

Recent Advances in the Application of Natural Flavonoids in the Pharmaceutical Field

Chujun Liu

*Science Department, Santa Catalina School, Monterey, USA
chujunliu1@gmail.com*

Abstract. Natural flavonoids are widely distributed plant polyphenols that have attracted increasing attention as potential pharmaceutical agents because of their diverse biological activities. This review summarizes recent advances in the pharmacological activities, therapeutic applications, and translational challenges of natural flavonoids. Current evidence indicates that flavonoids can exert antioxidant effects through direct reactive oxygen species scavenging and regulation of the nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element (ARE) pathway, while their anti-inflammatory actions involve pathways such as nuclear factor kappa B (NF- κ B) and mitogen-activated protein kinase (MAPK). Several flavonoids also show antitumor potential by influencing apoptosis, cell proliferation, angiogenesis, and signaling pathways, including the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway and the Wingless-related integration site (Wnt)/ β -catenin pathway. Their potential applications have been investigated in cardiovascular diseases, neurodegenerative disorders, diabetes, and other metabolic conditions. However, many findings are still based on cell and animal studies, and clinical translation remains limited by poor water solubility, low stability, extensive metabolism, weak systemic absorption, and variation among studies. Emerging delivery approaches, including nanocarriers and other formulation strategies, may improve flavonoid stability and bioavailability. Future research should emphasize standardized pharmacokinetic evaluation, safety assessment, quality control, and well-designed clinical trials to clarify therapeutic efficacy and support the development of reliable flavonoid-based pharmaceutical products.

Keywords: natural flavonoids, antioxidant activity, anti-inflammatory activity, pharmaceutical applications, bioavailability

1. Introduction

Natural flavonoids are a type of secondary metabolite of polyphenols, which are ubiquitous in plants and are usually produced in fruits, vegetables, tea, traditional Chinese medicine, and other plant-based foodstuffs. On the basis of chemical structure, flavonoids can be classified into flavones, flavonols, flavanones, isoflavones, and anthocyanidins. Besides contributing to the coloration and stress resistance of plants, these compounds exhibit diverse biological activities and are thus an important focus of interest in natural drug research in recent years. With the increase in chronic diseases, tumors, and neurodegenerative disorders, there has been an increase in the interest

in bioactive compounds of natural origin, with lower toxic side effects. Natural flavonoids have been found to exhibit, in many studies, a wide range of pharmacological activities, such as antioxidant, anti-inflammatory, antitumor, antibacterial, neuroprotective, and cardioprotective activities, presenting a broad spectrum of potential for the prevention and treatment of diseases.

In recent years, studies on flavonoids have moved from pure activity screening to focus on understanding their modes of action and their clinical potential. Flavonoids have been shown to have pleiotropic effects on several targets and pathways, such as oxidative stress, inflammatory responses, apoptosis, and signaling pathways, with increasing studies demonstrating these effects. But many common problems, such as low bioavailability and poor stability, are hampering their clinical application. Therefore, it is highly desirable to compile the pharmacological properties, therapeutic applications, and prospects of natural flavonoids in a systematic way as a natural drug.

2. Main pharmacological activities of natural flavonoids

2.1. Antioxidant effects

Oxidative stress is frequently a pathological mechanism of initiation and progression of several chronic diseases. Reactive oxygen species (ROS) are harmful compounds that, when elevated, result in lipid peroxidation, protein oxidation, and deoxyribonucleic acid (DNA) damage that affects cellular homeostasis. Natural flavonoids have some structural features, such as phenolic hydroxyl groups, that can donate hydrogen atoms or electrons to some free radicals and exhibit strong antioxidant potential. Zahra et al. reported that the antioxidant activity of flavonoids can be accomplished in two ways: the first is direct antioxidant free radical scavenging activity, and the second is regulation of the intracellular antioxidant defense mechanisms [1].

Flavonoids can directly function as ROS scavengers, as well as ROS pathway modulators of the nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element (ARE) signaling pathway. In response to activation and nuclear translocation, Nrf2 promotes the expression of cytoprotective genes, such as heme oxygenase-1 (HO-1), NAD(P)H quinone dehydrogenase 1 (NQO1), and glutathione-related enzymes, and leads to an increase in endogenous antioxidant capacity. Huang et al. have reviewed findings suggesting that several dietary flavonoids can regulate antioxidant responses via pathways including interference with Kelch-like ECH-associated protein 1 (Keap1)-Nrf2 binding, kinase regulation, and modulation of Nrf2 stability [2]. So, the effects of flavonoids are not only in the chemical scavenging of radicals, but also in the cellular regulation of signaling.

Different flavonoids have different structures, which also affect their antioxidant activity. For instance, flavonols with several hydroxyl groups, like quercetin, are generally found to have a powerful electron-donating ability. By limiting oxidative stress, flavonoids may also reduce inflammation and cellular damage, which provides a shared pharmacological basis for their application in cardiovascular, neurological, and metabolic diseases [1, 2].

2.2. Anti-inflammatory effects

Atherosclerosis, diabetes, arthritis, and some cancers are among the diseases that can develop and progress due to chronic inflammation. Natural flavonoids have been shown to regulate inflammatory responses via several mechanisms, of which the nuclear factor kappa B (NF- κ B) and mitogen-activated protein kinase (MAPK) pathways are best studied for their role in inflammation. According to Al-Khayri et al., quercetin, apigenin, kaempferol, genistein, and epigallocatechin

gallate (EGCG) have all been shown to influence NF- κ B, activator protein 1 (AP-1), and MAPK-mediated pathways, which consequently lead to a decrease in the production of several pro-inflammatory mediators [3].

Flavonoids can help reduce the production of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF- α), interleukin-1 beta (IL-1 β), and interleukin-6 (IL-6), and inhibit the expression and/or activity of inflammation-related enzymes such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) [3]. These effects help reduce the triggering of inflammatory mediators and limit tissue damage from chronic inflammation. As oxidative stress triggers activation of inflammatory pathways, and inflammation further triggers oxidative stress, flavonoids will have a multi-target action profile.

2.3. Antitumor effects

The main anti-tumoral activities of natural flavonoids are: the inhibition of abnormal proliferation, the induction of apoptosis, the inhibition of the cell cycle, the inhibition of migration, and the inhibition of vascularization. Several studies indicate that some signaling pathways, including phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt), MAPK, and Wingless-related integration site (Wnt)/ β -catenin, might play pivotal roles in the anti-tumor activity of flavonoids. Wei and Zhang also reviewed research on the anti-tumour effects of flavonoids on tumor angiogenesis in 2024, including pathways such as hypoxia-inducible factor 1-alpha (HIF-1 α)/vascular endothelial growth factor (VEGF)/vascular endothelial growth factor receptor 2 (VEGFR2)/PI3K/Akt and the Wnt/ β -catenin pathway [4].

Experimental evidence, largely in vitro and animal studies, has shown that quercetin, luteolin, apigenin, and genistein possess anti-tumor activity. Several flavonoids are also being studied for their potential to improve the efficacy or decrease the toxicity of conventional anti-cancer treatments, but the optimal dose, pharmacokinetics, and long-term safety of these flavonoids need further validation in clinical trials [4]. Therefore, they should be considered promising natural active molecules for anti-cancer activity, not as clinically proven anti-cancer drugs in themselves.

The main pharmacological activities and related signaling pathways of natural flavonoids are summarized in Figure 1.

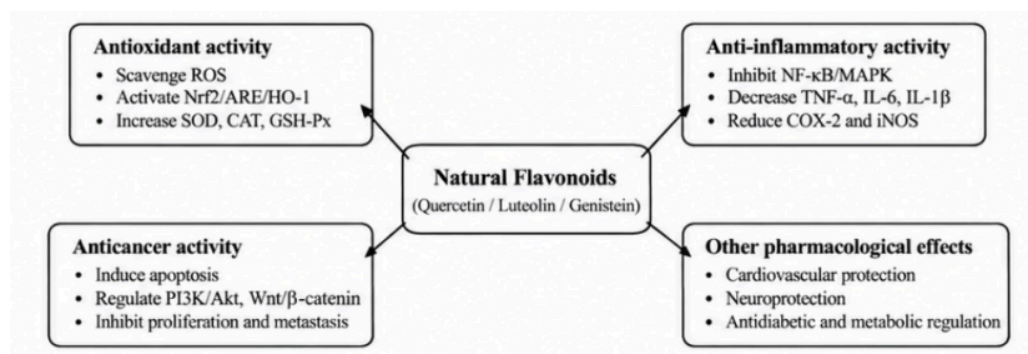


Figure 1. Schematic illustration of the main pharmacological activities and related signaling pathways of natural flavonoids (compiled from references [1-4])

(Picture credit: Original)

3. Applications of natural flavonoids in the pharmaceutical field

3.1. Cardiovascular diseases

Studies on natural flavonoids for the prevention and treatment of cardiovascular diseases have mainly focused on antioxidant and anti-inflammatory activities, improvements in vascular endothelial function, regulation of lipid metabolism, and myocardial protection. In this regard, Zhang and colleagues examined the latest research on quercetin in disease models, including atherosclerosis, myocardial infarction, ischemia-reperfusion injury, heart failure, hypertension, and arrhythmia, and attempted to clarify the potential applications of quercetin, including its actions as an antioxidant, on cholesterol levels and on the protection of endothelial cells [5].

Other flavonoids—such as anthocyanins and hesperidin—have also been studied in relation to cardiovascular risk factors in addition to quercetin. The multi-target action of flavonoids is very suitable for the complex pathophysiological mechanisms of cardiovascular diseases, but the data are still mainly from animal and pre-clinical experiments. Further investigations are needed to standardize human trials and determine effective doses, target populations, and the safety of various flavonoids when combined with standard drugs [5].

3.2. Neurodegenerative diseases

Oxidative stress, inflammation, dysfunction of synapses, and abnormal protein aggregation are all common features of neurodegenerative diseases, including Alzheimer's and Parkinson's. Flavonoids are thought to be useful for neuroprotective studies because of their antioxidant, anti-inflammatory, and cell-signaling modulation properties. Ramezani et al. reported from preclinical and clinical evidence that flavonoids may support learning and memory through effects on neurotransmitter systems, neurogenesis, synaptic plasticity, and neuronal survival [6].

It is to be noted that not all flavonoids are equally able to permeate the central nervous system, and their metabolites in vivo may also be responsible for actual effects. So, it's not quite true to say that flavonoids can cross the blood-brain barrier. More accurately, some flavonoids and metabolites have been identified as potentially crossing the blood-brain barrier (BBB) and/or affecting brain signaling in experimental studies. At present, there is insufficient clinical data, and future research should assess their actual therapeutic potential by incorporating pharmacokinetics, brain concentrations, and long-term intervention studies [6].

3.3. Diabetes and metabolic disorders

Natural flavonoids have also received considerable research attention in the areas of diabetes, obesity, and metabolic syndrome. The mechanisms they act through include improving insulin sensitivity, influencing glucose and lipid metabolism, decreasing oxidative stress and inflammation, and modulating pathways of energy metabolism such as adenosine monophosphate-activated protein kinase (AMPK). In recent years, the gut microbiota has emerged as a key target of interest in studies of the metabolic effects of flavonoids. As stated above, Du et al. observed that the anthocyanins, when they reach the colon, may interact with the gut microbes, and this bidirectional interaction may be responsible for controlling obesity, type 2 diabetes, and other diseases related to metabolic syndrome [7].

Thus, the benefits of flavonoids in metabolic diseases may not depend on a single target but rather on a complex interplay among host metabolism, the inflammatory state, and the gut

microbiota. The results of these studies provide new evidence for the use of natural flavonoids as a metabolic intervention, but inter-individual variation in gut microbiome composition and large variation in flavonoid absorption and metabolism indicate that systematic and standardized clinical trials are necessary to verify reproducibility and the real therapeutic effect [7].

The major disease areas in which natural flavonoids have potential pharmaceutical applications are summarized in Figure 2.

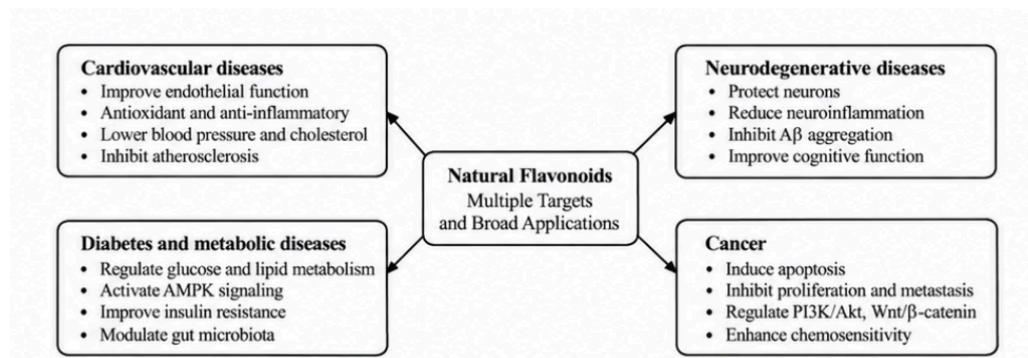


Figure 2. Potential applications of natural flavonoids in major disease areas (compiled from references [5-7])

(Picture credit: Original)

4. Existing issues and future outlook

Despite the multiple pharmacological activities found in natural flavonoids, their clinical application is still hampered by both pharmacokinetic factors and the quality of evidence. Firstly, many flavonoids are poorly water-soluble and therefore are not very stable or well absorbed in the gastrointestinal tract, and may be extensively metabolized during first-pass metabolism through the liver, such that systemic exposure following oral administration may be inadequate. Yuan et al. noted that the low solubility, high metabolism, and weak systemic absorption of dietary flavonoids are important issues that prevent clinical application of these compounds [8]. This means that the effective concentrations observed in vitro may not always be achieved in human target tissues.

In recent years, to overcome this problem, researchers have sought to enhance the solubility, stability, and delivery efficiency of flavonoids through solid dispersions, emulsions, complexes, crystal engineering, and various nanocarriers [8]. Zahra et al. have also summarised the potential of nanomedicine for the delivery of flavonoids, in which nanoformulations can improve the stability, targeting ability, and bioavailability of flavonoids [1]. However, new delivery systems also must undergo testing for how safe the materials are; how repeatable and reproducible the preparations are; how toxic the materials are over the long term; and whether or not the systems can be produced on a large scale; they should not be judged on the basis of whether or not the materials are absorbed more effectively.

Second, many current flavonoid studies are still conducted in cell and animal models, with large discrepancies in flavonoid purity, doses, routes of administration, and methods of measurement across studies, making it difficult to compare results and draw conclusions. Future experiments are needed that are based on high-quality randomized controlled trials (RCTs), using more standardized pharmacokinetics, safety assessments, and quality control procedures. During the transition, using strategies like structural modifications, prodrug development, and targeted delivery systems can be used to optimize exposure, and the type and dose of flavonoids used can be individualized for the

disease and patient. Only when progress is made in mechanistic research, optimization of formulation, and clinical trials will natural flavonoids be given the best opportunity to move beyond the concept of "bioactive natural compounds" to quality-controlled pharmaceutical products backed by solid research [8].

The major challenges and future research directions for the clinical translation of natural flavonoids are summarized in Figure 3.

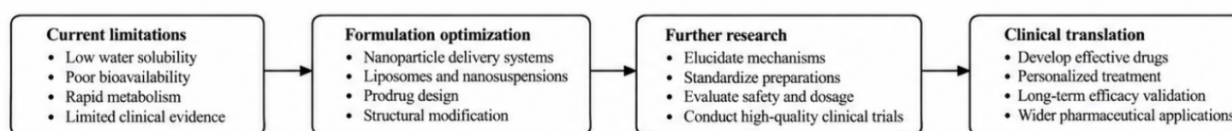


Figure 3. Major challenges and future research directions in the clinical translation of natural flavonoids (compiled from references [1, 8])

(Picture credit: Original)

5. Conclusion

Natural flavonoids possess diverse pharmacological activities and show potential for applications in cardiovascular, neurodegenerative, metabolic, and cancer-related research. Their effects are associated with multiple mechanisms, including the regulation of oxidative stress, inflammation, apoptosis, angiogenesis, cellular signaling, and host-microbiota interactions. Nevertheless, the transition from experimental findings to pharmaceutical use remains limited by low solubility, poor stability, extensive metabolism, insufficient systemic exposure, and inconsistent experimental designs. Formulation optimization, nanocarrier-based delivery, structural modification, and targeted delivery may help improve exposure and bioavailability, but these strategies also require careful evaluation of safety, reproducibility, long-term toxicity, and scalability. Future studies should combine mechanistic research with standardized pharmacokinetic assessment, quality control, and high-quality clinical trials. Such efforts will be necessary to determine effective doses, appropriate target populations, and long-term safety, and to support the development of natural flavonoids from promising bioactive compounds into reliable, quality-controlled pharmaceutical products.

References

- [1] Zahra, M., Abrahamse, H., & George, B. P. (2024). Flavonoids: Antioxidant powerhouses and their role in nanomedicine. *Antioxidants*, 13(8), 922.
- [2] Huang, W., Zhong, Y., Gao, B., Zheng, B., & Liu, Y. (2023). Nrf2-mediated therapeutic effects of dietary flavones in different diseases. *Frontiers in Pharmacology*, 14, 1240433.
- [3] Al-Khayri, J. M., Sahana, G. R., Nagella, P., Joseph, B. V., Alessa, F. M., & Al-Mssallem, M. Q. (2022). Flavonoids as potential anti-inflammatory molecules: A review. *Molecules*, 27(9), 2901.
- [4] Wei, Q., & Zhang, Y. H. (2024). Flavonoids with anti-angiogenesis function in cancer. *Molecules*, 29(7), 1570.
- [5] Zhang, W., Zheng, Y., Yan, F., Dong, M., & Ren, Y. (2023). Research progress of quercetin in cardiovascular disease. *Frontiers in Cardiovascular Medicine*, 10, 1203713.
- [6] Ramezani, M., Zeinaddini Meymand, A., Khodaghali, F., et al. (2023). A role for flavonoids in the prevention and/or treatment of cognitive dysfunction, learning, and memory deficits: A review of preclinical and clinical studies. *Nutritional Neuroscience*, 26(2), 156–172.
- [7] Du, L., Ding, X., Tian, Y., Chen, J., & Li, W. (2024). Effect of anthocyanins on metabolic syndrome through interacting with gut microbiota. *Pharmacological Research*, 210, 107511.
- [8] Yuan, D., Guo, Y., Pu, F., et al. (2024). Opportunities and challenges in enhancing the bioavailability and bioactivity of dietary flavonoids: A novel delivery system perspective. *Food Chemistry*, 430, 137115.