Flavonoid-rich foods (FRF): A promising nutraceutical approach against lifespan-shortening diseases

Alhamzah Hasan Waheed Janabi 1, Asghar Ali Kamboh 2, Muhammad Saeed 3, Lu Xiaoyu 1, Jannat BiBi 4, Fatima Majeed 5, Muhammad Naveed 6, Muhammad Jameel Mughal 7, Nazar Ali Korejo 8, Rubina Kamboh 9, Mahmoud Alagawany 10, Huixia Lv 1*

1 State Key Laboratory of Natural Medicines, School of Pharmacy, China Pharmaceutical University, Nanjing 211198, Jiangsu Province, PR China
2 Department of Veterinary Microbiology, Faculty of Animal Husbandry and Veterinary Sciences, Sindh Agriculture University Tandojam 70060, Pakistan
3 Faculty of Animal Production and Technology, Cholistan University of Veterinary and Animal Sciences, Bahawalpur 6300, Pakistan
4 Department of Physical Education, Shaanxi Normal University, Xi’an, Shaanxi Province, PR China
5 School of Public Health, Nanjing Medical University, Jiangsu Province, 211166, PR China
6 School of Pharmacy, Nanjing Medical University, Jiangsu Province, 211166, PR China
7 School of Pharmacy, Nanjing Medical University, Jiangsu Province, 211166, PR China
8 Department of Veterinary Medicine, Faculty of Animal Husbandry and Veterinary Science, Sindh Agriculture University, Tandojam 70060, Pakistan
9 Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan
10 Department of Poultry, Faculty of Agriculture, Zagazig University, Zagazig 44511, Egypt

ABSTRACT

It is well documented that life expectancy in developed countries at birth is going to surpass the 20th century. However, regrettably, a potential decline in life expectancy has been proposed for these nations in the 21st century due to a rapid upsurge in the prevalence of fatal degenerative diseases like cardiovascular diseases (CVD), cancer and diabetes. Collectively, these three diseases accounted for 65% of all deaths in urbanized societies and were considered as a dynamic issue for shortening the genetically determined lifespan through increased mortalities, morbidities, disabilities, immense sufferings, and premature aging. These fatal degenerative diseases and premature aging are closely associated with oxidative stress produced by the free radicals in the body. In epidemiologic studies, flavonoid-rich foods (FRF) like fruits, vegetables, and beverages have been associated as protective agents against these diseases. These also have been observed for their geroprotective effects and help in preventing premature aging and deterioration of brain function, which is related to Alzheimer's disease and dementia. In this review, we presented a comprehensive overview of the FRF for their potential role against lifespan-shortening complications, i.e., CVD, cancer and diabetes. We also have drawn the future perspective and dietary guidelines to reduce the fatal disease burden in urban populations.

Introduction

Food concept in the world is changing from a past emphasis on hunger satisfaction, the absence of the classical nutrient deficiency diseases and survival to an increasing focus on foods promising use as functional ingredients to provide better well-being and health (1). Substantial data from epidemiological surveys and nutritional intervention studies indicate that different components of food have biological characteristics that exhibit activities in modulating animal and human metabolism in a manner favorable for the longevity and several fatal disease prevention (2-4), and foods containing these components are called “functional foods”, which are sometimes dubbed as ‘superfoods’ in medical communities (5, 6). The term “superfood” has been valuable for marketing purpose, having no precise scientific definition (6). Nevertheless, it is rising in the scientific literature with the sense of plant foods that contain phytochemicals that confer remarkable health benefits thus potentially increasing life expectancy. Until recently, the relationship between diet and lifespan has been hardly understood. Nevertheless, animal studies have revealed that dietary manipulation could extend the mean and maximum lifespan and significantly slow down the progression or even completely prevent the age-dependent pathologies (7).

It is well documented that life expectancy at birth in developed countries has been increasing by three months per year since 1850 (8). Life expectancy at birth was 47.3 years at the beginning of the 20th century, but now after a dramatic increase in the past 100 years, it is nearly 77 years, because of reduced mortalities from infections, increased income of people, and several other dietary, lifestyle-, and health-related factors (6, 7, 9). Regrettably, in the 21st century, a potential decline in life expectancy has been proposed for developed nations (10) due to rapid trends in the prevalence of fatal diseases like cardiovascular diseases, cancer, and diabetes (10, 11), which accounted for 65% of all deaths in the USA. These diseases shorten life expectancy through increased mortalities, disabilities, and enormous sufferings and undermine health conditions (11). There is growing evidence that oxidative stress produced by some reactive oxygen compounds as...
well as free radicals such as nitric oxide (\(^{\text{NO}}\)) radical, hydroxyl (\(^{\text{OH}}\)) radical, lipid peroxyl (LOO*) radical, and superoxide (\(O_2^{-}\)) radical are the causative agents for a number of human diseases (12, 13). Therefore, particular attention is given to search for powerful antioxidant agents to attenuate the incidence and progression of lifespan-shortening diseases and to reinforce the genetically determined lifespan (13).

Among natural antioxidants, phytochemicals which are ubiquitous in plants with their major nutraceutical part called flavonoids (14), are considered as potent natural antioxidants. Over 8000, various natural flavonoids have been already described as mentioned by Croft (15), and this list is still growing. Some health-oriented biological effects are attributed to their antioxidant potency (16). Flavonoids have been shown to possess antioxidant properties within \textit{in vitro} experimental systems (4) and anti-inflammatory (17), immune-modulator (16), antiviral (18), antiallergic (19), and anticarcinogenic properties (20). Their antioxidant and inflammatory properties help in toxin-mediated stress and chronic disease prevention (21). Due to their surprising biological health effects, flavonoids are considered ‘disease-preventing, health-promoting dietary supplements’ (22). So, more than 30000 publications/year in the past few years were focused on health-promoting impacts of flavonoids (23). Foods containing these flavonoids have also been attracting considerable attention in the medical and public communities because of evidence from various literature which suggest that consumption of Flavonoid-rich foods (FRF) could potentially improve human health and well-being (24). Numerous dietary intervention studies have proven that consumption of plant products (e.g., fruits and vegetables) declines the development of pathological condition risks, which include genetic and nervous system disorders, inflammatory and cardiovascular diseases, and cancer (25, 26). A series of studies in China indicated that high intake of fruits and vegetables could prevent breast cancer (27), coronary heart disease (28), cataracts, diabetes, Alzheimer’s disease, and even asthma (29, 30). According to the world health report, 4.4% of the overall disease burden including disability and mortality in Europe could be attributed to low fruit and vegetable intake (31).

All these studies revealed that plant-derived FRF could reinforce life expectancy by cutting or preventing the risk of chronic lifespan-shortening disorders including diabetes, cancer, and cardiovascular diseases (10, 11) by dropping their associated risk factors, which positively affect the lifespan (32). The present review has focused on the evidence and mechanisms involved in the protective role of FRF against global lifespan-shortening complications including cardiovascular diseases, cancer, and diabetes. We also have drawn the evidence-based dietary guidelines for the readers to minimize the effects of aging, reduce the occurrence of degenerative diseases, and to get the genetically determined lifespan. Moreover, we have proposed a future perspective to identify priorities in food for a particular condition.

**Sources and phytochemistry**

Flavonoid-rich foods, based on their surprising health effects are well described as superfoods. These include all plant origin foods mainly tea, fruit, vegetables, grains, legumes, nuts, and wine (33). Tea and wine are the primary dietary sources of flavonoids in eastern and western societies, respectively. Besides, leafy vegetables, onions, apples, berries, cherries, soybeans, and citrus fruits are considered an important source of dietary flavonoids (34-36). The content of flavonoids in different food sources is shown in Figures 1, A-E.

**Figure 1.** A. Mean concentration of flavonols (mg/100 g) in different food sources. B. Mean concentration of flavanones (mg/100 g) in various food sources. C. Mean concentration of flavanols (mg/100 g) in different food sources. For green and black tea, leaves to water ratio are 1:20 (w/v). D. Mean concentration of anthocyanins (mg/100 g) in different food sources. E. Mean concentration of flavones (mg/100 g) in various food sources (37)
The chemical structure of flavonoids consists of a 15-carbon skeleton, which contains two phenyl (A & B) rings and (C) heterocyclic ring. The carbon skeleton can be abbreviated C6-C3-C6. According to the IUPAC nomenclature, they can be categorized into three categories: flavonoids or bioflavonoids, isoflavonoids (3-phenyl-1,4-benzopyrone), and neoflavonoids (4-phenyl-1,2-benzopyrone) (33, 34). Flavonoids could be further classified into flavonols (e.g., quercetin, rutin), flavonols (e.g., naringenin, hesperidin), flavanones (e.g., quercetin, rutin), flavanones (e.g., naringenin, hesperidin), flavanones (e.g., naringenin, hesperidin), and anthocyanins (e.g., pelargonidin, malvidin). The typical examples of isoflavonoids (also called isoflavone) are genistein and daidzein; whereas, neoflavonoids occur in the form of isoflavones and are rarely found in plant foods (24). The chemical structure and types of flavonoids are shown in Figure 2.

Mechanism of action of FRF

Significant work has been conducted in recent years to explore the working mechanisms by which FRF exert their effects against pathological conditions. Most of the investigations have communicated that beneficial activity of these foods from anti-mutagenicity to anti-aging are attributed to antioxidant potency of flavonoids (38, 39). These flavonoids exert their anti-oxidative action in several ways including direct trapping and scavenging of free radicals, decreasing leukocyte immobilization, and regulation of nitric oxide and xanthine oxidase activity (40, 41). Several flavonoids, including quercetin, have been reported for the reduction in ischemia-reperfusion injury by interfering with inducible nitric-oxide synthase activity (42). Nitric oxide itself can be viewed as a radical, and it was reported that nitric oxide molecules are directly scavenged by flavonoids. Therefore, it has been speculated that nitric oxide scavenging plays a role in the therapeutic effects of flavonoids (41). The significant effects of flavonoids are due to radical scavenging but another possible mechanism by which flavonoids act is through interaction with various enzyme systems such as superoxide dismutase, catalase, and glutathione peroxidase (41). Furthermore, in vitro studies have declared the anti-proliferative activity of flavonoids through inhibition of polyamine biosynthesis and signal transduction enzymes like protein tyrosine kinase (PTK), protein kinase C (PKC) and phosphoinositide 3-kinases (PI3K), induction of apoptosis and cell cycle arrest at G1/G2, differentiation of transformed cells, and rehabilitation of cellular homeostasis (43, 44).

Pharmacokinetics of flavonoids

The absorption, distribution, and biotransformation of flavonoids from FRF are crucial for their biological effects against lifespan-shortening degenerative diseases as shown in Figure 3. The majority of flavonoids found in FRF are in the form of β-glucosides, and hydrolysis of the glycoside moiety is an essential
step for absorption. Hydrolysis occurs in the cecum and colon by enterobacteria, aglycones are absorbed by gut epithelial cells and entered the circulation to metabolize in the liver (45). It is also reported that lactase-phlorizin hydrolase (LPH, EC 3.2.1.62), which is found on the brush border of the mammalian small intestine for the breakdown of lactose, is responsible for hydrolysis of flavonoids (46). By using healthy ileostomy volunteers in an experiment, it is demonstrated that sodium-dependent glucose transporter-1 (SGLT-1) is responsible for the transport of quercetin glucosides from intestinal epithelial cells (46).

Conversely, in another experiment, it was claimed that quercetin glucosides are entirely hydrolyzed to their aglycone form before transport from the intestinal tract in ileostomy patients (47). Overall, the intestinal absorption, distribution, and metabolism of flavonoids are not well elucidated at present; thus, the events in the intestinal tract should be clarified to observe the desirable health effects of FRF. Moreover, research on the mechanisms for aglycone transfer across the gut wall need to be illuminated.

It has been observed that bioavailability of flavonoids is very low, i.e., 2–20% on an intake of FRF like vegetables, fruit juices, and beverages (48). Therefore, this area of research needs more attention to find possible ways for enhancement of flavonoids absorption.

Food matrix also plays a vital role in the bioavailability and pharmacokinetics of flavonoids from FRF. A liquid matrix yields a faster absorption rate and higher peak plasma concentrations than a solid matrix, whereas aglycones in fermented foods are absorbed more rapidly than glucoside conjugates (49). Dietary fat (3–5 g/meal) is also reported as an enhancer for the absorption of phytochemicals from vegetables in children (50).

It is also well established that processing (mechanical or heat treatment) could increase the biological activity of FRF by promoting the bioaccessibility of polyphenols in food matrix (51). Tomato polyphenols (e.g., naringenin) are trapped in the cutin matrix of the membrane of the ripe fruit where it strongly interacts with insoluble polyesters. Mechanical and heat treatments may break the interactions, thus improving flavonoids bioaccessibility in vivo (52). Nevertheless, a few studies have reported the adverse effect of processing on garlic’s ability to alter the bioactivation of a known experimental mammary carcinogen (53). This might indicate the different response of each FRF to processing. Thus, studies are needed to unravel the individual response of processing for all FRF with significant insight into processing time. Some creative tools are required to explore the exact relationship of FRF with other components of diet and food matrix to make their possible synergisms and to avoid antagonistic combinations to enhance their bio-functionality against lifespan-shortening complications.

Pharmacological values and therapeutic properties

At the end of the 20th century, it was concluded for the first time that traditional Mediterranean diet meets several important criteria (Figure 4), which is responsible for extended lifespan (54) and low incidence of fatal degenerative diseases like cardiovascular diseases, cancer, and diabetes (55, 56). This conclusion was drawn by intriguing evidence accumulated over the last three decades that supported the Mediterranean diet having a high amount of FRF, i.e., olive oil, legumes, cereals, vegetables, and fruits for these effects. In Greece, in addition to high vegetable diet, the wild edible greens are eaten frequently in the form of pies and salads and contain a very high concentration of flavonoids (more than those in torn or wine) as reported by a study (54). The antioxidants found in these foods (FRF) such as polyphenolic flavonoids correct the free radicals generated in all cells from normal oxidative reactions, which if left uncorrected may damage cellular proteins, lipids, and nucleic acids, resulting in the onset of lifespan-shortening diseases (Table 1).

Fatal degenerative diseases including CVD, cancer, and diabetes are the primary health burdens, which reduce the average life expectancy and impair the health status. CVD is the leading cause of death followed by cancer, and both together account for almost one-half of all deaths (9) whereas, collectively all three (cardiovascular diseases, cancer, and diabetes) account for nearly two of every three persons in the USA and comprise 32% health cost of total illness costs (11). A summary of studies indicating the effects of FRF in reducing mortalities have been summarized in Table 2.

Protective effect against diabetes

Diabetes is an epidemic health concern in both developed and developing countries, characterized by impaired insulin production and function. In the United States, 7.8% of the population have diabetes, 35.4% have impaired fasting glucose (IFG) levels, 15.4% have impaired glucose tolerance (IGT), and 40.1% have prediabetes (IFG, IGT, or both) (57), while in China 9.7% and 15.5% of people are positive for diabetes and prediabetes, respectively (58). Diabetes could reduce life expectancy up to 15 years and account as a significant cause of mortalities in both developed and developing countries (59). It is also associated with other chronic

Figure 4. The schematic overview of the therapeutic properties of flavonoid-rich foods

Dietary flavonoids in lifespan-shortening diseases Waheed Janabi et al.
Diseases like stroke, heart diseases, nervous system disorders, kidney diseases, and vision problems. Its prevention is more accessible than a cure. In randomized trials, it was consistently observed that increased physical activity and dietary manipulation are the ideal approaches to prevent diabetes (56).

Numerous physiological studies had declared that free radicals might contribute to the autoimmune destruction of pancreatic β cells, leading to diabetes (60), and may impair insulin action (61). Fruits, vegetables, and whole grains possess strong scavenging ability against these radicals resulting in reduced risk of type I and type II diabetes mellitus (62, 63). It was also hypothesized that plant-derived foods like fruits and vegetables are low in carbohydrate contents, therefore could prevent the rise of blood sugars (56). Other dietary factors that have been related to reducing the risk of type II diabetes include coffee (64), berries (63), and tea (65). High intakes of quercetin and myricetin, mainly from dietary consumption of apples and berries also associated with reduced risk of type 2 diabetes (20). Among European adult persons who drank coffee frequently (≥7 cups/d) had a 29% to 52% reduced risk for diabetes compared with those who drank less coffee (≤2 cups/d or no cups/d) (64, 66). Moreover, in another study in Japan, it was reported that consumption of

| Type of flavonoids rich-food | Biological and pharmacological effects | References |
|------------------------------|----------------------------------------|------------|
| Fruits/vegetables           | Anti-hypertension, reduced risk of diabetes, anti-hypercholesterolemia, anti-obesity, ↓ cardiovascular diseases, ↓ breast cancer, ↓ coronary heart diseases | (27, 28, 62, 93, 94, 95, 97) |
| Whole grains                | Reduced risk of diabetes, anticancer   | (63, 82)  |
| Coffee                      | Reduced risk of type 2 diabetes        | (64)      |
| Berries                     | ↓ Prostate cancer, reduced risk of type 2 diabetes | (20, 63) |
| Green tea                   | Reduced risk of type 2 diabetes, ↓ blood glucose, anticancer | (65, 68, 79) |
| Apple                       | Reduced risk of type 2 diabetes, ↓ breast cancer, ↓ cardiovascular diseases | (20, 36) |
| Black tea                   | ↓ Blood glucose, ↓ total and LDL cholesterol, ↓ myocardial infarction, reduced risk of coronary heart disease | (69, 89, 121) |
| Onion                       | Antihyperglycemic effects, ↓ breast cancer | (20, 70) |
| Garlic                      | Anti-platelet aggregation, modification of LDL, anti hypertensive effects, anticancer | (70, 82) |
| Cruciferous vegetables      | Anticancer                             | (73)      |
| Cabbage                     | Anticancer, ↓ vascular diseases        | (20, 76) |
| Broccoli                    | Anticancer, ↓ prostate cancer          | (76)      |
| Cauliflower                 | Anticancer, ↓ prostate cancer          | (76)      |
| Brussels sprouts            | Anticancer                             | (76)      |
| Soy                         | Reduced risk of breast and prostate cancer | (77) |
| Citrus fruits               | Antiproliferative, ↓ vascular diseases | (20)      |
| Tomato                      | ↓ Prostate cancer                      | (78)      |
| Turmeric                    | Anti-hepatocarcinogenesis, anticancer  | (80, 81) |
| Ginger                      | Inhibit platelet aggregation, anticancer, anti-thrombotic | (82, 122) |
| Carrots                     | Anticancer                             | (82)      |
| Pomegranate                 | Anticancer                             | (44)      |

↓: decreased; LDL: low-density lipoprotein
green tea, coffee, and large total caffeine was associated with a reduced risk for type 2 diabetes (67).

Furthermore, antidiabetic (blood glucose reducing) effect of green tea (68) and black tea (69) has also been observed, indicating them as potent preventive and curative agents. Onion and garlic also have been found to have antihyperglycemic effects (70), probably based on their phytochemical contents. The antidiabetic results of FRF have been summarized in Figure 5.
Protective effect against cancer

The oxidative stress from exposure to industrial chemicals, air pollutants, ionizing radiation, or ultraviolet light, might overwhelm the antioxidant system of the body and cause oxidative damage of nuclear acids and proteins, which leads to cancer initiation in addition to other degenerative diseases as explained by another study (13). Until now, no data are available assuring anticarcinogenic impacts of foods in humans. However, there are many rodent in vivo and in vitro studies confirming chemopreventive impact of certain plant foods against early stages of cancer (72). Epidemiological studies are also supporting FRF for their cancer preventing effects particularly, cruciferous vegetables due to the abundant presence of anticarcinogenic compounds such as polyphenols and isothiocyanates (73, 74). Verhoeven et al. (75) claimed inverse associations between intake of crucifer and the incidence of skin, pancreas, lung, prostate, bladder, stomach, colon, and thyroid cancers. In case-control studies, inverse associations between risk of cancer and intakes of broccoli, cauliflower, brussels sprouts, or cabbage were noted in 70%, 56%, 67%, and 29%, respectively (76). A Finnish study specified that risk of prostate cancer lowered at higher intakes of myricetin (from berries), and risk of breast cancer lowered at higher intakes of quercetin (from apples and onions) (20). Soybean consumption is demonstrated as a contributing factor in lowering prostate and breast cancer in Japanese men and women, respectively (76). A Finnish study specified that risk of prostate cancer lowered at higher intakes of myricetin (from berries), and risk of breast cancer lowered at higher intakes of quercetin (from apples and onions) (20). Soybean consumption is demonstrated as a contributing factor in lowering prostate and breast cancer in Japanese men and women, respectively. This effect is considered due to isoflavone genistein that functions as an estrogen antagonist and reduces the risk of estrogen-sensitive tumors (77). Tomato and tomato products are also being investigated for their significant role in cancer chemoprevention, especially in prostate cancer (78). In another animal study, the chemopreventive effect of tea was observed for various types of cancers and recognized for the antioxidant property of polyphenolic components known as catechins (79). Among spices, chemopreventive effects of turmeric against cancers of the skin, mouth, fore stomach, liver, and colon are well documented (80, 81). These spices contain several natural water-soluble phenolic acids and flavonoids, such as caffeic acid and quercetin that attribute to these effects by inhibition of procarcinogen activators or induction of carcinogen deactivation enzymes (72). The National Cancer Institute, after five years of research, revealed the anticancer potential of plant foods. The foods and herbs with the highest anticancer activity include garlic, soybeans, cabbage, ginger, carrots, celer, cilantro, parsley, and parsnips, while those with a modest level of cancer-protective activity include onions, citrus, turmeric, cruciferous vegetables (broccoli, brussels sprouts, cabbage, and cauliflower), tomatoes, peppers, and whole wheat (82) and their anticancer effects have been summarized in Figure 6.

Estrogenic effect

Some dietary flavonoids (including isoflavones and prenyllflavonoids) are known as phytoestrogens, which can interact with estrogen receptors (ER) or modulate estrogen action in vivo. These phytoestrogens (e.g., genistein) are non-steroidal in chemical structure, but due to the presence of phenolic rings, particularly the 4'-hydroxyl, they can bind estrogen receptors. At specific concentrations, which may depend on many factors including receptor numbers, occupancy, and competing for estrogen concentration, they may antagonize and inhibit estrogen action (83).

There are inconsistent reports for the effects of phytoestrogens found in FRF on breast cancer. Setchell (83) demonstrated that soy isoflavones could stimulate the growth of ER-positive breast cancer cells through...
the ER singling pathway; while, some other studies stated the putative effect of isoflavones to inhibit carcinogenesis (84, 85). These chemopreventive effects may be through impairment of protein tyrosine kinases (86) or topoisomerase II inhibition (87). From the reports in support of the positive and negative effects of phytoestrogens on breast cancer, it is indicated that more clinical studies are warranted to clarify this critical issue. Other factors like hormonal status, age, the timing of exposure, and individual metabolism should also be considered. At this stage, recommendation of nutritionists to avoid soy foods is not logical (83), and the use of phytestrogens as supplements will be entirely acquitted.

**Protective effect against cardiovascular diseases**

Potential health benefits of chocolate (88) and tea (89) regarding heart health have been well-documented and attributed to flavonoid procyanidins, which reduce low-density lipoprotein (LDL) cholesterol by 11.1%. This LDL is oxidized directly by peroxynitrite, which is produced by the reaction of nitric oxide with free radicals. The nitric oxide release through the constitutive nitric oxide synthase activity is essential in the maintenance of blood vessels dilation (40). Flavonoids are capable of affecting different cells included in atherosclerosis development, one of the leading reasons for cardiovascular diseases. The chemokine monocyte chemotactic protein 1 (MCP-1) is well known to mediate macrophage recruitment to infection or inflammation sites, and direct involvement of MCP-1 on atherogenesis has been established. Furthermore, flavonoids could inhibit aggregation of TRAP-induced platelet (90) and protect endothelial cells from CD40-induced pro-inflammatory signaling as found by a study (91).

Several epidemiological studies proved that diets rich in specific antioxidants from fruits, some vegetable oils, and vegetables diminish the relative risk of premature death from CVD (25, 92) as shown in Figure 7. Findings of observational population studies support the hypothesis

---

**Figure 6.** The schematic overview of the anticancer effects of flavonoid-rich foods. CYP1: cytochrome P450; BCRP: breast cancer resistance protein; AhR: aryl hydrocarbon receptor; Erβ: estrogen receptor β; ROS: reactive oxygen species

**Figure 7.** The cardioprotective effect and implicated mechanisms of flavonoids. (IHD) indicates ischemic heart disease and (LDL), low-density lipoprotein cholesterol (92)
that fruit and vegetable consumption have a regulating effect on hypertension (93), hypercholesterolemia (94), and obesity (95), which are important cardiovascular risk factors. In a study related to Dietary Approaches to Stop Hypertension (DASH), it was concluded that intake of 1-2 cups of vegetable juice daily is associated with a reduction of blood pressure in subjects who were prehypertensive at the start of the trial (96). Furthermore, the decreasing trend for ischemic heart disease mortality was observed with the consumption of apples and onions (20). These findings are consistent with a large prospective study of postmenopausal women with 16 years follow-up that indicated dietary intakes of apples, pears, and red wine were associated with a lower risk of all-cause mortality, death due to coronary heart disease (CHD), and death due to CVD (36). In a cohort study of about 100,000 people, it was concluded that five servings of fruits and vegetables daily cause 28% reduction in risk of cardiovascular diseases (97), which is also in agreement with American Heart Association (AHA) recommendation for consuming at least five servings of fruits and vegetables per day (98).

**FRF as geroprotective**

Aging is an essential part of life, which is directly proportional to lifespan. It may not be eliminated from life, but it could be potentially accelerated or decelerated (99). Target health issues related to the aging process include the process of oxidation, the promotion of bone health, memory retention and cognition. Decrements in motor function and memory are two main behavioral parameters that altered senescence in both humans and animals; however, they appear due to increased amounts of inflammatory markers and/or enhanced susceptibility to oxidative stress caused by reactive species from oxygen and nitrogen and subsequent induction of peroxidative reactions that result in damage to biomolecules (100).

The potential substances that can slow down the aging process, prevent premature aging, and increase life expectancy, are known as geroprotectors (99). Natural antioxidants such as flavonoids have been observed as efficient geroprotectors and lifespan extending compounds through down-regulating the progression of degenerative diseases (101), and are also called lifespan-essential ingredients (102). Therefore, the use of FRF with strong antioxidant potential may reduce age-related disorders. This may be achieved by scavenging damaging ROS, preventing the formation of lipid peroxides, protecting proteins and DNA from oxidative damage, decreasing inflammation, and protecting against ROS-mediated apoptosis (103). In addition to free radical scavenging, anti-inflammatory role of flavonoids is also crucial for overreaction of microglial cells for signals thus reducing the production of cytokines causing behavioral pathology, including cognition and restore the population of microglial brain cells to put the elder brain in the youthful state (104). It was also observed that these FRF could directly alter the neuronal communication, calcium buffering, neuroprotective stress shock proteins, and stress signaling pathways for the amelioration of age-related deficits (105).

The role of diet in minimizing the adverse effects of aging has been extensively investigated. It has been concluded that nutritional interventions, via the polyphenolics present in plant foods like fruits and vegetables, may correct the age deficits and age-related deterioration of brain function (17, 106). Furthermore, Joseph and coworkers expressed that anthocyanin-rich fruits such as blueberry, spinach, and strawberry may help reverse the course of neuronal and behavioral aging (107). Moreover, by using transgenic mice as a model for Alzheimer's disease, the same group reported the beneficial effect of blueberry extracts on the outcome of this neurodegenerative illness (108). Studies also suggested the antiaging and brain protective role of garlic linked to dementia and Alzheimer's disease (103). In another study, green tea and its flavonoids constituents were proven for efficacy as prophylactic and neuroprotective agents against age-related neurodegenerative and neuroinflammatory diseases such as Parkinson's disease and multiple sclerosis (109). The study also confirmed that (-)-Epigallocatechin gallate inhibits lipopolysaccharide-induced microglial activation and protects against inflammation-mediated dopaminergic neuronal injury, Alzheimer's disease via modulation of cell survival/death genes, and mitochondrial function, which contributes to neuronal viability (109).

**How to get maximum health benefits from FRF**

Epidemiological and clinical evidence indicate that like essential nutrients of foods (e.g., vitamins), which are vital for several physiological and pathological conditions, flavonoids are necessary for full genetically-determined lifespan through down-regulation of chronic degenerative diseases (102). Therefore, it is essential to intake the optimum amount of flavonoids by including the reference quantity of FRF on the regular menu.

Flavonoid-rich green tea, isoflavone-rich soy, flax seed, flavonol quercetin, and isoflavones are popular supplements among consumers. People are showing their interest in these supplements because they assume that they are not consuming sufficient quantities of dietary flavonoids and flavonoids supplements are devoid of toxicity because these compounds are “natural.” However, there is evidence, which indicates the harmful effects of flavonoids supplements. In both animal and human studies, anti-thyroid and goitrogenic activities were observed by a high dose of green tea extracts and isoflavones (110, 111). Likewise, another adverse effect of high flavonoids doses includes inhibition of vitamin C transport, decreased trace element bioavailability, and impaired folate uptake (112).

Feeling the gravity of this ambiguous situation it is advisable to use all flavonoid supplements with the guidelines of a health practitioner/nutritionist because these are providing hundreds of times higher doses than a regular diet and only use the optimum amounts of fresh fruits and vegetables. A large body of nutritionists, medical experts, and the American Heart Association (AHA) (97, 98) also suggests this. The instructions of regulatory bodies like WHO (world health organization), AHA, ACS (American cancer society), and ADA (American diabetes association) should strictly be followed for consumption of at least 5 servings of fresh fruits and vegetables, whole grains, legumes, flavonoid-
rich beverages, and fruit juices to get the potential health benefits from these FRF. It is also acceptable to take a moderate amount of wines, meat, milk, and other dairy products to keep in mind the possible role/effects of these substances in the food matrix. A moderate amount of heart-healthy fat (proportional monounsaturated and polyunsaturated fats) should also be included in the dietary menu for its helping role in the absorption of FRF. To ensure the maximum health benefits of FRF, healthy lifestyle, including regular exercise, should also be adapted to maintain the active physiological status of the body.

**Biomarkers**

Intake biomarkers are useful for reflecting the amount of food or metabolites present in the body cells or fluids, but there is a need to know the best time for their measurement after consumption. Evidence is emerging that some biomarkers for cardiac health and other fatal degenerative diseases have been used successfully to differentiate disease and non-disease states and to predict the association between dietary intake and future susceptibility to infections (113, 114). For evaluation of the merits of nutritional habits, many genes, associated products, and receptors have been investigated for fatal degenerative and age-related diseases (like cancer, diabetes, Parkinson’s disease, etc.) as markers of genetic susceptibility including p53, PAR-α, APOA1, OB, and BCL (115, 116). Overall, authentic intake and susceptibility biomarkers are probably needed to develop a profile for an individual to approach health and longevity and significantly reduce the incidence of diet-related diseases through improved management of disease and ultimately its prevention. However, the relationship between dietary intake and lifespan related biomarkers is often highly complex.

**Dietary/lifestyle patterns**

Dietary factors are seen as contributing to the leading causes of death of urban people, including CHD, diabetes, and certain types of cancers. Inappropriate dietary habits are responsible for poor health and reduced lifespan, which are also a major reasons for public interest in the use of alternative medicines and functional foods (117). Advances in nutritional genomics like development of the concept of gene-nutrient interaction gets significant emphasize from dietetics profession particularly the clinical dietitians to suggest appropriate foods to their patients. Unquestionably, dietary habits are not the sole determinant of disease states, because adjusting the dietary menu with FRF represents a significant way of reducing risk. Further studies are recommended to characterize the strength of diet–health association, its generalizability, the dose-response relationship, and the timing of diet for potential benefits.

Some reviews have been published on the potential role of FRF in the prevention of cancer (73, 75) and other lifestyle-related diseases like hypertension, diabetes, obesity, and aging (118). However, there is much diversity in the cultural dietary patterns and lifestyles such as the degree of physical activity and consumption of low fat and low-calorie diet, which adds complexity in understanding the exact biological role of FRF in disease prevention. Therefore, more epidemiological studies are needed in different geographical locations to correlate the dietary patterns with cultural and individual habits and to minimize the wide divergence of the population.

**DRI in terms of effective dosages**

Regrettably, dietary reference intake (DRI) for flavonoids could not be established until now due to insufficient data regarding flavonoid contents of different foods and variations in different varieties and cultivars and grown in different environmental conditions, production methods (organic/conventional), post-harvest processing, and storage effect on flavonoids concentration of foods (48). Another difficulty is the unavailability of authentic and certified means for determining the flavonoid contents of several foods (FRF). On the other hand, there is growing interest in developing dietary supplements containing flavonoids or flavonoid-rich foods. In such dietary supplements usually, active components (a mixture of polyphenols) from FRF were purified or concentrated to boost the antioxidant status of the consumer (119). Nevertheless, presently all dietary recommendations by scientific communities like AHA for consumption of five servings of fruits and vegetables per day are based on nutritional epidemiological surveys or in vitro studies but not supported by in vivo clinical literature. Therefore, there is a need to use the tools of food science and technology to establish a data bank for flavonoid contents of all foods with an estimated difference of biological and physical factors to determine the therapeutic/preventive dosages/amount of FRF for fatal degenerative diseases. Clinical trials are also necessary to know the relationship between specific FRF and lifespan-shortening disorders. Consequences of long-term intake of FRF should also be explored.

**Conclusion and future perspectives**

Dietary factors play a vital role in the development and preclusion of premature aging, and some fatal degenerative diseases ultimately shorten the genetically determined lifespan. These life-threatening neurodegenerative diseases and age-related metabolic disorders are closely associated with oxidative stress produced by free radicals in the body. It has been estimated that free radicals are involved in the etiology of several (>100) human diseases and the aging process. Based on their potent antioxidant properties, flavonoids protect against these diseases and could potentially modulate life expectancy. Clinical evidence supports the health promoting, disease preventing, and life-extending effects of FRF like fruits including citrus fruits, berries, apples, vegetables particularly deep-colored green vegetables and onion, beverages such as tea and red wine, and cocoa that make these foods approach the superfoods of the millennium. It is strongly recommended that consumers eat 5 to 10 servings (one serving: about 40 g) of a wide variety of fruits and vegetables daily to reduce the risk of fatal degenerative lifespan-shortening diseases and to meet the nutrient requirements for optimum lifespan. However, one should keep in mind that FRF are not “magic bullets” for disease-free long life (120). It is only one part of a comprehensive lifestyle, which should be adjoined by physical activity (at least 30 min/day), smoking...
avoidance, stress reduction, moderate consumption of alcohol, meat, eggs, and dairy products, low consumption of fat and sugars, maintaining healthy body weight (BMI: <25 kg/m²), maintenance of healthy environment, and other positive health practices. When all of these issues are addressed together, then RRF becomes part of an efficient strategy to maximize lifespan and cut the risk of lifespan-shortening degenerative diseases.

Acknowledgment

We are thankful to Chinese Scholarship Council (CSC) for funding our research scholar FATIMA Majeed in her doctoral studies. Furthermore, all authors of this paper thank and acknowledge their respective Universities and Institutes.

Conflicts of Interest

The authors declare that there are no conflicts of interest. All authors read and approved the final manuscript.

Competing Interest

The authors declare that there are no competing financial interests.

References

1. De Leo F, Del Bosco F. Citrus flavonoids as bioactive compounds: Role, bioavailability, socio-economic impact and biotechnological approach for their modification, 9th ICABR International Conference on Agricultural Biotechnology: Ten Years Later, Ravello, Italy; 2005.
2. Shen J, Ng LJ, Ho SW. Therapeutic potential of phytochemicals in combination with drugs for cardiovascular disorders. Curr Pharm Des 2017;23:961-966.
3. Kamboh AA, Arain MA, Mughal MJ, Zaman A, Arain ZM, Soomro AH. Flavonoids: health promoting phytochemicals for animal production - a review. J Anim Health Prod 2015;3:6-13.
4. Kris-Etherton PM, Harris WS, Appel LJ. Omega-3 fatty acids and cardiovascular disease. Arterioscler Thromb Vasc Biol 2003;23:151-152.
5. Setchell KD, Radd S. Soy and other legumes/‘Bean’ around a long time but are they the ‘superfoods’ of the millennium and what are the safety issues for their constituent phytoestrogens? Asia Pac J Clin Nutr 2000;9:1-10.
6. Hancock RD, McDougall GJ, Stewart D. Berry fruit as ‘superfood’: hope or hype, Biologist 2007;54:73-79.
7. Bishop NA, Guarente L. Genetic links between diet and lifespan: shared mechanisms from yeast to humans. Nat Rev Genet 2007;8:835-844.
8. Tuljapurkar S, Li N, Boe C.A universal pattern of mortality decline in the G7 countries. Nature 2000;405:789-792.
9. Murphy SL, Xu J, Kochanek KD. National vital statistics reports. National vital statistics reports. 2013;8:61.
10. Olshansky SJ, Passaro DJ, Hershov R, Layden J, Barnes BA, Brody J. et al. A potential decline in life expectancy in the United States in the 21st century. N Engl J Med 2005; 352:1138-1145.
11. Eyre H, Kahn R, Robertson RM, Clark NG, Doyle C, Gansler T, et al. Preventing cancer, cardiovascular disease, and diabetes: a common agenda for the American Cancer Society, the American Diabetes Association, and the American Heart Association. CA Cancer J Clin 2004;54:190-207.
12. Kehrer JP, Klotz LO. Free radicals and related reactive species as mediators of tissue injury and disease: implications for Health. Crit Rev Toxicol 2015;45:765-798.
13. Mojsilovic G, Kuchta M. Dietary flavonoids and risk of coronary heart disease. Physiol Res 2001;50:29-535.
14. Yang X, Jiang Y, Yang J, He J, Sun J, Chen F, et al. Prelymted flavonoids, promising nutraceuticals with impressive biological activities. Trends Food Sci Technol 2015;44:93-104.
15. Croft KD. The chemistry and biological effects of flavonoids and phenolic acids. Ann N Y Acad Sci 1998; 854:435-442.
16. Catoni C, Schaefer HM, Peters A. Fruit for health: the effect of flavonoids on humoral immune response and food selection in a frugivorous bird. Funct Ecol 2008;22:649-654.
17. Shukitt-Hale B, Galli RL, Metroko V, Carey A, Bielinski DF, McGhee T, et al. Dietary supplementation with fruit polyphenolics ameliorates age-related deficits in behavior and neuronal markers of inflammation and oxidative stress. Age (Dordr) 2005;27:49-57.
18. Saravanan D, Thirumalai D, Asharani IV. Anti-HIV flavonoids from natural products: A systematic review. Int J Res Pharm Sci 2016;6:248-255.
19. Liang Q, Chen H, Zhou X, Deng Q, Hu E, Zhao C, Gong X. Optimized microwave-assistant extraction combined ultrasound pretreatment of flavonoids from Periploca forrestii Schltr. and evaluation of its anti-allergic activity. Electrophoresis 2017; 38:1113-1121.
20. Knekt P, Kumpulainen J, Jarvinen R, Rissanen H, Heliovaara M, Reunanen A, et al. Flavonoid intake and risk of chronic diseases, Am J Clin Nutr 2002;76:560-568.
21. AlDrak N, Abu-dawood M, Hamed SS, Ansar S. Effect of rutin on proinflammatory cytokines and oxidative stress in toxin-mediated hepatotoxicity. Toxim Rev 2017;37:1-8.
22. Middleton J, MD E. Biological properties of plant flavonoids: an overview, Int J Pharm 1996;34:344-348.
23. Scalbert A, Johnson IT, Saltmarsh M. Polyphenols: antioxidants and beyond. Am J Clin Nutr 2005;81:215-217.
24. Kamboh AA. Flavonoid-rich Foods - Super Foods of the Millennium, LAP LAMBERT academic publishing Deutschland, Germany; 2012.
25. Behzd S, Sureda A, Barreca D, Nabavi SF, Rastrelli L, Nabavi SM. Health effects of phloretin: from chemistry to medicine. Phytochem Rev 2017;16:527-533.
26. Stanner S, Hughes J, Kelly C, Buttress J. A review of the epidemiological evidence for the ‘antioxidant hypothesis’. Public Health Nutr 2004;7:407-422.
27. Malin AS, Qi D, Shu XO, Gao YT, Friedman JM, Jin F, et al. Intake of fruits, vegetables and selected micronutrients in relation to the risk of breast cancer, Int J Cancer 2003;105:413-418.
28. Zhang X, Shu XO, Gao YT, Yang G, Li Q, Li H, et al. Soy food consumption is associated with lower risk of coronary heart disease in Chinese women. J Nutr 2003;133:2874-2878.
29. Huang SL, Lin KC, Pan WH. Dietary factors associated with physician-diagnosed asthma and allergic rhinitis in teenagers: analyses of the first Nutrition and Health Survey in Taiwan. Clin Exp Aller 2001;31:259-264.
30. Liu RH. Health benefits of fruit and vegetables are from additive and synergistic combinations of phytochemicals. Am J Clin Nutr 2003;78:517-520.
31. WHO. The world health report: reducing risks, promoting healthy life, World Health Organization; 2002.
32. Pallafu K, Duckstein N, Rinbach G. A literature review of flavonoids and lifespan in model organisms. Proc Nutr Soc 2017;76:145-162.
33. Harborne JB, Williams CA. Advances in flavonoid research since 1992. Phytochemistry 2000; 55:481-504.
34. Liu RH. Health-promoting components of fruits and vegetables in the diet. Adv Nutr 2013; 4:3845-3925.
35. Butt MS, Imran A, Shariff MK, Ahmad RS, Xiao H, Imran M, et al. Black tea polyphenols: a mechanistic treatise. Crit Rev Food
Bioavailability of naringenin, chlorogenic acid, lycopene and et al.

52. Bugianesi R, Salucci M, Leonardi C, Ferracane R, Catasta 1998; 80:353-361.

51. Porrini M, Riso P, Testolin G. Absorption of lycopene from single or daily portions of raw and processed tomato. Br J Nutr 2001; 86:119-125.

50. Jalal F, Nesheim MC, Agus Z, Sanjur D, Habicht JP. Serum retinol concentrations in children are affected by food sources of beta-carotene, fat intake, and anthropometric drug treatment. Am J Clin Nutr 1998; 68:623-629.

49. Porrini M, Riso P, Testolin G. Absorption of lycopene from single or daily portions of raw and processed tomato. Br J Nutr 1998; 80:353-361.

48. Martin KR, Appel CL. Polyphenols as dietary supplements: a double-edged sword. Nutr Diet Suppl 2010; 2:1-12.

47. Centers for Disease Control and Prevention CDC. National diabetes fact sheet: general information and national estimates on diabetes in the united states, 2007. Atlanta, GA: U.S. Department of health and human services, centre for disease control and prevention; 2008.

46. Day AJ, Canada FJ, Kroon PA, McMullan R, Faulds SB, et al. Flavonoid and isoflavone glycosides are dietary flavonoids in lifespan-shortening diseases Waheed Janabi et al.}

45. Gonzales GB, Snaggle G, Grootaert C, Zotti M, Raes K, Camp JV. Flavonoid interactions during digestion, absorption, distribution and metabolism: a sequential structure-activity/property relationship-based approach in the study of bioavailability and bioactivity. Drug Metab Rev 2015; 47:175-190.

44. Atef Y, El-Fayoumi HM, Abdel-Mottaleb Y, Mahmoud MF. Quercetin and tin protoporphyrin attenuate hepatic ischemia reperfusion injury: role of HO-1. Naunyn-Schmiedeberg's Arch Pharmacol 2007; 369:1-12.

43. Ren W, Qiao Z, Wang H, Zhu L, Zhang L. Flavonoids: promising antitumor agents. Med Res Rev 2003; 23:519-534.

42. Atef Y, El-Fayoumi HM, Abdel-Mottaleb Y, Mahmoud MF. Quercetin and tin protoporphyrin attenuate hepatic ischemia reperfusion injury: role of HO-1. Naunyn-Schmiedeberg's Arch Pharmacol 2007; 369:1-12.

41. Abarikwu SO, Olufemi PD, Lawrence CJ, Wekere FC, Ochulor AC, Barikuma AM. Rutin an antioxidant flavonoid, induces apoptosis and inhibits proliferation and invasion of glioblastoma multiforme (GBM) cells and confers protection against ethanol induced oxidative stress in the testis of adult rats. Andrologia 2017; 49:7.

40. Nijveldt RJ, van Nood E, van Hoorn DE, Boelens PG, van Norren K, van Leeuwen PA. Flavonoids: a review of probable mechanisms of action and potential applications. Am J Clin Nutr 2001; 74:418-425.

39. de Pascual-Teresa S, Sanchez-Ballesta MT. Anthocyanins: from plant to health. Phytochem Rev 2008; 7:281-299.

38. Giampieri F, Forbes-Hernandez TY, Gasparrini M, Alvarez-Suarez JM, Afrin S, Bompadre S, et al. Strawberry as a health promoter: an evidence based review. Food Funct 2015; 6:1386-1398.

37. Bhagwat S, Haytowits DB, Holden JM. USDA Database for the flavonoid content of selected foods. Nutrient Data Laboratory, Beltsville Human Nutrition Research Center Agricultural Research Service U.S. Department of Agriculture 2011; 1:119.

36. Mink PJ, Scafford CG, Barraj LM, Harnack L, Hong CP, Nettleton JA, et al. Flavonoid intake and cardiovascular disease mortality: a prospective study in postmenopausal women. Am J Clin Nutr 2007; 85:905-909.

35. The PREDIMED-Mediterranean diet intervention randomized trial. Nutr Med 2008; 4:205-206.

34. Asmat U, Abad K, Ismail K. Diabetes mellitus and oxidative stress-a concise review. Saudi J Pharm Sci 2016; 24:547-553.

33. Wang PY, Fang JC, Gao ZH, Zhang C, Xie SY. Higher intake of fruits, vegetables or their fiber reduces the risk of type 2 diabetes: A meta-analysis. J Diabet Invest 2016; 7:56-69.

32. Meinilä J, Valkama A, Koivusalo SB, Stach-Lempinen B, Lindström J, Kautiainen H, et al. Healthy Food Intake Index (HFI)-Validity and reproducibility in a gestational-diabetes-risk population. BMC Public Health 2016; 16:600-609.

31. Tuomilehto J, Hu G, Bidel S, Lindström J, Jousilahti P. Coffee consumption and risk of type 2 diabetes mellitus among middle-aged Finnish men and women. JAMA 2004; 291:1213-1219.

30. Huxley R, Lee CM, Barzi F, Timmermeister L, Czernichow S, Perkovic V, et al. Coffee, decaffeinated coffee, and tea consumption in relation to incident type 2 diabetes mellitus: a systematic review with meta-analysis. Arch Intern Med 2009; 169:2053-2063.

29. Rosengren A, Dotevall A, Wilhelmsen L, Thelle D, Johansson S. Coffee and incidence of diabetes in Swedish women: a prospective 18-year follow-up study. J Intern Med 2004; 255:89-95.

28.iso H, Date C, Wakai K, Fukui M, Tamakoshi A, Watanabe K. Coffee intake and incidence of diabetes in Japanese men and women: JAMA 2004; 291:1213-1219.

27. Tuomilehto J, Hu G, Bidel S, Lindström J, Jousilahti P. Coffee consumption and risk of type 2 diabetes mellitus among middle-aged Finnish men and women. JAMA 2004; 291:1213-1219.

26. Wang PY, Fang JC, Gao ZH, Zhang C, Xie SY. Higher intake of fruits, vegetables or their fiber reduces the risk of type 2 diabetes: A meta-analysis. J Diabet Invest 2016; 7:56-69.

25. Meinilä J, Valkama A, Koivusalo SB, Stach-Lempinen B, Lindström J, Kautiainen H, et al. Healthy Food Intake Index (HFI)-Validity and reproducibility in a gestational-diabetes-risk population. BMC Public Health 2016; 16:600-609.

24. Io H, Date C, Wakai K, Fukui M, Tamakoshi A. The relationship between green tea and total caffeine intake and risk for self-reported type 2 diabetes among Japanese adults. Ann Intern Med 2006; 144:554-562.

23. Saeed M, Naveed M, Arif M, Kakar MU, Manzoor R, Abd EHM, et al. Green tea (Camellia sinensis) and l-theanine: Medicinal values and beneficial applications in human-s: A comprehensive review. Biomed Pharmacol 2017; 95:1260-1275.

22. Satoh T, Igarashi M, Yamada S, Takahashi N, Watanabe K. The Healthy Food Intake Index (HFI)-Validity and reproducibility in a gestational-diabetes-risk population. BMC Public Health 2016; 16:600-609.

21. Asmat U, Abad K, Ismail K. Diabetes mellitus and oxidative stress-a concise review. Saudi J Pharm Sci 2016; 24:547-553.

20. Wang PY, Fang JC, Gao ZH, Zhang C, Xie SY. Higher intake of fruits, vegetables or their fiber reduces the risk of type 2 diabetes: A meta-analysis. J Diabet Invest 2016; 7:56-69.

19. Meinilä J, Valkama A, Koivusalo SB, Stach-Lempinen B, Lindström J, Kautiainen H, et al. Healthy Food Intake Index (HFI)-Validity and reproducibility in a gestational-diabetes-risk population. BMC Public Health 2016; 16:600-609.
Waheed Janabi et al. Dietary flavonoids in lifespan-shortening diseases

12:60-79.
72. Bahmani M, Nejad ASM, Shah NA, Shah SA, Rafieian-Kopaei M, Mahmoudnia L. Survey on ethnotobanical uses of anti-cancer herbs in Southern region of Ilam, West Iran. J Biol Res-BollettinodellaSocietàitaliana di Biologia Sperimentale 2017; 90:19-25.
73. Higdon JV, Delage B, Williams DE, Dashwood RH. Cruciferous vegetables and human cancer risk: epidemiologic evidence and mechanistic basis. Pharmacol Res 2007; 55:224-236.
74. Lam TK, Gallicchio L, Lindeley K, Shieh M, Hammond E, Tao XG, et al. Cruciferous vegetable consumption and lung cancer risk: a systematic review. Cancer Epidemiol Biomarkers Prev 2009; 18:184-195.
75. Verhoeven DT, Goldbohm RA, van Poppel G, Verhagen H, van den Brandt PA. Epidemiological studies on brassica vegetables and cancer risk. Cancer Epidemiol Biomarkers Prev 1996; 5:733-748.
76. Keck AS, Finley JW. Cruciferous vegetables: cancer protective mechanisms of glucosinolate hydrolysis products and selenium. Integr Cancer Ther 2004; 3:5-12.
77. Tian T, Li J, Li B, Wang Y, Li M, Ma D, et al. Genistein exhibits anti-cancer effects via down-regulating FoxM1 in H446 small-cell lung cancer cells. Tumor Biol 2014; 35:4137-4145.
78. Giovannucci E, Rimm EB, Liu Y, Stampfer MJ, Willett WC. A prospective study of tomato products, lycopene, and prostate cancer risk. J Natl Cancer Inst 2002; 94:391-398.
79. Hayakawa S, Saito K, Miyoshi N, Oishi T, Oishi Y, Miyoshi M, et al. Anti-cancer effects of green tea by either anti-or pro-oxidative mechanisms. Asian Pacific J Cancer Preve 2016; 17:1649-1654.
80. Mandal S. Curcumin, a promising anti-cancer therapeutic: it's bioactivity and development of drug delivery vehicles. Inter J Drug Res Technol 2017; 6:14.
81. Volate SR, Davenport DM, Muga SJ, Wargovich MJ. Modulation of aberrant crypt foci and apoptosis by dietary herbal supplements (quercetin, curcumin, silymarin, ginseng and rutin). Carcinogenesis 2005; 26:1450-1456.
82. Caragay AB. Cancer-preventive foods and ingredients. Arthritis Rheum 1992; 25:15:10.
83. Setchell KD. Soy isoflavones-benefits and risks from nature's selective estrogen receptor modulators (SERMs). J Am Coll Nutr 2001; 20:354S-362S.
84. Harris J. The anti-inflammatory and anti-carcinogenic effects mediated by Genistein in breast cancer, Doctoral dissertation, Cardiff Metropolitan University; 2017.
85. Tse G, Eslick GD. Soy and isoflavone consumption and risk of gastrointestinal cancer: a systematic review and meta-analysis. Eur J Nutr 2016; 55:63-73.
86. Jung H, Ahn S, Kim BS, Shin SY, Lee YH, Lim Y. Isoflavones as modulators of adenosine monophosphate-activated protein kinase. Appl Biol Chem 2016; 59:217-225.
87. Salti G, Grewal S, Mehta RR, Gupta TD, Boddie Jr AW, Constantinou AI. Genistein induces apoptosis and topoisomerase II-mediated DNA breakage in colon cancer cells. Eur J Cancer 2000; 1:36:79-802.
88. Kwok CS, Boekholdt SM, Lentjes MA, Loke YK, Luben RN, Yeong JK, et al. Habitual chocolate consumption and risk of cardiovascular disease among healthy men and women. Heart 2015; 101:1279-1287.
89. Di Lorenzo A, Curti V, Tenore GC, Nahavi SM, Daglia M. Effects of tea and coffee consumption on cardiovascular diseases and relative risk factors: an update. Curr Pharm Des 2017; 23:2474-2487.
90. Rechner AR, Kroner C. Anthocyanins and colonic metabolites of dietary polyphenols inhibit platelet function. Thromb Res 2005; 116:327-334.
91. Xia M, Ling W, Zhu H, Wang Q, Ma J, Hou M, et al. Anthocyanin prevents CD40-activated proinflammatory signaling in endothelial cells by regulating cholesterol distribution. Arterioscler Thromb Vasc Biol 2007; 27:519-524.
92. Haseeb S, Alexander B, Baranchuk A. Wine and cardiovascular health: A comprehensive review. Circulation 2017; 136:1434-1448.
93. Dauchet L, Kesse-Guyot E, Caermichow S, Bertras S, Estouqio C, Peneau S, et al. Dietary patterns and blood pressure change over 5-y follow-up in the SUN.VLMAX cohort. Am J Clin Nutr 2007; 85:1650-1656.
94. Ramadath DD, Padhi EM, Sarfaraz S, Renwick S, Duncan AM. Beyond the cholesterol-lowering effect of soy protein: a review of the effects of dietary soy and its constituents on risk factors for cardiovascular disease. Nutrients 2017; 9:324.
95. Hughes LA, Arts IC, Ambergen T, Brants HA, Dagnelie PC, Goldbohm RA, et al. Higher dietary flavone, flavonol, and catechin intakes are associated with less of an increase in BMI over time in women: a longitudinal analysis from the Netherlands Cohort Study. Am J Clin Nutr 2008; 88:1341-1352.
96. Shenoy SF, Kazaks AG, Holt RR, Chen HJ, Winters BL, San khoo C, et al. The use of a commercial vegetable juice as a practical means to increase vegetable intake: a randomized controlled trial. Nutr J 2010; 9:38-48.
97. Hung HC, Joshihpura KJ, Jiang R, Hu FB, Hunter D, Smith-Warner SA, et al. Fruit and vegetable intake and risk of major chronic disease. J Natl Cancer Inst 2004; 96:1577-1584.
98. Krauss RM, Eckel RH, Howard B, Appel LJ, Daniels SR, Deckelbaum RJ, et al. AHA scientific statement: AHA dietary guidelines Revision 2000: A statement for healthcare professionals from the nutrition committee of the american heart Association. J Nutr 2001; 131:1:32-146.
99. Anisimov VN. Life span extension and cancer risk: myths and reality. Exp Gerontol 2001; 36:1101-1136.
100. Ferrari CK. Functional foods, herbs and nutraceuticals: towards biochemical mechanisms of healthy aging. Biogerontology 2004; 5:275-289.
101. Koltov V. Antioxidant medicine: from free radical chemistry to systems biology mechanisms. Russ Chem Bull 2010; 59:37-42.
102. Williamson G, Holst B. Dietary reference intake (DRI) value for dietary polyphenols: are we heading in the right direction? Br J Nutr 2008; 99:55-58.
103. Grosso G, Estruch R. Nut consumption and age-related disease. Maturitas 2016; 84:11-16.
104. Jang S, Johnson RW. Can consuming flavonoids restore old microglia to their youthful state? Nutr Rev 2010; 68:719-728.
105. Shukitt-Hale B, Lau FC, Joseph JA. Berry fruit supplementation and the aging brain. J Agric Food Chem 2008; 56:636-641.
106. Shukitt-Hale B, Carey A, Simon L, Mark DA, Joseph JA. Effects of Concord grape juice on cognitive and motor deficits in aging. Nutrition 2006; 22:295-302.
107. Joseph JA, Shukitt-Hale B, Denisova NA, Bielinski D, Martin A, McEwen JJ, et al. Reversals of age-related declines in neuronal signal transduction, cognitive, and motor behavioral deficits with blueberry, spinach, or strawberry dietary supplementation. J Neurosci 1999; 19:8114-8121.
108. Joseph JA, Denisova NA, Arendash G, Gordon M, Diamond D, Shukitt-Hale B, et al. Blueberry supplementation enhances signaling and prevents behavioral deficits in an Alzheimer disease model. Nutr Neurosci 2003; 6:153-162.
109. Sutherland BA, Rahman RM, Appleton I. Mechanisms of action of green tea catechins, with a focus on ischemia-induced neurodegeneration. J Nutr Biochem 2006; 17:291-306.
110. Milovera J, Cerovska J, Zamrazil V, Bilcik O, Hampl V. Beyond the cholesterol-lowering effect of soy protein: a review of the effects of dietary soy and its constituents on risk factors for cardiovascular disease. Nutrients 2017; 9:324.
Dietary flavonoids in lifespan-shortening diseases

Waheed Janabi et al.

111. Chandra AK, De N. Goitrogenic/antithyroidal relation of green tea extract in relation to catechin in rasts. Food Chem Toxicol 2010; 48:2304-2311.

112. Egert S, Rimbach G. Which sources of flavonoids: complex diets or dietary supplements? Adv Nutr 2011; 2:8-14.

113. Mateos R, Lecumberri E, Ramos S, Goya L, Bravo L. Determination of malondialdehyde (MDA) by high-performance liquid chromatography in serum and liver as a biomarker for oxidative stress: Application to a rat model for hypercholesterolemia and evaluation of the effect of diets rich in phenolic antioxidants from fruits. J Chromatogr B Analyt Technol Biomed Life Sci 2005; 827:76-82.

114. Medina-Remón A, Barrionuevo-González A, Zamora-Ros R, Andres-Lacueva C, Estruch R, Martínez-González MA, et al. Rapid Folin–Ciocalteu method using microtiter 96-well-plate cartridges for solid phase extraction to assess urinary total phenolic compounds, as a biomarker of total polyphenols intake. Anal Chim Acta 2009; 634:54-60.

115. Schatzkin A. Dietary change as a strategy for preventing cancer. Cancer Metastasis Rev 1997; 16:377-392.

116. Ferguson LR. Nutrigenomics approaches to functional foods. J Am Diet Assoc 2009; 109:452-458.

117. Biglari B, Galati F. Innovation trends in the food industry: the case of functional foods. Trend Food Sci Technol 2013; 31:118-129.

118. Feeney MJ. Fruits and the prevention of lifestyle-related diseases. Clin Exp Pharmacol Physiol 2004; 31:11-13.

119. Weisburger JH. Chemopreventive effects of cocoa polyphenols on chronic diseases. Exp Biol Med (Maywood) 2001; 226:891-897.

120. Duthie GG, Gardner PT, Kyle JA. Plant polyphenols: are they the new magic bullet?. Proc Nutr Soc 2003; 62:452-458.

121. Biglari B, Galati F. Innovation trends in the food industry: the case of functional foods. Trend Food Sci Technol 2013; 31:118-129.

122. Nurtjahja-Tjendraputra E, Ammit AJ, Roufogalis BD, Tran VH, Duke CC. Effective anti-platelet and COX-1 enzyme inhibitors from pungent constituents of ginger. Thromb Res 2003; 111:259-265.

123. Bellavia A, Larsson SC, Bottai M, Wolk A, Orsini N. Fruit and vegetable consumption and all-cause mortality: a dose-response analysis. Am J Clin Nutr 2013; 98:454-459.

124. Zhang X, Shu XO, Xiang YB, Yang G, Li H, Gao J. Cruciferous vegetable consumption is associated with a reduced risk of total and cardiovascular disease mortality. Am J Clin Nutr 2011;94:240-246.

125. Leenders M, Sluijs I, Ros MM, Boshuizen HC, Siersema PD, Ferrari P. Fruit and vegetable consumption and mortality European prospective investigation into cancer and nutrition. Am J Epidemiol2013;178:590-602.

126. Andersen LF, Jacobs DR, Carlsen MH, Blomhoff R. Consumption of coffee is associated with reduced risk of death attributed to inflammatory and cardiovascular diseases in the Iowa Women's Health Study. Am J Clin Nutr 2006; 83:1039-1046.

127. Kurijama S, Shimazu T, Ohmori K, Kikuchi N, Nakaya N, Nishino Y, et al. Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: the Ohsaki study. JAMA 2006; 296:1255-1265.

128. Nagura J, Iso H, Watanabe Y, Maruyama K, Date C, Toyoshima H, et al. Fruit, vegetable and bean intake and mortality from cardiovascular disease among Japanese men and women: the JACC Study. Br J Nutr 2009; 102:285-292.

129. Sahyoun NR, Jacques PF, Zhang XL, Juan W, McKeown NM. Whole-grain intake is inversely associated with the metabolic syndrome and mortality in older adults. Am J Clin Nutr 2006; 83:124-131.

130. Sauvaget C, Nagano J, Hayashi M, Spencer E, Shimizu Y, Allen N. Vegetables and fruit intake and cancer mortality in the Hiroshima/Nagasaki Life Span Study. Br J Cancer 2003; 88:689-694.

131. Genkinger JM, Platz EA, Hoffman SC, Comstock GW, Helzlsouer KJ. Fruit, vegetable, and antioxidant intake and all-cause, cancer, and cardiovascular disease mortality in a community-dwelling population in Washington County, Maryland. Am J Epidemiol 2004; 160:1223-1233.

132. Tucker KL, Hallfrisch J, Qiao N, Muller D, Andres R, Fleg JL. The combination of high fruit and vegetable and low saturated fat intakes is more protective against mortality in aging men than is either alone: the Baltimore Longitudinal Study of Aging. J Nutr 2005; 135:556-561.

133. Bazzano LA, He J, Ogden LG, Loria CM, Vupputuri S, Myers L, et al. Fruit and vegetable intake and risk of cardiovascular disease in US adults: the first National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. Am J Clin Nutr 2002; 76:93-99.

134. Strandhagen E, Hansson PO, Bosaeus I, Isaksson B, Eriksson H. High fruit intake may reduce mortality among middle-aged and elderly men. The Study of Men Born in 1913. Eur J Clin Nutr 2000; 54:337-341.

135. Rissanen TH, Vuolilainen S, Virtanen JK, Venho B, Vanharanta M, Mursu J, et al. Low intake of fruits, berries, and vegetables is associated with excess mortality in men: the Kuopio Ischaemic Heart Disease Risk Factor (KHD) Study. J Nutr 2003; 133:199-204.