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Review

GENERAL PROPERTIES, BIOSYNTHESIS, PHARMACOLOGICAL PROPERTIES, BIOLOGICAL ACTIVITIES AND DAILY USES OF LUTEOLIN

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ABSTRACT

Phenolic molecules are secondary metabolites that facilitate several biological processes. Secondary metabolites are non-nutritive substances that hold significant medicinal value. Our study combined the biological activities, general features, daily usage conditions, and biosynthesis of luteolin as reported in the literature. The literature review revealed that luteolin exhibits biological activities including antioxidant, antibacterial, anticancer, and anti-inflammatory properties. It was observed that it exerts effects on illnesses including cardioprotection, cholesterol regulation, neuroprotection, autistic spectrum disorders, gastrointestinal issues, obesity, insulin sensitivity, anxiety/depression, and arthritis. In this regard, luteolin was identified as a significant molecule for pharmacological applications.

KEYWORDS: Phenolic compounds, antioxidant, anticancer, luteolin.

1. Introduction

Secondary metabolites are molecules generated in natural items that lack nutritional value yet possess significant medicinal importance. A multitude of secondary metabolites is generated, particularly in plant species [1, 2]. These chemicals account for the biological functions of plants [3]. Numerous studies have demonstrated that plants exhibit various biological activities, including antioxidant, antimicrobial, anticancer, antiproliferative, antiaging, hepatoprotective, and DNA protective effects, attributable to their bioactive compounds [4-8]. In this context, assessing the potential qualities of bioactive substances is crucial for their application.

2. Luteolin and its properties

Luteolin is prevalent in consumable plants utilized in traditional medicine. Luteolin holds a significant position within the flavonoid category. Flavonoids, classified as secondary metabolites, are distinguished by their diphenylpropane (C6-C3-C6) structure [9, 10]. Luteolin is also referred to as tetrahydroxyflavone. Luteolin possesses a mostly planar $C_{15}H_{10}O_6$ structure, characterized by a dihedral angle between the pyrone ring system and the endocyclic atoms. A hydrogen connection exists between the carbonyl and hydroxy groups at C4 and C5. The crystal structures of hydroxyflavones encompass cirsimaritin, pacipodol, and 5-hydroxy-3,7,4-trimethoxyflavone [11]. Luteolin is commonly present in plants both in its pure form and as a derivative. Pure luteolin is prevalent in the families *Asteraceae, Simaroubaceae, Arecaceae, Lamiaceae, Mimosaceae, Asphodelaceae, Ranunculaceae, Ledocarpaceae, Begoniaceae, Geraniaceae, Scrophulariaceae, Brassicaceae, Moraceae, Apiaceae, Fabaceae, Capparaceae, Caesalpiniaceae, Colchicaceae, Leguminosae, Cynomoriaceae, Poaceae, Boraginaceae, Berberidaceae, Equisetaceae, Ginkgoaceae,*

Flacourtiaceae, *Clusiaceae*, *Balsaminaceae*, *Malvaceae*, *Lythraceae*, *Melastomataceae*, *Campanulaceae*, *Caprifoliaceae*, *Ochnaceae*, *Rubiaceae*, *Bignoniaceae*, *Papaveraceae*, *Plantaginaceae*, *Anacardiaceae*, *Labiatae*, *Combretaceae*, and *Zosteraceae* [12].

3. Biosynthesis of luteolin

Flavone synthases catalyze the oxidation of flavanones to flavones by introducing a double bond between carbon atoms 2 and 3 of the C ring. Flavonoids in plants are derived from phenylpropanoids. A membrane-bound cytochrome P450-dependent mono-oxygenase, flavone synthase II, is present in numerous plant families, whereas the soluble dioxygenase flavone synthase I has thus far been identified exclusively in members of the *Apiaceae* family. The three stages that transform L-Phe into 4-coumaroyl-CoA constitute a mechanism universal to all flavonoids. The three prevalent stages are facilitated by 4-coumaroyl CoA ligase, phenylalanine ammonia lyase, and cinnamate 4-hydroxylase [13, 14]. The closure of heterocycle C is catalyzed by chalcone isomerase. Luteolin (a flavone), eriodictyol (a flavanone), and naringenin, the precursor of apigenin, are synthesized. Flavone synthase oxidoreductase is essential for the synthesis of apigenin. Apigenin subsequently serves as the substrate for flavonoid 3-hydroxylase, facilitating the synthesis of luteolin [15]. The production of luteolin in certain microorganisms, such as *Streptomyces albus* and *Escherichia coli*, requires six enzymes: TAL, 4CL, CHS, CHI, FNS, and F30H [15]. The main recognized derivatives of luteolin are cynaroside (luteolin 7-O-glucoside), orientin (luteolin 8-C-glucoside), and isoorientin (luteolin 6-C-glucoside) [12].

4. Pharmacological and Therapeutical effects

Many studies have been conducted in the literature on the pharmacological and therapeutic effects of luteolin. The findings are shown in figure 1.

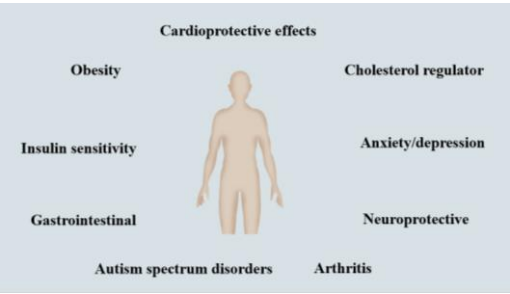

Fig 1. Pharmacological and therapeutic effects of luteolin

A literature review of luteolin revealed studies from China, Japan, and Taiwan indicating that luteolin preserves cardiac function following ischemia/reperfusion injury in rats, diminishes infarct size and cardiomyocyte apoptosis, enhances FGFR2 and LIF expression, activates the PI3K/Akt pathway, significantly lowers serum triglycerides, total cholesterol, LDL, malondialdehyde, creatine kinase, lactate dehydrogenase, and myocardial CTGF, inhibits cholesterol absorption in human embryonic kidney 293T cells, and markedly reduces the incidence and duration of ventricular tachycardia and ventricular fibrillation, as well as mortality during myocardial ischemia [16-21]. Research undertaken in Germany, the United States, China, and South Korea indicated that luteolin inhibited the production of proinflammatory markers in microglia and induced extensive alterations in the microglial transcriptome, with over 50 differently expressed transcripts. It markedly enhanced secondary brain damage, encompassing neurological impairments, cerebral water content, and neuronal death resulting from traumatic brain injury. It possesses the capacity to mitigate neuroinflammation in Alzheimer's disease. It can regulate amyloid-beta accumulation. Among children with autism, 50% exhibited eye contact and attention, 25% demonstrated social interaction, and around 10% experienced a resumption of speech. Serum levels of IL-6 and TNF were markedly diminished relative to baseline levels by the conclusion of the treatment period [22-28]. Studies conducted in Taiwan, China and the United States have shown that luteolin inhibits the growth of Helicobacter pylori by arylamine N-acetyltransferase (NAT) and 2-Aminofluorene (AF) or P-aminobenzoic acid (PABA), and significantly reduces colon damage in ulcerative colitis (UC) mice. It has been shown to improve glucose metabolism in mice fed a high-fat diet (HFD). It has also been reported to significantly improve insulin resistance in mice fed a high-fat diet (HFD) and to significantly increase peroxisome proliferator-activated receptor γ (PPARγ) transcriptional activity in 3T3-L1 adipocytes [29-33]. Various studies in Italy have documented the impact of luteolin on depression-like behavior across multiple paradigms, including open field, novelty suppressed feeding, forced swim test, and elevated plus maze. Additionally, luteolin ameliorated clinical manifestations of erosive hindpaw arthritis between days 26 and 35 and enhanced the histological condition of the joint and paw [34, 35].

5. Biological activities

Bioactive compounds are secondary metabolites responsible for many biological activities [36]. In our study, biological activity studies of luteolin reported in the literature were compiled. The findings are shown in Table 1 [37-81].

Table 1. Biological activities of luteolin [37-81].

Biological activities	Geographic regions	Ref.
Antioxidant, antimicrobial, anticancer, cytotoxic, anti-inflammatory, anti-allergic, antipruritic, anti-diabetic, antiviral, acetylcholinesterase, hepatoprotective, DNA protective	USA, Poland, South Korea, India, Taiwan, Portugal, China, Japan, South Africa, Canada, Thailand, Scotland, Saudi Arabia, Brazil, Slovakia	[37-81].

5.1. Antioxidant activity of luteolin

Antioxidants are crucial in mitigating the impact of free radicals. Free radicals are oxidizing agents generated from metabolic processes [82]. As the concentrations of these chemicals rise, cellular harm may ensue. Antioxidants contribute to mitigating and inhibiting these effects [83]. Nevertheless, in certain instances, this equilibrium tilts towards oxidant chemicals, resulting in oxidative stress. Oxidative stress can lead to severe diseases in humans, including cancer, cardiovascular problems, Alzheimer's disease, Parkinson's disease, diabetes, and multiple sclerosis [84-86]. Supplemental antioxidants can effectively mitigate the potential adverse effects of oxidant substances. Researchers concentrated on novel sources of antioxidants. Our study collated

literature on the antioxidant properties of luteolin. A study conducted in the USA examined the antioxidant properties of luteolin using H_2O_2, O_2^{*-}, and lipid peroxidation assays. Upon conclusion of the study, the LC_{50} values obtained from the tests were documented as 6, 5.2, and 45 µM, respectively [37]. A study in Poland examined the catechol O-methylation results for the pH-dependent radical scavenging characteristics of luteolin through both experimental and theoretical methods. The study's comparison of pKa values with pH-dependent TEAC profiles indicated that O-methylation influences TEAC and alters the impact of pH variations on radical scavenging activity by affecting the pKa for deprotonation [45]. A study conducted in the USA examined luteolin's capacity to inhibit the Fenton reaction associated with the iron-ATP complex. The study revealed that luteolin hindered the voltammetric catalytic wave linked to the iron-ATP complex in the presence of H_2O_2. Luteolin was discovered to entirely inhibit the catalytic wave of the iron-ATP/H_2O_2 system upon achieving a minimal iron-ATP ratio of 1.5:1. Furthermore, the study indicated that luteolin could inhibit the Fenton reaction [40]. A study in South Korea examined the impact of a luteolin derivative derived from *Sasa borealis* leaves on NF-E2-related factor-2 (Nrf2), a transcription factor that governs antioxidant and phase II detoxification genes. The study indicated that isoorientin (luteolin 6-C-glucoside) upregulated and activated Nrf2, demonstrating protective efficacy against oxidative damage induced by reactive oxygen species in HepG2 cells [55]. A study in India administered 0.2 mg/kg body weight/day of luteolin orally to rats over a duration of 15 days. The study reported a reduction in lipid peroxidation levels, conjugated dienes, lipid hydroperoxides, and enzymatic antioxidant activities of superoxide dismutase (SOD) and catalase (CAT). Additionally, elevated levels of glutathione and glutathione-dependent enzymes, including reduced glutathione (GSH), glutathione peroxidase (GPx), glutathione-S-transferase (GST), and glutathione reductase (GR), as well as non-enzymatic antioxidants, were observed [48]. A study in Taiwan examined the antioxidant properties of isoorientin-6″-O-glucoside, a luteolin derivative extracted from *Gentiana arisanensis*. The investigation indicated that isoorientin-6″-O-glucoside had greater potency than Trolox, probucol, and butylated hydroxytoluene (BHT) in neutralizing the stable free radical DPPH [39]. A study in India indicated that luteolin elevated the incidence of aberrant crypt foci (ACF), thiobarbituric acid reactive substances (TBARS), and hydroxy radical ($OH^{\cdot}$) levels in the plasma and colon of rats, while diminishing glutathione (GSH) and vitamins C, E, and A [57]. A separate study in India examined the antioxidant status of orally administered luteolin in Swiss albino mice. The study reported a concurrent reduction in the levels of enzymatic antioxidants, including superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), glutathione peroxidase (GPx), and glutathione-S-transferase (GST), as well as non-enzymatic antioxidants [77].

5.2. Antimicrobial activity of luteolin

In recent years, the struggle against microbial infections has intensified [87]. The primary factors contributing to this phenomenon include the rise of resistant microbes resulting from the indiscriminate use of antimicrobial agents [88, 89]. Researchers have concentrated on the identification of novel antimicrobial agents [90]. The potential adverse effects of synthetic medications have prompted researchers to explore natural antibacterial agents [91, 92]. This study aggregated literature on the antibacterial properties of Luteolin. A study in China examined the antibacterial properties of luteolin derivatives against *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas fluorescens*, and *Escherichia coli*. The study indicated that the minimum inhibitory concentration (MIC) values of the strains utilized ranged from 1.562 to 6.25 µg/mL [59]. A study in Japan examined the antibacterial effects of luteolin extracted from *Scutellaria barbata* against methicillin-resistant *Staphylococcus aureus*. The study indicated that the MIC value ranged from 62.5 to 125 µg/mL [41]. A study in Portugal indicated that luteolin and its derivatives derived from the 'alcaparra' table olive exhibited inhibitory effects at a low concentration of 0.05 mg/mL against strains of *Bacillus cereus, B. subtilis, Staphylococcus aureus*, *Escherichia coli, Klebsiella pneumoniae*, *Candida albicans*, and *Cryptococcus neoformans*, with the exception of *Pseudomonas aeruginosa* [52]. A study in South Africa reported that the highest minimum inhibitory concentration (MIC) value of luteolin, isolated from *Anredera cordifolia, Elaeodendron transvaalense*, *Elephantorrhiza burkei, Senna petersiana, Terminalia sericea*, and *Rauvolfia caffra*, was 1.0 mg/mL against strains of *Bacillus cereus, B. pumilus, B. subtilis, Staphylococcus aureus, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa*, *Serratia marcescens*, and *Enterobacter aerogenes* [49]. A study in Canada examined the antibacterial efficacy of luteolin against methicillin-resistant *Staphylococcus aureus* (MRSA), *Klebsiella pneumoniae*, and *Staphylococcus epidermidis*. The study found a zone of inhibition value of 10.5-11.5 mm only against methicillin-resistant *Staphylococcus aureus* (MRSA) [42]. A separate study in Japan indicated that the MIC value of luteolin against *Streptococcus mutans, S. sobrinus, S. salivarius, S. oralis, S. mitior, S. sanguis,* and *Porphyromonas gingivalis* ranged from 12.5 to 800 µg/mL [43]. A study in China revealed the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values of luteolin against *Staphylococcus aureus* and *Listeria monocytogenes* to be 16-64 µg/mL and 32-128 µg/mL, respectively [81]. A study in Portugal reported the LC25 value range of luteolin derivatives against *Bacillus cereus*, *Bacillus subtilis, Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Candida albicans,* and *Cryptococcus neoformans* to be 0.12-0.73 mg/mL [53].

5.3. Anticancer activity of luteolin

In recent years, the incidence of cancer cases has markedly risen. Numerous adjunctive products are utilized for supportive therapies in cancer patients [93]. Our study gathered the anticancer properties of luteolin as described in the literature. A study in South Korea examined the anticancer efficacy of luteolin on the lung cancer (H292) and head and neck (SCCHN, Tu212) carcinoma cell lines. The study revealed that the LC50 value of nano-luteolin in Tu212 cells was 4.13 µmol/L, while that of luteolin was 6.96 µmol/L. The LC50 value of luteolin was reported as 15.56 µmol/L, while that of nano-luteolin was 14.96 µmol/L in H292 cells [74]. A study in China determined that luteolin enhances TRAIL-induced cytotoxicity in A549 and HeLa cells, correlating with enhanced apoptotic activation

[67]. A study in China reported that luteolin enhances the sensitivity of cancer cells to therapeutic cytotoxicity by inhibiting cell survival pathways, including phosphatidylinositol 3'-kinase (PI3K)/Akt, nuclear factor kappa B (NF-κB), and X-linked inhibitor of apoptosis protein (XIAP), while also activating the tumor suppressor p53 [56]. A separate study in China demonstrated that luteolin diminished the viability of SMMC-7721 cells in a time- and dose-dependent manner, induced G0/G1 phase arrest, and flow cytometry analysis along with Hoechst 33342 staining revealed a significant increase in the number of apoptotic cells following luteolin treatment. Furthermore, qRT-PCR and western blotting studies indicated that luteolin therapy elevated caspase 8 levels and reduced bcl-2 levels in mRNA [79]. A study in Thailand examined the anticancer effects of luteolin on human CCA, KKU-M156 cells. The study found LC50 values of 10.50 and 8.7 Mm for CCA cells at 24 and 48 hours, respectively, and reported that luteolin administration inhibited interleukin-6 (IL-6)-induced JAK/STAT3 activation in KKU-M156 cells [70]. A study in South Korea examined the inhibitory effect of luteolin on the growth of MDA-MB-231 estrogen receptor (ER) negative breast tumors, utilizing both in vitro and in vivo methodologies. The study revealed that it inhibited 3H thymidine incorporation, signifying cell growth suppression, which was associated with cell cycle arrest and apoptotic activity in the G2/M and S phases [62]. A study in India indicated that the LC_{50} values of luteolin in human immortalized keratinocytes (HaCaT) and human melanoma (A375) cells were 37.1 and 115.1 µM, respectively [68]. A study in India reported that luteolin reduced the frequency of tumors in induced mammary carcinogenesis in Wistar rats and dramatically decreased tumor volume without altering the total body weight of the subjects [51]. A study in India demonstrated that 100 µg/mL luteolin exerted a cytotoxic effect on hepatocellular carcinoma (HCC) with 48.23% inhibition [72]. A study in Scotland showed luteolin displaying a negligible protective effect against TNF cytotoxicity in L-929 tumor cells [38]. A study in Taiwan revealed that luteolin treatment elevated the amounts of apoptotic proteins and activated caspase 9 and 3, which co-cleaved poly-ADP-ribose polymerase (PARP). Combination therapy with luteolin and paclitaxel enhanced the cytotoxic efficacy of paclitaxel in SCC-4 cells, whereas sustained luteolin administration inhibited the formation of xenograft tumors in nude mice [58]. A study conducted in China showed that luteolin pretreatment suppressed apoptosis and augmented the production of heme oxygenase-1 (HO-1). Furthermore, the study indicated that it enhanced the binding of Nrf2 to the antioxidant response element, facilitating an adaptive survival response to oxidative cytotoxicity induced by H_2O_2 [66]. A study in the USA shown that luteolin suppressed NF-κB suppression and augmented JNK activity, while significantly diminishing the synergistic cytotoxicity associated with TNF co-treatment [54]. A study conducted in China suggested that luteolin may reduce UPEC-induced cytotoxicity in human bladder epithelial cell lines, particularly T24 cells, with the inhibitory impact of luteolin on UPEC-induced cytotoxicity confirmed using ethidium bromide/acridine orange staining [75]. A study in Japan indicated that luteolin is efficient against human lung embryonic fibroblasts (TIG-1) and human umbilical vein endothelial (HUVE) cells [49]. A study in China showed the cytotoxic LC_{50} value of luteolin on the lung carcinoma cell line (A549) to be 40.2 µM [60].

5.4. Anti-inflammatory activity of luteolin

A study in Japan demonstrated that luteolin extracted from *Perilla frutescens* suppresses ear edema [44]. A study in South Korea indicated that luteolin derived from *Perilla frutescens* inhibits the secretion of inflammatory cytokines, including interleukin-1ß (IL-1ß) and tumor necrosis factor-α (TNF-α), from human mast cells (HMC-1) stimulated with a single dose of phorbol myristate acetate and calcium ionophore A23187 [73]. A distinct investigation conducted in Japan demonstrated a significant reduction of acute paw edema caused by carrageenan [61]. A study conducted in South Korea shown that luteolin and its derivatives significantly suppressed nitric oxide production and the expression of inducible nitric oxide synthase protein in RAW 264.7 cells [71]. A study in China shown that luteolin protected mice from severe acute pancreatitis (SAP) by enhancing HO-1 levels and suppressing the activation of the NF-κB pathway in an anti-inflammatory manner [78]. A study in Saudi Arabia indicated that the luteolin-treated group (50 mg/kg, orally, daily) showed enhanced release and expression of proinflammatory cytokines (tumor necrosis factor alpha and interleukin-1 beta), inducible nitric oxide synthase, and nuclear factor kappa B in response to liver damage caused by lead acetate (PbAc) exposure in male Wistar rats [80]. A study from South Korea shown that luteolin alleviated lipopolysaccharide (LPS)-induced inflammation more effectively than luteolin-7-O-glucoside, possibly due to differential activation of NF-κB/AP-1 [69]. A Brazilian investigation indicated that luteolin effectively inhibited hypertonicity-induced secretion of the proinflammatory interleukin-8 from human corneal epithelial cells and restored reductions in transepithelial electrical resistance [65]. A study conducted in South Korea shown that luteolin significantly suppressed the differentiation of both bone marrow mononuclear cells and Raw264.7 cells into osteoclasts [62].

5.5. Other activities of luteolin

A study in Japan indicated that luteolin derived from *Perilla frutescens* inhibits oxazolone-induced allergy edema [44]. A study in South Korea revealed that luteolin derived from *Perilla frutescens* dramatically diminished histamine release from rat peritoneal mast cells activated by compound 48/80, a powerful histamine liberator. Luteolin treatment was found to dramatically suppress scratching behavior and vascular permeability triggered by pruritogens as compound 48/80 or serotonin in ICR mice [73]. A study conducted in South Korea revealed that luteolin and its derivatives demonstrated the highest inhibitory efficacy against PTP1B and rat lens aldose reductase, with an LC50 value of 6.70 µM for anti-diabetic effects [71]. A study in China found that the LC50 value of luteolin against the Japanese encephalitis virus (JEV) was 4.56 µg/mL [77]. A research in Japan shown that luteolin extracted from *Rosmarinus officinalis* increased acetylcholinesterase (AChE) activity, an indicator of neuronal growth, and raised total choline and acetylcholine concentrations [64]. A study in China indicated that luteolin derivatives derived from Ixeris chinensis inhibited the elevation of glutamic pyruvic transaminase (GPT), glutamic oxaloacetic transaminase (GOT), malondialdehyde (MDA), and 8-hydroxydeoxyguanosine (8-OHdG), while also preventing the reduction of GSH in a dose-dependent manner. It was additionally discovered

to mitigate hepatocyte injury in vitro [46]. A study in Slovakia indicated that 20 µM luteolin had DNA protective effects against H_2O_2 in human melanoma HMB-2 cells [47].

6. Daily use and absorbation of luteolin

Luteolin, a flavonoid, is prevalent in various plants and fruits, including apples, carrots, artichokes, radishes, mint, broccoli, peppers, spinach, beans, chives, thyme, cauliflower, tea, cabbage, and celery (Figure 2). The daily consumption of flavonoids has been documented to range from 8.88 to 47.44 mg/day [18, 94, 95]. A research study in the Netherlands indicated that the mean daily consumption of mixed flavonoids was 23 mg [96]. Other investigations indicated that the average daily intake of various vegetables and fruits containing luteolin ranged from 0.01 to 0.20 mg/day or 0.0349 to 0.698 µmol/day [97]. A separate study found that the average luteolin intake associated with sage eating was 1.32 µg/day [98]. Flavonoids are absorbed either in their free form or by being converted into a glycosylated form. A portion of the flavonoid luteolin is absorbed, while 6.6% is excreted in urine and 31.3% in feces [99, 100].

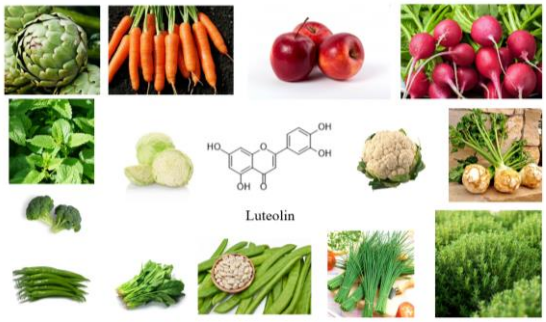

Fig 2. Luteolin sources

7. Conclusions

In our study, a comprehensive literature review of luteolin was conducted. As a result of the literature review, luteolin may play an important role in the prevention and treatment of global health problems. It was observed that luteolin has biological activities such as antioxidant, anticancer, antimicrobial, and anti-inflammatory. In this context, although it is seen that it has biological activity, the mechanisms of action that affect human health should also be considered. As a result, it is recommended to focus on pharmacological studies. It is also recommended to consider the use of luteolin in individuals receiving treatment with traditional treatment methods. Addition, it is recommended to increase the dose studies and determine the most appropriate dose level. As a result, it is thought that luteolin may be an important pharmacological compound.

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