Research Article

Oxidative Stress and Carcinogenesis: Prevention by Antioxidative Phytochemicals Acting on Different Molecular Targets

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ABSTRACT

Overproduction of reactive oxygen species (ROS) through endogenous or exogenous insults can cause oxidative stress. In carcinogenesis also, the unregulated or prolonged production of reactive species damages critical biomolecules and eventually results in several biological effects ranging from alterations in signal transduction and gene expression to mitogenesis, transformation, mutagenesis and cell death. ROS including hydroxyl radicals, superoxide anion, hydrogen peroxide and nitric oxide are very transient species due to their high chemical reactivity that leads to lipid peroxidation and oxidation of DNA and proteins which have been implicated in the etiology of a wide array of human diseases, including cancer. Oxidative stress can be ameliorated by the consumption of antioxidants containing fruits and vegetables which prevent chronic diseases including cancer by eliminating ROS. Both positive and negative correlations are seen between antioxidant and anticancer activity of these antioxidant phytochemicals. Many *in vitro* and *in vivo* studies of whole plant extracts and bioactive components have also proved their anti oxidative and anticancer effects on cancer cell lines and animal models. In particular, signal transduction pathways, including NF-κB, COX-2, cyclin dependent kinases, Bcl_2 etc. are known to be activated by ROS, and they lead to the transcription of genes involved in cell growth regulatory pathways which in turn cause tumorigenesis. In this review we have primarily focused on the role of phytochemicals in the inhibition of the oxidative stress for the prevention of cancer by acting on different molecular targets.

Keywords: Antioxidant phytochemicals, Cancer, Oxidative stress.

INTRODUCTION

Cells are constantly exposed to a variety of oxidizing agents, some of which are necessary for life. Metabolic activity within the cells may produce these oxidants and their overproduction can cause an imbalance, leading to oxidative stress and the possible damage of DNA, producing mutations that initiate tumor and sustain progression.[1-2] Antioxidants have the property of neutralizing free radicals by donating or accepting electron(s).There are many antioxidants such as vitamin C and vitamin E which directly react with or neutralize hydroxyl (·OH), alkoxyl (RO·) and lipid peroxyl (ROO·) radicals and form H_2O, alcohol and lipid hydroperoxides, respectively. In food industry there are some synthetic antioxidants such as tert-butylhydroxyltoluene (BHT), tert-butylhydroxyanisole (BHA) and tert-butyl hydroquinone (BHQ) which retard lipid oxidation. Many models have been established to study the mechanisms of action of antioxidants as well as to identify the new antioxidants; especially from natural substances.[3-5] The present review is an attempt to highlight the importance of different phytochemicals that have been known to regulate carcinogenesis through varied molecular targets.

OUTLINE OF OXIDATIVE STRESS AND ANTIOXIDANTS

Reactive oxygen species (ROS) are produced by both endogenous and exogenous sources and antioxidants are the substances which eliminate the ROS or oxidants by different protective mechanisms.[6] Natural antioxidants are primarily present in fruits and vegetables which help in eliminating these ROS. Oxidative stress can be prevented by the consumption of antioxidants present in fruits and vegetables. Experimental studies support the role of reactive oxygen species in cancer, at least in part and the dietary antioxidants such as vitamin E, vitamin C, selenium, carotene, and other phytochemicals, as well as endogenous antioxidants including superoxide dismutase (SOD), catalase (CAT) and glutathione (GSH), neutralize or trap reactive oxygen species.[7-8]

Dietary antioxidants have the ability to induce programmed cell death (apoptosis), thus act as adjuvant in cancer therapy.[9] Daidzein, one of the well-known isoflavonoids, has been evaluated on its chemo-preventive action, by enhancing antioxidant enzymes against breast cancers in prepubertal rats.[10] Anticancer therapeutic role of polyphenolic tea constituents in hepatocarcinoma cells (HCC) rests on their potent antioxidant and inflammatory properties as well as on their ability to modulate a multitude of signaling mechanisms and enzymatic pathways which are implicated in the process of hepatocarcinogenesis.[11] Some *in vitro* studies showed that growth of various cell lines including those of the stomach, prostate, colon and breast were strongly inhibited by raspberry, blueberry, blackberry and cranberry extracts.[12-14] Resveratrol, a type of polyphenol found in the skin of grapes and in wine, is currently being widely studied as a cancer preventive agent. In fact, it has been found to inhibit human cancer cell growth in the breast, blood and lung.[15]

Though fruits and vegetables are recommended for the prevention of cancer, mechanism (at molecular level) of their bioactive components is not well understood yet. There are many bioactive components of fruits and vegetables that commonly are known for the prevention of cancer (Figure 1). Carcinogens are believed to regulate anti-apoptotic proteins (e.g., Akt, Bcl-2, Bcl-XL), transcription factors (e.g., NF-kB, AP-1), cell cycle proteins (e.g., cyclins, cyclin-dependent kinases), pro-apoptotic proteins (e.g., caspases), protein kinases (e.g., EGFR), COX-2, and growth factor signalling pathways. Daidzein and biochanin A show significant enhancement of mammary gland differentiation and caspase 3 and decrease of ER-α expression.[16-17] Glyceollins synergistically activates the Nrf2 signaling pathway and subsequently the expression of phase 2 antioxidant enzymes in the presence of buthionine sulfoximine (BSO), suggesting that BSO induced oxidative stress and glyceollins regulate the expression of phase 2 antioxidant enzymes through different mechanisms.[18]

Role of Oxidative Stress in Carcinogenesis

Oxidative stress and reactive oxygen species

Approximately 35% of humans have cancer by age 85 and it has been hypothesized that this is largely due to a lifetime attack by reactive species (RS) generated endogenously and sometimes in addition by certain exogenous carcinogens, including cigarette smoke.[20] ROS including $O_2^{\bullet-}$, H_2O_2, $^{\bullet}OH$ and O_2 are totally harmless molecules as each one has two unpaired electrons with parallel spin which makes it paramagnetic and, hence unlikely to participate in reactions with organic molecules unless it is activated. Excess of ROS is inactivated by forming biologically inert products by cellular antioxidant enzymes, such as superoxide dismutase, catalases, glutathione peroxidase (GPx) and glutathione-S-transferase.[21-23]

Role of high level of reactive oxygen species in cancer

ROS damage critical biomolecules and eventually result in several biological effects ranging from alterations in signal transduction and gene expression to mitogenesis, mutagenesis and cell death.[24-25] ROS normally damage DNA and thus have mutagenic activity that promotes carcinoma initiation and progression. However, low concentrations of superoxide and hydrogen peroxide actually stimulate proliferation and enhance survival in a wide variety of cell types.[26-28]

Role of phytochemicals in oxidative stress

Recently, natural foods and food-derived components such as antioxidative vitamins and phenolic phytochemicals, have received a great deal of attention because they are believed to be safe and some of these are known to function as chemopreventive agents against oxidative damage. Whereas polyphenolics contribute significantly to the total antioxidant capacity of fruits, cellular system may be protected from oxidative stress through phenolics and carotenoids and also may lower the risk of chronic diseases such as cancer.[30]

A previous report suggests that it may not be only a single bioactive phytochemical, but the whole mixture exert the anti-carcinogenic activity.[31] Diallyltrisulfide (DATS) selectively inhibits growth of human melanoma A375 cells and basal cell carcinoma (BCC) cells by inducing G2/M arrest, endoplasmic reticulum (ER) stress, and mitochondria-mediated apoptosis, including the caspase-dependent and independent pathways.[32]Green tea extract reduces oxidative stress produced by neutrophils from cancer patients.[33]*Centellaasiatica* extract may ameliorate H_2O_2-induced oxidative stress by decreasing lipid peroxidation via alteration of the antioxidant defence system of the rats.[34] Garlic extract induced cytotoxicity and apoptosis in HL-60 cells involve phosphatidyl serine externalization, caspase-3 activation and nucleosomal DNA fragmentation associated with the formation of malondialdehyde (MDA), a by-product of lipid peroxidation and biomarker of oxidative stress.[35]

Methanolic extract of *Salviya officinalis* is reported to have a protective effect against cyclophosphamide (CYP)-induced oxidative stress and genotoxicity through its antioxidant property.[36] *Vernonia amygdalina* has been attributed to its abilities to scavenge free radicals, induce detoxification, inhibit stress response proteins and interfere with DNA binding activities of some transcription factors. Phytochemicals such as alkaloids, anthraquinones, coumarins, edotides, flavonoids, lignans, phenolic acids, saponins, sesquiterpenes, steroids, terpenes and xanthones have been extracted and isolated from *Vernonia amygdalina.* These compounds elicit various biological effects including cancer prevention.[37]

Different parts of *Phaleria macrocarpa* fruit showed appreciable antioxidant activity such as 2, 2-diphenyl-1-picrylhydrazyl (DPPH), ferric reducing antioxidant power, NO scavenging activity and cytotoxic activities against HT-29, MCF-7, HeLa and chang cell lines.[38]Jatropa (*Jatropha podagrica*) act as antioxidant with less efficiency but showed significant antitumor activity against the A549 and PC12 cells.[40] Both positive and negative correlations are seen between antioxidant capacity and anticarcinogenic activity (Table 1).

Phytochemicals and Molecular Targets of Cancer

Although fruits and vegetables are recommended for the prevention of cancer, the mechanism of action of active molecules or the whole complex is less understood. Number of transcription factors including NF-κB, p53, PPAR-γ, HIF-1α, β-catenin/Wnt, AP-1 and Nrf2 are activated by oxidative stress (Figure 2). These activated transcription factors can lead to the expression of different genes, including those for growth factors, chemokines, cell cycle regulatory molecules, inflammatory cytokines, and anti-inflammatory molecules.[39]

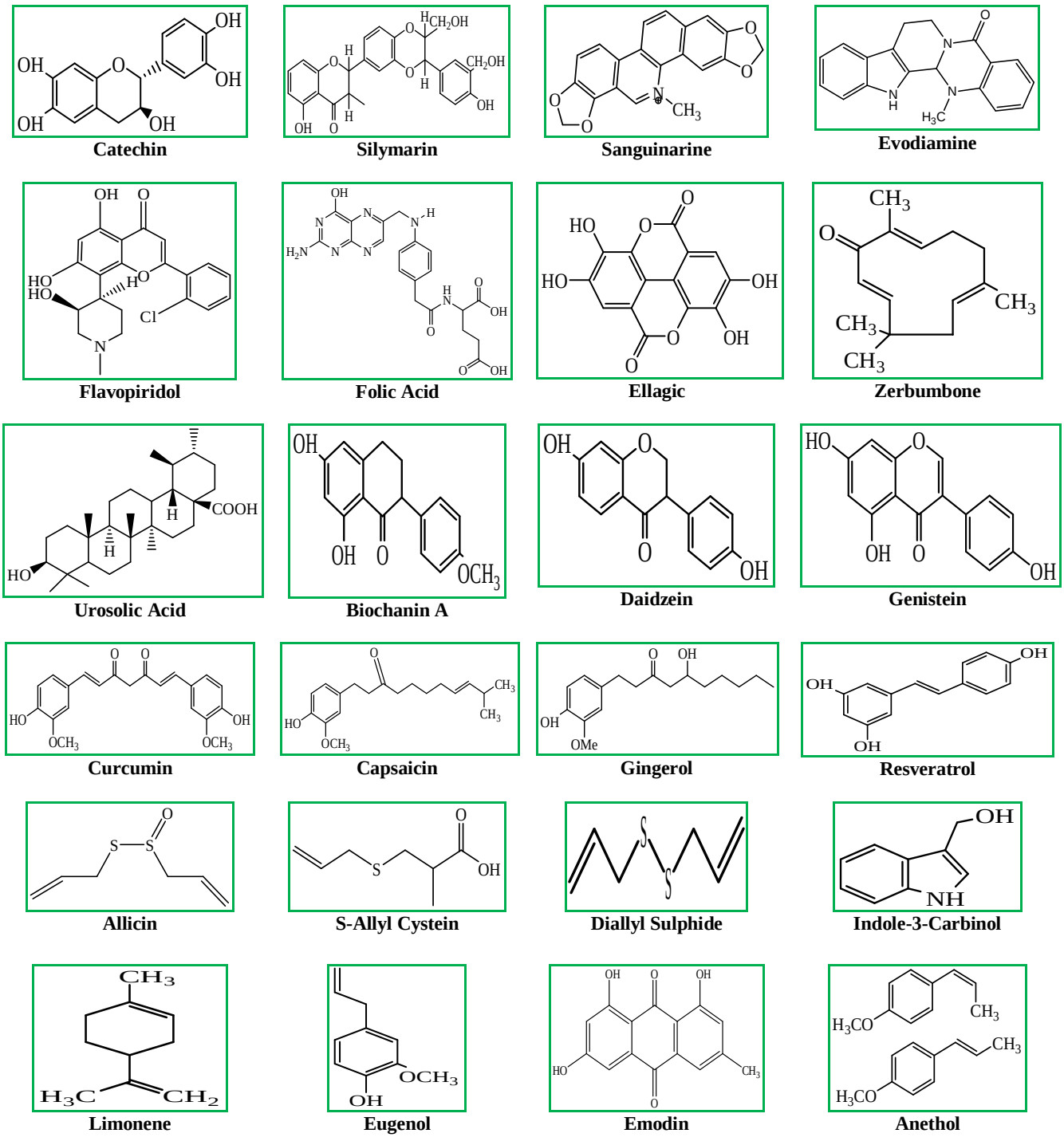

Figure 1: Chemical structures of major dietary compounds exhibiting antioxidant and antiproliferativepotential.[19]

Table 1: Positive and negative correlation of antioxidants and anticancer activities of different plants

Plants used	Antioxidant activity	In vitro/In vivo model	Observation
Jatropa *(Jatropha podagrica)*	DPPH, Reducing power, Superoxide scavenging, Lipid peroxidation	A549, PC12	It act as antioxidant but with less efficiency and showed significant antitumor activity.[40]
Wampee (*Clausena lansium*)	DPPH	SGC-7901, HepG-2, A 549	Its peel extract showed antioxidant and anticancer activities. [41]
Red raspberry (*Rubusidaeus*)	TOSC	HepG2	No relationship between anti proliferative activity and the antioxidant activity.[42]
Apples (*Malus domestica*)	NA	MCF-7 , MDA-MB-231	Significant inhibition of cell proliferation.[43]

Table 1: Positive and negative correlation of antioxidants and anticancer activities of different plants (Continued.....)

Plants used	Antioxidant activity	In vitro/In vivo model	Observation
Ginger (*Boesenbergia armeniaca*, *B.pulchellavar. attenuate* and *B. rotunda*)	ABTS, DPPH	CaOV3, HeLa, MCF-7, MDA-MB-231, HT-29	Antioxidant activities were in trend *B. pulchella*var. attenuata>*B. rotunda* >*B. armeniaca*. *B. rotunda* showed the most prominent anti proliferative effect.[44]
Pomegranate (*Punica granatum*)	NA	MCF-7	Significant cytotoxic and growth inhibition effects.[45]
Pomposia (*Syzygium cumini*)	DPPH	AML	A linear relationship between anti- oxidant and anti-proliferative activity.[46]
Longan (*Dimocarpus longan*)	DPPH	HepG2, A549, and SGC 7901	Lognan showed excellent antioxidant and anticancer activities.[41]
Ginger (*Zingiber officinale*)	TBA	MCF-7 and MDA-MB-231	Extract of its rhizomes with the highest anticancer activity on MCF-7 cancer cells.[47]
Different fruits	TOSC	HepG2	Positive correlation.[48]
Strawberries (*Fragaria ananassa*)	TOSC	HepG2	No relationship between anti proliferative and antioxidant activity.[49]
Red pitaya (*Hylocereus polyrhizus*)	DPPH, ABTS, TEAC	B16F10	Flesh and peel were both rich in polyphenols and were good sources of antioxidants.[50]
Walnut (*Juglans regia* L.)	Total antioxidant C capacity	WRL, HEPG-2 , KB,Caco2, MCF-7	No correlation between anti proliferative and antioxidant activity.[51]
Wampee (*Clausena lansium*)	DPPH	HepG2, A549, HeLa	Its ethyl acetate fraction with antioxidant activity and inhibitory effect on different cell line.[52]
Cacao (*Theobroma cacao* L.)	ABTS, ORAC	murine lymphoma L5178Y in BALB/c mice	Antitumor and antioxidant activity with no correlation.[53]
Rambutan (*Nephelium lappaceum*), Mangosteen (*Garcinia mangostana*), and Coconut (*Cocos nucifera*)	ABTS, FRAP	CaCO-2, KB, PBMC	This selective anti proliferation with no correlation with its antioxidant activity.[54]
Cherry extracts (*Prunus avium*)	ORAC	HT29	No relationship was indicated between antioxidant and anti proliferative activity.[55]

Antioxidant Assays: ABTS-2, 2'-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid); DPPH-2, 2-diphenyl-1-picrylhydrazyl; FRAP-ferrous reducing antioxidant property; *ORAC-Oxygen radical absorbance capacity;* TBA- Thiobarbituric acid; TOSC-Total oxyradical scavengering activity. ***In vitro/In vivo models:*** A549- Adenocarcinoma human alveolar basal epithelial cells; AGS- Human Caucasian gastric adenocarcinoma;AML- Acute myeloid leukemia cell lines*;* B16F10- Mouse melanoma cell line; Caco-2- Human epithelial colorectal adenocarcinoma cells; CAOV3- Ovarian cancer cell line*;* DU145-Human prostate cancer cell line*;* HeLa-Cervical cancer cell line; HEPG2-liver hepatocellular cellsHT-29- Human colon adenocarcinoma grade II cell line; KB- Human squamous cell carcinoma cell line; LS174-Human colon carcinoma cell line; MCF-7- Breast cancer cell line; MDA-MB-231- Human breast adenocarcinoma; PBMC-Peripheral blood mononuclear cells; PC-3- Human prostate cancer cell lines;PC12- rat pheochroma cytoma; SGS-7901- Human gastric cancer cell line; WRL68-hepatic fetal human epithelial cells.

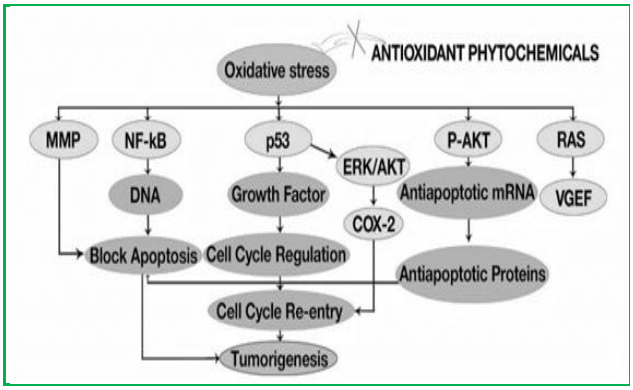

Figure 2: Activation of transcription factors by oxidative stress inducing tumor genesis

Research over the last decade has shown that several micronutrients in fruits and vegetables reduce cancer. Polyphenols in peach and plum have been identified as chemo preventive agents against estrogen-independent breast cancer cells.[56] Pomegranate phytochemicals exert chemoprevention of hepatic cancer through anti proliferative and pro-apoptotic mechanisms by modulating Wnt/β-catenin signaling.[57]

Previous reports showed that dietary intake of natural products contribute to the prevention and treatment of breast cancer by regulating specific miRNAs. Natural products, including stilbenes, curcumin, and glyceollins could alter the expression of specific miRNAs, which may

lead to increased sensitivity of cancer cells to conventional anti-cancer agents and, therefore, lead to tumor growth inhibition.[58]

Various environmental carcinogens for tumerogenesis, are responsible for the expression of various transcription factors such as NF-kB, AP-1, Akt, Bcl-2, Bcl-XL, caspases, EGFR, cyclins, cyclin-dependent kinases, cell adhesion molecules, COX-2, and growth factor signalling pathways, tumour necrosis factor (TNF) and tumor promoters. Several dietary agents are believed to suppress the inflammatory processes that lead to transformation, hyper proliferation, and initiation of carcinogenesis. Their inhibitory influences may ultimately suppress the final steps of carcinogenesis as well, namely angiogenesis and metastasis. Based on some studies the mechanism of crude extract on different molecular targets responsible for cancer are described in Table 2.

Phytochemicals acting on Nuclear Transcription Factor (NF-kB)

NF-κB is a protein complex that transcribes DNA and is widely expressed in almost all cells. Under resting condition NF-κB resides in cytoplasm and is activated by free radicals, inflammatory stimuli, cytokines, carcinogens, tumor promoters, endotoxins, ultraviolet (UV) light and X-rays.[72-73] NF-κB induces expression of more than 200 genes on activation, which suppress apoptosis and induce proliferation, invasion, metastasis, chemo-resistance, cellular transformation and inflammation.[74] Cruciferous vegetables contain a biologically active compound, sulforaphane that suppresses tumor necrosis factor-α (TNF-α), which in turn, activates NF-κB in a variety of human tumor cell lines, including human leukemia (U937, THP-1, HL60 and K562), human prostate carcinoma (PC-3), human breast carcinoma (MCF-7) as well as human hepatoma (HepG2) cells.[75] Many phytochemicals are found to be potent inhibitors of NF-kB.[76-89]

Phytochemicals acting on cell cycle arrest

Many proteins regulate the cell cycle arrest and show anti-cancer properties. Cyclins and cyclin–dependent kinase are the major protein of cell cycle and phytochemicals play major role in down regulating their proteins in cell cycle phases (G1, S and G2).[90-92] At different stages of cell cycle, resveratrol inhibits proliferation of cells by inhibiting cell cycle progression.[93-94] Resveratrol down regulates cyclin D1/Cdk4 in colon cancer cell lines.[95] Epigallocatechingallate (EGCG) causes cell cycle arrest and promotes apoptosis by up regulation of p21/Waf1, p27Kip1, and p16/INK4A, and down-regulation of proteins such as cyclin D1, cyclin E, Cdk2 and Cdk4.[96] In a variety of human cancer cell lines proliferation is inhibited and induction of apoptosis and G2 arrest is done by genistein.[97] Six dietary isothiocyanates (ITCs) from cruciferous vegetables were examined for their effects on cell cycle progression.[98] The dietary flavonoid apigenin induces G2/M phase arrest in two p53-mutant cancer cell lines, HT-29 and MG63, in parallel with a marked increase in the production of p21/WAF1.[99]

In vitro studies of whole cranberry extract on DU145 human prostate cancer cells decreases the proportion of cells in the G2-M phase of the cell cycle and increased the proportion of cells in the G1 phase of the cell cycle.[100] Components isolated from *Centipeda minima* showed stronger inhibitory activity through cell cycle arrest at G2/M phase.[101] S-allylcysteine a potent phytochemical suppressed the proliferation of prostate Cancer-3 cells and led to cell cycle arrest at the G0/G1 phases.[102] 3,3-diindolyl methane(DIM) is a potential cancer preventive phytochemical isolated from Brassica vegetables causes cell cycle arrest by down-regulating protein levels of cell-cycle related kinases CDK1, CDK2, CDK4, and CDK6, as well as cyclin B1 and Cdc25A.[67]

The induction of cell cycle arrest and the ultimate apoptotic death by some phytochemicals have been observed in different types of tumor cells, including colon carcinoma HT-29 cells,[91] human hepatocellular liver carcinoma Hep G2 cells[90] and HL-60 promyelocytic leukemia cells.[103]

Table 2: Plants and their molecular targets

Plant types	Molecular targets
Commiphora mukul	NF-κB, COX-2.[59]
Zanthoxylum nitidum	cyclin D1, VEGF, STAT3-dependent target genes, Janus kinase 2, Bcl-xL.[60]
Orthosiphon stamineus	VEGFR.[61]
Psoralea corylifolia	Akt, PTEN, PI3K, NF-κB, Bcl-2and Bcl-xL.[62]
Brassica sp.	CDK2, CDK6, p27.[63]
Glycine max	Caspase-3 and -9.[64]
Bryophyllum pinnata	c-Fos, c-Jun, Bcl-2, caspase-3 and PARP-1.[65]
Nitraria retusa	caspase-3 and caspase-8.[66]
Brassica sp.	CDK1, CDK2, CDK4, and CDK6.[67]
Leonurus japonicus	iNOS, COX-2, PGE-2, NF-κB, p-JNK, p38 and p-ERK.[68]
Epilobium sp.	COX-1 and COX-2.[69]
Caryopteris odorata	Lipoxygenase.[70]
Curcuma longa	protein kinase C, MMP-9, PKC.[71]

Abbreviations

AKT- Protein Kinase B (PKB), BRCA1-breast cancer type 1, BRCA2- breast cancer type 2, CDK- Cyclin-dependent kinases, COX- Cyclooxygenase, EGF- Epidermal growth factor, ERK- Extracellular signal-regulated kinases, ERK- Extracellular signal-regulated kinases, iNOS- Inducible NO synthase, MMP- Matrix metalloproteinase, NF-kB- Nuclear factor kappa light chain enhancer of activated B cells, Nrf 2- NF-E2-related factor 2, p53- Tumor protein 53 (tumor suppressor protein), PARP- Poly (ADP-ribose) polymerase, PGE-2-prostaglandin E2, PI3-K- Phosphatidylinositol 3-kinases, PKC- Protein kinase C, PTEN- Phosphatase and tensin homolog, STAT3- Signal transducer and

activator of transcription 3, TGFB- Transforming growth factor *beta,* VEGF- Vascular endothelial growth factor.

Phytochemicals acting on apoptosis

Apoptosis is a programmed cell death in which cells are eliminated without damaging neighbouring cells. Plants derived flavonoids have been shown to cause apoptosis through induction of Bax and suppression of Bcl_2.[104] Study showed that *Nitraria retusa* extracts appear to contain compounds with, anti-proliferative and apoptotic properties on human leukaemia lymphoma.[66] Similarly raspberry shows apoptotic activity both *in vitro* and *in vivo*.[105] Curcumin is known to down-regulate the expression of apoptosis suppressor proteins, such as Bcl-2 and Bcl-XL, in several cancer cell lines.[106] In BL41 Burkitt's lymphoma cells apoptosis is induced by *Bryonia dioica* aqueous extract through mitochondrial intrinsic pathway.[107] In prostate cancer genistein isoflavone (4', 5', 7-trihydroxyisoflavone) is a dietary phytochemical that shows anti-tumor activity primarily through apoptosis, *via* the activation of caspase-3 and 9 which are involved in the intrinsic pathway.[108] Nimbolide, a neemlimonoid induce apoptosis in human hepatocarcinoma (HepG2) cells.[109]

Phytochemicals acting on angiogenesis

Angiogenesis is the process of growth of new blood capillaries. These capillaries grow either from pre-existing vessels or by intersucception. Angiogenesis starts with cancerous tumor cells releasing molecules that send signals to surrounding normal cells and these signals activate certain protein which in turn initiates the process of forming new blood vessels. Number of angiogenic proteins such as vascular endothelial growth factors (VEGF), platelet derived growth factor (PDGF), fibroblast growth factors (FGF), tumour necrosis factor-α, transforming growth factor-β and interleukin 8 and non-angiogenic factors such as endostatin, angiostatin, tissue inhibitor of metalloproteinase, platelet factor 4, thrombospondin 1 and pentosan polysulfate known but most commonly found in tumor are basic fibroblast growth factor (BFGE)[110] and vascular endothelial growth factor (VEGF).[111-112] Some studies revealed that many phytochemicals act as anti-angiogenic agents.[113-119]

Phytochemicals acting on endogenous antioxidants

Phytochemical antioxidants also enhance the level of endogenous antioxidants such as glutathione, catalase and superoxide dismutase which help in balancing ROS.[120] Plant extracts namely *Salvia officinalis* (sage) extract, *Camellia sinensis* (oolong tea) extract and *Paullinia cupana* (guarana) extract increase in total glutathione concentrations, glutathione peroxidase and superoxide dismutase enzyme activities.[121] Natural phytochemical sulforaphane, (-) 1-isothiocyanato-4R-(methylsulfinyl)-butane, present in cruciferous vegetables, elevates hepatic glutathione S-transferase and quinine reductase.[122] Allicin in garlic up-regulates the glutathione level in a concentration and time-dependent manner up to 8-fold at a concentration of 10-20 μM.[123] Resveratrol increases nitric oxide synthases which induces accumulation of p53 and p21 and suppresses bovine pulmonary artery endothelial cell proliferation by distressing progression through S and G2.[124] Hydroperoxides, hydrogen peroxide and superoxide anions are decomposed by elevated glutathione peroxidase, catalase and superoxide dismutase induced by polyphenols.[120]

Phytochemicals acting on other molecular targets

There are other molecular targets such as activator protein-1 (AP-1), cell survival kinase Akt, chemokines and metastasis, cyclooxygenase-2 (COX-2), DNA methylation, lipoxygenase, mitogen activated protein (MAP) kinase, signal transducer and activator of transcription (STAT) and tumor suppressor gene (p53) on which natural phytochemicals act to prevent cancer.[19] Understanding the limitation of topic we have discussed only few, as above.

CONCLUSION

Numerous agents in fruits and vegetables can interfere with multiple cell-signalling pathways. These agents can be used in their natural form for the prevention or in their pure form for the therapy. Most modern medicines currently available for treating cancers are very expensive, toxic, and not highly effective in treating the disease. Thus, it is necessary to investigate further in details the agents derived from natural sources, described traditionally, for the prevention and treatment of cancer and disease. More clinical trials are also needed to validate the usefulness of these agents either alone or in combination with existing therapy.

Although there is evidence that phytochemicals decrease the incidence of breast and other cancer, many observations are only phenomenologic, and much work needs to be done to explore basic mechanisms and the strategic explanation of their interactions. The multiplicity of phytochemical actions at different sites in the process of tumorigenesis may eventually lead to the development of a multi-agent strategy designed to maximize the complementary effects of different agents. It is also very important to investigate the absorption, distribution, metabolism and excretion of chemopreventive phytochemicals in the human body to clarify the interaction with anticancer drugs at the site of drug action, in the tumor tissues and cancer cells. Therefore, dietary chemopreventive phytochemicals can be considered promising lead compounds for designing the more potent, but less toxic chemosensitizing agents to develop better chemotherapeutic alternatives for the treatment of cancer patients.

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