, are gingerols, zingerones, shogaols, and erumbone exerted promising effects in several cancer cell lines (105). By suppression of cyclin A, cyclin-dependent kinase (Cdk) and NF-□- regulated gene expression, via affecting the extracellular signal-regulated kinases (ERK) pathway, 6-gingerol regulated tight junction-related proteins and inhibited invasion and metastasis of pancreatic cancer cells (PANC-1 cells) (106). Weng et al showed that by inhibition of MMP-2/-9 and uPA and suppression of MAPK and PI3k/Akt pathways, along with downregulation of NF-□B and STAT3 activity, 6-shogaol and 6-gingerol effectively inhibited invasion and metastasis of hepatocellular carcinoma (107). The underlaying mechanism of these two bioactive molecules of ginger i.e. 6-Gingerol and 6-shogaol are modulation of NF-□B, STAT3, MAPK, cyclin A, Cdk and caspase-3/7, PI3k/Akt Ca2+ signals, COX-2, cyclin D1, survivin, Bcl-2 and MMP-9.

(vi) Broccoli (*Brassica oleracea*)**:** Broccoli is one of the healthy edible plants in the family of Brassicas, containing the principal compound sulforaphane, an isothiocyanate, found to have promising effect in pancreatic cancer and breast cancer (108-110). In case of prostate cellular models, sulphorphane induced the acetylation of histone H3 protein at the p21 promoter, which showed reduction in HDAC (Histone deacetylase) protein activity to promote the acetylation of alpha-

tubulin for attaining the neoplastic cell death (111). Several studies shown that Broccoli sprouts became much more beneficial for anti proliferative activity (112).

(vii) Mushroom: Edible mushrooms have high nutritional value and various therapeutic effects including anti-diabetic, anti-cancer, immunomodulatory because of their high contents of carbohydrates, protein, dietary fiber, vitamins and minerals (113). Cytotoxic bioassay revealed the immense activity of *Pleurotus ostreatus*, known as oyster mushroom, over several cancers (114). It was reported that via suppression of MMP-2 and MMP-9 expression *P. ostreatus* polysaccharide extract prohibited the invasion of colon cancer cell lines (Caco-2 cell), through the basement membrane (115). Another bioactive component, carboxymethylated P-glucan, from the mushroom *Pleurotus tuberregium,* reduced the proliferation of MCF-7 breast cancer cells via G1 phase cell cycle arrest in a dose-response manner (116). Pan, et al. in 2015 did research on mushroom *Amauroderma rude*, which on treatment with mice model reduced tumor growth through the modulation of immune system (117). *Antrodia cinnamomea*, a treasured mushroom, altered the PI3K/AKT/mTOR signaling pathway and promoted apoptosis in T47D breast cancer cell lines (1118).

(viii) Green tea (*Camellia sinensis*)**:** Green tea is one of the healthiest beverages on the planet. Epigallocatechin-3-gallate (EGCG) is the most abundant catechin in green tea and potentially active against tumorigenesis (119). It blocked NF□B signaling pathway via modulatin of interleukin in gastric adenocarcinoma cells for prohibition of metastasis and induction of apoptosis (120). Several studies shown that EGCG reduced proliferation and angiogenesis in colon cancer cell via regulation of different signaling pathway such as AKT, p38 and ERK1/2 (121).

(ix) Coffee: The most desired brewed drink worldwide after water is coffee, a mixture of bioactive components, exhibited potent chemopreventive activity (122). Very recently, from the Moli-sani cohort and cellular models, it was found that caffeine, the chief constituent of coffee, exhibited protective response over prostate cancer. In a time and dose dependent manner caffeine mediated suppression of cell proliferation by triggering the deterioration of G1 to S cell cycle progression in human PC-3 and DU145 prostate cancer cell lines (123). Via altering the ER (**Estrogen receptor)** and IGFIR (Insulin-like growth factor-I receptor) levels caffeic acid, another bioactive component of coffee, suppressed the cell cycle growth through inducing apoptosis in breast cancer cells (124).

(x) Honey: In addition to important role of natural honey in the traditional medicinal system, during the past few decades, it was subjected to laboratory and clinical investigations by several research groups and it has taken a place in modern medicine for its immense activity against several diseases such as leukemia, colorectal cancer, breast cancer and also in inflammation, cough, cold etc. Polyphenol in honey possesses tremendous anti-tumor activity in various clinical trials (125). Via induction of apoptosisthrough downregulation of VEGF (Vascular endothelial growth factor) expression tualang honey suppressed 7,12-dimethylbenz(α) anthracene (DMBA)-induced breast cancer in rats (126). By modulation of gene expression associated with Ras/ERK and PI3K/AKT pathways, combination of gelam honey and ginger shown promising response over tumor invasion in HT29 colon cancer cells (127).

Marine products that fight cancer:

From the past few decades oceanic resources like sponge, bacteria, seaweed, fungi and others have possessed a diverse range of biological activities and have attracted the attention of those, who has been trying to develop new lead compounds, specifically anticancer drugs (128). Fucoidan, a natural component from brown seaweed, suppressed the cycllin D1, cyclin D2 and Cyclin-dependent kinase 4 (CDK4) in carcinogenic cell and fucoidan from Fucus vesiculosus arrested cell cycle in G0/G1 phase via repression of CDK2 and CDK4 expression in human bladder cancer 5637 cells (129-131). Very recently, it was found that Lipastrotethya sp., a marine sponge, extract (LSSE) has noticeable antiproliferative effect on wild-type p53 (WT) and p53 knockout (KO) HCT116 cells; where, cell viability and cell death was more in HCT116 p53 KO cells than the HCT116 WT cells. In HCT116 WT cells, LSSE induced apoptosis via modulation of p53 and in HCT116 p53 KO cells, LSSE induced autophagy via decreasig mTOR and Bcl-2 (13). A bis-indole, fascaplysin, was isolated from a marine sponge and it demonstrated anti-neoplastic response via downstream regulation of CDK4 signaling pathway and modulation of phosphoproteins in human lung cancer cell lines (A549) (133).

Textiles in cancer treatment:

Cancer patients with surgery, chemotherapy, and radiation therapy, new medical textile

materials are developed. The new generation of applicational products (textiles) is intended for targeted local delivery of drugs to the lesion site (e.g., to tumour tissues) in a strictly defined effective concentration, specific for each of the drugs, whose accumulation in intact tissues and organs is minimized. The technology of textile printing is used for preparation of two types of medical materials: textile-based applications with hydrogel composition and hydrogel biopolymer based materials comprised of polymer thickeners with a drug impregnated thereon, intended for introduction into cavities: proctologic, gynecologic, etc. The drug is introduced into the thickened composition by a procedure similar to that used in printing textile (134). For creation of medical materials destined to improve the effectiveness of radiation therapy, were used 5-fluorouracil, a cytostatic agent possessing radiomodifying properties, and metronidazole, a radiosensitizing agent, for prevention and treatment of radioreactions. Molybdenum trioxide, which has anticancer effect, is used as a flame retardant in textiles, (135). The use of textiles for sun protection has been underestimated from long time. It has been found that one-third of commercial summer clothing items provide a UV protection factor (UPF) less than 15. Various textile parameters have an influence on the UPF of a finished garment. Important parameters are the fabric porosity, type, color, weight and thickness (136).

Scottish researchers developed headwear that uses smart textiles for women with cancer related hair loss. Micro-encapsulated textiles, that produce extra comforts and aroma-therapeutic effects to cancer patients, are now being used in a luxury handmade headwear range (137). Silver-coated conductive yarns were fabricated into hollow fiber-based non-woven fabrics which were used in drug delivery to the breast cancer. These non-woven fabrics are useful in designing a specially made textile wearable for breast cancer (138). The anticancer and cytotoxic activities of poly(propylenimine) dendrimers was observed against HeLa and Lep-3 human tumor cell lines. These dendrimers deposited cotton fabrics used in textile industry. (139). Sericin, a silk protein, has anticancer property. This property makes sericin-treated fabrics suitable for use as medical textiles (140).

Conclusion and future prospective:

Attempt has been made through this comprehensive review to focus the recent progresses and milestones accomplished in cancer therapies using various natural compounds from plant source, functional food and marine source with their mechanism of action on nuclear and cellular factors**.** Natural anticancer agents are the main focus due to their low cost and reliability over adverse effect resulted from existing marketed drugs. Based on the literature survey, we have concluded that natural therapeutic agents serve as promising and effective research area with bright future. It is expected those in coming years, much more novel entities from nature will enter into the commercial drug market as anticancer agent. There are still many of these entities under clinical trials. Moreover, huge research work should be execute on these novel entities to assess their toxicological and particular genotoxic profile against a vast range of cancer and finally to bring them in the market as anti-cancer drug either alone or in combination.

Conflict of interest

The authors declare no conflict of interest.

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