© SEP 2025 | IRE Journals | Volume 9 Issue 3 | ISSN: 2456-8880
DOI: https://doi.org/10.64388/IREV9I3-1710424-1486

Flavonoids and Their Synthetic Derivatives, Chemistry and Biological Applications - A Review

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Abstract- The emergence of drug-resistant microbes has created an urgent need for new antimicrobial agents. Flavonoids, a diverse group of polyphenolic plant metabolites, have shown great promise in this regard due to their wide range of biological activities. While naturally occurring, flavonoids are the most extensively studied, semi-synthetic and synthetic flavonoid derivatives have demonstrated remarkable antimicrobial potential, often inhibiting or killing microbes at concentrations below 1 μg mL⁻¹. Their substitution patterns frequently include hydroxyl groups, halogens, or heteroatomic rings such as pyridine, piperidine, or 1,3-dithiolium cations, though the diversity of substituents, this complicates the establishment of clear structure–activity relationships. First isolated in 1930 from oranges and initially misclassified as vitamin P, flavonoids are now recognized as key plant secondary metabolites, with over 10,000 identified to date. They are abundant in fruits, grains, vegetables, tea, and wine, and have found applications across nutraceutical, medicinal, cosmetic, and pharmaceutical industries. The broad utilization of flavonoids can be attributed to their antioxidant, anti-inflammatory, antimutagenic, and anticancer properties, as well as their ability to modulate cellular enzyme functions. Chemically, flavonoids are hydroxylated phenolic compounds synthesized by plants in response to microbial infection, and their activity is strongly influenced by structural class, degree of hydroxylation, substitution, conjugation, and polymerization. Based on chemical structure, flavonoids are classified into six subclasses: flavonols, flavones, flavanols, flavanones, isoflavones, and anthocyanins, each with distinct biological profiles. This review highlights the chemistry and biological applications of flavonoids and their synthetic derivatives, emphasizing their potential as novel antimicrobial agents in the fight against drug-resistant pathogens.

Index Terms -Flavonoids; Synthetic derivatives, antimicrobial agents, Drug resistance, Polyphenolic compounds, Antioxidant activity, Nutraceuticals.

I. INTRODUCTION

The term "flavonoid" is derived from the Latin word flavus, meaning "yellow." These compounds are widely distributed across the plant kingdom, particularly in fruits, flowers, vegetables, and herbs, where they serve as pigments responsible for colors ranging from yellow to red to blue. Flavonoids constitute a major class of polyphenolic compounds characterized by a benzo-γ-pyrone backbone and are universally present in plants. They are biosynthesized through the phenylpropanoid pathway. Reports indicate that phenolic secondary metabolites, including flavonoids, are largely responsible for a wide spectrum of pharmacological properties.

Flavonoids are hydroxylated phenolic molecules synthesized by plants in response to microbial infection, with their biological activities being highly structure-dependent. Their chemical properties are influenced by structural subclass, degree of hydroxylation, nature of substitutions and conjugations, and extent of polymerization. Recent scientific interest in flavonoids is largely due to their significant antioxidant potential. Functional hydroxyl groups mediate antioxidant effects primarily by scavenging free radicals or by chelating metal ions. Such metal chelation prevents radical formation that would otherwise damage critical biomolecules.

As important dietary constituents, flavonoids are associated with health-promoting properties in both in vivo and in vitro systems, owing to their high antioxidant capacity. They are also known to induce protective enzyme systems in humans. Numerous studies suggest that flavonoids provide protective effects against infectious diseases (bacterial and viral) as well as degenerative conditions, including cardiovascular disorders, cancers, and age-related pathologies.

In plants, flavonoids act as a secondary antioxidant defense system under abiotic and biotic stress conditions. They are localized in the mesophyll cell nuclei and within ROS generation centers, and they also play a regulatory role in plant growth factors such as auxin. Advances in metabolic engineering have enabled the assembly of biosynthetic gene clusters in bacteria and fungi for enhanced microbial production of flavonoids.

This review focuses on flavonoids and their synthetic derivatives, the chemistry and biological applications.

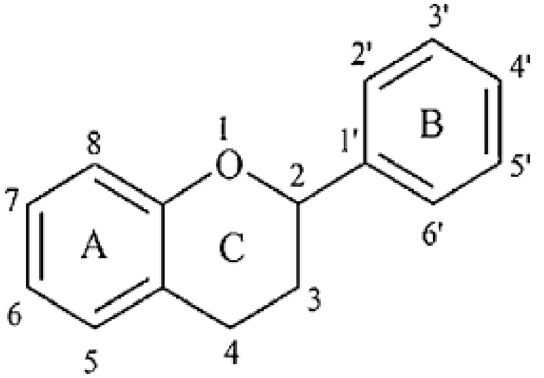


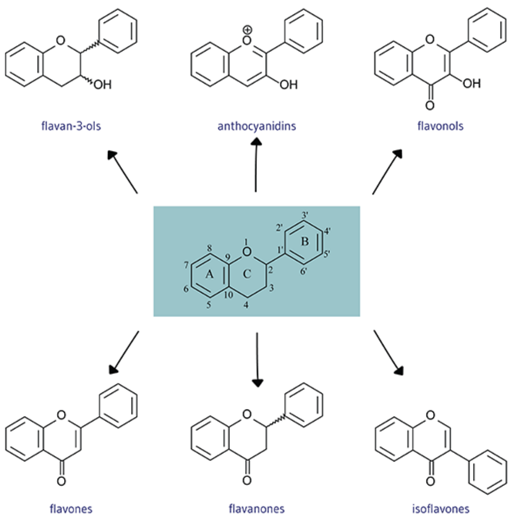
Figure 1. Basic Flavonoid Struture

II. LITERATURE REVIEW

2.1 The Chemistry of flavonoids

The chemical nature of flavonoids is determined by their structural class and the extent of substitutions and conjugations. Despite differences in the structure of the heterocyclic oxygen-containing ring, all flavonoids share a characteristic C6–C3–C6 carbon framework (Yao et al. 2004). This structure consists of two benzene rings (A and B) connected by an oxygenated heterocyclic ring (C).

Structurally, flavonoids are grouped into two major families: 3-hydroxyflavonoids and 3-desoxyflavonoids. The 3-hydroxyflavonoids contain a hydroxyl group at the C-3 position of the C-ring and include subclasses such as flavonols, leucoanthocyanidins, anthocyanidins, and catechins. In contrast, the 3-desoxyflavonoids which encompass flavanones and flavones lack the hydroxyl substitution at the C-3 position. Within these families, further classification is defined by the pattern and position of additional hydroxyl or methoxy substituents on the aromatic rings.



Physical Properties of Flavonoids

Flavonoids, a diverse group of polyphenolic compounds, exhibit characteristic physical properties that are influenced by their hydroxylation pattern, glycosylation, conjugation, and degree of polymerization.

Appearance and Color

- Flavonoids generally occur as crystalline solids and are often responsible for the yellow, red, orange, or blue pigmentation of plants.
- The coloration is mainly attributed to their extended conjugated π-electron system (Harborne & Williams, 2000).

Solubility

- Aglycones (non-sugar forms) are sparingly soluble in water but dissolve well in organic solvents such as ethanol, methanol, acetone, and DMSO.
- Glycosylation increases water solubility due to the presence of polar sugar groups (Yao et al., 2004).

Melting Point

- Flavonoids typically have high melting points (often >200 °C), reflecting their stable polyphenolic structures and hydrogen bonding capacity (Kumar & Pandey, 2013).

UV–Visible Absorption

- Flavonoids show characteristic absorption spectra due to conjugation:
- Band I (300–380 nm): associated with the B-ring cinnamoyl system.
- Band II (240–280 nm): associated with the A-ring benzoyl system.
- These absorption features are useful for structural characterization (Markham, 1982).

Stability

- Flavonoids are sensitive to pH, light, heat, and oxygen.
- Anthocyanins, for instance, appear red in acidic pH but may shift to purple, blue, or colorless under neutral or alkaline conditions (Panche et al., 2016).

Crystallinity and Taste

- Many flavonoids crystallize in pure form.
- Subclasses such as catechins and tannins impart a bitter or astringent taste, commonly observed in tea and certain fruits (Manach et al., 2004).

Chemical Properties of Flavonoids

Flavonoids possess unique chemical properties arising from their polyphenolic backbone, conjugation, and hydroxylation patterns. These features govern their stability, reactivity, and biological activity.

Acid–Base Behavior

- The multiple hydroxyl (-OH) groups in flavonoids can act as weak acids, donating protons to form phenoxide ions.
- Their pKa values typically range between 7–10, depending on the position and number of hydroxyl groups (Bors et al., 1990).
- This contributes to their antioxidant and radical-scavenging activity.

Redox Properties

- Flavonoids are strong reducing agents due to their phenolic structure.
- They readily donate electrons or hydrogen atoms to neutralize reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Rice-Evans et al., 1996).
- Their redox potential is influenced by conjugation and hydroxylation on the B-ring.

Chelation of Metal Ions

- Flavonoids form stable complexes with transition metals such as Fe^{2+}, Cu^{2+}, and Zn^{2+} through hydroxyl and carbonyl groups.
- Metal chelation reduces free radical generation via the Fenton reaction, enhancing antioxidant defense (Pietta, 2000).

Conjugation and Tautomerism

- The C2–C3 double bond conjugated with the 4-oxo group allows electron delocalization, stabilizing flavonoid radicals.
- Flavonoids may also exist in tautomeric forms (keto–enol tautomerism), which affect their reactivity (Kumar & Pandey, 2013).

Glycosylation and Acylation

- Glycosylation of flavonoids (commonly at hydroxyl groups) increases stability and solubility in water, while acylation with organic acids enhances lipophilicity.

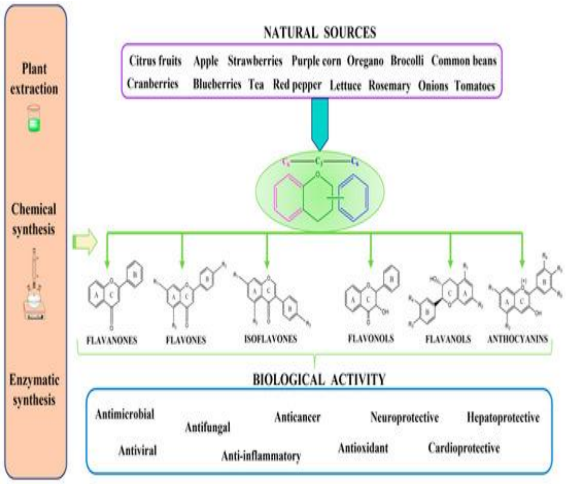
- These modifications influence their bioavailability and metabolic fate (Yao et al., 2004).

Reactivity Toward Oxidation

- Flavonoids are prone to oxidation in the presence of light, heat, or enzymes like polyphenol oxidases.
- Oxidized flavonoids may form quinones or polymerized products, which alter their biological activity (Heim et al., 2002).

Flavonoids represent the most abundant class of phenolic compounds present in plants, particularly in those capable of photosynthesis. They contribute to organoleptic properties such as taste and color, while also playing important roles in inhibiting lipid peroxidation and protecting vitamins and enzymes from oxidative damage. The distribution and accumulation of flavonoids within plants are influenced by several factors, including species variation and light exposure. For instance, high light intensity promotes the biosynthesis of highly oxidized flavonoid derivatives.

Although flavonoids are detected in humans and animals, they are not synthesized endogenously; rather, they are obtained through dietary intake of plant-derived foods (Clifford & Cuppett, 2000; Yao et al., 2004). Based on structural variations, naturally occurring flavonoids are categorized into ten distinct chemical classes, with major groups including flavanones, flavones, and flavans (flavanols).



Synthesis of Flavonoids

Just as in nature, 2′-hydroxychalcones serve as key intermediates for the synthesis of other flavonoid classes, including flavonols, flavones, and flavanones. Synthetically, these compounds can be obtained through several pathways such as Claisen–Schmidt condensation, Friedel–Crafts acylation, and Heck coupling reactions (Figure 2).

In the Claisen–Schmidt reaction, an aromatic aldehyde reacts with a substituted acetophenone under basic catalysis to form the chalcone scaffold (Scheme A, Figure 2). The efficiency of this process can be significantly improved by employing microwave or ultrasound irradiation, which increases yields while reducing reaction times.

The Friedel–Crafts acylation route involves the condensation of (E)-3-phenylprop-2-enoyl chloride with phenols in the presence of $AlCl_3$ as a catalyst, generating the 2′-hydroxychalcone framework (Scheme B, Figure 2).

Alternatively, the Heck coupling method utilizes the reaction between an aryl α, β-unsaturated ketone and iodobenzene, ultimately producing the desired chalcone structure

(Scheme C, Figure 2)

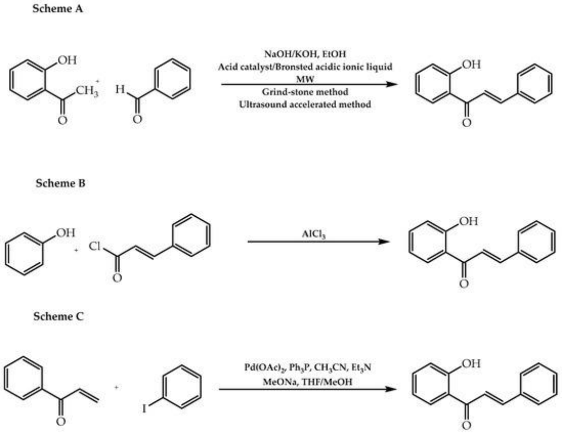
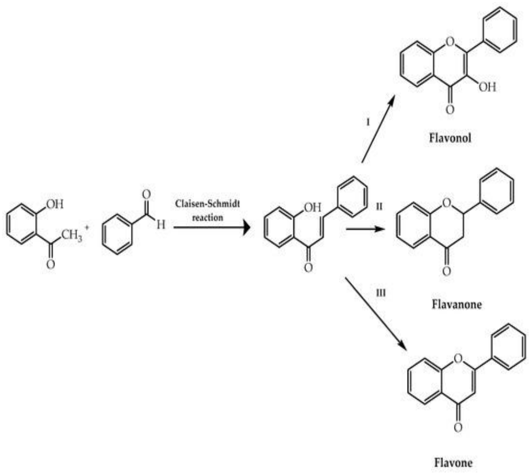


Figure 2. Synthetic methodologies of 2′-hidroxychalcones. Scheme A: Claisen–Schmidt reaction; Scheme B: Friedel–Crafts condensation; Scheme C: Heck coupling reaction.

The Algar–Flynn–Oyamada (AFO) reaction involves the oxidative cyclisation of 2′-hydroxychalcones into flavonols (route I, Figure 3), typically mediated by hydrogen peroxide in an alkaline medium Beyond this pathway, 2′-hydroxychalcones also act as versatile precursors for the synthesis of flavanones (route II, Figure 3) and flavones (route III, Figure 3). For flavanones, synthesis can be achieved through intramolecular cyclisation under either acidic or basic conditions Additional methods include thermolysis, electrolysis, photolysis, microwave-assisted reactions, eco-friendly catalytic systems, and palladium (II)-catalyzed cyclisation.

In the case of flavones, oxidative cyclisation of chalcones has been reported under diverse reaction conditions. Traditional methods include the I_2–DMSO protocol or NH_4I-mediated cyclisation in solvent-free systems. Other strategies involve the use of phenyliodinium acetate (PIDA), selenium (IV) reagents under microwave irradiation, indium (III) halides supported on gel-silica, and CuI-catalysis in the ionic liquid [bmim][NTf_2]. Furthermore, diphenyl disulfide at elevated temperatures and oxalic acid-mediated catalysis have also been applied for the efficient synthesis of flavones from chalcones.



III. BIOLOGICAL ACTIVITIES OF FLAVONOIDS

3.1. Antioxidant Activity - Flavonoids exhibit diverse biochemical activities, but their most widely recognized property across nearly all subclasses is their antioxidant potential. This activity is strongly influenced by the structural arrangement of functional groups within the flavonoid nucleus. Specifically, the configuration, degree of substitution, and the total number of hydroxyl groups play a critical role in determining antioxidant mechanisms such as free radical scavenging and metal ion chelation. Among these, the hydroxyl configuration on the B-ring is particularly important for reactive oxygen species (ROS) and reactive nitrogen species (RNS) scavenging. This is due to its ability to donate both a hydrogen atom and an electron to radicals such as hydroxyl, peroxyl, and peroxynitrite, thereby stabilizing them and generating a relatively stable flavonoid radical.

3.2. Hepatoprotective Activity - Several flavonoids, including catechin, apigenin, quercetin, naringenin, rutin, and venoruton, have been reported to exhibit hepatoprotective activities. Chronic metabolic disorders such as diabetes can contribute to hepatic complications, where expression of glutamate-cysteine ligase catalytic subunit (Gclc), glutathione levels, and ROS balance are often impaired in the liver of diabetic models. Anthocyanins have gained considerable attention due to their protective effects against multiple disease conditions. demonstrated that the anthocyanin cyanidin-3-O-β-glucoside (C3G) enhances hepatic Gclc expression by elevating intracellular cAMP levels, thereby activating protein kinase A (PKA). Activated PKA subsequently upregulates phosphorylation of cAMP response element-binding protein (CREB), promoting CREB-DNA interaction and increasing Gclc transcription. Enhanced Gclc expression reduces hepatic ROS accumulation and attenuates pro-apoptotic signaling. In addition, C3G treatment suppresses hepatic lipid peroxidation, downregulates pro-inflammatory cytokine release, and provides protection against hepatic steatosis.

3.3. Antibacterial Activity - Flavonoids are secondary metabolites synthesized by plants as part of their defense mechanism against microbial invasion. Consequently, it is not unexpected that these compounds exhibit significant antimicrobial activity in vitro against a broad spectrum of microorganisms. Numerous studies have demonstrated that flavonoid-rich extracts from diverse plant species possess pronounced antibacterial properties. Specific flavonoid subclasses—including apigenin, galangin, flavones, flavonol glycosides, isoflavones, flavanones, and chalcones—have been identified as potent antibacterial agents.

3.4. Anti-Inflammatory Activity- Inflammation is a physiological defense response triggered by tissue injury, microbial infection, or chemical irritation. The process begins with the migration of immune cells from the bloodstream and the release of mediators at the site of damage. This is followed by recruitment of inflammatory cells and the release of reactive oxygen species (ROS), reactive nitrogen species (RNS), and proinflammatory cytokines to eradicate pathogens and facilitate tissue repair. Under normal conditions, inflammation is rapid and self-limiting; however, impaired resolution or prolonged activation leads to chronic inflammatory disorders.

The immune response can be modulated by diet, pharmacological agents, environmental pollutants, and naturally occurring phytochemicals, particularly flavonoids. Several flavonoids, including hesperidin, apigenin, luteolin, and quercetin, have demonstrated significant anti-inflammatory and analgesic properties. Mechanistically, flavonoids target enzyme systems central to inflammation, particularly protein tyrosine kinases and serine/threonine kinases, by competitively binding with ATP at their catalytic domains. These kinases are key regulators of intracellular signaling cascades and immune cell activation.

Moreover, flavonoids suppress the expression of inducible nitric oxide synthase (iNOS), cyclooxygenases (COX), and lipoxygenases (LOX), thereby reducing the biosynthesis of nitric oxide, prostanoids, leukotrienes, and other inflammatory mediators such as cytokines, chemokines, and adhesion molecules. Inhibition of phosphodiesterases further attenuates immune cell activation. Importantly, many flavonoids downregulate cytokine-driven adhesion of leukocytes to injured tissues and strongly inhibit prostaglandin production, thereby mitigating excessive inflammatory signaling.

3.5. Anticancer Activity - Dietary components are recognized as key modulators in cancer prevention, with flavonoid-rich fruits and vegetables extensively reported as cancer chemopreventive agents. Epidemiological studies indicate that regular consumption of onions and apples both rich in the flavonol quercetin is inversely correlated with the incidence of prostate, lung, stomach, and breast cancers. Similarly, moderate intake of wine, another dietary source of flavonoids, has been associated with reduced risks of lung, endometrial, esophageal, gastric, and colorectal cancers. The protective role of fruit and vegetable intake in cancer prevention has been consistently documented, highlighting the potential for significant public health benefits through increased consumption of these foods. The chemopreventive action of flavonoids has been linked to several biochemical and molecular mechanisms affecting the initiation and promotion stages of carcinogenesis. These include: (1) downregulation of mutant p53 protein expression, (2) induction of cell cycle arrest, (3) inhibition of protein tyrosine kinases, (4) suppression of heat shock protein activity, (5) modulation of estrogen receptor binding, and (6) inhibition of Ras protein expression.

3.6. Antiviral Activity - Natural products remain a critical source for the identification and development of novel antiviral agents due to their natural abundance and relatively low toxicity. Flavonoids, in particular, have been reported to exhibit antiviral activity since the 1940s, with numerous studies highlighting their potential against different viral systems. The urgent demand for effective therapeutic agents against human immunodeficiency virus (HIV) has intensified research on compounds capable of targeting viral enzymes essential for replication. Structure–activity relationship (SAR) studies have demonstrated a clear link between flavonoid structural features and their enzyme inhibitory potential. For example, Gerdin and Srensso reported that flavan-3-ol displayed greater efficacy compared to flavones and flavanones in selectively inhibiting HIV-1, HIV-2, and related immunodeficiency viruses. Additionally, baicalin, a flavonoid isolated from Scutellaria baicalensis (Lamiaceae), has been shown to inhibit both HIV-1 infection and replication. Other flavonoids, such as baicalein, robustaflavone, and hinokiflavone, also exhibit inhibitory effects on HIV-1 reverse transcriptase.

CONCLUSION

Flavonoids can be easily produced and functionalized, according to the findings. The current review has shown that Flavonoids can be used to successfully synthesize a wide range of derivatives of medicinal relevance. Flavonoids -containing compounds have a wide range of activities. As a result, synthetic scientists and chemists have a lot of room to create new compounds with varied substitutions. The research on this ring can still be carried out, and the flavonoid moiety's therapeutic value can be investigated.

AUTHORS' CONTRIBUTIONS All the authors have contributed to the study design. The authors declare that they have no competing interests.

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