

Mechanistic Insights into the Pharmacological Actions of Flavonoids: A Comprehensive Review

Natural Product Communications
Volume 21(2): 1-15
© The Author(s) 2026
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1934578X261416331
journals.sagepub.com/home/npx



Abdur Rasheed¹, Gowhar Ali¹, Md. Rezaul Islam², Abdur Rauf³ , Rahaf Ajaj⁴, Hassan A. Hemeg⁵ and Marcello Iriti^{6,7}

Abstract

Flavonoids, a diverse group of polyphenolic chemicals found in plants, have significant attention for their diverse pharmacological actions and therapeutic potential. Their ability to target multiple pathways, modulate oxidative stress, and regulate inflammatory mediators is crucial in preventing and managing chronic diseases like cancer, cardiovascular disorders, diabetes, and neurodegenerative diseases. Flavonoids have multitargeted actions, providing a safer and general therapeutic approach compared to single-targeted synthetic drugs. This review provides a comprehensive understanding of flavonoids' biological effects, focusing on their modulation of key molecular signaling pathways such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), mitogen-activated protein kinases (MAPK), phosphatidylinositol 3-kinase (PI3 K)/protein kinase B (AKT), nuclear factor erythroid 2-related factor 2 (Nrf2), oxidative stress, inflammation, and apoptosis. Their anticancer potential is supported by their ability to induce apoptosis, modulate autophagy, and influence gene expression, while their anti-inflammatory and antioxidant properties aid in cytoprotection. Certain hydroxylation and glycosylation patterns enhance their biological efficacy based on structure-activity connections. The review demonstrates the various benefits of these substances, including their hepatoprotective, neuroprotective, anticancer, antidiabetic, and cardioprotective properties, based on both experimental and clinical evidence. It discusses the structure-activity relationship (SAR) that supports their bioefficacy as well as issues with metabolism, bioavailability, and therapeutic translation. It also provides a comprehensive understanding of flavonoids as potential agents for chronic disease prevention and management, integrating pharmacological findings with molecular facts. A method was used to identify works published in reputable journals. Every search result came from PubMed, Scopus, Web of Science, ScienceDirect, Google Scholar, etc. The terms flavonoids, pharmacological properties, disease, and mechanism of action were utilized. We selected and investigated research papers, review articles, and original studies that were published up until 2025. Future research should focus on improving flavonoids' bioavailability using advanced drug delivery methods like conjugates, liposomes, and nanoparticles, with extensive clinical trials needed for validation. Furthermore, the potential of flavonoids in therapeutic interventions will be enhanced through the use of computational techniques such as molecular docking, network pharmacology, and precision medicine. Future perspectives emphasize the need for advanced drug delivery systems, clinical trials, and molecular docking techniques to enhance their therapeutic efficacy.

Keywords

flavonoids, pharmacological mechanisms, oxidative stress, inflammation, signaling pathways, chronic diseases

Received: October 29, 2025; accepted: January 2, 2026

¹Department of Pharmacy, University of Peshawar, Peshawar, Pakistan

²Department of Pharmacy, Faculty of Health and Life Sciences, Daffodil International University, Dhaka, Bangladesh

³Department of Chemistry, University of Swabi, Swabi, Pakistan

⁴Department of Environmental and Public Health, College of Health Sciences, Abu Dhabi University, Abu Dhabi, United Arab Emirates

⁵Department of Medical Laboratory Technology, College of Applied Medical Sciences, Taibah University, Madinah, Saudi Arabia

⁶Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy

⁷National Interuniversity Consortium of Materials Science and Technology (INSTM), Firenze, Italy

Corresponding Authors:

Abdur Rauf, Department of Chemistry, University of Swabi, Swabi, Anbar, 23430, Khyber Pakhtunkhwa (K.P.), Pakistan.
Email: mashaljc@yahoo.com

Marcello Iriti, Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy.
Email: marcello.iriti@unimi.it



Introduction

Phytochemicals from plants, especially flavonoids, are utilized to treat and prevent various diseases. These plant-derived substances feature a benzopyrone ring and include over 6000 distinct types, categorized as flavones, flavanones, flavanols, isoflavones, anthocyanidins, and catechins. Extensive experimental studies have showcased their versatile pharmacological properties, such as antioxidant, anti-inflammatory, antibacterial, antifungal, antiviral, and several others, contributing to health benefits across numerous conditions.¹ Flavonoids are chemically defined polyphenolic structures, widely distributed in plants, vegetables, fruits, and leaves.² Additionally, flavonoids, or bioflavonoids, are polyphenolic substances found in fungi and plants. They serve various pharmaceutical purposes and biological roles in plants. Although not recognized as nutrients, regular consumption of flavonoids is beneficial for human health. They have various pharmacological properties, including anti-inflammatory, anti-cancer, anti-inflammatory, anti-Parkinson, anti-depressant, anti-bacterial, and anti-diabetic effects.³ Flavonoids possess multiple activities, like antioxidant, anti-inflammatory, analgesic, hepatoprotective, and gastroprotective activities.^{4,5} Further, flavonoids inhibit enzymes, regulate hormones, and exhibit anti-inflammatory properties in both proliferative and exudative stages of inflammation.⁶ Naringenin has strong pharmacological properties and therapeutic potential. It has potential therapeutic uses in neurological, cardiovascular, gastrointestinal, rheumatological, metabolic, and malignant conditions.⁷ Quercetin's strong antioxidant properties absorb ROS, nitrogen species, and chlorine species. Its structure contains five functional hydroxyl groups, catching free radicals. It demonstrates anti-inflammatory, antiviral, antihypertensive, and carcinostatic effects, prevents LDL oxidation, and inhibits angiogenesis.⁸ Kaempferol has shown potential neuroprotective effects on central nervous system (CNS) diseases by modifying proinflammatory signaling pathways. It modulates proinflammatory signaling pathways like β -catenin, p38MAPK, NF- κ B, and AKT. KPF and its glycosylated derivatives have a multipotential neuroprotective function in CNS diseases.⁹ Fisetin alters Bcl-2 family protein expression in various cancer cell lines, inhibits cell growth, induces apoptosis, and reduces cancer cell stages. It decreases NF- κ B activation and inhibits TET1 expression.¹⁰ Apigenin has therapeutic potential in preventing infectious diseases and suppressing tumor growth. Using apigenin with anti-cancer medications can maintain the cell cycle, inhibit mobility, boost immunity, and inhibit mTOR activity.¹¹ A study explores the anti-inflammatory properties of flavones luteolin and luteolin-7-O-glucoside, which interact with NF- κ B and JAK/STAT3 pathways. These compounds also impact inflammatory metabolic pathways, including lipid peroxidation, diabetes, and cancer cells.¹² Baicalin and baicalein have chemopreventive and therapeutic uses in managing inflammatory and cancerous conditions.¹³ Epigallocatechin gallate (EGCG) has shown potential in preventing diseases by influencing physiological processes like inflammation and lipid metabolism. It can alter cell signaling pathways related to oxidative stress (OS), apoptosis, and immunological modulation. It also has potential

therapeutic approaches for chronic diseases like cancer, heart disease, and metabolic syndromes.¹⁴ Genistein has anticancer, cardiovascular disease, postmenopausal relief, and osteoporosis protection. This study demonstrates genistein's toxicity profile and anti-inflammatory properties, focusing on signaling pathways and mediators involved in the inflammatory response. Genistein suppresses multiple pathways, including NF- κ B, prostaglandins, iNOS, proinflammatory cytokines, and reactive oxygen species (ROS).¹⁵ A study explores the biological effects of daidzein, a compound involved in chronic diseases like cancer, osteoporosis, cardiovascular disease, and neurodegenerative diseases (NDs). It regulates inflammatory mediators, activates antioxidant pathways, and modulates oestrogen receptors, potentially reducing OS, enhancing bone mineral density, and stopping cancer cell growth.¹⁶ In the review, flavonoids, which modulate cellular signaling pathways, have therapeutic effects like anti-inflammatory, anti-cancer, antioxidant, and neuroprotective properties. They also have potential for treating chronic diseases like cancer, heart disease, and neurodegeneration by modifying gut flora and enhancing metabolic processes.

This review conducted a literature search of major databases (PubMed, Scopus, Web of Science, ScienceDirect, Google Scholar) using the keywords 'flavonoids,' 'pharmacological properties,' 'disease,' and 'mechanism of action.' Research articles, review articles, and original studies published up to 2025 were selected and analyzed.

Chemical Structure and Bioavailability

Flavonoids are naturally occurring phenolic metabolites that are primarily found in plants. Flavonoids are found in various plant tissues, both externally and internally.¹⁷ Additionally, flavonoids have various health benefits, including antimalarial, cytotoxic, and cancer-fighting properties, and are beneficial in treating diabetes, Alzheimer's disease (AD), and age-related conditions.^{17,18} Flavonoids possess characteristics such as selective protein binding, scavenging free radicals, and chelating metals. A fifteen-carbon skeleton connected to two benzene rings, A and B, by a C (heterocyclic pyrene) ring is the fundamental component of flavonoids. Chemical classes vary in A and B-ring substitution sequence, while flavonoid classes differ in oxidation degree and C-ring arrangement.¹⁷ Furthermore, flavonoids can be classified into subgroups based on carbon in the C ring, oxidation, and substitution degree, and other factors. Isoflavones have a B ring in the third position, while neoflavonoids have a B ring in the fourth position. Flavonoids include flavanols, catechins, anthocyanins, flavonols, flavones, flavanones, and chalcones.¹⁹ Ninety percent of total anthocyanins are glycosylated with various sugar units and hydroxylation and methylation patterns on the B ring.²⁰ Flavanonols, also known as dihydroflavonols, are a subgroup of flavonoids comprising flavanones and their 3-hydroxy derivatives, distinguished by the saturation of the C ring in flavanones. Eriodictyol, hesperetin, and naringenin are the flavanones that are most frequently reported. Citrus fruits typically contain flavanones.²¹ Flavones are the largest subgroup of polyphenols. They have a ketone at position 4 and double

bonds between positions 2 and 3. Flavones include luteolin, tangeretin, isoorientin, apigenin, baicalein, and polymethoxylated flavones like tangeretin, nobilletin, and sinensetin.²² Moreover, flavanols, also known as flavan-3-ol, are formed by attaching a hydroxyl group at ring C's position 3, lacking a C4 carbonyl and a double bond between C2 and C3. They can have two chiral centers, resulting in four potential diastereoisomers.^{23,24} Flavonoids are known for their increased bioactivity, bioavailability, and stability. Flavonoids are converted into glycosides through the enzyme glycosyltransferase, which combines a sugar moiety with an aglycone portion. Methylation of flavonoids significantly alters their pharmacological and biological properties, similar to how methyltransferase binds methyl moieties to aglycone, forming C-methylated or O-methylated compounds.²⁵ Fat consumption enhances intestinal absorption and improves flavonoid bioavailability by increasing bile salt output, which increases the incorporation of flavonoids in the micellar.²⁶ Protein consumption can decrease the bioavailability of flavonoids, affecting the efficacy of antioxidants and the digestibility of proteins.²⁷ Aglycones, being lipophilic, pass-through passive diffusion into intestinal epithelial cells, while intestinal epithelial transporters regulate the uptake of glycosides. Microbes that divide their heterocyclic oxygen-containing ring break down unabsorbed flavonoids in the colon, which may be absorbed as hydroxylated phenyl carboxylic acids.²⁸

Pharmacological Activities of Flavonoids

Antinociceptive Effect

Cistus species extracts have been used to treat inflammatory conditions like kidney and rheumatism. Two *in vivo* models showed the extracts' effects on inflammation in mice. Three active components, 3-O-methylquercetin, 3-O-dimethylquercetin, and 3-O-dimethylkaempferol, were identified as the primary active components. These flavonoids showed strong antinociceptive properties and were found to be safe without acute toxicity or stomach damage.²⁹ 7-Hydroxyflavone, 3-hydroxyflavone, and 2-hydroxyflavanone effectively reduce nociceptive and neuropathic pain by targeting inflammatory mediators like TNF- α , IL-6, IL-12, and protein kinases.^{4,5} A Chinese study found that safflower and kaempferol glycosides effectively suppressed nociception and reduced paw edema from cinnamon aldehyde, while also reducing inflammation during both carrageenan-induced phases.³⁰ Black mulberry suppresses pro-inflammatory cytokines, demonstrating their anti-inflammatory and antinociceptive properties. The dry weight total flavonoid content was 20.9 mg/g, and the fruit contained two anthocyanins.³¹ A study analyses the differences in terpenoids and flavonoids among ethyl acetate extracts from ten locations and evaluates their antinociceptive potential. Despite variations in metabolite content, the antinociceptive effects of *Salvia semitrata* at a dose of 300 mg/kg were consistent, validating its traditional use as an analgesic.³²

Anti-Inflammatory Effect

Flavonoids, found in various plants, have numerous therapeutic benefits. They activate antioxidant pathways, inhibit lysozymes and β -glucuronidase release, and control cytokine expression and gene expression. Flavonoids also inhibit pro-inflammatory enzymes.³³ Flavonoids can regulate these inflammatory responses, inhibiting inflammatory indicators and preventing brain damage. This anti-inflammatory activity is mainly associated with microglial cell control via NF- κ B signaling pathways and MAPKs.³⁴ Naringenin reduces inflammation by decreasing OS, NF- κ B activation, MPO pathway, and MAPK signaling activation.³⁵ Flavonoids such as quercetin, genistein, apigenin, kaempferol, and epigallocatechin 3-gallate modulate the expression and activation of cytokines like IL-1 β , TNF- α , IL-6, and IL-8, along with the gene expression of various pro-inflammatory molecules, including NF- κ B, AP-1, ICAM, VCAM, and E-selectins. They also inhibit pro-inflammatory enzymes like inducible nitric oxide synthase, cyclooxygenase-2, and lipoxigenase.³³

Antidiabetic Activity

Flavonoids can reduce hyperglycemia through different mechanisms. Boswellic acid, ellagic acid, quercetin, and rutin reduce hyperglycemia by inhibiting glucose transport, increasing uptake in isolated cells (Figure 1).³⁶ Apigenin, cosmosin, and quercitrin have a significant hypoglycemic effect as compared to metformin.³⁷ Baicalein reduced advanced glycation end-products (AGEs) and tumor necrosis factor (TNF) levels, suppressed NF- κ B activity, and mitigated histopathological damage.³⁸ Furthermore, quercetin lowers glucose levels, improves glucose tolerance, reduces insulin resistance, and maintains beta cell structure in mouse models.^{39,40} Protein Tyrosine Phosphatase 1B (PTP1B) is a promising target for treatment due to its role in insulin resistance. DPP-4 inhibitors are a new treatment, but flavonoids' antidiabetic properties have not yet been explored. The study aims to identify beneficial flavonoids for inhibiting PTP1B and DPP-4.⁴¹ A study investigates flavonoids as inhibitors of PTP1B and DPP-4 activities, focusing on their inhibition types, experimental conditions, and structure-activity relationships. These enhance their potential as therapeutic agents for Type 2 Diabetes.⁴¹

Antibacterial Activity

Flavonoids are a diverse group of phenolic secondary metabolites known for their antibacterial properties. These may exert antibacterial effects by damaging cytoplasmic membranes, inhibiting energy metabolism, and interfering with nucleic acid synthesis.⁴² A study evaluated the antibacterial properties of six organic acids and thirteen common flavonoids using clinical strains of four pathogenic bacteria. Salicylic acid had the strongest inhibitory effect, but its biological activity was modest or low. Flavones, chrysin, apigenin, and luteolin showed no effect on antibacterial activity.⁴³ Flavonoids are increasingly recognized

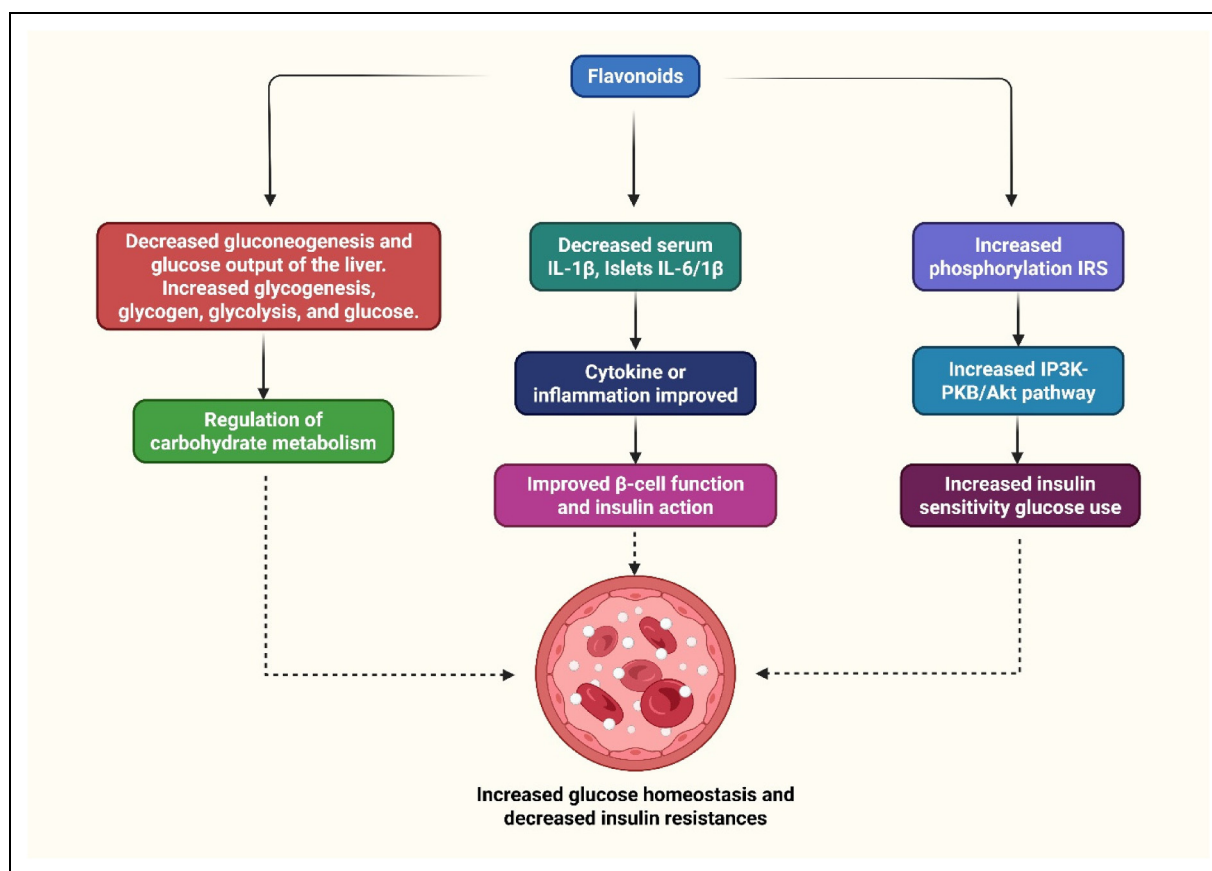


Figure 1. The diagram illustrates how flavonoids can potentially aid in managing blood sugar levels in diabetics. Flavonoids reduce insulin resistance and improve glucose homeostasis by several mechanisms. These promote glycogenesis and glycolysis while inhibiting gluconeogenesis and glucose output in the liver. These also decrease inflammatory cytokines (IL-1 β , IL-6), which enhances insulin action and β -cell function. Additionally, these improve insulin sensitivity and glucose consumption by activating insulin signaling pathways, including insulin receptor substrate (IRS) phosphorylation and the phosphatidylinositol 3-kinase (PI3 K)-protein kinase B (PKB)/Akt pathway.

for their antibacterial properties. Two regression equations were recognized, revealing that flavonoids have a minimum inhibitory concentration (MIC) against gram-positive bacteria. The MICs are estimated to be around 10.2, with flavonoids primarily affecting gram-positive bacteria through cell membrane degradation, ATP synthesis suppression, and respiratory chain disruption.⁴⁴

Antifungal Activity

Baicalin and myricetin have potent inhibitory effects on *Candida* sp., with MICs of 1.9–21 and 3.9–64 μ g/mL, respectively.⁴⁵ Curcumin has potential anti-candidal activity against various clinical isolates of *C. albicans* and *C. gattii*.⁴⁶ Flavonoid phytoalexins are formed in grasses infected by fungi, but little is known about their induction in maize. Researchers found biosynthetic enzymes contributing to the production of O-methylflavonoids in maize. Two tautomers of xilonenin were found to significantly suppress maize diseases. Two O-methyltransferases (OMTs) were found, with unique regiospecificity on various flavonoid classes. A cytochrome P450 monooxygenase functioned as a flavanone 2-hydroxylase.⁴⁷ Flavonoid metabolism in maize affected by fungi, key biosynthetic enzymes

responsible for O-methylflavonoid formation. Identified two O-methyltransferases, FOMT2 and FOMT4, that exhibit distinct regiospecificity among flavonoids, as well as a cytochrome P450 monooxygenase from the CYP93G subfamily acting as a flavanone 2-hydroxylase, which is essential for FOMT2's xilonenin production. Overall, diverse O-methylflavonoids with antifungal properties are produced in maize upon fungal exposure.⁴⁷

Antiviral Activity

Flavonoids are known for their antiviral properties, targeting viral infections at various stages. They are effective against various disease-causing viruses, including SARS, hepatitis, AIDS, the flu, and herpes. Despite their potential, there are currently no viable therapies for these diseases. A study examined various flavonoids *in vitro*, *in vivo*, and *in silico* testing settings. Some flavonoids showed stronger antiviral activity compared to commercially available medications.⁴⁸ EGCG has a dose-dependent effect against influenza A and B. Baicalin inhibits various stages of replication of Japanese Encephalitis virus. Quercetin and baicalin inhibitory potential have been reported in some studies. Naringenin, silymarin,

apigenin, ladanien and sorbifolin, and epigallocatechin are studied as effective against HCV.⁴⁸ Flavonoids like apigenin, vitexin, quercetin, rutin, and naringenin have antiviral properties due to altering viral proteins and inhibiting viral neuraminidase, proteases, and DNA/RNA polymerases. Recent drug delivery techniques have overcome the poor bioavailability of flavonoids, making it crucial to test flavonoid cocktails' antiviral properties to prevent viral infections and enhance existing treatments.⁴⁹ A study investigates the antiviral activity of flavonoids against the Chikungunya virus (CHIKV), a mosquito-borne disease. The compounds were tested using various assays, including Western blotting, immunofluorescence, and quantitative reverse transcription polymerase chain reaction (qRT-PCR). Baicalein, fisetin, and quercetagenin showed strong suppression of CHIKV infection with negligible cytotoxicity. These impacted CHIKV RNA synthesis and viral protein expression, providing the intracellular anti-CHIKV activity.⁵⁰

Antimalarial Properties

Rhodiola fastigiata contained nine known flavonoids (Figure 2), including herbacetin-8-O- β -D-xylopyranoside, kaempferol, herbacetin-8-methylether, and others, along with a new flavonoid glycoside, herbacetin-8-O-methyl glucuronide. Notably, herbacetin-8-O- β -D-xylopyranoside exhibited strong in vitro antimalarial activity against *Plasmodium falciparum* 3D7 at 50 μ M, significantly reducing mitochondrial membrane potential.⁵¹ Another study utilized UPLC-ESI-MS/MS to identify chemicals in marigold flower methanol extract (MFE) and quantified flavonoids hesperidin and rutin via RP-HPLC-DAD. Antileishmanial potential was tested against *Leishmania major* using both promastigotes and amastigotes, while a 4-day in vivo antimalarial test against *Plasmodium berghei* used infected mice. Molecular docking studies evaluated flavonoids' binding mechanisms to *Leishmania major*'s enzymes, and in silico assessment revealed antimalarial properties against *Plasmodium falciparum*. UPLC-ESI-MS/MS identified twenty compounds in MFE, highlighting hesperidin (36.17 mg g⁻¹) as significantly more abundant than rutin (3.65 mg g⁻¹). The IC₅₀ values against *Leishmania major* showed hesperidin, rutin, and MFE exhibit substantial antileishmanial activity.⁵² *Cissampelos pareira* is notable for its pleiotropic medicinal uses and unique pharmacological properties, primarily attributed to its isoquinoline alkaloids and flavonoids. Traditional applications include using flavonoid-rich leaf juice to treat malarial fever. In silico molecular docking studies revealed strong binding affinities of flavonoids, particularly quercetin-3-O-sophoroside, to key Plasmodium proteins. Pharmacokinetic analyses indicate these compounds meet several ADME-Tox criteria, and molecular dynamics simulations show stable interactions with PfLDH and other targets. *Cissampelos pareira* is a broad-spectrum antimalarial agent for developing innovative treatments against malaria.⁵³

Anti-Atherosclerotic Effect

Flavone 3',4',3,5,7-pentahydroxyflavone enhances aorta vasorelaxation, lowers systolic blood pressure. Quercetin improves

dyslipidemia, decreases OS by stimulating lipolysis activity, and regulates adipocyte gene expression, thereby increasing beta oxidation.⁵⁴ Kaempferol (30-150 mg/kg/day) in high-cholesterol rabbits increased antioxidant enzyme Superoxide dismutase, and decreased lipid-peroxidation marker MDA.⁵⁵ Flavonoid has anti-atherosclerotic potential and potential use as a functional food additive for atherosclerosis patients.⁵⁶ A study investigates the protective effects of alfalfa flavonoid extract (AFE) against atherosclerosis in rats on a high-fat diet and HUVEC cells treated with lipopolysaccharide. It inhibits the NF- κ B and MAPK pathways and reduces proinflammatory factors. It also lowers triglycerides and cholesterol while increasing high-density lipoprotein, thereby mitigating vascular endothelial damage. It promotes lipid catabolism through CYP7A1 and downregulates lipid production and uptake genes, improving hepatic steatosis. It is also a functional food to aid patients with atherosclerosis by addressing inflammation and lipid metabolism issues.⁵⁶ Another study using the thoracic aorta vascular ring formed an AS model that assessed blood vessel morphology, VSMC proliferation, and inflammatory markers. These inhibited VEGF, CRP, JNK2, p38, and NO expression at varying levels. The primary anti-inflammatory mechanism involved lowering CRP expression, blocking JNK2 and p38 kinase activity, and suppressing the MAPK pathway.⁵⁷

Anticancer Activity

Cancer is a global disease-causing mortality. Traditional treatments include antitumor medications, surgical excision, and radiation therapy. However, developing intelligent, targeted anti-cancer medications has been challenging. The emergence of medication resistance, tumor recurrence, and metastasis highlights the need for innovative therapeutic approaches. Flavonoids, dietary substances, and herbs are being used in complementary therapies for cancer patients. This study highlights the molecular processes behind flavonoids' pharmacological actions and discusses potential approaches to creating anticancer treatment by fusing traditional drugs with flavonoid nutraceuticals.⁵⁸ Flavonoids have potential anticancer effects. They inhibit various biological targets, such as topoisomerases, protein kinases, angiogenesis, apoptosis, cell cycle arrest, multidrug resistance, and anti-oxidative properties, which can impede the growth of malignant cells. The study highlights the structural characteristics and mechanisms of flavonoids' anticancer effects, including their inhibition of protein kinases, P-gp regulation, antiangiogenesis, and topoisomerase inhibition.⁵⁹ Quercetin inhibits tyrosine kinases, an enzyme family responsible for transmitting growth signals to the nucleus and overriding cell growth. Quercetin inhibits the growth of various types of carcinomas in various organs such as the lung, colon, prostate, and breast. Quercetin's growth inhibitory potential is attributed to its ability to induce apoptotic induction and arrest cancer cell cycle.⁶⁰ Quercetin reduced intracellular ROS levels and inhibited the growth of HepG2 cells, which are responsible for hepatocellular carcinoma.⁶¹ Additionally, kaempferol used ROS-mediated mitochondrial targeting to cause cytotoxicity in rat hepatocellular carcinoma cells.⁶²

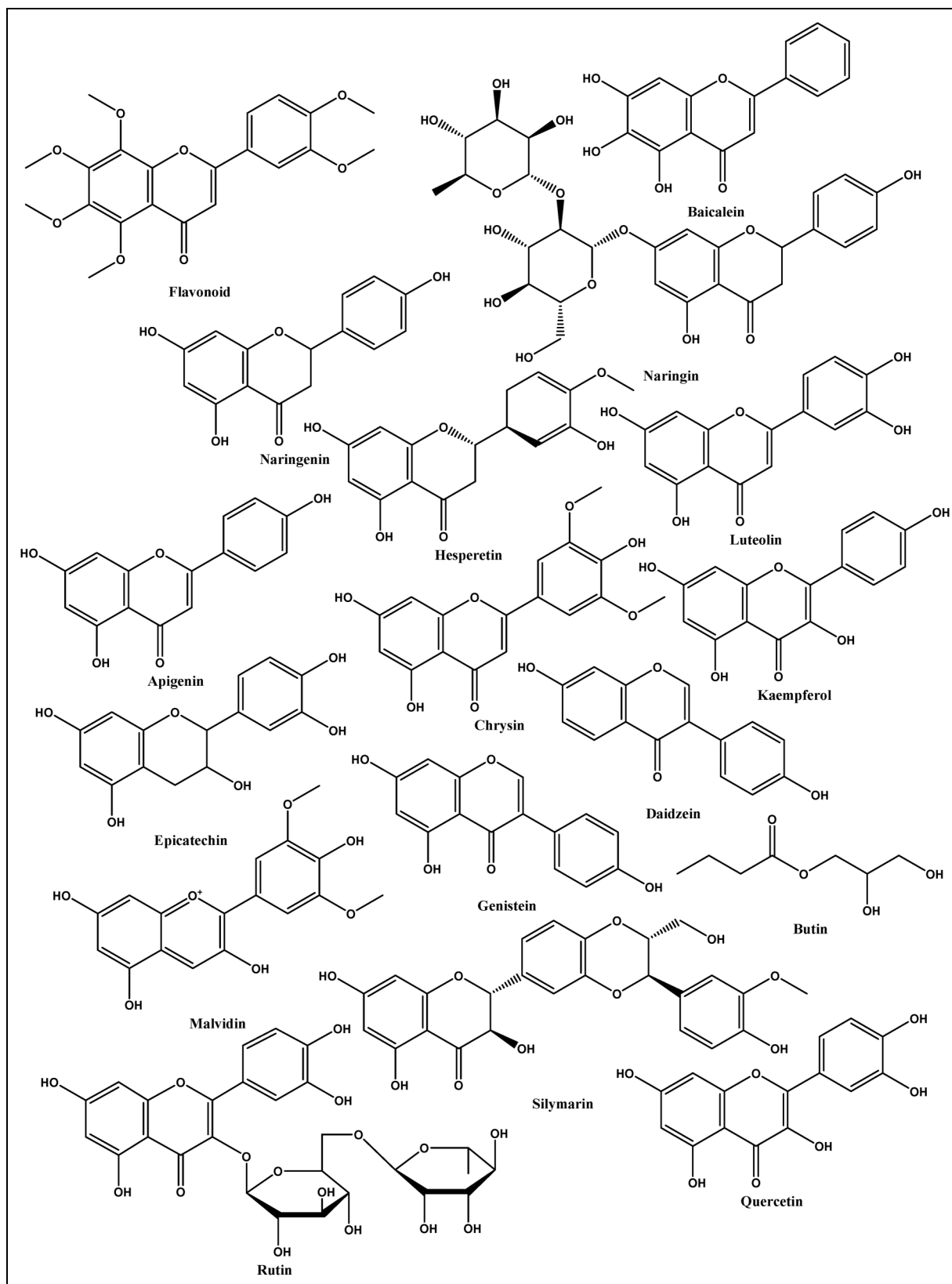


Figure 2. It demonstrates the chemical structure of flavonoids in pharmacological action. These have pharmacological action in the different types of diseases.

Anti-Alzheimer Activity

Alzheimer's disease (AD) is a severe ND affecting the elderly due to genetic, environmental, and lifestyle factors. The buildup of neurofibrillary tangles and A β peptides causes cognitive dysfunction and behavioral impairment. Flavonoids can enhance cognitive performance and prevent AD aggregation. Consuming foods high in flavonoids boosts cognitive function and delays the senescence cycle. Flavonoids interact with multiple signaling pathways, producing beneficial neuroprotective effects and slowing the progression of NDs.⁶³ Flavonoids decrease amyloid beta protein synthesis and scavenge ROS.⁶⁴ Okinwa propolis and its main components demonstrated *in vitro* inhibition of acetylcholine esterase.⁶⁵ Rhoifolin has been investigated in an animal model of streptozotocin-induced AD. It significantly enhanced memory, cognition, and spatial learning in AD animals.⁶⁶ EGCG has neuroprotective potential against AD by reducing A β protein accumulation and promoting α -secretase and β -secretase activity.⁶⁷ Flavonoids (Figure 3) can reduce AD progression by reducing insulin resistance, enhancing mitochondrial dysfunction, reducing OS, and improving memory impairment through molecular pathways alteration.⁶⁸ Resveratrol reduced cognitive impairment in AD mice by activating the first stage of autophagy. Quercetin eliminated A β aggregates, reduced brain damage, and postponed paralysis by triggering macroautophagy *in vitro* and *in vivo*.⁶⁹ Moreover, quercetin, silibinin, and wogonin have efficacy in removing amyloid by inducing autophagy via the ULK1/mTOR pathway.⁷⁰

Anti-Parkinson's Effect

Parkinson's disease (PD) is an ND causing symptoms like rigidity, tremor, and bradykinesia, influenced by OS, neuroinflammation, mitochondrial dysfunction, and insufficient neurotrophic support.⁷¹ Flavonoids reduce the risk of PD by promoting antioxidative stress, anti-inflammatory, and anti-apoptotic mechanisms.⁷² Baicalein inhibits α -synuclein formation, a presynaptic neuronal protein, instigating neuronal death.⁷³ Furthermore, baicalein inhibits autophagy and increases α -synuclein aggregates in rats exposed to 1-methyl-4-phenylpyridinium (MPP+), a neurotoxin used to cause PD in animal models.⁷⁴ Apigenin reduced DA neuronal loss and behavioural abnormalities in a rotenone-induced rat model of PD. These outcomes were linked to the inhibition of OS-induced apoptosis and neuroinflammation. Apigenin also increased dopamine production and dopamine D2 receptor expression, which regulated DA neurotransmission and reduced α -synuclein aggregation.⁷⁵ Furthermore, quercetin mitigates the loss of striatal dopamine and mitochondrial complex I activity in a rotenone model of PD.⁷⁶ Moreover, a study on a rat model of PD using a 6-OHDA lesion showed that troxerutin has neuroprotective properties. The troxerutin pretreatment reduced the latency and overall time on the narrow beam task, while also improving the bias caused by apomorphine-induced rotational behavior. The beneficial effects were eliminated by centrally administering an ER β antagonist or PI3 K inhibitor. Additionally, troxerutin reduced striatal lipid peroxidation, ROS, astrogliosis, and apoptosis

and stopped the death of nigral TH-positive neurones. Troxerutin is a potent neuroprotective drug against PD by reducing OS, apoptosis, and astrogliosis. Troxerutin's positive effects may be influenced by PI3 K/ER β signaling.⁷⁷

Anti-Epileptic Activity

Epilepsy is a condition that affects millions of people throughout the world. The primary pathophysiological pathways include OS, neuroinflammation, and neuropathies. Flavonoids are highly recommended for their potential to disrupt inflammatory functions and help prevent various diseases.⁷⁸ Additionally, epilepsy is often caused by an imbalance between excitatory and inhibitory neurotransmitters, with GABA receptor malfunction leading to inadequate inhibition and glutamate receptor abnormalities causing excessive neuronal excitation, resulting in seizures. Current anti-epileptic medications have drawbacks like drug resistance and high costs. Flavonoids have neuroprotective effects in epilepsy by interacting with signaling pathways and modifying their activity. These have potential as multitargeted, accessible, and affordable substitutes for traditional anti-epileptic drugs.⁷⁹ Flavonoids treat epilepsy by addressing multiple pathophysiological mechanisms. These block inflammatory mediators and strengthen antioxidant defenses. These also provide neuronal protection by blocking important inflammatory mediators and pathways. Enzymes are regulated to enhance the body's natural antioxidant defenses. Furthermore, flavonoids affect important antioxidant response pathways such as Nrf2, PKA, JNK, and PI3 K/AKT.⁸⁰ Furthermore, baicalein's anti-inflammatory effect in TRM rats was linked to ERK activation, p-JNK and MAPK inhibition, and NF- κ B activation.⁸¹

Gastroprotective Activity

Nobeletin protects gastric mucosa from ethanol and HCl/ethanol injuries, but weakly prevents aspirin-induced ulcers. Flavonoids like quercetin and myricetin decrease glutathione content, potentially causing DNA damage.⁸² The cure rate of *H. pylori* infections was significantly increased when outpatients with peptic ulcers and *H. pylori* infections were treated with sofalcone and a triple therapy.⁸³ A study investigated the gastroprotective effects of a crude extract from *Pulicaria odora* in a mouse model of ethanol-induced ulcers. In vitro antioxidant activity was assessed using DPPH and ABTS techniques, while anti-inflammatory properties were evaluated through human red blood cell membrane stabilization and bovine serum albumin denaturation methods. The extract showed a significant dose-dependent inhibition of ulcer formation, reducing it by up to 99.91% at 200 mg/kg. The aqueous fraction exhibited the highest gastroprotective efficacy, with 95.56% inhibition at 50 mg/kg. Additionally, the extract demonstrated strong anti-inflammatory effects with IC₅₀ values comparable to ascorbic acid and high free radical scavenging capacity. LC-ESI-MSn analysis identified nine flavonoid derivatives, which may inhibit stomach acid production by affecting the proton pump.⁸⁴ Flavonoid-rich subfraction of

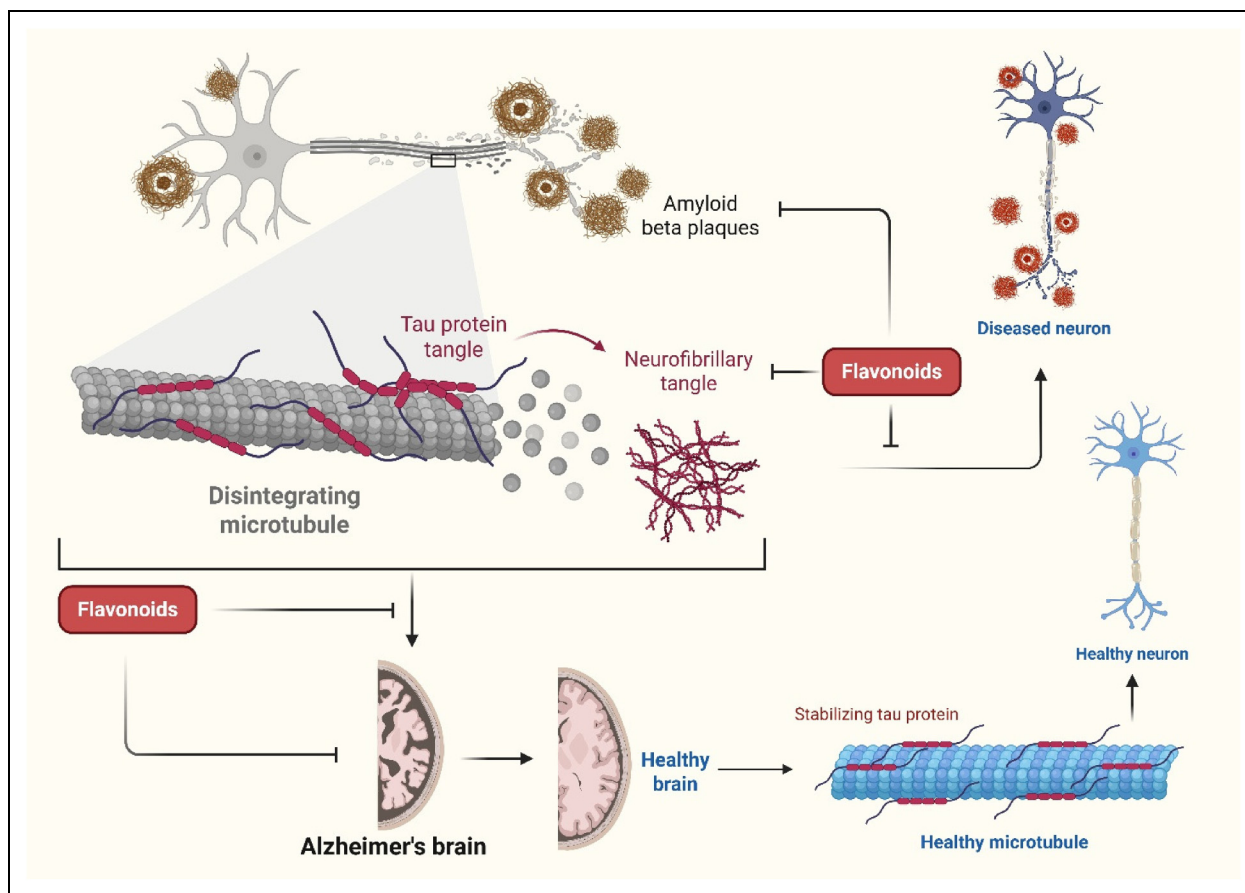


Figure 3. Flavonoids demonstrate anti-AD properties. These protect against AD by reducing neuronal degeneration. These also prevent the production of neurofibrillary tangles and $A\beta$ accumulation, preserve tau protein structure, and stabilize microtubules, enhancing healthy neuron survival. Consequently, these contribute to restoring neuronal integrity and improving brain health and function affected by Alzheimer's.

Fridericia chica exhibits gastroprotective properties. In experiments with rats, *Fridericia chica*, administered at 30 mg/kg, significantly reduced ethanol-induced gastric ulcerations by 81% and piroxicam-induced ulcerations by 77%. Antioxidant benefits were noted through the maintenance of GSH and LPO levels, as well as SOD and CAT activity, comparable to non-ulcerated controls. *Fridericia chica* also prevented increases in TNF, IL-6, IL-4, and IL-10 levels, alongside myeloperoxidase activity. Additionally, it enhanced mucin staining in ulcerated rats. The gastroprotective mechanism involves both antisecretory actions and interactions with nitric oxide (NO) and nonprotein sulfhydryl compounds (NP-SH). *Fridericia chica* interacts with NO synthase and cyclooxygenase-1.⁸⁵

Hepatoprotective Activity

Quercetin has potent antioxidant and anti-inflammatory properties. It significantly reduced serum liver enzymes, lipid peroxidation, and histological damage in CCl_4 and acetaminophen-induced liver injury models, while enhancing antioxidant enzyme levels. Silymarin consists primarily of flavonolignans and is a clinically recognized hepatoprotective agent. It stabilizes hepatocyte membranes, inhibits lipid

peroxidation, and stimulates ribosomal RNA polymerase, enhancing protein synthesis and regeneration of hepatocytes.⁸⁶ Naringenin and Naringin are effective against hepatotoxicity induced by alcohol, CCl_4 , and high-fat diets. Naringenin modulates lipid metabolism, enhances antioxidant enzyme expression, and reduces steatosis and inflammation in NAFLD models.⁸⁷ Five flavonoids, including reduced nitric oxide synthase, heme-oxygenase-1, luteolin, hesperetin, chrysin, and apigenin, enhance antioxidant capacity, prevent NF- κ B phosphorylation, and prevent proinflammatory cytokines. These also prevent liver damage from D-GalN/LPS.⁸⁸ Flavonoids (Table 1) have hepatoprotective, antioxidant, anti-inflammatory, and antihistamine properties. Kaempferol, quercetin, myricitrin, malvidin, luteolin, apigenin, epicatechin, and hesperetin were found to be effective against liver damage. Furthermore, lowering malondialdehyde and nitric oxide reduces NLRP3 inflammasome, regulates Nrf2 signaling, and prevents autophagy, oxidative effects, and apoptosis.^{88–90} In cases of cholestatic liver damage, quercetin may be useful. Cholestatic liver diseases lead to the depletion of platelets, loss of granules, and impaired function of their intended function. ORAI-1 gene expression affects platelet hypofunction in the bile duct ligation model, suggesting quercetin as a potential therapeutic target in haemostatic diseases due to its calcium entry

Table 1. The hepatoprotective actions of key flavonoids are summarized based on various *in vitro* and *in vivo* models. The table demonstrates the role of various flavonoids in mitigating liver injury through alterations in molecular pathways, including OS regulation, inflammation suppression, apoptosis inhibition, and activation of signaling pathways. Findings include reduced inflammatory cytokines, strengthened antioxidant defenses, enhanced platelet function, inhibition of fibrosis indicators, and mitigation of toxin-induced damage. Flavonoids can be therapeutically utilized to prevent liver damage by targeting various molecular pathways.

Flavonoids	Liver injury	Mechanism	Finding	Ref.
Hesperetin	Mouse liver is induced by alcohol and lipopolysaccharide-stimulated RAW264.7 cells.	In two <i>in vivo</i> and <i>in vitro</i> models, an increase in NLRP12, which inhibits the production and phosphorylation of P65 proteins and reduces inflammatory factors.	Reduced inflammation and liver damage by stimulating NLRP12 via NF- κ B.	⁹⁵
Quercetin	Rats with cholestatic liver damage	Boost the expression of the ORAI-1 gene	In a bile duct ligation model of cholestasis in rats, increased ORAI-1-mediated SOCE improves platelet function.	⁹¹
Epicatechin	By preventing oxidative and inflammatory damage to the liver, hepatic sinusoidal obstruction syndrome	Rats treated with epicatechin showed increased Nrf-2 translocation and increased expression of downstream antioxidant genes.	Decreased hepatic sinusoidal syndrome by lowering OS and hepatic inflammation at a dose of 0.02–0.04 g/kg.	¹⁰²
Genistein	Chronic liver damage and hepatic fibrosis in rats caused by D-galactosamine	Inhibited decreased α -SMA expression, collagen matrix deposition, and blood serum AST and ALT levels.	Inhibited the histopathological changes caused by D-GLN (5 mg/kg BW).	¹⁰³
Apigenin	In the rat liver and kidney, edifenphos caused toxicity by altering the caspase signal pathway, OS, and mitochondrial dysfunction.	Mitigated the oxidative damage caused by edifenphos.	Reduced liver damage caused by OS.	⁹⁸
Daidzein	Effects of LPS on Hepatotoxicity	Reduced AST, ALT, IL-6, IL-1 β , and TNF levels to inhibit inflammation and OS. Increase SOD levels by upregulating and downregulating Keap-1.	Mitigated inflammation and OS in the process of LPS-induced hepatotoxicity.	¹⁰⁰
Malvidin	Liver damage caused by lipopolysaccharide	Reduced inflammation by inhibiting proinflammatory cytokines and mediators, NLRP3 inflammasome activity, apoptosis, autophagy, and oxidative damage.	Reduced autophagy and hepatocyte death by upregulating the Nrf2 signaling pathway.	⁸⁹

enhancement.⁹¹ Additionally, quercetin's therapeutic properties include its hepatoprotective activity against triptolide-induced liver damage. It can prevent Triptolide-induced liver damage by restoring the balance between Th17 and Treg cells, inhibiting the TLR4-MyD88-NF- κ B signaling pathway, retinoid-related orphan receptor-t, proinflammatory cytokines, and the Th17 transcription factor, thereby preventing liver damage.⁹² Hyperoside is a quercetin derivative that exhibits hepatoprotective properties. In liver diseases, it prevents hepatic OS by operating antioxidant activity.⁹³ It was found that by blocking CYP4502E1, hyperoside, at a dose of 60000 μ g/kg, can protect the liver from oxidative damage and regulate glutathione-related metabolites and enzymes. Hyperoside reduces QKI expression, YY1 complex activity, and hepatic tumor cell proliferation and metastasis, inhibiting cell growth and stopping the cell cycle.⁹⁴ HD-4d, a hesperetin derivative, showed anti-inflammatory properties in RAW264.7 cells and liver damage in C57BL/6J mice, by increasing NLRP12, suppressing inflammatory factors, and inhibiting p65 protein phosphorylation.⁹⁵ A study using TUNEL showed that hesperetin significantly reduced liver

hepatocyte apoptosis caused by APAP. Acetaminophen overdose significantly increased liver caspase 3 activity in mice, but dose-dependent hesperetin inhibited this increase in the liver of mice exposed to lethal acetaminophen dosage.⁹⁶ Hesperetin derivative (HD-16) shows hepatoprotective and anti-inflammatory benefits on a range of hepatic diseases at doses of 25000, 50000, and 100000 μ g/kg. HD-16 demonstrated antifibrotic effects on LX-2 cells stimulated by TGF- β 1 and mouse hepatic fibrosis caused by carbon tetrachloride *in vitro* and *in vivo*. HD-16 was found to have an antifibrotic effect by controlling the AMPK/SIRT3 pathways. Additionally, HD-16 reduced inflammation and damage in the mouse liver fibrosis caused by CCl₄.⁹⁷ Another study found that a weekly dose of 0.1–0.2 g/kg P.O. of a substance called apigenin reduced liver failure severity and enzyme concentration. Apigenin pretreatment reduces hepatic NF- κ B levels, increases liver protein expression of PPAR γ and Nrf-2. Apigenin exhibits anti-inflammatory, antioxidant, and protective properties against hepatic lesions in mice caused by D-galactosamine/lipopolysaccharide. It may work via modulating NF- κ B/PPAR γ -mediated inflammation

and increasing Nrf-2-mediated antioxidant enzymes.⁹⁰ Furthermore, apigenin, by protecting hepatic cells and reducing mitochondrial degradation, mitigates the liver damage caused by edifenphos (EDF). Oral EDF disrupted the intracellular antioxidant system, leading to the production of intracellular ROS. EDF can lead to negative effects like DNA damage, OS, mitochondrial membrane potential reduction, ROS production, caspase 3/9 activation, and histo-renal histopathology anomalies. Apigenin reduced oxidative damage and apoptosis caused by EDF. An effective dietary antioxidant that reduces OS brought on by EDF is apigenin.⁹⁸ Epicatechin proved effective in treating an amoebic liver abscess in hamsters. Syrian golden hamsters were given intraperitoneal injections of *Entamoeba histolytica* trophozoites. Epicatechin dose (10 mg/100 g, I.P.) slowed the progression of the liver abscess and helped remove trophozoites to repair the liver.⁹⁹ Daidzein improves hepatotoxicity caused by LPS. The substance reduces inflammation and OS, thereby reducing the damage caused by LPS to hepatocytes. The mechanism by which daidzein affects hepatocyte injury was investigated. At 100 μ M, daidzein reduces AST and ALT expression levels without causing cytotoxicity.¹⁰⁰ Another study found that chicory, daidzein, and their combination dramatically lower the expression of the cyclin A/CDK2 and cyclin D1/CDK4 axis in liver tissue. Growth is prevented by inducing cell cycle arrest, inhibiting Ki-67 expression, and causing apoptosis through Bcl-2 downregulation.¹⁰¹

NLRP12: NOD-Like Receptor Family Pyrin Domain Containing 12, P65: RelA (p65 Subunit of NF- κ B), NF- κ B: Nuclear Factor- κ B, ORAI-1: Calcium Release-Activated Calcium Channel Protein 1, SOCE: Store-Operated Calcium Entry, Nrf-2: Nuclear Factor Erythroid 2-Related Factor 2, α -SMA: Alpha-Smooth Muscle Actin, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, D-GalN: D-Galactosamine, BW: Body Weight, OS: Oxidative Stress, LPS: Lipopolysaccharide, IL-6: Interleukin-6, IL-1 β : Interleukin-1 Beta, TNF: Tumor Necrosis Factor, SOD: Superoxide Dismutase, Keap-1: Kelch-Like ECH-Associated Protein 1, NLRP3: NOD-Like Receptor Family Pyrin Domain Containing 3.

Anti-Neuropathic Activity

Neuropathic pain is a chronic, multifactorial pathological sensation resulting from a lesion or disease affecting the somatosensory system's anatomy or physiology.^{4,5} Neuropathic pain is characterized by paroxysmal pain, independent of stimulus, and can be triggered by sympathetic activity. Peripheral nerve injury can lead to a chronic, multi-symptom, and heterogeneous form of pain called neuropathic pain. Chronic inflammation in central and peripheral nerves is the major cause of the induction and maintenance of neuropathic pain.¹⁰⁴ Naringenin has ameliorative potential against diabetes induced neuropathy and spinal nerve ligation-induced neuropathy.¹⁰⁵ Flavonoids reduce pro-inflammatory biomarkers in the neuropathic pain model, with single diosmin treatment reducing IL-1 β , IL-33, and St2 expressions, while sustained therapy decreases TNF α , IL-1 β , IL-33, and St2. A single treatment reduced oligodendrocyte

and microglia expression, while a longer treatment reduced astrocytes, microglia, and oligodendrocytes.¹⁰⁶ Fisetin, when administered to animals with CCI, effectively reduced spinal monoamine levels and 5-HT/5-HTP ratio while simultaneously lowering MAO-A. The study found that co-administration of a 5-HT7 receptor antagonist reduced fisetin's antihyperalgesic effect, indicating its role in its antinociceptive activity.¹⁰⁷ A study found that the combination of hesperidin and diosmin, when combined with naloxone, bicuculline, and haloperidol, did not significantly reduce its antihyperalgesic effect. The receptors are involved in the antihyperalgesia induced by hesperidin and diosmin in the CCI model of neuropathic pain.¹⁰⁸ Flavonoids inhibit diabetic neuropathy pathways, including the inhibition of α -glucosidase enzyme and the reduction of OS.¹⁰⁹

Anti-Addictive and Modulating Effects

Fisetin influences key transmitter systems related to alcohol use disorder, such as dopamine and NMDA. In a study using conditioned place preference (CPP) with 50 mice, fisetin was administered before ethanol conditioning (2 g/kg) over eight days to assess its effects on ethanol motivation. Fisetin (20 and 30 mg/kg) facilitated the extinction of CPP and reduced its acquisition (30 mg/kg). It reduced the reinstatement of CPP triggered by ethanol. It is also a therapeutic agent to curtail ethanol-seeking behavior and decrease relapse risk.¹¹⁰ A study impacts on adolescent mice regarding ethanol-induced conditioned place preference (ethanol-CPP). Mice received intraperitoneal ethanol to induce CPP and were treated with varying doses of quercetin before ethanol injections. Quercetin pretreatment decreased acquisition and reinstatement of ethanol-CPP and expedited its extinction. It has potential as an adjunct therapy in ethanol addiction management.¹¹⁰ Another study utilized CPP tests to investigate the effects of myricetin on ethanol reward and addiction. Mice received ethanol (2 g/kg, i.p.) during the conditioning phase, while myricetin was administered before ethanol to evaluate its impact on alcohol addiction. Myricetin (5 and 10 mg/kg, i.p.) significantly inhibited the development of ethanol addiction ($p < 0.05$) and promoted extinction while reducing reinstatement post-contextual exposure. Notably, neither ethanol nor myricetin affected motor coordination or locomotor activity. Thus, myricetin demonstrates potential as an adjunct therapy for alcohol addiction by attenuating its rewarding properties in mice.¹¹¹ Furthermore, a study investigates the neuroprotective and anti-inflammatory effects of naringenin, focusing on its role in reducing ethanol-induced neuroinflammation and craving via TRPM3 involvement. Adolescent male Sprague-Dawley rats received daily naringenin (50 mg/kg, i.p.) before ethanol administration (2 g/kg, i.p.) for two weeks. Behavioral assessments through open field tests and conditioned place preference were conducted. Ethanol increased dopamine levels in the AcbSh, preference scores, locomotion, TRPM3 expression, and inflammatory markers (TNF- α and IL-6). Naringenin reversed these effects, suggesting its potential anti-addictive properties and supporting TRPM3 as a treatment target for alcohol use disorder.¹¹²

Conclusion and Future Perspectives

Flavonoids, a class of natural polyphenols, are highly researched due to their exceptional pharmacological diversity and therapeutic significance. Studies have demonstrated their ability to regulate OS, inhibit pro-inflammatory mediators, induce apoptosis, alter autophagy, and interact with key signaling pathways like NF- κ B, MAPK, PI3 K/Akt, and Nrf2. These processes have positive effects on various chronic diseases like cancer, cardiovascular issues, diabetes, metabolic syndromes, and neurodegenerative pathologies. Flavonoids' SAR offers a deeper understanding of how specific hydroxylation, glycosylation, and methoxylation patterns influence their potency and bioactivity. Flavonoids are being identified as potential multitarget therapeutic agents that could bridge the gap between curative and preventive medicine. However, despite promising preclinical and experimental data, there are significant obstacles in transforming flavonoids into successful treatments. Their therapeutic efficacy in humans is limited by their low bioavailability, poor solubility, fast metabolism, and inconsistent absorption. The integration of these drugs into mainstream medicine is inhibited by the absence of large-scale randomized controlled trials and standardized dosage schedules. Furthermore, current research primarily focuses on individual chemicals, but there is limited understanding about the synergistic effects of dietary patterns high in flavonoids. Future research should explore nanotechnology-based delivery systems like micelles, liposomes, nanoparticles, and polymer conjugates for resolving pharmacokinetic issues. Flavonoids may enhance therapeutic efficacy and reduce side effects when combined with current pharmacological and chemotherapeutic treatments. Further clinical trials are urgently required to ensure safety, effectiveness, and optimal dosage in diverse patient populations. To predict multitarget interactions and direct precision-based therapies, computational techniques like molecular docking, network pharmacology, and systems biology must be integrated. Nutrigenomics and personalized medicine advancements enable new methods for determining patient-specific reactions to flavonoid therapy, enhancing their use in therapeutic and preventive methods. In conclusion, flavonoids hold significant potential as next-generation therapeutic agents for combating degenerative and chronic diseases through multitargeted approaches. Flavonoids can transform from dietary supplements into clinically proven pharmacological interventions through interdisciplinary research, innovative formulation technologies, and clinical validation. This will bridge the gap between natural product research and modern medicine.

Acknowledgment

The authors are thankful to the Department of Chemistry, University of Swabi, for supporting this project.

ORCID iDs

Abdur Rauf  <https://orcid.org/0000-0003-2429-5491>
 Marcello Iriti  <https://orcid.org/0000-0002-5063-1236>

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Yunusoğlu O, Ayaz İ, Dovankaya EH. Pharmacological, medicinal and biological properties of flavonoids: a comprehensive review. *Journal of Research in Pharmacy*. 2025;29(2):561–584.
2. Agrawal AJIIPSN. Pharmacological activities of flavonoids: a review. *Int J Pharm Sci Nanotechnol*. 2011;4(2):1394–1398.
3. Rana AC, Gulliya B. Chemistry and pharmacology of flavonoids-A review. *Indian Journal of Pharmaceutical Education & Research*. 2019;53(1).
4. Ullah R, Ali G, Rasheed A, et al. The 7-hydroxyflavone attenuates chemotherapy-induced neuropathic pain by targeting inflammatory pathway. *Int Immunopharmacol*. 2022;107(1):108674.
5. Ullah R, Ali G, Subhan F, et al. Attenuation of nociceptive and paclitaxel-induced neuropathic pain by targeting inflammatory, CGRP and substance P signaling using 3-hydroxyflavone. *Neurochem Int*. 2021;144(1):104981.
6. Rathee P, Chaudhary H, Rathee S, Rathee D, Kumar V, Kohli K. Mechanism of action of flavonoids as anti-inflammatory agents: a review. *Inflammation & Allergy-Drug Targets (Formerly Current Drug Targets-Inflammation & Allergy) (Discontinued)*. 2009;8(3):229–235.
7. Rani N, Bharti S, Krishnamurthy B, et al. Pharmacological properties and therapeutic potential of naringenin: a citrus flavonoid of pharmaceutical promise. *Curr Pharm Des*. 2016;22(28):4341–4359.
8. Carrillo-Martinez EJ, Flores-Hernández FY, Salazar-Montes AM, Nario-Chaidez HF, Hernández-Ortega LD. Quercetin, a flavonoid with great pharmacological capacity. *Molecules*. 2024;29(5):1000.
9. Silva dos Santos J, Goncalves Cirino JP, de Oliveira Carvalho P, Ortega MM. The pharmacological action of kaempferol in central nervous system diseases: a review. *Front Pharmacol*. 2021;11(6):565700.
10. Imran M, Saeed F, Gilani SA, et al. Fisetin: an anticancer perspective. *Food Sci Nutr*. 2021;9(1):3–16.
11. Abid R, Ghazanfar S, Farid A, et al. Pharmacological properties of 4', 5, 7-trihydroxyflavone (apigenin) and its impact on cell signaling pathways. *Molecules*. 2022;27(13):4304.
12. Caporali S, De Stefano A, Calabrese C, et al. Anti-inflammatory and active biological properties of the plant-derived bioactive compounds luteolin and luteolin 7-glucoside. *Nutrients*. 2022;14(6):1155.
13. Hu Z, Guan Y, Hu W, Xu Z, Ishfaq M. An overview of pharmacological activities of baicalin and its aglycone baicalein: new insights into molecular mechanisms and signaling pathways. *Iran J Basic Med Sci*. 2022;25(1):14.
14. Capasso L, De Masi L, Sirignano C, et al. Epigallocatechin gallate (EGCG): pharmacological properties, biological activities and therapeutic potential. *Molecules*. 2025;30(3):654.

15. Goh YX, Jalil J, Lam KW, Husain K, Premakumar CM. Genistein: a review on its anti-inflammatory properties. *Front Pharmacol*. 2022;13(1):820969.
16. Praisthy LJ C, Kushwah R, Dubey S, Kumar V, Jain S. Pharmacotherapeutic potential of daidzein: insights into mechanisms and clinical relevance. *Inflammopharmacology*. 2025;33(9):1–27.
17. Rakha A, Umar N, Rabail R, et al. Anti-inflammatory and anti-allergic potential of dietary flavonoids: a review. *Biomed Pharmacother*. 2022;156(1):113945.
18. Sharma A, Virmani T, Sharma A, et al. Potential effect of DPP-4 inhibitors towards hepatic diseases and associated glucose intolerance. *Diabetes, Metab Syndr Obes: Targets Ther*. 2022;15(1):1845–1864.
19. Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. *J Nutr Sci*. 2016;5(13):47.
20. McCallum JL, Yang R, Young JC, Strommer JN, Tsao R. Improved high performance liquid chromatographic separation of anthocyanin compounds from grapes using a novel mixed-mode ion-exchange reversed-phase column. *J Chromatogr, A*. 2007;1148(1):38–45.
21. Kawai S, Tomono Y, Katase E, Ogawa K, Yano M. Quantitation of flavonoid constituents in citrus fruits. *J Agric Food Chem*. 1999;47(9):3565–3571.
22. Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. *Am J Clin Nutr*. 2004;79(5):727–747.
23. Prior RL, Lazarus SA, Cao G, Muccitelli H, Hammerstone JF. Identification of procyanidins and anthocyanins in blueberries and cranberries (*Vaccinium* spp) using high-performance liquid chromatography/mass spectrometry. *J Agric Food Chem*. 2001;49(3):1270–1276.
24. Si W, Gong J, Tsao R, Kalab M, Yang R, Yin Y. Bioassay-guided purification and identification of antimicrobial components in Chinese green tea extract. *J Chromatogr, A*. 2006;1125(2):204–210.
25. Koirala N, Thuan NH, Ghimire GP, Van Thang D, Sohng JK. Methylation of flavonoids: chemical structures, bioactivities, progress and perspectives for biotechnological production. *Enzyme Microb Technol*. 2016;86(1):103–116.
26. Gonzales GB, Smaghe G, Grootaert C, Zotti M, Raes K, Camp JV. Flavonoid interactions during digestion, absorption, distribution and metabolism: a sequential structure–activity/property relationship-based approach in the study of bioavailability and bioactivity. *Drug Metab Rev*. 2015;47(2):175–190.
27. Świeca M, Gawlik-Dziki U, Dziki D, Baraniak B, Czyż J. The influence of protein–flavonoid interactions on protein digestibility in vitro and the antioxidant quality of breads enriched with onion skin. *Food Chem*. 2013;141(1):451–458.
28. Cassidy A, Minihane A-M. The role of metabolism (and the microbiome) in defining the clinical efficacy of dietary flavonoids. *Am J Clin Nutr*. 2016;105(1):10.
29. Küpeli E, Yesilada E. Flavonoids with anti-inflammatory and antinociceptive activity from *Cistus laurifolius* L. Leaves through bioassay-guided procedures. *J Ethnopharmacol*. 2007;112(3):524–530.
30. Wang Y, Chen P, Tang C, Wang Y, Li Y, Zhang H. Antinociceptive and anti-inflammatory activities of extract and two isolated flavonoids of *Carthamus tinctorius* L. *J Ethnopharmacol*. 2014;151(2):944–950.
31. Chen H, Pu J, Liu D, et al. Anti-inflammatory and antinociceptive properties of flavonoids from the fruits of black mulberry (*Morus nigra* L). *PLoS one*. 2016;11(4):e0153080.
32. Ortiz-Mendoza N, San Miguel-Chávez R, Martínez-Gordillo MJ, Basurto-Peña FA, Palma-Tenango M, Aguirre-Hernández E. Variation in terpenoid and flavonoid content in different samples of *Salvia Semiatrata* collected from Oaxaca, Mexico, and its effects on antinociceptive activity. *Metabolites*. 2023;13(7):866.
33. Al-Khayri JM, Sahana GR, Nagella P, Joseph BV, Alessa FM, Al-Mssallem MQ. Flavonoids as potential anti-inflammatory molecules: a review. *Molecules*. 2022;27(9):2901.
34. Spagnuolo C, Moccia S, Russo GL. Anti-inflammatory effects of flavonoids in neurodegenerative disorders. *Eur J Med Chem*. 2018;153(4):105–115.
35. Ferraz CR, Carvalho TT, Manchope MF, et al. Therapeutic potential of flavonoids in pain and inflammation: mechanisms of action, pre-clinical and clinical data, and pharmaceutical development. *Molecules*. 2020;25(3):762.
36. Jadhav R, Puchchakayala GJG. Hypoglycemic and antidiabetic activity of flavonoids: boswellic acid, ellagic acid, quercetin, rutin on streptozotocin-nicotinamide induced type 2 diabetic rats. *Group*. 2012;1(2):100.
37. Van LV, Pham EC, Nguyen CV, Duong NTN, Le Thi TV, Truong TNJPB. In vitro and in vivo antidiabetic activity, isolation of flavonoids, and in silico molecular docking of stem extract of *Merremia tridentata* (L.). *Biomed Pharmacother*. 2022;146(1):112611.
38. El-Bassossy HM, Hassan NA, Mahmoud MF, Fahmy AJP. Baicalein protects against hypertension associated with diabetes: effect on vascular reactivity and stiffness. *Phytomedicine*. 2014;21(12):1742–1745.
39. Li D, Jiang C, Mei G, et al. Quercetin alleviates ferroptosis of pancreatic β cells in type 2 diabetes. *Nutrients*. 2020;12(10):2954.
40. Bule M, Abdurahman A, Nikfar S, Abdollahi M, Amini M. Antidiabetic effect of quercetin: a systematic review and meta-analysis of animal studies. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association*. Mar 2019;125(10):494–502.
41. Proença C, Ribeiro D, Freitas M, Carvalho F, Fernandes E. A comprehensive review on the antidiabetic activity of flavonoids targeting PTP1B and DPP-4: a structure-activity relationship analysis. *Crit Rev Food Sci Nutr*. 2022;62(15):4095–4151.
42. Tan Z, Deng J, Ye Q, Zhang Z. The antibacterial activity of natural-derived flavonoids. *Curr Top Med Chem*. 2022;22(12):1009–1019.
43. Adamczak A, Ożarowski M, Karpiński TM. Antibacterial activity of some flavonoids and organic acids widely distributed in plants. *J Clin Med*. 2019;9(1):109.
44. Yuan G, Guan Y, Yi H, Lai S, Sun Y, Cao S. Antibacterial activity and mechanism of plant flavonoids to gram-positive bacteria predicted from their lipophilicities. *Sci Rep*. 2021;11(1):10471.
45. Salazar-Aranda R, Granados-Guzmán G, Pérez-Meseguer J, González GM, Waksman de Torres NJM. Activity of polyphenolic compounds against *Candida glabrata*. *Molecules*. 2015;20(10):17903–17912.

46. Alalwan H, Rajendran R, Lappin DF, et al. The anti-adhesive effect of curcumin on *Candida albicans* biofilms on denture materials. *Front Microbiol.* 2017;8(9):659.
47. Förster C, Handrick V, Ding Y, et al. Biosynthesis and antifungal activity of fungus-induced O-methylated flavonoids in maize. *Plant Physiol.* 2022;188(1):167–190.
48. Badshah SL, Faisal S, Muhammad A, Poulson BG, Emwas AH, Jaremko M. Antiviral activities of flavonoids. *Biomed Pharmacother.* 2021;140(1):111596.
49. Ninfali P, Antonelli A, Magnani M, Scarpa ES. Antiviral properties of flavonoids and delivery strategies. *Nutrients.* 2020;12(9):2534.
50. Lani R, Hassandarvish P, Shu M-H, et al. Antiviral activity of selected flavonoids against chikungunya virus. *Antiviral Res.* 2016;133(6):50–61.
51. Liu B-C, Gou L, Sun H, et al. Flavonoids from *Rhodiola fastigiata* and their antimalarial activities. *Revista Brasileira de Farmacognosia.* 2024;34(6):1377–1381.
52. Al-Huqail AA, Bekhit AA, Ullah H, Ayaz M, Mostafa NM. Antimalarial and antileishmanial flavonoids from *Calendula officinalis* flowers. *Agronomy.* 2023;13(11):2765.
53. Suresh PS, Kesarwani V, Kumari S, Shankar R, Sharma U. Flavonoids from aerial parts of *Cissampelos pareira* L. As antimalarial agents: computational validation of ethnopharmacological relevance. *S Afr J Bot.* 2023;163(5):10–19.
54. Saleh A. Efficiency of some antioxidants in reducing cardiometabolic risks in obese rats. 2011.
55. Kong L, Luo C, Li X, Zhou Y, He HJLiH. Disease. The anti-inflammatory effect of kaempferol on early atherosclerosis in high cholesterol fed rabbits. *Lipids Health Dis.* 2013;12(9):1–12.
56. Kang Y, Chen X, Long Q, et al. Anti-atherosclerotic effect of alfalfa flavonoid extract by regulating inflammation and oxidative stress in HUVEC cells and rats. *J Funct Foods.* 2024;121(7):106426.
57. Mao Z, Gan C, Zhu J, et al. Anti-atherosclerotic activities of flavonoids from the flowers of *Helichrysum arenarium* L. MOENCH through the pathway of anti-inflammation. *Bioorg Med Chem Lett.* 2017;27(12):2812–2817.
58. Kikuchi H, Yuan B, Hu X, Okazaki M. Chemopreventive and anticancer activity of flavonoids and its possibility for clinical use by combining with conventional chemotherapeutic agents. *Am J Cancer Res.* 2019;9(8):1517.
59. Shah S, Narang R, Singh VJ, Pilli G, Nayak SK. A review on anticancer profile of flavonoids: sources, chemistry, mechanisms, structure-activity relationship and anticancer activity. *Current Drug Research Reviews Formerly: Current Drug Abuse Reviews.* 2023;15(2):122–148.
60. Asgharian P, Tazekand AP, Hosseini K, et al. Potential mechanisms of quercetin in cancer prevention: focus on cellular and molecular targets. *Cancer Cell Int.* 2022;22(1):257.
61. Jeon J-S, Kwon S, Ban K, et al. Regulation of the intracellular ROS level is critical for the antiproliferative effect of quercetin in the hepatocellular carcinoma cell line HepG2. *Nutr Cancer.* 2019;71(5):861–869.
62. Seydi E, Salimi A, Rasekh HR, Mohsenifar Z, Pourahmad J. Selective cytotoxicity of luteolin and kaempferol on cancerous hepatocytes obtained from rat model of hepatocellular carcinoma: involvement of ROS-mediated mitochondrial targeting. *Nutr Cancer.* 2018;70(4):594–604.
63. Minocha T, Birla H, Obaid AA, et al. Flavonoids as promising neuroprotectants and their therapeutic potential against Alzheimer's disease. *Oxid Med Cell Longevity.* 2022;2022(1):6038996.
64. Kaur R, Sood A, Lang DK, et al. Potential of flavonoids as anti-Alzheimer's agents: bench to bedside. *Environmental Science and Pollution Research.* 2022;29(18):26063–26077.
65. Shahinozzaman M, Taira N, Ishii T, Halim MA, Hossain MA, Tawata SJM. Anti-inflammatory, anti-diabetic, and anti-Alzheimer's effects of prenylated flavonoids from Okinawa propolis: an investigation by experimental and computational studies. *Molecules.* 2018;23(10):2479.
66. Huang X, Wu S, Wei Y, Meng S, Jiang RJTJoPR. Effect of the plant flavonoid, rhoifolin, on memory and cognition in a rat model of Alzheimer's disease. *Trop J Pharm Res.* 2021;20(7):1481–1487.
67. Youn K, Ho C-T, Jun MJFS, Wellness H. Multifaceted neuroprotective effects of (-)-epigallocatechin-3-gallate (EGCG) in Alzheimer's disease: an overview of pre-clinical studies focused on β -amyloid peptide. *FSHW.* 2022;11(3):483–493.
68. Shimmyo Y, Kihara T, Akaike A, Niidome T, Sugimoto H. Epigallocatechin-3-gallate and curcumin suppress amyloid beta-induced beta-site APP cleaving enzyme-1 upregulation. *Neuroreport.* 2008;19(13):1329–1333.
69. Zaplatic E, Bule M, Shah SZA, Uddin MS, Niaz K. Molecular mechanisms underlying protective role of quercetin in attenuating Alzheimer's disease. *Life Sci.* 2019;224:109–119.
70. Zhang X-W, Chen J-Y, Ouyang D, Lu J-H. Quercetin in animal models of Alzheimer's disease: a systematic review of preclinical studies. *Int J Mol Sci.* 2020;21(2):493.
71. Jung UJ, Kim SRJJomf. Beneficial effects of flavonoids against Parkinson's disease. *J Med Food.* 2018;21(5):421–432.
72. Kumar S, Pandey AKJTswj. Chemistry and biological activities of flavonoids: an overview. *Sci World J.* 2013;2013(1):162750.
73. Lee JS, Lee S-JJJomd. Mechanism of anti- α -synuclein immunotherapy. *J Mov Disord.* 2016;9(1):14.
74. Hung K-C, Huang H-J, Wang Y-T, Lin AM-Y. Baicalein attenuates α -synuclein aggregation, inflammasome activation and autophagy in the MPP+-treated nigrostriatal dopaminergic system in vivo. *J Ethnopharmacol.* 2016;194:522–529.
75. Anusha C, Sumathi T, Joseph LD. Protective role of apigenin on rotenone induced rat model of Parkinson's disease: suppression of neuroinflammation and oxidative stress mediated apoptosis. *Chem-Biol Interact.* 2017;269(3):67–79.
76. Karuppagounder S, Madathil S, Pandey M, Haobam R, Rajamma U, Mohanakumar K. Quercetin up-regulates mitochondrial complex-I activity to protect against programmed cell death in rotenone model of Parkinson's disease in rats. *Neuroscience.* 2013;236(2):136–148.
77. Baluchnejadmojarad T, Jamali-Raeufy N, Zabihnejad S, Rabiee N, Roghani M. Troxerutin exerts neuroprotection in 6-hydroxydopamine lesion rat model of Parkinson's disease: possible involvement of PI3 K/ER β signaling. *Eur J Pharmacol.* 2017;801(5):72–78.

78. Yahfoufi N, Alsadi N, Jambi M, Matar CJN. The immunomodulatory and anti-inflammatory role of polyphenols. *Nutrients*. 2018;10(11):1618.
79. Pradhan P, Jana K, Ghosh S, et al. Recent advances in bioactive flavonoids-based nanotherapeutics as promising neuroprotectants in epilepsy. *Curr Aging Sci*. 2025.
80. Zhang Y, Hu X, Zou L-Q. Flavonoids as therapeutic agents for epilepsy: unveiling anti-inflammatory and antioxidant pathways for novel treatments. *Front Pharmacol*. 2024;15(1):1457284.
81. Mao X, Cao Y, Li X, et al. Baicalein ameliorates cognitive deficits in epilepsy-like tremor rat. *Neurol Sci*. 2014;35(8):1261–1268.
82. de Lira Mota KSDL, Dias GEN, Pinto MEF, et al. Flavonoids with gastroprotective activity. *Molecules*. 2009;14(3):979–1012.
83. Isomoto H, Furusu H, Ohnita K, Wen C-Y, Inoue K, Kohno S. Sofalcone, a mucoprotective agent, increases the cure rate of *Helicobacter pylori* infection when combined with rabeprazole, amoxicillin and clarithromycin. *World J Gastroenterol*. 2005;11(11):1629.
84. Boudebbaz K, Brouk M, Laalem R, Zabaiou N. Gastroprotective properties of flavonoid-rich extract of *Pulicaria odora* against ethanol-induced gastric ulcer in mice. *Heliyon*. 2025;11(1).
85. Miorando D, Steffler AM, Vecchia CAD, et al. Gastroprotective role of a flavonoid-rich subfraction from *Fridericia chica* (Bonpl.) LG Lohmann: a medicinal plant used in the Amazon region. *Inflammopharmacology*. 2024;32(5):3499–3519.
86. Liao Y, Lv F, Quan T, Wang C, Li JJFiP. Flavonoids in natural products for the therapy of liver diseases: progress and future opportunities. *Front Pharmacol*. 2024;15(1):1485065.
87. Flores-Peña R, Monroy-Ramirez HC, Caloca-Camarena F, et al. Naringin and naringenin in liver health: a review of molecular and epigenetic mechanisms and emerging therapeutic strategies. *Antioxidants*. 2025;14(8):979.
88. He Y, Xia Z, Yu D, et al. Hepatoprotective effects and structure-activity relationship of five flavonoids against lipopolysaccharide/d-galactosamine induced acute liver failure in mice. *Int Immunopharmacol*. 2019;68(5):171–178.
89. Fan H, Cui J, Liu F, et al. Malvidin protects against lipopolysaccharide-induced acute liver injury in mice via regulating Nrf2 and NLRP3 pathways and suppressing apoptosis and autophagy. *Eur J Pharmacol*. 2022;933(1):175–252.
90. Zhou R-J, Ye H, Wang F, Wang J-L, Xie M-L. Apigenin inhibits d-galactosamine/LPS-induced liver injury through upregulation of hepatic Nrf-2 and PPAR γ expressions in mice. *Biochem Biophys Res Commun*. 2017;493(1):625–630.
91. Nassef NA. Quercetin improves platelet function and ultrastructure in cholestatic liver injury in rats: role of ORAI1 gene expression. *Gene Reports*. 2019;17(1):100485.
92. Wei C-B, Tao K, Jiang R, Zhou L-D, Zhang Q-H, Yuan C-S. Quercetin protects mouse liver against triptolide-induced hepatic injury by restoring Th17/Treg balance through Tim-3 and TLR4-MyD88-NF- κ B pathway. *Int Immunopharmacol*. 2017;53(5):73–82.
93. Jang E. Hyperoside as a potential natural product targeting oxidative stress in liver diseases. *Antioxidants*. 2022;11(8):1437.
94. Xu S, Chen S, Xia W, Sui H, Fu X. Hyperoside: a review of its structure, synthesis, pharmacology, pharmacokinetics and toxicity. *Molecules*. 2022;27(9):3009.
95. Niu X-n, Zhang Y-l, Cheng M, et al. 7-O-(2-(Propylamino)-2-oxoethyl) Hesperetin attenuates inflammation and protects against alcoholic liver injury by NLRP12. *Int Immunopharmacol*. 2022;110(4):109006.
96. Wan J, Kuang G, Zhang L, et al. Hesperetin attenuated Acetaminophen-induced hepatotoxicity by inhibiting hepatocyte necrosis and apoptosis, oxidative stress and inflammatory response via upregulation of heme oxygenase-1 expression. *Int Immunopharmacol*. 2020;83(1):106435.
97. Li J-J, Jiang H-C, Wang A, et al. Hesperetin derivative-16 attenuates CCl₄-induced inflammation and liver fibrosis by activating AMPK/SIRT3 pathway. *Eur J Pharmacol*. 2022;915:174530.
98. Ahmad A, Kumari P, Ahmad M. Apigenin attenuates edifenphos-induced toxicity by modulating ROS-mediated oxidative stress, mitochondrial dysfunction and caspase signal pathway in rat liver and kidney. *Pestic Biochem Physiol*. 2019;159:163–172.
99. Velásquez-Torres M, Shibayama-Salas M, Pacheco-Yépez J, et al. (–)-Epicatechin protects from amebic liver abscess development in hamster. *Exp Parasitol*. 2021;224(9):108103.
100. Yu Z, Yang L, Deng S, Liang M. Daidzein ameliorates LPS-induced hepatocyte injury by inhibiting inflammation and oxidative stress. *Eur J Pharmacol*. 2020;885(3):173–399.
101. Abdel-Hamid NM, Zakaria S, Nawaya RA, Eldomany RA, El-Shishtawy MM. Daidzein and chicory extract arrest the cell cycle via inhibition of cyclin D/CDK4 and cyclin A/CDK2 gene expression in hepatocellular carcinoma. *Recent Pat Anti-Cancer Drug Discovery*. 2023;18(2):187–199.
102. Huang Z, Jing X, Sheng Y, et al. (–)-Epicatechin attenuates hepatic sinusoidal obstruction syndrome by inhibiting liver oxidative and inflammatory injury. *Redox Biol*. 2019;22(1):101117.
103. Ganai AA, Husain M. Genistein attenuates D-GalN induced liver fibrosis/chronic liver damage in rats by blocking the TGF- β /Smad signaling pathways. *Chem-Biol Interact*. 2017;261(3):80–85.
104. Chen K, Zhang Z-F, Liao M-F, Yao W-L, Wang J, Wang X-RJJotns. Blocking PAR2 attenuates oxaliplatin-induced neuropathic pain via TRPV1 and releases of substance P and CGRP in superficial dorsal horn of spinal cord. *J Neurol Sci*. 2015;352(1–2):62–67.
105. Salehi B, Fokou PVT, Sharifi-Rad M, et al. The therapeutic potential of naringenin: a review of clinical trials. *Pharmaceuticals*. 2019;12(1):11.
106. Bertozzi MM, Rossaneis AC, Fattori V, et al. Diosmin reduces chronic constriction injury-induced neuropathic pain in mice. *Chem-Biol Interact*. 2017;273:180–189.
107. Zhao X, Wang C, Cui W-G, Ma Q, Zhou W-H. Fisetin exerts antihyperalgesic effect in a mouse model of neuropathic pain: engagement of spinal serotonergic system. *Sci Rep*. 2015;5(1):9043.
108. Carballo-Villalobos AI, González-Trujano M-E, Pellicer F, López-Muñoz FJ. Antihyperalgesic effect of hesperidin improves

- with diosmin in experimental neuropathic pain. *BioMed Res Int*. 2016;2016(1):8263463.
109. Sood A, Kumar B, Singh SK, et al. Flavonoids as potential therapeutic agents for the management of diabetic neuropathy. *Curr Pharm Des*. 2020;26(42):5468–5487.
110. Yalniz Y, Yunusoğlu O, Berköz M, Demirel ME. Effects of fisetin on ethanol-induced rewarding properties in mice. *Am J Drug Alcohol Abuse*. 2024;50(1):75–83.
111. Yunusoğlu O, Shahzadi A, Türel CA, Demirkol MH, Berköz M, Akkan AG. Investigation of the pharmacological potential of myricetin on alcohol addiction in mice. *Journal of Research in Pharmacy*. 2022;26(4):722–733.
112. Awathale SN, Shirasath KR, More BR, Pardeshi GN, Goyal SN, Nakhate KT. Naringenin prevents ethanol-induced reward behavior in adolescent rats through inhibition of TRPM3-dependent inflammation in the pVTA. *J Nutr Biochem*. 2025;146(3):110078.