Journal of Applied Pharmaceutical Research
Volume 14 Issue 2, Year of Publication 2026, Page 01 – 12
DOI: https://doi.org/10.69857/joapr.v14i2.1486

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Review Article

JOURNAL OF APPLIED PHARMACEUTICAL RESEARCH | ***JOAPR***
www.japtronline.com ***ISSN: 2348 – 0335***

FLAVONOIDS AS CHEMOPREVENTIVE AGENTS: METABOLISM, APOPTOSIS, AND OXIDATIVE STRESS MODULATION

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Article Information
Received: 17th November 2025
Revised: 8th February 2026
Accepted: 16th February 2026
Published: 15th March 2026

Keywords
Flavonoids, Anticancer properties, Gut microbiota, Metabolism

ABSTRACT
Background: Liposomes are widely used as drug delivery systems because of their reduced systemic toxicity. Over the past few decades, numerous drug-loaded liposomes have been approved for clinical use in the treatment of cancer, viral, and fungal infections. Various liposomal formulations have progressed to later phases of clinical trials. Liposomes are spherical vesicles composed of a single or multiple phospholipid bilayers surrounding an aqueous core. Drug-loaded liposomes can exhibit controlled or targeted drug delivery, low immunogenicity, high biocompatibility, biodegradability, prolonged drug half-life, increased efficiency, reduced systemic toxicity, and enhanced pharmacokinetic properties. **Methodology:** This review article addresses the characteristics and types of liposomes; novel methods for their preparation, such as the Supercritical Anti-solvent Method and the Dual Asymmetric Centrifugation Method; lipid preferences; future directions for liposomes; marketed liposomal formulations; and associated patents. **Results and Discussion:** It has the potential to protect the drug against degradation. The aforementioned drug delivery system increases in vivo drug distribution toward target sites. PEGylated liposomes can prolong circulation time. It requires expertise in techniques, such as thin-film hydration and reverse-phase evaporation, for preparation. It has been utilized in nanomedicine. This particular delivery system requires characterizations like size, drug loading, drug release, etc. **Conclusion:** Liposome-embedded delivery systems advance nanotechnology and biopharmaceutics. The role of modern medicine has continued to expand, particularly in the management of chronic diseases.

INTRODUCTION

Primary metabolites are a class of compounds that are generally synthesized by living organisms, mainly plants, fungi, and microorganisms. These types of compounds are necessary for photosynthesis and for energy production and consumption. In addition to these basic substances, a diverse range of secondary metabolites exists, including alkaloids, flavonoids, polyketides, terpenoids, and phenylpropanoids. In most instances, they are recognized as capable of withstanding

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adverse conditions, such as potential attacks by parasitic microorganisms or predators [1]. Secondary Metabolites come from naturally occurring compounds that are essentially smaller than 3000 Da in molecular mass and derived from primary metabolites during plant development. Diverse plant species have distinct metabolite compositions and chemical properties [2]. Key dietary polyphenols, such as flavonoids, are present in a wide range of plant-based foods and beverages. A novel material was found in oranges in 1930. It was considered to belong to a newly identified class of vitamins at the time, known as vitamin P. This specific material was later determined to be a flavonoid (rutin), and there are currently around 4000 distinct types of flavonoids known to exist [3]. Relying on the kind of heterocycle involved, the flavonoids, which have a typical structure consisting of an oxygenated heterocycle (ring C) formed by joining two aromatic rings containing 3 carbon atoms (A and B), can be further divided into six different categories: flavones, flavonols, flavanones, isoflavones, flavonols (catechins and proanthocyanidins), and anthocyanidins. Nearly all of the flavonoids identified in food are found in their glycosidic forms, which are made up of multiple sugar molecules attached to hydroxyl groups at the C-3 position or phenolic groups. The aglycon structure and the type of sugar moiety attached to flavonoids have a considerable influence on their bioavailability [4]. A complex microbial community resides in the human gut tract [5]. The relationships between metabolism and the intestinal microbiota affect human health and disease. The majority of flavonoid glycosides are not readily absorbed in the mammalian gut after consumption and instead interact with the intestinal microbiota. The gut bacteria metabolise these substances [6]. Bioavailability is essential for understanding how dietary flavonoids are metabolised and absorbed in the digestive tract, thereby informing our understanding of their physiological functions and biological activity in vivo [7].

Several research projects have established that flavonoids can scavenge free radicals, control cellular metabolism, and fend off oxidative stress-related diseases [8]. These bioactive substances exhibit diverse biochemical properties, including anti-inflammatory, antiviral, antifungal, antibacterial, and anticancer effects. Flavonoids have been shown in epidemiological studies to have chemopreventive properties when incorporated into the human diet [9]. Consuming the flavonoid has been linked to a decreased chance of acquiring certain tumours, including colorectal, breast, prostate, and stomach cancers [10].

This paper provides an integrated perspective that links metabolism, microbiota interactions, and anticancer pathways, in contrast to other reviews that focus on flavonoid chemistry or biological activities in isolation. A thorough description of flavonoid chemistry is combined with an integrated microbial and enzymatic perspective that outlines the flavonoid-specific metabolic pathways, microbial changes associated with disease, and a comprehensive list of enzymes that control their biotransformations. Additionally, the study links these metabolic processes to subsequent biological outcomes, including the regulation of oxidative stress and apoptosis. It covers intrinsic and extrinsic apoptotic mechanisms, protein-level alterations including Bax overexpression and Bcl-2 reduction across different cancer cell lines, and modulation of PI3K/Akt, NF-κB, and p53 signalling. Furthermore, molecular and cellular insights link flavonoid metabolism to their anti-inflammatory and cardioprotective functions through oxidative stress. By clarifying how metabolic changes coordinate the anticancer efficacy of flavonoids, this comprehensive framework distinguishes the current review from prior research.

METHODOLOGY

A thorough search of leading scientific databases, such as PubMed, ScienceDirect, and Google Scholar, was conducted to gather pertinent material. Boolean operators (AND/OR) were combined with terms like "flavonoids," "gut microbiota," "flavonoid metabolism," "anticancer mechanisms," "apoptosis," and "oxidative stress." Articles published in English between 2021 and 2025 were accounted for in the search. Studies on oxidative processes, microbial or enzymatic metabolism, flavonoid chemistry, and anticancer properties were included; those unrelated to metabolism or from non-peer-reviewed sources were excluded. Based on their methodological quality and mechanistic focus, 69 current and highly relevant research papers were selected from an initial pool of 127. To integrate metabolic pathways, microbial interactions, and flavonoid anticancer processes, a rigorous review of the selected literature was conducted.

CHEMISTRY OF FLAVONOIDS

All flavonoids share a 15-carbon phenylpropanoid chain as their fundamental flavan skeleton, which partitions into two aromatic benzene rings (A and B) and a heterocyclic pyran ring (C) with 6 carbons in the number one ring, followed by 3 carbons in the number two ring with one oxygen, and 6 carbons in the last. Figure 1 depicts the general structure of flavonoids.

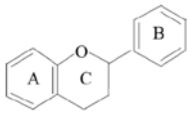

Figure 1: Basic Structure of Flavonoid

The proportion of oxidation, unsaturation in the interconnecting chain, and chemical structure of the following main classes of flavonoids might all be applied to classify them further. Multiple types of flavonoids can be identified, including flavones. These include apigenin, flavone, and luteolin, flavonols (quercetin, myricetin, fisetin, and kaempferol), flavanones, chalcones, and anthocyanidins (Figure 2a-2f) [11]. Although flavonoids share a common C_3–C_3–C_4 skeleton, the oxidation state and substitution pattern of the central heterocyclic (C) ring vary, resulting in distinct subclasses with different physiological behaviours. While flavonols (like quercetin and kaempferol) have an extra hydroxyl group at C3, flavones (like apigenin and luteolin) have a C2–C3 double bond and a C4 carbonyl group. While flavonols, like taxifolin, combine this saturated structure with a C3 hydroxyl, flavanones, like naringenin and hesperetin, lack the C2–C3 double bond, resulting in a saturated C-ring and nonplanar structure. The most reduced flavan-3-ols, such as catechin and epicatechin, exhibit considerable antioxidant activity because they lack the C4 carbonyl group but possess a C3 hydroxyl group. In isoflavones, such as genistein and daidzein, the B-ring is attached at the C3 position rather than the C2 position.

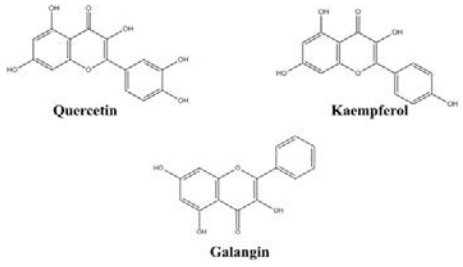

Figure 2a: Structure of Flavonol derivatives

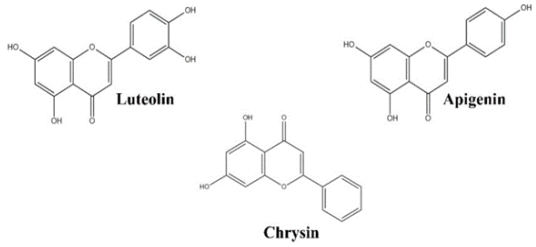

Figure 2b: Structure of Flavone derivatives

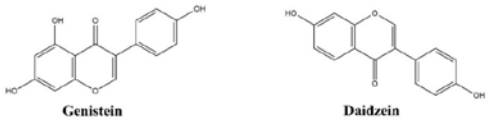

Figure 2c: Structure of Isoflavone derivatives

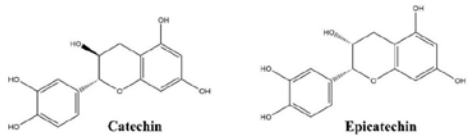

Figure 2d: Structure of Flavan-3-ols derivatives

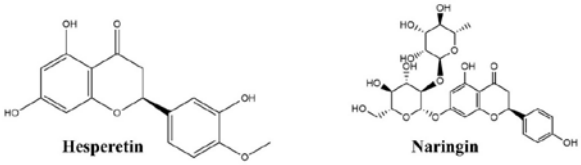

Figure 2e: Structure of Flavanone derivatives

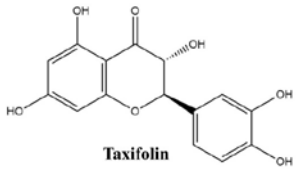

Figure 2f: Structure of Flavanonol derivatives

Figure 2: (a-f) Chemical structures of major flavonoid derivatives

Flavonoids are frequently observed as aglycones, glycosides, and methylated derivatives. The building block of the flavonoid molecule is aglycone (Figure 1). A α-pyrone that includes flavonols and flavanones, and its dihydroderivative (flavonols and flavanones) are the two categories of six-member rings that are fused with the benzene ring. The flavonoid class is separated into flavonoids (2-position) and isoflavonoids (3-position) based on the location of the benzenoid substituent. A hydroxyl group at the 3-position and a double bond in between C2 and C3 set flavonols apart from flavanones [12].

ABSORPTION AND METABOLISM OF FLAVONOIDS

The human gut is thought to harbour up to trillions of microorganisms, including more than 1,000 distinct bacterial species, as well as viruses, fungi, protozoa, bacteriophages, and other organisms that collectively constitute the human microbiome. To have different effects, the gut maintains a dynamic balance between harmful and beneficial microbes. Influencing host metabolism, intestinal host immunity, and intestinal barrier function are the three basic elements of intestinal bacteria's functions[13]. The gut microbiota has a vast gene pool and high metabolic capacity, enabling it to catalyse a variety of processes in the intestinal tract. This also holds for the gut's conversion of flavonoids. Because of the correlation between diseases and the results of contemporary physiological and omics-based research, together with cellular investigations and animal tests, additional research on the health implications of flavonoid-gut microbial interactions should be encouraged.

Overall, the gut microbiota can hydrolyse flavonoids via various biochemical pathways to produce glycosides, glucuronides, sulphates, amides, esters, and lactones. Figure 3 provides a summary of flavonoid ADME[14]. Flavonoids go through phase I metabolism in the epithelium, and the portal vein carries the metabolites to the liver. Phase I metabolism, along with phase II metabolism in the liver, produces additional polar molecules that mediate a broad spectrum of biological actions in target tissues. The kidney, intestinal epithelium, and bile excretion are the three ways that flavonoids leave the body. Microbial enzymes act on flavonoids released into the duodenum through the biliary system, where they may undergo enterohepatic recycling and reabsorption, as shown in Figure 3.

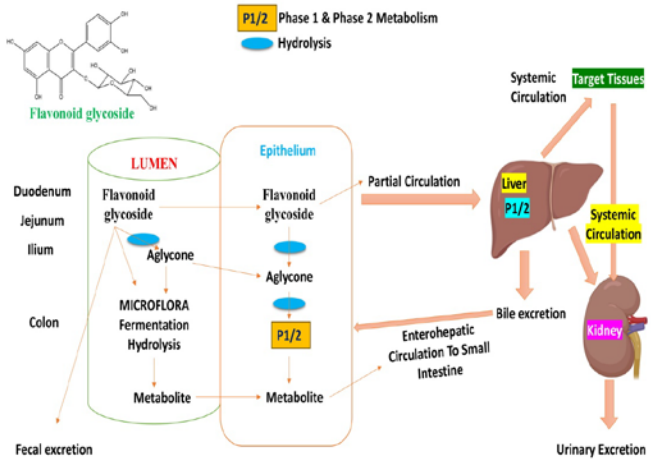

Figure 3: Metabolic Pathway of Flavonoid Glycosides

Flavonoids that are formed with bile in the digestive tract and those that the small intestine is unable to absorb are broken down by intestinal bacteria in the colon. (Figure 4). As a consequence of stomach acid, oligomeric flavonoids may hydrolyse into monomers and dimers. Bigger molecules reach the colon, where microorganisms break them down.

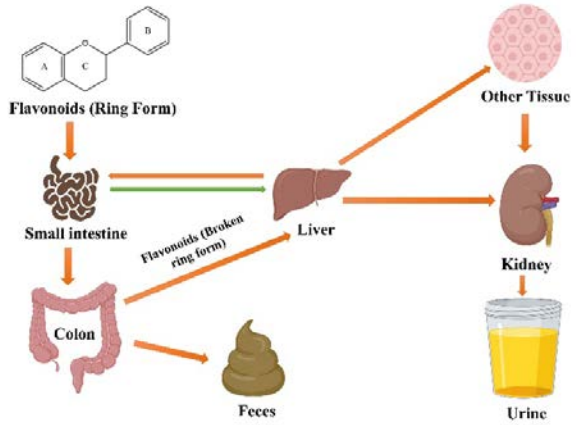

Figure 4: Compartmental Dynamics of Flavonoid Processing and Excretion

To control the illnesses, various beneficial and harmful metabolites are produced, including lipopolysaccharides, peptidoglycans, trimethylamines, and secondary bile[15] Plant tissues often contain and store flavonoids in a variety of derivative forms, primarily as sugar O-conjugates at locations C7 (flavanones, isoflavones, and flavones), C3 (flavonols, anthocyanidins, and flavan-3-ols), or C2 (chalcones). Xylose, galactose, rutinose, arabinopyranose, rhamnose, and arabinofuranose are the most frequently occurring bound sugars. Sugar moieties (like quercetin-3-glucoside) are cleaved from the phenolic backbone within the intestines and absorbed thereafter by consuming flavonoids.

Plants that are attached to sugars as β-glycosides include nearly every flavonoid, except the catechin subcategory (Figure 5). Aglycones are passively permeated into epithelial cells via the enterocyte membrane lactase phlorizin hydrolase (LPH) and other enzymes, or via β-glucosidase (CBG) in the cytosol, for polar glycosides. These enzymes hydrolyse glycosylated flavonoids. Although for the rhamnose-linked flavonoids to be absorbed, they need to get to the colon and participate in hydrolysis by the α-rhamnosidases released by the colon microbiota (as *Bifidobacterium dentium*)[16].

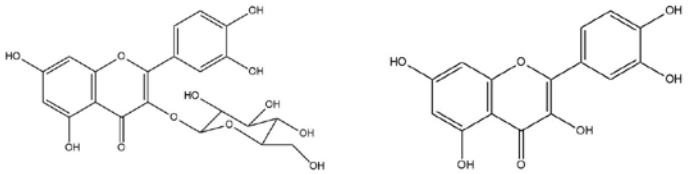

Figure 5: Structure of flavonoid glycoside and aglycone flavonoid

As flavonoids approach the hindgut, gut bacteria anaerobically degrade them, leading to glycoside hydrolysis, decarboxylation, dehydroxylation, and demethylation. By promoting the release of more rapidly absorbed unbound aglycones and the subsequent synthesis of new metabolites, this increases flavonoid metabolic activity. Glycosylated flavonoids could potentially work as the only carbon source available to intestinal bacteria, which first break down the glycosidic fraction to dispose of the O-glycosylation of flavonoids. Specifically, strains of the prominent family Eggerthellaceae in the gutmicrobiota are capable of converting into equol isoflavones[17]. The digestion of flavonoids by intestinal microbes depends on the microbial species and the flavonoid structure. For example, the intestinal flora is necessary for the synthesis of equol. Germ-free animals cannot produce equol; instead, activated flora, such as *Streptococcus intermedius* ssp. and *Bacteroides ovatus* spp., are necessary for equol production [18].

Table 1: Comparative insights between different classes of flavonoids [12, 14, 17]

Class of Flavonoid	Bioavailability	Potency	Examples
Isoflavones	Highly active as they occur as β-glucosides and get readily hydrolyzed by intestinal β-glucosidases into absorbable aglycones.	High (phytoestrogenic, apoptosis induction)	Genistein, Daidzein
Flavanones	Moderate to Low bioavailability due to their hydrophilicity and large molecular size.	High (anti-inflammatory, antioxidant, apoptosis)	Naringenin, Hesperetin
Flavones	Moderate bioavailability due to their poor water solubility, limited intestinal absorption, and extensive phase II metabolism	Moderate to High (protein kinase inhibitors)	Apigenin, Luteolin, Chrysin
Flavanonols	Low due to extensive phase II metabolism	Moderate (antioxidant, apoptosis induction; less studied)	Taxifolin, Dihydrokaempferol
Flavonols	Moderate to Low bioavailability due to their limited solubility, extensive metabolism, and low intestinal permeability.	Moderate to High (inhibiting oxidative stress, inflammation, and modulating cell signaling)	Quercetin, Kaempferol
Flavan-3-ols	Moderate due to extensive phase II metabolism	Moderate to High (pro-apoptotic, signaling modulation)	Catechin

ROLE OF MICROBIOTA AND ENZYMES IN THE BIOTRANSFORMATION OF DIETARY FLAVONOIDS

In the gastrointestinal tract, flavonols, such as kaempferol, present in tea, berries, and cruciferous vegetables, undergo deglycosylation. The production of metabolites, including 2-(3,4-dihydroxyphenyl)acetic acid, 2-(4-hydroxyphenyl) propionic acid, and 2-(3-hydroxyphenyl) acetic acid, results from this process, which β-glucosidase aids. Reduced Proteobacteria and elevated Prevotellaceae are among the microbiota implicated [19] Green tea, broccoli, and citrus fruits contain quercetin, which is primarily metabolised in the small intestine by the enzyme LPH via O-deglycosylation. The main microbial alterations are increases in Lactobacillus and Bifidobacterium, and decreases in Staphylococcus aureus and Escherichia coli. 3-(3-hydroxyphenyl)propionic acid and 3-(3,4-dihydroxyphenyl)propionic acid are among the metabolites that have been found [20].

The large intestine is where myricetin, present in tomatoes, parsley, pepper, and garlic, is degraded. β-glucosidase hydrolyses and deglycosylates the transformation. Metabolites, including 2-(3-hydroxyphenyl)acetic acid and 2-(3,5-dihydroxy phenyl)acetic acid, are produced as a result. Actinobacteria, Allobaculum spp., Lachnospiraceae, Brachybacterium, B. paraconglomeratum, Lactobacillus spp., Nocardiaceae, Turicibacter spp., and Lactobacillus intestinalis are among the microbiota that have changed [21].

Flavones: β-glucosidase hydrolyses apigenin, which is found in parsley and chamomile, in the small intestine. It produces metabolites such as 3-(3-hydroxyphenyl)-propionic acid and 4-hydroxycinnamic acid. Increased Bifidobacteria and Lactobacilli, and reduced Escherichia coli and Helicobacter pylori are among the microbiota involved [22].

Flavanones: Naringenin, which is present in pomelos, lemons, sweet limes, and mandarin oranges, is broken down in the colon by chalcone isomerase by O-deglycosylation. Three-(4-hydroxyphenyl) propionic acid is the main metabolite. Elevated Bifidobacterium catenulatum levels are linked to its metabolism [23].

Anthocyanins: In the small intestine, β-glucosidase O-deglycosylates cyanidin, which is found in large quantities in blackberries and blueberries, to create cyanidin-3-glucoside. Increased concentrations of Bifidobacterium lactis BB-12, Lactobacillus plantarum, and Lactobacillus casei indicate microbial activity [24].

Flavan-3-ols: Catechol-O-methyltransferase in the small intestine dehydroxylates catechin, which is present in kiwis, red wine, and green tea. As a result, 3-(3-hydroxyphenyl)propionic acid is created. Adlercreutzia equolifaciens JCM 14793T is the primary microorganism [37]. Isoflavones β-glucosidase deglycosylates daidzein, which is present in soybeans and soy

products like tofu, in the colon. S-equol is the main metabolite. Elevated amounts of Lachnospiraceae, Pseudoflavonifractor, and Slackia are linked to this metabolic pathway [25].

FLAVONOIDS' ROLE IN CANCER TREATMENT

Cancer is swiftly establishing itself as a dominant global health challenge, reshaping the landscape of disease prevalence in modern times. Flavonoids are believed to exert biological effects on cancer regulation, including angiogenesis, apoptosis, cell proliferation, differentiation, and other processes (Table 1). Flavonoids present in vegetables and fruits have been recognisedas chemopreventive agents for cancer[26]Ples and onions are two prominent foods that contain the flavonol quercetin, which has a negative correlation with the likelihood of breast, stomach, lung, and prostate cancer. Moderate wine users appear to be less likely to acquire cancers of the colon, stomach, oesophagus, endometrium, and lungs[27]. It is well established that consuming more fruits and vegetables can help prevent cancer. It has already been suggested that significantly raising the intake of these foods might significantly improve public health[28]. Numerous theories have been put forth to explain how flavonoids impact the initiation and course of carcinogenicity, including impacts on development and hormone action[29]. Flavonoids' predominant molecular mechanisms of action typically involve downregulation of proteins, such as the mutant p53 protein; inhibition of enzymes, including tyrosine kinases; inhibition of HSPs; and inhibition of Ras protein expression. It has been proven that the flavanol epigallocatechin-3-gallate hinders the fundamental functions of lipogenesis and fatty acid synthase (FAS) in prostate cancer cells. This activity is closely linked to both cell death and growth arrest [30]. FAS is upregulated at an early stage of tumour formation and becomes even more pronounced in later advanced tumours [31]. It is known that quercetin induces lymphoid cells to enter cell-cycle arrest. Apart from its antitumor properties, quercetin inhibited the proliferation of multiple cell lines of malignant tumours in vitro. P-388 leukaemia cells, gastric cancer cells (HGC-27, NUGC-2, NGN-7, and MKN-28), gastric cancer cells (HGC-27, NUGC-2, NGN-7, and MKN-28), ovarian cancer cells, colon cancer cells (COLON320DM), and human squamous breast cancer and gliosarcoma cells were reported amongst them [32].

Markaverich et al. suggest that quercetin's association with nuclear type II estrogen-binding sites (EBS) may underlie its anticancer activity. There is evidence that quercetin has antiproliferative attributes that have substantially lowered the elevated signal transduction in human breast cancer cells [33]. It has been tested and found that hesperidin, a flavanone glycoside, inhibits azoxymethanol in rats' colon and breast tumours [34]. Carroll et colleagues have examined the anticancer potential of flavonoids found in citrus fruits [35]. The most significant classes of flavonoids have strong antimutagenic qualities (Figure 5) [36]. It was discovered that the flavone nucleus's C-4 acarbonyl function was crucial to its action. Moreover, flavone-8-acetic acid's anticancer properties have been verified [37]. The results of earlier research indicate that ellagic acid, quercetin, robinetin, and myricetin inhibit the growth of tumours caused by BP-7, 8-diol-9, and 10-epoxide-2 on mouse skin [38].

Flavonoids have multifaceted anticancer mechanisms, including modulation of ROS-scavenging enzyme activities, modulation of signaling pathways, regulation of non-coding RNAs, induction of apoptosis, and inhibition of cancer cell growth and invasion [39]. Table 2 provides brief descriptions of the mechanisms of action and the diverse cancer cell lines targeted by different flavonoids, highlighting their promising anticancer properties. Each flavonoid employs distinct yet overlapping biochemical and cellular pathways to exert cytotoxic effects on cancer cells. Hesperidin and naringenin are potent in elevating reactive oxygen species (ROS) levels, reducing mitochondrial potential, and inducing DNA damage, ultimately activating apoptosis via intrinsic and extrinsic pathways. Epicatechin and epigallocatechin gallate demonstrate efficacy by modulating critical signaling enzymes, including Akt and nuclear factor κB (NF-κB), thereby inhibiting angiogenesis and inducing oxidative stress. Quercetin and kaempferol predominantly affect apoptotic pathways, damaging mitochondrial integrity and inducing cell death by increasing pro-apoptotic factors, such as caspases and Bax, and decreasing anti-apoptotic proteins, such as B-cell lymphoma 2 (Bcl-2). By blocking the Akt pathway and reducing survival proteins such as Bcl-xL, myricetin promotes mitochondrial apoptosis and enhances its anticancer activity.

Apigenin's ability to reduce histone deacetylase (HDAC) activity, induce G2/M cell cycle arrest, and regulate apoptotic proteins is among its most noteworthy characteristics, making it a promising target for aggressive tumours. Cyanidin, on the other hand, efficiently halts cell cycle progression by inducing caspase-independent apoptosis via activation of apoptosis-

inducing factor (AIF). The promising potential of these flavonoids as natural anticancer agents is underscored by their ability to disrupt tumour growth, proliferation, and survival across a variety of cancer cell lines.

Table 2: Flavonoids with their mechanism on cancer cell lines

Flavonoid	Mechanism of Action	Cell Lines	Ref
Hesperidin	Elevates ROS, reduces mitochondrial potential, induces DNA fragmentation, upregulates Bax, and downregulates Bcl-2,	Eca109, HT-29, MCF-7,Gastric cancer cells, H522, MDA-MB-231, HT-20	[40]
	reduces GSH concentrations, and cell cycle arrest typically occurs at the G0/G1 or G2/M phases.	Gastric cancer cells, HT-20, H522	
Naringenin	Elevates ROS, reduces mitochondrial potential, induces DNA damage, and overexpresses Fas and FADD ligands	SGC-7901 (gastric cancer)	[41]
Epicatechin	Modulates signaling enzymes, contributes to apoptosis, prevents angiogenesis, and induces oxidative stress	HeLa, MKN-45, HCT-116, renal tubular carcinoma	[42]
	Targets proliferative signaling NF-κB and Akt, exhibits synergistic effects with cisplatin or panaxadiol.	HCT-116, renal tubular carcinoma	
Epigallocatechin Gallate	Induces TRAIL-mediated apoptosis, increases caspase-3, Bax/Bcl-2, p53, p21, caspases-3 and -9, PTEN, downregulates PI3K, AKT, Bcl-2	Prostate carcinoma, lung carcinoma, T47D, HFF, MDA-MB-231, HS578t	[43]
	Stimulates p21, p27, reduces Ki-67, cell cycle arrest at G1, reduces VEGF, modulates Akt, ERK1/2, p38 MAPK	Eca-109, Te-1, HT-29, SW837, 293T, A549, MCF-7, NF639, SMF, colon cancer	
Quercetin	Induces apoptosis via Bax, caspase-3, decreases Bcl-2, triggers necroptosis, targets RIPK1, RIPK3, intrinsic mitochondrial pathway	MCF-7, BT-474, HL-60, NB-4	[44]
Kaempferol	Induces DNA fragmentation, increases p53, caspases, disrupts cell proliferation signaling, and prevents angiogenesis	MDA-MB-453, A2780, OVCAR-3, HL-60, NB-4	[45]
Myricetin	Induces DNA condensation, suppresses Bcl-xL and Bcl-2, releases AIF, inhibits the Akt pathway, triggers mitochondrial apoptosis	HCT-15, UVB-induced HaCaT, SKOV3, OVCAR-3, A2780	[46]
Apigenin	Inhibits HDAC activity, increases Bax, caspases, p21, p27, induces G2/M cell cycle arrest, reduces glutathione	PC-3, 22Rv1, DU145, T24, SW480, BCPAP	[46]
Cyanidin	Induces cell cycle arrest, inhibits proliferation via VEGF, and caspase-independent apoptosis (AIF pathway)	DU145, LnCap, U87	[47]

FLAVONOIDS IN OXIDATIVE STRESS

The majority of chronic inflammatory diseases, neurological problems, cancer, and metabolic disorders are known to be directly or indirectly caused by oxidative stress (OS). The biochemical scavenger theory posits that nutritional polyphenols, also known as flavonoids, are effective scavengers of reactive oxygen species (ROS) and free radicals owing to their aromatic structures, densely conjugated systems, and large numbers of hydroxyl groups. They can reduce tissue inflammation and prevent oxidative damage to biomolecules (lipids, proteins, and DNA) by blocking cellular OS or eliminating ROS [48]. ROS can be generated by a wide range of external agents, including metal-catalyzed reactions, X-rays, γ-rays, UV irradiation, environmental contaminants, and carcinogens. Exogenous sources of ROS include heavy metals and transition metals, nicotine, alcohol, solvents, certain medications, food (such as rancid oil, fat-rich foods, and meat cooked at high temperatures), and radiation. On the other hand, cytochrome P450 metabolism, peroxisomes, mitochondrial processes, and inflammatory cell activation are examples of endogenous sources of ROS. Both endogenous and exogenous ROS can oxidatively damage or modify biological

macromolecules when produced in excess. When cells produce excessive ROS, these oxidants typically damage proteins, lipids, DNA, and carbohydrates. This has led to the aetiology of many human diseases, such as diabetes, cancer, heart disease, inflammatory diseases, and brain dysfunction [49].

Consuming a diet rich in antioxidants mitigates the adverse effects of ageing and neurological diseases. Brightly coloured fruits such as oranges, tomatoes, and berries are rich in anthocyanins, which possess potent anti-inflammatory and antioxidant properties. They also inhibit cyclo-oxygenase (COX-1 and COX-2) pathways and lipid peroxidation [50].
About their antioxidant properties, tea catechins may have anti-aging effects. The in vitro impact of tea catechins on erythrocytes decreased malondialdehyde (MDA), membrane sulphydryl (SH-) group, and glutathione (GSH) [51]. They additionally prohibit smooth muscle fibres from entering the arterial wall and multiplying there [52]. Consuming polyphenol-rich foods reduces the incidence of CVDs [53]. According to recent research, polyphenols also help vascular diseases by reducing blood pressure, strengthening antioxidant defences, reducing inflammation, boosting endothelial cell function, preventing platelet aggregation, and preventing low-density lipoprotein (LDL) from oxidizing [54]. By selectively inhibiting cyclooxygenase 1 (COX-1), which raises the synthesis of thromboxane A2, a vasoconstrictor inducer, resveratrol inhibits platelet aggregation [55].

FLAVONOIDS IN APOPTOSIS

The two principal signalling cascades of apoptosis are intrinsic (mitochondrial pathway) and extrinsic (related to the TNF superfamily and its primary signalling molecule, caspase 8). Caspases 9, 3, and 7 are triggered by Bcl-2 family proteins in the former. Apoptosis, or programmed cell death, is frequently triggered by a range of pro-apoptotic proteins and signal transduction pathways, including Bcl-2 family proteins and caspases. Flavonoids are pro-oxidants that may inhibit the growth of cancer cells by blocking the actions of protein kinase B (Akt), phosphatidylinositide 3-kinases (PI3K), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and epidermal growth factor receptor/mitogen-activated protein kinase (EGFR/MAPK) [30].

Because flavonoids such as genistein and daidzein alter key cellular signalling pathways, they play a significant role in activating programmed cell death (PCD). PI3K/Akt/mTOR, caspases, JAK/STAT, Bcl-2 family proteins, and NF-κB are among the pathways that they control. Hesperetin is a flavanone that activates caspases 3 and 9, thereby inducing apoptosis and reducing the Bax/Bcl-2 ratio in gastric cancer cells [56]. Naringenin brings about apoptosis by enhancing p53 expression, cleaving Bax and caspase-3, and downregulating Bcl-2 and surviving in SGC-7901 cells[57]. It also induces extrinsic apoptosis by overexpressing TNF-family proteins. Kaempferol encourages apoptosis of HeLa cells by elevating the Bax/Bcl-2 ratio [58].Apigenin exerts dual apoptotic effects in HCT-116 cells and demonstrates estrogenic activity [59].

Epigallocatechin gallate (EGCG) has shown pro-apoptotic effects in cancers, including leukemia[60], prostate[61], gastric [62], preadipocytes [63], as well as colon[64]and fibroblasts[65]. These findings highlight the potential of flavonoids as modulators of apoptosis across various cell lines. As evidenced by research, ingesting more phytoestrogens, such as isoflavones and other flavonoids, reduces the incidence of prostate cancer [66]. To fully understand the underlying mechanisms, more research is necessary. Flavonoids have a notable impact on metastasis and on signalling pathways at the onset or progression of cancer.

FORMULATION STRATEGIES TO ENHANCE FLAVONOID BIOAVAILABILITY

Flavonoids often exhibit poor oral bioavailability due to low solubility, limited permeability, and instability. However, nanotechnology-based delivery technologies have emerged as a possible solution. Nanoscale carriers offer a more efficient solution by significantly increasing surface area, saturation solubility, and dissolution rate, even though methods such as prodrug modification, particle-size reduction, and pH adjustment can also improve dissolution. Recent studies have demonstrated the potential of various nanoformulations to enhance the medicinal efficacy of flavonoids. To improve the solubility and controlled release of the anti-inflammatory flavonoid rhoifolin, for example, a polymeric nanocarrier system made of PLGA nanoparticles with PEG-tannic acid surface modification was created (Al-Shalabi, 2022); amphiphilic dextran-based nanomicelles greatly increased quercetin's cellular uptake, addressing its poor aqueous solubility (He, 2023); and hesperetin-loaded nanosponges integrated into a topical gel demonstrated superior anti-inflammatory efficacy

(Rodrigues, 2022). Taken together, these developments demonstrate the increasing utility of nanotechnology as a platform for enhancing flavonoid bioavailability and therapeutic outcomes [67,68,69].

CONCLUSION

Flavonoids, as naturally occurring dietary compounds, can offer a safer alternative to many synthetic anticancer agents, with minimal adverse interactions due to their long-standing presence in human diets and beverages. Through liver-mediated bio-transformations and gut microbiota, they produce bioactive compounds that regulate ROS, signalling pathways, apoptosis, and cancer cell growth. However, flavonoids exhibit low bioavailability due to rapid metabolism, conjugation, and poor intestinal absorption, while inter-individual variation in the gut microbiota further contributes to inconsistent pharmacological outcomes. Differences in experimental models and analytical methods also contribute to variability across studies. Hence, integrative in vitro–in vivo studies, human microbiota-based models, and advanced formulation strategies are needed to enhance their stability, bioavailability, and therapeutic relevance in cancer prevention and treatment. This study not only summarises current knowledge but also offers a framework for utilising flavonoids as readily available, natural, and potent medicines in modern cancer prevention and treatment efforts, incorporating insights into metabolism, bioavailability, and molecular processes. Future studies should focus on addressing the current pharmacokinetic and pharmacological barriers that prevent the use of flavonoids in therapeutic settings. Techniques such as prodrug design, targeted delivery systems, and nanoformulation could increase therapeutic efficacy and bioavailability. Validating the molecular roles of flavonoid biotransformation to their anticancer potential requires carefully planned in vivo and clinical investigations. The intricate relationship between gut microbial diversity and flavonoid metabolism may be better understood by combining metabolomics, microbiome sequencing, and computational modelling. Furthermore, customised strategies that account for interindividual variation in gut microbiota composition may enable flavonoid-based treatments.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Faruk Alam conceptualized the review, conducted the literature searches, and critically reviewed and approved the final manuscript. Surabhi Mandal carried out the literature review, drafted the manuscript, and was responsible for its final content. Bhupendra Shrestha provided critical guidance and contributed to the manuscript's writing, review, and editing. Barasha Bharadwaj and Bramhajit Chatterjee assisted with the literature review and manuscript preparation and were responsible for the structure and figures.

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