Medicinal uses and chemistry of flavonoid contents of some common edible tropical plants

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ABSTRACT

Flavonoids are wide range of phytochemical with various pharmacological effects including antioxidant, anti-inflammation, anti-platelet, anti-allergic, cytotoxicity, reduce risk for heart disease or cancer etc. These flavonoids inhibited various enzymes such as prostaglandin synthase, lypoxygenase, cyclooxygenase, and induced detoxifying enzyme systems such as glutathione S-transferase. Flavonoids have significant vitamin C sparing activity and powerful antioxidants than the traditional vitamins such as quercetin, myricetin, rutin and apigenin. In vegetables, quercetin glycosides predominate, but glycosides of kaempferol, luteolin, and apigenin are also present. Fruits exclusively contain quercetin glycosides, whereas kaempferol and myricetin glycosides are found only in trace quantities. In this article we mainly discussed on three major flavonols (kaempferol, quercetin, and myricetin) and two major flavones (luteolin and apigenin) of edible tropical plants.

Keywords: Flavonoids; myricetin; quercetin; kaempferol; luteolin; apigenin

INTRODUCTION

Today we appears to be increasingly interested in the health benefits of foods and look beyond the basic nutritional benefits of food stuffs to disease prevention and health enhancing ingredients. Traditional systems of medicine be indebted their significance to the bioactive components from natural sources and most of them were associated with food habits. Plants have aromatic substances, most of which are phenols or their oxygen substituted derivatives [1]. Most are secondary metabolites, of which at least 12000 have been isolated, a number estimated to be less than 10% of the total [2]. In many cases these substances serve as plant defense mechanism against microorganisms, insects and herbivores. Polyphenols are widely distributed plant derived dietary constituents and implicated as the active components in a number of medicines [3]. More than 5000 plant polyphenols have been identified and several of them are known to possess a wide spectrum of biological activities [4] such as antiinflammatory, anti-microbial, anti-carcinogenic, anti-HIV, cardioprotective and neuroprotective influence etc. In view of their wide range of pharmacological activities they seem to have a great therapeutic potential.

Chemical Structure

Flavonoids are the major polyphenols present in wide variety of plants. 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 six membered 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 [5]. Flavonoids are often hydroxylated at positions 3,5,7,2',3',4',5'. 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 L rhamnose, D-glucose, gluco-rhamnose, galactose or arabinose [6].

Sources and Bioavailability

For any chemical moiety to exert a biological effect, it should be bioavailable and have the potential to exert effects in vivo. Most of the polyphenols are known to be readily absorbed [7,8] but these compounds are prone to be modified into other forms inside biological systems, one such common chemical modification being conjugation [9]. Curcumin undergoes metabolic O-conjugation to curcumin glucuronide and curcumin sulfate and bioreduction to tetrahydrocurcumin, hexahydrocurcumin, and hexahydrocurcuminol [10]. Certain curcumin metabolites, such as tetrahydrocurcumin, possess anti-inflammatory [11] and antioxidant activities [12] 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 [13]. Isoflavones such as genistein are undergo conjugation with glycosides and is metabolized in human intestine to dihydrogenistein and 6'-hydroxy-O-desmethylangolensin. Concentration of genistein has been shown to be higher in individuals consuming soy rich diet [14] and as a result genistein and its metabolites have been detected in plasma, breast aspirate and prostatic fluid [15]. Similarly, other polyphenols are also known to be absorbed and metabolized into various end products which may or may not posses the biological effects of the parent compound.

Antioxidant compounds in food play an important role as a health-protecting factor. Antioxidants reduce the risk for chronic diseases including cancer and heart disease. Primary sources of naturally occurring antioxidants are whole grains, fruits and vegetables. Plant sourced food antioxidants like vitamin C, vitamin E, carotenes, phenolic acids, phytate and phytoestrogens having the potential to reduce disease risk. Most of the antioxidant compounds in a typical diet are derived from plant sources and belong to various classes of compounds with a wide variety of physical and chemical properties. Some compounds, such as gallates, have strong antioxidant activity, while others, such as the mono-phenols are weak antioxidants. The main characteristic of an antioxidant is its ability to trap free radicals. Highly reactive free radicals and oxygen species are present in biological systems from a wide variety of sources. These free radicals may oxidize nucleic acids, proteins, lipids or DNA and can initiate degenerative disease. Antioxidant compounds like phenolic acids, polyphenols and flavonoids scavenge free radicals such as peroxide, hydro peroxide or lipid peroxyl and thus inhibit the oxidative mechanisms that lead to degenerative diseases. The number of studies suggesting that the antioxidants in fruits, vegetables, tea and red wine are the main factors for the observed efficacy of these foods in reducing the incidence of chronic diseases including heart disease and some cancers. Flavonoids possess wide range of biochemical and pharmacological effects including anti-oxidation, anti-inflammation, anti-platelet, anti-thrombotic action, and anti-allergic effects [16,17]. They can inhibit enzymes such as prostaglandin synthase, lypoxygenase, and cyclooxygenase, closely related to tumorigenesis [18], and induce detoxifying enzyme systems such as glutathione S-transferase [19]. Quercetin inhibited oxidation and cytotoxicity of low-density lipoprotein (LDL) [20], and can reduce risk for heart disease or cancer [21]. Quercetin, myricetin, and rutin are being more powerful antioxidants than the traditional vitamins [22]. Flavonols and flavones possess antioxidant and free radical scavenging activity in foods [23], and have significant vitamin C sparing activity [16], with myricetin being one of the most active. In vegetables, quercetin glycosides predominate, but glycosides of kaempferol, luteolin, and apigenin are also present. Fruits almost exclusively contain quercetin glycosides, whereas kaempferol and myricetin glycosides are found only in trace quantities. Flavonoids are polyphenols with diphenylpropanes skeletons. The four major classes are the 4-oxoflavonoids (flavones, flavonols, etc.), anthocyanins, isoflavones, and the flavan-3-ol derivatives (catechin and tannins) [24]. Flavonoids are a large family of over 4000 secondary plant metabolites, many being present as sugar conjugates. Epidemiological studies have indicated a relationship between a diet rich in flavonols and a reduced incidence of heart disease [25]. Three major flavonols (kaempferol,

quercetin, and myricetin) and two major flavones (luteolin and apigenin) of some edible tropical plants are studied. These tropical plants were studied such as guava (*Psidium guajava*), Chinese cabbage (*Brassica oleracea*), cabbage (*Brassica oleracea*), broccoli (*Brassica oleracea*), cauliflower (*Brassica oleracea*), winged bean (*Psophocarpus tetragonolobus*), French beans (*Phaseolus vulgaris*), French peas (*Pisum sativum*), lady fingers (*Hibiscus esculentus*), string beans (*Vigna sinensis*), bell pepper (*Capsicum annum*), bird chili (*Capsicum frutescens*), green chili (C*apsicum annum*), red chili (*Capsicum annum*), carrot (*Daucus carota*), white radish (*Raphanus sativus*), garlic (*Allium sativum*), lemongrass (*Cymbopogon citratus*), betel (*Piper betle*), Chinese chives (*Allium odorum*), onion (*Allium fistulosum*), drumstick leaves (*Moringa oleifera*), wolfberry (*Lycium chinense*), limau purut (*Citrus hystrix*), red spinach (*Amaranthus gangeticus*), kangkung (*Ipomoea aquatica*), sweet potato (*Ipomoea batatas*), tapioca (*Manihot utilissima*), cashew (*Anacardium occidentale*), fern (*Diplazium esculentum*), papaya (*Carica papaya*), yam (*Colocasia esculentum*), pegaga (*Hydrocotyle asiatica*), selom (*Oenanthe javanica*), brinjal (*Solanum melongena*), angular loofah (*Luffa acutangula*), pumpkin (C*ucurbita maxima*), sengkuang (*Pachyrrhizus erosus*), snake gourd (*Trichosanthes anguina*), mung bean (*Phaseolus aureus*), soy bean (*Glycine max*), mint (*Mentha arvensis*), oyster mushrooms (*Pleurotus sajor-caju*), peria (*Momordica charantia*), petai (*Parkia speciosa*), asam gelugur (*Garcinia atroviridis*), black tea (*Camellia chinensis*), turmeric (*Curcuma longa*), plaintain (*Musa sapientum*), bunga kantan (*Phaeomeria speciosa*) perilla (*Perilla frutescences*). In these above edible plants, five major food flavonoids, viz quercetin, kaempferol, myricetin, apigenin, and luteolin, were determined in dried plant samples of the flavonoid glycosides.

Vegetables

The total phenol contents in the vegetable subgroup were very low as compared to berries. The major phenolics were chlorogenic and *p*-coumaric acids [26]. The difference in antioxidant activity between potato varieties may result partly from the presence of anthocyanins, although pelargonin has been reported to show poor antioxidant activity [27]. Methanolic extracts of purple potatoes as well as other anthocyanin-rich plant products, such as blueberries, sweet cherries, purple sunflower hulls, and red onion scales, showed strong antioxidative activities in a *â*-carotene bleaching method [28]. In the present study, the antioxidant activity order was approximately similar at both tested concentration levels, which indicates that the yield of the vegetable extract was good. However, while the total phenol content of many vegetable extracts was extremely small. Sugar removal could have increased the antioxidant activities of some of the vegetable extracts.

Cereals

The concentrations of total phenolic compounds in cereals were even lower than the concentrations in vegetables. Cereal extracts did not show remarkable antioxidant activity. Oat bran exerted a moderate effect. In oat flour, *p*-hydroxybenzoic, protocatechuic, vanillic, *trans*-*p*-coumaric, (*p*-hydroxyphenyl)-acetic, syringic, *trans*-sinapic, caffeic, and ferulic acids were found, with ferulic acid being the most abundant [29]. Ferulic acid is also the dominant form of phenolic acid in rye, wheat, and barley. Ferulic acid showed moderate, caffeic acid showed strong, and *p*-coumaric acid showed neglibigle antioxidant activity [30]. In addition, oats contain a series of anionic substituted cinnamic acid conjugates, avenanthramides, which also are potential antioxidants [31]. The processing seems to be important when evaluating the antioxidant activity of cereals as brans were more active than other products from the same cereal species. This is obviously due to the localization of the phenolics in the grain: the outer layers of the grain (husk, pericarp, testa, and aleurone cells) contain the greatest concentrations of total phenolic, whereas their concentrations are considerably lower in the endosperm layers. About 80% of the *trans*-ferulic acid of both rye and wheat grain was found in the bran [29].

Polyphenolics

Flavanoids are polyphenols, the most widespread class of metabolites in nature, and their distribution is almost ubiquitous. It is estimated that 100,000 to 200,000 secondary metabolites exist. They generate the majority of the natural phenolics, such as flavonoids. Although, monophenols, such as *p*-coumaric acid, are not polyphenols, they have been same properties and characteristics as functional

polyphenols. Although a large variety of plant phenols exists, most of these compounds arise from a common origin: the amino acids phenylalanine or tyrosine. This well established antioxidant activity of flavonoids is also responsible for other biological activities. For example, the anticancer activity of some compounds is due to their ability to scavenge free radicals, thus avoiding the early stages of cancer promotion [32]. Besides this mechanism, flavonoids have also been reported to act as anticancer agents, modulation of enzyme activity related to detoxification, oxidation and reduction, stimulation of the immune system and DNA repair, and regulation of hormone metabolism. Some other flavonoid classes as potent molecules for the treatment of other pathologies that do not involve in the antioxidant activity. The some isoflavones, whose estrogen-like capacity is now well established, is related with their similarity to estradiol estrogen for the treatment of conditions in which the agonist effect in estrogen receptors is beneficial, such as menopause conditions. The venoprotective properties of flavonoids are also explored for the enhancement of micro-circulation in pathological conditions in which this function is compromised [32].

Flavonoids

Flavonoids are characterized by a phenylbenzopyran chemical structure. The general structure includes a C15 (C6-C3-C6) skeleton joined to a chroman ring (benzopyran moiety). The heterocyclic benzopyran ring is known as the C ring, the fused aromatic ring as the A ring, and the phenyl constituent as the B ring. The A ring can be of two types: a phloroglucinol type that is *meta*trihydroxylated, or a resorcinol type that is *meta*-dihydroxylated. The B ring can be monohydroxylated, *ortho*-dihydroxylated or vicinal-trihydroxylated. The center heterocycle most commonly exists in one of three forms: pyran, pyrilium, or γ-pyrone. According to the position of the aromatic ring to the benzopyrane moiety, flavonoids can be grouped in four classes: major flavonoids (2-phenylbenzopyrans), isoflavonoids (3-benzopyrans), neoflavonoids (4-benzopyranes) and minor flavonoids. In plants, these compounds occur in nearly all species. Increasingly, flavonoids have been reported to possess many useful properties, including anti-inflammatory, oestrogenic, enzyme inhibition, antimicrobial, antiallergic, vascular and cytotoxic antitumour activity, but the antioxidant activity is, without a doubt, the most studied one attributed to flavonoids.

Berries and Fruits

Overall, berries exhibited high total phenolic contents and high antioxidant activity. Berries with a strong purple color, such as crowberry, aronia, bilberry, and whortleberry, had clearly higher phenolic contents than the yellowish rowanberries and cloudberries. The strongly colored berries are rich in anthocyanins. The bilberry, cranberry, and cowberry are rich in flavonols, mainly quercetin, while strawberry, red raspberry, and cloudberry have an especially high content of ellagic acid, and rowanberry contains high amounts of ferulic acid [33]. In addition, bilberries are also especially rich in hydroxycinnamic acid derivates, which have been shown to exert antioxidant activity [34,35]. Extracts of black currants along with red currants, blackberries, blueberries, and black and red raspberries possessed also a remarkably high scavenging activity toward chemically generated superoxide radicals [36]. The total phenol contents of the two apple varieties studied were almost similar but lower than the contents in berries. However, apples exerted strong antioxidant activities.

Flavonoid Contents

The contents of five types of flavonoids, namely myricetin, quercetin, luteolin, kaempferol, and apigenin, in methanol extracts of common edible plants. All the species showed significant amounts of flavonoids except sweet potato shoots, winged bean, string bean, petai, peria, bayam duri, betel leaves, plaintain flower, and oyster mushroom. The results clearly indicated that some of the tested plants were rich in these natural antioxidant flavonoids, and the qualities and quantities of the flavonoids in these plants seemed to be very different among the kinds of samples used.

Flavonoids in Some Consumed Plants

Some of the locally consumed plants such as papaya shoot, tapioca shoot, cashew shoot, pegaga, maman, kesom leaves, bunga kantan, and daun turi are found to be rich in flavonoid content. *Piper betel* (Piperaceae) leaves are chewed alone or with other plant materials including the areca nut, *Areca catechu L.* Seven phenols were identified in *P.*

betel flowers. Safrole was the major phenol, followed by hydroxychavicol, eugenol, methyl eugenol, isoeugenol, flavone, and quercetin [37]. Flavonoids such as isorhamnetin, hyperoside, and persicarin were isolated from *Oenanthe javanica* [38]. The fruits and leaves of box thorn or Wolfberry leaves (*Lycium chinense*) have been used as foods, tea, and medicine. Box thorn leaves are known to be capable of reducing the risk of certain diseases such as arteriosclerosis, essential arterial hypertension, diabetes, and nightblindness [39] contained the anti-aging ascorbic acid and tocopherols [40]. The box thorn leaves contained rutin (1.1-2.7% dry weight basis), a preventive phytochemical for hypertension and stroke. Rhizomes of *Curcuma spp.,* such as *C. longa* are used in traditional medicine. The rhizomes of *C. longa* are also used as a yellow coloring additive for food because it contains curcuminoids [41]. Flavonoid extracted from the fruits of *Solanum melongena* showed hypolidemic action.

Flavonols in the Plants Tested

The quercetin is a potent anticancer agent in man. Myricetin, with its three adjacent hydroxyl groups was one of the most active antioxidants. Myricetin is not only a good antioxidant, but also been shown to be a potent anticarcinogen and antimutagen [42]. Quercetin is also a strong antioxidant that can contribute to the prevention of atherosclerosis [22,23]. Quercetin is a suppressing chemopreventive and chemotherapeutic agent that can relieve local pain caused by inflammation, headache, oral surgery, and stomach ulcer. Recently, quercetin has been shown to reduce the carcinogenic activity of several cooked food mutagens, enhance the antiproliferative activity of anticancer agents, and inhibit the growth of transformed tumorigenic cells [43]. Currently, kaempferol is in interest because of its antioxidant [22], antitumor, antiinflammatory, and antiulcer activity [44], and its inhibitory activity of HIV protease [45]. The flavones had the poorest antioxidant activity because of lack of *o*-dihydroxy groups. Kaempferol and its derivative have been identified in various vegetables, fruits, and beverages such as French beans [46], onions [47], teas [48], and honey [49-51]. there was variation in the levels of quercetin in cherry tomatoes purchased at different times. The concentrations of flavones and flavonols, like those of all secondary plant metabolites, vary within certain limits and are dependent on a number of factors: for example, growing condition, degree of ripeness, size of the fruit, and variety [52]. The consumption of controlled diets high in fruits and vegetables increased significantly the antioxidant capacity of plasma, and the increase could not be explained by the increase in the plasma R-tocopherol or carotenoid concentration [53]. On a milligram-per-day basis, the intake of the antioxidant flavonoids still exceeds that of the antioxidant *â*-carotene and vitamin E. Thus, flavonoids represent an important source of antioxidant activity in the human diet [54]. Supplementation of these natural antioxidants through a balanced diet could be much more effective and economical than supplementation of an individual antioxidant, such as ascorbic acid or R-tocopherol, in protecting the body against various oxidative stresses. Polyphenols are effective hydrogen donors, particularly flavonols such as quercetin [55]. Studies on the natural antioxidants flavonoids and phenolics compounds in temperate edible plants are quite established [56]. These foods include tea, alliums, tomatoes, lettuce, and celery [24,52], apples, vegetables, fruits, citrus fruit juices such as fresh orange, grapefruit, and lemon juices [54]; beer, coffee, chocolate milk, white wine, tea infusion, and red wine [57,58]; apple juice, tomato juice, grape juice, orange juice, grapefruit juice and lemon juice, cauliflower, radish, pea, broccoli, Chinese cabbage, and carrot [50]; sixteen leafy vegetables and fruits such as *Colocasia,* cabbage, and *Hibiscus sabdariffa*; lettuce, kale, chive, garlic chive, leek, horseradish, red radish, and red cabbage tissues; soybean sprouts, Japanese radish, grapefruit, and burdock root [51]; citrus fruits [59]; juices of orange, apple, pineapple, peach, apricot, pear, grape [58,60] and citrus fruits contain almost exclusively flavanones [59]. Quercetin was also found in some of the citrus fruit juices such as fresh orange, grapefruit, and lemon juices [48]. Flavanones, flavones, and flavonols are the flavonoids present in citrus. However, flavones and flavonols were in low concentration in citrus tissues in relationship to flavanones. These types of compounds have been shown to be powerful antioxidants and free radical scavengers [61].

Effect of Drying Temperature on Flavonoid Content

Phenolic compounds are usually susceptible to different factors (eg., acidic solution and high temperature) during the extraction process. Drying at temperatures below 50 ℃ yields the highest amount of total phenolics. Drying at room temperature may enhance the enzymatic degradation and thus lower the amount of phenolics in the samples. Increasing the temperature above 60 ℃ lowered the phenolic amount considerably. At high temperatures, certain phenolics may decompose/combine with the other plant components. Cooking lowered the quercetin content of both tomatoes and onions, with greater reduction being detected following microwaving and boiling than after frying [52]. This could be due to flavonoid breakdown during cooking and/or conjugated quercetin being extracted from the tomato and onion tissues by hot water more effectively than with hot oil used in the study. There are only little gross changes in either the overall level or the composition of quercetin glucosides during normal commercial storage [62]. Boiling and frying do not result in gross changes in glucosides composition, although an overall loss of up to 25% is found for both processes, in the former by leaching into the cooking water and in the latter by thermal degradation into products.

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 plant-derived 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. 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 everchanging variants [63]. 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 [64]. 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 [65]. 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) [66]. 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 [67]. Chrysin, a flavonoid has been characterized as a potent inhibitor of HIV-1 transcription in chronically infected cells [65]. The flavonoid halts the transcription by inhibiting casein kinase-II (CK-II) activity [68]. 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 [69]. 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 [70]. 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 [71]. Inhibition of viral adsorption by flavonoids such as epicatechin has been attributed to an irreversible interaction with gp120 [72]. 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 [73]. 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 [74]. 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 [75]. 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 [76]. Phenolics present in plants are known to be toxic to microorganisms [77] . 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 [78]. 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 [79]. Flavonoids are known to be synthesized by plants in response to microbial infections [80] 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 posses antimicrobial activity [81] and that they contain a mixture of catechin compounds. These compounds inhibited *Vibrio cholerae* as products of fermentation [82], *Streptococcus mutans* [83], *Shigella* [84] and other bacterial strains in vitro. The catechins have been found to inactivate the cholera toxin from *V. cholerae* [76] and inhibit isolated bacterial glucosyl transferase in *S. mutans* [85]. 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 [1]. 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 [86] often leading to inactivation of the protein via loss of function. This has been attributed for the wide range of quinone anti-microbial effects [87]. 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.

Cardioprotective 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 [88]. 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 [89]. Regular, moderate consumption of red wine is linked to a reduced risk of coronary heart disease [90]. Resveratrol, a component of red wine has been linked to a number of potentially cardioprotective effects [91]. Anthocyanidins have also been found to have antioxidant potential [92]. Studies suggest that EGCG can suppress reactive oxygen species and thereby prevent the development of cardiac hypertrophy [90]. 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 [93]. Lipid-lowering activity has also been reported in tea flavonoids [90]. 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 [94]. Resveratrol has been found to promote vasodilation by enhancing the production of NO [95]. Genistein, one of the major isoflavones in soy protein, binds to estrogen receptor b with much higher affinity than to ERa [96] and can elicit endothelium dependant vasorelaxation in vitro [97] and in vivo [98]. Other isoflavones such as dihydrodaidzeins have also been reported to enhance endothelial function [99]. 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 [100]. As documented above, it is evident that natural polyphenolic compounds possess antioxidant, vasorelaxant and antihypertensive properties that are beneficial to cardio-vascular 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 [101]. 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 [102]. 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 [103]. 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) [104], Huntington's disease (HD) and Schizophrenia [105] 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 [106]. Polyphenols such as EGCG, curcumin, extracts of blue berries and Scutellaria are also known to help in AD [107]. In vitro studies show that green tea extract rich in catechins could protect neurons from the amyloid beta-induced damages in AD [108]. EGCG is also found to be of use in ALS [109,110] and PD [111]. Extract of Scutellaria stem and polyphenols such as curcumin and naringenin also exhibit neuroprotection in PD [112]. 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 and also inhibits amyloid beta fibril formation [113]. Dietary polyphenols have potential as protective agents against neuronal apoptosis, through selective actions within stress activated cellular responses including protein kinase signaling cascade [114]. Several dietary supplements with blueberries extracts have been

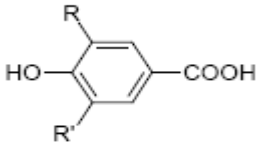
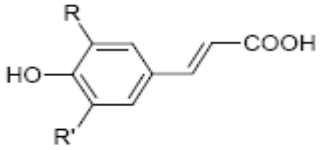
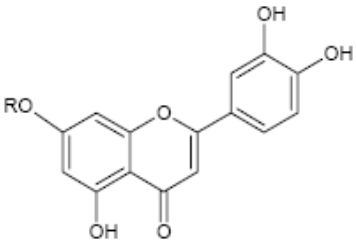
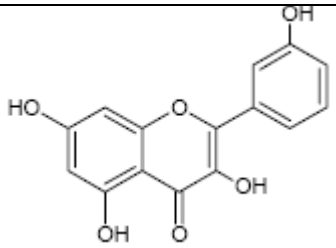
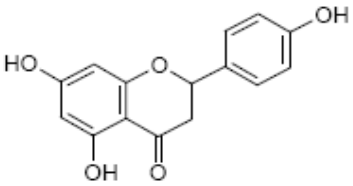
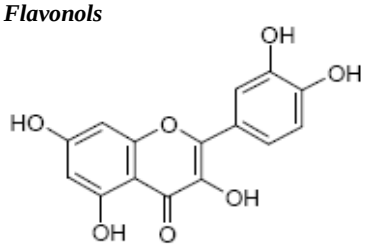
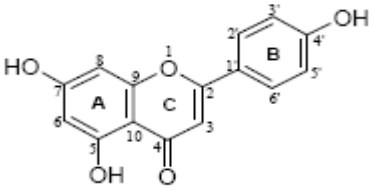
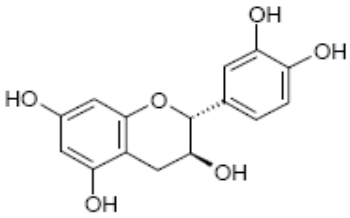
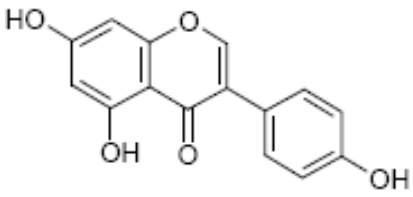
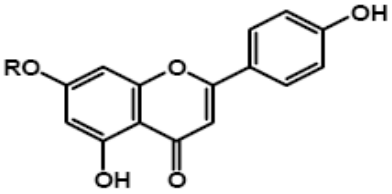
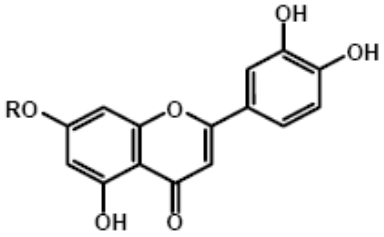
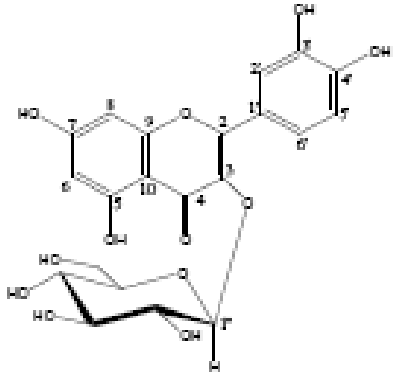
reported to reduce some neurological deficits in aged animal models. Blueberries are a rich source of polyphenols such as catechins, epicatechins and anthocyanins. Recent studies investigating the effect of polyphenols in cognitive performance have demonstrated that dietary supplementation with blueberries extracts reversed cognitive deficits in Morris water maze performance test and Y-maze test in aged mice models [115,116]. The studies therefore present a promising class of compound for possible application as health supplements and nutraceuticals for neuroprotection.

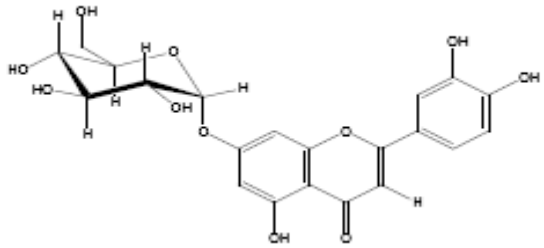
Anti-Carcinogenic Properties

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 [117].Various classes of dietary polyphenols are under investigation for their anticancer properties in order to design novel strategies for chemoprevention [118]. 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 [119]. Pretreatment with genistein, potentiated cell killing induced by radiation in human PC-3 prostrate cancer cells in vitro [120] and prostate tumor growth in vivo [121]. 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 [122], myeloid leukemia [123] and pancreatic tumor cells [124]. 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 [125]. Protein tyrosine kinases (PTKs) are known to play key roles in carcinogenesis, cell growth and apoptosis [126]. Genistein has been identified as a PTK inhibitor [127]. 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 [128]. 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 [129]. Curcumin, a natural phenolic compound found in turmeric have been shown to have antiproliferative action against colon cancer, breast cancer and myeloid leukemia [130,131]. Antitumor activity of curcumin is believed to be in part due to its ability to block the NF kappa B pathway [132]. 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 [133]. 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 [134]. Androgen independent DU145 human prostate cancer cells manifest resistance to radiation-induced apoptotic death [135]. Scarlatti et al have reported that pre-treatment with resveratrol significantly enhances radiation induced cell death in DU145 cells [136]. 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 [137]. 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 [138]. 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

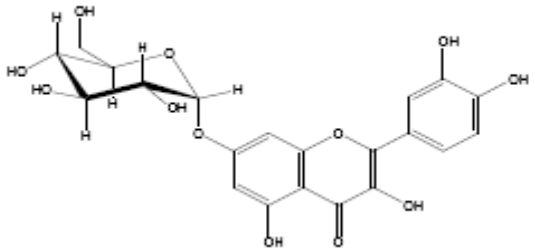
luteolin may also account for the antiproliferative properties of plant polyphenols [139].

Figure 1. Chemical Structures of major Polyphenolic Compounds

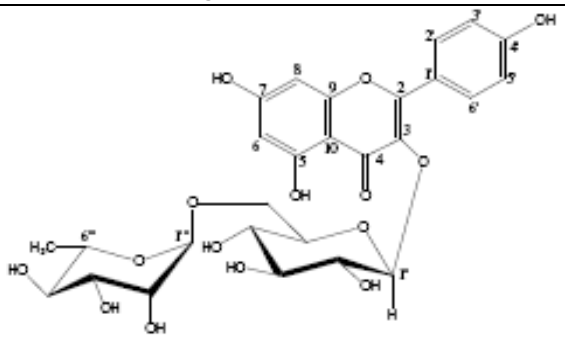
<table>
<tr><th colspan="3">Chemical classes of polyphenolic compounds.</th></tr>
<tr><td>PHENOLIC ACIDS
Benzoic acid derivatives
 
R =R' =H; p-hydroxybenzoic acid
R=OH,R' =H; protocatechuic acid
R = OCH3, R' = H; vanillic acid
R = R' = OH; gallic acid
R = R' = OCH3; syringic acid</td><td>Cinnamic acid derivatives
 
R = R' = H; p-coumaric acid
R = OH, R' = H; caffeic acid
R = OCH3, R' = H; ferulic acid
R = R' = OCH3; sinapic acid</td><td> 
R=H, Luteolin
R=Glc, Luteolin-7-O-glucoside</td></tr>
<tr><td> 
Kaempferol</td><td>Flavanones
 
Naringenin</td><td>Flavonols
 
Quercetin</td></tr>
<tr><td>FLAVONOIDS: Flavones
 
Apigenin</td><td>Flavan-3-ols
 
(+)-catechin</td><td>Isoflavones
 
Genistein</td></tr>
<tr><td> 
R=H Apigenin
R=Glu-Caf Apigenin 7-O-caffeoylglucoside
R=GlcU-GlcU Apigenin 7-O-diglucuronide</td><td> 
R=H Luteolin
R=GlcU Luteolin 7-O-glucuronide
R=GlcU-GlcU Luteolin 7-O-diglucuronide</td><td> 
Quercetin
3-O-4C1-D-glucopyranoside</td></tr>
</table>



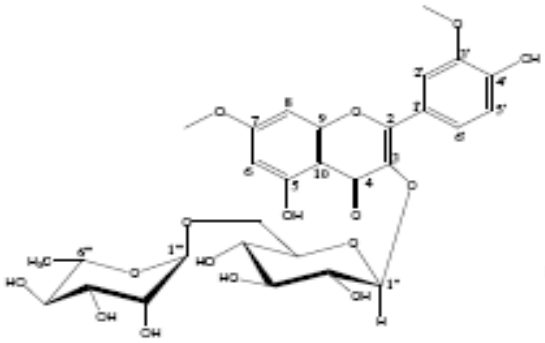
Luteolin 7-*O*-4C1-D-glucoside



Quercetin 7-*O*-4C1-D-glucoside



Kaempferol-3-*O*-[6"-*O*-L-rhamnopyranosyl]-D-glucopyranoside (nicotiflorin).



7,3` dimethoxy quercetin 3-*O*-[6"-*O*-L-rhamnopyranosyl]-D-glucopyranoside (rhamnazin 3-O-rutinoside)

Another convincing antiproliferative mechanism includes the oxidative DNA breakage by the prooxidant action of plant polyphenols in the presence of transition metals especially copper [140-142]. Flavonoids are recognized as naturally occurring antioxidants and this property has been implicated for their anticancer activity [143]. However, evidence in the literature suggests that antioxidant properties of plant polyphenols may not fully account for their anticancer effects [144]. In the context of copper being an essential constituent of chromatin (Bryan, 1979) and that the copper levels in tissues [145] and serum [146] 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 [147]. 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 [148]. Isoflavones such as biochanin A, daidzein [149] and green tea polyphenol EGCG [150] 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 $SKOV_3$ and ES-2 [151]. The above findings suggest that the plant polyphenols have indeed emerged as an area of great promise for delineating innovative strategies in cancer chemoprevention.

DISCUSSION

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 Plant polyphenols mobilize endogenous copper in human peripheral polyphenols and their associated health benefits. However, the issue of bioavailability has to be addressed before any targeted therapy could be designed effectively [152-160]. On the basis of what is known about the bio availabilities, 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 [160-165]. 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. However, for better and mechanism-based understanding of the potential health benefits of dietary polyphenols further studies are warranted. Flavanoids compounds in food play an important role as a health-protecting factor and reduce the risk for various chronic diseases including cancer and heart diseases. Primary sources of naturally occurring flavanoids are whole grains, fruits and vegetables. Edible plant sourced food antioxidants like vitamin C, vitamin E, carotenes, phenolic acids, phytate and phytoestrogens have been recognized as having the potential to reduce disease risk. Most of the flvanoids in a diet are derived from plant sources and belong to various classes of compounds with a wide variety of physical and chemical properties. Some compounds, such as gallates, have strong antioxidant activity, while others, such as the mono-phenols are weak antioxidants. The main characteristic of an antioxidant is its ability to trap free radicals. Highly reactive free radicals and oxygen species are present in biological systems from a wide variety of sources. These free radicals may oxidize nucleic acids, proteins, lipids or DNA and can initiate degenerative disease. Antioxidant compounds like phenolic acids, polyphenols and flavonoids scavenge free radicals such as peroxide, hydroperoxide or lipid peroxyl and thus inhibit the oxidative mechanisms that lead to degenerative diseases [166-170]. There are a number of clinical studies suggesting that the flavanoids are the main factors for the observed efficacy of these foods in reducing the incidence of chronic diseases including heart disease and some cancers.

CONCLUSION

The last two decades have witnessed a major drift in the interests of the scientific community towards explaining better means to containing the health risks of the human race. The century old chemotherapies against various disorders have never been a success, albeit not a total failure. Such therapies have a major drawback of side effects that give rise to unseen disorders that emerge as a new challenge. In this regard, the concept of foodstuffs as natural medicines is very attractive. Epidemiological studies suggest that the vegeteranian food habit is associated with reduced risk of cancer, cardiovascular and neurodegenerative disorders. Consistent with this hypothesis is the fact that the incidence of these disorders is least in Asian populations where fruits, vegetables and spices are the major elements in the human diet. Recent research has shown that plant-derived polyphenolic

compounds are promising nutraceuticals for control of various disorders such as cardiovascular, neurological and neoplastic disease. The richness of the polyphenolic contents of green tea and red wine has made them popular choice for associated anticancer and cardiovascular health benefits. The present article is a brief review of the promises plant polyphenols, bioactive components of our food, hold for the future.

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