CHAPTER 04

Flavonoids: Antioxidant Powerhouses in Disease Prevention and Therapy

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ABSTRACT: Flavonoids are the major type of polyphenols present in fruits, grains, green vegetables, bark, roots, stems, flowers, tea and wine. Flavonoids have applications as nutraceuticals, pharmaceuticals, and medicinal agents and they are also used in cosmetics. They exhibit anti-oxidative, anti-inflammatory, anti-mutagenic and anti-carcinogenic properties. These bioactive compounds scavenge reactive oxygen species (ROS), suppress oxidative stress that is one of the key pathogenic agents in the development of many long-term disorders, such as cardiovascular diseases, neurodegenerative disorders, diabetes, and cancer. Flavonoids modulate key signaling pathways, such as NF-κB and MAPK and regulate the expression of genes involved in inflammation and apoptosis. In addition, flavonoids can also enhance vascular health, improve endothelial physiology and decrease lipid peroxidation. Recent pharmacological studies have emphasized the bioavailability, mechanisms of action, and the effects of flavonois. Nonetheless, some issues, including poor bioavailability and stability, require an in-depth examination of innovative carriers including nanoparticles and liposomes. This chapter focuses on the central role of flavonoids in both health and disease prevention, and the use of flavonoids in both dietary and therapeutic management.

Keywords: Flavonoids, Cardiovascular health, Antioxidant, Anti-inflammatory, Diabetes

Flavonoids belong to one of the major categories of natural products; they are an essential class of secondary metabolites that have a polyphenolic structure and are obtained from plants, i.e., tea, fruits, red wine, vegetables, cereals, and certain beverages (Panche et al., 2016). The flavonoid structure is based on 15 carbon atoms combined in the form of C6-C3-C6 with two benzene rings linked by a central oxygen-containing heterocyclic ring. Flavonoids are synthesized at specific sites in plants primarily in photosynthetic tissues and reproductive organs like flowers. Flavonoids are further categorized as flavonols, flavanones, flavanols, isoflavones, flavones, and anthocyanins based on the variations in their structures (Brodowska, 2017).

Flavonoids with biological activity are usually referred as bioflavonoids (Brodowska, 2017). Flavonoids protect the cells of human as well as animals from oxidative damage induced as a result of free radicals due to their anti-oxidant activity. They display anti-oxidative, anti-inflammatory, anti-mutagenic as well as anti-carcinogenic characteristics. Moreover, they have the potential to influence the functions of key cellular enzyme (Panche et al., 2016). They play a vital role in the prevention of lipid peroxidation which is a major cause of multiple disorders, i.e., diabetes, inflammation, hepatotoxicity and atherosclerosis as well as ageing. The anti-allergic, antiviral, therapeutic, and cytotoxic effects of natural flavonoids and their analogues are among their many essential features. Some flavonoids have hormone-like characteristics and resemble steroid hormones, specifically estrogen (Brodowska, 2017).

They are also involved in a broad array of health-improving activities. Positive effects on human as

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well as animal health have been attributed to flavonoids, and the present focus is on chemoprevention and disease treatment (Panche et al., 2016). Due to their characteristics and ability to modulate critical cellular activities, they are critical components of pharmacological, medicinal, nutritional, and cosmetic uses (Walker et al., 1984). The anti-fungal and anti-bacterial activities of these elements are also identified. Numerous flavonoids and their natural as well as synthetic derivatives have been investigated as anti-malarial, anti-HIV, (Brodowska, 2017) and anti-COVID-19 agents (Ngwa et al., 2020). The dietary flavonoids possess good anti-oxidant features via acting as reactive oxygen species (ROS) as well as reactive nitrogen species (RNS) scavengers. Moreover, they effectively inhibit the development of inflammation via suppressing inflammatory mediators as well as regulating signaling pathways (Crasci et al., 2018; Ahmed et al., 2025).

The aim of this chapter is to explore the multifaceted roles of flavonoids in combating oxidative stress and their therapeutic ability in disease control and management. By delving into their chemical properties, mechanisms of action, and interactions within biological systems, this chapter aims to highlight flavonoids as critical natural compounds for improving health outcomes and addressing prevalent medical challenges.

CHEMISTRY AND CLASSIFICATION OF FLAVONOIDS

Flavonoids are polyphenolic-polyhydroxy substances, that are synthesized by plants in the phenylpropanoid synthetic pathway (Dretcanu et al., 2022). Carbon skeleton that originated from flavan system (C6-C3-C6) is an element that all flavonoids share in their chemical structure. The hydroxylation of ring B and a C2-C3 double bond joined by a C-3 hydroxyl group and a C-4 carbonyl group are the structural components of the flavonoid molecule that are most crucial for hydroxyl radical scavenging. The activity of a flavonoid is increased by the presence of gallate and galacturonate substituents on its skeleton, as well as by the hydroxylation of its A-ring. The biosynthesis of these compounds is of mixed origin: the A-ring is formed by the polyacetate pathway and the B-ring by the shikimate pathway, whereas the intermediates of the two pathways combine to form the central C-ring. Based on the differences in the oxidation state and substituent patterns of this central ring, flavonoids can be grouped into several major categories such as Flavonols, Flavones, Flavanones, Flavanols, Anthocyanins as well as Isoflavones (Symonowicz & Kolanek 2012).

Flavonols are a subclass of flavonoids, they impart color to the food and flavor and prevent oxidation of fat. Flavonols including quercetin, myricetin, kaempferol, fisetin, rutin and astragalin are highly functional. Kaempferol and quercetin are the primary types of flavonols and are richly found in onions, apples and broccoli. Quercetin and kaempferol have antioxidant and anti-inflammatory activities. Moreover, they also exhibit protection and antihypertensive effects in animals. Furthermore, quercetin is an antioxidant, which blocks most of the enzymes and kaempferol enhances cell viability and suppresses apoptosis in the pancreatic beta-cells (Tutunchi et al., 2020).

Flavones, a subclass of flavonoids, are normally found in glycosylated form with a hydroxylated B-ring. During the past few years, flavonoids as well as flavones have been of great scientific interest because of their reported anti-inflammatory, antimicrobial and anticancer activity. As luteolin that blocks the activity of Rho GTPases, thereby decreasing the infiltration of leukocytes and protecting inflammation and damage to nerve cells. The capacity of flavones to reduce cell migration is of particular significance in cancer where it implies potential treatment modalities that could minimize metastasis. Moreover, it has been revealed that apigenin, which is also an important flavone, can lower the migration of breast cancer cells (Lee et al., 2008).

The highest contents of flavonoid in plants occur in the citrus plants, especially the flavonoid flavanone subgroup. Important flavonoids isolated in citrus fruits are naringin, narirutin, nobiletin, naringenin and hesperidin. The compounds have shown strong antioxidant and anti-inflammatory effects in both *in vitro* and *in vivo* studies. Naringin is also a strong anti-oxidant, this property of naringin is due to the existence of a sugar moiety in naringin, which produce a steric hindrance around the active site that leads to its antioxidant capacity (Renugadevi & prabu 2009). It can play a cardioprotective role because of its antioxidant, anti-inflammatory, lipid-lowering activities as well as antifibrogenic and anticancerous properties. Hesperidin has a variety of biological characteristics. It is noteworthy that it has vitamin-like impacts especially one similar to vitamin P, in causing lowered capillary permeability, leakiness and fragility. Moreover, hesperidin possesses antioxidant, anti-inflammatory, anticarcinogenic and antiallergic effects, which indicates its therapeutic potential in health (Salehi et al., 2019).

Most common foods contain flavanols e.g. tea, cocoa, grapes, apples as well as beers. Flavanols have been found to have antioxidant activity in addition to their therapeutical potential in neurodegenerative diseases and neurodegenerative disorders by helping to reduce oxidative stress as well as inflammation (Qiang et al., 2018). One of the most significant representatives of the flavanol is catechin and prevents oxidation of proteins by its high free radical scavenging capacity. Also, it has the ability to limit the covalent modification of proteins that occurs due to the presence of ROS and this limits the damage of cellular proteins. Also, catechin has anti-atherosclerotic effects and has been demonstrated to prevent low-density lipoprotein (LDL) oxidation, decrease endothelin levels, and prevent platelet aggregation, a process that is helpful in cardiovascular protection (Murphy et al., 2003).

Anthocyanins are also a subclass of flavonoids, and these are secondary metabolites of plants. They are becoming sought after food, beverage, cosmetic, and nutraceutical ingredients. Teas, fruits, vegetables, and in particular berries such as blueberries and strawberries are high in anthocyanins. The nutraceutical properties of anthocyanins have revealed that they have potential health benefits that can be useful due to antioxidant, anti-inflammatory, anti-cancer and cardioprotective effects (Sivamaruthi et al., 2018). A flavonoid compound with a unique and significant subclass is isoflavone. They possess a wide distribution in legumes, mainly soy, but were also reported in green split peas, chickpea, blackbeans, lima beans, clover sprouts, and sunflower seeds However, isoflavone compounds seem to be effective in the management of cardiovascular and menopausal health, as well as in the prevention of cancer. There is also a possibility of isoflavones to exhibit antioxidant protection in the blood vessels (Yeung and Yu 2003). Classification and therapeutic properties of flavonoids has been demonstrated in Fig. 1.

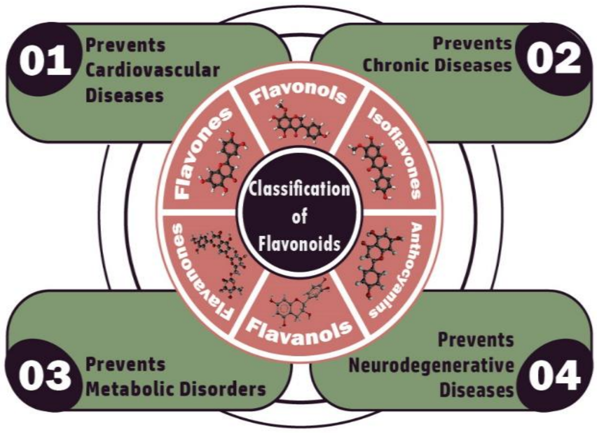

Fig 1. Classification and Therapeutic Properties of Flavonoids

MECHANISMS OF ANTIOXIDANT AND THERAPEUTIC ACTION

Oxidative stress occurs when ROS are generated in excess as compared to the capacity of the antioxidant system of body. ROS are small molecules that are usually generated in radical reactions and have the ability of interfacing with the structures of the cells in a quick manner (Ma, 2010). They can easily damage nucleic acids, proteins as well as lipids. The molecules attacked by ROS are damaged, destroyed or their functions are modified. Free radicals are molecules that have unpaired electrons, and they are therefore highly reactive. Because of this reactive property, the molecule either transfers or accepts electrons from neighboring molecules to achieve a stable state. Positive contributions of flavonoids to the prevention of illness are associated with either their antioxidant or, in fact, prooxidant effects. These activities can be expressed in the form of the ability to scavenge free radicals, activate antioxidant enzymes, chelate redox-active metal ions, regenerate vitamin E in the form of its radical, relieve the oxidative stress generated by nitric oxide, inhibit oxidases, and other positive actions (Prochazkova et al., 2011).

Many of the plant flavonoids can form stable complexes with metals based on their multiple OH and where present, a carbonyl functional group

(Psotova et al., 2003). Flavonoids have the capability to chelate trace metals, which take part in the reactions that produce ROS. Iron can catalyze the Fenton reaction which yields the hydroxyl radical. Besides, copper and iron can enhance the formation of lipid radicals via the process of lipid peroxidation. Iron ions occur in ferrous (Fe^{2+}) and ferric (Fe^{3+}) forms, which are significant in the start of the lipid peroxidation process (Mira et al., 2002). Flavonoids containing a hydroxyl group at C3 and the carbonyl group at C4 can coordinate iron in a 2:1 stoichiometry. In addition, a catechol group in ring B (3′ and 4′ positions), a hydroxyl group in ring A on C5, and a 2, 3-double bond increase iron chelation. Three possible sites of chelation exist in such flavonoids; the 3′−4′ catechol moieties, the 3-hydroxyl and 4-carbonyl groups, and the 5-hydroxyl and 4-carbonyl groups. Chelation is favored at the 5-hydroxyl and 4-carbonyl positions because it entails a 6-membered ring which imparts increased stability (Leopoldini et al., 2006). This is corroborated by computational analysis where the energy has been calculated to decrease by 10 kcal/mol in such compounds compared to five-membered ring complexes bound elsewhere. The complex with a ferrous ion involves a single deprotonated flavonoid, while the complex with a ferric ion requires a doubly deprotonated flavonoid. Nevertheless, it is necessary to mention that flavonoids have a superior binding affinity for ferrous cation (Mira et al., 2002).

Flavonoids possess the ability to regulate a variety of intracellular signaling pathways, including JAK-STAT, MAPK and NF-κB. The transcription factor NF-κB has a critical influence on the modulation of both adaptive and innate immunity. This is achieved by controlling the expression of many genes that are stimulated in response to inflammation. (Jeong et al., 2012). NF-κB regulates the synthesis of cytokines (IL-8, IL-6, and TNF-α) as well as cyclooxygenase 2 (COX-2) expressions. ROS play a basic part in pro-inflammatory reactions by activating redox-sensitive transcription elements i.e., activator protein-1 (AP-1) and NF-κB, and their up-regulating kinases including MAPK as well as PI3K (Teng et al., 2016). ROS that activates redox-sensitive NF-κB play a role in the overproduction of various pro-inflammatory cytokines such as TNF-α, IL-12, IL-6, IL-2, and IL- IL-1β. Nrf2 signaling pathway activating compounds would have the same potential to down-regulate the excessive production of pro-inflammatory cytokines, i.e. TNF-α, IL-6, and IL-1β. Because ROS activates NF-κB and AP-1, the idea behind reducing inflammation using flavonoids is to lower intra-cellular level of ROS (Kim et al., 2011).

However, it has come to light that flavonoids may modulate signaling processes within cultured cells and perhaps also *in vivo* (Williams et al., 2004). These polyphenols may be able to prevent oxidative damage by activating transcription factors known to be redox-sensitive as nuclear factor (erythroid-derived 2)-like 2 (Nrf2). Although Nrf2 regulates genes that encode proteins which suppress oxidative stress and detoxification of xenobiotics, it can also modulate genes that play a role in metabolism, adipocyte differentiation as well as cell survival (Chorley et al., 2012). In the normal circumstances, Nrf2 binds to the Kelch-like-ECH-associated protein 1 (Keap1) which inhibits the entrance of the former to the nucleus. However, flavonoids interfere with this interaction to enhance translocation of Nrf2 thereby causing activation of EpRE. Inflammation is significant in MAPK pathway. When activated, MAPK becomes phosphorylated and numerous transcription factors including Nrf-2, PPAR, and NF-κB become activated to express their target genes and inflammatory mediators. Various MAPKs possess varied substrate specificities i.e. interaction of different MAPKs cascades is of vital significance to combine the messages and activate a different set of genes. Therefore, blocking MAPKs may result in an anti-inflammatory effect by regulating the extent of pro- and anti-inflammatory agents (Kaminska, 2005).

Inflammation represents a body response to a foreign agent. Excellent anti-inflammatory properties are known to be found in flavonoids. Another key to flavonoid action is the flavonoid structure in terms of the anti-inflammatory process. Pre-treatment of cells with apigenin was observed to inhibit the TNF-α-stimulated IL-1β, IL-6, as well as prostaglandin E_2 (Santangelo et al., 2007). Numerous flavonoids inhibit pro-inflammatory cytokines, including IL-1β, IL-6, IL-8 and TNF-α. Flavonoids are also strong suppressor of phospholipase A_2, NOS, cyclooxygenase, and arachidonic acid. This minimizes the synthesis of NO, prostaglandins, and leukotrienes that are the main inflammatory mediators. Flavonoids disrupt several signal transduction pathways during carcinogenesis therefore restricting cell growth, angiogenesis, and spreading or inducing apoptosis. The use of flavonoid mostly induces apoptosis through the intrinsic apoptotic pathway. Also, there are reports that the flavonoid and flavonoid-classical anticancer drugs combination products have a better cancer treatment capabilities (Teng et al., 2016). Mechanisms of antioxidant and therapeutic action of flavonoids has been illustrated in Fig. 2.

such as quercetin, myricetin, kaempferol, fisetin, rutin and astragalin, act on cardiovascular system by targeting hypertension, ischemic heart disease, stroke and myocardial infarction. Flavonoids have numerous health effects that have been revealed with the best being anti-inflammatory, antihypertensive, antiplatelet, antioxidant, and anti-ischemic actions. Functional endothelium, a single layer of cells located between the circulating blood and vascular smooth muscle, is a central determinant of cardiovascular health. Endothelium is known to control the homeostasis of the vascular system through its ability to generate and release signaling molecules in response to physical and

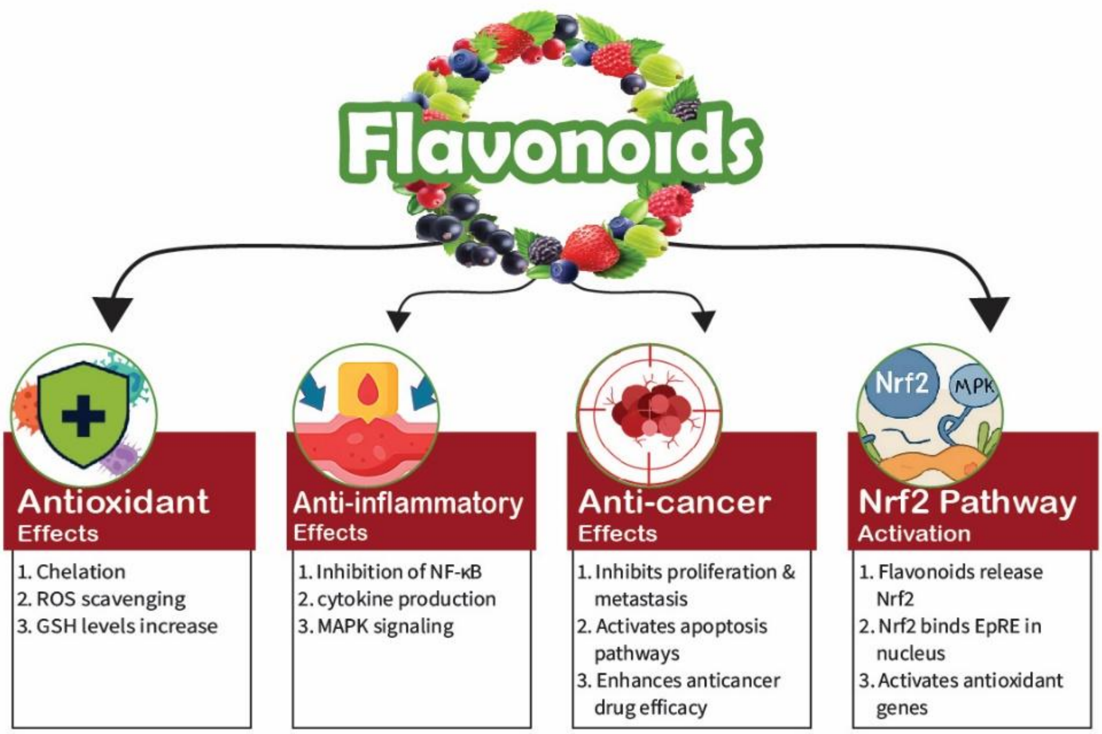

Fig 2. Mechanisms of Antioxidant and Therapeutic Action of Flavonoids

ROLE OF FLAVONOIDS IN DISEASE PREVENTION AND THERAPY

Cardiovascular Diseases

Cardiovascular events are significant health concerns associated with aging. They are a leading cause of mortality as well as morbidity worldwide, mainly driven by factors such as, high plasma cholesterol levels, arterial stiffness, and peripheral vascular resistance (Mehra et al., 2020). Flavonoids

chemical signals. Nitric oxide produced by endothelial cells has a vital part in the regulation of vascular tone, integrity as well as the cardiovascular system. It has been found out that flavonoids help prevent chronic health situations, especially cardiovascular disorders. Among their major mechanisms of actions is their development of vasodilation due to the release of NO by endothelium (Zhang et al., 2018). NO enters vascular smooth muscle cells (VSMCs), wherein, it activates the cyclic guanase signaling pathway, that acts through cyclic guanosine monophosphate-dependent protein kinase (cGMP-PKG). The activation of these channels leads to the opening of intracellular Ca^{2+}-activated potassium channels, causing the cell membrane to hyperpolarize. This, in turn, inhibits the entry of extracellular Ca^{2+} and its release from the endoplasmic reticulum. The outcome of all these events is vasodilation. Cardioprotective effect of flavonoids is attributed to several mechanisms such as lowering of blood pressure/hypertension, and increasing coronary blood flow (CBF), which is ultimately linked to reduced chances of cardiovascular disorders (Rees, 2018).

Over-accumulation of ROS may be harmful and damage other biomolecules, e.g. lipids. In atherosclerosis, ROS take central stage in atheromatous plaque formation and development, increasing monocyte-endothelial interaction, facilitating low-density lipoprotein (LDL) oxidation, and encouraging proliferation and growth factor synthesis by smooth muscle cells. Flavonoids have great antioxidant implications, and thus may reduce oxidative damage and its cardiac related implications (Rees, 2018). The positive functions of flavonoids are mostly explained by anti-oxidant properties, especially the inhibitory action on the oxidation of low-density lipoproteins (LDL), which leads to a positive effect on the lipid profile. The LDL lipid peroxidation can be decreased by flavonoids in several ways via scavenging ROS and RNA, chelating transition metal ions, and preserving LDL associated antioxidants. They also moderate oxidative stress in macrophages by suppression of cellular oxygenases as well as activity of endogenous antioxidant systems (Ciumarnean, 2020).

Metabolic Disorders

Metabolic disorders are diseases that alter the standard functioning and metabolism of macro nutrients such as proteins, fats and carbohydrates (Oteiza, 2018). Diabetes mellitus is an illness that increases the level of glucose in blood caused by failure to failure to produce or release insulin, an inability to bind with cell receptors. Flavonoids in their natural form have been seen to exhibit antidiabetic effects and can even prevent diabetes and its complications. The antidiabetic effect of flavonoids is associated with the regulation of three most important metabolic processes including the regulation of the insulin signaling with insulin secretion together with the glucose intake, carbohydrate digestion and deposition in the adipose tissue. Flavonoids have the potential to affect production as well as the secretion of insulin by the β-cells. Flavonoids directly act on a number of metabolic molecular mechanisms, including insulin secretion, β-cell proliferation stimulation, and hyperglycemia alleviation through the control of the hepatic glucose metabolism (Zeka, 2017).

Malnutrition and poor eating habits along with the lack of physical activities interfere with the metabolic homeostasis state and lead to obesity. The ill effects of obesity are that it reduces the functionality of various organ systems and significantly increases the risk of various disorders, i.e., type 2 diabetes, cardiovascular disorders, hypertension, and neurological disorders, diseases of the liver and kidney, and cancer (Mahboob et al., 2023). Flavonoids are considered a novel approach in research to produce beneficial and safe therapeutic formulations against obesity and diabetes. Flavonoids possess important antioxidant, hypocholesterolemic, and antidiabetic potentials that may control different metabolic issues. The study of other flavonoid metabolites is therefore promising towards the discovery of compounds that may assist in the cure of certain metabolic disorders. These compounds have huge therapeutic potential and therefore further exploration of molecular mechanisms involved is imperative (Zeka, 2017).

Neurodegenerative Diseases

The issue of neurological and neurodegenerative disorders have become significant worldwide health concerns, especially as the population keeps aging. Even though research progress is already being made, available pharmacological interventions are not necessarily curative. A wide spectrum of disorders, such as functional diseases including depression as well as progressive neurodegenerative diseases such as Alzheimer disease (AD), Parkinson disease (PD), Huntington disease, Multiple sclerosis and amyotrophic lateral sclerosis, are present in humans. Oxidative stress, inflammation, and cytotoxicity are some of the main contributors since they amplify neuronal dysfunction and tissue degeneration (Bellavite, 2023). Flavonoids have been used in traditional and complementary medicine over the years which emphasizes its therapeutic significance (Melrose, 2023).

The endothelium of brain micro vessels forms the blood that is called the blood brain barrier (BBB), and this barrier remains suited in the control of nearby cells especially astrocytes. CNS exhibits a high oxidative metabolism rate relative to other tissues as it derives approximately 15 percent of the cardiac output and comprises up to 30 percent of the total metabolic rate. This metabolic requirement renders the CNS more vulnerable to the effect of oxidative stress. It can be countered by dietary antioxidant and anti-inflammatory substances. It is notable that the consumption of flavonoids has demonstrated to considerably enhance the flow-mediated dilation and lower the blood pressure that produces a positive impact on vascular health (Suen et al., 2016).

Alzheimer's disease (AD) is a progressive brain disorder that causes dementia, memory loss, and cognitive decline due to the breakdown and death of nerve cells. The polyphenolics antioxidants have the potential to reverse or prevent the onset of AD and other neurodegenerative pathologies (Bellavite, 2023). Flavonoids have anti-amyloid and anti-inflammatory properties due to which they may regulate AD. These substances are beneficial for memory enhancement, cognitive support, and neurodegeneration protection. Parkinson disease (PD) is a neurological condition and results in the development of various symptoms like tremors, muscle rigidity, balance and coordination difficulties. Flavonoids have been found to be useful in the management of PD. Their neuroprotective effect in PD is mostly related to their capacity to attenuate the oxidative stress and their capacity to block pathways leading to neuronal cell death (Tian et al., 2021).

CLINICAL STUDIES ON FLAVONOID-RICH DIETS

Clinical studies are carried out on the general public to provide new information by outlining the effects of treatments designed to enhance the recognition, prevention and management of human ailments. Significant evidence from nutritional intervention studies and epidemiological surveys shows that various food ingredients have biological properties that show activities in modifying animal and human metabolism in a way that promotes longevity and the prevention of several lethal diseases. These foods are identified as "functional foods" or "superfoods" in the medical community (Zabor et al., 2020). Flavonoid-rich foods (FRF) are often referred to as superfoods due to their remarkable health benefits. These comprise all foods derived from plants such as wine, tea, fruit, vegetables, grains, legumes and nuts. Consuming plant products has been shown in several dietary intervention studies to lessen the chance of the emergence of unhealthy conditions, including cancer, inflammation and cardiovascular diseases, and abnormalities of the neurological and genetic systems (Shen et al., 2017).

According to several epidemiological studies, diets high in some antioxidants from fruits, vegetables and some vegetable oils reduce the relative risk of premature mortality from cardiovascular diseases (CVD) (Hancock et al., 2007). A type of flavonoids that lowers blood cholesterol in people at high risk for CVD is anthocyanins, which are present in berries and cherries. Numerous preclinical studies have demonstrated the functional and molecular benefits of blueberry supplementation, including improvements in cerebral blood flow, neuronal resilience and endothelial protection, as well as the reversal of age-related declines in cognitive and motor performance. Additionally, studies have demonstrated that blueberry therapy has hippocampal-specific cognitive and neurotrophic effects, which are especially relevant in the context of late-life dementia (Harborne & Williams, 2000).

A recent epidemiological study, specifically the Nurses' Health Study, which involved about 70,000 women, revealed an inverse relationship between the risk of cerebral ischaemia and flavanone intake (Behzad et al., 2017). This is particularly noteworthy when comparing women who have high levels of flavanones (>63 mg/day) to those who consumed low levels (<13.7 mg/day). A growing proportion of research shows that taking flavonoids rich diet minimizes the chance of getting cancer, mainly breast cancer. Asian nations often have lower rates of breast cancer than do North American and European nations (Shukitt-Hale et al., 2015). It might be explained by Asian populations consuming more soy, which is a rich source of isoflavones. A meta-analysis of 22 observational studies revealed that, among Asian populations as opposed to Western ones, a high consumption of isoflavones was associated with a lower risk of breast cancer (Williams et al., 2008).

For the first time, it was determined in the 20th century that the traditional Mediterranean diet fulfils a number of critical requirements, contributing to a longer lifetime and a lower prevalence of degenerative illnesses that cause death. The findings of a meta-analysis on the relationship between food, dietary habits, and supplements and PD were released in 2024 (Wu et al., 2024). From 1989 to 2022, 24 randomized and crossover clinical studies were included in the study. The quantitative insulin sensitivity check index was found to be moderate but statistically significantly impacted by food and dietary supplements. It has been observed that low-protein diets considerably reduced motor symptoms, while Mediterranean, low-fat, and ketogenic diets considerably decreased the overall Unified PD Rating Scale (UPDRS) score (Cassidy et al., 2012).

With varying kinetics, gallic acid and isoflavones are the polyphenols that are best absorbed by humans, followed by quercetin glucosides, catechins, and flavanones. Anthocyanins, galloylated tea catechins, proanthocyanidins and are the polyphenols that are least readily absorbed (Manach et al., 2005). It has been noted that when consuming FRF-containing foods and drinks, such as vegetables and fruit juices, the bioavailability of flavonoids is extremely low, ranging from 2 to 20%. The pharmacokinetics and bioavailability of flavonoids derived from FRF are also significantly influenced by the food matrix (Xie et al., 2013). Aglycones in fermented foods are absorbed more quickly than glucoside conjugates, whereas a liquid matrix produces greater peak plasma concentrations and a quicker absorption rate than a solid matrix. Moreover, it has also been observed that dietary fat (3–5 g/meal) improves children's absorption of phytochemicals from vegetables (Salas-Salvado et al., 2011). Table 1 demonstrates the outcomes of some flavonoid rich diets.

Table 1. Clinical studies on Flavonoid-Rich diets

Flavonoid	Dosage	Duration	Study Design	Outcome	Reference
Dietary flavonoids	Not Specified	Conducted in 10 European countries and 477,312 adult participants contributed for 11 years	Prospective cohorts study	No linkage was found among total flavonoids intake or flavonoid subclasses and Colorectal cancer	Zamora-Ros et al., 2017
Naringenin	10–160 µM	24–72 hours	In vitro study on gastric cancer SGC7901 cell line	Induces apoptosis by increased apoptotic proteins, decreased AKT signaling	Li et al., 2023
Regular green tea drinking	Green tea extract @0.9 g/day	12 months	Randomized clinical trial	Lowered the incidence of metachronous adenoma	Shin et al., 2018
Quercetin	15 mg/day	Not specified	Population-based, case-control study	Reduced lung cancer risk by decreased CYP1A1 expression	Li et al., 2023

BIOAVAILABILITY AND METABOLISM CONSIDERATIONS

Flavonoids found in diet are predominantly found as glycosides. Depending on the nature of the sugar moiety, deglycosylation emerges in the intestinal region. It has been shown that two enzymes in the small intestine, β-glucosidases, can hydrolyze flavonoid monoglucosides (Day et al., 2003). Lactase-phlorizin hydrolase (LPH) is the first enzyme found on brush borders, and this enzyme breaks down lactose into glucose and galactose. Cytosolic 2-glucosidase (CBG) is the other enzyme, found in the enterocytes. Therefore, de-glycosylation in the small intestine after a meal is potentially relevant for enhancing the bioavailability of flavonoid monoglucosides. However, this step may not be essential, as the gut microbiome might be able to compensate for its absence. With the non-monoglucosidic glycosides, including rutin and hyperoside (quercetin-3-O-galactoside), the intestinal β-glucosidases cannot hydrolyze the sugar component. The microbiota of the intestines has the ability to produce absorbable aglycon in the cecum and in the large intestine. The microbiota resulting product is called the aglycon which is taken up by large intestine and delivered into circulation (Erlund et al., 2000). After the introduction of flavonoid aglycons to intestinal epithelial cells, the respective conjugated hydrolysates are formed by phase II enzymes. Three classes of phase II enzymes have been reported to carry out the metabolism of flavonoids including catechol-O-methyltransferases (COMT), uridine-5′-diphosphate-glucuronosyltransferases (UGT) as well as sulfotransferases (SULT) (Van der et al., 2004).

Digestion of flavonoids in gut occurs in the form of aglycones containing no attached sugar molecules or glycosides containing attached sugars. Based on the nature of the sugary moiety attached, there is significant metabolism by the intestinal microbiota and the host tissue (Chen et al., 2014). Upon intake, flavonoids glycosides are mostly absorbed by the upper GI tract estimated at levels of about 10%, and the rest passes to the colon as non-absorbed and non-metabolized flavonoids. In the small intestine, flavonoids undergo various preparatory processes before they enter the colon. These processes include oxidation, reduction, and decarboxylation, and can also involve their conversion into other types of flavonoids. After reaching the colon, the microbiota generates colonic enzymes that remove glycosides to produce flavonoid aglycones. These are then further converted into the products of ring fission (Murota et al., 2018). Another location of Phase II metabolism is the liver. After conjugation in the intestine, the absorbed flavonoids travel to the portal vein or the lacteal. Further conjugation- sulfation and methylation- takes place in liver and several conjugates are formed. Metabolism of flavonoids involves other organs and tissues, however, other than the liver, it occurs in the intestinal mucosa and kidney, as well as in other tissues (Liu et al., 2017).

Recently, global interest has grown in the flavonoid products created by the intestinal microbiota and their potential physiological significance (Duda-Chodak et al., 2015). New clinical potentials to improve the effectiveness of multiple drugs, including substances of flavonoid derivatives, may be provided by the regulation of the certain reactions induced by bacterial enzymes produced by intestinal microbiota. Recent studies exemplify the entire findings on the biological activity of flavonoids metabolites produced through phase I metabolic pathway and phase II metabolic pathways associated with biotransformation of flavonoids by the gut microbiota (Luca et al., 2020).

The exposure of flavonoids to the microbiome has massive potential in terms of human health, both locally (within the gut) and generically (within the body). The promise of this is a broad spectrum of disease related to dysbiosis being treated with diet-based therapies facilitated by the ability of flavonoids to modulate micro biome. Polyphenols in orange and apples have the capacity to change the microbiome of patients with systemic lupus erythematosus with flavanones enhancing Lactobacillus and dihydroflavonols enhancing Bifidobacterium in the patients implying that dysbiosis of systemic lupus erythematosus may be reversible by flavonoid based dietary interventions (Cuervo et al. 2015). Interaction between flavonoid and microbiome can also be useful in treating infectious diseases. Recent research demonstrates that the gut bacterium Clostridium orbiscindens metabolizes dietary flavonoids, producing desaminotyrosine (DAT) which strengthens type 1 interferon signaling in mice infected with the influenza virus, leading to reduced lung damage and improved survival rates. Baiclin related flavone is also seen to have inhibited influenza plaque assay and would require favorable conversion into aglycone baicalein to be absorbed, and this would be microbiota dependent (Steed et al. 2017).

CONCLUSION

Flavonoids have strong antioxidant, anti-inflammatory properties as well as therapeutic powers. They have free radical scavenging properties due to which they act as strong protective agents against various disorders. Flavonoids have ability to modulate important enzymes, inhibit pro-inflammatory mediators, and stimulate indigenous defense against oxidation. Although rich in fruits, vegetables and tea, the clinical significance of flavonoids is closely associated with their bioavailability, metabolic stability, and means of effective concentration of the target sites. However, an integrative study design is necessary to reveal the maximum therapeutic potential of flavonoids due to their potential applications in nutrition science, pharmacology, and clinical medicine. The future research must focus on the optimization of flavonoid-based interventions, establishment of dose protocols, and confirmation of their effectiveness with regard to well-designed human studies. By highlighting these interdisciplinary partnerships, it will be easier to translate flavonoid-rich diets into practical methods for disease prevention and treatment.

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