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# Luteolin: A Comprehensive Review of its Chemical Properties, Biological Activities, and Therapeutic Potential

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**ABSTRACT: Luteolin (3', 4', 5, 7-tetrahydroxyflavone) is a naturally occurring flavonoid abundant in herbs, vegetables, and citrus fruits, contributing to its presence in the human diet. This flavonoid has garnered significant interest due to its extensive biological activities, including antioxidant, anti-inflammatory, anticancer, neuroprotective, and cardiovascular benefits. Its molecular structure, characterized by hydroxyl groups at specific positions on a flavone backbone, underpins its potent bioactivities. However, luteolin's therapeutic application is limited by poor water solubility and low bioavailability, which has prompted research into advanced delivery systems such as nanoparticles and liposomal formulations. This review provides an in-depth analysis of luteolin's chemical properties, biological effects, and potential therapeutic applications. Key findings highlight its ability to scavenge reactive oxygen species, modulate inflammatory signaling pathways, inhibit cancer cell proliferation and angiogenesis, protect neuronal cells from oxidative stress, and enhance cardiovascular health. Despite promising preclinical results, further studies, particularly clinical trials, are essential to validate luteolin's efficacy and safety in human health. This review underscores luteolin's potential as a therapeutic agent for managing chronic diseases, including cancer, neurodegenerative disorders, and cardiovascular diseases.**

**Keywords:** Antioxidant, Anti-inflammatory, Anticancer, Bioavailability, Luteolin.

## INTRODUCTION

Luteolin (3', 4', 5, 7-tetrahydroxyflavone) is a naturally occurring flavonoid, belonging to the flavone subclass of polyphenolic compounds, widely distributed in the plant kingdom. It is commonly found in a variety of dietary sources, including herbs (such as parsley, thyme, and rosemary), vegetables (like celery, broccoli, and carrots), fruits (particularly citrus fruits), and even olive oil and tea. These sources make luteolin an integral component of the regular human diet, contributing to its potential health benefits (Zhao *et al*., 2020). Due to its presence in diverse food items, luteolin has been studied extensively for its various biological effects and its role in maintaining overall health. The interest in luteolin has grown significantly in recent years due to its broad spectrum of pharmacological activities. It exhibits remarkable antioxidant, anti-inflammatory, anticancer, antimicrobial, and neuroprotective properties, making it a promising candidate for therapeutic applications (Zhang *et al.,* 2023). Structurally, luteolin consists of a flavone backbone with hydroxyl groups at positions 3', 4', 5, and 7, which play a crucial role in its biological activities. These hydroxyl groups contribute to its potent free radical scavenging ability, which is essential in reducing oxidative stress—a major factor in the progression of chronic diseases (Cho and Dua 2022). As oxidative stress and inflammation are key contributors to various pathological conditions, luteolin's dual antioxidant and anti-inflammatory properties make it a compelling subject of research. Numerous studies have highlighted luteolin's potential in the treatment and prevention of chronic diseases. For instance, its anticancer effects have been demonstrated in various cancer models, including breast, lung, prostate, and colorectal cancers, where it has been shown to inhibit tumor growth, induce apoptosis, and suppress metastasis (Wang *et al.,* 2023). Similarly, its cardioprotective effects are attributed to its ability to reduce oxidative damage, improve endothelial function, and regulate lipid metabolism, which are crucial in preventing cardiovascular diseases (Sun *et al.,* 2021). Additionally, its neuroprotective potential has been explored in the context of neurodegenerative disorders such as Alzheimer's and Parkinson's diseases, where it has been found to mitigate neuronal damage and inhibit neuroinflammation (Han *et al.,* 2021). Given the increasing prevalence of chronic diseases worldwide, there is a strong need to explore naturally derived bioactive compounds with minimal side effects. Luteolin stands out as a promising candidate due to its multi-targeted mechanisms and bioavailability from commonly consumed dietary sources. However, despite

extensive research, there remain gaps in understanding its pharmacokinetics, bioavailability enhancement strategies, and precise molecular interactions. This review aims to provide an in-depth understanding of luteolin chemical properties, biological effects, therapeutic potential, Pharmacokinetics and Bioavailability based on recent studies.

## CHEMICAL PROPERTIES

Luteolin is a flavonoid with a distinct chemical structure that contributes to its bioactivity. It is part of the flavone class, which is characterized by the presence of a benzopyrone ring system. The hydroxyl groups at the 3', 4', 5', and 7' positions of the molecule enhance its antioxidant and anti-inflammatory properties by providing sites for electron donation to reactive species. The hydroxyl groups also influence its ability to form metal-chelating complexes, which may further contribute to its biological effects (Li *et al.*, 2020; Wang *et al.*, 2023). One key feature of luteolin is its poor water solubility, which limits its bioavailability. This low solubility is typical of many flavonoids, which are highly hydrophobic. However, luteolin is soluble in organic solvents like ethanol, methanol, and acetone, allowing it to be extracted from plant sources. Recent studies have explored various methods to improve its bioavailability for therapeutic use, such as nanoparticle-based delivery systems, liposomal formulations, and phospholipid complexes, which enhance its absorption and stability (Zhao *et al.*, 2020; Patel *et al.*, 2023).

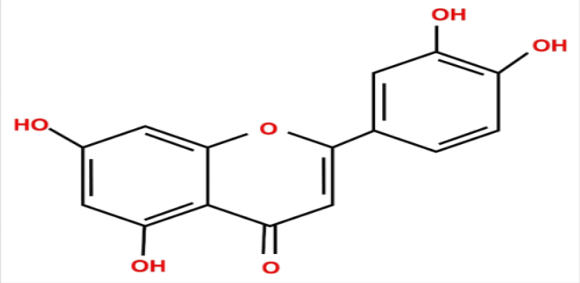


**Fig. 1.** Chemical Structure of luteolin (Bekhit *et al.*, 2016).

## BIOLOGICAL ACTIVITIES OF LUTEOLIN

**Antioxidant Activity.** Luteolin is a potent antioxidant due to its ability to scavenge free radicals and reduce oxidative stress. The hydroxyl groups on the flavonoid structure make luteolin an effective radical scavenger, able to neutralize harmful reactive oxygen species (ROS) like superoxide anion, hydrogen peroxide, and hydroxyl radicals. These ROS are implicated in the pathogenesis of a variety of diseases, including cancer, cardiovascular diseases, and neurodegenerative disorders (Choudhary *et al.*, 2021; Liu *et al*., 2023). A comprehensive review by Zhang *et al.* (2023) discusses luteolin antioxidant and anti-inflammatory mechanisms, emphasizing its potential in mitigating oxidative stress-related diseases. Luteolin's antioxidant effects extend beyond direct free radical scavenging; it also modulates cellular antioxidant defense mechanisms. For instance, it upregulates the expression of antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, which help to protect cells from oxidative damage. Recent studies highlight the role of luteolin in activating the Nrf2 (nuclear factor erythroid 2-related factor 2) signaling pathway, which regulates antioxidant responses (Wang *et al.*, 2023).

**Anti-inflammatory activity.** Anti-inflammatory Effects Inflammation is a fundamental biological response to injury or infection, but chronic inflammation is a contributing factor to many diseases, including arthritis, cardiovascular disease, and cancer. Luteolin's anti-inflammatory activity is well-documented in the literature, and it operates through several mechanisms. One of the key pathways it affects is the NF-κB signaling pathway, which plays a central role in regulating the expression of inflammatory cytokines and enzymes like COX-2 (cyclooxygenase-2) and iNOS (inducible nitric oxide synthase) (Lee *et al.*, 2020; Cho and Dua 2022). Luteolin has been shown to inhibit the activation of NF-κB, thereby reducing the expression of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β. This makes luteolin a promising agent for managing chronic inflammatory conditions such as rheumatoid arthritis, inflammatory bowel disease (IBD), and asthma. Additionally, luteolin has been found to down regulate other pro-inflammatory pathways, including those involving the MAPK (mitogen-activated protein kinase) family and the JAK/STAT (Janus kinase/signal transducer and activator of transcription) signaling cascade (Lee *et al.*, 2020).

**Anticancer Activity.** The anticancer properties of luteolin have garnered significant attention due to its ability to target multiple hallmarks of cancer. Luteolin inhibits cancer cell proliferation, induces apoptosis (programmed cell death), and suppresses metastasis (the spread of cancer to other tissues). It achieves these effects by modulating various signaling pathways involved in cell survival, growth, and migration. A recent publication by Cho and Dua (2022) provides an overview of luteolin's molecular mechanisms in cancer therapy, highlighting its role in modulating signaling pathways involved in cell cycle regulation and apoptosis. Luteolin has been shown to inhibit key oncogenes such as the AKT and ERK (extracellular signal-regulated kinase) pathways, which are crucial for cell survival and proliferation in many cancer types. Additionally, luteolin induces cell cycle arrest at the G1/S phase transition, preventing cancer cells from progressing through the cell cycle. New findings suggest that luteolin may also enhance the efficacy of conventional chemotherapeutic drugs by sensitizing cancer cells to apoptosis (Zhao *et al.*, 2021; Patel *et al.*, 2023). Moreover, luteolin suppresses the process of angiogenesis, the formation of new blood vessels that

supply tumors with nutrients, by inhibiting the expression of vascular endothelial growth factor (VEGF). By targeting multiple mechanisms involved in cancer progression, luteolin has the potential to serve as an adjunct to conventional cancer therapies, enhancing their effectiveness (Zhao *et al*., 2021).

## PHARMACOKINETICS AND BIOAVAILABILITY

Luteolin's therapeutic efficacy is significantly constrained by its low bioavailability, primarily due to its poor water solubility and rapid metabolism (Zhao *et al*., 2020). After oral administration, luteolin undergoes extensive first-pass metabolism in the liver and intestines, leading to reduced systemic availability (Zhao *et al.*, 2020). To overcome these challenges, recent studies have explored various strategies to enhance luteolin's bioavailability, including the use of nanoparticles, micelles, and liposomal formulations (Choudhary *et al.*, 2021). These approaches aim to improve luteolin's solubility, stability, and absorption, thereby prolonging its circulation time and enhancing its therapeutic potential.

Nanoparticle-based delivery systems have been developed to encapsulate luteolin, thereby increasing its solubility and protecting it from enzymatic degradation. For instance, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) have been utilized to enhance the dissolution rate and stability of luteolin, leading to improved intestinal permeability and prolonged systemic circulation time. Similarly, liposomal formulations, which involve encapsulating luteolin within phospholipid bilayer vesicles, have been shown to enhance its solubility, protect it from metabolic degradation, and facilitate controlled drug release (Choudhary *et al*., 2021). This approach not only increases luteolin's bioavailability but also allows for targeted delivery to specific tissues, thereby enhancing its therapeutic efficacy.

Micelle-based formulations represent another promising strategy to improve luteolin's bioavailability. By incorporating luteolin into micelles, which are self-assembled amphiphilic molecules, its solubility in aqueous environments is significantly enhanced. This facilitates better absorption in the gastrointestinal tract and protects luteolin from rapid degradation. Additionally, the use of self-emulsifying drug delivery systems (SEDDS) has been investigated to improve the oral bioavailability of luteolin. SEDDS are lipid-based formulations that form fine oil-in-water emulsions upon contact with gastrointestinal fluids, enhancing the solubilization and absorption of hydrophobic compounds like luteolin (Wang & Liu 2023). Furthermore, the formation of luteolin–phospholipid complexes, known as phytosomes, has been explored to improve its solubility and permeability. Phytosomes enhance luteolin's affinity for cell membranes, facilitating its absorption across the intestinal barrier and increasing its plasma concentration and half-life (Zhao & Liu 2021). Prodrug approaches, which involve chemically modifying luteolin to improve its solubility and metabolic stability, have also been investigated (Patel & Patel 2023). These prodrugs undergo enzymatic conversion in the body, releasing the active luteolin molecule in a controlled manner, thereby bypassing rapid metabolism and enhancing systemic circulation (Patel & Patel 2023).

## CONCLUSIONS

Luteolin is a naturally occurring flavonoid with significant pharmacological potential due to its diverse biological activities, including antioxidant, anti-inflammatory, anticancer, and neuroprotective properties. Its ability to modulate multiple molecular pathways makes it a promising candidate for the prevention and treatment of chronic diseases such as cancer, cardiovascular diseases, and neurodegenerative disorders. However, despite its broad therapeutic potential, luteolin’s clinical application is significantly hindered by its poor bioavailability, primarily due to its low water solubility, extensive metabolism, and limited systemic absorption. Recent advancements in drug delivery strategies have focused on improving luteolin's pharmacokinetic profile to enhance its bioavailability and therapeutic efficacy. Innovative approaches such as nanoparticle-based formulations, liposomes, micelles, self-emulsifying drug delivery systems (SEDDS), and phytosomes have demonstrated promising results in increasing luteolin’s solubility, stability, and absorption. These strategies not only enhance its systemic circulation but also enable targeted delivery, thereby optimizing its therapeutic potential. Additionally, prodrug formulations have emerged as an effective means to overcome rapid metabolism, ensuring sustained release and prolonged biological activity. Despite these advancements, further research is required to optimize luteolin-based formulations for clinical applications. Future studies should focus on developing multifunctional drug delivery systems that integrate various bioavailability enhancement strategies while ensuring safety, efficacy, and minimal side effects. Additionally, pharmacokinetic and clinical trials are essential to validate the effectiveness of these formulations in human subjects. As research continues to advance, luteolin holds great promise as a bioactive compound with the potential to revolutionize therapeutic strategies for various chronic diseases.

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**Conflict of Interest.** None.

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