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Flavonoids and Age Related Disease: Risk, benefits and critical windows

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Abstract

Plant derived products are consumed by a large percentage of the population to prevent, delay and ameliorate disease burden; however, relatively little is known about the efficacy, safety and underlying mechanisms of these traditional health products, especially when taken in concert with pharmaceutical agents. The flavonoids are a group of plant metabolites that are common in the diet and appear to provide some health benefits. While flavonoids are primarily derived from soy, many are found in fruits, nuts and more exotic sources, e.g., kudzu. Perhaps the strongest evidence for the benefits of flavonoids in diseases of aging relates to their effect on components of the metabolic syndrome. Flavonoids from soy, grape seed, kudzu and other sources all lower arterial pressure in hypertensive animal models and in a limited number of tests in humans. They also decrease the plasma concentration of lipids and buffer plasma glucose. The underlying mechanisms appear to include antioxidant actions, central nervous system effects, gut transport alterations, fatty acid sequestration and processing, PPAR activation and increases in insulin sensitivity. In animal models of disease, dietary flavonoids also demonstrate a protective effect against cognitive decline, cancer and metabolic disease. However, research also indicates that the flavonoids can be detrimental in some settings and, therefore, are not universally safe. Thus, as the population ages, it is important to determine the impact of these agents on prevention/attenuation of disease, including optimal exposure (intake, timing/duration) and potential contraindications.

Keywords

soy; kudzu; metabolic syndrome; complimentary medicine; dietary supplements

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Introduction

Flavonoids are important secondary metabolites of plants that are the most common group of polyphenolics in the human diet (Figure 1). They are subdivided into several other groups including flavone, flavonol, flavanone, and isoflavones. Isoflavonoids differ from other flavonoids by having ring B attached to C-3 position of ring C. In plants, they are especially important in guarding against oxidant damage, and they provide to the plant the color that attracts pollinators and repels attacks by insects and microbes. Recent research suggests that in humans, these plant polyphenols provide important health benefits related to metabolic syndrome, cancer, brain health and the immune system. While many of these effects are of interest in youth, they are even of greater interest for treating the fastest growing sector of the population, i.e., aging adults. The relatively low toxicity and potential efficacy of most of these agents make them attractive to a large sector of the population. Further, there has been a growing public openness to non-traditional therapies such as botanical supplements. An estimated 42% of adults in the US take some form of dietary supplement for their health [1] and most studies suggest that about 33% of women regularly take a botanical supplement [2].

Research investigating botanical compounds focuses on elucidating beneficial and adverse effects, as witnessed by the publication in 2009 of over 60 scientific review articles on the health effects of dietary botanicals. The emerging scientific evidence indicates that many of these compounds are effective and have few adverse effects, but some adverse effects and adverse drug interactions have been identified [3,4]. No polyphenol has been identified as a primary treatment for any disease, but many flavonoids appear to provide potentially important adjuvant and preventative treatments. In response, there has been phenomenal rise in use of isoflavones over the last decade. While soybeans and soy products have been the major sources of commercially available isoflavones, increasing consumer interest led to supplements based on soy, red clover, and kudzu. Similarly, these sources have been the target of many ongoing studies investigating their roles in the prevention/delay of age-related diseases, such as atherosclerosis [5], cancer [6,7] and osteoporosis [8,9].

This paper reviews the broad health effects of flavonoids in disease, but it also focuses more specifically on their role in the metabolic syndrome and its tripartite contributors, i.e., diabetes, hypercholesterolemia (and obesity) and hypertension. Whereas there is an extraordinary rise in the incidence of type 2 diabetes and insulin resistance among teens, the incidence of type 2 diabetes is increasing nearly as rapidly among the aging and is highest among aged Hispanics and African-Americans (>70% greater than in age-matched Caucasians [10]). Further, lifestyle modifications that decrease diabetes in the young (e.g., weight loss, smoking cessation and increased exercise) are often unavailable or not well tolerated in older adults. In aged adults, compared to youth, hypertension and dyslipidemia are much more likely to synergize with diabetes to produce the metabolic syndrome, thus requiring many daily medications and. It is well established that an increase in anti-diabetic medications leads to a concomitant decrease in compliance in adults [11]. In contrast, adults appear to much more consistently take botanical supplements than pharmaceuticals [1]. Thus, botanical supplements that exhibit anti-diabetic actions may be an important component of successful diabetes therapy.

Flavonoid biochemistry

To verify the *in vivo* health effects of isoflavones, it is important to understand how isoflavones are absorbed from the gastrointestinal tract and why some isoflavones are absorbed more efficiently than others. Equally important is the determination of how much and how long isoflavone exposure is required to provide health effects. Although there has been substantial progress in the elucidation of the pharmacokinetics and bioavailability of isoflavones, there is yet no clear understanding of why isoflavones have relatively poor bioavailability.

Uptake and bioavailability of isoflavones

Soy products, the major source of dietary isoflavones for most people, contain 12 known isoflavone compounds (three aglycones, three glucosides, three acetyl-ester glucosides, and three malonyl-ester glucosides). Genistein (5,7,4'-trihydroxyisoflavone) and daidzein (7,4'-dihydroxyisoflavone) are the primary isoflavones and are commonly regarded as phytoestrogens because of their estrogenic-like properties. A series of reports from *in vivo* studies document the bioavailability of these two isoflavones at target tissues, but the bioavailability is much lower than the concentration typically used for *in vitro* studies that are designed to evaluate the botanicals' biological effects, e.g., antioxidant properties [12], estrogen receptor binding [13,14] and antiproliferative and growth inhibiting effects [15]. Since most isoflavones undergo extensive metabolism *in vivo*, much of the *in vitro* data are complicated to interpret relative to *in vivo* systems. Therefore, a clear understanding of uptake, metabolism and bioavailability of these compounds is crucial to elucidating their health benefits/adverse effects.

Most common isoflavones exist as O-glucosides (e.g., daidzein and genistein), and, compared to their aglycones form, the glycoside forms are poorly absorbed from the small intestine into the blood due in large part to their high hydrophilicity [16,17]. Intestinal uptake of majority of isoflavones is by non-ionic passive diffusion, and the glycosidic moieties of isoflavone glucosides are substantial hydrophilic, thus reducing passive transport across the membrane. Some flavonoid glucosides may utilize the Na⁺-dependent glucose transporters [18,19]. Interestingly, soy may inhibit glucose transport in isolated rat intestinal vesicles via inhibition of GLUT2 [20].

Poor absorption of O-glycosylated isoflavones poses a potential barrier for their clinical application. Like other flavonoids, isoflavones undergo intestinal absorption and first-pass metabolism before entering the peripheral blood compartment and reaching most target organs. Isoflavones are substrates for β -glucosidase, UDP-glucuronosyltransferase, and sulfotransferase in the small intestine as well as for a number of phase I and II enzymes. Lactase phlorizin hydrolase (LPH) is a membrane-bound β -glucosidase enzyme located in the brush-border of small intestine and is primarily responsible for hydrolysis of lactose and glycosides. Isoflavones in blood circulation mostly exist in the form of glucuronide conjugates. For example, oral bioavailability of genistein in cats is 1.379% for free form and 29.85% for the conjugated forms [21]. It is also important to note that genistein and its principal metabolite, genistein 7-O- β -glucuronide are well absorbed from the intestine and transported from portal blood into the liver and bile and thus undergo enterohepatic circulation [22,23]. In view of enterohepatic circulation of genistein and its metabolites, genistein is highly bioavailable in rats as it may accumulate within gastrointestinal tract [22].

Ingested isoflavones are subjected to hydrolysis and degradation in the colon due to microbial enzyme catalysis. The pharmacokinetic behavior of isoflavones genistein and daidzein and their respective β -glucosides in healthy humans was first studied by Setchell [24]. The studies indicated that the peak plasma concentrations (T_{max}) for aglycones genistein and daidzein were 5.2 and 6.6 h, respectively, whereas in the case of their β -glucosides, the T_{max} values were delayed to 9.3 and 9.0 h, respectively [24]. According to this study, daidzein showed extensive tissue distribution compared to genistein as the apparent volume of distribution of daidzein is 236 L compared with genistein (161 L). These data indicate that the systemic bioavailability of genistein (plasma concentration) is higher than daidzein, and the half life (T_{1/2}) for daidzein and genistein are about 9.3 h and 7.1 h, respectively.

In contrast to isoflavone O-glucosides, puerarin (daidzein 8-C-glucoside) an isoflavone C-glucoside found in kudzu root, is resistant to intestinal hydrolysis and absorbed intact. Puerarin is rapidly absorbed into the blood, reaching a maximum and then declining within 1 h [25]. It

undergo limited phase I and phase II reaction and widely distributes to various organs such as liver, kidney, lungs, pancreas, heart, brain and eyes [26,27]. The mechanism for this action may involve intestinal glucose co-transporters (SGLT1 and/or GLUT2). These observations clearly demonstrate that deconjugation of isoflavone-C-glycosides is not a prerequisite for its absorption in rats. Schematic of possible mechanism involved in intestinal transport of puerarin and daidzin is shown in Fig. 2.

Colonic metabolism of isoflavones by the large number of microorganisms in the lumen of the colon is a major factor affecting their bioavailability. After intestinal hydrolysis, the aglycone daidzein undergoes extensive reductive metabolism to make dihydrodaidzein, dihydrogenistein, O-desmethylangolensin (O-DMA) and equol. Equol-a potential ligand for estrogen receptor (ER)beta, was first identified in urine and blood as metabolites of daidzein [28]. It has attracted interest for its potential application in hormone-dependent therapeutic and is under development as a nutraceutical [29]. Metabolism of genistein includes dihydrogenistein, 6'-hydroxy-O-DMA, 2-(4-hydroxyphenyl)-propionic acid, and 4-ethyl phenol [30] (Fig. 3). The extraction output of these metabolites varies tremendously among individual's gut microbial ecology, i.e. equol producer or non producer. Only 30-40% of the Western populations are equol producers [31].

Bacterial metabolism of isoflavones is important relative to generating chiral metabolites from achiral molecules. Setchell has shown that in human the naturally occurring isomer of equol is the S(-)- enantiomer [32]. It is interesting to note that only daidzein metabolites are detected in the prostate of male rats [7]. Because of the differences in absorption and metabolism of each of the isoflavones, the isoflavone composition of soy preparations or dietary supplements plays crucial roles in determination of their health beneficial effects.

Metabolic Syndrome and Botanicals

The metabolic syndrome has three major contributors: hypertension, dyslipidemia/obesity and hyperglycemia/hyperinsulinemia, all of which act synergistically to greatly increase morbidity and mortality. While the incidence of all three contributors is increasing exponentially in adults, a parallel rise is also occurring in children [33]. It is estimated that clustering of these metabolic risk factors occurs in up to 50% of overweight adolescents, leading to an increased appearance in early onset type-2 diabetes and cardiovascular disease [34].

The treatment of metabolic syndrome in both young and aging populations has greatly increased pharmaceutical expenditures, and antihyperglycemic drugs are projected to become the largest single component of all prescription drug spending in the near future [35], making the metabolic syndrome a very significant burden on individual health and the economy. Research is increasingly exploring the ability of botanical supplements to reduce metabolic syndrome risk factors, since these compounds could provide greater efficacy and tolerability at lower cost, compared to current pharmaceutical options (Fig. 4).

Metabolic syndrome displays a strong gender disparity. Relative to age-matched males, the rate of metabolic syndrome is significantly lower in premenopausal women, but after menopause women display a large increase in dyslipidaemia, arterial pressure and other risk factors, so that their risk profile for metabolic syndrome approximates that observed in age-matched males [36]. This lends support to the hypothesis that estrogen protects premenopausal women from metabolic disease, adds interest to the search for alternatives to estrogen therapy to reduce metabolic disease and increases interest in flavonoids as potential estrogen mimetics.

Hypertension and Botanicals

A major contributor to metabolic syndrome is hypertension, which also significantly increases the incidence of heart disease and stroke, amplifies the adverse effects of other cardiovascular risk factors and is highly age-related [37,38]. Hypertension is present in 30% of all adults and in more than 60% of adults over 65 years of age [39]. The mechanisms underlying the development of most hypertension are polygenic, and most are only partially understood.

The prevalence of hypertension is also sexually dimorphic. Premenopausal females consistently have lower blood pressure than age-matched males; however, during the perimenopausal period, arterial pressure increases rapidly in females and by age 60 the average arterial pressure is equal to that in males [36,40]. These observations have long suggested that circulating estrogen and/or progesterone exert cardioprotective effects on premenopausal women and that loss of this protective estrogenic effect at menopause contributes to the rapid increase in arterial pressure, hypertension and cardiovascular disease. In response to these findings, during the last 2 decades of the 20th century there was a tremendous expansion in the use of hormone replacement therapy (HRT) to decrease cardiovascular disease in postmenopausal women; however, the findings of the Women's Health Initiative indicated significant potential adverse effects of HRT [41]. These findings increased interest in the use of alternative methods, especially dietary supplements that were estrogen-like, but appeared to lack the associated adverse effects of estrogen.

Probably the most studied and most widely used botanical for cardiovascular protection is soy, largely due to the ability of soy isoflavones to activate estrogen receptors. A number of studies indicate that dietary soy lowers arterial pressure in both postmenopausal women and age-matched men, e.g., [42,43], regardless of whether individuals have established hypertension or are normotensive [44]. Several studies have tried to elucidate the roles of genistein and daidzein in these effects. Both genistein and daidzein bind estrogen receptors (ER), especially ER β receptors [45,46], and the antihypertensive effects of both of these isoflavones mirrors the effects of whole soy in clinical [47,48] and animal studies [49,50]. Our laboratory has focused on the effects of soy isoflavones on blood pressure control in spontaneously hypertensive rats (SHR) and stroke prone SHR (SHRSP), both commonly used genetic model of hypertension that exhibit gender disparity similar to that observed in human subjects [51, 52]. These findings suggested that both estrogen and flavonoid “phytoestrogens” exert a protective effect on arterial pressure in these models. Soy flavonoids are present in high concentrations in normal commercial rodent diet (typically soy based), and they decrease blood pressure in ovariectomized SHR that are on an otherwise phytoestrogen-free diet [52]. Supplementation of the diet with genistein alone at dietary concentrations (0.06% w/w) causes a 50% (>30 mm Hg) decrease in the hypertensive response to a high NaCl diet in these animals [53], and the protective effect of soy isoflavones on salt-sensitivity also extends to male rats and thus the effect is not gender specific [53].

Grape seed extract is another well studied flavonoids, largely due to epidemiological observations that the red wine drinking French display better vascular health and lower cardiac mortality rates relative to their American counterparts, despite consuming a diet similar in fat [54], i.e., the “French Paradox” [55]. These observations suggest that the flavonoids in red wine might confer a protective effect against coronary heart disease. Results from ensuing studies indicate that red grapes (both skins and seeds) contain a significant number of polyphenolic compounds, including phytoalexins (e.g., resveratrol), proanthocyanidins and flavonoids, that significantly reduce cardiovascular disease and stroke [54,56].

Grape seed extract is composed of multiple polyphenolic compounds, including monomeric catechins and proanthocyanidins (oligomeric or polymeric catechins). Similar to soy flavonoids, in combination with a otherwise flavonoids-free diet, grape seed extract reduces

NaCl-sensitive hypertension in male and female SHR and decreases blood pressure in ovariectomized SHR on a basal NaCl diet [57]. It appears that these actions are not mediated by estrogenic pathways. In contrast, grape seed extracts provide significant antioxidants and may reduce the amount of reactive oxygen species, which are elevated in cardiovascular disease and cancer along. A similar study using grape skin extract demonstrated that dietary supplementation lowered arterial pressure in both DOCA-NaCl and L-NAME-induced hypertensive rats, likely as a result of vasodilatory effects of grape skin polyphenols [58]. Taken together, these rodent studies indicate that the polyphenolic compounds found in both the skin and seeds of red grapes favorably impact hypertension and control of arterial pressure.

Kudzu root is a botanical that has been extensively used in traditional Asian cultures for centuries. In the SHR, kudzu root extract (compared to control diet) induces a relatively small (< 15 mm Hg) decrease in hypertension compared to that provided by other flavonoids [59]. Further, kudzu root show no greater effect in SHR on a high salt diet, old SHR or male versus intact female versus ovariectomized female rats. Other flavonoids tested have a greater effect in many of these settings. Together, these findings suggest that the mechanisms of action of these botanicals differ, with grape seeds favorably affecting hypertension and control of arterial pressure.

Botanicals and Dyslipidemia

Dyslipidemia, including elevated plasma concentrations of total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol (and/or reduced high-density lipoprotein [HDL]), is strongly associated with cardiovascular disease, peripheral vascular disease and stroke[60]. Further, many observational studies have demonstrated that populations consuming plant-based diets typically have significantly lower TC and LDL levels, corresponding to reduced rates of heart disease compared to the general population. These observations have resulted in dietary guidelines that limit total and saturated fats and dietary cholesterol and are higher in plant products.

Early results indicate that multiple botanical compounds may improve plasma lipid profiles, e.g., plant stanols and sterols, tea-based catechins and theaflavins [61], although clinical data related to the efficacy of many of these substances is lacking. One dietary substance that demonstrates potent beneficial effects on lipid profile is niacin, which increases HDLs and decreases LDL levels. Given the number of clinical studies supporting an effect of niacin on lipid profile (e.g., [62]), it has been increasingly used in hyperlipidemia therapy. Other supplements that demonstrate early clinical success in improving lipid profiles include red yeast rice extract [63,63] and omega-3 fatty acids[61].

In Asia, where diets generally contain relatively large amounts of soy, lipid profiles and coronary heart disease are low compared to Western societies. Studies have demonstrated that soy isoflavones reduce LDL levels [64-71], triglycerides[72-75] and apolipoprotein B plasma concentrations[76] while increasing HDL levels[77]. In addition, soy intake also lowers body weight and BMI in obese individuals[78].

The mechanism(s) by which soy isoflavones act may include both estrogen-like effects and alternative pathways. Similar to estrogen, the phytoestrogen genistein activates ER β receptors, decreasing the activity of lipoprotein lipase and thereby decreasing lipogenesis[79]. Soy isoflavones may also positively influence lipid levels through PPAR-mediated pathways, which control the transcription of several genes involved in lipid catabolism and adipocyte differentiation, and as a tyrosine kinase inhibitor by which they can block phosphorylation of elements necessary for adipocyte differentiation[79]. Consumption of red grapes and red wine also has been shown to improve plasma lipid profiles and reduce vascular damage and atherosclerosis[80]. Whether these effects are a broad result of general alcohol intake, including

white wine or other forms of alcohol, or are more specific to the red grape polyphenols has been widely studied, and most studies indicate that red wine polyphenolic extracts exert the strongest effects[80]. Research to date has indicated that red wine polyphenols improved plasma lipid profiles by increasing HDL cholesterol levels and improve LDL oxidation [81-83]. Further, polyphenols in red wine decrease lipoprotein oxidation in human subjects [84,85] and increase cellular and plasma antioxidant levels, increasing resistance to oxidative stress[86,87] and reducing oxidative LDL-induced dysfunction of endothelial cells[88]. The net result of these effects is a decrease in the risk of major cardiovascular events[81].

But, while light to moderate alcohol intake improves risk factors for cardiovascular disease, intake of more alcohol does not potentiate the positive effects on lipid profiles and antioxidant status. It is increasingly clear that a J- or U-shaped curve exists regarding alcohol intake and occurrence of risk factors such as arterial pressure, dyslipidemia, blood glucose levels and markers of oxidative stress[89,90].

Flavonoid effects on glucose control

Type-2 diabetes has increased greatly in frequency over the last decade resulting in an increased interest of patients in using dietary supplements to improve glycemic control; approximately one third of diabetic individuals use some type of botanical supplement or complementary therapy[91]. Despite a vast array of plant products used in controlling blood glucose levels, such as the botanical alkaloid berberine[92], Russian tarragon[93], plant anthocyanins[93], there is very little research in either diabetic individuals or rodent models of diabetes as to the efficacy or safety of most of these compounds.

The spice cinnamon has demonstrated a strong potential for improving diabetic control in limited number of clinical studies, e.g., [94,95] The mechanisms by which cinnamon exerts this effect is currently under investigation, with studies suggesting activation of PPAR signaling [96], and regulation of genes related to insulin signaling and lipogenesis in adipose tissue[97]. Similarly, the trace element chromium also improves glycemic control in diabetic individuals, and chromium deficiency induces reversible diabetes[98]. Research from our laboratory has focused on the anti-glycemic effects of extracts derived from kudzu (*Pueraria lobata*). Kudzu, originally imported from Japan in 1876, is an invasive species. Kudzu root extract contains several isoflavons, including puerarin (the most dominant compound) and daidzin and genistein (similar to that found in soy). In control and diabetic ob/ob mice, whole kudzu extract and puerarin supplementation improve glucose tolerance (unpublished data). We similarly demonstrated that glycemic control is improved by both acute and long-term puerarin supplementation in stroke-prone SHR[59]. Whether kudzu elicits similar anti-glycemic effects in diabetic individuals remains to be determined.

Flavonoid effects on other age-related diseases

Osteoporosis

Aging decreases bone mass in all adults, but this loss is much more significant in postmenopausal women who do not take replacement therapy or an alternative. While many women take botanical products to reduce bone loss (either by increasing bone formation or decreasing bone resorption), the effectiveness of these agents remains debatable. Yamaguchi suggests that various carotenoids, β -cryptoxanthin from *Citrus unchiu* MARC increases bone formation and inhibits bone resorption, thus potentially stabilizing bone mass in osteoporosis rat models and perhaps in humans[99]. He indicates that extracts from wasabi, marine alga and bee pollen and *p*-hydroxycinnamic acid also preserve bone integrity in aged rat and in humans [99]. Soy is by far the most used isoflavone and has been touted for its positive effects on bone health in aging woman, largely due to its putative estrogenic effects. Several groups have shown

that soy isoflavones (especially genistein) have a positive effect on bone health in postmenopausal woman[4,31,100-103]. However, these effects appear to be modest compared to the effects of estrogen replacement[104], and the animal studies are almost exclusively in young ovariectomized rats. The findings of the NIH Women's Health Initiative suggest that timing is everything in hormone replacement therapy, and by analogy for flavonoid therapy, e.g.[41,105]. Data from animals suggest that very high intake of soy isoflavones, especially if initiated long after menopause (a time when estrogen receptors are altered in their responsiveness) can worsen bone loss, thus suggesting that flavonoids may be a double-edged sword[104].

Cancer

The use of flavonoids for both cancer prevention and treatment has also increased dramatically over the past decade[106], in general due to the belief that such treatments are effective and much safer than alternative pharmaceutical treatments. Both of these assumptions must be considered with care. Clearly, preclinical and clinical data demonstrate the potential for some botanicals and flavonoids to be beneficial against cancers. In humans, genistein appears to negatively regulate the proliferation of hormone-sensitive breast cancers[107-109], likely by acting directly on estrogen pathways. However, other reports indicate that in rodent models genistein increases the growth of estrogen-positive breast tumors[110,111]. A similar debate also surrounds the use of soy isoflavones and other botanicals in the prevention and treatment of prostate cancer.

In colorectal cancer, green tea consumption is reported to have a protective effect that is directly correlated with duration of exposure to the green tea catechins[112]. In contrast, soy supplementation appears to increase colon cell proliferation. Curcumin induces apoptosis in colon cell cancer lines, but not in normal colon cells[113], and green tea causes apoptosis in oral cancer cells but not normal oral cells[113].

All of these studies point out clearly that the effects of botanicals on cancers are greatly influenced by dosage, duration and timing of the botanical, supplement type, experiment design (e.g., *in vivo* or *in vitro*) and the type of cancer line tested. The mechanisms of these anti-carcinogenic and anti-mutagenic effects of polyphenols appears to be in large part due to the antioxidant and anti-inflammatory properties of these agents and their bioavailability and molecular targets, e.g., NK- κ B, caspases, cytokines, angiogenic regulators, etc.[25,114].

Clearly, there is no single botanical that can be considered efficacious or even safe for all cancer patients. Further, as indicated by Cassileth, et al., there are significant interactions between botanicals and anti-cancer pharmaceuticals that can appreciably decrease the potency of the drugs or even worsen the cancers[115]. Also, each botanical seems to act uniquely in the setting of each cancer[115]. Thus, an agent that protects against one cancer may potentiate another. Further, many of the botanicals act differently depending on circulating hormones or sex steroid sensitivity of the cancer. Better differentiation of the genotype and phenotype of each cancer should greatly improve the effective use of botanicals as complimentary agents in the prevention and amelioration of cancer.

The brain

As longevity dramatically increases in the population, the number of individuals displaying neurodegenerative diseases is greatly increasing. Most of these diseases like Alzheimer's disease (AD) and Parkinson disease (PD) are relatively slow in onset and progression in the over 65-year-old population, but once these individuals become incapacitated from normal competencies of everyday life, they become both a massive burden to the caregiver(s) and a tremendous economic burden, in that the caregiver often must exit the workforce and long-

term care typically moves to institutional care as the individual progresses into late stages of the disease. Many of these patients are otherwise healthy, and thus live with AD and to a lesser extent PD for a decade or more. Thus, any mechanism that could delay the onset of neurodegenerative disease or decrease its severity would greatly benefit the health and economic welfare of everyone.

Perhaps the best-publicized example of polyphenols protecting the brain comes from the work of James Joseph and colleagues on blueberries. That work demonstrates that feeding aged rodents blueberries or strawberries significantly reverses age-related motor and cognitive dysfunction[116-118]. While these effects were initially considered to be the result of antioxidative actions of the botanicals, the effects of the botanicals were greater than would that produced by antioxidant treatment alone[116]. These treatments appear to both delay and reverse the age-related decline of rodent brain function.

Compared to their premenopausal counterparts, postmenopausal women are at relatively higher risk for cognitive impairment. The standard therapy of a decade ago promoted the pharmaceutical replacement of the lost hormones in these women; however, extensive studies have demonstrated that long-term use of HRT is associated with significant adverse effects in many women[41,119], (see[120] for counterpoint). In contrast, dietary polyphenols appear to provide some of the beneficial effects of hormone replacement therapy without appreciable adverse effects.

Grapes (*Vitis vinifera*) are one of the most widely consumed fruits worldwide and are rich in polyphenols. Grape seed polyphenols have antihypertensive and cognitive enhancement effects in ovariectomized, aged female rodents similar to the effects of several other polyphenols [57]. While the mechanism(s) remains unclear, several lines of evidence suggest that they do not primarily act via estrogen receptor binding[121-123]. Grape seed polyphenols are powerful antioxidants with greater potency than vitamin E and C[124], and upregulation of reactive oxygen species (ROS) appears to play an important role in some forms of cardiovascular diseases, including hypertension, e.g., [125-127]. Grape seed proanthocyanidins can significantly reduce vascular endothelial superoxide production in the body and importantly in the brain.

Treatment of aging normotensive rats with angiotensin converting enzyme inhibitors improves memory despite negligible effects on arterial pressure[128]. and chronic antihypertensive treatment of hypertensive rats with hydralazine does not improve their age-related memory impairment [129]. Thus, it seems unlikely that arterial pressure is the only factor underlying the improved spatial learning performance of the rats supplemented with grape seed or other isoflavones.

Potential toxicities and quality control of dietary supplements

While there is an increased interest in the use of flavonoids alone or in combination with other medicines, there is a possibility of botanical-drug interactions. For example, silybin- a flavonoid from milk thistle inactivates cytochromes P450 3A4 and 2C9 and inhibits major hepatic enzymes glucuronosyltransferases [130]. When this compound is taken alone or in dietary supplements in high doses, there is a concern of potential drug-drug interaction. Similarly, G. biloba extract or supplements containing quercetin or kaempferol may inhibit intestinal or hepatic glucuronidation of mycophenolic acid [131]. Kava-kava (*Piper methysticum*) is well known for its hepato-toxicity, and flavonoid C-glycosides isolated from Kava extract show mutagenic effects [132]. These results indicate that some dietary flavonoids may have the potential to negatively interact with clinical drugs.

Toxicity associated with botanical dietary supplements in part, may result from fungal or bacterial contamination or contamination with pesticides, herbicides, and heavy metals. There are plethora of botanical products are being marketed in the United States with little or no regulation regarding their validation of chemical composition and efficacy [3]. Proper identification and quantification of major bioactive principles is crucial for preclinical and clinical application of dietary supplements. Studies by Prasain, et al., indicated that some manufactures of kudzu dietary supplements did not state puerarin as the most abundant compound; the compound assumed to be daidzin was in fact puerarin [133].

Summary

Flavonoids show promise as useful adjuvants to prevent, delay and/or ameliorate several chronic diseases in aging humans. Recent studies have elucidated their bioavailability, a first step in understanding their mechanisms of action. *In vivo* experiments have demonstrated that they are effective in reducing disease burden in humans and in animal models of disease, including cancer, cardiovascular disease, cognitive impairments. Perhaps the greatest future impact of botanicals in age-related disease will be related to reducing the impact of the three major contributors to the metabolic syndrome, since each of them is very closely linked to diet (e.g., excess fat and carbohydrate ingestion). Studies are also elucidating the mechanisms by which botanicals act. However, not all botanicals are effective nor are they all beneficial for all aged individuals. Given the high percentage of aging individuals regularly taking these flavonoids, it is incumbent on the medical community to more clearly understand the benefits, adverse effects and related dosing and timing issues, so that flavonoids can compliment other mechanisms to increase patient health.

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Figure 1.
Chemical structures of some dietary flavonoids.

Figure 2.

Schematic outline of uptake and metabolism of daidzin (isoflavone O-glucoside) and puerarin (isoflavone C-glucoside). SGLT1 = sodium dependent glucose transporter 1, GULT2 = glucose transporter 2, LPH = lactase phlorizin hydrolase, UDPGT = uridine diphosphate glucuronosyl transferase,, SULT = sulfotransferase.

Figure 3.

Bacterial metabolism of isoflavones daidzein and genistein. Daidzein and genistein undergo reduction to form their dihydro metabolites and further metabolize to O-DMA and 6'-hydroxy-O-DMA, respectively. Daidzein is converted to equol, whereas genistein is metabolized to 2,4,6-trihydroxybenzoic acid, p-ethylphenol and 2-(4-hydroxyphenyl)-propionic acid.

Figure 4.

Mechanisms by which flavonoids are most likely to reduce the three main contributors to metabolic syndrome in aging adults.