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Exploring the Therapeutic Power of Flavonoids on Chronic Disease: Unraveling the Mechanisms of Action Especially by Following MAPKs/ NF-KB Signaling Pathways

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Abstract

This book chapter addresses the potential of flavonoids as a promising therapeutic intervention in the amelioration of chronic diseases, specifically through their regulatory influence on the MAPK and NF-κB signaling cascades. Chronic diseases pose an overwhelming global burden, urging the need for effective therapeutic strategies. Flavonoids, polyphenolic compounds ubiquitous in plant-based diets, have historically displayed vast medicinal attributes, including anti-inflammatory, antioxidant, and anticancer activities. However, the precise mechanisms underlying these therapeutic effects remain relatively elusive. This chapter focuses on the biochemical interaction of flavonoids with the complex MAPKs/NF-KB pathways, known for their fundamental role in cell survival, inflammation, and immunity. The existing preclinical and clinical evidence elucidates the compelling potential of flavonoids as therapeutic agents in the management of chronic diseases. By intervening in the MAPKs/NF-KB pathways, flavonoids may suppress inflammatory responses, enhance cellular antioxidant defenses, and induce apoptosis in cancer cells, providing an innovative approach to disease management. Potential

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therapeutic applications, comparative analysis with existing treatments, potential side effects, and future research directions are extensively discussed, underscoring the promise and challenges in utilizing the power of flavonoids. This comprehensive book chapter provides a platform for further research into the molecular mechanisms of flavonoids, ultimately contributing to our fight against chronic diseases.

Keywords: Molecular pathway, signaling cascade, MAPK, NF-KB

1.1 Introduction

The profound health and economic burdens imposed by chronic diseases necessitate new therapeutic approaches and discovery of new drugs entities. Drugs developed against specific molecular targets have proven efficacious for some conditions with minimal side effects. However, most of these drugs are often reported to have adverse effects and fail to address the complex and multifaceted pathogenesis of chronic diseases like metabolic diseases such as diabetes, hypertension, and cancer. Flavonoids are a large and diverse class of polyphenolics a phytochemical abundantly found in various fruits, vegetables, and plant-based food supplements. These bioactive plant compounds present a promising efficacy and opportunity to influence multiple disease pathways simultaneously. It is abundantly present in consumed foods and beverages and have an excellent safety profile and with reduced morbidity [1].

It is composed of a universal class of plant secondary metabolites categorized into six major subclasses: flavanols, flavones, flavan-3-ols, flavanones, isoflavones, and anthocyanidins. The foundational structure of a flavonoid is characterized by a bifurcated arrangement of aromatic rings, which are interconnected by a tri-carbon linear chain. Structural variations in this core chemical scaffold differentiate the subclasses and contribute to the wide variability in flavonoid bioactivity and biological function [2]. While flavonoid content can vary considerably between plant species, commonly consumed foods rich in flavonoids include fruits, vegetables, tea, spices, herbs and cocoa [1].

In recent years, the complicated therapeutic capabilities of flavonoids have gathered considerable scholarly attention, given their wide-ranging biological activities that encompass anti-inflammatory, antioxidative, oncologic inhibitory, neuroprotective, and cardiovascular safeguarding effects [3]. A large body of evidence suggests that regular dietary intake of flavonoids may help prevent or mitigate various chronic diseases that currently affect millions of people worldwide. Chronic diseases such as cardiovascular disease, cancer, diabetes, and neurodegenerative disorders involve

complex, multifactorial pathophysiology. However, common underlying mechanisms including inflammation, oxidative stress, and abnormal cell signaling, are implicated in many of these disorders. An array of bioactive flavonoids found in foods like fruits, vegetables, tea, herbs and spices demonstrate significant activity to effectively modulate these pathways and diseases [4].

While the health benefits of flavonoids seem promising, their exact mechanistic activity are not yet well understood. Several investigators have probed that flavonoids can potentially inhibit key pro-inflammatory signaling molecules like NF-κB and MAPKs. By inhibiting these pathways, flavonoids may mitigate downstream effects like cytokine production, abnormal immune responses, and altered cellular behaviors that underlie this disease progression. However, most studies focus on specific flavonoid compounds or disease models in isolation. Comprehensive reviews integrating the wide-ranging effects of flavonoids across diverse chronic conditions are still required [5].

Therefore, an in-depth, mechanistic perspective into how bioactive flavonoids may exert therapeutic effects against major chronic diseases will be emphasized here. Emphasis will be placed on the detailed investigation of the molecular substrates and intracellular signaling sequences regulated by flavonoids, particularly in relation to the nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways in the context of chronic diseases. For each chronic disease, focus will be directed towards the anti-inflammatory and antioxidant characteristics of select flavonoid compounds, and clinical and epidemiological evidence are highlighted here. Finally, important future directions in flavonoid research are discussed, including improving bioavailability, elucidating lesser-known mechanisms of action, and conducting rigorous human studies. By specifying the therapeutic potential and biological effects of flavonoids, researchers will strive to generate further interest in these bioactive compounds with the aim of investigating their potential roles in mitigating and managing chronic medical conditions.

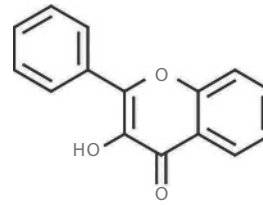
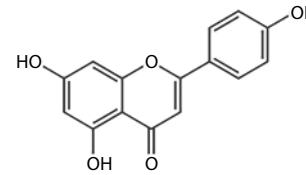
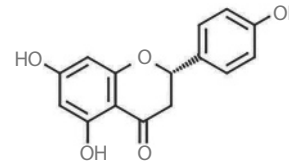
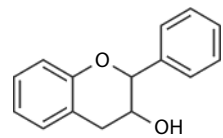
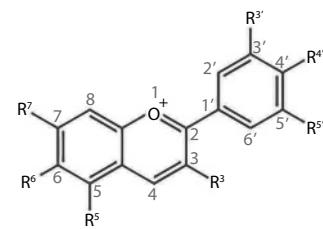
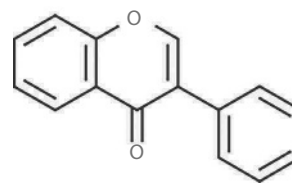
1.1.1 Structure and Classification of Flavonoids

Flavonoids belong to a class of non-nitrogenous biological compounds that are naturally abundantly present in plants. They represent a major class of plant secondary metabolites with over 6,000 identified subtypes. Flavonoids perform important functions in plants including pigmentation, UV filtering, signal transduction and microbial defense. Flavonoids not only contribute to the chromatic characteristics of a plethora of botanical

entities such as fruits, vegetables, and angiosperms but also manifest bioactive properties in vertebrate and human physiological systems, thereby inducing an array of pharmacological actions [1]. Flavonoids constitute a broad spectrum of polyphenolic entities naturally present in the plant kingdom. To date, these compounds have been systematically classified into six primary subcategories, according to their molecular configurations, as delineated in Table 1.1. The categorization of flavonoids is determined by several structural parameters: the attachment site of the B ring, the type of linkage on the C ring, and the specific attributes of the C ring itself. In the subclass known as isoflavones, the B ring is anchored at the 3-position on the C ring [6]. Notable examples are genistein and daidzein. Neoflavanoids represents another subclass, characterized by the connection of the B ring at the 4-p position of the C ring. For flavonoids where the B ring is fastened at the 2-position on the C ring, additional subcategories are established based on the degree of saturation and the presence of hydroxyl groups on the C ring [7].

a. In flavones, a conjugated double bond exists between the second and third carbon atoms, accompanied by a ketonic functional group at the fourth carbon of Ring C. Representative examples include luteolin and apigenin.
b. Flavonols are a variant of flavones, differentiated by the presence of a hydroxyl substituent at the third carbon of Ring C. Quercetin and kaempferol serve as key examples.
c. Contrasting flavones, flavanones feature a fully saturated bond between carbons 2 and 3 and lack a ketonic group at the fourth carbon in Ring C. Naringenin and hesperetin are illustrative compounds.
d. Flavanonols are a specific subtype of flavanones, uniquely characterized by a hydroxyl group attached to the third carbon in Ring C.
e. Known as flavanols or catechins, these compounds exhibit a saturated bond between the second and third carbons and feature hydroxyl groups at assorted positions on Ring C. Catechin and epicatechin are prototypical examples.
f. Anthocyanidins are distinct due to the positive charge localized on the oxygen atom of Ring C. Cyanidin and delphinidin are examples that epitomize this class.
g. Chalcones stand out for their unsealed Ring C configuration and function as the biosynthetic forerunners to all the other subclasses under consideration.

Table 1.1 Outlining the major classes and subclasses of flavonoids [8].

Flavonoid class	Subclasses	Structure
Flavonols	Kaempferol, quercetin, isorhamnetin, myricetin	
Flavones	Tangeritin, apigenin, luteolin, chrysin	
Flavanones	Naringenin, hesperetin, eriodictyol	
Flavan-3-ols	Catechins (epicatechin, epigallocatechin, epicatechin gallate, epigallocatechin gallate), proanthocyanidins	
Anthocyanins	Cyanidin, delphinidin, malvidin, peonidin, pelargonidin	
Isoflavones	Genistein, daidzein, glycitein	

1.1.2 Sources and Origins of Flavonoids

Flavonoid compounds can be readily found in an extensive array of naturally occurring foods and beverages. Among the most notable sources are fruits like citrus varieties and berries, as well as vegetables such as onions. Leguminous plants like soybeans also serve as a rich reservoir for these compounds. Additionally, various herbs and stalks, including parsley and celery, are significant contributors. In the realm of beverages, green tea stands out as a prominent source, alongside red wine. Lastly, cocoa is another crucial provider of flavonoids. However, the type and levels of flavonoids vary widely among different plant and fruit sources. For instance, flavonol content is highest in onions, kale and leeks while soy and soy products are uniquely rich in isoflavones. Therefore, individual exposure to flavonoids depends on eating patterns and food preferences. Understanding the distribution and variability of flavonoids in the diet provides important insights into their health benefits [9]. Table 1.2 describes the classification and sources of various flavonoids [10–15].

Table 1.2 Classification and sources of the major flavonoid subgroups.

Flavonoid subclass	Examples	Dietary sources	References
Flavonols	Quercetin, kaempferol, myricetin	Onions, kale, broccoli, berries, tea	[10]
Flavones	Luteolin, apigenin	Parsley, celery, chamomile	[11]
Isoflavones	Genistein, daidzein	Soybeans, soy products	[12]
Flavanones	Hesperetin, naringenin	Citrus fruits, mint	[13]
Flavan-3-ols	Catechin, epicatechin	Tea, cocoa, apples	[14]
Anthocyanidins	Cyanidin, delphinidin	Berries, cherries, red grapes	[15]

1.1.3 Flavonoid Bioavailability and Metabolism

The extent to which flavonoids are available for absorption and subsequent physiological action is influenced by the food source, digestive stability, intestinal absorption, distribution to tissues, and metabolic biotransformation. In general, aglycones and glycosides with fewer sugar units have better absorption than highly glycosylated flavonoids. However, glycosides can be deglycosylated by intestinal enzymes and gut microbiota. Once absorbed, flavonoids undergo extensive metabolic modification in the small intestine, liver, and colon [16]. Conjugation reactions (glucuronidation, sulfation, and methylation) facilitate elimination in bile and urine. The colonic microflora plays a key role through deglycosylation, degradation, and ring cleavage. Flavonoid metabolites circulating systemically can differ greatly from parent structures. Understanding factors influencing flavonoid bioavailability and metabolism will enable translation of their health benefits [17].

1.2 Chronic Diseases and Inflammation

1.2.1 Understanding Chronic Diseases

Chronic diseases are long-lasting pathological health conditions that typically progress slowly over time. These encompass cardiovascular disease, cancer, protracted pulmonary respiratory diseases, cerebrovascular stroke, metabolic diseases like diabetes, and degenerative neurological conditions such as Alzheimer's disease. These diseases are often complex and multifactorial, involving genetic factors, lifestyle, and various external environmental factors. According to global health data from the World Health Organization, chronic diseases are the predominant causes of mortality and morbidity, being responsible for an estimated 70% of worldwide deaths. Their growing prevalence and associated health care costs imposes a major societal burden [18]. Chronic diseases exhibit overlapping risk factors such as tobacco usage, suboptimal nutritional habits, sedentary lifestyle, and excessive intake of alcoholic beverages. However, their underlying pathophysiology often involves chronic inflammation and oxidative stress that drive disease initiation and progression. Persistent inflammatory responses characterized by cytokine release, immune cell infiltration, and tissue destruction contribute to insulin resistance, atherosclerosis, carcinogenesis, and neuronal injury over time [19].

1.2.2 Role of Inflammation in Chronic Disease

Inflammation is a normal physiological response to infection, injury or stress that facilitates tissue repair and removal of harmful stimuli. However, chronic low-grade inflammation can become deleterious if dysregulated. Sustained release of proinflammatory cytokines, including TNF-α, IL-1, IL-6, and various interferons, initiates a series of intracellular signaling pathways that modify cellular activities. It is now widely accepted in the scientific community that persistent inflammation serves as a crucial contributing factor in the etiology of various medical conditions, encompassing oncological disorders, cardiovascular ailments, metabolic diseases like diabetes, neurodegenerative issues, autoimmune responses, and respiratory complications such as asthma [20]. Biomarkers of systemic inflammation such as C-reactive protein (CRP) and various inflammatory cytokines, frequently display elevated levels long before the manifestation of symptoms associated with chronic diseases [21]. Inflammation contributes to insulin resistance, endothelial dysfunction, oxidative damage, and apoptosis. It also creates a microenvironment that promotes cellular proliferation, angiogenesis, metastasis, and reduced immune surveillance in cancer development. Anti-inflammatory and antioxidant approaches are emerging as potential therapies to mitigate chronic disease risk by targeting underlying inflammatory mechanisms [22].

1.2.3 MAPKs and NF-κB Mediated Inflammatory Signaling Pathways

The MAPK (mitogen-activated protein kinase) pathways, in conjunction with the NF-κB (nuclear factor kappa B) signaling system, serve as conserved and phylogenetically retained frameworks governing cellular reactions associated with inflammation. MAPKs including p38, JNK, and ERK1/2 coordinate activation of transcription factors, cytokines, and enzymes in response to stress signals, mitogens, and pro-inflammatory stimuli. Aberrant MAPK activation by reactive oxygen species (ROS), tumor promoters, and growth factors contributes to cancer, neurodegeneration, and metabolic disorders [23]. The NF-κB signaling cascade plays a pivotal role in modulating inflammatory gene transcription, immune cell responsiveness, and cellular longevity. In its dormant state, NF-κB remains sequestered by the inhibitory proteins known as IκB. Activation of the IKK complex in response to pro-inflammatory stimuli results in the phosphorylation of IκB, leading to its subsequent proteolytic breakdown [24]. Once liberated from IκB, NF-κB translocates into the cell nucleus, where it

facilitates the transcription of key effector molecules such as TNF-α, IL-1β, COX-2, and iNOS, all of which are instrumental in mediating inflammation. The aberrant regulation of the NF-κB pathway is associated with an array of chronic pathological conditions, and thus may cure diseases [25, 26]. Table 1.3 depicts the role of flavonoids linked to signaling pathways in chronic metabolic diseases [27–33].

Evidence indicates that flavonoids can modulate the synthesis and release of key pro-inflammatory markers such as TNF-α, IL-1β, IL-6, and IL-8. For example, quercetin, a type of flavonol, has been shown to attenuate LPS-triggered secretion of TNF-α in macrophages by hindering the transactivation of NF-κB. Similarly, the flavone apigenin curtailed the production of TNF-α and IL-6 in LPS-activated macrophages by restricting the phosphorylation of both p38 MAPK and ERK 1/2 [34]. Flavonoids further demonstrate the ability to downregulate the enzymatic activity of inflammation-related mediators such as COX-2 and iNOS [35]. For instance,

Table 1.3 Major subclasses of flavonoid with associated signaling pathways in various chronic diseases.

Flavonoid subclass	Pathways modulated	Associated chronic diseases	References
Flavonols (quercetin, kaempferol)	MAPK, NF-κB, Nrf2/ARE	Cancer, CVD, neurodegeneration	[27, 28]
Flavones (luteolin, apigenin)	NF-κB, MAPK, PI3K/Akt	Cancer, inflammation, diabetes	[29]
Isoflavones (genistein, daidzein)	NF-κB, MAPK, estrogen receptor	Cancer, osteoporosis, menopausal symptoms	[30]
Flavanones (hesperetin, naringenin)	NF-κB, inflammasomes	Atherosclerosis, inflammation	[31]
Flavan-3-ols (catechins, epicatechins)	MAPK, Nrf2, NF-κB	Cancer, CVD, neurodegeneration	[32]
Anthocyanidins (cyanidin, delphinidin)	MAPK, PI3K/Akt, VEGF	Cancer, CVD, diabetes	[33]

the flavan-3-ol catechin mitigated the expression of iNOS and COX-2 in LPS-challenged macrophages by obstructing the translocation of NF-κB to the cell nucleus [36]. The citrus flavanone naringenin also suppressed COX-2 transcriptional activation by interfering with NF-κB binding to DNA [37]. Dietary flavonoids have the potential to attenuate the persistent loop of chronic inflammation through several mechanisms. These include the neutralization of reactive oxygen species (ROS), the suppression of pro-inflammatory cytokine activity, and the modulation of enzymes involved in the inflammatory response [38]. Table 1.4 depicts NF-kβ- and MAPK-mediated anti-inflammatory mechanism of flavonoids [39–45].

1.2.4 Flavonoids as a Potent Modulator of MAPKs/NF-κB Signaling

The MAPK (mitogen-activated protein kinase) pathways along with the NF-κB (nuclear factor kappa B) signaling cascade serve as crucial regulatory frameworks governing the modulation of inflammatory processes. Flavonoids have emerged as promising modulators of these signaling cascades to mitigate inflammation [46]. Studies demonstrate that certain flavonoids suppress MAPK pathways like p38, JNK and ERK1/2. For instance, the flavonol kaempferol prevented LPS-induced JNK phosphorylation and IL-8 synthesis in human mast cells [47]. The flavan-3-ol EGCG also decreased JNK and p38 activation in hepatic stellate cells by suppressing upstream MAPKKs. By dampening MAPK cascade activation, flavonoids attenuate inflammatory cytokine production and signaling [48]. Flavonoids further exhibit potent inhibition of the NF-κB pathway. The citrus flavanone hesperetin prevented TNF-α-induced NF-κB activation in human breast cancer cells by suppressing IKK activity (Kim *et al.*, 2007). Similarly, the flavones chrysin and apigenin inhibited NF-κB nuclear translocation and DNA binding induced by LPS in macrophages (Liu *et al.*, 2008). This ultimately decreases transcription of NF-κB-targeted genes like COX-2, TNF-α, iNOS, and ICAM-1 that mediate inflammatory effects. Through concurrent modulation of MAPK and NF-κB signaling, dietary flavonoids potently mitigate inflammatory responses underlying chronic diseases like atherosclerosis, diabetes, neurodegeneration, and cancer [49].

1.2.5 Antioxidant Properties

The antioxidant effects of flavonoids arise largely from their chemical structure. Quercetin scavenged peroxynitrite radicals and hydroxyl radicals

Table 1.4 NF-kB- and MAPK-mediated anti-inflammatory mechanisms of different flavonoid subclasses.

Flavonoid subclass	Effects on inflammation	Representative studies
Flavonols	Inhibit NF-κB and MAPK activation; suppress TNF-α, IL-1β, IL-6, IL-8; downregulate COX-2 and iNOS	Quercetin inhibited LPS-induced TNF-α in macrophages by blocking NF-κB [39]
Flavones	Suppress TNF-α, IL-6 through effects on NF-κB, MAPKs; inhibit eicosanoid synthesis	Apigenin decreased TNF-α and IL-6 in macrophages stimulated by LPS, via MAPKs [40]
Isoflavones	Inhibit NF-κB and MAPKs; bind proinflammatory cytokines	Genistein suppressed LPS-induced iNOS and COX-2 in macrophages by inhibiting NF-κB [41, 42]
Flavanones	Downregulate NF-κB target genes like COX-2, iNOS, and cell adhesion molecules	Hesperetin inhibited TNF-α-induced NF-κB activation in breast cancer cells by suppressing IKK [43]
Flavan-3-ols	Suppress of NF-κB as well as MAPK pathways; enhance anti-inflammatory cytokines	EGCG decreased JNK and p38 activation in hepatic stellate cells by inhibiting upstream MAPKKs [44]
Anthocyanidins	Inhibit NF-κB activation and iNOS expression	Cyanidin-3-glucoside inhibited LPS-induced COX-2 and iNOS expression in macrophages by inhibiting NF-κB [45]

directly and in a dose-dependent manner *in vitro*, through its phenolic hydroxyl groups. In LDL oxidation assays, the flavones luteolin and apigenin displayed potent antioxidant activities compared to other flavonoid subclasses. Moreover, the intake of flavan-3-ols from green tea, specifically catechin, led to a decline in F2-isoprostanes plasma concentrations,

serving as an indicator of diminished oxidative injury, among a male healthy cohort [3]. Flavonoids can also manifest antioxidant capabilities through secondary mechanisms. For example, the activation of nuclear factor erythroid 2-related factor 2 (Nrf2) by quercetin leads to the upregulation of antioxidative enzymes such as glutathione peroxidase, glutathione-S-transferase, and glutathione reductase in liver cells. Through both direct and indirect mechanisms, dietary flavonoids help counteract oxidative stress implicated in inflammation, carcinogenesis, atherosclerosis, and neurodegeneration [4].

1.3 Interplay between Flavonoids and Inflammatory Mediators

Growing evidence indicates that flavonoids directly interact with key inflammatory mediators like pro-inflammatory cytokines and eicosanoids. Certain flavonoids have been found to inhibit tumor necrosis factor-α (TNF-α)-induced inflammatory effects by directly binding to TNF-α. One study demonstrated that the flavone apigenin binds to TNF-α with high affinity, inhibits its association with receptors, and suppresses downstream Akt activation [47]. Additionally, flavonoids like quercetin and galangin suppress inflammation by inhibiting the enzymatic activity of cyclooxygenase and lipoxygenase to reduce the production of inflammatory eicosanoids like prostaglandins and leukotrienes. Flavonoids also have the potential to augment the release of cytokines with anti-inflammatory properties, such as Interleukin-10 (IL-10) and Interleukin-4 (IL-4) [50]. By directly interacting with cytokines, eicosanoids, and immune cells, flavonoids can modulate the secretion and potency of both pro- and anti-inflammatory mediators. This multitarget strategy effectively disrupts the self-amplifying cascade of chronic inflammation. Further research into the direct interactions between flavonoids and inflammatory molecules may provide additional targets for therapeutic interventions. Table 1.5 describes flavonoids involved in molecular targets [51–53].

1.4 Estrogenic Activities of Flavonoids

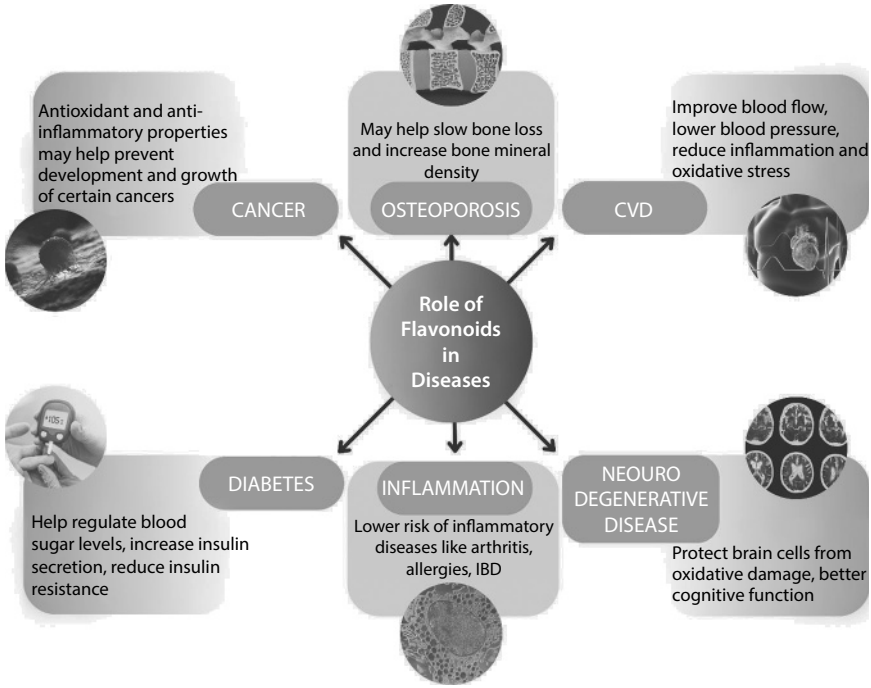
Some flavonoids, particularly isoflavones, may exert favorable biological effects through interaction with estrogen receptors. Genistein has

Table 1.5 Flavonoids and cellular/molecular targets.

Flavonoid compound	Cellular/molecular targets	Effects	Disease relevance
Quercetin	NF-κB, MAPKs, histone acetylation	Inhibits NF-κB and MAPK activation, reduces cytokine and adhesion molecule expression, increases histone H3 acetylation	Atherosclerosis, arthritis [51]
Apigenin	STAT3, NF-κB	Suppresses STAT3 and NF-κB transcriptional activity, lowering inflammatory mediators	Colitis, diabetes [52]
Genistein	NF-κB, Akt, MAPKs	Downregulates NF-κB and MAPK pathways, inhibits Akt activation, reduces inflammation	Metabolic disorders, cancer [41]
Cyanidin-3-glucoside	TLR4, NF-κB	Reduces TLR4 levels to attenuate NF-κB signaling, thereby mitigating the secretion of pro-inflammatory cytokines	Sepsis, diabetes [45]
Epigallocatechin gallate	26S proteasome, NLRP3 inflammasome	Inhibits proteasome activity to reduce NF-κB activation; suppresses NLRP3 inflammasome activation	Alzheimer's disease, diabetes [53]

preferential binding affinity for ERβ over ERα and can act as a selective estrogen receptor modulator (SERM). This estrogenic activity exerted by soy isoflavones may play a role in conditions like breast cancer, osteoporosis, and menopausal symptoms. However, the estrogenic and anti-estrogenic activities of flavonoids are complex, with differences based on compound class, receptor subtype interactions, and factors like endocrine context [54]. Further investigation is needed to elucidate the implications of estrogenic properties of certain flavonoids for disease prevention and health.

Impact of Flavonoids on Specific Chronic Diseases:



1.5 Chronic Diseases and Role of Flavonoids

1.5.1 Cardiovascular Diseases: Effects of Flavonoids on Heart Health

Cardiovascular disorders continue to be the predominant cause of mortality globally. Hypertension, atherosclerosis, and thrombosis underlie most cardiovascular conditions like heart failure, coronary artery disease, and stroke. Oxidative stress and chronic inflammation significantly contribute to CVD pathogenesis [55]. Flavonoids demonstrate promising cardioprotective effects through several mechanisms:

1.5.1.1 Antioxidant Activities

Flavonoids combat oxidative damage to LDL cholesterol that initiates atherogenesis. *In vitro* studies show that flavonoids protect LDL from oxidation by transition metal ions and free radicals. The flavan-3-ol catechin reduced Cu^{2+}-induced LDL oxidation more effectively than vitamin C and

E. Flavonoids also increase endogenous antioxidant defenses. Quercetin upregulated superoxide dismutase and glutathione peroxidase in diabetic rats [3].

1.5.1.2 Anti-Inflammatory Effects

Flavonoids inhibit inflammatory mediators like NF-κB, TNF-α, IL-1β, and COX-2 that promote endothelial dysfunction and plaque instability. The citrus-derived flavonoid, naringenin, attenuated the expression of vascular cell adhesion molecule-1 (VCAM-1) elicited by tumor necrosis factor-alpha (TNF-α) through the suppression of nuclear factor kappa B (NF-κB) activity [37].

1.5.1.3 Antiplatelet Activities

Flavonoids inhibit platelet aggregation by suppressing thromboxane A2, cyclooxygenase, and phosphodiesterase. The flavone apigenin strongly inhibited collagen-induced platelet aggregation via cyclooxygenase and thromboxane synthase [56].

1.5.1.4 Vasodilatory Effects

Flavonoids induce arterial relaxation by promoting endothelial nitric oxide (NO) production. Cocoa flavan-3-ols increased NO synthase activity and vasodilation. Quercetin also activates endothelial NO synthase (eNOS) to increase NO [57].

1.5.1.5 Lipid-Lowering Actions

Certain flavonoids lower LDL cholesterol while raising HDL levels. A meta-analysis found that soy isoflavone supplements significantly decreased LDL and total cholesterol. Flavonoids may act through cholesterol receptors like PPARα/γ and inhibition of cholesterol absorption [58].

Through these broad mechanisms, dietary flavonoids protect against major risk factors of atherosclerosis like endothelial dysfunction, inflammation, oxidative stress, hypertension, thrombosis, and dyslipidemia. Higher flavonoid intake is associated with reduced CVD mortality in epidemiological studies. Further clinical trials are warranted to validate their cardiovascular benefits. Table 1.6 describes the role of flavonoids in cardiovascular disorders [59–61].

Table 1.6 Effect of different flavonoid subclasses on cardiovascular health.

Flavonoid subclass	Cardioprotective mechanisms	Examples
Flavonols	Antioxidant activities, anti-inflammatory effects, vasodilation	Quercetin: Increased antioxidant enzymes and vasodilation by eNOS activation [59]
Flavones	Antiplatelet effects, vasodilation	Apigenin: Inhibited platelet aggregation by suppressing COX and thromboxane [40]
Isoflavones	Lipid-lowering actions	Soy isoflavones: Decreased LDL and total cholesterol in meta-analysis [60]
Flavanones	Vasodilation, anti-inflammatory effects	Hesperetin: Lowered blood pressure and inhibited NF-κB activation [43]
Flavan-3-ols	Antioxidant activities, vasodilation	Catechin: Protected LDL from oxidation and increased NO-mediated vasodilation [61]
Anthocyanins	Anti-inflammatory effects, vasodilation	Cyanidin-3-O-glucoside: Reduced CRP and increased NO production [45]

1.5.2 Neurological Disorders: Neuroprotective Role of Flavonoids

Neurodegenerative disorders such as Alzheimer's disease, Huntington's disease, and Parkinson's disease collectively impact millions of individuals worldwide. These chronic and debilitating illnesses result from progressive loss and dysfunction of neurons. Oxidative stress, neuroinflammation, abnormal protein aggregation, and excitotoxicity contribute to neuronal injury [62]. Growing evidence indicates that dietary flavonoids exert neuroprotective effects that could mitigate neurodegeneration. Key mechanisms include the following.

1.5.2.1 Antioxidant Activities

Flavonoids combat oxidative damage to brain cells by directly scavenging reactive oxygen species and upregulating antioxidant defenses like

glutathione and superoxide dismutase. The flavonol quercetin inhibited lipid peroxidation and increased antioxidant levels in n a rodent model focused on traumatic brain injury [63].

1.5.2.2 Anti-Inflammatory Effects

Flavonoids mitigate neuroinflammatory responses through the inhibition of microglial engagement, the restriction of pro-inflammatory molecular agents such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), as well as the modulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathways. Specifically, the citrus-derived flavanone naringin attenuates the expression levels of TNF-α, Interleukin-6 (IL-6), Cyclooxygenase-2 (COX-2), and inducible Nitric Oxide Synthase (iNOS) within a neurotoxicity framework, primarily through the suppression of NF-κB activity [34].

1.5.2.3 Modulating Neuronal Signaling

Flavonoids interact with important neuronal receptors and signaling proteins. For instance, the soy isoflavone genistein activates estrogen receptors to improve cognitive function. Flavonoids also activate Tr-κB receptors and PI3K/Akt pathways involved in neuron survival [62].

Inhibiting protein misfolding: Flavonoids like EGCG from green tea can inhibit aggregation of beta-amyloid and tau proteins implicated in Alzheimer's pathogenesis. They may also activate autophagy to clear misfolded proteins [38].

1.5.2.4 Enhancing Neurogenesis

Some evidence indicates that flavonoids like quercetin and fisetin stimulate neuronal progenitor cell proliferation and differentiation in the hippocampus, thus promoting neurogenesis [64]. Through these mechanisms, flavonoids may prevent or slow neurodegeneration. Higher flavonoid intake correlates with reduced risk of dementia and cognitive decline. However, more clinical trials are needed to establish effective doses, bioavailability, and long-term impacts on neurological disorders. Their multi-target mechanisms make flavonoids promising therapeutic candidates for supporting cognitive health. Table 1.7 describes flavonoids targeting neurological disorders involved in molecular targets [65–69].

Table 1.7 Flavonoids and molecular targets in neurological disorders.

Flavonoid	Molecular targets	Effects	Disease relevance
Quercetin	Nrf2, NF-κB	Activates Nrf2 signaling to induce antioxidant enzymes; inhibits NF-κB mediated inflammation	Alzheimer's, Parkinson's disease [65]
Luteolin	STAT3, NF-κB	Inhibits STAT3 and NF-κB activation to suppress inflammatory cytokines	Alzheimer's, multiple sclerosis [66]
Fisetin	ERK, PI3K/Akt	Activates ERK and PI3K/Akt pro-survival signaling in neurons	Alzheimer's, Huntington's [67]
EGCG	α-synuclein, Tau	Inhibits α-synuclein and tau aggregation; promotes clearance of misfolded proteins	Parkinson's, Alzheimer's [68]
Cyanidin	RAGE, PARP	Reduces binding of AGEs to RAGE receptor; inhibits PARP activation after excitotoxicity	Diabetic neuropathy, stroke [69]

1.5.3 Metabolic Syndrome: Flavonoids and Insulin Sensitivity

Metabolic syndrome includes a variety of interrelated risk factors such as abdominal fat, elevated blood pressure, lipid abnormalities and insulin resistance that predispose people to chronic diseases such as cardiovascular disease and type 2 diabetes [70]. Insulin resistance is considered the major underlying pathology. It is characterized by impaired responsiveness of peripheral tissues to insulin, resulting in defective glucose uptake and hyperglycemia. Persistent inflammation and oxidative stress significantly

contribute to the development of insulin resistance [71]. Emerging evidence suggests that certain dietary flavonoids may counteract insulin resistance through several mechanisms.

1.5.3.1 Alleviating Inflammation

Flavonoids target key signaling cascades such as mitogen-activated protein kinases (MAPK) and nuclear factor-kappa B (NF-κB) downstream signaling, which are often dysregulated in metabolic syndrome. Flavonoids have been shown to inhibit the activation of MAPKs and thereby reduce the expression of proinflammatory cytokines such as IL-6, TNF-alpha and CRP [72]. This modulation offers a promising therapeutic avenue for conditions such as insulin resistance and obesity, common components of metabolic syndrome. The flavan-3-ol catechin decreased CRP levels in individuals with metabolic syndrome [73] . Similarly, the NF-κB pathway is another important regulator of inflammatory reactions. Flavonoids have been found to inhibit the translocation of NF-κB into the nucleus, which is a crucial step in the activation of genes related to inflammation [74]. By blocking this translocation, flavonoids effectively dampen the inflammatory response, which is beneficial in treating metabolic syndrome.

1.5.3.2 Reducing Oxidative Stress

Flavonoids enhance endogenous antioxidant defenses and scavenge reactive oxygen species that impair insulin signaling. Quercetin reduced oxidative stress markers and improved antioxidant status in a rat model [3].

1.5.3.3 Preserving Pancreatic Beta Cell Function

Flavonoids help prevent glucotoxicity-induced damage to insulin-secreting pancreatic beta cells. Naringenin protected beta cells from apoptosis by modulating the IRS-2/PI3K/Akt pathway [75].

1.5.3.4 Regulating Glucose Uptake and Metabolism

Flavonoids may modulate pathways like AMPK, Akt, and GLUT4 to enhance insulin-stimulated glucose uptake. The soy isoflavone genistein increased glucose uptake in insulin resistant adipocytes via AMPK [76].

1.5.3.5 Improving Dyslipidemia

Certain flavonoids decrease serum triglycerides while raising HDL cholesterol through interactions with PPARs and modulation of lipid metabolism [77].

1.5.4 Cancer: Anticancer Potential of Flavonoids

Cancer remains one of the leading causes of death worldwide. Flavonoids have emerged as promising chemopreventive and chemotherapeutic agents against various cancers due to their abilities to modulate molecular pathways involved in carcinogenesis [78]. A crucial anticancer potential of flavonoids lies in their ability to modulate various biomarkers including mitogen-activated protein kinase (MAPK) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathways.

1.5.4.1 Anticancer Effect of Flavonoids Induced by MAPK Pathway

The MAPK pathway is implicated in cell proliferation, differentiation, and survival [79]. Aberrant activation of this pathway often contributes to oncogenic transformation and cancer progression [80]. Flavonoids such as quercetin and kaempferol have shown inhibitory effects on the MAPK pathway, specifically blocking the ERK1/2 and p38 MAPK sub-pathways. By down-regulating these pathways, flavonoids may inhibit cell proliferation and induce apoptosis in cancer cells [79, 81]

1.5.4.2 Targeting NF-κB Pathway in Cancer

The NF-κB pathway plays a critical role in immune response, inflammation, and cell survival (Hayden & Ghosh, 2008). Its dysregulation is linked to the promotion of cancer, making it an attractive target for anticancer therapies. Flavonoids like genistein and luteolin have demonstrated potent inhibitory effects on the activation of NF-κB [32]. By modulating this pathway, flavonoids can impact various aspects of cancer, from tumorigenesis to metastasis [82].

1.5.4.3 Dual Targeting of MAPK and NF-κB Pathway

Some flavonoids, such as apigenin, display dual inhibitory action on both MAPK and NF-κB pathways [83]. This dual targeting presents a multi-faceted approach, potentially enhancing the effectiveness of existing cancer

therapies and reducing side effects. Some other key anticancer mechanisms of flavonoids include the following.

1.5.4.4 Antioxidant and Anti-Inflammatory Effect in Cancer

Flavonoids display antioxidant properties by neutralizing reactive oxygen species (ROS), binding with redox-reactive metals, and boosting the body's own antioxidant mechanisms. This helps mitigate oxidative damage to DNA, proteins, and lipids that can cause mutagenesis. Flavonoids also broadly suppress cancer-promoting inflammation by downregulating pro-inflammatory mediators like NF-κB, COX-2, TNF-α, and IL-1β. The isoflavone genistein inhibited NF-κB transcriptional activity to reduce inflammation in a colitis-associated colon cancer model. Chronic intestinal inflammation promotes colon tumorigenesis [1].

1.5.4.5 Regulating Carcinogen Metabolism

The initiation phase of carcinogenesis involves biotransformation of procarcinogens by phase I enzymes like cytochrome P450s into reactive metabolites that can damage DNA. Certain flavonoids can inhibit specific CYP isoforms to reduce activation of cigarette smoke procarcinogens and heterocyclic amines from cooked meat. Flavonoids also stimulate the activity of phase II enzymes, such as glutathione S-transferases and UDP-glucuronosyltransferases, which helps in the more effective removal and neutralization of cancer-causing substances [78].

1.5.4.6 Cell Cycle Arrest by Flavonoids

Flavonoids have the ability to inhibit the growth cycle of cancerous cells by reducing the levels of specific cyclins (D1, A, and B1) and also cyclin-dependent kinases (CDKs), leading to a halt at various cell cycle stages such as G0/G1, S, or G2/M. For instance, apigenin has been shown to cause a G2/M phase stoppage in human cells related to prostate cancer, which is associated with a decline in the activity of the cyclin B1/cdc2 kinase. Flavonoids may also upregulate p53 and p21 expression to halt the cell cycle for DNA repair or promote senescence [84]. Research indicates that specific flavonoids, like quercetin, can disrupt the MAPK signaling pathway, resulting in halting of the cell cycle at the G2/M stage. In particular, flavonoids can inhibit the ERK1/2 pathway, a sub-pathway of MAPK, which subsequently affects the cyclin D and CDK4/6 complexes responsible for cell cycle progression [85]. This leads to the inhibition of cell

proliferation and the induction of apoptosis, as demonstrated by various cancer cell lines.

Similarly, the NF-κB signaling cascade has been observed to modulate the progression of the cellular cycle via the governance of cyclin D1, an integral protein involved in cell cycle regulation. Phytochemical compounds such as genistein and apigenin have demonstrated the capability to attenuate the activation of NF-κB, consequently resulting in the diminished expression of cyclin D1 and the induction of a halt in the cellular cycle at the G1 stage [86].

1.5.4.7 Anti-Proliferative Activities of Flavonoids

Abnormal proliferation is a hallmark of cancer cells. Flavonoids suppress signaling pathways that control growth and proliferation like MAPK, PI3K/Akt/mTOR, NF-κB and Wnt/β-catenin. For instance, the flavonol quercetin inhibited Akt and mTOR phosphorylation, reducing prostate cancer cell proliferation. Flavonoids also decrease growth factor receptors like EGFR and IGF-1R while activating tumor suppressor genes [87].

1.5.4.8 Inhibiting Angiogenesis and Metastasis

Tumor growth and metastasis require angiogenesis to supply nutrients and spread respectively in microenvironment. Flavonoids, such as luteolin, demonstrate the ability to inhibit such as vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs). The VEGF is a crucial signaling molecule that induces angiogenesis, which is essential for tumor growth. MMPs, on the other hand, are enzymes that degrade the extracellular matrix, facilitating the migration of endothelial cells to form new blood vessels. By suppressing these key molecular players, flavonoids can significantly affect the processes of endothelial cell migration, proliferation, and tubule formation. The modulation of these pathways has far-reaching implications for halting tumor growth and limiting metastatic potential [88]. Another perspective on the interaction between flavonoids and angiogenesis is evident through their modulation of the mitogen-activated protein kinase (MAPK) signaling cascade. MAPK is a critical cellular signaling pathway that can regulate various angiogenic factors like VEGF. Quercetin, a type of flavonoid, has been demonstrated to exert anti-angiogenic effects by inhibiting the activation of the MAPK pathway. This downregulation directly impacts VEGF expression, thereby providing an additional mechanism through which flavonoids can inhibit angiogenesis. nuclear factor-kappa B (NF-κB) serves as another noteworthy regulator

of angiogenesis. It primarily influences this process by upregulating pro-angiogenic factors such as interleukin-8 (IL-8) and VEGF. Flavonoids like genistein are known to act as NF-κB inhibitors. By blocking the activity of NF-κB, these compounds have been shown to successfully reduce angiogenesis in preclinical models, providing another strategic point of intervention to halt tumor growth and metastasis [89]. Inhibitors of NF-κB, such as the flavonoid genistein, have been shown to reduce angiogenesis in preclinical models [90].

1.5.4.9 Enhancing Apoptosis

Caspases constitute a class of enzymatic proteins pivotal in both the initiating and execution phases of programmed cell death, commonly referred to as apoptosis. Various flavonoids are capable of activating these caspases, thereby catalyzing the dismantling of cellular components, and leading to controlled cell death. This activation is particularly intriguing, given that many anti-cancer drugs aim to induce apoptosis through caspase activation. Thus, flavonoids could serve as a natural alternative or adjunct to existing therapies. Another molecular target of flavonoids is the Bcl-2 family of proteins, known for their role in the negative regulation of apoptosis. By inhibiting the action of these anti-apoptotic proteins, flavonoids can tip the cellular balance toward apoptosis, countering the pro-survival tendencies of cancerous cells [91]. Similarly, the realm of mitogen-activated protein kinase (MAPK) signaling pathways represents an area in which flavonoids have demonstrated considerable potential. This pathway is implicated in several cell processes, including survival, growth, and apoptosis. Dysregulation of MAPK often contributes to aberrant cell behavior, including unchecked proliferation and survival. Flavonoids appear to recalibrate this pathway, restoring its role in moderating cell survival and facilitating apoptosis. Inhibition of this particular pathway has the potential to shift the paradigm toward programmed cell death. For example, polyphenolic compounds such as quercetin have been demonstrated to encourage apoptotic processes by attenuating the enzymatic activity of ERK1/2, an integral element of the MAPK signaling cascade. This, in turn, results in the diminished expression of anti-apoptotic molecules like Bcl-2 [92, 93]. These broad anticancer effects make flavonoids promising supplemental therapies. However, improving bioavailability remains a major challenge for their clinical effectiveness. Further research should focus on validating their anticancer potential in humans through well-designed clinical trials. Table 1.8 describes the role of flavonoids against cancer [94–96].

Table 1.8 Flavonoids as hallmarks for targeting cancer.

Flavonoid	Targeted cancer hallmark	Mechanism of action	Targeted cancer
Apigenin	Evading apoptosis	Induced caspase-dependent apoptosis by inhibiting PI3K/Akt signaling	Prostate, leukemia [94]
EGCG	Limitless replicative potential	Caused senescence by upregulating p21 and p27	Skin, breast [95]
Quercetin	Sustained angiogenesis	Suppressed VEGF production and secretion	Ovarian, gastric [59]
Genistein	Tissue invasion and metastasis	Downregulated MMPs and inhibited cell motility	Prostate, melanoma [41]
Fisetin	Evading immune destruction	Increased tumor cell recognition by NK cells	Lung, pancreatic [67]
Anthocyanins	Genome instability	Reduced DNA damage by scavenging reactive oxygen species	Oral, esophageal [96]

1.6 Flavonoids' Role in Neurodegenerative Disorders

Neurological degenerative conditions, such as Alzheimer's disease and Parkinson's disease, exhibit characteristics of continual neuronal degradation and apoptosis. Factors such as oxidative imbalances and inflammatory processes are posited as fundamental mechanisms contributing to the advancement of neuronal degeneration. Flavonoids—plant pigments found in foods like tea, berries, cocoa, and onions—have emerged as promising bioactive compounds that may protect neurons and brain function [97]. Multiple lines of research, from epidemiological studies to clinical trials, have linked greater flavonoid intake to better cognitive performance, lower rates of cognitive decline in aging populations, and

reduced risk of dementia. Flavonoids' antioxidant and anti-inflammatory properties appear to counteract some of the damage to brain cells seen in Alzheimer's, Parkinson's, and other neurodegenerative disorders [98]. Specific flavonoids like anthocyanins in berries, catechins in tea, and quercetin in apples have exhibited neuroprotective effects in laboratory and animal studies. Proposed mechanisms include direct antioxidant activity, increasing endogenous antioxidant defenses, inhibiting neuron apoptosis, reducing neuroinflammation by modulating microglia, and decreasing tau hyperphosphorylation [99].

1.7 Mechanisms of Action

Several mechanisms have been proposed as to how flavonoids may attenuate neurodegeneration, such as:

- Antioxidant effects—The flavonoid compounds exhibits dual roles in antioxidant defense mechanisms, functioning both as reactive oxygen species (ROS) neutralizers and as facilitators in the upregulation of intracellular antioxidant enzymes such as superoxide dismutase and catalase. These activities collectively contribute to the mitigation of oxidative neuronal impairment [3].
- Anti-inflammatory effects—Flavonoids act as suppressors of pro-inflammatory cytokine secretion from microglial cells while concurrently diminishing the activation of neuroinflammatory signaling pathways, notably the NF-κB cascade. Consequently, these actions mitigate harmful inflammatory reactions within cerebral tissue [97].
- Anti-apoptotic effects—Flavonoids can inhibit apoptosis regulators like caspases, Bax, and p53, preventing programmed neuron death [93].
- Enhancing neurogenesis—Some evidence indicates that flavonoids may stimulate neuronal growth factors like BDNF to induce growth and proliferation of neurons [100].
- Inhibiting tau aggregation—Flavonoids may prevent accumulation and aggregation of phosphorylated tau proteins, a hallmark of Alzheimer's pathology [101] .
- Improving cerebrovascular function—Increased cerebral blood flow induced by flavonoids ensures that neuron energy demands are met [102].

- Neurotransmitter modulation—Flavonoids interact with receptors for neurotransmitters like GABA, serotonin, and acetylcholine to maintain signaling [103].

1.7.1 MAPK and NF-κB Pathway in Neurodegeneration

The MAPK (MAPK) signaling cascade regulates in cellular processes such as differentiation, proliferation, and cell viability. Anomalies in the regulation of this pathway are implicated in the onset of neurodegenerative disorders and apoptotic events in neuronal cells [104]. Various flavonoids, such as quercetin and resveratrol, have been shown to attenuate MAPK activation, thus reducing inflammation and neuronal apoptosis [105]. The NF-κB pathway is crucial in mediating in inflammatory reactions, and persistent activation of this pathway has been associated with the advancement of disorders characterized by neural degeneration [106]. Flavonoids like apigenin and luteolin can inhibit NF-κB activation, thus lowering the inflammatory response in neural tissues [107]. Some flavonoids like curcumin demonstrate dual inhibitory actions on both MAPK and NF-κB pathways, making them effective in reducing both neuroinflammation and neuronal apoptosis [108]. Among thousands of flavonoids, compounds like anthocyanins, catechins, proanthocyanidins, quercetin, and hesperidin have shown particular promise for neuroprotection [99]:

- Anthocyanins: Found in colored fruits and vegetables, protected against cognitive decline in animal studies.
- Catechins: Abundant in green tea, may prevent Alzheimer's pathogenesis by reducing amyloid-beta aggregation and tau phosphorylation.
- Proanthocyanidins: In grapes and cocoa, improve cerebral blood flow and vasodilation.
- Quercetin: Potent antioxidant found in apples, onions, tea; may reduce oxidative damage to neurons.
- Hesperidin: Found in citrus fruits, demonstrated anti-inflammatory and neuroprotective activities in preclinical studies.

1.7.2 Various Key Research Findings in Neurodegenerative Diseases Versus Flavonoids

While most research to date has been preclinical, some human trials have confirmed the potential for flavonoids to improve memory, limit cognitive

decline, and reduce neuroinflammation markers. However, optimal dosing and intake methods are still being investigated.

1. Animal studies show that flavonoid supplementation can prevent cognitive decline, improve learning and memory, reduce neuroinflammation and oxidative damage, and protect neuron viability in models of neurodegenerative disease [103].
2. Epidemiological studies in aging cohorts, consistent empirical evidence from epidemiological investigations suggests a negative correlation between habitual consumption of flavonoids and the incidence of cognitive deterioration, including neurodegenerative conditions such as Alzheimer's and Parkinson's disease [100].
3. Clinical trials demonstrate improved memory, attention, and information processing speed in older adults after flavonoid interventions. fMRI studies show enhanced brain connectivity and activation patterns [109].

However, human research remains limited with considerable variability in flavonoid doses and types, requiring further well-controlled trials. It is unclear which specific flavonoids are most potent, and what combinations achieve synergistic effects. The neuroprotective benefits of flavonoids likely depend on long-term, regular consumption of a variety of flavonoid-rich foods rather than short-term high doses. Further human-centric clinical investigations are imperative for establishing the optimal dosages and identifying the most efficacious nutritional origins. Nonetheless, prevailing data suggest that a diet abundant in flavonoids may constitute an essential element in mitigating neurodegenerative processes associated with aging, thereby sustaining cognitive functions in later life stages. Incorporating flavonoid-containing foods like berries, green tea, dark chocolate, and red wine into a balanced, healthy diet seems a profound step for maintaining neuron health and function well into old age. Though research continues, flavonoids look promising as natural compounds that could aid in staving off the damages of neurodegenerative disease.

1.8 *In Vitro* Experimental Approaches

In vitro studies involve the use of isolated cells or tissues to understand the cellular effects of specific compounds. *In vitro* studies demonstrate flavonoids' ability to inhibit molecular processes associated with Alzheimer's,

Parkinson's and dementia, including amyloid-beta and tau aggregation, imbalance of neurotransmitters, apoptosis, and microglia activation [110]. There are a variety of experimental techniques that are helpful to uncover the mechanism of action flavonoids and the underlying signaling pathways.

1.8.1 Use of Cell Culture Models for Assessment of Flavonoid Activity

Cell culture models serve as a cornerstone in investigating the underlying signaling pathways modulated by various drugs. In a nutshell the primary cells or cell lines are cultured under controlled environmental of temperature, pH, humidity, gases, and nutrients conditions. The cell line usually includes human cancer cells, immune cells, and endothelial cells, each with unique features for studying the complex activity of flavonoids. Flavonoids administered at different concentrations and durations shows different effects on cellular signaling [111].

1.8.2 Western Blotting for Protein Dynamics

Western Blotting is a sophisticated method that allows scientists to quantitatively assess protein levels in a given cell sample. When flavonoids are introduced into a cellular environment, it can elicit a range of responses that often involve changes in the expression of proteins. This process can yield both qualitative and quantitative concentration of protein expression. Thus, the influence of flavonoids on protein levels can be comprehensively studied using Western blot, offering insights into potential mechanisms of action [112].

1.8.3 PCR for Analysis of the Transcriptional Effects of Flavonoids

The application of real-time polymerase chain reaction (PCR) serves as an influential analytical methodology for the precise and sensitive examination of the transcriptional consequences elicited by flavonoid compounds on genetic expression. This technique enables researchers to quantitatively assess how genes expression occurs in response to flavonoid exposure [113].

1.8.4 Reporter Assays

Cells are genetically modified to express reporter genes under the control of specific signaling pathway promoters. Flavonoid treatments can then be assessed by measuring reporter gene expression [114].

1.8.5 High-Throughput Screening

This approach involves testing a large number of flavonoid compounds on multiple cell lines to identify potential candidates for further investigation [115].

1.9 *In Vitro* Studies on Flavonoid-Mediated Signaling Modulation

Experimental platforms utilizing cell cultures have been invaluable for elucidating the intricate molecular processes and signaling cascades that are modulated by flavonoid compounds. Key findings from *in vitro* studies include:

1.9.1 NF-κB Pathway Modulation

The flavonoid compound naringenin, commonly found in citrus fruits, attenuated the activation of NF-κB, induced by TNF-α, within a specific intestinal epithelial cell line. This inhibitory effect was mediated through the suppression of both IKK enzyme function and the phosphorylation and subsequent degradation of IκBα [116].

- In lipopolysaccharide (LPS)-stimulated macrophages, the flavone apigenin inhibited NF-κB nuclear translocation, binding to DNA, and subsequent transcription of inflammatory genes.

1.9.2 MAPK Signaling Effects

- Quercetin prevented MAPK pathway activation in breast cancer cells by suppressing MEK1 and Raf-1 kinase activities and blocking ERK1/2 and JNK phosphorylation.

- Genistein, an isoflavone derived from soy, suppresses the UVB-mediated activation of mitogen-activated protein kinase (MAPK) pathways as well as the consequent initiation of activator protein-1 (AP-1) transcriptional activity in human keratinocyte cells [117].

1.9.3 Modulating Apoptosis and Survival Pathways

- Luteolin instigated programmed cell death in hepatocellular carcinoma cells by inhibiting the phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling cascade and facilitating the activation of the phosphatase and tensin homolog (PTEN), a known tumor suppressor.
- Fisetin suppressed the expression of anti-apoptotic proteins such as B-cell lymphoma 2 (Bcl-2) and B-cell lymphoma-extra-large (Bcl-xL), while simultaneously attenuating the activity of the PI3K/Akt and mTOR pathways, thereby triggering apoptosis in cells of prostatic carcinoma [26]. The existing body of research provides compelling evidence that flavonoids can regulate critical signaling pathways implicated in inflammation, cell proliferation, survival, and programmed cell death, not only in oncological contexts but also in cells pertinent to other diseases.

1.10 Animal Models and Preclinical Investigations

In biomedical research, the utilization of animal-based experimental systems and preliminary studies serves as a crucial intermediary phase that facilitates the translation of foundational scientific inquiries into human clinical evaluations. Such investigations are instrumental in ascertaining not only the safety but also the effectiveness and the underlying biochemical pathways of prospective treatment modalities prior to their application in human participants.. This topic focuses on the methodologies, significance, and common experimental models in flavonoids research.

1.11 Animal Models and Methodologies

1. Choice of Animal Species. The selection of an animal model is critical for the success of the research. It is guided by the

physiological and genetic similarities between the animal and humans. Widely used animal models include mice, rats, rabbits, dogs, and even non-human primates. Each has its pros and cons depending on the specific aims of the study [118].

2. Disease Modeling. This involves replicating human disease conditions in animals either through genetic modification or exposure to specific environmental factors. This allows scientists to investigate how diseases develop and progress, which is crucial for evaluating the effectiveness of prospective treatments [119].
3. Pharmacokinetics and Pharmacodynamics: Animal models offer an indispensable platform to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of therapeutic agents. PK studies in animal models provide a comprehensive understanding of how a drug is absorbed, distributed, metabolized, and excreted (ADME) by the body. Researchers often employ techniques such as liquid chromatography-mass spectrometry (LC-MS) to quantify drug concentrations in biological matrices, thereby ascertaining bioavailability, half-life, and clearance rates. Concurrently, PD studies are conducted to delineate the biochemical and physiological effects of a drug at the cellular or systemic level. These can include the assessment of receptor binding, enzyme inhibition, and cellular signaling pathways. Combined PK/PD modeling allows researchers to link drug exposure levels with observed effects, paving the way for optimized dosing regimens and enhanced therapeutic efficacy [120].
4. Efficacy Studies: In the arena of preclinical research, the emphasis is not merely on how a drug interacts with the body, but also on its ability to exert the desired therapeutic effects. Animal models, chosen for their physiological and genetic similarities to humans, are instrumental for conducting efficacy studies. Through controlled interventions, which may include the administration of drugs or therapeutic regimens, the impact of these treatments on disease markers is meticulously monitored. Outcomes such as symptom relief, the arrest of disease progression, or even reversal of pathological changes are keenly observed. Advanced techniques like *in vivo* imaging, histological assessments, and molecular analyses are employed to quantify these outcomes, facilitating a

robust evaluation of treatment efficacy. Researchers administer potential interventions (drugs and therapies) and monitor the impact on disease progression, symptom relief, or other relevant outcomes [121].

5. Toxicology and Safety Assessments: A fundamental aspect of preclinical research involves toxicology and safety assessments. These studies in animal models aim to establish the therapeutic window, which is the range between the lowest effective dose and the dose that may cause adverse effects. A variety of biochemical, hematological, and histopathological tests are undertaken to identify potential toxicities, including hepatotoxicity, nephrotoxicity, or cardiotoxicity. Acute and chronic toxicity studies further delineate the safety profile of the drug, often necessitating dose adjustments or reformulation for subsequent clinical trials. Animal models aid in determining the safety profiles of interventions, identifying potential adverse effects, and establishing safe dosages [122].
6. Mechanistic Studies: Understanding the mechanisms underlying both disease progression and therapeutic intervention is crucial for the development of new treatments. Animal models are highly useful in mechanistic studies that probe the biological underpinnings of diseases and responses to therapies. These studies often focus on signaling pathways, gene expression profiles, and protein interactions, employing advanced techniques such as transcriptomics, proteomics, and metabolomics. The data generated offer valuable insights into target identification and validation, thereby providing a rational basis for the optimization of therapeutic strategies. Animal models provide insights into the underlying biological mechanisms involved in disease progression and response to interventions [123].

1.11.1 Significance of Animal Models

Research using animal models has been helpful in elucidating the biological functions and underlying pathways through which flavonoids exert their effects, as initially observed in *in vitro* studies. They allow researchers to manipulate variables, observe responses, and gather data that would not be feasible or ethical in human studies. Animal models contribute to our understanding of disease progression, drug pharmacokinetics, toxicology,

and the effects of interventions on whole systems. Common experimental models include the following.

1.11.2 Inflammation and Oxidative Stress Models

Investigation into animal-based models of oxidative stress and inflammation has disclosed intricate interrelations and underlying processes that hold significant implications for the understanding and treatment of metabolic disorders and persistent inflammatory conditions in humans.

1.11.3 Quercetin in Rat Models of Arthritis

The efficacy of quercetin was investigated in rat models exhibiting symptoms analogous to human arthritis. Administration of quercetin through oral routes revealed a dose-dependent suppression of joint inflammation and edema. This effect can be primarily attributed to a multi-faceted reduction of inflammation mediators. For instance, the inflammatory cytokines, which are protein signaling molecules involved in systemic inflammation, were found to be significantly lowered. Moreover, nitric oxide, a chemical compound implicated in pain and inflammation, was also reduced. Most notably, it has been ascertained that quercetin plays a role in attenuating the functional activity of nuclear factor kappa B (NF-κB), a protein assembly crucial for DNA transcription, cytokine synthesis, and cellular longevity. These comprehensive data suggest that quercetin may serve as an instrumental component in strategies aimed at combating persistent inflammatory conditions, including arthritis, through the regulation of various biochemical signaling pathways.

1.11.4 Naringenin in Mice Models of Obesity-Induced Inflammation

On a different spectrum of investigation, the effects of naringenin were explored concerning inflammation triggered by obesity in murine models. Mice subjected to a diet designed to induce obesity were simultaneously administered naringenin. Intriguingly, the results indicated that these mice exhibited diminished levels of systemic inflammation and enhanced insulin responsiveness in contrast to their non-supplemented control group.

The most salient features of this reduction were observed in adipose tissue—essentially fat storage cells where macrophage infiltration was considerably suppressed. Macrophages are white blood cells implicated in

inflammation, and their reduction suggests a lowering of adipose tissue inflammation. In addition, the levels of pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF-α) and Interleukin-6 (IL-6) exhibited a notable reduction. This is critical since both cytokines are implicated in the exacerbation of metabolic diseases.

Additionally, the naringenin-treated mice showed enhanced insulin signaling pathways, indicating improved insulin sensitivity. This not only reinforces the anti-inflammatory properties of naringenin but also underscores its potential role in mitigating complications related to insulin resistance, a common consequence of obesity [3].

1.11.4.1 Cancer Models

a) In mice with estrogen-induced mammary carcinogenesis, dietary genistein decreased tumor size and multiplicity by inducing apoptosis and inhibiting cell proliferation through modulation of Bcl-2 proteins and suppression of ERK and Akt signaling [78].
b) In a murine xenograft model simulating prostate malignancy, the administration of oral catechin hydrate resulted in notable tumor size reduction. This effect was mediated through dual mechanisms: (1) hindrance of cellular proliferation, as evidenced by its influence on the cyclin B1/cdc2 complex, and (2) suppression of angiogenic processes, demonstrated by the decreased expression of Vascular Endothelial Growth Factor (VEGF).

1.11.4.2 Neurodegeneration Models

a) In a rodent experimental model of Parkinson's disease induced by 6-hydroxydopamine lesions, the administration of hesperetin, effectively inhibited the neurodegeneration of dopaminergic neurons. Additionally, it attenuated markers of oxidative damage within the substantia nigra, potentially through its antioxidative properties [117].
b) Dietary anthocyanins from blackcurrants alleviated Alzheimer's disease-associated memory deficits in mice expressing human amyloid precursor protein through activation of autophagy pathways and reduction of neuronal inflammation. These representative preclinical studies provide important validation of

the bioactivities of flavonoids observed *in vitro*. Animal models will continue to be vital in elucidating flavonoid mechanisms of action and investigating their preventative and therapeutic potential for diverse chronic diseases.

1.12 Human Clinical Trials: Efficacy and Safety of Flavonoid Interventions

While animal and cell culture models support potential health benefits of flavonoids, confirmation in human trials is essential to translate findings into therapeutic recommendations. They help determine the optimal dosages, safety profiles, and potential therapeutic applications of flavonoid interventions in diverse populations. Some key clinical studies include the following:

1.12.1 Cardiovascular Disease

The significance of flavonoids in maintaining cardiovascular well-being has increasingly become a focal point of scholarly inquiry. As naturally occurring polyphenolic substances, flavonoids are predominantly found in produce such as fruits and vegetables, as well as in specific beverages including tea and wine. Notably, existing studies indicate that these compounds are instrumental in modulating cardiovascular pathologies [124].

a) In a controlled, randomized study conducted over a twelve-month period with metabolic syndrome patients, it was observed that the regular intake of anthocyanin-rich purple grape juice yielded statistically noteworthy ameliorations in systolic and diastolic blood pressure, low-density lipoprotein cholesterol levels, and additional cardiovascular health indicators when juxtaposed with a placebo beverage.
b) In a study focused on males diagnosed with coronary artery disease, a six-week regimen involving the daily intake of 366 mg of epigallocatechin gallate, sourced from green tea extract, exhibited positive effects on endothelial functionality and circulatory dynamics. Additionally, the research noted a reduction in the levels of oxidized low-density lipoprotein cholesterol and inflammatory indicators such as C-reactive protein.

1.12.2 Cancer

Numerous scientific studies have endeavored to assess the therapeutic potential of flavonoids in oncological interventions [93].

a) In men with prostate cancer, a low-fat diet combined with green tea catechin extracts (600 mg/day) for 3–6 weeks prior to prostatectomy reduced tumor markers like VEGF and prostate-specific antigen (PSA) compared to the control group.
b) Women with breast cancer randomized to receive 200 mg/day isoflavones including genistein for 2–3 weeks before surgery exhibited reduced cell proliferation rates in tumor samples compared to placebo.

1.12.3 Memory and Cognition

The influence of flavonoids on cognitive function and memory retention represents an emerging field of scholarly inquiry, particularly concerning age-related cognitive decline and neurodegenerative conditions. Recent clinical investigations have begun to elucidate the potential neuroprotective capacities of flavonoids, compounds abundantly found in an array of dietary sources such as fruits, vegetables, and tea [125].

Postmenopausal women who consumed a blueberry and grape juice mixture high in anthocyanins (2 servings/day) for 12 weeks showed increased neural activation during memory tasks as well as improved memory function versus placebo juice. Overall, clinical studies report excellent safety and tolerability of flavonoid interventions at doses of 30–600 mg/day up to 1 year. More large-scale, high-quality human trials are still needed to firmly establish therapeutic efficacy, optimal dosing, and long-term impacts on chronic disease outcomes. Nevertheless, current evidence supports potential benefits of flavonoids for human health.

1.13 Mechanism of Action

1.13.1 Modulation of MAPK Signaling Pathways

Mitogen-activated protein kinase (MAPK) signaling pathways represent a phylogenetically preserved mechanism essential for mediating cellular reactions to various external cues such as stress inducers, cytokines, and growth factors. Dysregulation of MAPK signaling contributes to cancer,

inflammation, and other chronic diseases. Flavonoids demonstrate promising abilities to modulate MAPK pathways like JNK, p38, and ERK1/2 to mitigate downstream effects. For instance, the flavonol quercetin inhibited JNK phosphorylation and TNF-α production in activated macrophages by blocking MAPK kinase kinase. The flavan-3-ol EGCG suppressed lipopolysaccharide-induced ERK1/2 activation in macrophages, attenuating release of IL-6 and TNF-α. Flavonoids may exert these effects by modulating upstream kinases, phosphatases, scaffold proteins, and cross-talk mechanisms within MAPK cascades. Elucidating the precise molecular targets of flavonoids within MAPK pathways may enable optimization of their therapeutic potential [26].

1.13.2 NF-κB Inhibition

The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) serves as a pivotal transcriptional regulator, governing processes such as immunological reactions, programmed cell death, cellular expansion, and inflammatory responses. Dysregulated activation of this transcription factor has been implicated in a myriad of pathological conditions, encompassing oncogenesis, neurodegenerative disorders, and chronic inflammatory states. Bioactive compounds known as flavonoids exhibit a robust inhibitory effect on NF-κB activation, exerting this influence through a diverse array of molecular pathways. In gastric carcinoma cells, quercetin obstructed the translocation of NF-κB into the nucleus by hindering the enzymatic activity of IKKβ, thereby averting the phosphorylation and subsequent degradation of IκBα. Similarly, genistein mitigated the activation of NF-κB induced by TNF-α through the suppression of p65 acetylation and its DNA-binding capacity. Additional hypothesized mechanisms encompass the direct immobilization of NF-κB subunits, attenuation of nuclear migration, and inhibition of interactions between NF-κB and DNA. By inhibiting NF-κB activity, flavonoids may mitigate inflammatory responses and disease progression [126].

1.13.3 Regulation of Pro-Inflammatory Cytokines

Flavonoids have been shown to exert strong inhibitory effects on the generation of pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and IL-8. These effects are partially attributed to the suppression of the NF-κB and MAPK signaling cascades. For instance, luteolin mitigates the release of TNF-α, IL-6, and IL-1β from stimulated microglia, which is linked to its capacity to obstruct the phosphorylation of ERK, p38, and JNK. Similarly,

apigenin attenuates the secretion of IL-6, IL-8, and TNF-α in monocytes exposed to LPS, a phenomenon correlated with the downregulation of NF-κB and AP-1 activity. Additionally, flavonoids may directly bind cytokines through interactions facilitated by their phenolic groups. By attenuating the release of inflammatory cytokines, flavonoids can disrupt positive feedback loops that amplify and sustain inflammation [127].

1.13.4 Alteration of Oxidative Stress Pathways

Flavonoids beneficially alter oxidative stress dynamics, which play a pivotal role in the pathogenesis of chronic ailments, by employing both immediate and mediated antioxidative mechanisms. Specific flavonoids exhibit the ability to counteract reactive oxygen species (ROS) and sequester redox-sensitive metals, which act as catalysts for the formation of free radicals. Additionally, flavonoids stimulate the body's intrinsic antioxidant defense systems. For instance, quercetin upregulated glutathione peroxidase, superoxide dismutase and catalase expression in hepatic cells by activating Nrf2 and blocking Keap1 inhibition. Other flavonoids like catechins may also boost mitochondrial function and quality control processes to reduce ROS emission. These synergistic mechanisms strengthen endogenous antioxidant capacity against oxidative insults [3].

1.13.5 Effects on Apoptosis and Cell Proliferation

Dysregulated cellular proliferation coupled with impaired apoptotic mechanisms constitute fundamental characteristics of cancerous states. Certain flavonoid compounds have shown potential in modulating these pathways, thereby exhibiting anti-cancer properties. Specifically, fisetin has been observed to initiate caspase-dependent apoptotic mechanisms in lung cancer cell lines by counteracting the PI3K/Akt/mTOR signaling cascade and reducing the levels of the anti-apoptotic protein, Bcl-2. Similarly, apigenin has been found to instigate apoptosis in pancreatic cancer cells, primarily by inhibiting the PI3K/Akt pathway and facilitating the enzymatic cleavage of caspase-3 and PARP. Moreover, flavonoids have been implicated in the regulation of cell cycle progression and growth restriction by altering the activities of cyclins, cyclin-dependent kinases (CDKs), and cell cycle checkpoint proteins. Further research into the apoptotic mechanisms of flavonoids could expand their therapeutic potential for cancer and other diseases of uncontrolled cell growth [93].

1.14 Future Research Directions for Improved Flavonoids Use

1.14.1 Improving Bioavailability of Flavonoids

The therapeutic efficacy of flavonoids depends on their bioavailability to reach target tissues and exert biological effects [128]. However, certain flavonoids have limited absorption and rapid metabolism/elimination. Strategies to enhance bioavailability could include the following:

1. Synthesis of flavonoid structural analogs with improved stability and membrane permeability
2. Formulation with absorption enhancers like lipids, emulsifiers, and nanocarriers
3. Design of prodrugs that promote intestinal uptake and bypass first-pass metabolism
4. Modulation of intestinal and hepatic metabolism through selective enzyme inhibition
5. Identification of metabolites with enhanced potency compared to parent compounds

1.14.2 Elucidating Mechanisms of Action

While some mechanisms of action have been defined for certain flavonoids, many details remain unclear. Further research could:

1. Elucidate precise molecular targets of flavonoids within signaling cascades
2. Investigate poorly understood mechanisms like epigenetic modulation
3. Examine effects of flavonoids on cell processes like proteostasis, mitochondrial function, and the microbiome
4. Use omics approaches to identify novel cellular pathways and targets affected
5. Integrate computational modeling to predict flavonoid interactions with biomolecules

1.14.3 Exploring Synergistic Effects with Other Compounds

Investigating combinations of flavonoids with other bioactive could reveal synergistic interactions that enhance efficacy. Potential areas include:

1. Flavonoid-flavonoid combinations capitalizing on complementary mechanisms
2. Formulations with other polyphenols like curcumin to improve bioavailability
3. Nutraceutical formulations combining flavonoids with vitamins, minerals, probiotics etc.
4. Integration into existing therapeutic regimens to bolster treatment effects

1.14.4 Further Epidemiological and Intervention Studies

More rigorous clinical data are critical to validate the therapeutic potential of flavonoids. Additional well-controlled trials should be performed taking into consideration:

1. Recruitment of large and more diverse patient cohorts.
2. Use accurate biomarker quantification and pharmacokinetic analysis.
3. Test optimized flavonoid formulations for bioavailability and efficacy.
4. Examine sustained, long-term outcomes in target populations.
5. Systematically assess dose–response relationships.

Further observational studies should also clarify associations between flavonoid intake and disease risk.

1.14.5 Emphasis on the Therapeutic Potential of Flavonoids

In total, the broad-spectrum bioactivities of flavonoids highlighted herein in conjunction with their clinical safety verify their potential to address the multifactorial and intersecting etiologies underlying most chronic diseases. As multi-target molecules capable of interacting with numerous proteins and signaling networks, flavonoids are uniquely equipped to influence disease progression in a holistic manner. Their abilities to selectively suppress aberrant inflammatory and oncogenic signaling while activating protective pathways make flavonoids ideal adjunctive or preventative therapies.

Flavonoids may prove especially impactful for chronic conditions precipitated by inflammation and oxidative stress like cardiovascular and neurodegenerative diseases where current pharmaceutical interventions remain limited. Additionally, the synergistic actions of different flavonoid subclasses could be harnessed through selective combinations for enhanced therapeutic benefit. Intensified interdisciplinary research efforts promise to open new vistas into the optimal application of these elegant polyphenolic compounds for fundamental health promotion and disease mitigation.

1.14.6 Importance of Continued Research in the Field

While incredible strides have elucidated activities and mechanisms of action of flavonoids, much work remains to fully realize their potential in enhancing human health. Improving bioavailability through novel formulations remains key, as most flavonoids have limited absorption. Better understanding of how metabolism affects circulatory and tissue levels of active flavonoids versus inactive metabolites will clarify optimal dosing strategies. Large-scale human trials with clinical endpoints are imperative to firmly establish efficacy. Systems biology and multi-omics approaches incorporating metabolomics, proteomics, and transcriptomics will help unravel the full extent of flavonoid interactions within interconnected molecular networks during disease processes. As research continues to fervently investigate these bioactive phytochemicals, the future looks bright for flavonoids to fulfill their promise as potent, versatile nutraceuticals for combating some of the most pervasive and burdensome chronic diseases afflicting global populations.

1.15 Conclusion

Extensive *in vitro* evidence outlines the abilities of flavonoids to favorably modulate practically all of the major pathogenic mechanisms underlying conditions like cancer, cardiovascular disease, neurodegeneration, diabetes, and osteoporosis. Flavonoids have been shown to mitigate long-term inflammatory responses by modulating key intracellular signaling cascades such as nuclear factor-kappa B (NF-κB), mitogen-activated protein kinases (MAPK), and Janus kinase/signal transducer and activator of transcription (JAK/STAT). These pathways play a critical role in regulating the synthesis of pro-inflammatory cytokines. Additionally, flavonoids exhibit strong antioxidative capacities through the activation of native antioxidant

enzymes, neutralization of free radical species, and complexation of redox-reactive metallic ions. They regulate apoptosis and proliferation by targeting PI3K/Akt, mTOR, Wnt/β-catenin, and other oncogenic cascades. They beneficially interact with receptors, kinases, and transcription factors crucial to neuronal function and survival.

Animal studies provide pivotal support for the translation of these molecular activities into actual disease prevention and treatment. Human clinical trials, while still limited in number and scale, have yielded promising results such as improved endothelial function, blood pressure, cognition, and markers of cardiovascular risk, cancer proliferation, and neuroinflammation. The excellent safety profile displayed by flavonoids further adds to their appeal as therapeutic agents.

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