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Review

A Comprehensive Review of Biological Properties of Flavonoids and Their Role in the Prevention of Metabolic, Cancer and Neurodegenerative Diseases

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Abstract

Dietary flavonoids are emerging as multifunctional bioactive compounds with significant implications for the prevention and management of chronic diseases. Integrating the latest experimental, clinical, and epidemiological evidence, this review provides a comprehensive synthesis of flavonoid classification, chemistry, dietary sources, and bioavailability, with special attention to their structural diversity and core mechanisms. Mechanistic advances related to antioxidant, anti-inflammatory, antimicrobial, anti-obesity, neuroprotective, cardioprotective, and anticancer activities are highlighted, focusing on the modulation of critical cellular pathways such as PI3K/Akt/mTOR, NF-κB, and AMPK. Evidence from in vitro and in vivo models, supported by clinical data, demonstrates flavonoids' capacity to regulate oxidative stress, inflammation, metabolic syndrome, adipogenesis, cell proliferation, apoptosis, autophagy, and angiogenesis. An inverse correlation between flavonoid-rich dietary patterns and the risk of obesity, cancer, cardiovascular, and neurodegenerative diseases is substantiated. However, translational challenges persist, including bioavailability and the optimization of delivery strategies. In conclusion, a varied dietary intake of flavonoids constitutes a scientifically grounded approach to non-communicable disease prevention, though further research is warranted to refine clinical applications and elucidate molecular mechanisms.

Keywords: chronic disease prevention; antioxidant; anti-inflammatory; anticancer; neuroprotection; bioavailability; PI3K/Akt/mTOR signaling; dietary polyphenols

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1. Introduction

Flavonoids are a diverse group of natural compounds with variable phenolic structures. They are classified as plant secondary metabolites and are ubiquitously found in our diet through fruits, vegetables, grains, bark, roots, stems, flowers, tea, and wine. Due to their wide-ranging health benefits, flavonoids are now considered essential components in a variety of nutraceutical, pharmaceutical, and medicinal applications. Their value stems from powerful biological properties, including being anti-oxidative, anti-inflammatory, anti-mutagenic, and anti-carcinogenic. In nature, flavonoids are not just passive components. They play active roles in the life of plants. They are crucial for growth and provide a defense against pests. They are responsible for the vibrant colors and aromas of flowers that attract pollinating insects and also protect plants from various stresses like UV radiation, drought, and frost. All flavonoids share a common chemical backbone: a 15-carbon skeleton consisting of two benzene rings (labeled A and B) connected by a three-carbon heterocyclic C ring. The incredible diversity of over 6000 known flavonoids comes from variations in this basic structure. They are divided into different subgroups based on the carbon of the C ring to which the B ring is attached, as well as the degree of oxidation and unsaturation of the C ring. There are seven main classes of flavonoids. One of them are flavones, which are widely found in leaves, flowers, and fruits, with major dietary sources including celery, parsley, red peppers, and chamomile. Another is flavonols, which are one of the most common flavonoid subgroups in fruits and vegetables. Onions, kale, apples, grapes, tea, and red wine are particularly rich sources. Flavanones are generally found in citrus fruits and are responsible for the bitter taste of their peels and juice. Oranges, lemons, and grapes are primary sources. Isoflavonoids are a distinctive group which is found predominantly in soybeans and other leguminous plants. Because their structure is similar to estrogen, they are often called phyto-oestrogens. Anthocyanins are the pigments that give many plants and fruits their red, purple, and blue colors. They are abundant in berries, red grapes, and black currants. Flavanols (or catechins) unlike many other flavonoids, lack a double bond between the 2nd and 3rd carbons in the C ring. They are found in high concentrations in bananas, apples, blueberries, and peaches. Chalcones are unique because they are open-chain flavonoids that lack the characteristic C ring of the basic flavonoid skeleton. They are found in tomatoes, pears, and strawberries [1].

Currently, human health is seriously threatened by both infectious and chronic non-communicable diseases, presenting significant obstacles in the search for new therapeutic agents that are effective and exhibit minimal side effects. This situation has greatly intensified the challenges facing modern drug discovery and development. The growing integration of nutritional and food sciences into medical research has underscored the pivotal role of functional plant-derived foods in chronic disease prevention [2,3]. Flavonoids exert their health-promoting effects through several mechanisms, primarily by acting as powerful antioxidants and enzyme inhibitors. Almost all flavonoids have the capacity to act as antioxidants. They protect the body's cells and tissues from damage caused by free radicals and reactive oxygen species (ROS), which are produced during normal metabolism. Flavonoids can directly scavenge free radicals. Due to the high reactivity of their hydroxyl groups, they can react with a radical, making it more stable and less reactive, thereby neutralizing the threat. This action helps prevent cellular membrane damage and inhibit LDL (bad cholesterol) oxidation, which is a key factor in atherosclerosis. Flavonoids can inhibit xanthine oxidase (XO), an enzyme that produces superoxide free radicals. By inhibiting XO, flavonoids like quercetin and luteolin reduce oxidative injury to tissues. Flavonoids are known to be potent inhibitors of several key cellular enzymes. They possess anti-inflammatory action. Inflammation is often driven by the enzyme cyclo-oxygenase (COX), which exists in two forms. COX-2 is induced during an inflammatory response, while COX-1 helps maintain the gastric lining. Some flavonoids have been found to act as preferential inhibitors of COX-2, allowing them to reduce inflammation with fewer gastrointestinal side effects. Flavonoids have neuroprotective effects. In neurodegenerative diseases like Alzheimer's, a key therapeutic strategy is to inhibit the enzyme acetylcholinesterase (AChE). Studies have shown that flavonoids such as quercetin and macluraxanthone can effectively inhibit AChE in a concentration-dependent manner. A diet rich in flavonoids is associated with a reduced risk of cardiovascular disease. They help improve vascular health by enhancing endothelial function. Many flavonoids have been identified with antifungal, antiviral, and antibacterial properties, making them valuable in food safety and nutrition. Flavonoids are known to have anti-carcinogenic properties, partly because they can induce apoptosis (programmed cell death) in cancer cells and regulate carcinogen metabolism.

Oxidative stress and chronic inflammation are recognized as key contributors to the development of conditions such as obesity, cancer, and neurodegenerative disorders [4,5]. Flavonoids, due to their pronounced antioxidative and anti-inflammatory effects, are gaining recognition as promising agents in the therapeutic management of these diseases [6]. Multiple mechanisms underpin the actions of flavonoids, affecting tissues and cells as diverse as skeletal muscle, liver, pancreas, adipocytes, immune system elements, and neural cells within the brain, all of which are relevant to the etiology of these chronic health problems [7]. Compelling studies illustrate the impact of specific flavonoids: apigenin, a flavone sourced from chamomile tea and celery, exhibits significant anti-adipogenic properties that confer protection against obesity. Genistein—the primary isoflavone found in soy—has demonstrated both antioxidative and neuroprotective activities in a variety of experimental models. Epidemiological data further suggest an inverse association between circulating isoflavone levels and the risk of certain cancers, including breast cancer in women and prostate cancer. While earlier reviews have predominantly summarized the broad effects and mechanisms by which flavonoids influence disease pathways, this article aims to synthesize and critically assess the most recent and innovative advances in flavonoid research. Special emphasis is placed on elucidating molecular mechanisms, as well as evaluating how the dosage and duration of flavonoid supplementation modulate their efficacy in the prevention and adjunctive management of obesity, cancer, and neurodegenerative conditions. While the evidence for the health benefits of flavonoids is strong, many studies have been conducted in vitro (in a lab setting) or in silico (via computer simulation). There is a clear need for more in vivo studies to confirm these effects in living organisms. Key challenges for future research include the heterogeneity of flavonoid structures and the lack of comprehensive data on their bioavailability—how well they are absorbed and used by the body. Furthermore, data on the long-term consequences of chronic flavonoid intake is still scarce, making it too early to form specific dietary recommendations beyond advising a diet rich in fruits and vegetables [1].

The primary aim of this review is to deliver a multidirectional and integrative synthesis of contemporary scientific evidence elucidating the role of dietary flavonoids in the prevention and adjunctive management of obesity, cancer, and neurodegenerative disorders. Moving beyond a simple catalog of biological effects, this work is distinguished by its mechanism-driven framework, which critically analyzes how flavonoids modulate core cellular signaling networks to link their molecular actions directly to therapeutic outcomes. A key objective is to bridge the gap between foundational science and clinical application. This is achieved by first establishing the chemical diversity and structure-activity relationships of flavonoids, then critically evaluating the significant translational barrier of bioavailability, and finally exploring innovative solutions like nanocarriers and structural modifications. By synthesizing evidence across three distinct yet interconnected chronic diseases, this review uniquely highlights the multi-target nature of flavonoids, revealing the shared molecular pathways that position them as versatile and powerful agents for promoting human health in the context of modern medicine.

2. Methodology

2.1. Data Retrieval Strategy

A comprehensive literature search was performed using primary academic databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search utilized combinations of keywords and Medical Subject Headings (MeSH) related to flavonoids (e.g., "flavonoids," "polyphenols," "bioflavonoids"), biological activities ("antioxidant," "anti-inflammatory," "antimicrobial," "anticancer," "neuroprotective," "anti-obesity," "cardioprotective"), mechanisms ("PI3K/Akt/mTOR," "NF-κB," "AMPK," "apoptosis," "autophagy"), and clinical or preclinical models ("in vitro," "in vivo," "clinical trial," "epidemiology").

This review is based exclusively on published and publicly available sources, which are comprehensively cited within the references. All data analyzed are accessible through the cited literature. No new experimental data or proprietary datasets were generated for this work. The time frame of the publications used spans from 2000 to 2025 but a significant majority of the references are from the last decade (2015–2025). This aligns with the stated methodology of prioritizing recent, high-impact publications to capture the most current scientific advances.

All study types relevant to the biological activities of dietary flavonoids were considered, including original research articles (in vitro, in vivo, and clinical studies), meta-analyses and systematic reviews. Inclusion required that studies present original data or comprehensive analyses on the structural, mechanistic, or clinical aspects of flavonoids related to chronic disease prevention, signaling pathways, or bioavailability.

Publications focusing solely on synthetic derivatives without biological testing, non-peer-reviewed communications, case reports, and conference abstracts without sufficient methodological detail were excluded to ensure scientific rigor.

2.2. Data Extraction and Synthesis

Eligible records were screened by title, abstract, and full text. Relevant details—including flavonoid class, source, molecular structure, model/system used, dosage, duration, primary endpoints, mechanistic findings, and clinical correlations—were systematically extracted and summarized. Special attention was given to high-quality recent studies elucidating molecular mechanisms (particularly PI3K/Akt/mTOR, NF-κB, AMPK, and related regulatory networks) and to robust epidemiological data linking flavonoid intake with disease risk or outcomes. The synthesis was qualitative, focusing on the mapping and critical analysis of emerging patterns, controversies, and knowledge gaps, and highlighting translational opportunities and unresolved barriers, such as bioavailability and interindividual variability. Representative data were tabulated for clarity.

2.3. Data Classification and Prioritization Strategy

The retrieved literature was systematically classified and prioritized. Our synthesis prioritized recent, high-impact publications, with a strong emphasis on studies that elucidated molecular mechanisms, followed by robust clinical and epidemiological evidence. To construct a rigorous and impactful synthesis, the retrieved literature was systematically organized using a multi-tiered classification and prioritization strategy designed to emphasize scientific recency, methodological quality, and mechanistic depth. Primary emphasis was placed on high-impact publications from the last five to seven years to ensure the review captures the latest scientific advances. This temporal filter was complemented by a focus on studies published in reputable, peer-reviewed journals, characterized by robust experimental design and significant contributions to the field. Following this initial filtering, the selected articles were prioritized according to a clear evidence-based hierarchy. In line with this review's core objective, the highest priority was given to mechanistic studies. This included in vitro and in vivo research that clearly elucidated the molecular mechanisms of flavonoid action, particularly those investigating the direct modulation of key signaling pathways like PI3K/Akt/mTOR, NF-κB, and AMPK, as these provide the foundational evidence for how flavonoids exert their biological effects. The next tier of priority comprised clinical trials, systematic reviews, and meta-analyses due to their direct translational relevance in evaluating the efficacy of flavonoids in human populations. Subsequently, epidemiological and robust preclinical evidence was prioritized to provide real-world correlational data and essential physiological context that bridges cellular mechanisms with human clinical outcomes. Finally, foundational and highly cited review articles were utilized to establish the broader scientific context for flavonoid chemistry, classification, and general biological properties.

2.4. Data Quality Assurance

To enhance validity and objectivity, source identification, screening, and data extraction were independently performed by the authors of this review. Disagreements were resolved by joint review and consensus. Seminal literature and controversial findings were cross-checked with multiple sources to ensure balanced interpretation.

3. Flavonoids-Chemistry, Biological Properties and Role in the Prevention of Diseases

3.1. Classification of Flavonoids

Naturally occurring molecules from medicinal plants, particularly flavonoids, are gaining prominence for their broad pharmacological effects and favorable safety profiles. These bioactive flavonoids are synthesized via the phenylpropanoid pathway and ubiquitously occur in the plant kingdom, contributing critically to the regulation of plant physiological functions and development. Flavonoids are present as glycosidic ligands, methylated ethers, or aglycone forms, reflecting their adaptive diversity as secondary metabolites shaped through long-term natural selection [2,3]. They are widely distributed across roots, stems, leaves, flowers, and fruits of higher plants. Given their presence in nature and their valuable role in potentially treating both infectious and non-communicable diseases, flavonoids remain a focus of intense research as promising molecular candidates for innovative drug development. The mounting awareness of health-related concerns has driven an increased demand for flavonoids within both the healthcare and medical sectors, ensuring that these compounds continue to be a major focus in research on natural bioactive molecules.

To date, the scientific community has characterized an immense diversity of over 10,000 distinct flavonoid compounds [8]. These vital secondary metabolites are ubiquitously present in the plant kingdom, with notable concentrations in fruits, vegetables, herbs, cereals, flowers, and seeds [9]. The broad range of health benefits associated with flavonoids is largely credited to their well-established biological activities, including anti-oxidative, anti-inflammatory, anti-mutagenic, and anti-carcinogenic actions, in addition to their capacity for modulating critical cellular enzymes [1]. Such properties confer beneficial biochemical and antioxidant effects that show therapeutic potential against numerous pathologies, including cancer, neurodegenerative disorders, and cardiovascular disease [10]. Consequently, due to this wide spectrum of health-promoting effects, flavonoids have become essential components in a multitude of pharmaceutical, nutraceutical, cosmetic, and medicinal formulations.

Based on variations in their chemical structure, such as the degree of unsaturation and the oxidation of their carbon ring, flavonoids are categorized into several classes, including flavones, flavanones, isoflavones, flavonols, chalcones, flavanols, and anthocyanins; all of these types are ubiquitously distributed in nature [11]. In plants, these compounds typically accumulate in the flowers, fruits, leaves, and seeds, where they are responsible for the plant's characteristic color, fragrance, and flavor profiles [12]. Functioning as important secondary metabolites, plant flavonoids are involved in diverse physiological processes, from regulating auxin transport and ensuring male fertility to aiding in pollination, seed development, flower coloring, and allelopathy [13]. Furthermore, flavonoids have protective functions against both abiotic stressors—such as ultraviolet radiation, cold, salt, drought, and heavy metals—and biotic threats, including herbivores, bacteria, and fungi [14]. The biological significance of these compounds is extensive, as flavonoids exhibit a variety of activities in plants, animals, and bacteria [15]. Chemically, all flavonoids are synthesized via the phenylpropanoid metabolic pathway and are defined by a 15-carbon skeleton arranged into a three-ring (C6-C3-C6) structure, labeled A, B, and C [16]. Based on structural variations in their core skeleton, flavonoids are categorized into seven distinct subclasses: flavones, flavanones, isoflavones, flavonols, chalcones, flavanols, and anthocyanins [17] (Figure 1). Within the plant cell, these compounds predominantly accumulate in the vacuoles, where they are typically present as either C-glycosides or O-glycosides [18].

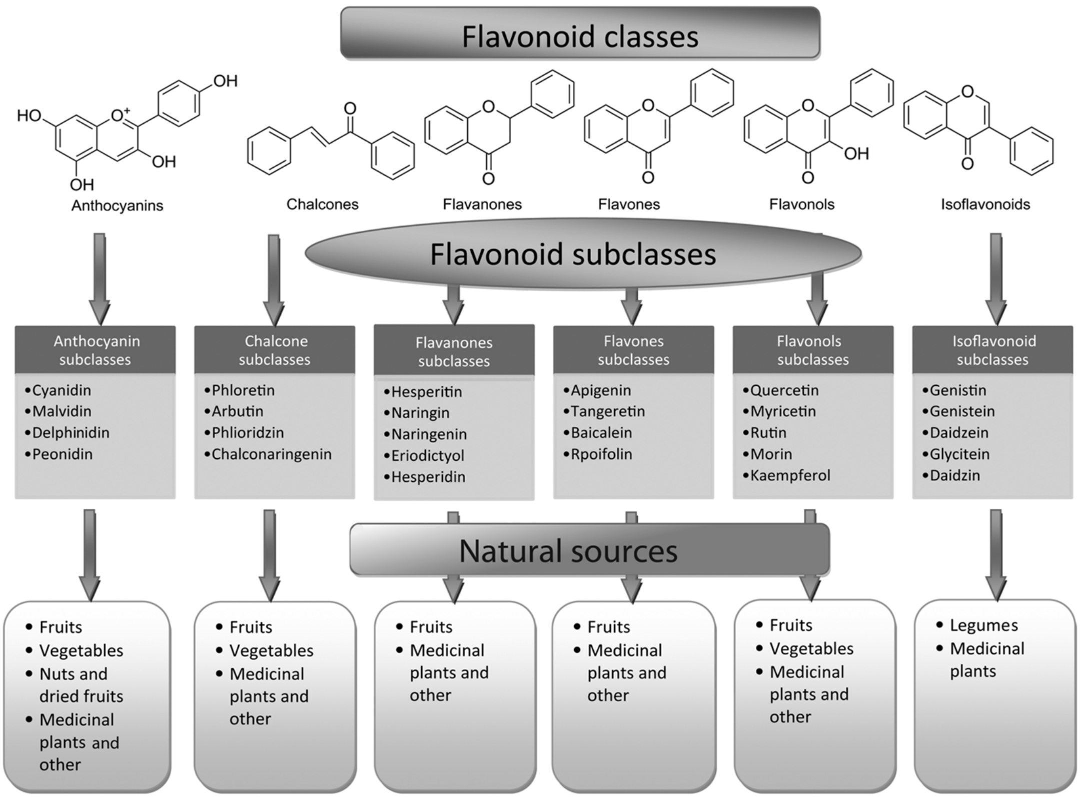

Figure 1. Flavonoid classes, subclasses and their natural sources [1].

3.1.1. Flavones

Apigenin and luteolin are two of the most common examples of flavones, which make up one of the largest subclasses of flavonoids. Apigenin, in particular, shows significant therapeutic potential. It is known to scavenge free radicals, help regulate antioxidant enzyme activity in pancreatic cells, and can lessen inflammation in conditions like cancer, neuroinflammation, and cardiovascular disease [19]. In nature, you will typically find apigenin in a glycosylated state. This means a sugar molecule is attached to its core structure, either through a hydroxyl group (O-glycosides) or directly to a carbon atom (C-glycosides) [20]. Its main natural derivatives include the glycosides apiin, vitexin, isovitexin, and rhoifolin. More broadly, flavones are abundant in many plants and herbs—like celery, parsley, red pepper, chamomile, mint, and ginkgo—where they usually occur as 7-O-glycosides [9,21]. The chemical backbone that defines all flavones is a 4H-chromen-4-one structure that has a phenyl substituent attached at the second position.

3.1.2. Flavanones

Flavanones are found almost exclusively in citrus fruits, including oranges, lemons, mandarins, grapefruits, clementines, and limes [22]. The primary dietary flavanones, naringenin and hesperetin, are particularly abundant in this group of fruits [22,23]. These compounds exhibit notable biological activities. For example, naringin has been shown to increase the activity of antioxidant enzymes and to enhance the immune system. Furthermore, both naringenin and hesperetin have demonstrated the ability to recover impaired thyroid function in rat models. Depending on their specific structural differences, other examples of flavanones include hesperidin, pinocembrin, likvirtin, and eriodictyol [24]. The unique chemical identity of flavanones, also known as dihydro-flavones, is determined by a saturated C-ring. The saturation of the double bond between positions 2 and 3 in this C-ring represents the sole structural feature that distinguishes flavanones from other classes of flavonoids [25]. A defining characteristic of their structure is a disaccharide moiety linked to the seventh position of the aglycone [26]. They also typically possess hydroxyl groups at positions 5 and 7 on the A-ring and feature hydroxyl or methoxy substituents at the C3 or C4 positions of the B-ring [27].

3.1.3. Isoflavones

A significant characteristic of isoflavones is their function as phytoestrogens; these plant-derived compounds exhibit potent estrogenic activity. The molecular structure of isoflavones shares a remarkable similarity with animal estrogens, particularly the human hormone 17-β-estradiol, which enables them to bind to estrogen receptors [28]. In addition to this hormonal activity, isoflavones possess strong antioxidant properties that may reduce the risk of certain cancers by inhibiting free radical-induced DNA damage. Isoflavones are generally classified into three primary groups: genistein, daidzein, and glycitein. The sole chemical feature that distinguishes this subclass from other flavonoids is the attachment point of the B-ring; for isoflavones, it is connected at the C3 position of the heterocyclic C-ring, as opposed to the C2 position typical for other flavonoids [29]. These compounds are characteristic metabolites of leguminous plants and are essential for processes such as microbial signaling and nodule induction in legumes [30].

3.1.4. Flavonols

Four principal types of flavonols—namely quercetin, galangin, kaempferol, and myricetin—are widely distributed in various vegetables and fruits, such as asparagus, onions, lettuce, broccoli, tomato, and apples [31]. These compounds exhibit a diverse range of significant biological activities, including antioxidant, antibacterial, cardioprotective, anticancer, and antiviral properties. Notably, dietary intake of flavonols has been correlated with a significantly reduced risk of gastric cancer, particularly in female and smoking populations. Chemically, flavonols are also referred to as 3-hydroxy flavones and can be identified by specific substitutions on their A- and B-rings, which are connected by a three-carbon chain [32]. A common structural feature of flavonols is the presence of hydroxyl groups at positions 5 and 7 of the A-ring. In plants, these compounds are primarily concentrated in epidermal cells, where they function to protect DNA against damage induced by UV radiation [33].

3.1.5. Chalcones

Chalcones function as biosynthetic precursors to other flavonoids and isoflavonoids. Chemically, they are defined as open-chain flavonoids, formally named 1,3-diaryl-2-propen-1-ones, and are characterized by a structure that can carry up to three modified or unmodified C5, C10, or C15 prenyl moieties on both their A and B-rings. These bioactive products are widely distributed in plant families such as Fabaceae, Moraceae, Zingiberaceae, and Cannabaceae. This class of compounds exhibits a wide spectrum of pharmacological effects, including antioxidant, antibacterial, anthelmintic, antiulcer, antiviral, antiprotozoal, and anticancer activities [34]. Due to their prominent bioactivity and the relative ease with which their structural features can be constructed from simple aromatic compounds, chalcones have inspired extensive research. This has led to the synthesis of numerous chalcone analogs and structurally modified natural chalcones, forming a large collection of bioactive derivatives [34]. Xanthohumol and isbavirachalone are two representative derivatives that exhibit abundant biological and pharmacological activity [35]. The bioactivity of flavonoids is largely determined by the number and position of hydroxyl (-OH) groups on their benzene rings. For instance, the most effective radical scavengers are flavonoids possessing the 3′,4′-dihydroxy substitution pattern on the B-ring and/or a hydroxyl group at the C-3 position. The presence of a 3-OH group, in particular, significantly enhances bioactivity. Notably, the C2=C3 double bond is not a prerequisite for high activity, as demonstrated by certain flavanols that lack this bond yet still display strong activity.

3.1.6. Flavanols

A flavanol-rich diet can facilitate the permanent improvement of endothelial function and may prevent the development of cardiovascular diseases [36,37]. Flavanols can also protect blood vessels from tobacco-induced damage by increasing the content of nitric oxide (NO). A variety of these compounds, including catechin, gallocatechin, epicatechin, and their gallate derivatives (e.g., catechin 3-gallate and epicatechin 3-gallate), are widely distributed in many fruits, such as apples, bananas, pears, and blueberries [38]. Chemically, flavanols, also called catechins or flavan-3-ols, are defined by two primary structural characteristics. They lack a double bond between positions 2 and 3 in the C-ring. Additionally, they are characterized by a hydroxyl group at position 3 of the C-ring [39].

3.1.7. Anthocyanins

Anthocyanins are a group of soluble vacuolar pigments, classified as glycosylated polyphenolic compounds, which are responsible for a range of colors in plants—from orange, red, and purple to blue. The expressed color is dependent on the pH of the microenvironment within flowers, seeds, fruits, and vegetative tissues [40]. Consequently, anthocyanins are commonly utilized as natural food colorants. In human health, anthocyanins play important roles, including contributing to visual acuity, cholesterol decomposition, and a reduced risk of cardiovascular disease [41]. These compounds are mainly found in the outer cell layer of various fruits and vegetables, such as blackcurrants, grapes, and berries [42]. The structural diversity of anthocyanins is extensive, with over 650 distinct types identified in plants [43]. This variety arises from the position and number of hydroxyl and methoxyl groups present as substituents on the core flavylium structure. These compounds are grouped into five primary classes—cyanidin, delphinidin, malvidin, pelargonidin, and peonidin—and their corresponding derivatives [44]. The antioxidant capacity of anthocyanins is associated with their ring orientation and the position and number of free hydroxyl groups surrounding the pyrone ring.

3.2. The Biological Activities and Therapeutic Potential of Flavonoids

3.2.1. Antioxidant Mechanisms of Flavonoids

The antioxidant capacity of flavonoids is fundamentally dependent on their chemical structure, particularly the number and position of hydroxyl groups, which determines their stability and function in different matrices [45,46]. Specific structural motifs, such as the orthodihydroxy configuration on the B-ring, enhance this activity by enabling electron delocalization within flavonoid phenoxyl radicals (Figure 2). This effect is further promoted by features such as double bonds in the phenolic ring, hydroxyl side chains, and the glycosylation of anthocyanidins [13]. Moreover, the polymerization of flavonoid monomers, as seen in proanthocyanidins, can increase antioxidant capacity due to a greater number of available hydroxyl groups [47]. Flavonoids exert their antioxidant effects through several molecular mechanisms. One of the primary pathways is the direct scavenging of reactive oxygen species (ROS). Another direct mechanism is metal-chelating activity, which can reduce the toxicity of redox-active transition metal ions [48]. The capacity of hydroxyflavones to chelate metal cations varies significantly based on the number and position of their hydroxyl substituents [49]. For instance, quercetin, catechin, and rutin have demonstrated high antioxidant activity against Fe(III) [50], while kaempferol can chelate Cu(II) ions to suppress the formation of oxidants and radicals [51].

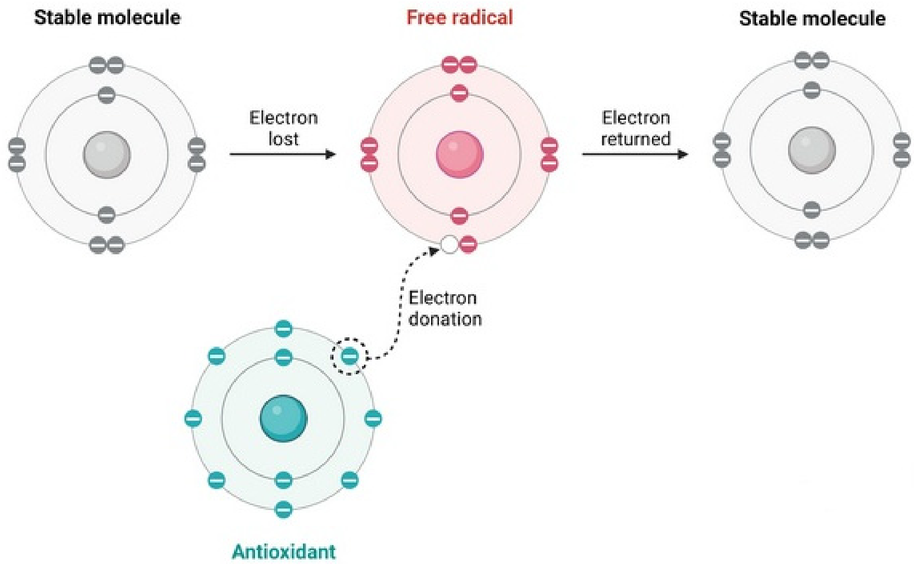

Figure 2. Antioxidant Mechanism of Flavonoids (created with BioRender.com).

The structural basis for this activity often involves the formation of stable complexes between the flavonoid's carbonyl moiety and its hydroxyl groups. Quercetin possesses three potential bidentate binding sites for creating stable metallic complexes, and catechin is capable of chelating a wide array of metal ions, including Mn(VI), Fe(II), Fe(III), Cu(II), Zn(II), and Al(III) [52]. In addition to direct actions, flavonoids modulate enzymatic activity. They can inhibit pro-oxidant enzymes, thereby reducing the production of free radicals. For example, they inhibit the activity of oxidases such as xanthine oxidase (XO) and protein kinase C, both of which catalyze the production of superoxide anions. Fisetin, for example, has been reported to reduce oxidative damage by inhibiting XO activity [53].

Other enzymes inhibited by flavonoids include cyclooxygenase, NADH oxidase, microsomal monooxygenase, and lipoxygenase [14]. Conversely, flavonoids can activate defensive antioxidant enzymes. This includes the induction of phase II detoxifying enzymes such as NAD(P)H-quinone oxidoreductase, glutathione S-transferase, and UDP-glucuronosyltransferase, which are critical for defense against electrophilic toxicants and oxidative stress. This activation can occur via the electrophile-responsive element (EpRE), as flavonoids have been shown to activate EpRE-mediated gene expression. Flavonoids also interact with specific biological systems to mitigate oxidative stress. In the context of the free radical-driven lipid peroxidation of low-density lipoprotein (LDL), a process associated with human health [54], flavonoids can play a protective role by acting as hydrogen donors to α-tocopherol radicals.

Several flavonoids, including quercetin, epigallocatechin gallate, and naringin, have shown strong inhibitory activity against LDL oxidation in vitro [55]. Finally, flavonoids can mitigate oxidative stress resulting from nitric oxide (NO). Although NO is crucial for vasodilation, its loss can cause oxidative stress in the vasculature [56]. The interaction of NO with O_2 can form the potent oxidant peroxynitrite, which causes pathological damage. Flavonoids can counteract this by inhibiting the production of NO in certain lipopolysaccharide-activated cells through the inhibition of inducible NOS expression [57]. Some flavonoids can also suppress the activities of other free radical-generating enzymes such as nitric-oxide synthase [58].

3.2.2. The Role of Flavonoids in the Inhibition of Inflammation

Inflammation, which can be caused by infections, injuries, and various diseases, is a critical physiological response [59]. However, chronic inflammation represents a common pathological basis for a range of age-associated diseases, including cardiovascular disease, diabetes, cancer, and Alzheimer's disease, highlighting the need for effective anti-inflammatory agents [60]. Flavonoids, a class of natural polyphenolic compounds, have demonstrated significant potential in modulating inflammatory pathways. Flavonoids exert their anti-inflammatory effects through a variety of molecular mechanisms, primarily involving the inhibition of pro-inflammatory mediators, the regulation of cytokines and adhesion molecules, and the reduction in immune cell infiltration (Figure 3).

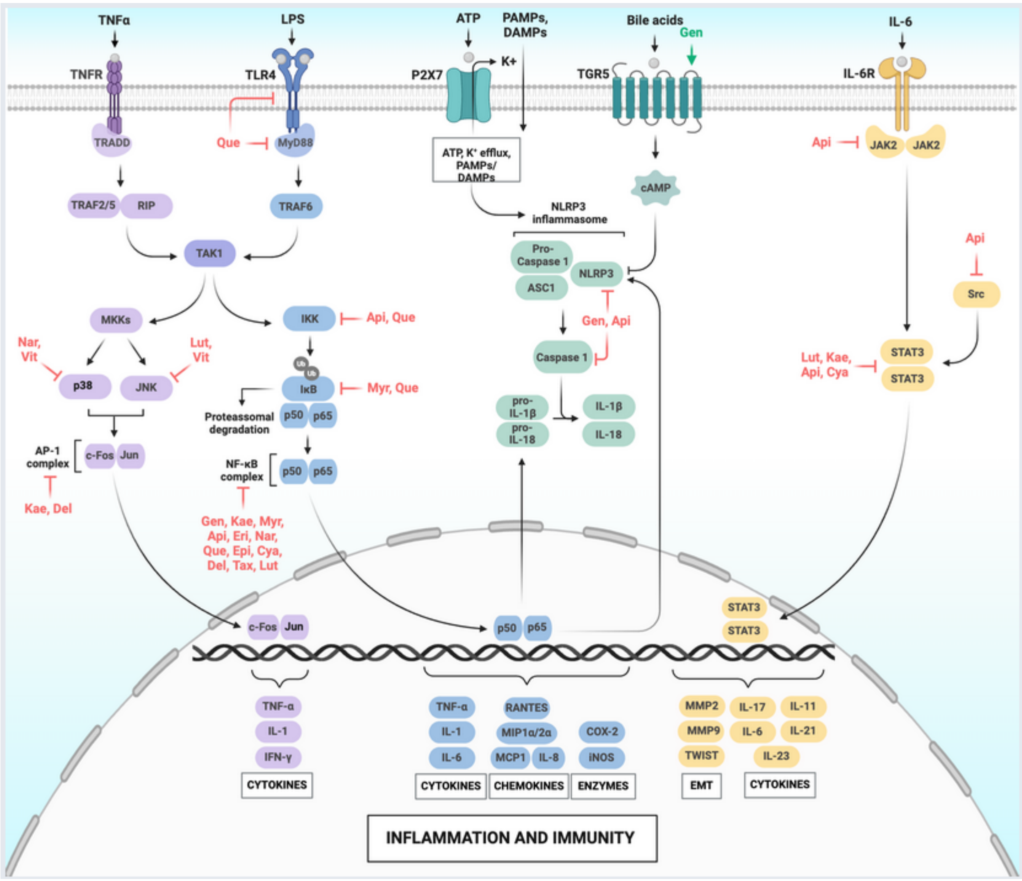

Figure 3. Flavonoid modulation of inflammation and immunity pathways in cancer (created with BioRender.com).

A key mechanism of flavonoid action is the suppression of the arachidonic acid pathway. Many flavonoids can decrease the production of arachidonic acid and inhibit the activities of crucial enzymes such as phospholipase A_2, cyclooxygenase (COX), and nitric oxide synthase (NOS). This inhibition leads to a subsequent decrease in the production of key inflammatory substances, including prostaglandins, leukotrienes, and nitric oxide (NO) [61]. Specific examples of this enzymatic inhibition are well-documented. Several flavonols, such as morin, quercetin, kaempferol, and myricetin, have been shown to inhibit the activity of lipoxygenase [62]. In a rat model of colitis, diosmin and hesperidin were found to inhibit leukotriene B4 (LTB4) biosynthesis, which contributed to a reduction in colitis [63]. Furthermore, flavonoids from Tartary buckwheat sprout (vitexin, orientin, and rutin) were observed to reduce NO production by inhibiting the expression of iNOS and COX-2 in both lipopolysaccharide (LPS)-induced RAW cells and in male BALB/c mice [64].

Flavonoids are potent modulators of inflammatory cytokines. Many have been shown to reduce the expression of pro-inflammatory cytokines, including TNF-α, IL-1β, IL-8, IL-6, and monocyte chemoattractant protein-1 (MCP-1), in various immune cell types such as Jurkat T cells, peripheral blood mononuclear cells, and RAW macrophages. Specific flavonoids like quercetin and catechins were found to increase the production of the anti-inflammatory cytokine IL-10 through the combined inhibition of TNF-α and IL-1β. Similarly, naringenin and several chalcones (e.g., trans-chalcone, hesperidin, and methyl chalcone) have demonstrated inhibitory activity against pro-inflammatory cytokines [65]. In addition to cytokine modulation, flavonoids can affect the expression of cellular adhesion molecules. Apigenin, for instance, can reduce the steady-state mRNA levels induced by TNF-α and downregulate the expression of intercellular adhesion molecule-1 (ICAM-1), E-selectin, and vascular cell adhesion molecule-1 (VCAM-1) on endothelial cells. By inhibiting the production of arachidonic acid metabolites and chemokines, flavonoids can effectively decrease leukocyte infiltration and edema [66]. This effect has been specifically reported for naringenin, which displayed anti-inflammatory activity by reducing leukocyte infiltration. Other anti-inflammatory mechanisms attributed to flavonoids include the chelation of metal ions and the suppression of complement system activation [67]. Additionally, quercetin has been shown to suppress the activity of heat shock factor (HSF), thereby reducing heat-induced cellular damage [68].

The therapeutic potential of flavonoids has been validated in several experimental models of inflammatory diseases. Genistein demonstrated efficacy in a guinea pig model of asthma by reducing airway hyper-responsiveness, ovalbumin-induced bronchoconstriction, and pulmonary eosinophilia. It also suppressed the inflammatory response and joint destruction in a model of collagen-induced arthritis in mice. In a general experimental model of chronic inflammation, quercetin, rutin, and hesperidin were shown to decrease inflammation, with results indicating that rutin played a particularly key role in the chronic phase [69]. Furthermore, in the context of cellular protection, quercetin and myricetin were found to protect 661W cells, a cone photoreceptor cell line, from the toxic effects of H_2O_2. These flavonoids also enhanced the gene expression of M and S opsins under conditions of oxidative stress, suggesting a protective role in retinal cells [70].

3.2.3. Flavonoids as Inhibitors of Bacterial and Fungal Pathogens

Flavonoids have been extensively studied for their antimicrobial properties and are considered promising candidates for the development of efficient, economical, and safe drugs to inhibit bacterial and fungal infections in humans [71]. The antimicrobial efficacy of flavonoids is attributed to a variety of mechanisms, including the disruption of microbial membranes, inhibition of essential biosynthetic pathways, and interference with cellular transport and energy production [72,73]. The broad-spectrum activity of these compounds has been demonstrated in numerous studies. For example, flavonoid extracts from *Coriolus versicolor* exhibited strong antibacterial effects against *Escherichia coli*, *Staphylococcus aureus*, and *Bacillus subtilis* [74]. Similarly, specific flavonoids show potent activity against a range of pathogens. Flavonoids isolated from licorice, such as glabrol and licochalcones A, C, and E, have shown high efficiency against methicillin-resistant *S. aureus* (MRSA) while displaying low cytotoxicity to mammalian cells. In the context of antifungal action, baicalein has demonstrated strong activity against *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Aspergillus fumigatus*, and *Candida albicans*, while wogonin was found to inhibit all these fungi except for *C. albicans*.

A primary target for the antimicrobial action of flavonoids is the cellular envelope, encompassing both the cell membrane and, in fungi, the cell wall. Flavonoids can exert their antibacterial and antifungal effects through the disruption of the plasma membrane [75]. For Gram-positive bacteria, the cell membrane is a principal site of action, where flavonoids can induce damage to phospholipid bilayers [72]. A specific example is glabrol, which exerts its bactericidal effect by increasing the permeability of the cell membrane and collapsing the proton motive force.

In fungi, flavonoids can also inhibit the generation of the cell wall [76]. Glabridin, for instance, has been shown to inhibit the biosynthesis of essential fungal cell wall components, namely β-glucans and chitin [77].

Flavonoids can interfere with critical biosynthetic processes in both bacteria and fungi, including the synthesis of nucleic acids, proteins, and ATP [8,14]. In bacteria, flavonoids have been shown to suppress the biosynthesis of nucleic acids and ATP, as well as disrupt electron transport [73]. Specific compounds such as quercetin, myricetin, baicalein, and luteolin have been found to suppress DNA replication in bacteria [78], while epigallocatechin gallate and baicalein have been shown to inhibit the biosynthesis of ATP [77]. The inhibition of the respiratory chain is another related mechanism observed in Gram-positive bacteria [72]. Similar inhibitory effects are observed in fungi, where flavonoids can suppress cell division and the biosynthesis of RNA and proteins [79]. Myricetin, quercetin, kaempferol, naringenin, genistein, and luteolin have all been reported to suppress the synthesis of DNA, RNA, and protein in fungal cells, while apigenin has also been shown to control the fungal cell cycle [80].

The modulation of cellular stress responses and the induction of mitochondrial dysfunction are key aspects of the antifungal activity of flavonoids [81]. Some flavonoids, including those from *Glycyrrhiza glabra* (isoflavones and chalcones), induce bactericidal effects by regulating the expression of phosphatidylserine decarboxylase, which leads to a loss of mitochondrial membrane potential and subsequent cell membrane disruption [82]. The role of reactive oxygen species (ROS) in these mechanisms is complex. Some flavonoids, such as baicalein and apigenin, exert their antifungal effects by regulating ROS levels, decreasing lipid peroxidation, and preventing membrane disruption [83]. Similarly, quercetin can inhibit oxidative phosphorylation and suppress the production of ROS. In contrast, other flavonoids utilize an opposing strategy; baicalein and wogonin, extracted from *Scutellaria* roots, can induce apoptosis-like programmed cell death through the overproduction of ROS. Additionally, flavonoids can inhibit efflux-mediated pumping systems in fungi, preventing the extrusion of antimicrobial agents [79]. A significant mechanism of antibacterial action for many flavonoids is the inhibition of biofilm formation [73]. Several flavonoids have been identified as potent inhibitors of this process. Quercetin, apigenin, naringenin, chrysin, genistein, kaempferol, daidzin, and daidzein have all been found to effectively block the formation of bacterial biofilms [78].

3.2.4. Flavonoids as Potent Agents Against Viral Pathogens

Flavonoids have demonstrated notable antiviral activities across a range of experimental models, including in vitro, in vivo, and in silico studies [84]. The mechanisms underlying these effects are multifaceted. Flavonoids are known to be effective antivirals by interfering with multiple stages of the viral life cycle, such as blocking the replication, transcription, and translation of the viral genome [85]. Additionally, some flavonoids can attach to viral surface proteins, thereby inhibiting viral entry into host cells. They may also modulate the host immune system to reduce the overall viral load [86].

Specific flavonoids exhibit activity against a wide array of viruses. Apigenin, for instance, has shown broad-spectrum antiviral effects against both RNA and DNA viruses, including herpes simplex virus types 1 and 2, African swine fever virus, and hepatitis B and C viruses [87]. Similarly, kaempferol can inhibit the replication of HIV-1 in host cells and also prevent the entry of herpes simplex viruses 1 and 2. Other examples include baicalein, which can block the replication of the avian influenza H5N1 virus in humans [88], and luteolin, which inhibits HIV-1 reactivation. Genistein has also been shown to suppress HIV-1 infection in CD4+ T cells and macrophages [89].

3.2.5. The Role of Flavonoids in the Inhibition of Carcinogenesis

Epidemiological studies have indicated that a diet rich in flavonoids may decrease the risk of developing various human cancers, including breast, lung, colon, prostate, and pancreas tumors. The anticancer properties of flavonoids are often linked to their anti-inflammatory activity, which influences key processes such as carcinogen inactivation, antiproliferation, cell cycle arrest, apoptosis induction, and the inhibition of angiogenesis [90]. A multitude of flavonoid compounds isolated from medicinal plants—including quercetin, rutin, hesperetin, genistein, and cyanidin have been shown to exert genoprotective, cytotoxic, anti-proliferative, and/or proapoptotic actions in various tumor cell lines [90,91] (Table 1).

Table 1. Overview of Major Dietary Flavonoids: Groups, Core Properties, Mechanisms, and Natural Sources.

Flavonoid Name	Flavonoid Group	Key Properties	Mechanism of Action	Natural Source	Literature Source
Apigenin	Flavones	Antioxidant, anti-inflammatory, anti-cancer	ROS scavenging, enzyme regulation, cytokine modulation	Celery, parsley, chamomile, mint, red pepper, ginkgo	[1,19]
Luteolin	Flavones	Antioxidant, anti-inflammatory	ROS scavenging, enzyme inhibition, apoptosis induction	Celery, parsley, chamomile, mint, red pepper, ginkgo	[1,92]
Naringenin	Flavanones	Antioxidant, immune-enhancing, vasodilator, anti-inflammatory, anti-cancer	Antioxidant enzyme activation, inhibition of leukocyte infiltration, cell migration suppression	Citrus fruits (oranges, lemons, mandarins)	[22,23,93]
Hesperidin	Flavanones	Anti-inflammatory, anti-proliferative, vasoprotective	Inhibits leukotriene B4 biosynthesis, cell cycle regulation, inhibits inflammation	Citrus fruits	[63,94]
Hesperetin	Flavanones	Antioxidant, supports endothelial health	Antioxidant enzyme activation; thyroid function recovery	Citrus fruits	[22]
Genistein	Isoflavones	Phytoestrogen, antioxidant, anti-cancer, anti-inflammatory	Estrogen receptor binding, induction of apoptosis, cell cycle arrest	Leguminous plants (soybeans, beans)	[28,89,91]

Table 1. *Cont.*

Flavonoid Name	Flavonoid Group	Key Properties	Mechanism of Action	Natural Source	Literature Source
Daidzein	Isoflavones	Phytoestrogen, antioxidant	Estrogen receptor binding, DNA protection	Leguminous plants	[29]
Liquiritigenin	Isoflavones	Anticancer, pro-apoptotic	Increases p53/Bax, caspase activation, reduces Bcl-2	Licorice	[95]
Quercetin	Flavonols	Antioxidant, anti-inflammatory, antibacterial, anticancer, cardioprotective	ROS scavenging, metal chelation, cytokine modulation, cell cycle arrest, enzyme inhibition	Onions, apples, broccoli, lettuce, tomato, asparagus	[33,96]
Kaempferol	Flavonols	Antioxidant, anticancer, UV-protective	ROS scavenging, cell cycle arrest, DNA/RNA inhibition	Various vegetables/fruits, onions, apples	[31,97]
Myricetin	Flavonols	Antioxidant, anti-inflammatory, antibacterial	Lipoxygenase inhibition, cell cycle control, oxidative protection	Asparagus, onions, lettuce, apples, broccoli	[62,92]
Galangin	Flavonols	Antioxidant, antibacterial	Enzyme inhibition, ROS scavenging	Honey, propolis, Alpinia officinarum	[31]
Chalcone	Chalcones	Antioxidant, antibacterial, antiviral, anti-cancer	Radical scavenging, signaling modulation	Fabaceae, Moraceae, Zingiberaceae, Cannabaceae plants	[34]
Xanthohumol	Chalcones	Antioxidant, anti-inflammatory, anticancer, cardioprotective	Radical scavenging, signal pathway modulation, induction of apoptosis	Hops	[35,98]
Isbavirachalone	Chalcones	Anti-cancer	Radical scavenging, signal pathway modulation, induction of apoptosis	Hops and related species	[35]
Baicalein	Flavones *	Anti-inflammatory, antifungal, antiviral, anticancer	ROS regulation, apoptosis induction, DNA replication inhibition, ATP biosynthesis inhibition	*Scutellaria baicalensis*, other roots	[83,88]
Catechin	Flavanols	Potent antioxidant, antibacterial	NO modulation, ROS scavenging, metal chelation	Apples, bananas, pears, berries, tea	[38,39]
Epicatechin	Flavanols	Antioxidant, endothelial protection	NO content increase, ROS scavenging	Fruits (apples, berries), tea	[36,37]
Gallocatechin	Flavanols	Antioxidant, antibacterial	ROS scavenging, membrane action	Tea, cocoa, fruits	[38]

Table 1. *Cont.*

Flavonoid Name	Flavonoid Group	Key Properties	Mechanism of Action	Natural Source	Literature Source
Cyanidin	Anthocyanins	Antioxidant, anti-cancer, colorant, visual acuity	Free radical scavenging, apoptosis induction, colorant	Blackcurrant, grape, berries, red cabbage	[44,99]
Delphinidin	Anthocyanins	Antioxidant, colorant, cardioprotective	Free radical scavenging, apoptosis induction, colorant	Blackcurrant, grape, berries, red cabbage	[42,43]
Malvidin	Anthocyanins	Antioxidant, food colorant	Free radical scavenging, apoptosis induction, colorant	Grapes, berries	[44]
Pelargonidin	Anthocyanins	Antioxidant, colorant	Free radical scavenging, apoptosis induction, colorant	Red fruits, berries, vegetables	[44]
Peonidin	Anthocyanins	Antioxidant, colorant	Free radical scavenging, apoptosis induction, colorant	Blueberries, cranberries, red grapes	[43,44]

* Sometimes also classified as flavonone/chalcone-related.

A primary mechanism of flavonoid-mediated anticancer activity is the induction of cell cycle arrest and apoptosis. Several flavonoids cause growth arrest in cancer cells; for example, the isoflavone genistein promotes breast cancer cell arrest at the G2/M phase [91], an effect also observed with kaempferol in human breast cancer cells [97]. Hesperidin suppresses cell cycle progression in MG-63 human osteosarcoma cells [94], while epigallocatechin-3-gallate (ECGG) causes growth arrest in prostate cancer cells [100]. In vitro studies have shown that quercetin can cause cell cycle arrest and DNA damage in leukemia, colon, breast, and ovarian cancer cell lines [96]. This cell cycle arrest is often followed by the activation of apoptosis. Genistein induces ROS-dependent apoptosis [21], while liquiritigenin has been shown to promote apoptosis in HeLa cells by increasing p53 and Bax gene expression, decreasing Bcl-2 expression, releasing cytochrome c, and elevating caspase-9 and -3 activity [95]. Similarly, apigenin and luteolin induce apoptosis in several ovarian cancer cell lines through alterations in ROS signaling [92], and cyanidin induces apoptosis in human epithelial colorectal adenocarcinoma cells [99].

Flavonoids can effectively inhibit the proliferation and spread of tumor cells. Isorhamnetin and acacetin, for instance, suppress the proliferation of human breast cancer cells [99]. Naringenin inhibits the proliferation and migration of MG-63 human osteosarcoma cells by inhibiting ROS formation and improving the activity of antioxidant enzymes like SOD, CAT, and GSH [93]. Furthermore, resveratrol and procyanidins have been shown to synergistically inhibit the growth of breast cancer cells [101]. Flavonoids isolated from *Dimorphandra mollis* and *Croton betulaster* have been shown to inhibit the proliferation of human glioblastoma cells and concurrently reduce the expression of *VEGF* and *TGF-β1* genes [102].

A combination of resveratrol and grape seed proanthocyanidins significantly reduced the activities of DNMT and HDAC in breast cancer cell lines [103]. A range of flavonoids and related compounds, including EGCG, genistein, and resveratrol, exhibit cancer-preventive effects through the epigenetic regulation of tumor suppressor genes [104]. Furthermore, flavonoids can regulate non-coding microRNAs (miRNAs). They can alter miRNA levels by inhibiting oncogenic miRNAs, activating tumor-suppressive miRNAs, or affecting miRNA transcription and processing [105]. For example, a therapy combining SAHA and EGCG was found to significantly reduce the expression levels of miR-221/222 while increasing the expression of p27, ERα, and other tumor suppressor genes in carcinogenic cells [106].

3.2.6. Cardiovascular Effects of Flavonoids

The consumption of dietary flavonoids is associated with a markedly lower risk of death from cardiovascular causes in the population [107]. The cardioprotective capacity of these compounds stems from a variety of biological activities, including the ability to modulate oxidative stress and inflammation, promote vasodilation, and regulate the apoptosis of endothelial cells [108]. Several studies have highlighted the positive impact of flavonoids on vascular function and hemodynamics. Investigations in both in vitro and animal models have confirmed that certain flavonoids possess vasodilatory effects, which contribute to their capacity to lower blood pressure [109]. Specifically, compounds such as naringenin, quercetin, and hesperetin have been identified as having potent vasodilator properties, and further research has demonstrated that naringenin, in particular, can reduce high blood pressure by actively promoting vasodilation [110]. In addition to these effects, flavonoids have been shown to ameliorate endothelial dysfunction, improve insulin resistance, and exert protective effects against both platelet aggregation and atherosclerosis [109,111].

Flavonoids also exert significant influence over lipid metabolism and related metabolic disorders. They have been observed to prevent hepatic steatosis, dyslipidemia, and insulin sensitivity, achieving these effects primarily by inhibiting the synthesis of hepatic fatty acids while concurrently increasing their oxidation [111]. A notable example is the anthocyanin subclass, which has been shown to reduce the risk of myocardial infarction (MI) in humans. This benefit is linked to improvements in systolic blood pressure as well as reductions in the levels of triglycerides, total cholesterol, and low-density lipoprotein cholesterol [112]. Furthermore, specific flavonoids have been implicated in the prevention and management of distinct cardiovascular pathologies. For instance, isoflavones appear to shield against inflammatory vascular diseases by inhibiting the adhesion of monocytes to endothelial cells. Baicalin has been noted to improve cardiac dysfunction and inhibit apoptosis within the heart. Quercetin provides atheroprotective activity and also exerts cardioprotective effects against ischemia–reperfusion injury in cardiac tissue [113].

At the molecular level, the cardioprotective actions of flavonoids are linked to the modulation of key cellular signaling pathways. For example, xanthohumol confers protection against isoprenaline-induced myocardial hypertrophy and fibrosis in murine models by enhancing PTEN expression and inhibiting AKT/mTOR phosphorylation [98]. Similarly, flavonoids extracted from *Myrica rubra* have been found to mitigate oxidative damage and cardiomyocyte apoptosis by modulating the PI3K/Akt/GSK3β pathway [98]. Another critical target is the sirtuin 1 (SIRT1) enzyme, a key regulator of physiological functions whose reduced expression is often associated with age-related cardiovascular conditions like myocardial infarction, myocardial hypertrophy, and endothelial dysfunction. Long-term administration of the citrus flavonoid naringenin (NAR) to mice was shown to enhance SIRT1 expression. This upregulation was associated with a significant reduction in reactive oxygen species (ROS) in myocardial tissue and lower levels of the cardiovascular inflammatory markers TNF-α and IL-6, indicating that nutritional therapy with NAR may help to ameliorate myocardial aging and preserve cardiac function [114].

3.3. Flavonoid Absorption, Metabolism and Advanced Delivery Strategies

Flavonoids are a class of natural polyphenolic compounds with a wide range of beneficial biological activities, including antioxidant, antitumor, and anti-inflammatory effects. Despite their therapeutic promise, the clinical application of flavonoids is frequently hindered by their low bioavailability in vivo. This limitation arises from their structural characteristics, which lead to poor absorption, extensive metabolic breakdown, and rapid clearance from the body. Consequently, their bioactivity is largely dependent on overcoming these pharmacokinetic challenges [115]. To address this bottleneck, modern research has focused on two primary avenues: the development of advanced pharmaceutical formulations and the chemical modification of the flavonoid structure itself.

The physiological journey of flavonoids after oral ingestion is complex. Most of these compounds are consumed as glycosides, which must be processed before they can be effectively absorbed. This process begins in the small intestine, where flavonoid glycosides are either hydrolyzed by brush border enzymes into their more lipid-soluble aglycone forms for passive diffusion into epithelial cells, or transported directly by membrane carriers such as the sodium-dependent glucose transporter 1 (SGLT-1) [116,117]. Once inside the enterocytes, and subsequently in the liver, flavonoids undergo extensive Phase I and Phase II metabolism. These reactions, which include glucuronidation, sulfation, and methylation, are designed to increase the water solubility of the compounds to facilitate their excretion via urine and bile. This metabolic conversion is a key factor that limits the systemic concentration of active flavonoids. Flavonoids that are not absorbed in the small intestine continue to the colon. There, the gut microbiome plays a crucial role by cleaving their core pyranone rings and performing reactions like dehydroxylation and decarboxylation. This microbial processing breaks down the flavonoids into smaller metabolites, which can then be absorbed into circulation or excreted [118].

To protect flavonoids from degradation and enhance their systemic uptake, modern formulation techniques leveraging nanotechnology have been developed. These nanomedicine preparations are designed to improve the pharmacokinetic profile and therapeutic efficacy of the encapsulated compounds [119]. By formulating flavonoids into nanosuspensions, liposomes, solid lipid nanoparticles (SLNs), or micelles, their bioavailability can be markedly improved compared to the raw compounds [120]. These nanocarrier systems work by shielding the flavonoid from the harsh enzymatic and pH conditions of the digestive system, increasing their solubility, and facilitating their transport across the intestinal epithelium. For example, research has demonstrated that encapsulating flavonoids like luteolin and naringenin in lipid-based nanoparticles can significantly increase their systemic circulation time and overall bioavailability [121,122]. The use of such technologies allows for more efficient delivery, ensuring that a greater concentration of the active compound reaches its target sites within the body.

In addition to advanced formulations, direct chemical modification of the flavonoid skeleton is another powerful strategy to enhance its drug-like properties. These modifications aim to optimize the compound's solubility, stability, and permeability, thereby improving its absorption and distribution. Acetylation involves converting the hydroxyl groups on the flavonoid structure into acetamide groups. The addition of methylene and amide components increases the compound's lipophilicity, which in turn improves its ability to cross the lipid bilayer of cell membranes, leading to enhanced bioavailability [123,124]. Similarly to acetylation, esterification and acylation are used to increase the lipophilicity of flavonoids. By converting hydroxyl or carboxyl groups into esters with fatty acids or alcohols, the modified flavonoid gains a higher affinity for cell membranes. Studies have shown that baicalin ester derivatives exhibit significantly greater absorption efficiency than the parent molecule in cell models [125]. Likewise, acylated flavonoids have demonstrated superior pharmacological activity, as the modification facilitates easier absorption by cells [126]. Many flavonoids possess multiple active phenolic hydroxyl groups, which, while crucial for their bioactivity, are also primary targets for metabolic conjugation, leading to reduced bioavailability. The methyl etherification pathway converts these hydroxyl groups into more stable methyl ether derivatives. This modification can protect the flavonoid from rapid metabolism, thereby increasing its systemic exposure and efficacy [127]. The impact of adding sugar moieties (glycosylation) to a flavonoid aglycone is complex. While most flavonoid glycosides must be hydrolyzed before absorption, some studies have found that specific glycosylation patterns can actually increase bioavailability. For instance, quercetin glucoside has been observed to have a higher absorption efficiency than its aglycone form [128]. The effect of glycosylation ultimately depends on the type of sugar, the number of sugar units, and the nature of the glycosidic bond [129]. By employing these sophisticated nanocarrier systems and structural modification techniques, it is possible to overcome the inherent pharmacokinetic limitations of natural flavonoids, paving the way for their successful development as effective therapeutic agents.

3.4. Obesity Prevention with Flavonoids

According to the World Health Organization (WHO), obesity is defined as excessive or abnormal fat accumulation that impairs health. The prevalence of this complex condition—shaped by the interplay of diet, genetic predispositions, and behavioral patterns—has escalated worldwide, currently affecting over 1.9 billion individuals. A key pathological event involves hypertrophy of adipocytes, where surplus energy is stored as triglycerides, ultimately triggering both chronic low-grade inflammation and the development of insulin resistance [130]. It is well established that dietary patterns abundant in flavonoids are positively correlated with healthier body mass regulation and improved metabolic outcomes [131]. Beyond these epidemiological associations, experimental research has elucidated the multifaceted roles played by flavonoids in combating adipose tissue expansion through anti-adipogenic activity, promoting energy expenditure, and enhancing insulin sensitivity across various models (Table 2). In the following synthesis, we present a critical review of the evidence regarding how distinct flavonoids influence obesity onset and progression, with particular emphasis on established mechanisms, effective dosing and treatment duration, as well as their observable impacts on physiological and metabolic parameters.

Table 2. Summary of Flavonoid Actions in Experimental Obesity Models.

Flavonoid	Dose	Duration	Experimental Model	Observed Effect	Underlying Mechanism	Reference
Luteolin	0.01%	84 days	Mice (high-fat diet)	Promotes browning and thermogenesis	Activates AMPK/PGC1α pathway	[132]
Genistein	20 pM	12–42 days	Adipose-derived mesenchymal stem cells	Inhibits adipogenesis	Wnt/β-catenin signaling modulation	[133]
Daidzein	20 pM	12–24 days	Adipose-derived mesenchymal stem cells	Anti-adipogenic	Wnt/β-catenin signaling modulation	[133]
Fisetin	25 pM	0–2 days	3T3-L1 cells	Reduces adipocyte differentiation	SIRT1 upregulation, PPAR-γ downregulation	[134]
Apigenin	50 pM	2 days	3T3-L1 cells	Suppresses adipogenesis	Regulates adipogenic gene expression, affects cell cycle	[135]
Anthocyanins	50 pg/mL	1–3 days	3T3-L1 cells	Inhibits adipocyte formation	Downregulates PPAR-γ expression	[136]

Table 2. *Cont.*

Flavonoid	Dose	Duration	Experimental Model	Observed Effect	Underlying Mechanism	Reference
Flavan-3-ols	10 mg/kg BW	20 h	AR blocker-treated mice	Enhances energy expenditure	Stimulates sympathetic nerve activity	[137]
Epigallocatechin-3-gallate	0.2%	32 days	Mice (high-fat diet)	Increases thermogenesis and mitochondrial biogenesis	Promotes mitochondrial DNA replication and AMPK activation	[138]
Epigallocatechin-gallate	1.0%	4–7 days	Mice (high-fat diet)	Increases energy excretion, fat oxidation	Alters food digestibility, promotes fat oxidation	[139]
Genistein	1 mg/kg BW	45 days	Mice (high-fat, high-fructose diet)	Improves insulin sensitivity	Enhances IRS phosphorylateon, PI3K/Akt pathway	[140]
Myricetin	1 mg/kg BW	14 days	Mice (high-fructose diet)	Improves insulin resistance	Affects IR and IRS1 phosphorylation, activates PI3K/Akt, binds μ-opioid receptor	[141]
Hesperidin	0.2 g/kg BW	35 days	Mice (type 2 diabetes)	Stimulates glycogen synthesis	Increases glucose kinase (GK) activity	[142]
Naringin	0.2 g/kg BW	35 days	Mice (type 2 diabetes)	Inhibits gluconeo-genesis	Reduces PEPCK and G6P expression	[143]
Procyanidins	80 mg/kg BW	35 days	Mice (high-fat diet)	Reduces insulin resistance	Elevates GK and hepatic glycogen content	[144]

AMPK—AMP-activated protein kinase; PGC1α—peroxisome proliferator-activated receptor-gamma coactivator-1α; IRS—insulin receptor substrate; PI3K/Akt—phosphatidylinositol 3-kinase/protein kinase B; PPAR-γ—peroxisome proliferator-activated receptor-gamma; Wnt—wingless-type MMTV integration site family.

The foundational pathogenesis of obesity development is adipose hyperplasia. The process of adipogenesis, through which this occurs, involves two distinct stages of differentiation. The first is the determination stage, where multipotent mesenchymal stem cells (MSCs) are committed to the preadipocyte lineage. This is followed by a terminal differentiation stage, in which preadipocytes develop the characteristic metabolic features of mature adipocytes [144,145]. A substantial body of emerging evidence demonstrates that flavonoids can modulate adipogenesis via a variety of mechanisms. A primary strategy by which flavonoids exert anti-adipogenic effects is through the modulation of key transcription factors. Peroxisome proliferator-activated receptor-gamma (PPARγ), which is highly expressed in adipose tissue, is a central target involved in the anti-adipogenesis activity of flavonoids due to its critical role in regulating adipocyte differentiation [146]. For instance, fisetin can inhibit adipogenesis by suppressing the transcriptional activity of PPARγ through the activation of NAD+-dependent deacetylase SIRT1 [147,148]. Similarly, anthocyanins derived from black soybeans have been shown to inhibit the terminal differentiation of preadipocytes by reducing the expression of PPARγ [136,149].

Flavonoids also regulate adipogenesis by influencing major signaling pathways that control these master regulators. There is evidence that flavonoids such as isorhamnetin, genistein, and daidzein can regulate the differentiation potential of preadipocytes into mature adipocytes by acting on the wingless-type MMTV integration site family/canonical (Wnt/β-catenin) pathway [149]. In the crosstalk among these signaling molecules, the binding of Wnt to cell surface receptors triggers the transfer of β-catenin into the nucleus.

Within the nucleus, β-catenin interacts with transcription factors to suppress members of the CCAAT/enhancer-binding protein (C/EBP) family as well as PPARγ [150].

Other anti-adipogenic mechanisms of flavonoids involve processes such as cell-cycle arrest and the activation of central energy sensors like AMP-activated protein kinase (AMPK). Apigenin, a major flavone present in herbs, serves as a representative example, as it can arrest the cell cycle at the G0/G1 phase by lowering the expression of both cyclin D1 and CDK4 [151]. This same compound can also decrease adipogenic expression through the activation of the AMPK pathway [151]. The full scope of flavonoid action also includes the inhibition of mitotic clonal expansion, reduction of C/EBPα-GLUT4 signaling, and inhibition of mTOR signaling [152].

Numerous experimental studies have revealed that flavonoids can significantly improve insulin sensitivity by modulating signaling pathways associated with glucose and insulin. A primary mechanism involves the restoration of defective upstream insulin signaling cascades. For example, genistein has been shown to improve signaling in mice fed a high-fat-high-fructose diet by restoring both the phosphorylation of the insulin receptor substrate (IRS) and the PI3K/Akt pathway [153]. Myricetin, another common flavonoid, also enhances insulin sensitivity by directly restoring the phosphorylation of the insulin receptor (IR) and IRS1, or alternatively, through an indirect mechanism involving the binding of the μ-opioid receptor [154]. Flavonoids also exert powerful effects on hepatic glucose metabolism. In the livers of type-2 diabetic mice, for instance, naringin and hesperidin have been reported to inhibit gluconeogenesis by decreasing the mRNA levels of phosphoenolpyruvate carboxykinase (PEPCK) and glucose 6-phosphate (G6P) [142]. Concurrently, these compounds promote glycogen synthesis by increasing the expression of glucokinase (GK). Similarly, supplementation with grape seed-derived procyanidins, which are formed from catechin and epicatechin, improves insulin sensitivity by increasing the expression of GK and the concentration of hepatic glycogen in both mice and HepG2 cells [143].

Improving glucose uptake in peripheral tissues is another key strategy by which flavonoids enhance insulin sensitivity. For example, green tea extract, which is rich in various catechins, significantly improves this process by enhancing the function of glucose transporters. These therapeutic actions are crucial for counteracting insulin resistance, a pathological condition that drives metabolic abnormalities in obesity and diabetes. In this state, defective insulin signaling leads to the inhibition of the PI3K/Akt pathway and IRS phosphorylation [140]. This impairment, in turn, damages AMPK phosphorylation and the translocation of GLUT4 to the cell membrane, resulting in decreased glucose uptake in skeletal muscle and adipose tissue [154]. In the liver, the defective PI3K/Akt pathway dysregulates metabolism, promoting gluconeogenesis by upregulating PEPCK and G6P while simultaneously inhibiting glycogen synthesis through the suppression of GK and glycogen synthesis kinase (GSK). This pathology is often initiated in obese individuals, where adipose tissue releases increased amounts of hormones, glycerol, pro-inflammatory cytokines, and non-esterified fatty acids. The resulting insulin resistance can then create a vicious cycle, further contributing to obesity by decreasing glucose transport metabolism in peripheral tissues and increasing hepatic glucose production.

Flavonoids demonstrate several anti-obesity mechanisms, notably enhancing energy expenditure and facilitating adipose tissue remodeling. The conversion of white adipose to thermogenically active brown-like (beige) adipose tissue has been identified as an important factor in increased energy dissipation and reduced fat accumulation [155]. Numerous studies report that, in experimental obesity models, administration of flavonoids prevents body weight gain without affecting either food intake or nutrient absorption—an effect that strongly suggests the involvement of enhanced metabolic activity. One prominent molecular mechanism involves the activation of the AMPK/PPAR-γ pathway within the sympathetic nervous system, triggering browning and thermogenic gene expression in both brown and subcutaneous fat depots. In models utilizing high-fat-fed mice, luteolin has been shown to upregulate AMPK/PGC-1α signaling and drive the expression of thermogenic genes, resulting in increased metabolic rate and energy expenditure [137]. Flavan-3-ols, widely present in chocolate, promote sympathetic activity and adrenaline secretion, further enhancing AMPK and PGC-1α activity and, in turn, stimulating energy output. Mitochondrial biogenesis represents another crucial process governed by flavonoid intake. These compounds have been found to counteract the suppression of mitochondrial renewal frequently observed with obesity, thereby supporting robust thermogenic capacity in both adipose and muscle tissues. Epigallocatechin gallate (EGCG), for example, effectively reduces body weight in obese, high-fat-fed mice by promoting mitochondrial DNA replication and activating AMPK in brown adipose tissue, ultimately augmenting thermogenesis. In addition, both EGCG and other tea-derived catechins exhibit anti-obesity effects through the suppression of food digestibility and the facilitation of fat oxidation [139].

3.5. Neurodegenerative Diseases Prevention with Flavonoids

Flavonoids exhibit significant neuroprotective potential, partly due to their capacity to cross the blood-brain barrier and exert multiple biological effects within neural tissues [156,157]. The spectrum of neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease is characterized by progressive neuronal dysfunction localized to particular brain regions [158,159]. The underlying causes of these conditions are multifactorial and include oxidative stress, neuroinflammation, aberrant protein aggregation, mitochondrial failure, and increased apoptosis; these pathological mechanisms are further shaped by lifestyle, genetic predispositions, and environmental exposures [160,161]. Dementia is especially notable as a leading source of disability, institutionalization, and mortality. Given their ability to interact with diverse neurobiological pathways, flavonoids are considered promising candidates for the prevention and mitigation of neurodegenerative disorders (Table 3).

Table 3. Summary of Neuroprotective Effects of Flavonoids in Experimental Models.

Flavonoid	**Dose**	**Duration**	**Experimental Model**	**Observed Effect**	**Underlying Mechanism**	**Reference**
Chrysin	50 mg/kg	14 days	Huntington's disease rat model	Prevents mitochondrial dysfunction and neuronal apoptosis	Regulates Bcl-2, Bax, and Bad genes	[162]
Quercetin	25 mg/kg	90 days	Triple transgenic AD mice	Attenuates Alzheimer's pathology; enhances cognition and mood	Not specified	[163]
Fisetin	9 mg/kg	80 days	ALS transgenic mice	Reduces oxidative damage and supports neuroprotection	Engages ERK signaling	[164]
7,8-dihydroxyflavone	5 mg/kg	119 days	R6/1 transgenic mice	Improves cognitive and motor performance	Involvement of PLCγ1 pathway	[165]
Anthocyanins	20 mg/kg	84 days	R6/1 mice (HD model)	Boosts spatial learning and cognition	Improves oxidative status	[166]
Quercetin	50 mg/kg	14 days	PD mouse model	Antiparkinsonian effects	Enhanced AchE activity and antioxidant effect	[167]

Table 3. *Cont.*

Flavonoid	Dose	Duration	Experimental Model	Observed Effect	Underlying Mechanism	Reference
Genistein	40 µM	48 h	Amyloid-β-exposed hippocampal cells	Inhibits neuronal apoptosis	Antioxidant and estrogen receptor-related	[168]
EGCG and tea polyphenols	2 and 10 mg/kg	14 days	Parkinson's disease mice	Protects dopaminergic neurons	Antioxidant and iron chelation activity	[156]
Morin	1–10 µM	6 h	Human neuroblastoma cells	Blocks apoptosis and tau protein phosphorylation	GSK3β pathway	[169]
Fisetin	0.05%	180 days	Alzheimer's transgenic mice	Preserves cognitive ability	Modulates p25 and inflammatory cascades	[170]
7,8-dihydroxyflavone	5 mg/kg	75 days	ALS transgenic mice	Enhances motor function, motoneuron survival	Not specified	[165]
EGCG	10 mg/kg	91 days	ALS transgenic mouse model	Provides neuroprotection	Influences NF-κB and caspase-3	[171]

AD—Alzheimer's disease; ALS—amyotrophic lateral sclerosis; AchE—acetylcholinesterase; Bax—Bcl-2-associated X protein; Bad—Bcl-2-associated death promoter; Bcl-2—B-cell lymphoma 2; ERK—extracellular signal-regulated kinases; GSK3β—glycogen synthase kinase 3 beta; HD—Huntington's disease; PLCγ1—phospholipase C gamma 1; NF-κB—nuclear factor kappa-light-chain-enhancer of activated B cells.

3.5.1. Alzheimer's Disease

Alzheimer's disease (AD), which stands as the leading neurodegenerative disorder and a principal cause of mortality in the elderly, is associated with progressive memory impairment and decline in cognitive functions. A hallmark of AD pathology involves the accumulation of extracellular neuritic plaques, primarily composed of amyloid β (Aβ), and the presence of neurofibrillary tangles containing tau protein [172,173]. The etiology of AD and its complex neurological outcomes have propelled interest in natural compounds for therapeutic intervention, and many flavonoids have shown promising actions in this context. Long-term flavonoid supplementation has produced several neuroprotective benefits. In animal studies, administration of green tea catechins was reported to improve both cognitive capacity and learning performance in rats [174]. Likewise, green tea flavonoids were shown to mitigate Aβ-induced cytotoxicity in primary prefrontal cortical neurons [175]. Investigations in transgenic mice models of AD revealed that quercetin supplementation not only ameliorated cognitive and emotional deficits but also mitigated neuropathological markers, including tau aggregation, amyloid β deposition, microgliosis, and astrogliosis particularly in the amygdala and hippocampus. Fisetin's ability to preserve cognitive faculties has been linked to its regulatory effects on p25 and inflammation-related signaling pathways.

Flavonoids exert their neuroprotective activities through several molecular routes. Genistein, for instance, was found to counteract Aβ-induced apoptosis in hippocampal neurons through an estrogen receptor-dependent mechanism, even at nanomolar concentrations. The elevation of cellular resilience to oxidative stress is another dimension of flavonoid action: extracts rich in flavonoids from Ginkgo biloba were able to ameliorate toxicity caused by Aβ peptides or oxidative stress in hippocampal cells [175]. Furthermore, rutin was effective at suppressing oxidative damage by inhibiting malondialdehyde and glutathione disulfide formation in SH-SY5Y neuroblastoma cells. Morin, a flavonoid naturally present in apples and onions, has also shown considerable potential by blocking neuronal apoptosis and hindering GSK3β-mediated tau phosphorylation—effects confirmed both in neuroblastoma cells and mouse models of AD [169]. Collectively, these findings underscore the therapeutic promise of flavonoids as agents for preventing or slowing the progression of Alzheimer's disease through a combination of anti-amyloidogenic, antioxidant, anti-apoptotic, and anti-inflammatory actions [163].

3.5.2. Parkinson's Disease

Parkinson's disease (PD) ranks as the second most common neurodegenerative disorder affecting adults, with its pathogenesis driven by cumulative factors such as oxidative stress, mitochondrial dysfunction, and the progressive misfolding and aggregation of specific neuronal proteins. Characteristically, PD involves the degeneration of dopaminergic neurons in the substantia nigra, resulting in the formation of Lewy bodies and a pronounced loss of dopamine within the striatum, ultimately leading to hallmark symptoms such as bradykinesia, resting tremor, gait disturbances, cognitive decline, and olfactory deficits [176,177]. Remarkably, clinical manifestations do not become apparent until the majority of dopaminergic neurons—approximately 60% in the substantia nigra—are lost and striatal dopamine has declined by around 80%.

There is mounting evidence that flavonoids may intervene in multiple PD-related pathological pathways. One extensive epidemiological study, tracking approximately 130,000 participants over two decades, revealed that male subjects with the highest intake of flavonoid-rich foods (such as berries, apples, oranges, red wine, and tea) exhibited a 40% reduced risk of developing PD compared to those with the lowest consumption [178]. In experimental settings, extracts from Ginkgo biloba, known for their high flavonoid content, have been shown to protect dopaminergic neurons from degeneration in animal models of PD. Similarly, green tea and its principal catechin, EGCG, counteracted the loss of dopaminergic neurons in the substantia nigra and prevented striatal dopamine depletion in mouse models. The neuroprotective capacity of quercetin has also been substantiated: it shields mesencephalic dopamine neurons against apoptosis induced by oxidative insults in primary rat mesencephalic cultures. Furthermore, oral administration of quercetin significantly improved motor coordination and boosted the activity of antioxidant enzymes, such as Na-K ATPase, superoxide dismutase (SOD), and glutathione peroxidase, in PD mouse models [166]. Collectively, these findings highlight the therapeutic potential of flavonoids in targeting the underlying mechanisms of PD and provide compelling support for their use in disease prevention even before overt symptoms emerge.

3.5.3. Huntington's Disease

Huntington's disease (HD) is a hereditary autosomal disorder, stemming from the expansion of cytosine–adenine–guanine trinucleotide repeats in the Huntington gene [179]. The disease is typified by selective degeneration of striatal neurons, especially those producing γ-aminobutyric acid in the deeper layers of the cerebral cortex, which underlies many of its clinical manifestations [180]. Individuals with HD experience a progressive cascade of symptoms, beginning with involuntary movements and advancing to psychiatric changes, cognitive decline, choreoathetosis, and ultimately premature death. With continued research into novel preventive strategies for HD, flavonoids have garnered attention for their neuroprotective properties. For instance, daily oral supplementation of chrysin in rat models exposed to 3-nitropropionic acid (3-NP) was shown to foster survival of striatal neurons while inhibiting oxidative stress and neuronal death [166]. Likewise, chronic administration of 7,8-dihydroxyflavone (7,8-DHF) in HD mouse models has been found to stimulate neurotrophic signaling, mitigate inflammation, preserve striatal volume, and delay both motor and cognitive impairments. Furthermore, injections of kaempferol and genistein proved effective at reducing neuronal loss in the striatum, lessening cell death, and attenuating motor deficits associated with HD. Other flavonoids, such as quercetin, hesperidin, and naringin, have demonstrated protective effects against cognitive decline in HD mouse models treated with 3-nitropropionic acid [181]. Collectively, these findings underscore the ongoing potential for flavonoids to serve as therapeutic agents in the context of Huntington's disease.

3.5.4. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative condition marked by progressive weakening and paralysis due to the degeneration of anterior horn cells and cortical motor neurons. While the majority of ALS cases arise sporadically, approximately 10% are attributed to inherited mutations in the copper/zinc SOD1 gene. Because ALS involves complex and multifactorial etiologies, therapeutic approaches that can target multiple pathological processes are urgently needed. Among promising candidates are flavonoids, bioactive compounds shown to engage diverse neuroprotective mechanisms. Notably, the flavonoid 7,8-dihydroxyflavone (7,8-DHF) when administered from an early age, has demonstrated efficacy in preserving motor performance in SOD1-G93A mouse models of ALS [165]. Green tea-derived EGCG, given orally, has been observed to delay disease onset, extend lifespan, protect motor neurons, and suppress markers of neuroinflammation in the same model [171]. Additionally, the flavonol fisetin has been shown to shield neurons from reactive oxygen species (ROS)- induced injury and to ameliorate disease behaviors in mutant hSOD1 ALS mice through upregulation of the ERK signaling pathway [164]. Despite these favorable results, a more comprehensive understanding of how flavonoids can prevent or modify the clinical trajectory of ALS remains a significant goal for future studies.

3.6. Flavonoid Role in Cancer Prevention

Cancer remains one of the most pressing global health challenges and is a leading obstacle to increasing life expectancy worldwide [182]. Multiple lines of population-based and cohort research have demonstrated that flavonoids, a diverse class of plant-derived polyphenols, possess notable anti-carcinogenic activity across a variety of malignancies [183,184]. These protective effects have been identified in several cancer types, including but not limited to lung, breast, prostate, stomach, liver, and colorectal cancers [185,186] (Table 4).

Table 4. Summary of Anti-Cancer Effects of Flavonoids in in Clinical and Experimental Settings.

Flavonoid	Dose	Duration	Experimental Model	Observed Effect	Underlying Mechanism	Reference
Delphinidin	120–180 µM	48 h	Human prostate cancer cells	Inhibits cell proliferation	Stimulates autophagy	[187]
Hesperetin	100–300 µM	24–48 h	Esophageal cancer cells	Triggers apoptosis	Boosts ROS; activates caspase-9, caspase-3, Apaf-1	[188]
Quercetin	15 mg/day	—	Lung cancer case–control study	Decreased lung cancer incidence	Modulates CYP1A1	[189]
Methlut	1–100 µM	2–24 h	Mast cell system	Reduces inflammation	Alters intracellular calcium; inhibits NF-κB	[190]
Fisetin	40–120 µM	24–96 h	Prostate cancer cells	Enhances autophagy	Acts on mTOR signaling	[191]
Quercetin	20–100 µM	24–72 h	BT-474 breast cancer cells	Initiates extrinsic caspase-dependent apoptosis	Activates caspase-8, caspase-3; affects STAT3	[192]
Flavonols	15 mg/day	—	Italian breast cancer case–control study	Lower breast cancer association	Not specified	[193]

Table 4. *Cont.*

Flavonoid	Dose	Duration	Experimental Model	Observed Effect	Underlying Mechanism	Reference
Anthocyanin	30–150 µM	72 h	Oral cancer cell line	Anti-metastatic effects	Induces autophagy	[2]
Naringenin	10–160 µM	24–72 h	SGC7901 gastric cancer cells	Induces apoptosis	Alters AKT signaling; affects apoptotic proteins	[194]
Apigenin	12.5–50 µM	24 h	HCT116 colon cancer cells	Promotes apoptosis	Triggers autophagy	[195]
Naringenin	100 mg/kg	72 h	Murine breast cancer resection	Inhibits metastatic spread	Reduces Treg immunosuppression	[196]
Quercetin	25 mg/day	—	Finnish lung cancer case–control	Associated with reduced lung cancer risk	Not specified	[197]
Quercetin	30–90 µM	48 h	Human breast cancer cells	Drives autophagy	Promotes proteasome function; inhibits mTOR	[198]

AKT—protein kinase B; Apaf-1—apoptotic protease activating factor 1; CYP1A1—cytochrome P450 1A1; mTOR—mammalian target of rapamycin; NF-κB—nuclear factor kappa-light-chain-enhancer of activated B cells; ROS—reactive oxygen species; STAT3—signal transducer and activator of transcription 3; Treg—regulatory T cell.

The mechanistic underpinnings of flavonoid-mediated cancer prevention are multifaceted, influencing cellular pathways that govern DNA integrity, programmed cell death, the inflammatory tumor microenvironment, and the regulation of tumor angiogenesis. These findings collectively emphasize the expanding significance of dietary flavonoids as a preventive measure against the growing global burden of cancer. Their impact on cancer development and progression is largely attributed to their ability to regulate cell signaling pathways—such as the inhibition of NF-κB activity, modulation of the PI3K/Akt and MAPK cascades, and the induction of programmed cell death via apoptosis and autophagy [199,200]. Flavonoids also demonstrate potent antioxidant and anti-inflammatory activities: they scavenge reactive oxygen species (ROS), reduce pro-inflammatory cytokine signaling, and promote antioxidant-triggered apoptosis. Fruit-based flavonoids, in particular, are gaining attention for their stable fluorescence properties and unique roles within the food matrix, expanding their significance beyond nutrition to potential biosynthetic and diagnostic applications. Clinical trials now feature dietary flavonoids like quercetin as leading candidates for anticancer interventions, reflecting positive correlations between fruit rich in flavonoids and diminished cancer risk—especially for breast, colon, and liver malignancies. Experimental evidence further substantiates their role in inhibiting angiogenesis and cell proliferation in liver cancer, as well as blocking the NF-κB pathway to suppress lung tumorigenesis. In breast cancer, the protective effects of flavonoids are strongly linked to disruption of PI3K/Akt and MAPK signaling, while in colon cancer, anti-inflammatory and ROS-induced apoptotic mechanisms predominate [201].

The antineoplastic properties of flavonoids are underpinned by their ability to disrupt multiple cell signaling cascades that regulate cancer development and progression. A central aspect of their anticancer mechanism is the inhibition of angiogenesis, mediated in part by downregulating the expression and signaling of vascular endothelial growth factor (VEGF) [202,203]. Flavonoids exert much of their therapeutic efficacy by targeting the downstream elements of the PI3K tyrosine kinase growth receptor, interfering with activation loops that control cellular growth and survival. They notably affect the PI3K/Akt/mammalian target of rapamycin (mTOR) axis by inhibiting PI3K enzymatic function, disrupting the feedback and crosstalk between protein kinase B (Akt), PI3K, and other molecular targets such as ERK and phosphatase and tensin homolog (PTEN).

Another significant action involves the blockade of the ATP-binding domain within the PI3K complex, which perturbs the mechanical assembly of the mTORC2 signaling complex, thereby reducing Akt phosphorylation and promoting cellular antioxidant responses (Figure 4). These interactions attenuate oxidative stress damage—such as that induced by hydrogen peroxide—and increase apoptosis in targeted cells through PI3K/Akt pathway modulation. Flavonoids further influence the expression and function of regulatory proteins including glycogen synthase kinase-3 (GSK-3), and play a role in enhancing tumor necrosis factor-alpha (TNF-α)-induced apoptosis in human lung cancer cells. Additionally, they hinder tumor progression by suppressing the activity of signal transducer and activator of transcription 3 (STAT3) through inhibition of Src kinase phosphorylation, effectively blocking cancer cell proliferation and metastasis [204].

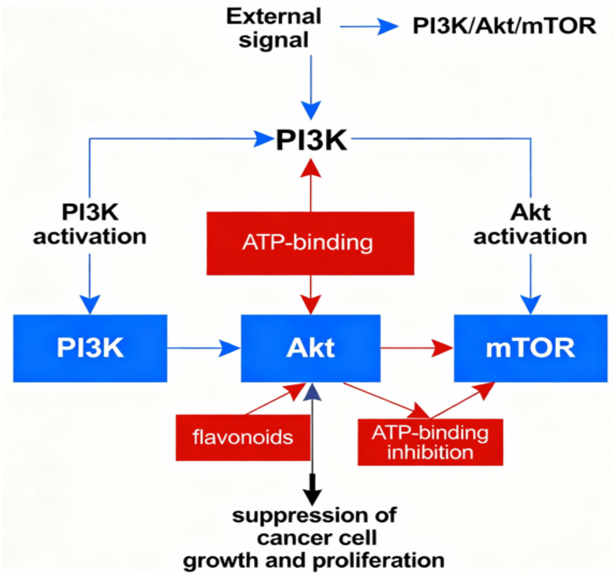

Figure 4. Flavonoid modulation of PI3K/Akt/mTOR pathway (PI3K—phosphatidylinositol 3-kinase, Akt—protein kinase B, mTOR—mammalian target of rapamycin; created with BioRender.com).

3.6.1. Trigering Programmed Cell Death

Apoptosis induction refers to the process of triggering or starting apoptosis, which is often called "programmed cell death." It's a natural and controlled way for the body to remove old, damaged, or unnecessary cells without causing inflammation, making it a critical process for tissue health and a key target in disease treatment. Because the failure of apoptosis (cellular self-destruction) is a key factor in cancer development, researchers are exploring therapies that can restart this process. These strategies often involve regulating key proteins, generating reactive oxygen species (ROS), or causing DNA damage. In this area, various flavonoids have shown promise as anticancer agents by activating the cell's death machinery. For instance, hesperetin triggers apoptosis in esophageal cancer by causing ROS to build up and activating an internal death pathway [188]. Flavonoids can also directly alter the balance of proteins that control apoptosis. Quercetin, for example, encourages cell death in breast cancer by raising the levels of pro-death proteins and lowering the levels of anti-death proteins. This effect is boosted when quercetin is used with other compounds like EGCG or metformin, which together reduce the ability of cancer cells to survive, move, and spread [192]. Another flavonoid, naringenin, induces apoptosis in gastric cancer cells while also halting their growth and spread [194].

The anticancer activities of a broad range of other flavonoids, including flavones, anthocyanidins, and isoflavonoids, have been associated with their ability to act through both the intrinsic and the extrinsic pathways of apoptosis. There are two principal pathways involved in this process. The intrinsic pathway is a response to diverse intracellular stresses, which leads to the formation of an apoptosome complex—comprising cytochrome c, Apaf-1, and caspase-9—through the regulation of BH3-only and Bcl2-like proteins, ultimately promoting cell death. The other is the extrinsic pathway, which is initiated when a ligand from the TNF family binds to death receptors on the cell surface. This action in turn activates caspase-8 and caspase-3 through the Fas-associated death domain protein (FADD), leading to cellular destruction. By leveraging these pathways, flavonoids help restore a critical biological process. Apoptosis is a form of programmed cell death that occurs in response to a variety of intracellular damage signals and is essential for maintaining tissue homeostasis [205].

3.6.2. Modulating the Autophagy Network

At its core, autophagy is a mechanism for the breakdown and reuse of a cell's internal components, typically activated by conditions such as nutrient deprivation or other forms of cellular stress. Therefore, alongside their influence on apoptosis, the capacity of flavonoids to manipulate this complex autophagic network represents a significant aspect of their anticancer effects, as confirmed by numerous studies. Beyond their influence on apoptosis, flavonoids are increasingly recognized for their crucial impact on cancer biology through the regulation of autophagy—a cellular recycling process activated in response to deprivation or stress [206].

Autophagy serves complex and sometimes opposing functions during cancer progression [207]. At the onset of tumorigenesis, it may prevent malignant transformation by suppressing cellular proliferation, yet in advanced cancers, autophagy can instead foster tumor cell adaptation and survival under hypoxic, nutrient-deficient conditions [208]. The fundamental PI3K-AKT-mTOR signaling axis orchestrates autophagic activity: class I PI3Ks inhibit autophagy via mTORC1 activation, whereas class III PI3Ks are essential to initiate the autophagic machinery. Flavonoids can modulate this pathway and, in early tumor development, promote autophagy to trigger cell death in cancer cells or amplify the effects of apoptosis, particularly in those with defective apoptotic signaling [209] (Figure 5). For instance, quercetin has been demonstrated to obstruct proteasome activity, enhancing macroautophagy in malignant cells and concurrently suppressing mTOR signaling. Fisetin, naturally occurring in plant-based foods, instigates programmed autophagic death in prostate cancer cells through the inhibition of both major mTOR complexes [191]. Similarly, compounds like genistein and baicalein act on PI3K-AKT-mTOR to induce autophagic cell death across diverse cancer types. As tumors progress, however, autophagy increasingly serves as a protective mechanism, enabling cells to resist apoptosis.

Accordingly, combining anthocyanins with autophagy inhibitors has been shown to heighten apoptosis in liver cancer cells, while similar inhibition strategies sensitize colon and breast cancer cells to apigenin-induced apoptotic death. Additionally, studies have shown that fisetin can kill human breast cancer cells (MCF-7) by blocking autophagy and facilitating apoptosis via caspase-7 activation, with no observed cytotoxicity in non-cancerous cells [193].

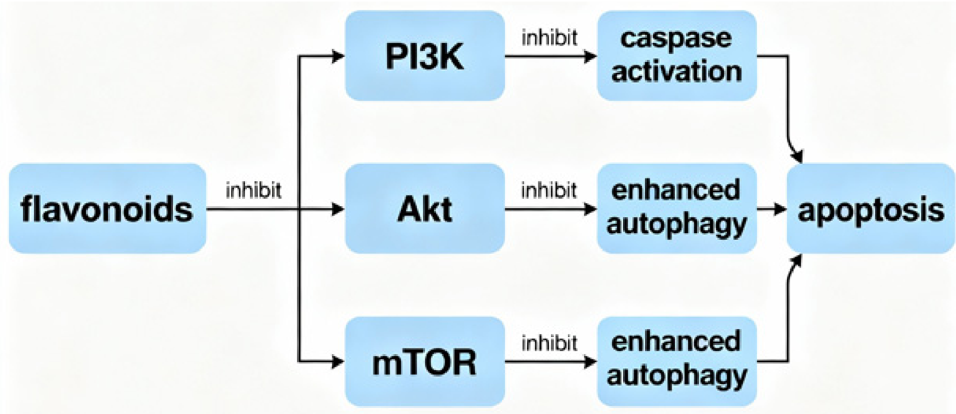

Figure 5. Flavonoid modulation of autophagy/apoptosis pathway (PI3K—phosphatidylinositol 3-kinase, Akt—protein kinase B, mTOR—mammalian target of rapamycin; created with BioRender.com).

3.6.3. Modulating the NF-kB Pathway

The NF-kB pathway is a central regulator at the intersection of immune and inflammatory processes, which strongly influence the onset and evolution of cancer [210]. Persistent inflammatory stimuli, including chronic infections, lead to the activation of NF-kB; the consequences of this activation vary depending on the cell type involved. In inflammatory cells, NF-kB often provokes oncogenic responses, while in epithelial cells, its activation can actually suppress tumorigenic processes [211]. The complexity of this signaling network is highlighted by research demonstrating that delphinidin inhibits human prostate cancer cell proliferation through NF-kB activation, yet without impacting normal prostate epithelial cells [187].

Conversely, other flavonoids can halt tumor progression by interfering with NF-kB signaling. For instance, anthocyanins derived from black rice have been reported to suppress metastasis formation in oral cancer by reducing NF-kB expression [212]. Rather than targeting NF-kB directly in every context, focusing on upstream immune or inflammatory triggers of this pathway may offer a more effective preventive strategy for cancer. Cyanidin provides such an example: it reduces inflammation mediated by IL-17A-producing TH17 cells, lessens airway hyperresponsiveness, and inhibits skin hyperplasia in models of severe asthma or steroid resistance, primarily by blocking the binding of IL-17A to its receptor IL-17RA [213].

The immunosuppressive tumor microenvironment also features elevated regulatory T cells (Tregs), which limit the anticancer efficacy of effector T cells by secreting cytokines such as IL-10 and TGF-β [214]. Naringenin has been shown to mitigate metastasis in mouse breast cancer resection models, in part by boosting T cell antitumor responses and reducing immunosuppression from Tregs [194]. In a further example, tetramethoxyluteolin, a flavone, diminishes inflammatory mediator release in human mast cells by both lowering intracellular calcium and inhibiting NF-kB transcriptionally and translationally, leading to strong anti-inflammatory effects [190].

4. Outcomes and Future Perspectives

This review has comprehensively synthesized the current literature on the chemical diversity, mechanistic breadth, and translational prospects of flavonoids as bioactive compounds in human health, with a core focus on metabolic disorders, neurodegenerative diseases, and cancer. Building on a robust base of experimental and clinical evidence, the discussion highlights how flavonoids—spanning subclasses from flavonols to anthocyanins—exert multi-dimensional protective effects. Classic phytochemical studies and more recent biochemical analyses agree that the structure–activity relationship of flavonoids is central to their biological roles [1,8]. The 15-carbon skeleton (C6-C3-C6) underpins a manifold of biological activities by enabling redox cycling, enzyme modulation, and diverse receptor interactions. Our review corroborates that specific substitutions such as hydroxylation patterns on the B and C rings are directly linked to antioxidant, anti-inflammatory, and enzyme-inhibitory effects.

Experimental findings consistently show strong ROS-scavenging, metal-chelating, and radical stabilization properties, especially in polyhydroxylated flavonols and anthocyanins. These direct antioxidant effects are complemented by the modulation of endogenous defensive enzymes and by the inhibition of pro-oxidant systems, giving flavonoids a unique versatility in counteracting oxidative stress a key pathomechanism in chronic and degenerative diseases. Notably, the polymerization of flavonoid subunits (e.g., in proanthocyanidins) further increases radical-scavenging capacity, reflecting the role of chemical complexity in functional potency [58].

Importantly, the discussed literature does not limit flavonoids' efficacy to direct antioxidant action. Their capacity to modulate critical signal transduction pathways—including PI3K/AKT/mTOR, MAPK, AMP-activated protein kinase, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)—anchors their broader biological and therapeutic profile. This review's focus on chronic diseases and cancer highlights that flavonoids may impact cell survival, apoptosis, differentiation, autophagy, angiogenesis, and inflammation—often through mutually reinforcing mechanisms [201,215].

Several well-characterized flavonoids (e.g., quercetin, apigenin, genistein) directly inhibit cell proliferation or promote programmed cell death through apoptosis and/or autophagy, by modulating both intrinsic (mitochondrial) and extrinsic (receptor-mediated) pathways. Many act on key regulatory checkpoints, such as cyclin-dependent kinases, caspases, and BCL-2 family members, shifting the balance between survival and cytotoxicity in favor of cellular homeostasis and tumor suppression. These observations align with our mechanistic understanding of flavonoids as multi-target agents whose efficacy emerges from systems-level modulation rather than single-target specificity.

Our working hypothesis—that the health-promoting potential of dietary flavonoids arises from their multitargeted regulation of cellular signaling and defense networks—is strongly supported by studies cited herein and across the nutritional pharmacology literature. Multiple epidemiological investigations, as referenced, reveal significant correlations between high flavonoid intake and reduced risks of chronic illnesses, including cardiovascular disease, certain cancers, and neurodegeneration. Notably, cohort and case–control studies suggest that frequent consumption of flavonoid-rich foods correlates with better metabolic outcomes and lower disease prevalence [178,185]. These population-level findings are mechanistically supported by in vivo and in vitro models showing anti-inflammatory, anti-apoptotic, and antiproliferative actions.

At the same time, our synthesis shows that the clinical translation of flavonoid supplementation is shaped by factors such as bioavailability, metabolic stability, and the complexity of human dietary patterns echoing limitations and caveats found in prior reviews [2,7]. The recognition of flavonoids as both beneficial and potentially bioactive at pharmacologically relevant concentrations is now widely accepted, yet their optimal dosing, delivery, and real-world efficacy remain active areas of inquiry.

Our critical overview underscores that flavonoids hold particular promise for the prevention and adjunctive management of metabolic disorders, neurodegenerative diseases, and cancer—a hypothesis aligned with growing research interest in plant-based therapeutics. In neurodegenerative models, flavonoids have demonstrated the capacity to cross the blood-brain barrier, decrease oxidative damage, inhibit protein aggregation, and modulate neuroinflammatory mediators. In the context of cancer, multiple subclasses exhibit potent anti-proliferative, pro-apoptotic, and anti-angiogenic activity through effects on multiple cellular signaling axes (NF-κB, PI3K/AKT/mTOR, STAT3), corroborated by cell studies and animal models.

Additionally, the review's discussion of metabolic syndrome and obesity highlights how flavonoids can regulate adipocyte differentiation, improve insulin signaling, modulate lipid metabolism, and increase energy expenditure—mechanisms with significant translational relevance given the global burden of obesity and diabetes. Several studies further confirm the cardioprotective effects of certain flavonoids, which act at the level of vascular function, atherogenesis, and endothelial protection.

Over the past few decades, research has successfully transitioned from identifying the in vitro properties of flavonoids to substantiating their health benefits in human populations. This progress is most evident in large-scale epidemiological studies and clinical observations that have established strong, consistent links between flavonoid-rich diets and reduced risk for major chronic diseases. A significant body of evidence now supports the cardioprotective effects of flavonoids. Multiple population-based studies have demonstrated that a high intake of dietary flavonoids is associated with a markedly lower risk of death from cardiovascular causes. Specifically, anthocyanins have been shown to reduce the risk of myocardial infarction (MI) in humans, an effect linked to improvements in blood pressure and lipid profiles. In the realm of cancer prevention, extensive cohort and case–control studies have revealed an inverse correlation between flavonoid consumption and the incidence of several malignancies. These protective associations have been identified for lung, breast, colorectal, and prostate cancers, highlighting the broad anti-carcinogenic potential of these compounds at a population level. Perhaps one of the most compelling findings comes from neuroprotection research. A landmark epidemiological study that followed approximately 130,000 participants for over two decades found that men with the highest habitual intake of flavonoids had a 40% lower risk of developing Parkinson's disease compared to those with the lowest intake. This powerful statistic underscores the profound, long-term impact that dietary flavonoids can have on neurological health. Collectively, this clinical and epidemiological progress provides a strong foundation for the therapeutic promise of flavonoids. While translational challenges such as bioavailability remain, these human studies validate the mechanistic findings and confirm that a diet rich in flavonoids is a scientifically supported strategy for mitigating the risk of major chronic diseases. Despite these favourable mechanistic and preclinical conclusions, our analysis—and that of prior reviews—recognizes several significant limitations and unresolved questions. Chief among these is the issue of bioavailability, which remains a major challenge for the clinical utility of many flavonoids. The typically poor solubility, chemical instability, and rapid metabolism of most naturally occurring flavonoids limit their systemic action and biological half-life. The recent technological innovations—including nanosystem delivery, micellar encapsulation, enzymatic methylation, and microcapsule-based approaches—show promising progress in improving flavonoid delivery and stability. However, further research and standardization are necessary to optimize these systems for clinical translation and to ensure target specificity and activity retention after oral, dermal, or parenteral administration.

Beyond these formulation challenges, a critical evaluation of existing clinical data reveals several fundamental gaps that temper direct therapeutic recommendations and guide future research priorities. Firstly, there is a significant lack of clarity regarding dose–response relationships. Current human trials often employ a wide range of doses and utilize flavonoids from varied sources (i.e., whole-food extracts versus isolated aglycones), making cross-study comparisons difficult and obscuring the distinction between a low-dose physiological effect and a high-dose pharmacological action. Future studies must move towards standardized interventions that systematically assess dose-dependent effects to identify optimal therapeutic windows. Secondly, interindividual population variability remains a major confounding factor. The efficacy of flavonoids is heavily influenced by genetic polymorphisms in metabolic enzymes, vast differences in gut microbiome composition, age, and underlying health status, yet few trials are designed with sufficient power to account for these variables. A shift towards personalized or stratified trial designs is necessary to understand which populations are most likely to benefit from flavonoid supplementation. Finally, the vast majority of clinical interventions are short-term, leaving the long-term efficacy and safety of sustained flavonoid intake largely unconfirmed. There is a pressing need for longitudinal studies that track not only surrogate biomarkers but also hard clinical endpoints over extended periods to validate the promising health correlations observed in epidemiological data.

Other research gaps include the tissue specificity of flavonoid effects, possible interactions with other dietary or pharmacological agents, interindividual genetic differences in metabolism, and the balance between physiologic and pharmacologic dosing—a recurring theme in current research. Additionally, although generally safe, certain flavonoids may possess rare but notable toxicities or provoke adverse effects, underlining the importance of further experimental and clinical toxicity studies, especially with new delivery forms or structural modifications.

5. Conclusions

Dietary flavonoids emerge as multifunctional bioactive compounds with substantial potential for the prevention and adjunctive management of chronic metabolic, neurodegenerative, and oncological diseases, as consistently demonstrated across epidemiological, experimental, and clinical studies. Their health-promoting actions are mediated by pleiotropic mechanisms—including antioxidative, anti-inflammatory, and regulatory effects on cell signaling pathways such as PI3K/Akt/mTOR, NF-κB, and AMPK—which collectively contribute to improved metabolic regulation, neuroprotection, and cancer prevention. Nevertheless, challenges regarding bioavailability, clinical translation, and interindividual variability underscore the need for continued research to optimize flavonoid efficacy and elucidate their nuanced molecular interactions. Integrating diverse, flavonoid-rich foods into dietary patterns remains a scientifically supported strategy for disease mitigation, while evolving advances in delivery systems and molecular targeting are expected to further enhance the translational impact of these key phytochemicals in public health and clinical contexts.

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