Asian Journal of Chemistry; Vol. 26, No. 16 (2014), 4929-4939

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2014.16547

REVIEW

Biophenols: The Abundant Redox-Active Dietary Molecules of Life

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Received: 19 October 2013; *Accepted*: 11 April 2014; *Published online*: 28 July 2014; AJC-15605

Plants, in general and functional food plants particularly, have been analyzed to be the rich sources of numerous redox-active secondary metabolites. Phytophenols are undoubtedly the ubiquitous class of bioactive constituents of the human diet manifesting both nutritional and health benefits mediated largely by their redox property, reactive species-scavenging and metal chelating capacities and can mitigate oxidative stress-induced tissue damage associated with chronic diseases. Though the therapeutic potentials and the antioxidant/pro-oxidant capacities of the individual biophenols are themselves potential topics of debate, an ever-expanding quantum of scientific evidence does tend to support their protective role, *via* diet, against the presently mushrooming age-related degenerative disorders. The present review attempts to portray the status quo of dietary biophenols in the health and longevity.

Keywords: Plant phenol, Dietary antioxidant, Cardiovascular health, Aging, Neurodegenerative disorders, Cancer chemopreventive.

INTRODUCTION

The use of plants, as a major source of nutrition for humans, is as ancient as human civilization. Food plants that manifest potential health benefits biosynthesize an extensively wide array of bioactive constituents. One can well recognize the significance of the therapeutic promises of food from the host of emerging hot research terms and disciplines such as functional foods, nutraceuticals, nutrapharmacology, nutrigenomics, nutriproteomics, medicinal foods, designer food, medical nutrition, *etc*. Conventionally, medical education and the practice of medicine focus largely on the treatment and cure of disease with considerably less attention being devoted to the prevention of the chronic diseases, particularly those of aging. With the ongoing discoveries in basic mechanisms of biochemistry, physiology, nutrition and molecular biology, there is a growing sense that the onset of many of the inevitable diseases of aging can be significantly delayed or reduced in intensity. As a result, the current focus of nutrition research is directed towards 'Preventive Medicine' and experts are of the opinion that nutrition will become the primary treatment modality in the 21st century[1]. Meta analysis of epidemiologic (case-control and cohort) studies of the recent past strongly favour the claim that the regular consumption of non-nutritive bioactive botanicals *via* plant-based diet can reduce the risk of a number of the prevailing lifestyle-mediated chronic disorders, including coronary heart disease, cancers and diabetes[2]. As the aging population is increasing steadily, there is greater demand for healthier aging. The stressful lifestyle and increased consumption of junk food have turned obesity into a worldwide epidemic. Overweight and obesity are the major predisposing factors for chronic diseases such as cardiovascular diseases (CVD), diabetes (DM), neurodegenerative disorders (NDD) and carcinogenesis[3]. Concomitantly, chronic diseases are also the leading cause of mortality worldwide[4]. The repeated failure of the approach of orthodox Western medicine to keep at bay the progression of such complex diseases, coupled with the adverse reactions of a number of the currently prescribed drugs, frequently create more serious issues than the very disease. Illnesses mediated by microbes are no better, especially with the increasing multi-drug resistant superbugs. Consequently, the need for more effective, safer and smarter alternatives has driven the searches back to the traditional systems in the light of the state-of-the-art probes at one's disposal.

Increased consumption of fruits and vegetables has consistently been observed to reduce the risk of chronic diseases including cardio- and cerebro-vascular diseases, certain forms of cancer, hypertension (HT), type 2 diabetes mellitus and stroke, worldwide. The protection is due, largely, to the plethora of bioactive metabolites, both nutritive and non-nutritive, biosynthesized by plants. Evidences accumulating to date from both laboratory and clinical studies tend to support that oxidative stress (OS), imposed by reactive oxygen, nitrogen and chlorine species, plays a pivotal role in the aging process and in the pathophysiology of age-related diseases, particularly atherosclerosis, neurodegenerative disorders, immune functions and all stages of carcinogenesis. These reactive species are generated as a result of natural cellular processes (such as mitochondrial electron transport and exercise), environmental stimuli (including ionizing radiation from the sun and pollutants) and lifestyle stressors. Plants have evolved with survival and defence mechanisms, in response to environmental stressors, pathogen-attack, competing-plants and herbivory[5]. This protection may be either mechanical or chemical in nature and the later is the result of the synthesis of the non-nutritive/anti-nutritive plant secondary metabolites. The ability to synthesize secondary compounds has been selected throughout the course of evolution in different plant lineages when such compounds addressed specific needs. Secondary metabolites apparently act as defence (against herbivores, microbes, viruses or competing plants) and signal (to attract pollinating or seed dispersing animals) compounds, as well as protecting the plant from ultraviolet radiation and oxidants. Therefore, they represent adaptive characters that have been subjected to natural selection during evolution. This requirement for secondary metabolites to have highly diverse biological activities has led plants to accumulate a vast number of such compounds. Over 200,000 known metabolites have been classified, according to their biosynthetic routes and structural features, into various chemical classes. Convincing evidences accumulating till date tend to drive one to believe that dietary antioxidant micronutrients accumulated in fresh fruits and vegetables assist in promoting good health, by protecting lipids, proteins and nucleic acids, against the oxidative damage initiated by reactive substances. Consequently, the control of 'redox' status with the properties of food and food components has emerged as a salient field of research today. Dietary interventions are, therefore, among the emerging trends to curtail physiological malfunctioning including cancer, diabetes mellitus, cardiac complications, hypertension and neurodegenerative disorders, apart from stimulating the immune system, improving drug metabolism and tissue regeneration. Antioxidation is frequently cited to be the key property underlying the prevention and/or reduction of these chronic and age-related disorders as well as skin deterioration by dietary plant phenolics and other plant phenol-containing commodities. The intention of the present review is to portray the status quo of the ubiquitous class of dietary antioxidants, better termed as 'biophenols', in offering such a protection against the inevitable age-related ailments.

A hand search of recently published journals of relevance as well as a search for the concerned documents available in the following databases were performed to compile the data presented in this review: Google Scholar, ISI Web of Knowledge, Science Direct, PubMed, MEDLINE (Medscape), Scirus and Phenol-Explorer. The figures presented reflect the status quo of the data accessed at the close of August 2013.

Plants, in general and functional food plants particularly, have been analyzed to be the rich sources of numerous redox-active secondary metabolites as well[6]. Based on their solubilities, these antioxidants have been partitioned into lipophilic and hydrophilic components. The common lipophilic antioxidants in the diet include the carotenoids, tocopherols and tocotrienols and some fatty acids and phenols. The antioxidant capacities of these constituents are acclaimed (rightly or wrongly) to explain their health-promoting characteristics. Hydrophilic dietary antioxidants such as uric acid, ascorbates, polyphenolic glycosides and glutathione protect cellular constituents against oxidation.

Dietary phenols: The most abundant class of bioactive dietary metabolites are undoubtedly the phenolics, which are a diversified group of plant-derived molecules, originated from the pentose phosphate, shikimate and phenylpropanoid pathways[7]. This class of secondary metabolites are produced by the plant kingdom, including certain algae and specific insects. In plants, they are distributed throughout most tissues and are essential and contribute significantly to the plant physiology. They play key roles in pigmentation, growth and reproduction and resistance to pathogens and predators due to their potent astringency and function as phytoalexins[8]. They are also the extremely important components of the human diet with both nutritional and medicinal benefits reported for animals and humans, mediated largely by their redox property, free radical scavenging capacity and the ability to mitigate oxidative stress-induced tissue damage associated with chronic diseases. They exhibit a remarkably diverse range of bio-physicochemical properties that make them rather unique and intriguing natural products. Unlike the classical nutrients, including vitamins and minerals, these phenolics are not required for vital body functions in humans, such as growth, reproduction, wound repair and development. As a result, nutritionists and food technologists of the past decades have brushed them off as 'non-nutrients' and frequently taunted as 'anti-nutrients', as these metabolites, in addition, bind to proteins and handicap their bioavailability. Yet, phenolics commendably occupy today a unique place in science as the only class of bioactive natural products that the general public has certainly heard about. The foremost reason for their ever-increasing recognition not only by the scientific community but also and most remarkably, by the general public being (i) their abundant availability in fruits, seeds/nuts, flowers, tubers, leaves, bark as well as in derived foodstuffs and beverages, (ii) the claim that regular consumption of these products is beneficial for the human health and (iii) their implication in the formulation of well-marketed cosmetic and parapharmaceutical products. It is their capacity to scavenge oxidatively generated free radicals and other reactive species (among the host of benefits) that has often been highlighted as the fundamental chemical event that underlies their utility in reducing the risk of several age-related degenerations and their capacity to delay the onset of the very aging process[9,10]. Fig. 1 illustrates the progressively increasing number of literature on polyphenols and reactive species/redox process-associated terms retrieved from ISI web of knowledge in the past five decades. As implied by Fig. 2, the quantum of polyphenol research always well correlate with the common redox-active tags such as antioxidants, free radicals, reactive oxygen species (ROS) and oxidative stress.

Nomenclature: Despite the fact that plant phenols constitute the largest group of secondary metabolites with ubiquitous distribution in angiosperms, a biochemically accurate, comprehensive and convincing term to describe this class of

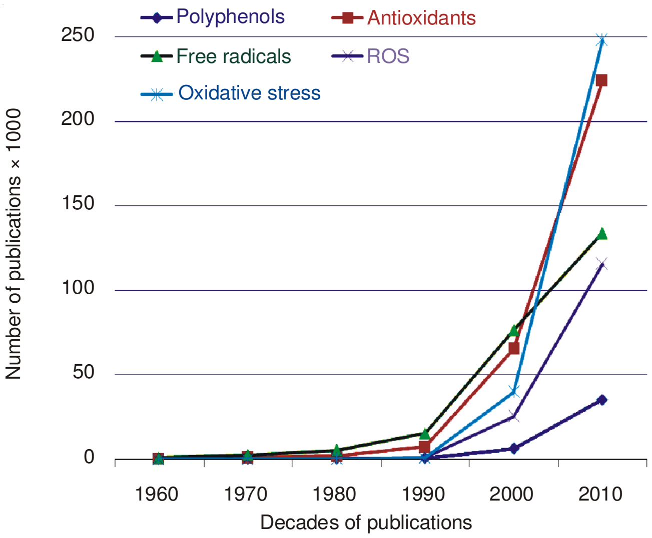


Fig. 1. Number of publications (English) cited in ISI web of knowledge

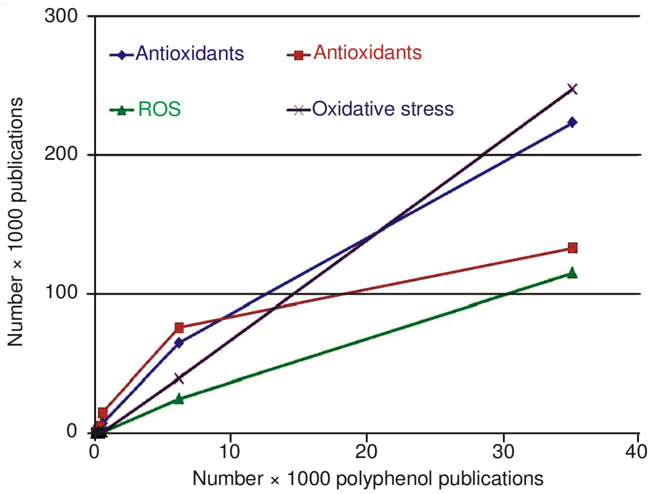


Fig. 2. Correlations of antioxidant polyphenol publications (English) cited in ISI web of knowledge

phytochemical is yet inconclusive. Plant phenols are more commonly cited in scientific literatures as 'polyphenols' and this term retrieved 216,000 hits in Google Scholar; 43,376 articles in Science Direct, 12,351 publications in PubMed and around 21,000 results in ISI Web of Knowledge (upto August 2013). Before being called as 'polyphenols', these plant-derived natural products have been referred to as 'vegetable tannins' worldwide, as a consequence of the utility of various phenolic-plant-extracts to convert animal skins to leather[11]. During the second half of the 20th century, research on polyphenols began to address objectives well beyond those related to leather manufacture. As a result, their significance, not only as the widespread plant secondary metabolites but also as compounds that manifest properties with numerous implications and potential exploitations in various domains of general public as well as in commerce, has gained enormously. Consequent to the understanding that all vegetable tannins are polyphenols, but the reciprocal is not necessarily true, a more meaningful delineation of the terms, tannins and polyphenols has resulted[11]. Several biologically active plant-derived monocyclic phenols (Fig. 3) have also unfortunately got clustered into this terminology, *viz*., 'polyphenols', not only in cosmetic, *para*-pharmaceutic and nutraceutic commercial advertisements, but also in the scientific literature, which has succumbed to today's fashionable use of the term. The much debated use of the term 'polyphenol' to refer even the monocyclic compounds containing single aromatic benzene ring may probably be inherited from the wine chemistry[12]. On the other hand, 'biophenols', first introduced by Romeo and Uccella in 1996 to describe the bioactive phenols in olives[13], appears to lend itself to be a more comprehensive and chemically appropriate name to describe plant phenols ranging from simple monocyclic phenols to complex polymeric molecules[12]. The prefix 'bio' more meaningfully addresses their biological origin as well as the manifested biological significance of these compounds in other living systems. Encompassing the phenolic isolates of natural origin and also those artefacts[14] derived out of the post-harvest processing and/or handling of plant tissues, biophenols may better be defined as plant secondary metabolites derived from shikimate-phenylpropanoid and/or polyketide pathway(s) including their derivatives, conjugates, degradation products and metabolites, featuring one or more phenolic rings that are devoid of any nitrogen-based functional group in their basic structural skeleton. This definition, however, restricts the use of the label, 'biophenols' to purely O-containing phenols and thereby excluding the N-containing ones. Structures consisting of a nitrogen system (such as pyridine, piperidine and pyrrolidine) linked to the 'A' ring of chromone (Fig. 4) are referred to as chromone alkaloids[15]. This group of compounds may be sub-divided into two types, *viz*., those in which the chromone nucleus exists as noreugenin [5,7-dihydroxy-2-methylchromone (chromone alkaloids)] and those which bear an aryl substituent at C-2 (**1**) called flavo-/flava-noid alkaloids or flavoalkaloids (Fig. 4). Chromone and flavonoid alkaloids are of interest not only due to their amphoteric nature (being both bases and phenols), but also because of the pronounced biological activity of some of the natural sources which contain

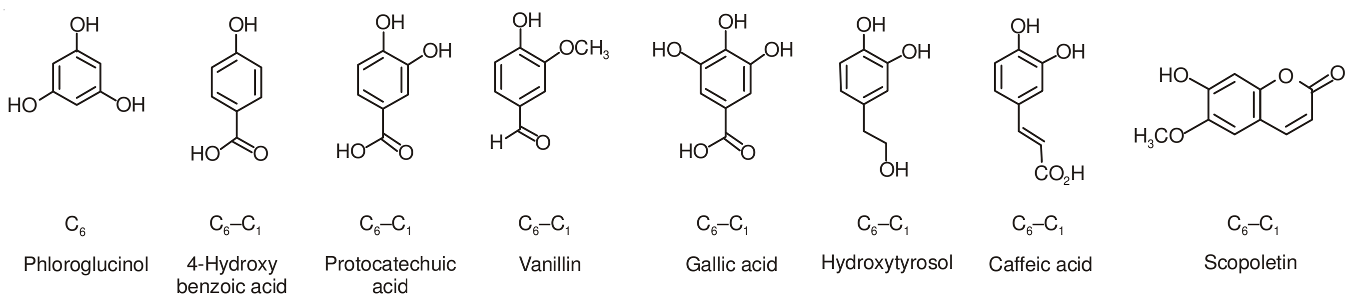


Fig. 3. Selected monocyclic phenols of plant origin

them[15]. Tocopherols and tocotrienols, collectively known as tocochromanols, are lipid-soluble dietary antioxidants that belong to the group of vitamin E compounds and play an essential role in human nutrition and health. Tocochromanols comprise of a chromanol ring system and a polyprenyl side chain, which is saturated in tocopherols and 3-fold unsaturated in tocotrienols (Fig. 5). Both subgroups are further classified into different homologues, *viz*., the α-, β-, γ- and δ-forms according to the number and position of methyl groups attached to the chromanol ring system. Their antioxidant activity has been attributed to the capacity of their heterocyclic chromanol ring system to donate the phenolic hydrogen to lipid free radicals, in a manner much similar to the phenolics. Yet, the vitamin E group compounds are generally not included in publications reporting phenolic antioxidant capacities.

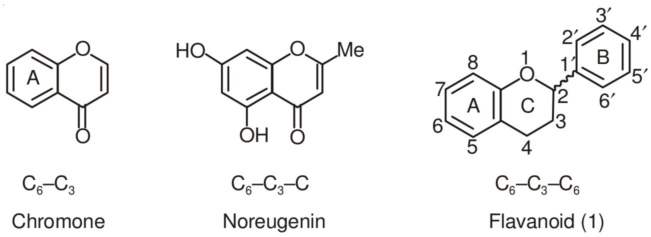
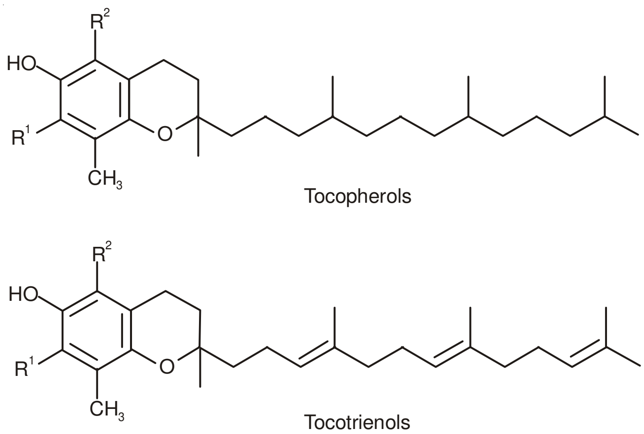


Fig. 4. Chromone and flavonoid core structures



R[1]	R[2]	Type
CH_3	CH_3	α
H	CH_3	β
CH_3	H	γ
H	H	δ

Fig. 5. Tocochromanol antioxidants of plant origin

Structural diversity: Plant phenolics are characterized by the presence of at least one aromatic ring with one or more hydroxyl groups directly bonded to the ring. They range from the naturally occurring simple, low molecular weight, single-aromatic-ring compounds (Fig. 3) to the large and complex tannins and 'derived polyphenols'. Tannins are the active ingredients of traditional plant extracts used to convert hides to leather and occur widely in foods and beverages too but at concentrations too low to tan hides. Phenolic compounds may be classified by the number and arrangement of their carbon atoms (Table-1) and are commonly found conjugated to sugars and organic acids, which facilitates their sap solubility. Traditionally processed foods and beverages, such as black tea, matured wine, coffee and cocoa and soy products, may contain phenolic transformation products that are best described as 'derived polyphenols'[14]. Phytophenols are stable as long as they are accumulated in living plant cells. When the tissues get exposed to physiological changes, such as fruit ripening and wounding of the tissue by herbivores or during commercial processing, some of them undergo chemical degradation to secondary polyphenols by enzymatic and non-enzymatic reactions[14]. Such post harvest chemical changes occur ubiquitously in vegetables and fruits to a greater or lesser extent. In most cases, the reactions involving the production of secondary polyphenols are complex and many of the reaction products still remain to be chemically identified[14,16].

TABLE-1
CLASSIFICATION OF PLANT PHENOLICS BASED ON THE CARBON SKELETON

Skeleton	Class
C_6	Simple phenols
C_6	Benzoquinones
C_6-C_1	Phenolic acids
C_6-C_2	Phenylacetic acids
C_6-C_2	Acetophenones
C_6-C_2	Secoiridoids
C_6-C_3	Hydroxycinnamic acids
C_6-C_3	Coumarins
C_6-C_3	Phenylpropenes
C_6-C_3	Chromones
C_6-C_4	Naphthoquinones
C_6-C_1-C_6	Xanthones
C_6-C_1-C_6	Benzophenones
C_6-C_2-C_6	Stilbenes
C_6-C_2-C_6	Anthraquinones
C_6-C_3-C_6	Flavonoids
C_6-C_3-C_6	Isoflavonoids
$(C_6$-$C_1)_n$	Hydrolyzable tannins
$(C_6$-$C_3)_2$	Lignans
$(C_6$-$C_3)_2$	Neolignans
$(C_6$-C_3-$C_6)_2$	Biflavonoids
$(C_6)_n$	Catechol Melanins
$(C_6$-$C_3)_n$	Lignins
$(C_6$-C_3-$C_6)_n$	Condensed tannins

The most productive plant metabolic route, in terms of the number of (poly)phenolic substances it produces, is without question that leading to the flava-/flavo-noids, a C_6-C_3-C_6 framework (Fig. 4, 6), with close to 10,000 structures characterized to date. These compounds are metabolic hybrids, as they are derived from a combination of the shikimate-derived phenylpropanoid (→ C_6-C_3) and the acetate/malonate-derived polyketide (→C_6) pathways. They contain a chroman ring (C-ring) with a second aromatic ring (B-ring) at the C-2, C-3, or C-4 position. The heterocyclic six-membered C-ring is sometimes replaced by the acyclic form *e.g*. chalcones (**2**) and dihydrochalcones (**3**) or by a five-membered ring *e.g*., aurones (**4**). The oxidation state of the C-ring is also used to classify flavonoids into different categories (Fig. 6). Andersen and Markham have described 8,150 flavonoids till the close of 2004 in their book[17]. The fifth[18] and the sixth[19] triennial reviews

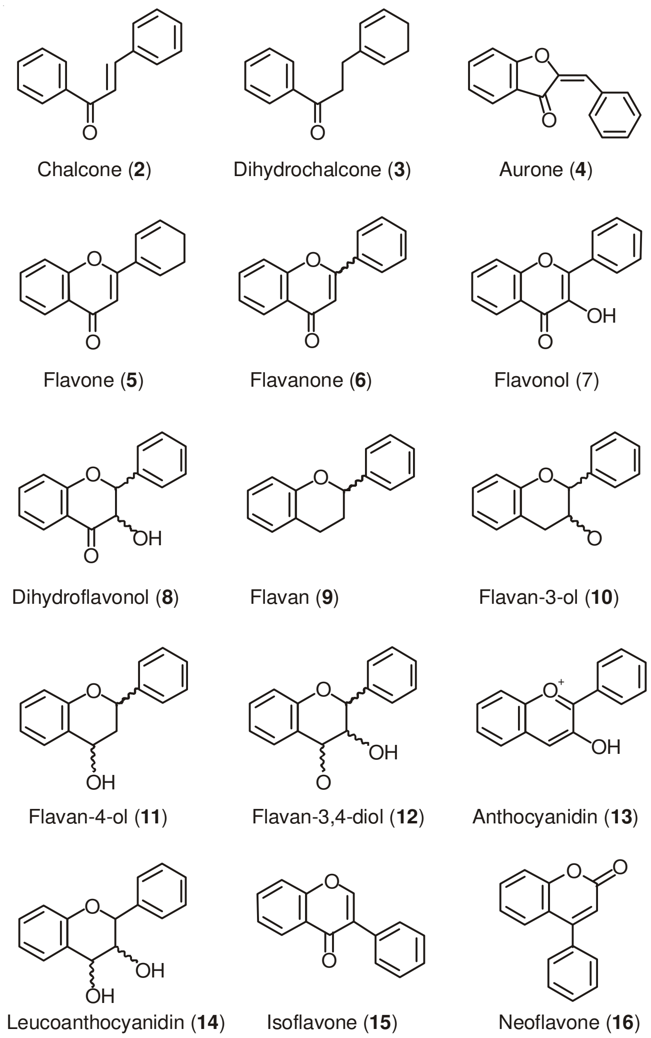


Fig. 6. Classes of flavonoid pigments

of the flavonoid literature have respectively quoted 600 and 796 new examples of naturally occurring flavonoids found either as aglycones or glycosides, comprising of flavones (**5**), flavanones (**6**), flavonols (**7**), dihydroflavonols (**8**), flavans (**9**), flavanols (**10-12**), anthocyanidins (**13**) and leucoanthocyanidins (**14**). More than 840 new examples of isoflavones (**15**), have been reported in the 15-years period from 1997-2011 alone, suggesting that interest in this area continues to remain at a high level[20]. Neoflavonoids (**16**) are not often found in food plants, but dalbergin (6-hydroxy-7-methoxy-4-phenylcoumarin) is a relatively widely distributed neoflavone in the plant kingdom.

Sources: The main source of biophenols in our diet is fruits and beverages such as fruit juice, tea, coffee, wine, beer and cocoa-rich products. Consumption of vegetables and cereals also contributes but to a lesser extent relatively. The average daily intake of total polyphenols has been estimated to be 1193 mg/d, although the authors have suggested that this may be a slight underestimate due to insufficient data on the polyphenol content of foods[21]. Flavonols are the most widespread of the flavonoids, being dispersed throughout the plant kingdom with the exception of a few algae and fungi. The distribution and structural variations of flavonols are extensive and have been well documented[17-19]. The major flavonol of our diet is quercetin (**17**), which is commonly encountered as its 3-*O*-glycoside, rutin or as quercetin itself. The mean intake of quercetin has been estimated to be 16 mg/d. Apple skins accumulate high levels of flavonoid 3-*O*-glycosides, particularly flavonol and anthocyanin galactosides. Flavanols exist in both the monomeric (*e.g.* catechin) and the polymeric (*e.g.* proanthocyanidin) forms. Catechins (5,7,3',4'-tetrahydroxyflavan-3-ol) are flavanols, commonly found in many types of fruits (apricot, which contains 250 mg Kg^{-1} fresh weight, is a rich source). Though they are also available in red wine, green tea and dark chocolates (cocoa-rich products) are by far the richest sources. An infusion of green tea (200 mL) contains up to 200 mg of catechins[22]. Black tea contains fewer monomeric flavanols, as these are oxidised during processing of tea leaves to more complex dimers (theaflavins) and polymers (thearubigins)[22].

Stilbenes (Fig. 7) such as resveratrol (**18**) and piceatannol (**19**) characterized from wine and grapes are also known to occur in a variety of plant foods and beverages, including dark chocolate, nuts and berries, though their concentrations are much lower than the other biophenols[23]. In human foods, flavanones are found in tomatoes and certain aromatic plants

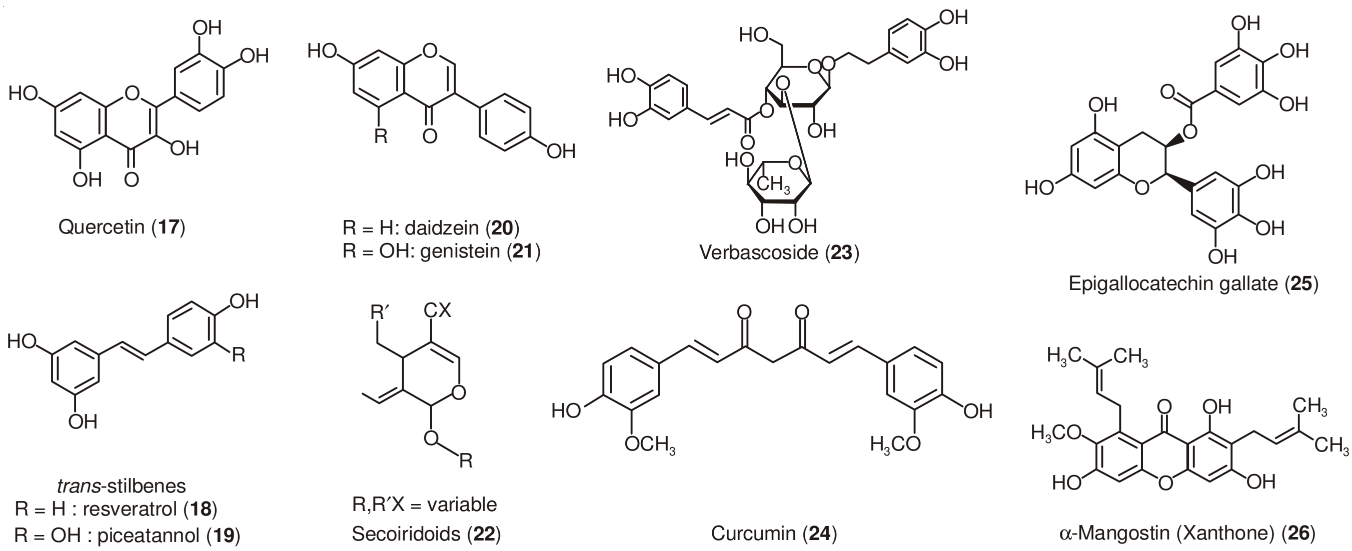


Fig. 7. Illustrative dietary biophenols

such as mint, but their presence is high only in citrus fruits. The main aglycones (the non sugar component that results from hydrolysis of glycoflavanones) are naringenin (5,7,4'-trihydroxyflavanone) in grapefruit, hesperetin (5,7,3'-trihydroxy-4'-methoxyflavanone) in oranges and eriodictyol ((S)- 5,7,3',4'-tetrahydroxyflavanone) in lemons. The Leguminosae, with an estimated 19,500 species, is the main source of naturally occurring isoflavonoids[20]. Soya and its processed products, red clover, chickpea and alfalfa are the main source of isoflavones in the human diet. Currants and raisins are also reported to be rich in daidzein (**20**) and genistein (**21**). The isoflavone content of soya and its manufactured products varies greatly as a function of geographic zone, growing conditions and processing[23]. Soybeans contain between 580 and 3,800 mg isoflavones Kg^{-1} fresh weight and soymilk contains between 30 and 175 mg L^{-1}. Isoflavones are relatively stable under most cooking conditions and do not normally get destroyed during food processing. The open-ring chalcones are found in fruits such as apples and hops or beers[24]. Neohesperidin dihydrochalcone (4'-*O*-β-neohesperidosyldihydrochalcone), derived from citrus, is an artificial sweetener. The compound is said to be roughly 1500-1800 times sweeter than sugar at threshold concentrations and around 340 times (w/w) sweeter than sugar.

The skins of the fruit or the outer edge of the vegetables as well as the leaves commonly constitute the major sources of phenolics than the edible portions as they tend to accumulate in the dermal tissues of plant body because of their potential role in the protection against UV rays, as attractants in fruit dispersal and also as defense chemicals against pathogens[23]. In addition, their content is also influenced by factors such as season, sunlight, climate and food preparation and processing. Anthocyanidins are the principal components of the scarlet, pink, purple and blue pigments of the majority of flower petals, fruits (such as berries, grapes and strawberries) and vegetables as well as certain special varieties of grains (black rice). Anthocyanidins, in plants, mainly exist as water-soluble glycosidic anthocyanins. A total of more than 500 anthocyanins are known depending on the hydroxylation, methoxylation patterns on the B ring and glycosylation with different sugar units[24]. Proanthocyanidins, also known as condensed tannins, are oligomeric or polymeric end-products of the flavonoid biosynthetic pathway. They are widespread in fruits, bark, leaves and seeds throughout the plant kingdom, where they provide protection against predation. They are also determinants of astringency or flavour in beverages and their presence in forage crops is a major quality factor. Dietary sources of proanthocyanidins include apples, pears, grapes and wines, tea and cocoa products.

Phenolic acids account for about one third of the total intake and flavonoids account for the remaining two thirds. Olive fruit and oil are reported to contain more than a dozen phenolic acids in addition to a number of phenolic alcohols, flavonols, hydroxytyrosol (Fig. 3), secoiridoids (**22**) and the hydoxycinnamic acid derivative, verbascoside (**23**)[25]. While fruits and vegetables also contain many free phenolic acids, in grains and seeds (particularly in the bran or hull), phenolic acids are often in the bound form[24]. It is possible to release these phenolic acids upon hydrolysis using an acid or an alkali or by enzymes. A number of published literatures, including the cited ones[11-30], describe the isolation, characterization and quantification of the various classes of dietary biophenols from food sources.

Phenol-Explorer is a comprehensive database on polyphenol content in foods. The database contains more than 35,000 content values for 518 polyphenols, belonging to six classes and 31 sub-classes in over 400 foods[31]. Release 2.0 of Phenol-Explorer[32] has added data on polyphenol metabolism. Pharmacokinetic data on 380 metabolites identified in biofluids after the consumption of polyphenol-rich sources are presented. The Release 3.0 of Phenol-Explorer[33] has attempted to introduce data on the effects of food processing and cooking.

Health implications: Among the different classes, 'polyphenols' are probably the most extensively probed secondary metabolites in the past two decades. Fig. 8 illustrates the publications/hit-results returned from the databases of Google Scholar, Science Direct, PubMed and MEDLINE upto August 2013 for the search-term 'polyphenols' in the context of a wide range of research areas[12]. As pointed out earlier, the tag 'polyphenols' lucidly encompass the scores of monocyclic phenols biosynthesized by the green kingdom too and hence is to be better addressed as biophenols. Results emerging from epidemiological studies involving short-term human interventions, experimental animals and *in vitro* studies tend to suggest that high dietary intake of polyphenols, especially the abundant flavonoids, is strongly linked with beneficial effects[34]. Cardiovascular health (CVH), ability to exert beneficial cognitive effects and to reverse specific age-related neurodegeneration, capacity to exert a variety of anti-carcinogenic effects (including an ability to induce apoptosis in tumour cells, inhibit cancer cell proliferation and prevent angiogenesis and tumour cells invasion) appear to be more promising than the others. They might also exert several other specific biological effects including inhibition of cholesterol uptake, modulation of different enzymes including telomerase, cycloxygenase (COX) and lipoxygenase (LOX) and might interact with several signal transduction pathways. They can also affect caspase-dependent pathways, cell cycle regulation, platelet functions and can also prevent endothelial dysfunctions[34,35]. Although the therapeutic potentials and the antioxidant/prooxidant

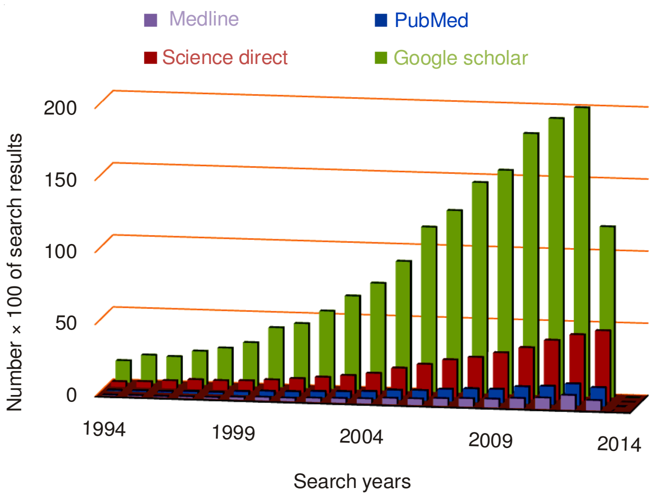


Fig. 8. Search-Results of publications (English) cited in MEDLINE, PubMed, Science Direct and Google Scholar databases (upto August 2013)

capacities of the individual biophenols are themselves potential topics of debate, an ever-expanding quantum of scientific evidence does support their protective effect on chronic degenerative disorders, such as cardiovascular diseases, neurodegenerative disorders and certain forms of cancers. The apparent shortcomings in the intervention literature (that poses the topics to debate, as understood today) primarily stem from a lack of (i) standardized biomarkers of intake, (ii) studies using homogenous isolates, (iii) long duration clinical interventions and (iv) studies quantifying biophenol dose, blood level or pharmacokinetics[36].

Heralded by the Zutphen Elderly Study[37,38], the Rotterdam Study[39] and the French paradox[40], research into possible biological pathways underling the vasoprotective properties of dietary flavonoids has undeniably gained renewed impetus. With respect to cardiovascular health, flavonoids are said to alter lipid metabolism, inhibit low-density lipoprotein oxidation, reduce atherosclerotic lesion formation, inhibit platelet aggregation, decrease vascular cell adhesion molecule expression, improve endothelial function and reduce blood pressure (BP)[41]. A wealth of flavonoid studies using biomarkers of cardiovascular diseases risk continues to flood the literature. During the 20 year period after the coinage of the term French paradox, a large section of studies (13,390 publications cited in Science Direct, 1,019 in PubMed and 42,200 hits in Google Scholar) have investigated the fascinating and overwhelmingly positive biological and clinical associations of polyphenol consumption with cardiovascular diseases and mortality. Reports claim that light to moderate intake of wine produced a kaleidoscope of potentially beneficial effects that target all phases of the atherosclerotic processes ranging from atherogenesis (early plaque development and growth) to vessel occlusion (flow-mediated dilatation and thrombosis). Such beneficial effects involve cellular signaling mechanisms, interactions at the genomic level and biochemical modifications of cellular and plasma components[42]. Red wine components, especially the intensively explored resveratrol (**18**) and its derivatives bearing catecholic B ring (**19**) as well as other phenolics[11], are believed to decrease oxidative stress, enhance cholesterol efflux from vessel walls and inhibit lipoproteins oxidation, macrophage cholesterol accumulation and foam-cell formation. These components are also most likely to increase nitric oxide bioavailability and thereby antagonizing the development of endothelial dysfunction, decrease blood viscosity, improve insulin sensitivity, counteract platelet hyperactivity, inhibit platelet adhesion to fibrinogen-coated surfaces and decrease plasma levels of von Willebrand factor, fibrinogen and coagulation factor VII[42].

Evidences also support the beneficial effects of fruit biophenols on cardiovascular diseases risk, although more human intervention studies examining a greater range of fruits, larger sample size and longer period of observations are much needed to establish these observations. Pomegranate, purple grapes and certain berries have been the most extensively investigated fruits and have been found to be effective in reducing cardiovascular diseases risk, particularly with respect to lowering blood pressure, inhibition of platelet aggregation and increasing vascular function. These fruits contain relatively high concentrations of flavonols, anthocyanins and procyanidins in addition to several other phenols and nutrients. On the other hand, fruits rich in flavanones such as oranges and grapes, though appeared to have limited impact on blood pressure, platelet and vascular function, have exhibited beneficial effects on blood lipid profiles[43].

Aging is a continuous process that commences in the fetus and advances throughout our entire life. Oxidative stress, systemic low-grade chronic inflammation and the impairment of hormonal, fibrinolytic and immunological status are the major risk factors underlying aging and age-related diseases such as neurodegenerative disorders, cognitive decline, cardiovascular diseases, cancer, type 2 diabetes mellitus, obesity, osteoarthritis, osteoporosis, metabolic syndrome and cerebrovascular diseases and others. Human life expectancy is growing continuously and by 2025, 10.4, 18.8 and 21 % of the World, USA and European populations, respectively, are projected[44] to be represented by senior citizens of age ≥ 65 y.

Aging leads to numerous transitions in brain physiology, including synaptic dysfunction and disturbances in cognition and memory. Neurodegenerative disorders comprise of a condition in which the nerve cells from brain and spinal cord degrade leading to either functional loss (ataxia) or sensory dysfunction (dementia). Mitochondrial dysfunctions, excitotoxicity and finally apoptosis have been reported as pathological cause for aging and neurodegenerative diseases such as Parkinson's disease (PD), Alzheimer's disease (AD), stroke, multiple sclerosis (MS), Huntington's disease (HD) and amyolotrophic lateral sclerosis (ALS). Emerging scientific evidences tend to suggest that neurodegenerative diseases are accompanied by oxidative stress, inflammation, metal accumulation and mitochondrial dysfunctions. Various physiological mechanisms are altered by these pathological changes which contribute to the etiology of neurodegenerative diseases[45]. With only a few available clinically relevant drugs, substantial portions of the aging population is at the risk of age-related neurodegenerative disorders and hence depend heavily on nutritional intervention[46]. Neurodegenerations have been speculated to be interplay of a number of factors including environmental and genetic predispositions. The prevention and treatment of these disorders with complex mechanisms require novel therapeutic strategies, targeted for multiple genes and proteins. However, redox-metal abuse appears to occupy a central role as most of the symptoms stems out of abnormal metal-metabolism. Oxidative stress and free radical generation, catalyzed by redox-metals, have been shown to play pivotal role in regulating redox reactions *in vivo* contributing reactive intermediates, particularly the oxygen and nitrogen ones. These intermediates are claimed to be the main culprits in the neurodegeneration. Biophenolic dietary antioxidants, as learnt from a number of pre-clinical animal experiments and limited clinical interventions, can remarkably control and modulate reactive species, metal-toxicity, inflammation, apoptosis, signal transduction, ion channels and neurotransmitters. Their multipotent ability can thus attenuate such complex physiology by modulating several therapeutic targets simultaneously. Dietary intake or their direct usage and dietary supplementation can attenuate oxidative stress and hence reduce the risk for Alzheimer's disease, stroke, multiple sclerosis, Parkinson's disease and Huntington's disease. Experimental and epidemiological study-reports suggest that dietary biophenols activate antioxidant pathways such as nuclear factor erythroid 2-related factor 2/heme oxygenase-1 (Nrf2/HO1) and down-regulate nuclear factor-kappa B (NFkB), metalloproteinases, peroxisome proliferator activated receptor, hypoxia inducible factor-1 (HIF-1) and signal transducer and activation of transcription pathways. Biophenols are also claimed to modulate immune response by inhibiting pro-inflammatory biomarkers such as chemokine (C-C motif) ligands (CCL17 and CCL22), chemokine receptors (CCR1 and CCR2), macrophage inflammatory proteins (MIP1α and MIP1β), chemokine (C-X-C motif) ligands -CXCL (9, 10, 11), interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α) and interleukin-IL (1β, 6, 17A, 22). These salient properties of biophenols help to reduce oxidative damage and inflammation, the hallmarks of neurodegeneration.

Biophenols are also claimed to protect mitochondria from pathological events by triggering pro-survival cell signaling. They have been found to elevate the amounts of antioxidant enzymes such as, catalase, superoxide dismutase (SOD1, SOD2) and pro-survival B-cell lymphoma 2 and pancreatic ER kinase pathways. Down regulation of BCL2-associated agonist of cell death/BCL2-associated X protein, c-jun, c-jun N-terminal kinase, COX-2, activator protein-1 (AP1) and caspase-3 also contributes to the survival of neurons. Biophenols also appear to help in improving cognitive abilities by inhibiting acetylcholinesterase and butyrylcholinesterase. The inhibition of these enzymes are claimed to play an important role in clinical medicine to treat Alzheimer's disease. Apart from their anti-acetylcholinesterase activity, biophenols also induce metal chelation and modulate autophagy and prion proteins. These features along with reduction of Aβtoxicity, reduction of neural lesions and activation of cell survival genes are of particular relevance to neurodegenerative diseases. The absence of observed toxic effect and easy availability from natural sources makes biophenols as clinically relevant therapeutics/preventives in neurodegeneration.

Evidence also suggests that consuming additional biophenols in the diet can lead to cognitive benefits, although the actual effects observed have been small[47]. Declarative memory and particularly spatial memory appear to be most sensitive to polyphenol consumption and effects might differ depending on the polyphenol source. Polyphenol-rich berry fruit juice consumption is claimed to be most beneficial for immediate verbal memory, whereas isoflavone based interventions have been associated with significant improvements for delayed spatial memory and executive function[47].

Despite a remarkable progress in the development of anticancer therapies, cancer still remains the second most abundant cause of death and hence a major public health problem in the world. The clinical management of cancer invariably involves diverse conventional modalities, including surgery, radiation and chemotherapy. As cell and tissue homeostasis are mediated by the balance between proliferation and apoptosis, controlling this balance is important for cancer chemoprevention. Cancer chemotherapy can be achieved by the use of natural, synthetic or biological sunstances that reverse, suppress or prevent the development of epithelial malignancies. Over 50 chemotherapeutic agents are currently being used as drugs for the treatment of cancer. Majority of these drugs cause severe side effects, posing physical and mental trauma to patients in addition to the complexity of cancer itself. Consequently, alternative management has become a necessity to improve the efficacy of therapeutic treatments and the quality of life of patients. According to estimates of the American Cancer Society, one-third of cancer deaths is related to lifestyle factors such as nutrition, obesity and lack of physical activity and hence is preventable[48]. Cancer is also considered a disease of aging since the risk for developing the disease considerably increases with age. It is estimated that 77 % of all cancers are diagnosed in people of age ≥ 55 y. Also, it takes several years from initiation to the development of detectable cancer in some instances. An advantage of such long latency is that it provides numerous opportunities for intervention. While intervention approaches cannot be geared towards a whole population, they can nevertheless be directed towards a defined group of people who have a greater relative risk for developing the disease. Thus, next to life style modification as a primary cancer prevention strategy, chemoprevention constitutes a means of cancer management in which the progression of the disease can be manipulated (to reverse, to suppress, or to prevent the process of carcinogenesis) through administration of specific natural and/or synthetic agents to decrease the incidence of cancer. An important aspect of chemoprevention is that agents can be designed for intervention at any stage during the multistage process of carcinogenesis. This process of slowing the progression of cancer is applicable to many cancers with long latency.

The idea of cancer prevention through the use of nontoxic agents, preferably from dietary sources, has emerged as a viable strategy for controlling the disease. A web search makes this fact more obvious since next to lifestyle (441,000 hits), wine (156,000), green tea (153,000), olive (147,000) and soy (111,000) are the words that occur frequently in conjunction with cancer in Google scholar. Strategies of cancer chemoprevention or therapy may also combine phytometabolites along with proven chemotherapeutic agents to inhibit tumour development[49]. A given constituent in a botanical can have an additive effect on prescribed anti-neoplastic agent, in addition to affecting absorption, distribution, metabolism, excretion and toxicity of prescription drugs. This interaction is particularly clinically important when hepatic enzymes, which are responsible for catabolising many drugs, are induced or inhibited.

Biophenols are one predominant class of botanicals that has consistently manifested to exert well-evidenced health benefits including chemopreventive/protective and anti-inflammatory effects in cell lines and experimental animal models[50,51]. However, when translated in the clinical domain, the effects that have been observed tend to pose more questions than results. A search in Google Scholar database for the search string 'Polyphenol+cancer' retrieved 68,100 results. Among individual phenolics, the ubiquitous dietary phenol, quercetin has been cited 57,100 times, while resveratrol of wine 52,400 times, curcumin (**24**) of *Curcuma longa* L. (turmeric) 48,200 times and the soy isoflavone: genistein 44,300 times. The green tea phenolics: catechin, epigallocatechin and epigallocatechin gallate (**25**) (EGCG) have, respectively retrieved 34,800, 29,500 and 28,900 results in the context of cancer. Dietary phenolics are known to decrease leukocyte immobilization, induce apoptosis and inhibit cell proliferation and angiogenesis, in addition to exhibiting phytoestrogenic activity[52]. They also interfere with signal transduction pathways related to the process of carcinogenesis, thereby acting as chemopreventive agents. These include the suppression of NFkB and AP1 activation, inhibition of the mitogen-activated proteins (MAPKs)-, protein kinases- and growth-factor receptor-mediated pathways, cell cycle arrest, induction of apoptosis, anti-oxidant and anti-inflammatory effects and suppression of angiogenesis[53].

The chemopreventive properties of a variety of compounds can be directly related to their pro-apoptotic properties, most probably exerted *via* the intrinsic (mitochondrial) apoptotic pathway[52]. Many studies have described the pro-apoptotic properties of dietary polyphenols in a varietry of human cancer cell lines derived from colon, prostate, lung, breast cancers and leukemia[54]. Resveratrol[55], piceatannol[56] and quercetin[57], for instance, are capable of acting in multiple ways through multiple pathways involved in the regulation of the cell cycle and the induction of apoptosis by modulating directly or indirectly (in a dose- and cell-status-dependent manner) either pro-survival or pro-apoptotic factors. These factors include hormone-regulated receptor signaling systems (say, estrogen receptors) and the expression and/or activity of numerous functional proteins such as the tumor-suppressor p53 and retinoblastoma (pRb) proteins, MAP kinases, cyclins and cyclin-dependent kinases, tyrosine kinases and certain other protein kinases, DNA polymerase (*in vitro*), carcinogenic phase I (say, cytochrome P450 monooxygenases, CYPs) and phase II enzymes, proinflammatory COXs, lipoxygenases (LOXs) and induced nitric oxide synthase (iNOS), both anti- and pro-apoptotic BCL2 proteins, proliferative transcriptional factors (say, NFkB, AP1, Egr1) and co-transcriptional factors such as the acetylase p300, known to activate the proliferative NFkB, as well as the apoptotic p53 and the deacetylase sirtuin 1 (SIRT1), presumed to exert the exact opposite effects. Some of them are found to exert an antimetastatic effect by blocking tumour cell adhesion to endothelial cells through the inhibition of the expression of ICAM-1, a glycoprotein cell-surface receptor involved in cell-cell interaction processes[58].

The apparent dichotomy that emerges from the reported data on resveratrol, piceatannol and quercetin (Fig. 7) does not help one to establish a clear picture of their effects on human health. However, they do at least unveil their conceivable and remarkable capacity to act as promoters of either cell death or survival by interacting with different target molecules to affect signaling pathways within cells in different ways, depending upon their status and related specific molecular settings. This ability of the compounds is remarkable and, as can be inferred from similar such data relating to the chemopreventive and/or chemotherapeutic actions of other biophenols, notably those found in green tea such as EGCG[59] or in turmeric such as curcumin[60,61] or in soy[62-64] (isoflavonoids), could be manifested by majority of biophenols. SIRT1 is a human NAD^+-dependent deacetylase that promotes cell survival by inactivating the p53 protein and thereby delaying apoptosis to give cells additional time to repair damage before cell death[11]. Resveratrol is reported to be the most potent activator and at low doses (0.5 μM) increased the survival of human embryonic kidney cells submitted to radiation-induced DNA-damaging conditions. A reverse effect, however, has been observed at higher concentrations (50 μM). Most intriguingly, resveratrol could also mimic calorie restriction in yeast by activating SIR2 (the yeast homologue of the human SIRT1), thus extending the average cell lifespan by 70 %[11]. The expression of SIRT1 and other related so-called "longevity" proteins have been reported by Mukherjee *et al.*[65], to get induced in rats fed with both red and white wines. The SIRT1 enzyme has also been shown to confer significant protection against age-related neurodegeneration, notably by rescuing neurons from Alzheimer's disease[66].

Promising results are also being realised *in vitro* and *in vivo* by the use of biophenols as adjuvant to existing chemotherapy regimens to improve efficacy and/or reduce drug-induced toxicity. This has opened up new avenues for exploring better cancer chemotherapeutic strategies, especially in the emerging therapeutic modalities like nanotechnology and photodynamic therapy[35,67,68]. EGCG has been found to synergistically enhance the anticancer effects of panaxadiol, a purified sapogenin of ginseng saponins in the inhibition of colon cancer cell growth[69,70]. In the study[69], the possible synergistic anticancer effects of panaxadiol and EGCG on HCT-116 and SW-480 human colorectal cancer cells have been evaluated by a modified trichrome stain cell proliferation analysis, in addition to exploring the potential role of apoptosis in the synergistic activities. EGCG[71,72] is reported to have shown the most potent antiproliferative effects and significantly induced cell cycle arrest in the G1 phase and cell apoptosis, suggesting that apoptosis might play an important role in the EGCG-enhanced antiproliferative effects of panaxadiol on human colorectal cancer cells.

The mechanism of anticancer efficacies and the synergistic effects of combining EGCG, resveratrol and α-mangostin (**26**) in the treatment with the anticancer drug 5-fluorouracil in three human colon cancer cell lines is also recently reported[73]. The numbers of viable cells have been observed to consistently decrease by the treatment at more than 10 μM in all three cell lines tested. All the compounds primarily have induced apoptosis and have suppressed the phosphatidylinositol-3 kinase, PI3K/Akt signaling pathway. Additionally, α-mangostin, which had the greatest PI3K/Akt-suppressing activity, also suppressed MAPK/ERK1/2 signaling (ERK:extra-cellular signal-regulated kinase). Importantly, the combination treatment with resveratrol and 5-fluorouracil has induced a remarkably synergistic enhancement of growth inhibition and apoptosis through the additional suppression of the MAPK/ERK1/2 signaling pathway in colon cancer DLD-1 cells. Interestingly, resveratrol has increased the intracellular expression level of miR-34a, which down-regulated the target gene E2F3 and its downstream SIRT1, resulting in growth inhibition, in the study. These findings are claimed by the authors to indicate that these compounds have functioned as chemosensitizers when combined with anti-cancer drugs through the modulation of apoptotic and growth-related signaling pathways. According to them, resveratrol has exerted its anti-cancer activity in part through a newly defined mechanism, *viz.*, the miR-34a/E2F3/SIRT1 cascade[73].

One major reason attributed to the poor performance of the dietary biophenols in the clinical front is the problem encountered with their short half-life and poor oral bioavailability, requiring modalities to directly deliver them to the target tissues. The use of encapsulation[74,75] and nano-particulation[76,77] are areas that are being exploited to enhance their delivery. Targeted and triggered drug delivery systems accompanied by nanoparticle technology are evolving as prominent solutions to augment the bioavailability and bioefficacy of these phenolic biomolecules. Nanoparticle (nanosphere and nanocapsule) formulations, liposome encapsulation, nanoemulsions, micellar encapsulation systems, are some of the platforms successfully developed to enhance the oral bioavailability and cellular uptake and superior biological efficacies *in vivo*.

The greater surface area, appreciable solubility and improved controlled release that enable better precision targeting of the encapsulated phytophenols complement the objectives of such studies. In addition, their sub-cellular dimensions permit nanoparticles to penetrate deep into tissues through fine capillaries and cross the fenestration present in the epithelial lining, thereby allowing efficient delivery of therapeutic agents to target sites in the body. To overcome the less favourable pharmacokinetic properties arising out of low water solubility, chemical instability (being rapidly and extensively metabolized and excreted) and poor bioavailability, nano and micro formulations for resveratrol encapsulation have been reported. These include liposomes, polymeric nanoparticles, solid lipid nanoparticles, lipospheres, cyclodextrins, polymeric microspheres, yeast cells carriers and calcium or zinc pectinate beads[78]. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), loaded with resveratrol have been claimed to have an average resveratrol entrapment efficiency of 70 % for both solid lipid nanoparticles and nanostructured lipid carriers[79]. Various nano-preparations of curcumin for cancer therapy, including nanoparticles, liposomes, micelles, nanoemulsions, cyclodextrin complexes, nanodisks, nanofibres, solid lipid nanoparticles and curcumin conjugates are overviewed in a recent literature[80].

Conclusion

In the past two decades or more, plant derived biophenols, belonging to various classes, have been drawing particular interest not only in the emerging dietary clinical interventions but also in dermatological/cosmeceutical, food processing and certain other prominent fields of research. Consensus on their protection against age-related ailments today is largely based on pre-clinical *in vitro* and experimental animal models. The future of biophenol research, thus, very much relies on the clinical establishment of these health claims. Furthermore, risk assessment and safety evaluation, particularly of nanobiophenol delivery must also be critically investigated.

ACKNOWLEDGEMENTS

The facilities provided by the following database managements are acknowledged with gratitude: Google Scholar, ISI Web of Knowledge, Science Direct, PubMed, MEDLINE (Medscape), Scirus and Phenol-Explorer.

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