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REVIEW ON ROLE OF BIOFLAVONOIDS IN TREATMENT OF METABOLIC SYNDROME

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ABSTRACT

The development of dietary flavonoids as multipurpose bioactive substances has important ramifications for managing and preventing chronic illnesses. This study offers a thorough synthesis of flavonoid taxonomy, chemistry, dietary sources, and bioavailability using the most recent experimental, clinical, and epidemiological data, paying particular emphasis to their structural variety and fundamental processes. With an emphasis on the regulation of vital cellular pathways such, NF-κB, and AMPK, mechanistic developments pertaining to antioxidant, anti-inflammatory, antibacterial, anti-obesity, cardioprotective, and anticancer actions are addressed. Clinical data and evidence from in vitro and in vivo models show that flavonoids can control oxidative stress, inflammation, metabolic syndrome, adipogenesis, and angiogenesis. There is evidence of an inverse relationship between dietary patterns high in flavonoids and the risk of obesity, cancer, cardiovascular disease, and neurological disorders. Translational issues still exist, nonetheless, including as bioavailability and delivery strategy improvement. In summary, a diverse dietary intake of flavonoids is a scientifically supported strategy for preventing non-communicable diseases, but more study is necessary to improve clinical applicability and clarify molecular mechanisms.

KEYWORDS: Dietary polyphenols, antioxidant; anti-inflammatory; anticancer, Antiobesity, Cardioprotective.

INTRODUCTION

A broad class of naturally occurring substances with a variety of phenolic structures is called flavonoids. They are widely present in our food through fruits, vegetables, cereals, bark, roots, stems, flowers, tea, and wine and are categorized as secondary metabolites of plants. Flavonoids are currently regarded as crucial elements in a range of nutraceutical, pharmacological, and medical uses because of their numerous health advantages. Their potent biological

qualities, such as their anti-oxidative, anti-inflammatory, anti-mutagenic, and anti-carcinogenic effects, are what give them their value. Flavonoids are more than just passive elements in nature. They actively participate in plant life. They offer protection from pests and are essential for growth. In addition to protecting plants from numerous stresses including UV radiation, drought, and frost, they are responsible for the vivid colors and fragrances of flowers that draw pollinating insects. The 15-carbon skeleton of all flavonoids is made up of two benzene rings (designated A and B) joined by a three-carbon heterocyclic C ring. Variations in this fundamental structure account for the remarkable diversity of the more than 6000 identified flavonoids. They are separated into various subgroups according to the degree of oxidation and unsaturation of the C ring, as well as the carbon of the C ring to which the B ring is linked. Flavonoids are divided into seven major classes. Celery, parsley, red peppers, and chamomile are some of the main dietary sources of flavones, which are commonly found in leaves, flowers, and fruits. One of the most prevalent flavonoid subgroups in fruits and vegetables are flavonols. Rich sources include onions, kale, apples, grapes, tea, and red wine.

Citrus fruits typically contain flavanones, which give their peels and juice their bitter flavor. The main sources are grapes, oranges, and lemons. Unique classes of compounds, isoflavonoids are mostly present in soybeans and other leguminous plants. They are frequently referred to as phyto-oestrogens because of their structural resemblance to estrogen. The pigments that give many plants and fruits their red, purple, and blue hues are called anthocyanins.

They are rich in black currants, red grapes, and berries. In contrast to many other flavonoids, flavanols (also known as catechins) do not have a double bond between the second and third carbons in the C ring. Bananas, apples, blueberries, and peaches all contain large amounts of them. Because they are open-chain flavonoids without the distinctive C ring of the typical flavonoid structure, chalcones are special. Strawberries, pears, and tomatoes all contain them.[1]

Both infectious and chronic non-communicable diseases pose a substantial danger to human health today, making it difficult to find novel therapeutic agents with few adverse effects. The difficulties associated with contemporary drug development and discovery have significantly increased as a result of this circumstance. The importance of functional meals produced from plants in preventing chronic diseases has been highlighted by the increasing integration of nutritional and food sciences into medical studies.[2,3]

Flavonoids work as potent antioxidants and enzyme inhibitors, among other ways, to promote health. The majority of flavonoids possess the ability to function as antioxidants. They shield the body's tissues and cells from harm brought on by reactive oxygen species (ROS) and free radicals, which are created during regular metabolism. Free radicals can be directly scavenged by flavonoids. Because their hydroxyl groups are highly reactive, they can react with a radical to make it less reactive and more stable, reducing the hazard. This effect inhibits the oxidation of LDL (bad cholesterol), a major contributor to atherosclerosis, and helps avoid damage to cellular membranes.

The enzyme xanthine oxidase (XO), which generates superoxide free radicals, can be inhibited by flavonoids. Flavonoids such as luteolin and quercetin lessen oxidative damage to tissues by blocking XO. It is well known that flavonoids are strong inhibitors of a number of important biological enzymes. They have the ability to reduce inflammation. The two variants of the enzyme cyclo-oxygenase (COX) are frequently responsible for inflammation. While COX-1 aids in maintaining the stomach lining, COX-2 is induced following an inflammatory response. It has

been discovered that certain flavonoids function as selective inhibitors of COX-2, which enables them to lessen inflammation with fewer adverse effects on the gastrointestinal tract.The effects of flavonoids are neuroprotective.

Acetylcholinesterase (AChE) inhibition is a crucial therapeutic approach for neurodegenerative illnesses such as Alzheimer's. According to studies, flavonoids including macluraxanthone and quercetin can efficiently inhibit AChE in a concentration-dependent way. A lower risk of cardiovascular disease is linked to a diet high in flavonoids. By boosting endothelial function, they contribute to better vascular health. Numerous flavonoids have been found to have antifungal, antiviral, and antibacterial qualities, which makes them useful for nutrition and food safety.

Because they can cause cancer cells to undergo apoptosis, or programmed cell death, and control the metabolism of carcinogens, flavonoids are known to have anti-carcinogenic qualities.Chronic inflammation and oxidative stress are known to play a major role in the development of diseases like obesity, cancer, and neurological problems.[4,5]

Flavonoids are becoming recognized as prospective medicines in the therapeutic management of various disorders because of their strong anti-inflammatory and antioxidative properties.[6] Flavonoids act on a variety of organs and cells, including skeletal muscle, the liver, the pancreas, adipocytes, immune system components, and brain neuronal cells, all of which are pertinent to the genesis of these long-term health disorders.[7]

Strong research demonstrates the effects of particular flavonoids: apigenin, a flavone found in celery and chamomile tea, has strong anti-adipogenic qualities that provide protection against obesity. The main isoflavone in soy, genistein, has shown neuroprotective and antioxidative properties in a range of experimental types. Additionally, epidemiological studies point to an inverse relationship between circulating isoflavone levels and the risk of several malignancies, such as prostate and breast cancer in women. This article attempts to summarize and critically evaluate the most current and creative developments in flavonoid research, whereas previous reviews have primarily highlighted the broad impacts and methods by which flavonoids alter disease pathways.

Clarifying molecular pathways and assessing how the duration and amount of flavonoid supplementation affect their effectiveness in the prevention and adjuvant treatment of obesity, cancer, and neurodegenerative disorders are given particular attention. Although there is substantial data supporting the health advantages of flavonoids, most of the research has been done in vitro (in a lab setting) or in silico (via computer simulation). Further in vivo research is obviously required to verify these effects in live things. The diversity of flavonoid structures and the dearth of thorough information on their bioavailability the degree to which the body absorbs and uses them are major obstacles for further study.It is also too early to develop particular dietary recommendations beyond suggesting a diet high in fruits and vegetables due to the lack of data on the long-term effects of chronic flavonoid intake.[1]

The only sources used in this review are those that have been published and are accessible to the public; these sources are fully referenced in the references. The cited literature provides access to all studied data. For this investigation, no private datasets or fresh experimental data were created. Although the articles used cover the years 2000 to 2025, the vast bulk of the references are from the most recent decade (2015–2025).This is consistent with the practice that prioritizes high-impact, recent publications in order to capture the most recent advancements in science.

Metaanalyses, systematic reviews, and original research articles (in vitro, in vivo, and clinical investigations) that were pertinent to the biological activities of dietary flavonoids were all taken into account. Studies must include unique data

or thorough analyses on the structural, molecular, or clinical features of flavonoids in relation to signaling pathways, bioavailability, or the prevention of chronic diseases in order to be included. To maintain scientific rigor, publications that exclusively addressed synthetic derivatives without biological testing, non-peer-reviewed communications, case reports, and conference abstracts lacking adequate methodological description were eliminated.

BIOLOGICAL PROPERTIES AND ROLE OF FLAVONOIDS

Flavonoids, which are naturally occurring compounds derived from medicinal plants, are becoming more well-known due to their good safety profiles and wide range of pharmacological activities. These bioactive flavonoids are widely distributed across the kingdom of plants and are produced through the phenylpropanoid pathway. They play a vital role in controlling the physiological processes and growth of plants. The adaptive diversity of flavonoids as secondary metabolites sculpted by long-term natural selection is reflected in their presence as glycosidic ligands, methylated ethers, or aglycone forms.[2,3] They are extensively dispersed throughout higher plants' roots, stems, leaves, flowers, and fruits. Flavonoids continue to be the subject of extensive investigation as prospective molecular targets for novel medication development because of their abundance in nature and their potential to cure both infectious and non-communicable diseases.

Flavonoids continue to be a prominent focus in research on natural bioactive molecules because of the growing demand for these chemicals in the healthcare and medical industries due to the growing awareness of health-related issues. Over 10,000 different flavonoid molecules have been identified by scientists thus far [8]. With significant amounts found in fruits, vegetables, herbs, cereals, flowers, and seeds, these essential secondary metabolites are found across the kingdom of plants.[9]

The well-established biological activities of flavonoids, such as their ability to modulate important cellular enzymes and their anti-oxidative, anti-inflammatory, anti-mutagenic, and anti-carcinogenic properties, are largely responsible for the wide spectrum of health advantages linked to them [1]. These characteristics provide advantageous biochemical and antioxidant effects that have therapeutic potential against a variety of maladies, such as cardiovascular disease, cancer, and neurodegenerative diseases [10]. As a result, flavonoids have become crucial ingredients in numerous pharmacological, nutraceutical, cosmetic, and medical compositions because of their broad range of health-promoting benefits.

Flavonoids are classified into a number of classes, including flavones, flavanones, isoflavones, flavonols, chalcones, flavanols, and anthocyanins, based on differences in their chemical structure, such as the degree of unsaturation and the oxidation of their carbon ring.[11] All of these types are widely found in nature. These compounds, which give plants their distinctive color, aroma, and flavor profiles, usually build up in the flowers, fruits, leaves, and seeds of plants.[12] Plant flavonoids are significant secondary metabolites that have a variety of physiological roles, including pollination, seed development, flower coloring, allelopathy, auxin transport regulation, and male fertility.[13]

Additionally, flavonoids defend against biotic hazards including bacteria, fungi, and herbivores as well as abiotic stresses like UV radiation, cold, salt, dehydration, and heavy metals.[14] These substances have a wide range of biological significance since flavonoids are active in microbes, plants, and mammals.[15]

Chemically, the phenylpropanoid metabolic pathway is used to generate all flavonoids, which are characterized by a 15-carbon skeleton structured into a three-ring (C6-C3-C6) structure, designated A, B, and C.[16] Flavonoids are divided into seven different subclasses based on structural differences in their core skeleton: flavones, flavanones, isoflavones, flavonols, chalcones, flavanols, and anthocyanins[17] (Figure 1). These substances mostly build up in the vacuoles of plant cells, where they are usually found as either C-glycosides or O-glycosides.[18]

1. FLAVONES

Two of the most prevalent examples of flavones, which comprise one of the largest subclasses of flavonoids, are apigenin and luteolin. Specifically, apigenin exhibits considerable therapeutic promise. It can reduce inflammation in diseases like cancer, neuroinflammation, and cardiovascular disease, scavenge free radicals, and assist control the activity of antioxidant enzymes in pancreatic cells.[19] Apigenin is usually found in nature in a glycosylated form. This indicates that a sugar molecule is joined to its core structure either directly to a carbon atom (C-glycosides) or via a hydroxyl group (O-glycosides).[20]

The glycosides apiin, vitexin, isovitexin, and rhoifolin are among its primary natural derivatives. More generally, a variety of plants and herbs, including celery, parsley, red pepper, chamomile, mint, and ginkgo, are rich in flavones, which are typically found as 7-O-glycosides [9, 21]. A phenyl substituent is connected to the second position of the 4H-chromen-4-one structure, which is the chemical backbone that characterizes all flavones.

2. FLAVANONES

Citrus fruits, such as oranges, lemons, mandarins, grapefruits, clementines, and limes, are nearly the only foods that contain flavanones.[22] This fruit group is especially rich in naringenin and hesperetin, the two main dietary flavanones.[22,23] These substances have significant biological activity. For instance, it has been demonstrated that naringin strengthens the immune system and increases the activity of antioxidant enzymes. Furthermore, in rat models, naringenin and hesperetin have both shown the capacity to restore compromised thyroid function. Other flavanones include hesperidin, pinocembrin, likvirtin, and eriodictyol, depending on their particular structural peculiarities.[24]

A saturated C-ring gives flavanones, often referred to as dihydro-flavones, their distinct chemical identity. The only structural characteristic that sets flavanones apart from other groups of flavonoids is the saturation of the double bond between positions 2 and 3 in this C-ring [25]. A disaccharide molecule connected to the aglycone's seventh position is a distinguishing feature of their structure [26]. Additionally, they usually have hydroxyl or methoxy substituents at the C3 or C4 locations of the B-ring and hydroxyl groups at positions 5 and 7 on the A-ring.[27]

3. ISOFLAVONES

The role of isoflavones as phytoestrogens plant-derived substances with strong estrogenic activity is a noteworthy feature. Isoflavones can bind to estrogen receptors because their chemical structure is remarkably similar to that of animal estrogens, especially the human hormone 17-β-estradiol.[28] In addition to this hormonal activity, isoflavones have potent antioxidant qualities that may lower the risk of some malignancies by preventing DNA damage caused by free radicals. The three main categories of isoflavones are genistein, daidzein, and glycitein.

The attachment point of the B-ring, which is attached at the C3 position of the heterocyclic C-ring for isoflavones rather than the C2 position common for other flavonoids, is the only chemical characteristic that sets this subclass apart

from other flavonoids.[29] These substances are typical metabolites of leguminous plants and are necessary for functions like nodule induction and microbial signaling in legumes.[30]

4. FLAVONOLS

Asparagus, onions, lettuce, broccoli, tomatoes, and apples are just a few of the many fruits and vegetables that contain the four main forms of flavonols: quercetin, galangin, kaempferol, and myricetin.[31] These substances have a wide range of important biological actions, such as antiviral, cardioprotective, antioxidant, antibacterial, and anticancer effects. Notably, dietary consumption of flavonols has been linked to a markedly lower incidence of stomach cancer, especially in smoking and female populations. Flavonols, also known chemically as 3-hydroxy flavones, are distinguished by certain substitutions on their A- and B-rings, which are joined by a three-carbon chain.[32]

The presence of hydroxyl groups at positions 5 and 7 of the A-ring is a frequent structural characteristic of flavonols. These substances are mostly found in the epidermal cells of plants, where they serve to shield DNA from UV-induced damage [33]. A diet high in flavanols may help avoid the development of cardiovascular illnesses and promote the long-term improvement of endothelial function.[34-37] By raising nitric oxide (NO) levels, flavanols can help shield blood arteries from harm caused by smoke.

Many fruits, including apples, bananas, pears, and blueberries, contain a variety of these chemicals, including as catechin, gallocatechin, epicatechin, and its gallate derivatives (such as catechin 3-gallate and epicatechin 3-gallate).[38] Chemically, flavanols also known as catechins or flavan-3-ols are distinguished by two main structural traits. They don't have a double bond in the C-ring between positions 2 and 3. They are also distinguished by the presence of a hydroxyl group at C-ring position 3.[39]

5. ANTHOCYANINS

Classified as glycosylated polyphenolic compounds, anthocyanins are a type of soluble vacuolar pigments that give plants a variety of colors, including orange, red, purple, and blue. The pH of the microenvironment in flowers, seeds, fruits, and vegetative tissues determines the expressed color.[40] Anthocyanins are therefore frequently used as natural food coloring. Anthocyanins have significant effects on human health, such as improving vision, breaking down cholesterol, and lowering the risk of cardiovascular disease.[41] These substances are mostly present in the outer cell layer of a variety of fruits and vegetables, including berries, grapes, and blackcurrants.[42]

Over 650 distinct forms of anthocyanins have been found in plants, demonstrating the structural variety of these compounds.[43] The location and quantity of hydroxyl and methoxyl groups that are substituents on the core flavylium structure give rise to this variation. Cyanidin, delphinidin, malvidin, pelargonidin, and peonidin, along with their related derivatives, are the five main families into which these chemicals fall.[44] Anthocyanins' ring orientation and the quantity and location of free hydroxyl groups surrounding the pyrone ring are related to their antioxidant potential.

ANTIOXIDANT MECHANISMS OF FLAVONOIDS

Flavonoids' stability and function in various matrices are largely determined by their chemical structure, specifically the quantity and location of hydroxyl groups, which also affects their antioxidant capability.[45,46] By permitting electron delocalization within flavonoid phenoxyl radicals, certain structural motifs, like the orthodihydroxy configuration on the B-ring, increase this activity (Figure 2). Features including hydroxyl side chains, double bonds in the phenolic ring,

and the glycosylation of anthocyanidins all contribute to this impact [13]. Furthermore, because there are more hydroxyl groups accessible, the polymerization of flavonoid monomers, as in proanthocyanidins, might boost antioxidant potential.[47]

Flavonoids use a variety of molecular pathways to provide their antioxidant properties. Direct scavenging of reactive oxygen species (ROS) is one of the main mechanisms. Metal-chelating activity is another direct method that can lessen the toxicity of transition metal ions that are redox-active.[48] The quantity and location of hydroxyl substituents in hydroxyflavones greatly affects their ability to chelate metal cations.[49] For example, kaempferol can chelate Cu(II) ions to prevent the production of oxidants and radicals,[51] whereas quercetin, catechin, and rutin have shown strong antioxidant activity against Fe(III).[50]

The development of stable complexes between the carbonyl moiety and hydroxyl groups of flavonoids is frequently the structural basis for this activity. Catechin can chelate a variety of metal ions, such as Mn(VI), Fe(II), Fe(III), Cu(II), Zn(II), and Al(III), while quercetin has three possible bidentate binding sites for forming stable metallic complexes.[52] Apart from their direct effects, flavonoids also influence the activity of enzymes. They can lessen the generation of free radicals by inhibiting pro-oxidant enzymes. For instance, they prevent oxidases like protein kinase C and xanthine oxidase (XO) from catalyzing the synthesis of superoxide anions.

For instance, it has been shown that fisetin inhibits XO activity to lessen oxidative damage.[53] Cyclooxygenase, NADH oxidase, microsomal monooxygenase, and lipoxygenase are further enzymes that flavonoids inhibit.[14] On the other hand, flavonoids have the ability to trigger protective antioxidant enzymes. In order to protect against electrophilic toxicants and oxidative stress, phase II detoxifying enzymes such NAD(P)H-quinone oxidoreductase, glutathione S-transferase, and UDP-glucuronosyltransferase must be induced. Since flavonoids have been demonstrated to activate EpRE-mediated gene expression, this activation may take place through the electrophile-responsive element (EpRE). Additionally, flavonoids interact with particular biological systems to reduce oxidative stress.

By serving as hydrogen donors to α-tocopherol radicals, flavonoids can provide protection against the free radical-driven lipid peroxidation of low-density lipoprotein (LDL), a process linked to human health.[54] Quercetin, naringin, and epigallocatechin gallate are among the flavonoids that have demonstrated potent inhibitory effect against LDL oxidation in vitro.[55] Lastly, nitric oxide (NO)-induced oxidative stress can be lessened by flavonoids. The reduction of NO can result in oxidative stress in the vasculature, despite the fact that NO is essential for vasodilation.[56]

The powerful oxidant peroxynitrite, which results in pathological damage, can be created when NO and O2 combine. By preventing the expression of inducible NOS in some lipopolysaccharide-activated cells, flavonoids can prevent the generation of NO.[57]

Certain flavonoids can also inhibit the activity of other enzymes that produce free radicals, like nitric oxide synthase.[58]

CARDIOVASCULAR EFFECTS OF FLAVONOIDS

The population's risk of dying from cardiovascular causes is significantly reduced when dietary flavonoids are consumed.[59] These substances have a range of biological actions that contribute to their cardioprotective potential, such as their capacity to control endothelial cell death, promote vasodilation, and modify oxidative stress and inflammation. Numerous studies have demonstrated the beneficial effects of flavonoids on hemodynamics and vascular

function. Certain flavonoids have been shown to have vasodilatory effects in both in vitro and animal models, which contribute to their ability to reduce blood pressure.[60]

Particularly, substances with strong vasodilator qualities include naringenin, quercetin, and hesperetin; additional studies have shown that naringenin, in particular, can lower high blood pressure by actively encouraging vasodilation.[61] Moreover, flavonoids have been demonstrated to improve insulin resistance, reduce endothelial dysfunction, and provide protection against atherosclerosis and platelet aggregation.[62,63] Additionally, flavonoids have a major impact on lipid metabolism and associated metabolic diseases. They have been shown to prevent insulin sensitivity, dyslipidemia, and hepatic steatosis. They do this mainly by preventing the synthesis of hepatic fatty acids while simultaneously enhancing their oxidation.[64]

One prominent example is the anthocyanin subclass, which has been demonstrated to lower human myocardial infarction (MI) risk. This advantage is associated with lower levels of triglycerides, total cholesterol, and low-density lipoprotein cholesterol as well as improvements in systolic blood pressure.[65] Additionally, some flavonoids have been linked to the management and prevention of several cardiovascular diseases. For example, by preventing monocytes from adhering to endothelial cells, isoflavones seem to protect against inflammatory vascular disorders. It has been observed that baicalin improves cardiac dysfunction and prevents heart apoptosis. In addition to having atheroprotective properties, quercetin protects heart tissue from ischemia-reperfusion injury.[66]

Flavonoids' cardioprotective effects are associated with the molecular regulation of important cellular signaling pathways. For instance, by increasing PTEN expression and blocking AKT/mTOR phosphorylation, xanthohumol protects against isoprenaline-induced cardiac hypertrophy and fibrosis in mouse models. Similarly, via modifying the PI3K/Akt/GSK3β pathway, flavonoids isolated from Myrica rubra have been shown to reduce oxidative damage and cardiomyocyte apoptosis.[67] The sirtuin 1 (SIRT1) enzyme, a crucial regulator of physiological processes whose decreased expression is frequently linked to age-related cardiovascular disorders like myocardial infarction, cardiac hypertrophy, and endothelial dysfunction, is another important target.

It has been demonstrated that giving mice the citrus flavonoid naringenin (NAR) over an extended period of time increases SIRT1 expression. This upregulation was linked to lower levels of the cardiovascular inflammatory markers TNF-α and IL-6 as well as a significant decrease in reactive oxygen species (ROS) in myocardial tissue, suggesting that nutritional therapy with NAR may help to prevent myocardial aging and maintain cardiac function.[67]

A class of naturally occurring polyphenolic chemicals known as flavonoids has a variety of advantageous biological properties, such as anti-inflammatory, anticancer, and antioxidant properties. Flavonoids have medicinal potential, but their limited in vivo bioavailability frequently prevents them from being used in clinical settings. Their structural features, which result in poor absorption, substantial metabolic breakdown, and quick removal from the body, are the cause of this limitation. As a result, resolving these pharmacokinetic issues is crucial to their bioactivity.[68] Modern research has concentrated on two main approaches to overcome this bottleneck: the creation of sophisticated pharmacological formulations and the chemical alteration of the flavonoid structure itself.

Following oral consumption, flavonoids undergo a complicated physiological trip. The majority of these substances are ingested as glycosides, which need to be broken down in order to be well absorbed. This process starts in the small

intestine, where flavonoid glycosides are either directly transported by membrane carriers like the sodium-dependent glucose transporter 1 (SGLT-1) or hydrolyzed by brush border enzymes into their more lipid-soluble aglycone forms for passive diffusion into epithelial cells.[69,70] Flavonoids go through substantial Phase I and Phase II metabolism after they enter the enterocytes and then the liver.

These processes, which include methylation, sulfation, and glucuronidation, are intended to make the chemicals more soluble in water so that they can be eliminated through bile and urine. One important factor limiting the systemic concentration of active flavonoids is this metabolic conversion. The colon receives flavonoids that are not absorbed in the small intestine. By cleaving their core pyranone rings and carrying out processes like dehydroxylation and decarboxylation, the gut microbiome plays a critical role there. The flavonoids are broken down into smaller metabolites by this microbial activity, which can either be eliminated or absorbed into the bloodstream.[71]

OBESITY PREVENTION WITH FLAVONOIDS

The World Health Organization (WHO) defines obesity as an excessive or abnormal build-up of fat that is harmful to one's health. Over 1.9 billion people worldwide are today afflicted by this complicated disorder, which is shaped by the interaction of nutrition, genetic predispositions, and behavioral habits. Adipocyte hypertrophy, where excess energy is retained as triglycerides, is a crucial pathogenic process that eventually triggers the development of insulin resistance and persistent low-grade inflammation.[71] Dietary patterns rich in flavonoids are known to be positively associated with better metabolic outcomes and better management of body mass.[72,73]

Beyond these epidemiological correlations, experimental studies have demonstrated the diverse functions of flavonoids in boosting energy expenditure, improving insulin sensitivity in a variety of models, and preventing the growth of adipose tissue through anti-adipogenic action. In the synthesis that follows, we provide a critical analysis of the data pertaining to the ways in which different flavonoids affect the development and course of obesity, with a focus on well-established mechanisms, appropriate dosage and duration of treatment, and their discernible effects on physiological and metabolic parameters. Adipose hyperplasia is the fundamental pathophysiology underlying the development of obesity. This is accomplished through two different stages of differentiation in the process of adipogenesis. First, multipotent mesenchymal stem cells (MSCs) commit to the preadipocyte lineage during the determination stage.

A terminal differentiation step ensues, during which preadipocytes acquire the distinctive metabolic characteristics of mature adipocytes.[74,75] Flavonoids can influence adipogenesis through a number of different methods, according to a large body of new research. Modulating important transcription factors is one of the main ways that flavonoids have anti-adipogenic effects. Because it plays a crucial role in controlling adipocyte differentiation, peroxisome proliferator-activated receptor-gamma (PPARγ), which is widely expressed in adipose tissue, is a key target in the anti-adipogenesis activity of flavonoids.[76] For example, fisetin inhibits adipogenesis by activating NAD+-dependent deacetylase SIRT1, which suppresses PPARγ transcriptional activity.[77,78]

Similarly, it has been demonstrated that anthocyanins from black soybeans impede preadipocyte terminal development by lowering PPARγ expression.[79,80] By affecting the main signaling pathways that govern these master regulators, flavonoids also control adipogenesis. By influencing the wingless-type MMTV integration site family/canonical (Wnt/β-catenin) pathway, flavonoids including isorhamnetin, genistein, and daidzein have been shown to control the ability of preadipocytes to differentiate into mature adipocytes.[81] When Wnt binds to cell surface receptors in the

crosstalk between these signaling molecules, β-catenin is transferred into the nucleus. β-catenin interacts with transcription factors in the nucleus to decrease PPARγ and members of the CCAAT/enhancer-binding protein (C/EBP) family.[82]

Cell-cycle arrest and the stimulation of central energy sensors like AMP-activated protein kinase (AMPK) are two additional anti-adipogenic actions of flavonoids. As an example, apigenin, a significant flavone found in herbs, can stop the cell cycle at the G0/G1 phase by reducing the production of CDK4 and cyclin D1.[83] By activating the AMPK pathway, this identical substance can also reduce adipogenic expression.[83] Inhibition of mTOR signaling, decrease of C/EBPα-GLUT4 signaling, and inhibition of mitotic clonal expansion are all part of the complete range of flavonoid action.[84]

Flavonoids can greatly increase insulin sensitivity by altering signaling pathways linked to insulin and glucose, according to a number of experimental investigations. Restoring damaged upstream insulin signaling cascades is one of the main mechanisms. For instance, genistein has been demonstrated to enhance signaling in mice fed a high-fat, high-fructose diet by reestablishing the PI3K/Akt pathway and the phosphorylation of the insulin receptor substrate (IRS).[85] Another common flavonoid, myricetin, likewise improves insulin sensitivity by either directly phosphorylating the insulin receptor (IR) and IRS1 or indirectly by attaching to the μ-opioid receptor.[86]

Additionally, flavonoids have a significant impact on the metabolism of glucose in the liver. For example, it has been shown that naringin and hesperidin suppress gluconeogenesis in the livers of type-2 diabetic mice by lowering the mRNA levels of glucose 6-phosphate (G6P) and phosphoenolpyruvate carboxykinase (PEPCK).[87] These substances also increase the expression of glucokinase (GK), which facilitates the synthesis of glycogen. Similarly, by raising the expression of GK and the amount of hepatic glycogen in both mice and HepG2 cells, supplementing with grape seed-derived procyanidins which are made from catechin and epicatechin improves insulin sensitivity.[88]

Another important way that flavonoids improve insulin sensitivity is via increasing glucose absorption in peripheral tissues. For instance, by boosting the activity of glucose transporters, green tea extract, which is abundant in different catechins, greatly enhances this process. In order to combat insulin resistance, a pathological condition that causes metabolic irregularities in obesity and diabetes, these therapeutic actions are essential. IRS phosphorylation and the PI3K/Akt pathway are inhibited in this condition due to impaired insulin signaling.[89] Skeletal muscle and adipose tissue absorb less glucose as a result of this impairment, which also impairs AMPK phosphorylation and GLUT4 translocation to the cell membrane.[90]

The malfunctioning PI3K/Akt system in the liver dysregulates metabolism, limiting glycogen synthesis by suppressing GK and glycogen synthesis kinase (GSK) and increasing gluconeogenesis by upregulating PEPCK and G6P. Obese people frequently develop this condition because their adipose tissue releases more hormones, glycerol, pro-inflammatory cytokines, and non-esterified fatty acids. By lowering peripheral tissue glucose transport metabolism and raising hepatic glucose synthesis, the ensuing insulin resistance can subsequently start a vicious cycle that exacerbates obesity. Flavonoids exhibit a number of anti-obesity strategies, including increasing energy expenditure and promoting the remodeling of adipose tissue.

Increased energy dissipation and decreased fat storage have been linked to the transformation of white adipose tissue into thermogenically active brown-like (beige) adipose tissue [91]. Flavonoids have been shown in numerous studies to reduce body weight gain in experimental obesity models without changing food intake or nutrient absorption. This effect clearly suggests that increased metabolic activity is involved. One well-known molecular mechanism is the activation of the sympathetic nervous system's AMPK/PPAR-γ pathway, which causes browning and thermogenic gene expression in subcutaneous and brown fat depots.

Luteolin has been demonstrated to boost metabolic rate and energy expenditure in models using high-fat-fed animals by driving the expression of thermogenic genes and upregulating AMPK/PGC-1α signaling.[92] Widely found in chocolate, flavan-3-ols increase adrenaline secretion and sympathetic activity, which further boosts AMPK and PGC-1α activity and increases energy production. Another important process controlled by flavonoid consumption is mitochondrial biogenesis. These substances have been shown to support strong thermogenic capacity in both muscle and adipose tissues by reversing the inhibition of mitochondrial regeneration commonly seen with obesity.

For instance, by stimulating mitochondrial DNA replication and activating AMPK in brown adipose tissue, epigallocatechin gallate (EGCG) effectively lowers body weight in obese, high-fat-fed rats, ultimately increasing thermogenesis. Additionally, by reducing food digestibility and promoting fat oxidation, EGCG and other tea-derived catechins show anti-obesity actions.[93]

FLAVONOIDS ROLE IN DIABETES AND CARDIOVASCULAR DISEASE

It is well known that diabetes mellitus raises cardiovascular disease morbidity and mortality.[94,95] Patients with diabetes are twice as likely to die following a myocardial infarction (MI) as those without the disease.[96] Following MI, diabetic patients who have had primary angioplasty and conventional therapy are also more likely to get heart failure (HF).[97] The most recent research on the connection between flavonoids and diabetic cardiovascular problems is highlighted in this section. Flavanones in a diabetic rat model of ischemic heart disease, hesperidin has cardioprotective effects through the PPAR-c pathway. Specifically, compared to controls, hesperidin pretreatment markedly increased mean arterial pressure, decreased left ventricular end-diastolic pressure, and enhanced both inotropic and lusitropic heart performance.[98] Flavanols., as previously mentioned, green tea leaves from the Camellia sinensis plant are the primary source of catechins, which are polyphenolic chemicals.[99]

The main conclusion of Bhardwaj et al.'s work is that catechin may protect STZ-diabetic rats from diabetes mellitus-induced experimental vascular endothelial damage by activating the PI3K and eNOS signaling systems.[100] As a class of flavonoids, anthocyanins are particularly prevalent in a variety of vibrant fruits, vegetables, red wine, and cereals.[101] In diabetic mice, anthocyanin cyanidin-3-O-β-glucoside enhances endothelial function and raises blood adiponectin concentrations.[102] In diabetic apolipoprotein E-deficient mice, cyanidin-3-o-b-glucoside supplementation also encourages endothelium repair and inhibits increased atherogenesis.[103] One of the primary ingredients of grape seed procyanidin extracts is dimeric procyanidin B2 (GSPB2). GSPB2 considerably reduced obesity in db/db mice in one research. Additionally, GSPB2 inhibited the rise in serum AGE levels seen in db/db mice, indicating that GSPB2 has an anti-non-enzymatic glycation action.

Furthermore, GSPB2 considerably lowered the high levels of total cholesterol and triglycerides. In the cardiac sections of db/db mice, GSPB2 inhibited myocardial hypertrophy and cardiac matrix remodeling.[104] Isoflavones. Puerarin has a

number of positive effects on cardiovascular conditions, including hypertension.[106] and myocardial infarction.[105] In streptozotocin-nicotinamide-induced diabetic mice following myocardial infarction, puerarin enhances heart function by controlling energy metabolism. Specifically, it was demonstrated that puerarin dramatically increased the survival rate, enhanced cardiac function, and increased GLUT4 expression and translocation while attenuating CD36 expression and translocation.[107]

The rhizome of Smilax china L. (Smilaceae) yields astilbin, an active flavonoid chemical that is frequently utilized in traditional Chinese medicine.[108] An intriguing study assessed Astilbin's anti-myocardial ischemia and reperfusion (I/R) injury effect on diabetic rats in vivo and clarified the possible mechanism in vitro. In a concentration-dependent way, astilbin markedly reduced hypoxia-induced cell damage. Astilbin treatment of H9c2 cells inhibited the production of high-mobility group box protein 1 (HMGB1), which in turn prevented NF-κB phosphorylation.

Astilbin administered intravenously to diabetic rats prevented myocardial I/R injury, as evidenced by decreased infarct volume, improved hemodynamics, and decreased myocardial damage. Additionally, the rats' serum levels of pro-inflammatory factors were lowered, and the expression of HMGB1 and phosphorylated NF-jB in ischemic myocardial tissue was decreased.[109] Flavones, in a recent study, insulin deficit (ID) and insulin resistance (IR) were established in male Wistar rats using either fructose or STZ, and the potential protective impact of baicalein was examined. higher blood pressure, enhanced vasoconstriction and impaired relaxation KCl, higher TNF-α and AGEs, NF-κB activation, significant leukocyte infiltration in the adventitia, pyknosis of endothelial cells, and significant collagen deposition were observed in both animals.

Baicalein avoided an IR model with excessive vasoconstriction, reduced BP rises in models, and enhanced relaxation in an ID model. In both models, baicalein prevented histopathological alterations, lowered TNF-α and AGE levels, and decreased NF-κB activation.[110] Glycyrrhizae radix is the source of the flavone molecule liquiritin. In human umbilical vein endothelial cells, liquiritin reduces advanced glycation end-product-induced endothelial dysfunction through the RAGE/NF-B pathway.[111] flavonoids. Quercetin has been demonstrated to lower high blood pressure and prevent diabetes-induced excessive vasoconstriction. Furthermore, quercetin prevented enhanced collagen deposition, endothelial pyknosis, and adventitial leukocyte infiltration linked to diabetes.[112]

FLAVONOID ROLE IN PREVENTION OF CANCER

Cancer continues to be one of the most important global health issues and a major barrier to raising life expectancy globally [113]. Flavonoids are a wide class of plant-derived polyphenols that have been shown in numerous lines of population-based and cohort studies to have significant anti-carcinogenic efficacy across a range of malignancies.[114, 115] Lung, breast, prostate, stomach, liver, and colorectal cancers are just a few of the cancer types in which these protective effects have been found[116,117] (Table 4). The molecular pathways that control DNA integrity, programmed cell death, the inflammatory tumor microenvironment, and the control of tumor angiogenesis are all impacted by the complex mechanisms underlying flavonoid-mediated cancer prevention.

Together, these results highlight the growing importance of dietary flavonoids as a preventive strategy against the rising incidence of cancer worldwide. Their ability to control cell signaling pathways, such as the inhibition of NF-κB activity, modulation of the PI3K/Akt and MAPK cascades, and induction of programmed cell death via apoptosis and autophagy, is largely responsible for their influence on the development and progression of cancer.[118,119]

Additionally, flavonoids exhibit strong anti-inflammatory and antioxidant properties: they increase antioxidant-triggered apoptosis, scavenge reactive oxygen species (ROS), and decrease pro-inflammatory cytokine signaling. Particularly, fruit-based flavonoids are becoming more well-known for their distinct roles in the food matrix and persistent fluorescent characteristics, which extend their importance beyond nutrition to possible biosynthetic and diagnostic uses. Dietary flavonoids, such as quercetin, are currently the most promising prospects for anticancer treatments in clinical trials. This is because fruit high in flavonoids has been linked to a lower risk of cancer, particularly liver, colon, and breast cancers.

Their involvement in suppressing lung carcinogenesis by blocking the NF-κB pathway and decreasing angiogenesis and cell proliferation in liver cancer is further supported by experimental findings. While anti-inflammatory and ROS-induced apoptotic pathways prevail in colon cancer, flavonoids' protective effects in breast cancer are closely associated with disruption of PI3K/Akt and MAPK signaling.[120]

The capacity of flavonoids to interfere with several cell signaling cascades that control the onset and spread of cancer is the basis for their antineoplastic qualities. The prevention of angiogenesis, which is partly achieved by downregulating the production and signaling of vascular endothelial growth factor (VEGF), is a key component of their anticancer mechanism.[121,122] By interfering with activation loops that regulate cellular growth and survival, flavonoids target the downstream components of the PI3K tyrosine kinase growth receptor, which accounts for a large portion of their therapeutic activity. By blocking PI3K enzymatic activity and interfering with the feedback and crosstalk between protein kinase B (Akt), PI3K, and other molecular targets like ERK and phosphatase and tensin homolog (PTEN), they significantly impact the PI3K/Akt/mammalian target of rapamycin (mTOR) axis.

Triggering Programmed Cell Death

The process of initiating apoptosis, often known as "programmed cell death," is referred to as apoptosis induction. It is an essential process for tissue health and a major target in the treatment of disease since it provides a natural and regulated means for the body to eliminate old, damaged, or superfluous cells without producing inflammation. Researchers are looking at treatments that might restart apoptosis, or cellular self-destruction, as it is a major contributing element to the development of cancer. These tactics frequently entail producing reactive oxygen species (ROS), controlling important proteins, or damaging DNA. By triggering the cell's death machinery, a number of flavonoids have demonstrated potential as anticancer drugs.

For example, hesperetin causes ROS to accumulate and activates an intrinsic death pathway, which causes apoptosis in esophageal cancer.[123] Additionally, the balance of proteins that regulate apoptosis can be directly changed by flavonoids. For instance, quercetin promotes cell death in breast cancer by increasing pro-death protein levels and decreasing anti-death protein levels. When quercetin is combined with other substances like metformin or EGCG, which collectively lessen the capacity of cancer cells to proliferate, migrate, and spread, this impact is amplified.[124] Naringenin, another flavonoid, stops the proliferation and spread of gastric cancer cells and causes them to undergo apoptosis.[125]

The capacity of a wide variety of different flavonoids, including as flavones, anthocyanidins, and isoflavonoids, to operate via both the intrinsic and extrinsic pathways of apoptosis has been linked to their anticancer properties. This procedure has two main routes. In response to various intracellular stressors, the intrinsic pathway regulates BH3-only

and Bcl2-like proteins, which ultimately promotes cell death by forming an apoptosome complex that includes cytochrome c, Apaf-1, and caspase-9. The other is the extrinsic pathway, which starts when a TNF family ligand attaches itself to cell surface death receptors.

Cellular death results from this action's subsequent activation of caspase-8 and caspase-3 via the Fas-associated death domain protein (FADD). Flavonoids aid in the restoration of a vital biological process by utilizing these pathways. Tissue homeostasis depends on apoptosis, a type of programmed cell death that happens in response to various intracellular damage signals.[122]

Fundamentally, autophagy is a process that breaks down and reuses a cell's internal components; it is usually triggered by circumstances like food restriction or other types of cellular stress.

Thus, in addition to their impact on apoptosis, flavonoids' ability to control this intricate autophagic network is a key component of their anticancer actions, as multiple investigations have demonstrated. Beyond their impact on apoptosis, flavonoids are becoming more widely acknowledged for their critical role in cancer biology by controlling autophagy, a cellular recycling process that is triggered in response to stress or deprivation.[125]

During the development of cancer, autophagy performs a variety of intricate and perhaps conflicting roles.[126] Autophagy may prevent malignant transformation at the beginning of carcinogenesis by inhibiting cellular proliferation, but in advanced malignancies, it may promote tumor cell adaptability and survival in hypoxic, nutrient-deficient environments.[127]

FUTURE PERSPECTIVES

With a primary focus on metabolic disorders, neurological illnesses, and cancer, this review has thoroughly summarized the present research on the chemical diversity, mechanistic breadth, and translational possibilities of flavonoids as bioactive chemicals in human health. The debate emphasizes how flavonoids which include subclasses ranging from flavonols to anthocyanins exert multifaceted beneficial effects, building on a solid foundation of experimental and clinical evidence. Both more recent biochemical investigations and traditional phytochemical research concur that the structure activity relationship of flavonoids is essential to their biological functions.[1,8] Numerous biological processes are supported by the 15-carbon skeleton (C6-C3-C6), which permits redox cycling, enzyme regulation, and a variety of receptor interactions.

Our analysis supports the clear correlation between antioxidant, anti-inflammatory, and enzyme-inhibitory actions and particular alterations, such as hydroxylation patterns on the B and C rings. Strong ROS-scavenging, metal-chelating, and radical stabilization capabilities are repeatedly demonstrated by experimental results, particularly in polyhydroxylated flavonols and anthocyanins.

The modulation of endogenous defensive enzymes and the inhibition of pro-oxidant systems complement these direct antioxidant activities, providing flavonoids a special adaptability in combating oxidative stress, a major pathomechanism in chronic and degenerative disorders. Significantly, the polymerization of flavonoid subunits (such as in proanthocyanidins) enhances the ability to scavenge radicals, indicating the significance of chemical complexity in angiogenesis, inflammation, and functional potency,[58] frequently through mutually reinforcing pathways.[101,109]

By modifying both internal (mitochondrial) and extrinsic (receptor-mediated) pathways, a number of well-characterized flavonoids (such as quercetin, apigenin, and genistein) directly decrease cell growth or promote programmed cell death by apoptosis and/or autophagy. Many influence the balance between survival and cytotoxicity in favor of cellular homeostasis and tumor suppression by acting on important regulatory checkpoints, such as cyclin-dependent kinases, caspases, and members of the BCL-2 family. These findings are consistent with our mechanistic understanding of flavonoids as multi-target drugs whose effectiveness results from modulation at the systems level as opposed to single-target specificity. Studies referenced here and throughout the nutritional pharmacology literature provide compelling evidence for our working hypothesis, which holds that the health-promoting effect of dietary flavonoids results from their multitargeted control of cellular signaling and defense networks.

Significant associations between high flavonoid intake and lower chances of chronic illnesses, such as cardiovascular disease, some types of cancer, and neurodegeneration, have been shown in numerous epidemiological studies, as mentioned. Notably, frequent consumption of foods high in flavonoids is linked to improved metabolic outcomes and decreased disease prevalence, according to cohort and case control studies.[102,104] In vitro and in vivo models demonstrating anti-inflammatory, anti-apoptotic, and antiproliferative effects mechanistically support these population-level findings. Simultaneously, our synthesis demonstrates that factors including bioavailability, metabolic stability, and the complexity of human dietary patterns impact the clinical translation of flavonoid supplementation, echoing limitations and cautions observed in previous reviews.[2,7]

Furthermore, given the prevalence of obesity and diabetes worldwide, the review's discussion of metabolic syndrome and obesity emphasizes how flavonoids can control adipocyte differentiation, enhance insulin signaling, alter lipid metabolism, and boost energy expenditure—mechanisms with substantial translational relevance. The cardioprotective benefits of certain flavonoids, which act at the level of vascular function, atherogenesis, and endothelial protection, are further supported by a number of research. Research has effectively moved from determining flavonoids' in vitro characteristics to proving their health benefits in human populations during the last few decades. Large-scale epidemiological research and clinical observations that have demonstrated robust, reliable associations between diets high in flavonoids and a lower risk of serious chronic illnesses are the best examples of this advancement.

The cardioprotective properties of flavonoids are now supported by a substantial body of evidence. A high dietary flavonoid consumption is linked to a significantly lower risk of dying from cardiovascular causes, according to numerous population-based studies. In particular, anthocyanins have been demonstrated to lower the risk of myocardial infarction (MI) in humans; this effect is associated with improvements in lipid profiles and blood pressure. In the field of cancer prevention, a number of malignancies have been found to be inversely correlated with flavonoid consumption, according to large cohort and case control studies. These protective relationships have been found for colorectal, lung, breast, and prostate cancers, demonstrating the chemicals' widespread anti-carcinogenic potential at the population level.

Research on neuroprotection has produced some of the most intriguing results. The tissue specificity of flavonoid effects, potential interactions with other dietary or pharmacological substances, genetic variations in metabolism between individuals, and the balance between physiologic and pharmacologic dosing a recurrent theme in current research are further study needs. Furthermore, although being usually safe, some flavonoids may have uncommon but

significant toxicities or cause negative side effects. This emphasizes the significance of additional experimental and clinical toxicity research, particularly with novel delivery methods or structural alterations.

CONCLUSIONS

Epidemiological, experimental, and clinical research have repeatedly shown that dietary flavonoids are multifunctional bioactive substances with significant promise for the prevention and adjuvant therapy of chronic metabolic, neurodegenerative, and oncological illnesses. Pleiotropic mechanisms, such as antioxidative, anti-inflammatory, and regulatory effects on cell signaling pathways like PI3K/Akt/mTOR, NF-κB, and AMPK, mediate their health-promoting actions. Together, these mechanisms improve metabolic regulation, neuroprotection, and cancer prevention.

However, difficulties with absorption, clinical translation, and interindividual variability highlight the need for more study to maximize flavonoid effectiveness and clarify their complex molecular interactions. While increasing advancements in delivery systems and molecular targeting are anticipated to further enhance the translational impact of these important phytochemicals in public health and clinical contexts, incorporating a variety of flavonoid-rich foods into dietary patterns is still a scientifically supported strategy for disease mitigation.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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