IJPSR (2015), Vol. 6, Issue 11 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 05 May, 2015; received in revised form, 25 August, 2015; accepted, 30 August, 2015; published 01 November, 2015

INVESTIGATION OF THE BIOCHEMICAL MECHANISM OF ACTION OF ANTIOXIDANTS IN THE PREVENTION OF CANCER

Kissi Mudie*, Atsbeha Gebregzabher and Desta Kassa

HIV/TB Research Directorate, Ethiopian Public Health Institute (EPHI), Addis Ababa, Ethiopia.

Keywords:

Cancer, antioxidants, chemoprevention, phytochemicals

Correspondence to Author:
Kissi Mudie

HIV/TB Research Directorate, Ethiopian Public Health Institute (EPHI), P.O. Box 1242, Addis Ababa, Ethiopia.

Email: kissimudiey@yahoo.com

ABSTRACT: The safe use of medicines is a critical issue for all health care professionals, **Background:** Cancer refers to a group of diseases that are associated with a disturbance in the control of cell growth and metabolism. Indeed, the unbalanced control of cellular proliferation is a primary characteristic of cancer cells and, as such, any molecule capable of inhibiting cancer cell proliferation may also be useful as a potential chemo-preventive agent. Throughout history, antioxidants have been the most significant source of anticancer and chemopreventing agents. More than 1,000 different phytochemicals are already proved to possess interesting chemopreventing activities. Antioxidants consist of a wide variety of biologically active phytochemicals including phenolics, flavonoids, carotenoids, etc. that have been shown to suppress early and late stages of carcinogenesis. **Objective:** To review recent biochemical and molecular mechanisms, in relation to natural and synthetic chemopreventing substances (antioxidants) for cancer control and management. **Major findings:** Antioxidants exert anticancer effects via a variety of mechanisms, including removal of carcinogenic agents, modulation of cancer cell signaling and cell cycle progression, promotion of apoptosis and modulation of enzymatic activities. **Conclusion:** This review provides an updated and comprehensive overview on the anticancer effects of antioxidants in-vitro and in-vivo animal models including recent intervention studies. Finally, possible mechanisms of action involving antioxidant and pro-oxidant activity as well as interference with cellular functions are discussed.

INTRODUCTION: Cancer is a broad group of various diseases, all involving unregulated cell growth. In cancer, cells divide and grow uncontrollably, forming malignant tumors, and invade nearby parts of the body. The cancer may also spread to more distant parts of the body through the lymphatic system or bloodstream [1]. It is fundamentally a disease of failure of regulation of tissue growth.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.6(11).4556-69

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(11).4556-69

In order for a normal cell to transform into a cancer cell, the genes which regulate cell growth and differentiation must be altered [2]. Cells can experience uncontrolled growth if there are damages or mutations to DNA, and therefore, damage to the genes involved in cell division. Four key types of gene are responsible for the cell division process: Oncogenes (genes which promote cell growth and reproduction), tumor suppressor genes (genes which inhibit cell division and survival), suicide genes (genes that control apoptosis and tell the cell to kill itself if something goes wrong), and DNA-repair genes (genes that instruct a cell to repair damaged DNA). Cancer occurs when a cell's gene mutations make the cell unable to correct DNA damage and unable to commit suicide [3].

Cancer is a growing health problem around the world, particularly with the steady rise in life expectancy. According to a recent report by the World Health Organization cancer is a leading cause of death worldwide, with 8.2 million deaths and an estimated 14.1 million new cases [4].

1.1. Oxidants, free radicals and antioxidants:

1.1.1. Oxidants and free radicals:

Most of the potentially harmful effects of oxygen are believed to be due to the formation and activity of reactive oxygen species acting as oxidants, that is, compounds with a tendency to donate oxygen to other substances. Many reactive oxygen species are free radicals. Free radicals are molecules with one or more unpaired electrons. Many free radicals are unstable and highly reactive [5].

Humans are constantly exposed to free radicals created by electromagnetic radiation from the manmade environment such as pollutants and cigarette smoke. Natural resources such as radon, cosmic radiation, as well as cellular metabolisms (respiratory burst, enzyme reactions) also add free radicals to the environment. The most common reported cellular free radicals are hydroxyl ($OH\cdot$), superoxide ($O_2^{-}\cdot$) and nitric monoxide ($NO\cdot$). Even some other molecules like hydrogen peroxide (H_2O_2) and peroxynitrite ($ONOO^{-}$) are not free radicals; they are reported to generate free radicals through various chemical reactions in many cases. Overproduction of free radicals can cause oxidative damage to biomolecules, (lipids, proteins, DNA), eventually leading to many chronic diseases such as atherosclerosis, cancer, diabetics, rheumatoid arthritis, post-ischemic perfusion injury, myocardial infarction, cardiovascular diseases, chronic inflammation, stroke and septic shock, aging and other degenerative diseases in humans [6].

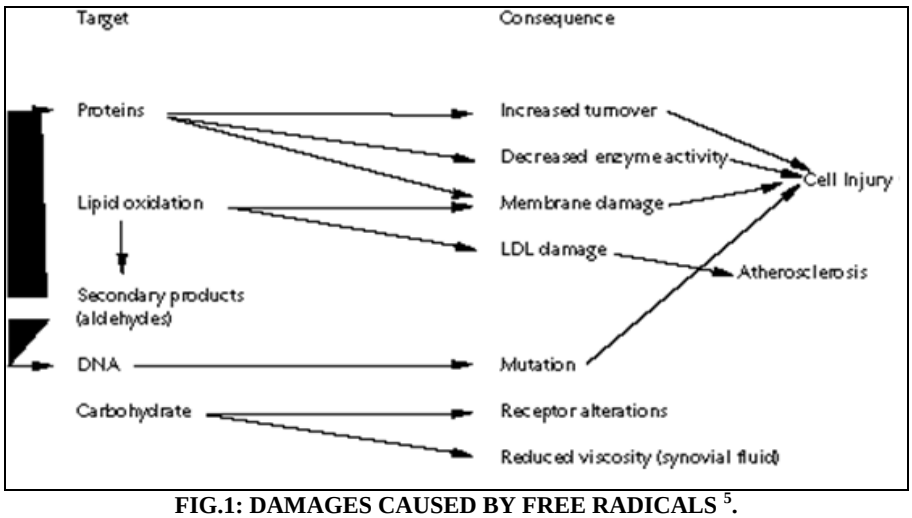

FIG.1: DAMAGES CAUSED BY FREE RADICALS [5].

1.1.2. Antioxidants:

Antioxidants are molecules that inhibits the oxidation of other molecules. Antioxidants terminate chain reactions by removing free radical intermediates, and inhibit other oxidation reactions [7]. In general, antioxidant systems either prevent reactive species from being formed, or remove them before they can damage vital components of the cell. However, reactive oxygen species also have useful cellular functions, such as redox signaling. Thus, the function of antioxidant systems is not to remove oxidants entirely, but instead to keep them at an optimum level [8].

Various antioxidants are supplied to human body through diet, both vegetarian as well as non-vegetarian. Vitamins C and E, β-carotene and coenzyme Q are the most famous antioxidants of diet. Plants (fruits, vegetables, medicinal herbs) may contain a wide variety of free radical scavenging molecules such as phenolic compounds (Phenolic acids, flavonoids, quinones, coumarins, lignans, stilbenes, tannins etc.), nitrogen compounds (alkaloids, amines, betalains etc.), terpenoids (including carotenoids) and some other endogenous metabolites which are rich in antioxidant activity [6].

TABLE 1: FOODS CONTAINING ANTIOXIDANTS [9]

Antioxidant compounds	Foods containing high levels of these antioxidants
Vitamin C (ascorbic acid)	Fresh Fruits and vegetables
Vitamin E (tocopherols, tocotrienols)	Vegetable oils
Polyphenolic antioxidants (resveratrol, flavonoids)	Tea, coffee, soy, fruit, olive oil, chocolate, cinnamon, oregano
Carotenoids (lycopene, carotenes, lutein)	Fruit, vegetables and eggs.

2. Role of antioxidants in the prevention of cancer:

The fact that millions of people die from various types of cancer every year raises an overwhelming demand to develop new, more potent and effective anticancer, as well as chemopreventing agents [10].

Additionally, the cancer problem and the failure of conventional chemotherapy to achieve a reduction in the mortality rates for common epithelial malignancies such as carcinomas of the lung, colon, breast, prostate and pancreas, indicates a critical need for new approaches to control cancer development. One of these approaches is chemoprevention. Chemoprevention is a pharmacological approach to intervene with the objective of arresting or reversing the process of multi-step carcinogenesis [11]. It is the use of specific natural (dietary) or synthetic agents to prevent, delay, or slow the carcinogenic process [12].

Intervention to slow down, arrest or reverse the process of carcinogenesis by the use of either natural or synthetic substances individually or in combination therapy has emerged as a promising and pragmatic medical approach to reduce cancer risk. A number of compounds naturally occurring in foods, particularly antioxidative compounds in plants, have shown promise as potential chemopreventive agents. The American National Cancer Institute has identified about 35 plant-based foods containing 1,000 different phytochemicals, which possess cancer-preventive properties. The most exciting findings have been achieved with antioxidant vitamins and their precursors, which are found in dark, leafy green vegetables and yellow/ orange fruit and vegetables [10, 11].

A large number of epidemiologic studies have suggested that a diet high in fruits, vegetables, and other foods derived from plants is associated with a lower risk of cancer. Antioxidant nutrients such as ascorbic acid, α- tocopherol, and the carotenoids (eg, beta carotene) that are present in plant-derived foods may have a major preventive role against carcinogenesis, and it has been suggested that they may suppress tumor cell growth and induce tumor cell apoptosis. A variety of grains, cereals, nuts, soy products, olives, beverages confer a protective effect against cancer. In particular, natural products consist of a wide variety of biologically active phytochemicals including phenolics, flavonoids, carotenoids, alkaloids and nitrogen containing as well as organosulfur compounds, which have been shown to suppress early and late stages of carcinogenesis [10, 13, 14].

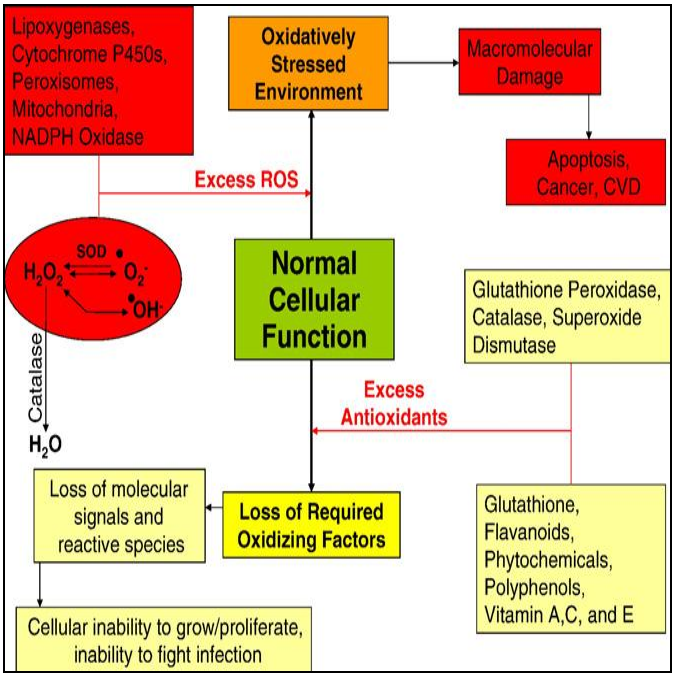

FIG.2: CELLULAR OXIDATIVE INTERACTIONS AND ROLE OF ANTIOXIDANTS [15].

2.1. Biochemical mechanism of action of antioxidants in the prevention of cancer:

Antioxidants act to suppress cancer development through various molecular targets that are involved in controlling cell proliferation, differentiation, apoptosis, or cell cycle. These targets may be

aberrantly activated or silenced, depending on each specific case, and thus allow initiated cells to survive and proliferate [16].

Molecular targets of Antioxidants:

Regulation of Nuclear factor kappa-B (NFκB):

NF-κB the is a heterodimeric transcription factor that regulates the expression of most anti-apoptotic gene products associated with the survival of the tumor; regulates the gene products linked with proliferation of tumors; and controls the expression of gene products linked with invasion, angiogenesis, and metastasis of cancer [10].

NFκB consists of a p50 and p65 subunit and, when active, promotes inflammatory gene expression, cell proliferation, cell survival and oncogenic processes. Inactive NFκB is normally found in the cytosol, bound to its inhibitory subunits (IκBs). Upon activation, IκBs are rapidly phosphorylated by IκB kinases (IKK), and ubiquitinated leading to IκB degradation and subsequent release of NFκB and translocation to the nucleus. Constitutive activation of NFκB is common in various human malignancies, including colon and prostate cancer, and leads to up-regulation of genes encoding adhesion molecules, inflammatory cytokines, growth factors, and anti-apoptotic genes. Thus, inhibition of NFκB activation has been postulated as a key target for cancer chemoprevention [16, 17, 18].

Regulation of Activator protein-1 (AP1):

AP1 is another transcription factor that regulates expression of genes that are involved in cellular adaptation, differentiation and proliferation. Functional activation of AP1 is associated with malignant transformation as well as tumor promotion [17].

The AP-1 family is comprised of heterogeneous and complex dimeric interacting partners, with divergent downstream targets depending on tissue context and cellular stimuli. Modulation of AP-1 members can have effects on both promoting and inhibiting carcinogenesis. These divergent responses observed are likely dependent on genetic background, cell type, tumor state, and signaling networks that are affected in response to specific agents [16]. Antioxidants suppress AP-1 activity by the inhibition of mitogen-activated protein kinase [19].

Regulation of Cyclooxygenase -2 (COX-2):

COX-2 is a rate limiting enzyme and is constitutively overexpressed in practically every premalignant and malignant condition involving the colon, liver, pancreas, breast, lung, bladder, skin, stomach, head and neck, and esophagus in response to various mitogens, tumor promoters, cytokines, growth factors and exposure to solar UV radiation [17]. Antioxidants play great role in down-regulation of COX-2 [18].

Regulation of Mitogen-activated protein kinases (MAPK):

MAPKs belong to the superfamily of serine/threonine kinases including the extracellular signal-regulated kinases (ERK), c-Jun NH2-termial kinases (JNK), and p38. Each is believed to play a role in carcinogenesis and cancer development [16].

MAPK signaling pathway is an important upstream regulator of transcriptional factor activities and their signaling affects a wide variety of extracellular stimuli into intracellular events and thus control the activities of downstream transcription factors implicated in carcinogenesis. UV-induced oxidative stress has been implicated in the activation of MAPK proteins [17].

MAPK signaling pathway also has been viewed as an attractive pathway for anticancer therapies, based on its central role in regulating the growth and survival of cells from a broad spectrum of human cancers, and its role in the transcriptional and post-transcriptional activation of COX-2 [20]. Antioxidants have been shown to inhibit the proliferation of human prostate cancer cells by regulating MAPK pathways [21].

Regulation of phosphatidylinositol- 3- kinase (PI3K/AKT):

The PI3K/Akt pathway plays critical role in mammalian cell survival signaling and has been shown to be activated in various cancers. A key downstream effector of PI3K is the serine-threonine kinase Akt, which in response to PI3K activation phosphorylates and regulates the activity of number of molecular targets [17].

Antioxidants have been shown to inhibit PI-3K/AKT pathways, the key survival cascade that are frequently aberrantly activated in human cancers [22, 23].

Regulation of Apoptosis:

Apoptosis, or programmed cell death, can be accomplished either through the death-receptor caspase cascades or the mitochondria caspase cascades [16]. Apoptosis plays a major role in establishing a natural balance between cell death and cell renewal in mature animals by destroying excess, damaged or abnormal cells. The activation of NF-κB promotes cell survival and proliferation, and down-regulation of NF-κB sensitizes the cells to apoptosis induction. Expression of several NF-κB-regulated genes such as Bcl-2, cIAP, survivin, TRAF have been reported to function by blocking the apoptosis pathway. The higher ratio of Bax/Bcl-2 leads to the cleavage of caspases and that stimulates the induction of apoptosis [17].

Treatment with antioxidants has shown to inhibit the growth of many different cancer cell lines by increasing apoptosis [24].

Regulation of Cell cycle arrest:

One hallmark of cancer is hyperproliferation due to loss of cell cycle regulatory mechanisms. Several proteins are known to regulate the timing of the events in the cell cycle. The key regulators of cell cycle progression are the cyclindependent kinases (CDKs), cyclins, and CDK inhibitors. The regulation of CDK complexes is dependent upon the phosphorylation status of the various components of the complex and whether or not CDK inhibitors are bound. The cyclin/CDK complexes promote cell cycle progression while the CDK inhibitors promote cell cycle arrest [16, 17].

Antioxidants inhibit the growth of many different cancer cell lines by inducing cell cycle delays and modulating intracellular signaling pathways [24].

Histone deacetylase (HDAC) inhibition:

Increased HDAC activity and expression is common in many cancer malignancies, and can result in repression of transcription that results in a de-regulation of differentiation, cell cycle and apoptotic mechanisms. Moreover, tumor suppressor genes, such as p21 appear to be targets of HDACs and are "turned off", or transcriptional silenced, by deacetylation. Effectiveness of chemopreventive agents reflects their ability to counteract certain upstream signals that leads to genotoxic damage, redox imbalances and other forms of cellular stress. Targeting malfunctioning molecules along the disrupted signal transduction pathway in cancer represents a rational strategy in chemoprevention [10].

2.1.1. Mechanism of cancer prevention by antioxidant enzymes

The human body has several mechanisms for defense against free radicals and other reactive oxygen species. The various defences are complementary to one another because they act on different oxidants or in different cellular compartments. One important line of defense is a system of enzymes, including glutathione peroxidases, superoxide dismutases and catalase, which decrease the concentration of the most harmful oxidants [5].

Superoxide dismutases are a family of antioxidant enzymes which are important in the catalytic decomposition of the superoxide radical to hydrogen peroxide and oxygen; Catalase specifically catalyses the decomposition of hydrogen peroxides; Glutathione peroxidases are a family of antioxidant enzymes containing selenium which are important in the reduction of hydroperoxidese, those that result from lipid oxidation (**Fig. 3**).

$$2O_2^{\cdot -} + 2H^+ \xrightarrow{\text{Superoxide dismutase}} H_2O_2 + O_2$$

$$2H_2O_2 \xrightarrow{\text{Catalase}} O_2 + 2H_2O$$

$$LOOH + 2GSH \xrightarrow{\text{Glutathione peroxidase}} LOH + H2O + GSSG$$

FIG. 3: ENZYMATIC ANTIOXIDANT DEFENCES (L = LIPID)

Nutrition plays a key role in maintaining the body's enzymatic defences against free radicals. Several essential minerals including selenium, copper, manganese and zinc are involved in the structure or catalytic activity of these enzymes. If the supply of these minerals is inadequate, enzymatic defences may be impaired. A second line of defence is small-molecular-weight compounds which act as antioxidants; that is, they react with oxidizing chemicals, reducing their capacity for damaging effects. Some, such as glutathione, ubiquinol and uric acid, are produced by normal metabolism [5].

2.1.2. Mechanism of cancer chemoprevention by carotenoids:

Carotenoids, which belong to the chemical group known as isoprenoid polyenes, are lipid-soluble, yellow-orange-red pigments found in all higher plants and some animals. Major carotenoids with antioxidant activity that have been extensively evaluated with regard to their cancer chemopreventive ability include: α- and β-carotenes, β-cryptoxanthin, lycopene, lutein and zeaxanthin [11].

The mechanisms underlying the anticancer and/or cancer chemopreventive activities of carotenoids may involve changes in pathways leading to cell growth or cell death. These include immune modulation, hormone and growth factor signaling, regulatory mechanisms of cell cycle progression, cell differentiation and apoptosis. The changes in the levels of many proteins suggest that the initial effect involves modulation of transcription. Such modulation can occur at the level of ligand-activated nuclear receptors or other transcription factors. Carotenoids have multiple targets that contribute to their efficacy as chemoprevention agents (**Fig.4**).

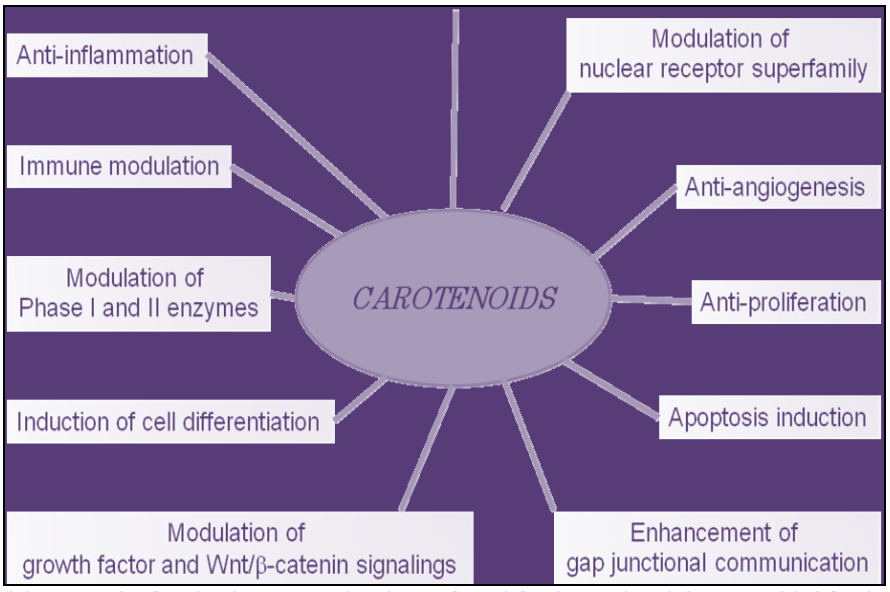

FIG.4: PROPOSED MECHANISMS BY WHICH CERTAIN CAROTENOIDS SUPPRESS CARCINOGENESIS

Gap Junctional Intercellular Communication:

Carotenoids increase gap junctional intercellular communication (GJIC) and induce the synthesis of connexin 43, a component of the gap junction structure. Loss of GJIC may be important for malignant transformation, and its restoration may reverse the malignant process [11].

Growth Factor Signaling:

Growth factors, either in the blood or as part of autocrine or paracrine loops, are important for cancer cell growth. Recently, insulin growth factor (IGF)-1 has been implicated as a major cancer risk factor and a target of potential for dietary intervention strategies for cancer prevention [25].

In mammary cancer cells, lycopene treatment markedly reduced IGF-1 stimulation of both tyrosine phosphorylation of insulin receptor substrate-1 and the DNA binding capacity of the activator 1 (AP-1) transcription factor. These effects were associated with an increase in

membrane-associated IGF binding proteins (IGFBPs) [26].

Cell Cycle Progression:

Growth factors have a major effect in promoting cell cycle progression, primarily during the G1 phase. Lycopene treatment of MCF-7 mammary cancer cells has been shown to slow down IGF-1-stimulated cell cycle progression [26], which was not accompanied by either apoptotic or necrotic cell death. Lycopene-induced delay in progression through the G1 and S phases has also been observed in other human cancer cell lines (leukemia and cancers of endometrium, lung and prostate) [27].

Similar effects of another carotenoid, α-carotene, was reported in human neuroblastoma cells. Likewise, β-carotene was found to induce a cell-cycle delay in the G1 phase in normal human fibroblasts. Fucoxanthin is reported to alter cell cycle progression [28]. In addition, metabolites of lycopene, apo-10'-lycopenoic acid and apo-12'-lycopenal can induce cell cycle arrest in cancer cells [29].

Differentiation-Related Proteins

Induction of malignant clonogenic cells to differentiate into mature cells with distinct functions similar to those of nonmalignant cells has been proposed as an alternative to cytotoxic chemotherapy, and may be useful for chronic chemoprevention. Lycopene alone induces differentiation of HL-60 promyelocytic leukemia cells. A similar effect has also been described for other carotenoids such as β-carotene, lutein and the saffron carotenoids. The differentiation effect of lycopene was associated with elevated expression of several differentiation-related proteins such as cell surface antigen (CD14) and oxygen burst oxidase [27]. Most importantly, carnosic acid and its combinations with 1,25(OH)2D3 and retinoic acid transcriptionally activated the expression of nuclear hormone receptors such as vitamin D3 receptor (VDR), retinoic acid receptor (RAR), and retinoid X receptor (RXR) [30].

Retinoic Acid Receptor (RAR):

The structural similarity between lycopene and β-carotene suggests that lycopene or some of its oxidized derivatives may activate retinoid-like receptors. Acyclo-retinoic acid, a hypothetical oxidation product of lycopene, is the open chain analog of retinoic acid [31].

Retinoids and carotenoids are important dietary factors which regulate cellular differentiation and growth, so that they are thought to be particularly effective at preventing the development of certain tumors. They play this role as ligands of the nuclear retinoic acid receptors, RAR and RXR. These ligand-activated nuclear receptors induce the transcription of target genes by binding to retinoic acid-responsive elements in the promoter regions. Among these target genes, the RARβ gene is of great interest, being able to encode a potential tumor suppressor [32].

β-Carotene and its oxidative metabolite, apo-14'-carotenoic acid, are reported to reverse the down-regulation of RARβ by smoke-borne carcinogens in normal bronchial epithelial cells. In addition, the transactivation of the RARβ promoter by β-apo-14'-carotenoic acid appears to occur via its metabolism to all-*trans*-retinoic acid. Therefore, the molecular mode of the action of β-carotene might be mediated by retinoic acid through transcriptional activation of a series of genes with distinct anti-proliferative or pro-apoptotic activity, which allows for the elimination of neoplastic and preneoplastic cells with irreparable alterations [33].

Peroxisome proliferator-activated receptors (PPARs):

PPARγ is expressed at significant levels in a variety of human primary and metastatic carcinomas. The presence of PPARγ receptors in various cancer cells, their activation by fatty acids, prostaglandins and related hydrophobic agents in the μM range makes this liganded transcription factor an interesting target for carotenoid derivatives [34].

Recently, a new molecular mechanism was reported by which lycopene regulates cigarette smoke-driven inflammation in human macrophages [35]. It has shown that lycopene inhibits the production of the pro-inflammatory cytokine interleukin (IL)-8 induced by cigarette smoke. More recently, one study demonstrated that the

anti-proliferative effect of lycopene on human prostate cancer cells (LNCaP) involves the activation of the PPARγ-LXRα-ATP-binding cassette transporter 1 (ABCA1) pathway [36].

AP-1 Transcriptional Complex:

The activation of the AP-1 transcriptional complex is a middle-term event (1–2 h) in the mitogenic signaling pathway of IGF-1 and other growth factors. The AP-1 complex consists of protein from the Jun (c-Jun, JunB and JunD) and Fos (c-Fos, FosB, Fra-1 and Fra-2) families, which associate as homo- (Jun/Jun) or heterodimers (Jun/Fos). These proteins are often induced by mitogenic stimuli and tumor-promoting agents. They bind to the AP-1 site, known also as the TPA response element (TRE), on the promoter of many genes that are related to cell proliferation such as cyclin-D [11].

Lycopene and retinoic acid reduce growth factor-induced stimulation of AP-1 transcriptional activity by altering the composition of AP-1 complexes that bind to DNA [37]. The expression of c-Jun and c-Fos genes in the lungs of ferrets, supplemented with high-dose β-carotene and exposed to tobacco smoke, was elevated 3- to 4-fold [38]. In addition, they observed a strong proliferative response in lung tissue and squamous metaplasia, as well as an increase in the level of a cell proliferation marker, proliferating cell nuclear antigen. In β-carotene-supplemented animals, this increase was enhanced further by tobacco smoke [11].

Wnt/β-Catenin Pathway:

The Wnt/β-catenin pathway has been demonstrated to modulate cell proliferation, migration, apoptosis, differentiation and stem cell self-renewal. It has been shown that Wnt/β-catenin signaling is implicated in the maintenance of stem cells in a variety of cancers, including colorectal cancer. Activated Akt was shown to be able to phosphorylate Ser9 on glycogen synthase kinase 3β (GSK3β), which may decrease the activity of GSK3β, thereby stabilizing β-catenin [39].

Furthermore, the PI3K/Akt pathway is important in regulating the mammary stem/progenitor cells by promoting β-catenin downstream events through the phosphorylation of GSK3β. In colon cancer cells, lycopene suppressed Akt activation and nonphosphorylated β-catenin protein levels, and augmented the phosphorylated form of β-catenin, which were associated with reduced protein expression of cyclin D. Hence, lycopene may inhibit Wnt/β-catenin signaling via the connection along the Akt/GSK3β/β-catenin [11].

Inflammatory Cytokines

Cancer frequently develops in inflamed tissues, suggesting that the inflammatory condition is closely related to carcinogenesis. Examples of this relationship are: chronic hepatitis (HBV and HCV infection) and liver cancer; Barrett dysplasia and esophageal cancer; chronic gastritis (*H. pylori* infection) and gastric cancer; and inflammatory bowel disease and colorectal cancer [11].

The common denominator of all these conditions is that chronic inflammation leads to an increased incidence of cancer. Thus, suppression of inflammatory cytokine expression leads to inhibition of carcinogenesis. These inflammatory cytokines include IL-1β, IL-6 and tumor necrosis factor (TNF)-α. Cytokine expression is mainly regulated by NF-κB. A recent study demonstrated that astaxanthin suppressed the expression of these inflammatory cytokines and NF-κB, and inhibited inflammation-associated colon carcinogenesis in mice. In addition, lycopene is reported to inhibit pancreatitis [40].

2.1.3. Mechanism of cancer chemoprevention by polyphenols:

Polyphenols are compounds possessing one or more aromatic rings with one or more hydroxyl groups. They are broadly distributed in the plant kingdom and are the most abundant secondary metabolites of plants, with more than 8,000 phenolic structures currently known, ranging from simple molecules such as phenolic acids to highly polymerized substances such as tannins.

Plant phenolics are generally involved in defense against ultraviolet radiation or aggression by pathogens, parasites and predators, as well as contributing to plants' colors. They are ubiquitous in all plant organs and are therefore an integral part of the human diet. Phenolics are widespread constituents of plant foods (fruits, vegetables, cereals, olive, legumes, chocolate, etc.) and

beverages (tea, coffee, beer, wine, etc.), and partially responsible for the overall organoleptic properties of plant foods [9].

Phenolic extracts or isolated polyphenols from different plant food have been studied in a number of cancer cell lines representing different evolutionary stages of cancer. For example, berry extracts prepared from blackberry, raspberry, blueberry, cranberry, strawberry and the isolated polyphenols from strawberry including anthocyanins, kaempferol, quercetin, esters of coumaric acid and ellagic acid, were shown to inhibit the growth of human oral (KB, CAL-27), breast (MCF-7), colon (HT-29, HCT-116), and prostate (LNCaP, DU-145) tumor cell lines in a dose-dependent manner with different sensitivity between cell lines [9].

Cancer development is a multistage process that involves a series of individual steps including initiation, promotion, progression, invasion and metastasis (**Fig. 6**).

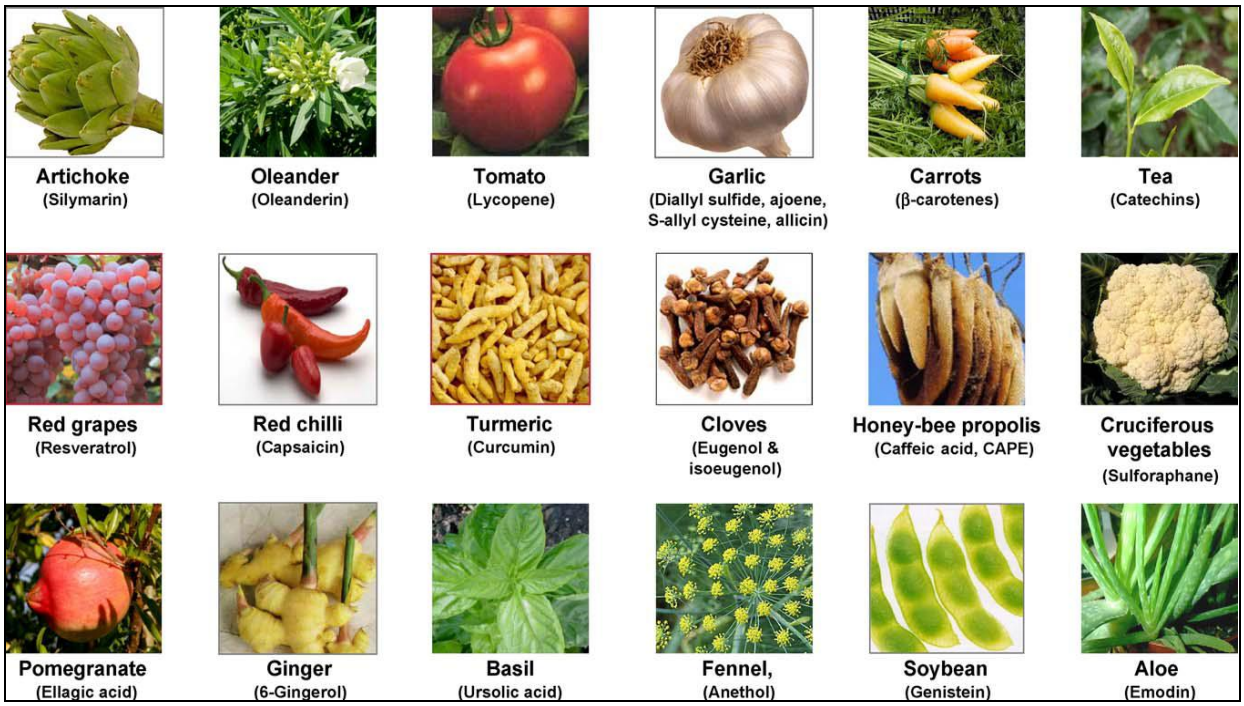

FIG. 5: BEST DIETARY SOURCES OF PHENOLIC COMPOUNDS.

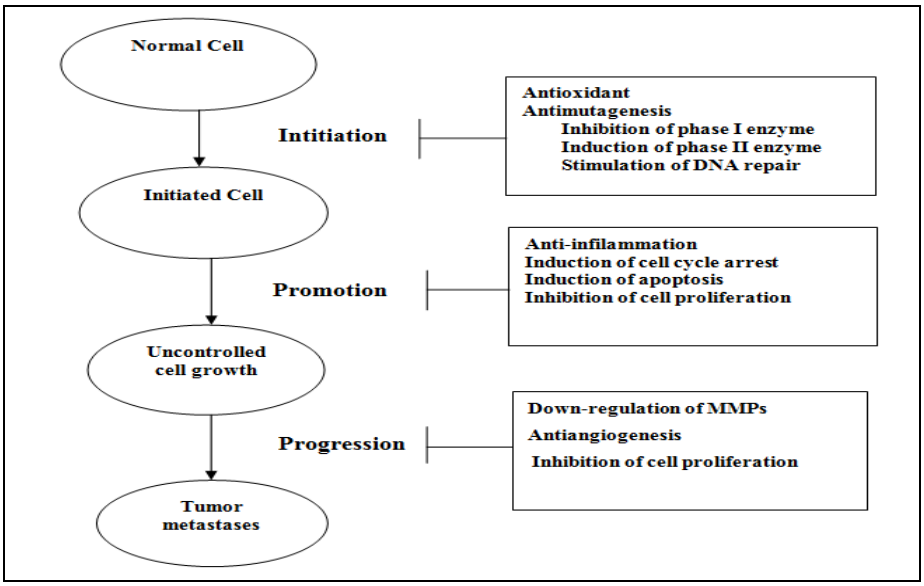

FIG.6: POTENTIAL ANTICANCER MECHANISMS OF PLANT PHENOLICS DURING CANCER DEVELOPMENT.

Tumor initiation begins when DNA, in a cell or population of cells, is damaged by exposure to carcinogens. If the DNA damage escapes repair, it can lead to genetic mutation. The resulting somatic mutation in a damaged cell can be reproduced during mitosis, which given rise to a clone of mutated cells. Tumor promotion is a selective clonal expansion of the initiated cells to form an actively proliferating multi-cellular premalignant tumor cell population. It is an interruptible or reversible and long term process. During progression, premalignant cells developed into tumors through a process of clonal expansion. In the late stages of cancer development, invasion and metastasis happens, where tumor cells detach from the primary tumor mass, migrate through surrounding tissues toward blood vessels or lymphatic vessels, and create a second lesion. Metastasis is the major cause of cancer mortality.

It is widely accepted that human cancer development does not occur through these discrete phases in a predictable manner, rather it is best characterized as an accumulation of alteration in cancer regulating genes, such as oncogenes, tumor suppressor genes, resulting in altered cellular processes, namely, decreased apoptosis, increased proliferation, and cell maturation and differentiation. The inhibitory effect of natural phenolics in carcinogenesis and tumor growth may be through two main mechanisms: modifying the redox status and interfering with basic cellular functions (cell cycle, apoptosis, inflammation, angiogenesis, invasion and metastasis) [41].

Epigenetic changes, such as DNA methylation, histone modifications and post transcriptional gene regulation by non-coding microRNAs (miRNAs) are easily influenced by dietary and environmental factors. These processes affect transcript stability, DNA folding, nucleosome positioning, chromatin compaction, and complete nuclear organization of the genetic material. Synergistically and cooperatively they determine whether a gene is silenced or expressed, as well as the timing and tissue-specificity of the expression of these genes. Dietary polyphenols can potentially impact all three epigenetic modifications, which in turn contribute towards their chemopreventive potential. Although epigenetic changes are heritable in somatic cells, these modifications are also potentially reversible, which makes them attractive and promising avenues for cancer preventive and therapeutic strategies. Dietary polyphenols from green tea, turmeric, soybeans, broccoli and others have shown to possess multiple cell-regulatory activities within cancer cells [10].

At the cellular level, there is good evidence that polyphenols present in tea, red wine, cocoa, fruit juices, and olive oil influence carcinogenesis and tumor development. For example, they may interact with reactive intermediates and activated carcinogens and mutagens, may modulate the activity of key proteins involved in controlling cell cycle progression and influence the expression of many cancer-associated genes [20].

Polyphenols may exert these anticancer effects via a variety of mechanisms, including removal of carcinogenic agents, modulation of cancer cell signaling and cell cycle progression, promotion of apoptosis and modulation of enzymatic activities. For example, the enhancement of glutathione peroxidase, catalase, NADPH-quinone oxidoreductase, glutathione S-transferase and/or cytochrome P450 enzyme activity by polyphenols may aid in the detoxification of carcinogenic agents. Furthermore, they may modulate the activity of signaling pathways (*i.e.*, MAPK kinase and PI3 Kinase), which are involved in cancer cell proliferation [20].

Chemopreventing phytochemicals:

Curcumin:

Curcumin (diferuloylmethane) is a major chemical component of turmeric (*Curcuma longa* Linn.) and is used as a spice to give a specific flavor and yellow color to food [10, 12].

The chemopreventive properties of curcumin are attributed to its effect on several targets including transcription factors, growth regulators, adhesion molecules, apoptotic genes, angiogenesis regulators, and cellular signaling molecules. In human prostate cancer cell line, curcumin reduced MDM2 protein and mRNA and enhanced the expression of the tumor suppressor p21/WAF1, a gene that encodes a potent cyclin-dependent kinase

inhibitor of cyclin-CDK2 and -CDK4 complexes, inducing apoptosis and inhibiting proliferation [12].

Epigallocatechin gallate (EGCG):
EGCG is an antioxidant and chemopreventive polyphenol that is found in green tea. It has been shown to suppress malignant transformation in a PMA-stimulated mouse epidermal JB6 cell line, which seemed to be mediated by blocking activation of Ap123 [10].

According to cell-culture studies, EGCG induced apoptosis and cell cycle arrest in many cancer cells without affecting normal cells. Particularly in prostate cancer cells, EGCG activates growth arrest and apoptosis primarily via p53-dependent pathway that involves the function of both p21 and Bax such that down regulation of either molecule confers a growth advantage to the cells [12].

Mechanisms for the action of tea polyphenols include inhibition of MAP kinases and the PI3K/AKT pathway, inhibition of NFκB- and AP-1-mediated transcription, inhibition of growth factor-mediated signaling, inhibition of aberrant arachidonic acid metabolism, and other activities [42].

Genistein: (4,5,7-trihydroxyisoflavone)
Genistein is the predominant isoflavone in human nutrition, derived mainly from soybeans but also from other legumes, including peas, lentils, or beans. Genistein has chemopreventive properties, and in particular genistein has been shown to inhibit growth of both androgen-dependent and -independent prostate cancer cells in vitro. Several mechanisms have been proposed for genistein anticarcinogenic activity: inhibition of protein-tyrosine kinase, with the result of alleviating the growth of cancer cells by inhibiting PTK-mediated signaling mechanisms; inhibition of topoisomerases I and II and protein histidine kinase with antiproliferative or proapoptotic effects; antioxidant effects, through inhibition of the expression of stress response related genes; inhibition of NF-κB and Akt signaling pathways; the inhibition of angiogenesis; the down regulation of transforming growth factor-beta (TGF-β), and the inhibition of epidermal growth factor (EGF) [12].

Resveratrol: (3,4,5-trihydroxy-*trans*stilbene)
Resveratrol is a phytoalexin present in grapes and a key antioxidant ingredient of red wine. The cardioprotective and cancer preventive actions of resveratrol may be attributable to anti-inflammatory effects such as the inhibition of synthesis and release of pro-inflammatory mediators, modifications of eicosanoid synthesis, inhibition of some activated immune cells, or inhibiting enzymes such as cyclooxygenase-1 (COX-1) or cyclooxygenase-2 (COX-2). Resveratrol inhibited experimental tumorigenesis in a wide range of animal models by targeting many components of intracellular signaling pathways including pro-inflammatory mediators, regulators of cell survival and apoptosis, tumor angiogenic and metastatic switches by modulating a distinct set of upstream kinases, transcription factors and their regulators [43].

Research from in vitro and in vivo studies indicate that resveratrol can overcome chemo-resistance in tumor cells by modulating apoptotic pathways, down-regulating drug transporters, down-modulating proteins involved in tumor cell proliferation, and inhibiting NF-κB and STAT-3 pathway [12].

Quercetin:
Quercetin is a flavonoid ubiquitously distributed in edible plant foods, caffeic acid phenethyl ester, sulphoraphane, silymarin, apigenin, emodin and anethole. It is the main representative of the flavonol class and a polyphenolic antioxidant found in a variety of fruits and vegetables, highly concentrated in onions, broccoli, apples, grapes (red wine), and in soybeans. This flavonoid, besides having antioxidant and anti-inflammatory activities, has been shown to possess potent antiproliferative effects against various malignant cells [12]. Quercetin has been reported to suppress the activation of NF-kB and AP1, which might contribute to their chemopreventive and/or cytostatic effects [10].

Quercetin treatment has been associated with selective antiproliferative effects and induction of cell death, predominantly through an apoptotic mechanism, in cancer cell lines. This compound seems to be able to induce apoptosis through multiple mechanisms: causing arrest in the G1

phase of the cell cycle or through interaction with cell cycle-regulated proteins, like cyclin D1 and CDK4; releasing cytochrome c and activating caspase-9 and caspase-3; through inhibition of PI3K, an enzyme involved in the pivotal cell survival pathway, synergizing the effect of ECGC. A study showed that this natural compound inhibits the expression of MMP 2 and 9 in prostate cancer cells (PC-3).

As it has been detected that MMP-2 and 9 expressions were regulated by MAP kinase signaling pathways and quercetin is an inhibitor of several kinases including MAP kinases and tyrosine kinases, it is reasonable to speculate that quercetin might have downregulated the expression of MMP-2 and -9 through inhibitions of protein kinases [12].

Proanthocyanidins:

Proanthocyanidins are naturally occurring phenolic compounds that are widely found in fruits, vegetables, nuts, seeds, flowers, pine bark, grape seed and red wines. Grape seed proanthocyanidins (GSPs) have been shown to be potent antioxidants and free radical scavengers. In addition to have anti-oxidant activity, GSPs have been shown to have anti-carcinogenic activity in different tumor models. A number of studies have shown that GSPs exert their anti-cancer effects through the suppression of NF-κB. *In vitro* treatment of human epidermoid carcinoma A431 cells with GSPs down-regulates the constitutive expression or basal level of NF-κB/p65 and IKKα in these cells and simultaneously inhibits the degradation of IκBα protein, a regulator of NF-κB [17].

TABLE 2: SUMMARY OF STUDIES ON POLYPHENOLS AND THEIR RESPECTIVE MECHANISMS OF ACTION.

Compound	Type of study	Mechanisms of action
Curcumin	*In vitro;* in humans	Reduction of MDM2 protein and induction of gene NKX3.; induction of apoptosis and the activation of procaspase-3 and -8 and caspase-9 and -3;reduction of MMP-2 and 9; decrease of PGE-2
Epigallocatechin-3-gallate	*In vitro; In vivo;* In humans	Activation of caspase-6 and -9; reduction of expression of androgen receptor; inhibition of (MMP-2 and -2) and VEGF
Resveratrol	*In vitro*	Inhibition of the formation of free radicals and induction of apoptosis.
Quercetin	*In vitro*	Activation of caspase-9 and caspase-3; induction of apoptosis; downregulation of the expression of MMP-2 and -9; suppression of androgen receptor
Genistein	*In vitro: In vivo:*	Inhibition of angiogenesis and downregulation of TGF-β and EGF; increase of the glutathione peroxidase (GPx)-1; decrease of metastases by 96% ; serum prostate specific antigen (PSA) decreased by 7.8%

CONCLUSION: Cancer chemoprevention is a rapidly expanding discipline that focuses on the discovery and identification of dietary agents and drugs that prevent or inhibit malignant tumor development.

Since approximately one-third of the overall risk of cancer is attributable to diet, a large number of dietary compounds have been tested to determine their chemopreventive ability using animal carcinogenesis models. The higher eukaryotic aerobic organisms, including man, cannot exist without oxygen, yet oxygen represents a danger to their very existence due to its high reactivity. This fact has been termed the paradox of aerobic life. A number of ROS are generated during normal aerobic metabolism such as the superoxide, hydrogen peroxide and the hydroxyl radical. In addition, singlet oxygen can be generated through photochemical events (in skin and eyes), and lipid peroxidation can lead to peroxyl radical formation. These oxidants collectively contribute to aging and degenerative diseases such as cancer and atherosclerosis through oxidation of DNA, proteins and lipids. Antioxidant compounds can decrease mutagenesis, and thus carcinogenesis, both by decreasing oxidative damage of DNA and by decreasing oxidant-stimulated cell division. The human body maintains an array of endogenous antioxidants such as catalase and superoxide dismutase.

Strong and consistent epidemiology evidence indicates a diet with high consumption of

antioxidant rich fruits and vegetables significantly reduces the risk of many cancers, suggesting that certain dietary antioxidants could be effective agents for the prevention of cancer incidence and mortality. These agents present in the diet are a very promising group of compounds because of their safety, low toxicity, and general acceptance.

Exogenous dietary antioxidants such as ascorbic acid (Vitamin C), α-tocopherol (Vitamin E) and carotenoids play important roles in reducing oxidative damage as well, and their serum levels have the potential to be manipulated. Major carotenoids with antioxidant activity that have been extensively evaluated with regard to their cancer chemopreventive ability include: α- and β-carotenes, β-cryptoxanthin, lycopene, lutein and zeaxanthin. The mechanisms underlying the anticancer and/or cancer chemopreventive activities of carotenoids may involve changes in pathways leading to cell growth or cell death. These include immune modulation, hormone and growth factor signaling, regulatory mechanisms of cell cycle progression, cell differentiation and apoptosis.

Phenolic compounds constitute one of the most numerous and ubiquitous group of plant metabolites, and are an integral part of the human diet. It was found that in addition to their primary antioxidant activity, this group of compounds displays a wide variety of biological functions which are mainly related to modulation of carcinogenesis. Various in vitro and in vivo systems have been employed to determine the anticarcinogenic and anticancer potential of these natural phenolic compounds or extracts. Natural phenolics have been found to intervene at all stages of cancer development. In addition to their antioxidant action, the inhibition of cancer development by phenolic compounds relies on a number of basic cellular mechanisms, involving a spectrum of cellular basic machinery.

Effectiveness of natural chemopreventive agents reflects their ability to counteract certain upstream signals, such as NF-kB, AP1, TNF, β-catenin, etc. Interestingly, dietary polyphenols can also potentially epigenetic modifications, such as DNA methylation, histone modifications and post transcriptional gene regulation by non-coding microRNAs (miRNAs). In addition, phenolic compounds possess antiangiogenesis effects, which is an important aspect in the inhibition of tumor growth, invasion and metastasis.

RECOMMENDATION: Cancer is a growing health problem around the world, particularly with the steady rise in life expectancy. It has become obvious, that chemoprevention in close relation to chemotherapy, enforced by edible phytochemicals is now considered to be an inexpensive, readily applicable, acceptable and accessible approach to cancer control and management. Hence, with healthcare costs being an international key issue today, I strongly recommend that it would be cost-effective to promote the awareness and consumption of phytochemicals as a cancer-preventive and therapeutic strategy, within the health system.

REFERENCES:

1. Anand P, Kunnumakkara AB, Kunnumakara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, Sung B, Aggarwal BB: Cancer is a preventable disease that requires major lifestyle changes. Pharm. Res. 2008; 25 (9): 2097–2116
2. Croce CM: Oncogenes and cancer. N. Engl. J. Med. 2008; 358 (5): 502–511.
3. Knudson AG: Two genetic hits (more or less) to cancer. Nat. Rev. Cancer 2001; 1(2): 157–162.
4. WHO Cancer worldwide. World Health Organization Report, 2012.
5. Langseth L: Oxidants, antioxidants and disease prevention. International life science institute (ILSI) Europe concise monograph series 1995; 1:1-13
6. Uttara B, Singh AV, Zamboni P, Mahajan RT: Oxidative Stress and Neurodegenerative Diseases: A Review of Upstream and Downstream Antioxidant Therapeutic Options. Current Neuropharmacology 2009; 7(1): 65-74
7. Sies H: Oxidative stress: Oxidants and antioxidants. Experimental physiology 1997; 82(2): 291–295.
8. Rhee SG: Cell Signaling: H_2O_2, a Necessary Evil for Cell Signaling". Science 2006; 312(5782): 1882–1883.
9. Dai J, Mumper RJ: Plant Phenolics: Extraction, Analysis and Their Antioxidant and Anticancer Properties. J.molecules 2010; 15:7313-7352
10. Karikas GA: Chemoprevention molecular and biochemical mechanisms involved in cancer control and management. Health Science Journal 2011; 5(2): 149-154
11. Tanaka T, Shnimizu M, and Moriwaki H: Cancer Chemoprevention by Carotenoids. J.molecules 2012; 17(1): 3202-3242
12. Cimino S, Sortino G, Favilla V, Castelli T, Madonia M, Sansalone S, Russo GI, Morgia G: Polyphenols: Key Issues Involved in Chemoprevention of Prostate Cancer. Oxidative Medicine and Cellular Longevity J. 2012; 1-8
13. Lin J, Cook NR, Albert C, Zaharris E, Gaziano J M, Denburgh MV, Buring JE, Manson JE: Vitamins C and E and Beta Carotene Supplementation and Cancer Risk: A Randomized Controlled Trial. Jnci oxford journals org. 2009; 101(1): 14-23

14. Siddiqui IA, Adhami VM, Ahmad N, and Mukhtar H: Nanochemoprevention: Sustained Release of Bioactive Food Components for Cancer Prevention. Nutr. Cancer 2010; 62(7): 883-890
15. Seifried HE, Anderson DE, Fisher EI, Milner JA: A review of the interaction among dietary antioxidants and reactive oxygen species. Journal of Nutritional Biochemistry 2007; 18: 567–579
16. Clarke JD, Dashwood RH, and Ho E: Multi-targeted prevention of cancer by sulforaphane. Cancer Lett. 2008; 269(2): 291–304.
17. Nandakumar V, Singh T, and Katiyar SK: Multi-targeted prevention and therapy of cancer by Proanthocyanidins. Cancer Lett. 2008; 269(2): 378–387.
18. Su CC, Chen GWEI, Lin JG, Wu LIITZU, and Chung JG: Curcumin inhibits cell migration of human colon cancer colo 205 cells through the inhibition of nuclear factor kappa B/p65 and down-regulates cyclooxygenase-2 and matrix metalloproteinase-2 expressions. Anticancer Res. 2006; 26(2A):1281-1288.
19. Kim AL, Zhu Y, Zhu H, Han L, Kopelovich L, Bickers DR, Athar M: Resveratrol inhibits proliferation of human epidermoid carcinoma A431 cells by modulating MEK1 and AP1 signalling pathways. Exp Dermatol. 2006; 15(7): 538-546.
20. Vauzour D, Rodriguez-Mateos A, Corona G, Oruna-Concha MJ and Spencer JPE: Polyphenols and Human Health: Prevention of Disease and Mechanisms of Action. J. Nutrients 2010; 2:1106-1131
21. Shukla S, Gupta S: Apigenin-induced cell cycle arrest is mediated by modulation of MAPK, PI3K/Akt, and loss of cyclin D1associated retinoblastoma dephosphorylation in human prostate cancer cells. Cell Cycle 2007; 6:1102–1114.
22. Fulda S: Modulation of apoptosis by natural products for cancer therapy. Planta Med., 2010; 76(11): 1075-1079.
23. Shaw RJ, Cantley LC: Ras, PI3K and mTOR signaling controls tumour cell growth. Nature 2006; 441(7092): 424-430.
24. Li W, Frame LT, Hirsch S, Cobos E: Genistein and hematological malignancies. Cancer lett., 2010; 296(1): 1-8.
25. Voskuil DW, Vrieling A, Van't Veer LJ, Kampman E, Rookus MA: The insulin-like growth factor system in cancer prevention: Potential of dietary intervention strategies. Cancer Epidemiol. Biomark. Prev. 2005; 14:195–203.
26. Karas M, Amir H, Fishman D, Danilenko M, Segal S, Nahum A, Koifmann A, Giat Y, Levy J, Sharoni Y: Lycopene interferes with cell cycle progression and insulin-like growth factor I signaling in mammary cancer cells. Nutr. Cancer 2000; 36:101–111.
27. Amir H, Karas M, Giat J, Danilenko M, Levy R, Yermiahu T, Levy J, Sharoni Y: Lycopene and 1,25-dihydroxyvitamin D3 cooperate in the inhibition of cell cycle progression and induction of differentiation in HL-60 leukemic cells. Nutr. Cancer 1999; 33:105–112.
28. Satomi Y, Nishino H: Implication of mitogen-activated protein kinase in the induction of G1cell cycle arrest and gadd45 expression by the carotenoid fucoxanthin in human cancer cells. Biochem. Biophys. Acta, 2009; 1790:260–266.
29. Ford NA, Elsen AC, Zuniga K, Lindshield BL, Erdman JW: Lycopene and apo-12'-lycopenal reduce cell proliferation and alter cell cycle progression in human prostate cancer cells. Nutr. Cancer; 2011; 63:256–263.
30. Danilenko M,Wang X, Studzinski GP: Carnosic acid and promotion of monocytic differentiation of HL60-G cells initiated by other agents. J. Natl. Cancer Inst., 2001; 93:1224–1233.
31. Stahl W, von Laar J, Martin HD, Emmerich T, Sies H: Stimulation of gap junctional communication: Comparison of acyclo-retinoic acid and lycopene. Arch. Biochem. Biophys., 2000; 373:271–274.
32. Pavan B, Biondi C, Dalpiaz A: Nuclear retinoic acid receptor β as a tool in chemoprevention trials. Curr. Med. Chem., 2006; 13:3553–3563.
33. Prakash P, Liu C, Hu KQ, Krinsky NI, Russell RM, Wang XD: β-Carotene and β-apo-14'-carotenoic acid prevent the reduction of retinoic acid receptor β in benzo[a]pyrene-treated normal human bronchial epithelial cells. J. Nutr. 2004; 134: 667–673.
34. Youssef J, Badr M: Peroxisome proliferator-activated receptors and cancer: Challenges and opportunities. Br. J. Pharmacol., 2011; 164:68–82.
35. Simone RE, Russo M, Catalano A, Monego G, Froehlich K, Boehm V, Palozza P: Lycopene inhibits NF-kB-mediated IL-8 expression and changes redox and PPARgamma signalling in cigarette smoke-stimulated macrophages. PLoS One, 2011; 6:e19652.
36. Yang CM, Lu IH, Chen HY, Hu ML: Lycopene inhibits the proliferation of androgen-dependent human prostate tumor cells through activation of PPARγ-LXR-ABCA1 pathway. J. Nutr. Biochem. 2012; 23:8–17.
37. Palozza P, Parrone N, Catalano A, Simone R: Tomato lycopene and inflammatory cascade: Basic interactions and clinical implications. Curr. Med. Chem. 2010; 17:2547–2563.
38. Wang XD, Liu C, Bronson RT, Smith DE, Krinsky NI, Russell M: Retinoid signaling and activator protein-1 expression in ferrets given β-carotene supplements and exposed to tobacco smoke. J. Natl. Cancer Inst., 1999; 91:60–66.
39. Schulenburg A, Cech P, Herbacek I, Marian B, Wrba F, Valent P, Ulrich-Pur H: CD44-positive colorectal adenoma cells express the potential stem cell markers musashi antigen (msi1) and ephrin B2 receptor (EphB2). J. Pathol. 2007; 213:152–160.
40. Kim H: Inhibitory mechanism of lycopene on cytokine expression in experimental pancreatitis. Ann. N.Y. Acad. Sci. 2011; 1229:99–102.
41. Kampa M, Nifli AP, Notas G, Castanas E: Polyphenols and cancer cell growth. Rev. Physiol. Biochem. Pharmacol. 2007; 159:79-113.
42. Yang CS: Antioxidative and anti-carcinogenic activities of tea polyphenols. Arch Toxicol. 2009; 83(1): 1-17.
43. Brown L, Kroon PA, Das DK, Das S, Tosaki A, Chan V, Singer MV, Feick P: The biological responses to resveratrol and other polyphenols from alcoholic beverages. Alcohol Clin Exp Res. 2009; 33(9): 1513–1523.

How to cite this article:
Mudie K, Gebregzabher A and Kassa D: Investigation of the Biochemical Mechanism of Action of Antioxidants in the Prevention of Cancer. Int J Pharm Sci Res 2015; 6(11): 4556-69.doi: 10.13040/IJPSR.0975-8232.6(11).4556-69.