" Pharmacological Significance of Flavones: From Natural Products to Drug Leads "

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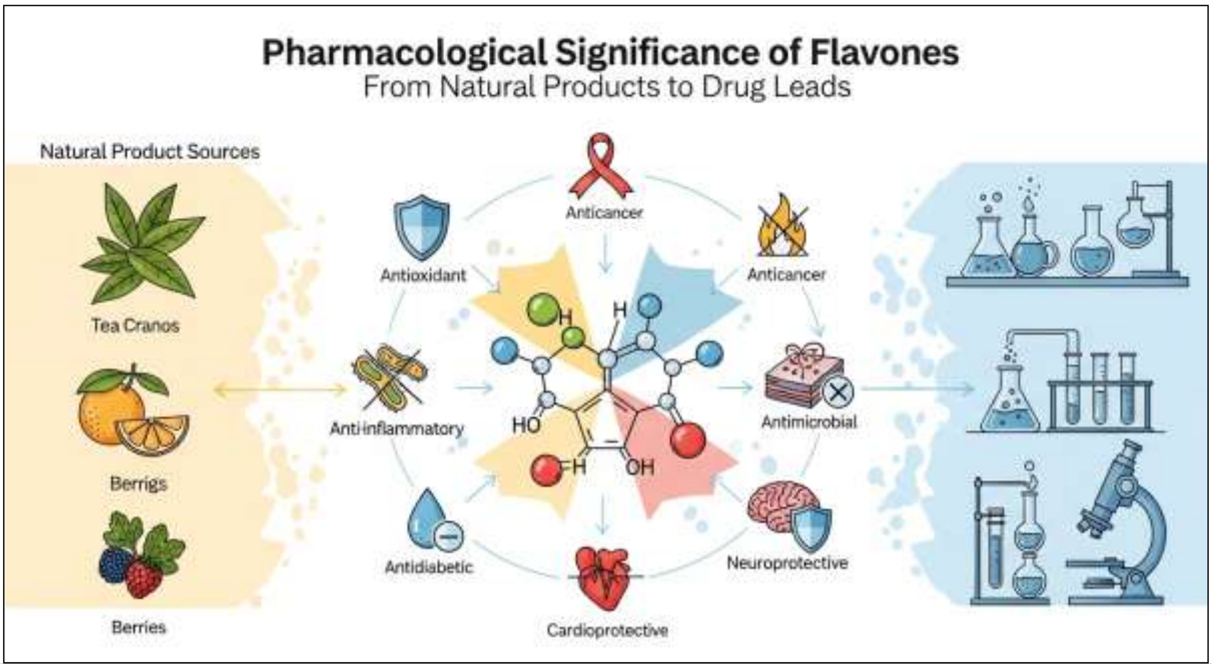
Graphical Abstract :



Abstract :

Flavones are a major subgroup of flavonoids that are widely present in edible plants and herbs, and have long been of interest because of their complex biological and pharmacological properties. From a structural perspective, flavones are characterized by a 2-phenyl-4H-chromen-4-one skeleton, which provides a rigid and planar structure that can easily interact with various biological targets. In addition to their well-documented antioxidant and anticancer properties, flavones have been shown to possess strong anti-inflammatory, antimicrobial, antiviral, antidiabetic, neuroprotective, and cardioprotective effects. These biological effects are achieved through the modulation of major signaling pathways, such as NF-κB, MAPK, PI3K/Akt, AMPK, and Nrf2, which play critical roles in the pathogenesis of chronic diseases.

Notably, flavones possess the ability to target multiple sites as modulators to simultaneously manage oxidative stress, inflammation, metabolism, and cell survival, providing a distinct advantage over traditional single-target drugs. Moreover, the natural availability of flavones, their favorable safety profile, and their long history of dietary exposure further contribute to

their translational potential. Furthermore, recent developments in synthetic modifications, hybrid drug design, and formulation approaches have greatly improved the bioavailability and pharmacokinetic properties of flavone derivatives. This review aims to provide an overview of the natural sources, diversity, biological functions, and pharmacological significance of flavones, highlighting their significance as multifunctional bioactive compounds. In summary, flavones represent an exemplary class of natural compounds with a simple structure that can have a dramatic biological effect and continue to provide valuable leads in contemporary medicinal chemistry.

Keywards: Flavones, Anti-oxidants, Anticancer, Biological Activities

Introduction :

Flavonoids are one of the most prevalent plant secondary metabolites, playing a major role in plant defense strategies and health-promoting activities in humans (1-3). Among the various subclasses of flavonoids, flavones have a unique status because of their chemical stability, planarity, and wide range of biological activities. Flavones are defined by a C_6-C_3-C_6 framework, which comprises two aromatic rings that are condensed through a heterocyclic pyrone ring system, with a specific double bond between C_2 and C_3 (4) (See Figure. 1).

This property distinguishes flavones from flavanones and provides molecular stability, extended conjugation systems, and high affinity for binding to enzymes and receptors (5). Various naturally occurring flavones, such as apigenin, luteolin, chrysin, baicalein, and wogonin, have been well-studied for their biological activities. Although the initial focus was on their antioxidant properties, mounting evidence indicates that flavones possess the ability to modulate multiple biological pathways as multi-target agents (6-8).

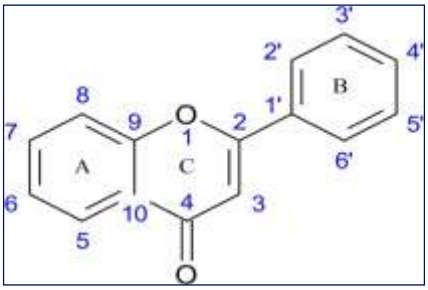


Figure 1. Structure of Flavone.

Natural Sources of Flavones

Flavones are found in common dietary plants and medicinal herbs, which have led to their use in ethnopharmacology (2,9). Dietary plants rich in flavones include parsley, celery, chamomile, thyme, mint, citrus peel, onions, and leafy vegetables, in which apigenin and luteolin are predominantly found (10). Medicinal plants like Scutellaria baicalensis are rich in baicalein and wogonin, which are commonly used in traditional Chinese medicine for their anti-inflammatory and antiviral properties (11). Moreover, flavones are found in herbal teas, especially chamomile tea, which justify their use as nutraceuticals with health benefits (12).

Structural Diversity of Flavones

The structural diversity of flavones can be attributed to differences in hydroxylation, methoxylation, glycosylation, and halogenation patterns of the A and B rings (13). The typical positions of substitution are the hydroxyl groups at C_5 and C_7 of ring A and C_3'/C_4' of ring B. Such modifications greatly affect solubility, redox properties, metabolic stability, and biological activity (14).

Glycosylated flavones are generally more soluble in water but less readily taken up by cells, while aglycones are often more biologically active (15). The chemical modification of the flavone skeleton has made it possible to produce flavone hybrids and analogs with optimized pharmacokinetic and pharmacodynamic properties, solidifying the position of flavones as scaffolds in medicinal chemistry (16).

Biological Activities of Flavones

Flavones have been found to exhibit a wide range of biological activities, such as antioxidant, anti-inflammatory, anticancer, antimicrobial, antidiabetic, neuroprotective, and cardioprotective properties. These properties are due to the ability of flavones to interact with various cellular targets and major signaling pathways. Therefore, flavones have been identified as multifunctional bioactive compounds with high therapeutic potential (See Figure. 2).

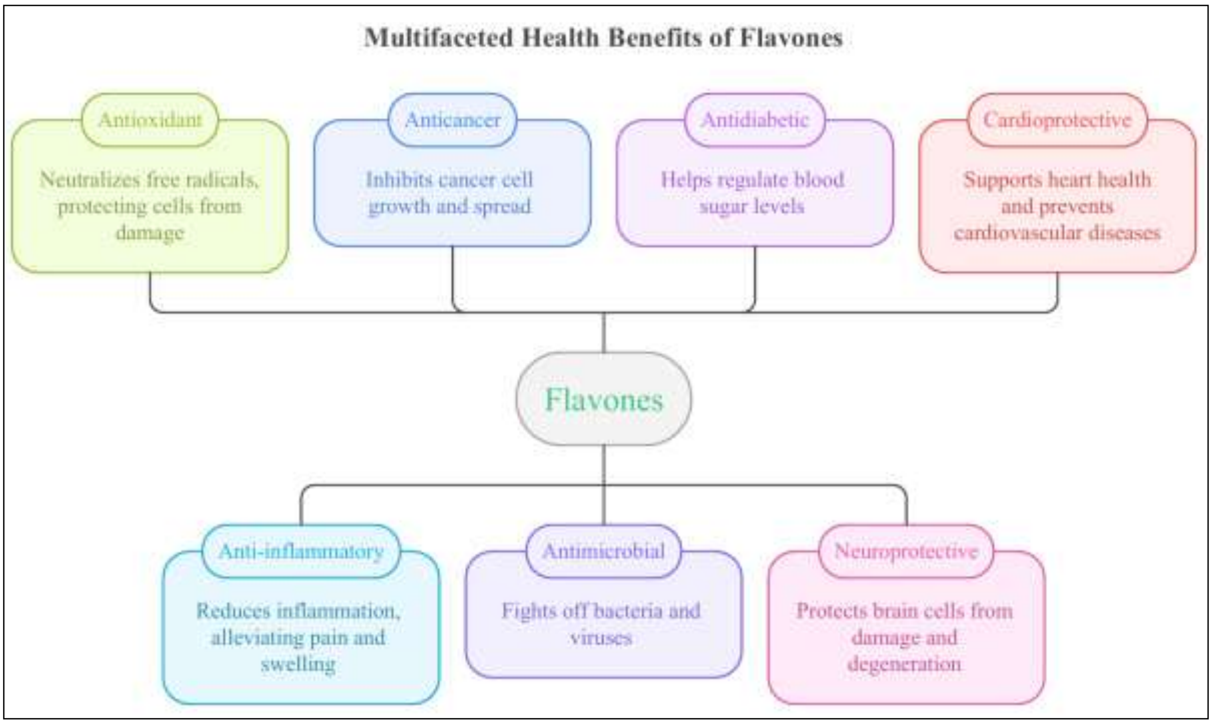


Figure 2. Biological activities of Flavones.

A) Antioxidant Activity

Flavones demonstrate antioxidant activity by direct scavenging of reactive oxygen species, chelation of metal ions, and modulation of endogenous antioxidant enzymes (17). Hydroxylated flavones, such as luteolin and baicalein, can efficiently delocalize free radicals by resonance. Notably, flavones can also activate the Nrf2 pathway, thus promoting the long-term defensive capabilities of cells against oxidative stress (18).

B) Anticancer Activity

Flavones have been shown to inhibit cancer cell proliferation through apoptosis, cell cycle arrest, and inhibition of angiogenesis and metastasis (6,19). The mechanisms of action involve the modulation of PI3K/Akt, MAPK, NF-κB, and STAT3 signaling pathways. Moreover, apigenin and luteolin have been shown to make cancer cells sensitive to conventional chemotherapeutic drugs, establishing their importance as adjuvants in cancer therapy (20).

C) Anti-Inflammatory Activity

Flavones exhibit strong anti-inflammatory properties through the inhibition of pro-inflammatory cytokines, nitric oxide, and prostaglandin production (21). The mechanisms of action involve the inhibition of cyclooxygenase-2 and inducible nitric oxide synthase expression, as well as the inhibition of NF-κB activation and MAPK phosphorylation (22). The combined antioxidant and anti-inflammatory properties of flavones make them highly effective in the treatment of chronic inflammatory and autoimmune diseases (23).

D) Antimicrobial and Antiviral Activity

Flavones have antimicrobial properties against bacteria, fungi, and viruses due to their ability to disrupt microbial membranes, inhibit nucleic acid synthesis, and interfere with viral replication enzymes (24). Some flavones have shown inhibitory activity against the influenza virus, HIV, and other RNA viruses, highlighting their use as broad-spectrum antimicrobials (25).

E) Antidiabetic and Metabolic Effects

Flavones play a role in regulating metabolism by inhibiting α-glucosidase and α-amylase enzymes, thus lowering postprandial hyperglycemia (26). They also increase insulin sensitivity by activating AMPK signaling pathways and regulating glucose transporter gene expression. Moreover, flavones safeguard pancreatic β-cells against oxidative and inflammatory injury, validating their use in type 2 diabetes mellitus (27).

F) Neuroprotective Effects

Flavones display neuroprotective properties through the reduction of neuroinflammation, acetylcholinesterase inhibition, and the protection of neurons against oxidative stress and excitotoxicity (28). The use of compounds such as luteolin and baicalein has been shown to inhibit microglial activation and amyloid-β toxicity, emphasizing their potential in the treatment of neurodegenerative disorders (29).

G) Cardiovascular and Vaso protective Effects

Flavones have been shown to improve cardiovascular function through the enhancement of endothelial function, vasodilation, inhibition of platelet aggregation, and prevention of lipid peroxidation (30). The cumulative effect of these properties is the reduced risk of atherosclerosis and thrombosis, thus supporting the cardioprotective role of flavones (31).

Pharmacological Relevance and Therapeutic Potential of Flavones

Flavones have been identified as pharmacologically interesting compounds because of their diverse range of biological properties, favorable safety profiles, and impressive ability to modulate multiple disease-related targets simultaneously. Unlike traditional small molecule drugs, which are generally designed to target a single molecular entity, flavones are multi-target regulatory compounds, which make them especially useful for the treatment of complex and multifactorial diseases. The therapeutic interest of flavones is based on a combination of structural, mechanistic, and translational diversity (32,33).

Multi-target modulation and disease network regulation

One of the most significant pharmacological properties of flavones is their ability to modulate interrelated signaling pathways instead of individual pathways. Flavones modulate major molecular pathways like NF-κB, MAPK, PI3K/Akt, AMPK, and Nrf2, which together regulate inflammation, oxidative stress, metabolism, apoptosis, and immune responses. This network-based modulation enables flavones to re-establish cellular homeostasis instead of triggering the sudden blockade of pathways, which is particularly beneficial in chronic conditions where there is pathway redundancy and compensatory feedback.

In diseases such as chronic inflammatory disorders, metabolic syndrome, cardiovascular diseases, and neurodegenerative disorders, the progression of the disease is mediated by overlapping molecular processes. The use of flavones, which target multiple points in these networks, provides a pharmacological advantage over single-target drugs, which are often restricted by adaptive resistance or toxicities (34).

Anti-inflammatory and immunomodulatory therapeutic potential

Chronic inflammation is a hallmark of numerous pathological conditions, such as arthritis, inflammatory bowel disease, atherosclerosis, diabetes, and neurodegenerative diseases. Flavones have immense therapeutic potential as anti-inflammatory compounds based on their mechanism of action, which includes the inhibition of pro-inflammatory cytokines, suppression of cyclooxygenase-2 and inducible nitric oxide synthase expression, and inhibition of NF-κB activation. Notably, flavones also modulate the function of immune cells by influencing macrophage polarization and T-cell activation, thus ensuring immune homeostasis rather than inducing immunosuppression (35).

From a therapeutic point of view, the immunomodulatory effects of flavones make them promising leads for the chronic treatment of inflammatory diseases, where sustained efficacy with reduced toxicity is a priority. The versatility of flavones, which can display antioxidant, anti-inflammatory, and cytoprotective properties simultaneously in a single molecule, further adds to their therapeutic potential.

Anticancer relevance beyond cytotoxicity

Although flavones are famous for their anticancer properties, their pharmacological significance is not limited to their cytotoxic effects. Flavones act as modulators of tumour initiation, promotion, and progression by regulating cell cycle checkpoints, triggering apoptosis, suppressing angiogenesis, and preventing metastasis. Moreover, flavones also regulate tumour-associated inflammation and oxidative stress, which are now being recognized as important drivers of tumour progression (36).

One of the most promising therapeutic applications of flavones is their use as chemosensitizers. By suppressing survival signals and drug resistance pathways, flavones can increase the efficacy of conventional chemotherapeutic drugs while possibly lowering their doses and toxicity. This complementary therapeutic approach is very much in line with the current trends in oncology, which emphasize the importance of combination therapy and personalized medicine.

Metabolic and antidiabetic therapeutic relevance

Flavones have shown great promise in the treatment of metabolic syndrome, type 2 diabetes mellitus, and obesity. The pharmacological properties of flavones include the inhibition of carbohydrate-digesting enzymes, the improvement of insulin sensitivity, the activation of AMP-activated protein kinase, and the modulation of lipid metabolism. The collective mechanisms of flavones contribute to the enhancement of glycemic control, the improvement of insulin sensitivity, and the attenuation of metabolic complications (37).

Unlike most antidiabetic agents that specifically target a particular metabolic pathway, flavones display a holistic mechanism of metabolic regulation, which targets hyperglycemia, dyslipidemia, and inflammation concurrently. The β-cell protective properties of flavones also highlight their importance in disease prevention and progression delay, making flavones promising leads in the development of multifunctional metabolic agents (35, 38).

Neuroprotective and central nervous system applications

Neurodegenerative disorders are known for their intricate pathological mechanisms, which include neuroinflammation, oxidative stress, mitochondrial impairment, protein aggregation, and neurotransmitter dysregulation. Flavones have been shown to possess neuroprotective properties due to their ability to suppress microglial activation, lower the secretion of inflammatory mediators, inhibit acetylcholinesterase activity, and prevent neuronal damage from oxidative and excitotoxic insults.

The permeability of some flavones across the blood-brain barrier improves their translational value in the treatment of central nervous system disorders. Moreover, the ability of flavones to modulate multiple pathological mechanisms, such as neuroinflammation, oxidative stress, and synaptic dysfunction, makes them conform to the new treatment approach that prefers multi-mechanism drugs for the management of neurodegenerative (39, 40).

Cardiovascular and Vaso protective significance

Flavones have been shown to play a role in cardiovascular protection through the enhancement of endothelial function, induction of vasodilation, inhibition of platelet aggregation, and prevention of lipid peroxidation. These mechanisms, taken together, work to lower the risk of atherosclerosis, thrombosis, and hypertension. Notably, flavones have been shown to affect nitric oxide availability and calcium signaling in vascular cells, which is fundamental to vascular homeostasis (37).

From a pharmacological perspective, flavones are promising agents for chronic cardiovascular treatment. The combination of antioxidant, anti-inflammatory, and lipid-modulating properties of flavones targets several factors that contribute to cardiovascular disease in a single molecule (35, 41).

Safety, bioavailability, and translational considerations

One of the key strengths of flavones is their favorable safety profile, which has been well supported by the extensive dietary exposure and preclinical data. Nevertheless, difficulties such as low aqueous solubility, high metabolism, and poor bioavailability have long been considered limitations for the clinical development of flavones. Recent progress in formulation science, such as nano-delivery systems, prodrug design, and structure hybridization, has greatly improved the pharmacokinetic properties and tissue targeting of flavones (19, 40).

The progress made has enabled the conversion of flavones from nutraceuticals to potential drug development candidates, thus filling the gap between natural product pharmacology and medicinal chemistry (18, 41).

Drug discovery and future therapeutic prospects

In modern drug development, there is a growing appreciation for the limitations of highly selective single-target drugs for complex diseases. Flavones represent a new class of therapeutically valuable compounds that integrate multi-target efficacy, flexibility, and safety. The flavone scaffold is rigid enough to be explored systematically for structure-activity relationships, allowing for rational design and optimization for particular disease targets (38). Future studies aimed at target validation, pharmacokinetic optimization, and translation to the clinic are anticipated to further establish the importance of flavones as useful tools for next-generation drugs. The flexibility of flavones in the inflammatory, metabolic, neurodegenerative, oncology, and cardiovascular areas reflects their continued pharmacological importance (42).

Integrative Perspective: Why Flavones Matter Pharmacologically

The pharmacological relevance of flavones cannot be merely attributed to the listing of discrete biological activities, but instead, it lies in their distinctive property of concomitantly modulating various disease-related pathways within a single, integrated molecular entity. Unlike traditional single-target drugs, flavones function as network-active molecules, which modulate interrelated signaling cascades that, in concert, regulate inflammation, oxidative stress, metabolism, cell survival, and immunity. This systems pharmacology approach is especially beneficial in multifactorial diseases like chronic inflammation, metabolic syndrome, neurodegenerative diseases, and cardiovascular diseases, in which pathway redundancy and compensatory mechanisms often render mono-target therapies ineffective (36-40).

From a medicinal chemistry perspective, flavones are a remarkable example of the synergy between structural simplicity and biological complexity. The rigid and flat 2-phenyl-4H-chromen-4-one core structure is a robust template for predictable structure-activity relationships, and small variations in hydroxyl, methoxy, or glycosylation patterns can be used to finely tune binding affinity, selectivity, and pharmacokinetic properties. The flavone core structure is rigid enough to bind to a variety of biological targets, such as enzymes, transcription factors, and membrane-associated receptors, while still being flexible enough to accommodate a variety of substitution patterns without compromising molecular integrity. As such, flavones have come to be recognized not only as biologically active natural products, but also as privileged structures for pharmacophore design (42).

One of the defining characteristics that emphasize the pharmacological significance of flavones is their ability to connect nutritional chemoprevention and pharmacological intervention. Some flavones are commonly ingested as part of the diet, and this has led to their chronic modulation of disease risk through low-level chronic exposure. On the other hand, purified flavone derivatives and synthetic flavones have shown significant pharmacological activity under therapeutic conditions. This ambivalence makes them more attractive, as their safety profile, which has been established through dietary exposure, can be harnessed in drug development pipelines (43).

Notably, flavones have a beneficial polypharmacology and selectivity profile. Although they target a variety of pathways, including NF-κB, MAPK, PI3K/Akt, AMPK, and Nrf2, their action is more regulatory than inhibitory, aiming to correct physiological homeostasis rather than cause pathway failure. This is especially useful in the case of chronic diseases, in which a constant correction of the pathological signaling state is more desirable than an aggressive inhibition. Consequently, flavones have great potential as therapeutic agents with a long-term action and as supplements that can increase the efficacy of traditional drugs while reducing their toxicities (4, 31,33).

The pharmacological relevance of flavones is further supported by the rapid progress of modern drug delivery and formulation technology. The long-recognized limitations of flavones, such as low aqueous solubility or high metabolism rates, are increasingly being overcome by nano-delivery systems, prodrug design, and structure hybridization. These developments have significantly improved bioavailability, tissue targeting, and metabolic half-life, and thus the practical applicability of flavone-based drugs (35).

In a general sense, flavones represent a new paradigm in drug discovery, in which multiple target modulation, safety, and flexibility are emphasized over high potency at a single molecular target. The ability to combine multiple mechanisms of action, including antioxidant, anti-inflammatory, metabolic, neuroprotective, and cardiovascular effects, into a single molecular package makes flavones important players in the new paradigm of next-generation drug therapies. Further research efforts in the areas of mechanistic understanding, pharmacokinetic optimization, and clinical validation are expected to further establish the importance of flavones as small molecules with high pharmacological impact (43)

Conclusion :

Flavones are a biologically and pharmacologically important sub-class of flavonoids with varied uses in medicine. The antioxidant, anticancer, anti-inflammatory, antimicrobial, antidiabetic, neuroprotective, and cardioprotective properties of flavones make them versatile bioactive compounds. The natural availability, diversity, and multi-target pharmacology of flavones make them important assets in the field of medicinal chemistry. The recent developments in the synthesis and delivery systems of flavones are expected to increase their importance in medicine.

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