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HEALTH BENEFITS OF POLYPHENOLS AND PREVENTION OF DISEASES IN HUMANS

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Abstract

Increased consumption of fruits and vegetables is associated with a lower risk of chronic disease such as cardiovascular disease, some forms of cancer, and neurodegeneration. Pro-oxidant-induced oxidative stress contributes to the pathogenesis of numerous chronic diseases and, as such, dietary antioxidants can quench and/or retard such processes. Dietary polyphenols, i.e., phenolic acids and flavonoids, are a primary source of antioxidants for humans and are derived from plants including fruits, vegetables, spices, and herbs. Based on compelling evidence regarding the health effects of polyphenol-rich foods, new dietary supplements and polyphenol-rich foods are being developed for public use. Consumption of such products can increase dietary polyphenol intake and subsequently plasma concentrations beyond expected levels associated with dietary consumption and potentially confer additional health benefits. Furthermore, bioavailability can be modified to further increase absorption and ultimately plasma concentrations of polyphenols. However, the upper limit for plasma concentrations of polyphenols before the elaboration of adverse effects is unknown for many polyphenols. Moreover, a considerable amount of evidence is accumulating which supports the hypothesis that high-dose polyphenols can mechanistically cause adverse effects through pro-oxidative action. Thus, polyphenol-rich dietary supplements can potentially confer additional benefits but high-doses may elicit toxicity thereby establishing a double-edge sword in supplement use.

INTRODUCTION

Today the world appears to be increasingly interested in the health benefits of foods and have begun to look beyond the basic nutritional benefits of food stuffs to disease prevention and health enhancing ingredients of the same. Traditional systems of medicine owe their significance to the bioactive components that have their origin in plant sources and most of them were associated with routine food habits. Plants have an almost limitless ability to synthesize aromatic substances, most of which are phenols or their oxygen substituted derivatives (Geissman, 1963). Most are secondary metabolites, of which at least 12000 have been isolated, a number estimated to be less than 10% of the total (Schultes,1978). In many cases these substances serve as plant defense mechanism against predation by microorganisms, insects and herbivores. Polyphenols are widely distributed plantderived dietary constituents and have been implicated as the active components in a number of herbal and traditional medicines (Wollenweber, 1988). More than 5000 plant polyphenols have been identified and several of them are known to possess a wide spectrum of pharmacological properties (Beretz et al, 1977). Polyphenols exhibit several biological effects such as antiinflammatory, anti-microbial, anti-carcinogenic, anti-HIV, cardioprotective and neuroprotective influence. In view of their wide range of pharmacological and biological activities they seem to have a great therapeutic potential for cancer.

Chemical Structure Flavonoids are the major polyphenols present in wide variety of plant sources. The basic structure of flavonoids contains a heterocyclic skeleton of flavan (2- phenylbenzopyrane). The structure is represented by a benzene ring (A), condensed with a heterocyclic sixmembered pyran or pyrone ring (C), which in the 2 or 3 position carries a phenyl ring (B) as a substituent (Figure 1). The constituent polyphenolic units are derived from the secondary plant metabolism of the shikimate pathway (Dewick, 1995). Flavonoids are often hydroxylated at positions 3, 5, 7, 2', 3', 4', 5'. Usually in the plant system, these flavonoids exist in conjugated forms, the most common being the glycosides. When glycosides are formed, the glycosidic linkage is normally

located at position 3 or 7 and the carbohydrate moiety can be Lrhamnose, D-glucose, gluco-rhamnose, galactose or arabinose (Middleson, 1984). Flavonoid is a major class of polyphenols found in plant sources.

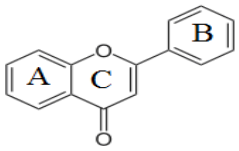

Figure 1 the basic structure of flavonoids

Figure 2 illustrates flavonoid subclasses along with their important members that are known to carry pharmacological benefits. Sources and Bioavailability For any chemical moiety to exert a biological effect, it should be bioavailable i.e. it must be readily absorbed into the bloodstream and reach concentrations that have the potential to exert effects in vivo. Most of the polyphenols are known to be readily absorbed (Scalbert and Williamson, 2000; Rowland, 2003) but these compounds are prone to be modified into other forms inside biological systems, one such common chemical modification being conjugation (Lambert et al, 2005). Curcumin undergoes metabolic O-onjugation to curcumin glucuronide and curcumin sulfate and bioreduction to etrahydrocurcumin, hexahydrocurcumin, and hexahydrocurcuminol in rats and mice in vivo and in suspensions of human and rat hepatocytes (Ireson et al, 2001). Certain curcumin metabolites, such as tetrahydrocurcumin, possess anti-inflammatory (Mukhopadhyay et al, 1992) and antioxidant activities (Sugiyama et al, 1996) similar to those of their metabolic progenitor. Dietary resveratrol is rapidly absorbed and predominantly present in plasma as glucoronide and sulphate conjugates. When administered in food, such as wine or grape juice, resveratrol metabolism is significantly inhibited by other polyphenols due to competitive reactions with metabolizing phase II enzymes resulting in an increased concentration of the free form (Wenzel and Somoza, 2005).

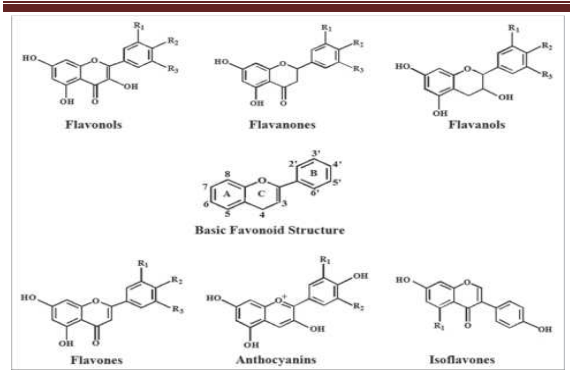

Figure 2 Chemical structures of sub-classes of flavonoids. Based on the variation in the type of heterocycle involved, flavonoids are divided into six major subclasses: flavonols, flavanones, flavanols, flavones, anthocyanins and isoflavones.

Isoflavones such as genistein are also known to undergo conjugation with glycosides and is metabolized in human intestine to dihydrogenistein and 6'-hydroxyO-esmethylangolensin.

Concentration of genistein has been shown to be higher in individuals consuming soy rich diet (Adlercreutz et al, 1993) and consequently genistein and its metabolites have been detected in plasma, breast aspirate and prostatic fluid (Mills et al, 1989). Similarly, other polyphenols are also known to be absorbed and metabolized into various end products which may or may not possess the biological effects of the parent compound. Therapeutic Potential exploring healing powers in plants is an ancient phenomenon. Traditional healers have long used plants to prevent or cure various diseased conditions. An insight into the investigations, both in vitro and in vivo, reveals the properties of plant polyphenols that could form the basis of their use in the prevention and cure of several disorders. Some of the important therapeutic properties of polyphenols with strong evidences from the existing literature have been discussed below.

Anti-HIV Properties

Human immunodeficiency virus (HIV), the etiologic agent for acquired immunodeficiency syndrome (AIDS) has been the most successful pathogen to challenge the humans in the last three decades. Globally, about 39.5 million adults are living with the syndrome (UNAIDS, WHO, 2006). In the past few years, several therapies have been tried but as of now, there is no conclusive treatment to eliminate this virus from the body once the infection has taken place. The efforts to develop vaccines against HIV have not been successful so far due to their ever-changing variants (Desrosiers, 2004). Flavonoids and

their derivatives have been reported to inhibit the growth and development of HIV by interrupting at several stages of its life cycle. Derivatives of hesperidin, particularly sulphonated and phosphorylated forms, have been studied by various scientists as hyaluronidase inhibitors and antimicrobial agent (Joyce et al, 1986).Acute HIV-1 infection has been shown to be suppressed by certain flavonoids and evidence for inhibition of HIV-1 protease, integrase and reverse transcriptase by flavonoids also exists (Critchfield et al,1996).Anti-HIV activity of scutellarin has been reported against three strains of human deficiency virus including laboratory-derived virus (HIV-1 IIIB), drug resistant virus (HIV-1 74V) and low passage clinically isolated virus (HIV-1 KM018)(Zhang et al, 2005). Scutellarin was found to inhibit several stages of HIV-1 replication with different potencies. It appeared to inhibit HIV-1 reverse transcriptase activity, HIV-1 particle attachment and cell fusion.

In cells harboring proviral HIV-1 DNA, viral transcription represents a potential therapeutic target, if selective inhibitors can be developed (Li et al, 1994). Chrysin, a flavonoid has been characterized as a potent inhibitor of HIV-1 transcription in chronically infected cells (Critchfield et al, 1996). The flavonoid halts the transcription by inhibiting casein kinase-II (CK-II) activity (Critchfield et al, 1997). CK-II may regulate HIV-1 transcription by phosphorylating cellular proteins involved in HIV-1 transactivation. Isoflavones have also been shown to inhibit transcription by repressing HIV-1 promotor activity (Wu et al, 1995). The multiple steps of the HIV-1 life cycle each lend themselves to potential therapeutic intervention. The interaction between the viral products and the host factors are critical to develop the host-pathogen relationship. HIV- 1 cellular entry via binding to CD4 and chemokine receptors well defines the principle of HIV-1 and host factor interaction (Fauci, 1996). Epigallocatechin-3-gallate (EGCG), the major polyphenol in tea has been reported to bind with CD4 receptor of TH cells, thus interfering with its ability to interact with gp120, an envelope protein of HIV-1 (Kawai et al, 2003). Inhibition of viral adsorption by flavonoids such as epicatechin has been attributed to an irreversible interaction with gp120 (de Clereq, 2003). This protective effect against HIV infection is mediated by

inhibiting virions from binding to the target cell surface. Recent studies documented that the beta-chemokine receptors, CCR2b, CCR3 and CCR5, and the alpha-chemokine receptors, CXCR1, CXCR2, and CXCR4 serve as entry coreceptors for HIV-1 (Verma et al, 2007).Grape seed polyphenols, proanthocyanidins, have been shown to down regulate HIV-1 entry coreceptors CCR2b, CCR3 and CCR5 gene expression by normal peripheral blood mononuclear cells (Nair et al, 2002).

These studies have clinical significance since the ability of polyphenols to interfere at multiple target sites of HIV might determine their successful use against ever changing variants. Antimicrobial Properties Microbiologists and natural product chemists are exploring the Earth for phytochemicals, which could be developed for the treatment of infectious diseases (Cowan, 1999). Polyphenols particularly, flavonoids are found to be effective antimicrobial agents against a wide array of microorganism. This is probably due to their ability to complex with extracellular and soluble proteins and also with the bacterial cell wall (Tsuchiya et al, 1996). Phenolics present in plants are known to be toxic to microorganisms (Mason and Wasserman, 1987). Many plant extracts derived from different parts of the plant have been analyzed for their active constituents possessing antibacterial activities. Antibacterial activity of leaf and stem bark of Pterocarpus santalinus was investigated for both gram-positive and gram-negative bacteria (Manjunatha, 2006). The stem bark and leaf extracts showed inhibitory activity against a number of infectious microbial strains including Enterobacter aerogenes and Staphylococcus aureus. The broadspectrum antibacterial activity exhibited by Pterocarpus santalinus may be attributed to its richness in isoflavone glucosides (Krishnaveni and Rao, 2000) .Flavonoids are known to be synthesized by plants in response to microbial infections (Dixon et al, 1983) and therefore, very obviously they have been found In vitro to be effective antimicrobial substance against a wide range of microorganisms. Catechins, an important group of flavonoids, have been extensively investigated due to their occurrence in oolong green teas. It has been reported in the past, that teas posse's antimicrobial activity (Toda et al, 1989) and that they contain a mixture of catechin

compounds. These compounds inhibited Vibrio cholerae (Borris, 1996), Streptococcus mutans (Batista et al, 1994), Shigella (Vijaya et al, 1995) and other bacterial strains in vitro. The catechins have been found to inactivate the cholera toxin from V. cholerae (Tsuchiya et al, 1996) and inhibit isolated bacterial glucosyl transferase in S. mutans (Nakahara et al, 1993). Many of the flavonoids are known to be hydroxylated and the site(s) and number of hydroxyl groups associated with the rings are thought to be related to their relative toxicity to microorganisms, with evidence that increased hydroxylation results in increased toxicity (Geissman, 1963). Catechol and pyrogallol both of which are hydroxylated phenols have been shown to be toxic to microorganisms. Inhibitory interaction between the polyphenols and protein or DNA has also been observed. Quinones are known to complex irreversibly with nucleophilic amino acids in proteins (Stern et al, 1996) often leading to inactivation of the protein via loss of function. This has been attributed for the wide range of quinone anti-microbial effects (Kazmi et al, 1994). The above references have well established the antimicrobial properties of plant polyphenols supporting their use to combat infective diseases. While 25 to 50% of current pharmaceuticals are derived from plants, none are used as antimicrobials, since our choice had been restricted to bacterial and fungal sources for these activities. However, with the increasing complexities of antibiotic resistance, the use of antibiotic needs to be checked and antimicrobial agents from plant origin be given a favourable insight for their therapeutic use.

Cardio protective properties

A longstanding tenet of nutrition holds that people with diets rich in fruits and vegetables enjoy better health than those eating few. Consequently, research has sought the components or compounds responsible for this apparent health benefit. Much of current research shows that free radicals are the connecting link between otherwise physiologically distinct diseases. As a result dietary antioxidants hold promise in at least delaying the onset/ progression of these diseases. The “French Paradox” – the observation that mortality from coronary heart disease is relatively

low in France despite relatively high levels of dietary saturated fat led to the idea that regular consumption of red wine (rich source of polyphenols) might provide additional protection from cardiovascular disease (Criqui and Ringel, 1994). In the prevention of cardiovascular disease, many of the observed effects of polyphenols can therefore be attributed to their recognized antioxidant and radical scavenging properties, which may delay the onset of atherogenesis by reducing chemically and enzymatically mediated peroxidative reaction (German and Walzem, 2000).Regular, moderate consumption of red wine is linked to a reduced risk of coronary heart disease (Li et al, 2006). Resveratrol, a component of red wine has been linked to a number of potentially cardioprotective effects (Szewczuk et al, 2004). Anthocyanidins have also been found to have antioxidant potential (Falchi et al., 2006). Studies suggest that EGCG can suppress reactive oxygen species and thereby prevent the development of cardiac hypertrophy (Li et al, 2006). Increase in LDL is taken as a parameter for the occurrence and susceptibility of cardiovascular diseases. Polyphenols such as dicvertin have been reported to produce a 12% decrease in LDL along with a 14% increase in HDL in coronary heart disease patients (Belaia et al., 2006). Lipid-lowering activity has also been reported in tea flavonoids (Li et al., 2006). Endothelial dysfunction is the pathophysiologic principle involved in the initiation and progression of arteriosclerosis. Some polyphenols have been shown to relax endothelium-denuded arteries. There have been several reports that extracts from grape and wine induce endothelium-dependent relaxation via enhanced and/ or increased biological activity of nitric oxide (NO) which leads to the elevation of cGMP levels (Andriambeloson, 1997). Resveratrol has been found to promote vasodilation by enhancing the production of NO (Wallerath et al, 2002). Genistein, one of the major isoflavones in soy protein, binds to estrogen receptor b with much higher affinity than to ERa (Kuiper et al, 1998) and can elicit endothelium dependant vasorelaxation in vitro (Figtree et al, 2000) and in vivo (Walker et al, 2001). Other isoflavones such as dihydrodaidzeins have also been reported to enhance endothelial function (Shen et al, 2006). Flavonoids have also

been found to be good hypochlorite scavenger in vitro and could have favorable effects in diseases such as atherosclerosis in which hypochlorite is known to play a significant role (Firuzi, 2004). As documented above, it is evident that natural polyphenolic compounds possess antioxidant, vasorelaxant and antihypertensive properties that are beneficial to cardiovascular health.

Neuroprotective properties

Neurodegenerative disorders are a heteregenous group of diseases of the nervous system, including the brain, spinal cord and peripheral nerves, which have different aetiologies. The multifactorial etiology of these diseases suggests that interventions having multiple targets such as polyphenols could have therapeutic potential for them. Moreover, epidemiological studies indicate that dietary habits and antioxidants from diet can influence the incidence of neurodegenerative disorders such as Alzheimer and Parkinson's diseases (Morris et al,, 2002). The nervous system is rich in fatty acids and iron. High levels of iron can lead to oxidative stress via the ironcatalyzed formation of ROS (Bauer and Bauer, 1999). In addition brain regions that are rich in catecholamines are vulnerable to free radical generation. One such region of the brain is the substantia nigra, where a connection has been established between antioxidant depletion and tissue degeneration (Perry et al, 2002). There is substantial evidence that oxidative stress is a causative or at least an ancillary factor in the pathogenesis of many neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS) (Ghadge et al., 1997), Huntington's disease (HD) and Schizophrenia (Philips et al, 1993) Flavonoids exhibit biological effects such as anti-inflammatory, antioxidant and metal chelating properties, which augment their role in neuroprotection. Reports also suggest that red wine that contains high levels of antioxidant polyphenols reduces the incidence of AD (Wang et al., 2006). Polyphenols such as EGCG, curcumin, extracts of blue berries and Scutellaria are also known to help in AD (Dai et al, 2006). In vitro studies show that green tea extract rich in catechins could protect neurons

from the amyloid beta-induced damages in AD (Bastianetto et al, 2006). EGCG is also found to be of use in ALS (Kohstl et al., 2006; Xu et al., 2006) and PD (Ramassamy, 2006). Extract of Scutellaria stem and polyphenols such as curcumin and naringenin also exhibit neuroprotection in PD (Shang et al., 2006). Alzheimer's disease is characterized by chronic inflammation and oxidative damages in the brain. Curcumin posses antioxidative and anti inflammatory properties and has thus been shown to exert a protective effect against oxidative damages initiated by divalent metals or suppress inflammatory damage by preventing metal induction of NF-κB and also inhibits amyloid beta fibril formation (Kim et al., 2005). Dietary polyphenols have potential as protective agents against neuronal apoptosis, through selective actions within stress activated cellular responses including protein kinase signaling cascade (Schroeter et al., 2006). Several dietary supplements with blueberries extracts have been reported to reduce some neurological deficits in aged animal models. Blueberries are a rich source of polyphenols such as catechins, epicatechins and anthocyanins. Recent studies investigating the effect of polyphenols in cognitive performance have demonstrated that dietary supplementation with blueberries extracts reversed cognitive deficits in Morris water maze performance test and Y-maze test in aged mice models (Joseph et al., 1999; Joseph et al., 2003). The studies therefore present a promising class of compound for possible application as health supplements and nutraceuticals for neuroprotection.

Anti-Carcinogenic Properties

Evidence in the literature suggests that the differential regulation (progression and prevention) of several disorders may be characterized through the food habits prevalent in different geopolitical regions of the world. Soybean food comprises a significant portion of Asian diet, providing 10% of the total per capita protein intake in Japan and China where the incidence of breast and prostate cancer is much less than that in the United States (Adlercreutz et al., 2003).Various classes of dietary polyphenols are under investigation for their anticancer properties in order to design novel strategies for chemoprevention (Ullah, 2008).Studies

have found that genistein, an isoflavone from soy can inhibit the growth of various cancer cell lines including leukemia, lymphoma, prostate, breast, lung and head and neck cancer cells (Alhasan et al., 1999). Pretreatment with genistein, potentiated cell killing induced by radiation in human PC-3 prostrate cancer cells in vitro (Hillman et al., 2001) and prostate tumor growth in vivo (Hillman et al., 2004). Another isoflavone present in soy, biochanin A has been found to have cytotoxic effect on cell growth in the mammary carcinoma cell line MCF-7 (Hsu et al., 1999), myeloid leukemia (Fung, 1997) and pancreatic tumor cells (Lyn et al., 1999). Biochanin A also induces a dose dependent inhibition of proliferation in LNCaP-cell and [3H] thymidine incorporation that is correlated with increased DNA fragmentation, indicative of apoptosis (Rike et al., 2002). Protein tyrosine kinases (PTKs) are known to play key roles in carcinogenesis, cell growth and apoptosis (Ulrich and Schlessinger, 1990). Genistein has been identified as a PTK inhibitor (Kyle et al., 1997). Transcription of genes is critical to cell growth and proliferation. Transcription factors interact with enhancer and promoter regions of target genes, which allow the binding of RNA polymerase and initiation of gene transcription process (Papavassiliou, 1995). Investigations have revealed that genistein treatment could inhibit DNA binding activity of a major transcription factor NF-kB in PC3 and LNCaP prostate cancer cells (Davis et al., 1999). Curcumin, a natural phenolic compound found in turmeric have been shown to have antiproliferative action against colon cancer, breast cancer and myeloid leukemia (Tsvetkov et al., 2005; Maheshwari et al., 2006). Antitumor activity of curcumin is believed to be in part due to its ability to block the NF kappa B pathway (Singh et al., 1995). Other studies have shown that curcumin inhibits cell growth and induces apoptosis in MCF-7, a human breast carcinoma cell line through modulation of insulin-like growth factor-1 (IGF- 1) system, including IGFs (IGF-1 and IGF-2), IGF-1R (IGF-1 receptor) and IGFBPs (IGF binding proteins), which have been implicated to play a critical role in the development of breast cancer (Xia et al., 2007). Resveratrol, the phenol antioxidant found in berries and grapes has been reported to posses anticancer properties (Aggarwal et al., 2004) and is able to inhibit

the formation of prostate tumors by acting on the regulatory genes such as p53 (Narayanan, 2006). Androgen independent DU145 human prostate cancer cells manifest resistance to radiation-induced apoptotic death (Yacoub et al., 2001). Scarlatti et al have reported that pre-treatment with resveratrol significantly enhances radiation induced cell death in DU145 cells (Scarlatti et al., 2007). Some polyphenols are known to inhibit the cancerous growth by arresting the cell cycle progression rather than inducing apoptosis. Genistein has been demonstrated to induce a G2/M cell cycle arrest in breast cancer cells, gastric adenocarcinoma cells and human melanoma cells (Casagrande and Darbon, 2000). Citrus fruit flavonoids, tangeretin and nobiletin have also been shown to inhibit human breast cancer cell lines MDAMB-435 and MCF-7 and human colon cancer cell line HT-29 by blocking cell cycle progression at G1 stage of the cell cycle (Morley et al., 2006). Such flavonoids which inhibit the growth and proliferation of cancer cell lines by arresting cell cycle are cytostatic and significantly block the proliferation without apoptosis. Inhibition of proliferation of human cancers without inducing cell death may be advantageous in treating tumors as it would restrict proliferation in a manner less likely to induce cytotoxicity and death in normal, non tumor tissues. Inhibition of tumor invasion and angiogenesis by popular flavonoids such as luteolin may also account for the antiproliferative properties of plant polyphenols (Bagli et al., 2004). Another convincing antiproliferative mechanism includes the oxidative DNA breakage by the prooxidant action of plant polyphenols in the presence of transition metals especially copper (Hadi et al., 2000; Azmi et al., 2006; Hadi et al., 2007). Flavonoids are recognized as naturally occurring antioxidants and this property has been implicated for their anticancer activity (Bors et al., 1998). However, evidence in the literature suggests that antioxidant properties of plant polyphenols may not fully account for their anticancer effects (Gali et al., 1992). In the context of copper being an essential constituent of chromatin (Bryan, 1979) and that the copper levels in tissues (Yoshida et al., 1993) and serum (Ebadi and Swanson, 1988) are considerably elevated in various malignancies, the mechanism of oxidative DNA breakage holds significance. In

addition to their potential as anticancer agents, an important role of plant polyphenols as natural modulators of cancer multidrug resistance (MDR) has been realized recently (Ullah, 2008). Resistance of recurrent disease to cytotoxic drugs is the principal factor limiting long-term treatment success against cancer. Flavonoids, a major class of plant polyphenol has been found to inhibit breast cancer resistance protein (BCRP), an ABC transporter, which plays an important role in drug disposition leading to chemoresistance in breast cancer (Shuzhong et al.,2005). Isoflavones such as biochanin A, daidzein (Chung et al., 2005) and green tea polyphenol EGCG (Feng et al, 2005) have also been shown to exhibit anti MDR activities in various drug resistant cancer cell lines such as doxorubicin resistant KB-A1 cells through the inhibition of P glycoprotein transporters. Curcumin has been reported to induce apoptosis in chemoresistant ovarian cancer cell lines SKOV3 and ES-2 (Wahl et al., 2007) the above findings suggest that the plant polyphenols have indeed emerged as an area of great promise for delineating innovative strategies in cancer chemoprevention.

CONCLUSION

Hippocrates (460-377B.C), the father of medicine recommended, “Let thy food be thy medicine and thy medicine be thy food”. Such an idea reflected the importance of dietary supplements for their therapeutic and preventive bioactive components due to their elevated margin of safety and desired range of efficacy. The above observation made centuries ago has now gained scientific verifications with epidemiological studies showing that the incidence of cancer and cardiovascular diseases are least in countries like India and China where vegetables, fruits and spices form an essential part of human diet. With regard to the extensive consumption of polyphenols in the diet, the biological activity of these compounds is an important area of scientific investigation. Given the potential therapeutic tendencies of these compounds, one would expect to observe their favourable effects in human population. The investigations, both in vitro and in vivo provide a definite link between the dietary intake of polyphenols and their

associated health benefits. However, the issue of bioavailability has to be addressed before any targeted therapy could be designed effectively. On the basis of what is known about the bioavailabilities, it seems likely that the organ sites that are most accessible to dietary polyphenols experience the protective effects of these compounds. Moreover, another way is to explore the biofactors that in combination with dietary polyphenols could stabilize and enhance their effects even under limited bioavailability. Nature has gifted us with numerous natural products, which we consume as food and which are the armamentarium of bioactive substances having diverse activities. Since diseases like cancer are multifactorial phenomenon in which many normal cellular pathways become aberrant, it is highly unlikely that one agent could prove effective against such disorders. In this regard foods, unlike drugs may have the advantage of simultaneously influencing various pathways that go awry in diseases like cancer. Another aspect that needs to be explored is that why the excessive use of fruits and vegetables is not harmful although they are routine part of human diet whereas an isolated compound may show detrimental effects as projected in various studies. Although, it is well understood that dose does determines whether a substance acts as a toxicant or not, it is important to note the significance of synergism among the components that are present together in a particular food. In this respect nutrient-nutrient interactions and synergism are required to be studied to augment their beneficial effects or otherwise reduce the side effects. The concept of food as medicine needs to be propagated to ensure healthy food habits.

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