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A Review on Flavonoid Luteolin: Phytochemistry, Pharmacognosy and Pharmacological activities

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Abstract

Background:

Natural products are secondary metabolites produced and used by organisms for defending or adapting purposes. Historically, plants and their components have been widely used since ancient times for the treatment of various ailments.

Objectives:

This paper uses recent research findings with a broad range of study models to comprehensively summarize the phytochemistry, pharmacognosy and pharmacological activities of Luteolin (LTL) reported to date.

Methodology:

Articles published in scientific journals by authors on LTL were analyzed for the study.

Results:

LTL has been known to play a wide range of pharmacological functions such as anticancer, anti-inflammatory, antioxidant, antiviral, hepato and neuroprotective properties.

Conclusion:

LTL plays several pharmacological processes. Although scientists have strongly reported the important functions of LTL, we conclude by emphasizing the further use of laboratory experiments to extend its application scope.

Keywords: Luteolin, Phytochemistry, Pharmacognosy, Pharmacology

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1. Introduction

Since ancient times, humans have used natural products, such as plants, animals, microorganisms, and marine organisms, in medicines to alleviate and treat diseases. (1,2) The World Health Organization (WHO) estimates that 80% of the population of some Asian and African countries presently use herbal medicines for some aspect of primary health care. (3) Plants have the ability to synthesize a wide variety of chemical compounds that are used to perform important biological functions and to defend against attack. (4) Natural products with diverse chemical scaffolds have been recognized as an invaluable source of compounds in drug discovery and development. (5) It has been estimated that approximately over half of the pharmaceuticals in clinical use today are derived from natural products. Some natural product-derived drugs that are a hallmark of modern pharmaceutical care include quinine, theophylline, penicillin G, morphine, paclitaxel, digoxin, vincristine, doxorubicin, cyclosporine and vitamin A among many other examples. (6) These natural plants and their products have been used as traditional healers for the treatment of fever, especially malarial fever, dysentery, cancer, asthma, hypertension, diabetes, antiinflammatory, antibacterial activity, antistress, growth promoters, appetiser and tonics. (7) The dominant source of knowledge of natural product uses from medicinal plants

is a result of man experimenting by trial and error for hundreds of centuries through palatability trials or untimely deaths, searching for available foods for the treatment of diseases. (8) *Many researches worldwide are focusing on natural products* for the discovery of new compounds.

Luteolin (3', 4', 5, 7-tetrahydroxyflavone) has been identified as commonly present in plants. It belongs to a group of naturally occurring compounds called flavonoids that possess substantial characteristics that can be exploited for the development of therapeutic agents targeting several chronic diseases. They have been seen to exert a wide range of pharmacological effects, such as anti-oxidant, anti-tumor, anti-viral, anti-allergic, anti-inflammatory, and anti-viral effects. These protective biological properties are mostly due to the phenolic structure of these flavonoids. (9) Here our aim is to provide a deeper understanding of knowledge regarding LTL and its phytochemistry, pharmacognosy and pharmacology which will be valuable for the scientists working in the field of natural compounds.

2. Phytochemistry

2.1. Chemical Structure

Belonging to the flavone group of flavonoids, luteolin has a C6-C3-C6 structure and possesses two benzene rings (A, B), a third, oxygen-containing (C) ring, and a 2−3 carbon double bond [Figure 1]). Luteolin also possesses hydroxyl groups at carbons 5, 7, 3', and 4' positions. Chemically it is 3', 4', 5, 7-tetrahydroxyflavone. (11)

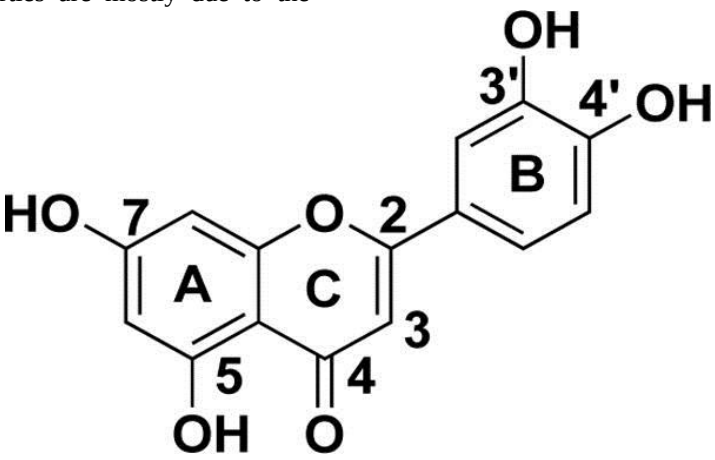

Figure 1. Chemical structure of Luteolin

2.3. Phytochemical testing

All the prepared extracts viz. methanol, ethanol, chloroform and dichloromethane showed the presence of flavonoids by Shinoda test. (12)

2.4. Structure activity relationship

The hydroxyl moieties and 2−3 double bond are important structure features in luteolin that are associated with its biochemical and biological activities. (13) As in other flavonoids, luteolin is often glycosylated in plants, and the glycoside is hydrolyzed to free luteolin during absorption and some portion of luteolin is converted to glucuronides when passing through the intestinal mucosa. Luteolin is heat stable and losses due to cooking are relatively low. (14-16)

2.5. Extraction of luteolin

Using four different extraction techniques (maceration, soxhlet, reflux and ultrasound assisted extraction), authors extracted LTL from the leaves of *Vitex negundo* L. Their results indicate that varying amount of extract yields was obtained with different solvents and extraction techniques. The maximum and minimum yield for ethanol extract (14.5% and 5.2%) were obtained by soxhlet and UAE techniques respectively, and the yield of methanol extract was found to be the highest by UAE technique. They concluded that reflux technique using methanol is better than the other extraction techniques and should be preferred for the extraction and isolation of luteolin from *V. negundo* leaves extract in research labs or industries. (11)

2.6. Quantitative estimation of luteolin by HPLC method

Quantification of different extracts of *V. negundo* L. through HPLC revealed that methanol is the best solvent for the extraction of luteolin. Luteolin content in methanol extract obtained through maceration, soxhelation, reflux and UAE techniques was found to be 1.020%, 1.075%, 6.340% and 0.640% respectively. Moreover, among various techniques employed for extraction and isolation of luteolin, reflux technique was found to be the most efficient. The results indicated that methanol is the most suitable solvent for luteolin extraction. (11) Four (4) markers such as eugenol, luteolin, ursolic acid, and oleanolic acid were quantified from the leaf of green and black varieties of *Ocimum sanctum* using HPLC with densitometry. The methods were found to be precise, with relative standard deviation (RSD) values for intraday analyses in the range of 0.77 to 1.29%, and for interday analyses in the range of 0.73 to 0.96% for luteolin. Instrumental RSD values were 0.39. (17) However, satisfactory recoveries in the range of 83.2% -89.1% with RSD ranging from 2.2% to 4.6% were achieved and thermoregulated extraction method was favorable for automated boronate affinity extraction, preventing degradation of the target and avoiding acidic elution for breaking Wulff-type boronate sites. (18)

3 Pharmacognosy

3.1. Natural sources

Luteolin, as a common flavonoid is abundantly present in many fruits, vegetables, and medicinal herbs [Table 1]. It has been extracted from several plants, such as broccoli, pepper, thyme, parsley, celery, and rosemary. (19)

Table 1. Plants containing *Luteolin* as an important constituent with its biological properties

Botanical name of the plant	Illustrating image of the plant	Common name	Biological activities	Refs.
Apium graveolens		Celery	Antioxidant Neuroprotection Hypolipidemic, Hypoglycemic, Anti-platelet aggregation Antiadhesive activity Anti-depression Larvicidal and mosquito repellent activity Hepatoprotective activity Anticancer activity Antidiabetic activity Anti-inflammatory activity Antimicrobial activity Analgesic Antiulcer Anti-spasmolytic Anti-infertility Antiplatelet Hypocholesterolemic Cardiotonic	(20-36)
Brassica oleracea		Broccoli	Antioxidant Anti-inflammatory Cancer chemopreventive agent	(37, 38)
Piper nigrum		Pepper	Antioxidant Anticancer Antidiabetic Anti-inflammatory, Immunomodulatory, analgesic, anticonvulsant, neuroprotective, anti-asthmatic, anti-carcinogenic, anti-ulcer, and anti-amoebic properties	(39, 40)
Thymus vulgaris		Thyme	Antiseptic	(41)
Allium cepa		Onion	Antioxidant Immunological biomarker Antidiabetic Macrophage activation inhibitor	(42, 43)

Daucus carota subsp. sativus		Carrots	Nephroprotective Antioxidant and hepatoprotective Glucose uptake improver cytoprotective Anti-angiogenic Antifungal	(44-47)
Chrysanthemum indicum		Mums or chrysanths	Anti-inflammatory Antiobesity NLRP3 and AIM2 inflammasome activation inhibitor Antibacterial, antiviral, anti-oxidant and immunomodulatory Anti-adipogenetic Natural skin-whitening agent Apoptotic	(48-52)
Malus domestica		Apple	Antibacterial α-Glucosidase Inhibitor Antioxidant Antimicrobial	(53-55)
Brassica napobrassica		Kohlrabi	Antioxidant Proapoptotic potential	(56)
Cynara scolymus		Artichoke	Antioxidant Hypolipidemic Anti-hyperglycemic Liver protective effect	(57-60)
Lactuca sativa		Red leaf lettuce	Phytogenic acaricide Antioxidant Anti-inflammatory	(61, 62)
Cichorium intybus var. intybus		Chicory greens	Antioxidant Antifungal	(63, 64)
Cucurbita maxima		Pumpkin	Urinary Disorder improver Antidiabetic Anti-obese potential	(65-67)

Capsicum annuum		Green hot chili pepper	Cardio protective, antilithogenic, antiinflammatory, analgesia, thermogenic	(68)
		Serrano pepper	Antioxidant	(69)
Cichorium intybus var. foliosum Endive		Radicchio	Antiinflammator	(70)

4. Pharmacology

Anti-inflammatory effects

Inflammation usually occurs when infectious microorganisms such as bacteria, viruses or fungi invade the body, reside in particular tissues and/or circulate in the blood. It may happen in response to processes such as tissue injury, cell death, cancer, ischemia and degeneration. Among the different biological activities of natural plant products that have been published until now, anti-inflammation is one of the most reported effects. (71-74)

Chronic pharyngitis is characterized as a common inflammation of the pharyngeal mucosa, and anti-inflammatory medications are the common treatment to relieve it.

Polysaccharides from Citrus grandis (PCG) associate with luteolin suppress the productions of pro-inflammatory cytokines interlukin-6 (IL-6), interlukin-12 (IL-12) and tumor necrosis factor alpha (TNF-α) in macrophages. Luteolin promotes macrophage M2 polarization by enhancing expressions of arginase (Arg1) and mannose receptor C type 1 (Mrc1). PCG with luteolin suppress nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation and interferon regulatory factor 1 (IRF1), interferon regulatory factor 5 (IRF5) expression. PCG together with luteolin relieves chronic pharyngitis by anti-inflammatory via suppressing NF-κB pathway and the polarization of M1 macrophage. (75)

Authors investigated the anti-inflammatory effects of luteolin and tangeretin in combination. Their results showed that combination produced synergistic inhibitory effects on LPS-stimulated production of nitric oxide (NO), caused stronger suppression on the LPS-induced overexpression of proinflammatory mediators, such as prostaglandin E2 (PGE2), interleukin (IL)-1β, and IL-6 than luteolin or tangeretin alone. Immunoblotting and Real-Time PCR analyses showed that luteolin and tangeretin combination significantly decreased LPS-induced protein and mRNA expression of inducible nitric oxide synthase and cyclooxygenase-2. (76)

Anticancer effects

Cancer is a severe metabolic syndrome and is one of the leading causes of death regardless of developments in the tools of disease diagnosis, treatment and prevention measures. It is one of the principal causes of mortality and morbidity around the globe and the numbers of cases are constantly increasing estimated to be 21 million by 2030. It is a frightful disease and represents one of the biggest health-care issues for the human race and demands a proactive strategy for cure. Plants are reservoirs for novel chemical entities and provide a promising line for research on cancer. (77-80) Luteolin, found in different plants such as vegetables, medicinal herbs, and fruits, acts as an anticancer agent against various types of human malignancies such as lung, breast, glioblastoma, prostate, colon, and pancreatic cancers. It also blocks cancer development in vitro and in vivo by inhibition of proliferation of tumor cells, protection from carcinogenic stimuli, and activation of cell cycle arrest, and by inducing apoptosis through different signaling pathways. Luteolin can additionally reverse epithelial-mesenchymal transition through a mechanism that involves cytoskeleton shrinkage, induction of the epithelial biomarker E-cadherin expression, and by down-regulation of the mesenchymal biomarkers N-cadherin, snail, and vimentin. Furthermore, luteolin increases levels of intracellular reactive oxygen species (ROS) by activation of lethal endoplasmic reticulum stress response and mitochondrial dysfunction in glioblastoma cells, and by activation of Endoplasmic reticulum stress-associated proteins expressions, including phosphorylation of eIF2α, PERK, CHOP, ATF4, and cleaved-caspase 12. (81) Additionally, Luteolin prevents tumor development by inactivating several signals and transcription

pathways essential for cancer cells. Its anticancer property is associated with the induction of apoptosis, and inhibition of cell proliferation, metastasis and angiogenesis. It sensitizes cancer cells to therapeutic-induced cytotoxicity through suppressing cell survival pathways such as phosphatidylinositol 3'-kinase (PI3K)/Akt, nuclear factor kappa B (NF-kappaB), and X-linked inhibitor of apoptosis protein (XIAP), and stimulating apoptosis pathways including those that induce the tumor suppressor p53. (82)

Lee J et al, 2019, (83) further investigated and compared differential effects of luteolin and its glycosides in MDA-MB-231 triple-negative breast cancer cells. They found that luteolin had both antimetastatic and cytotoxic effects on MDA-MB-231 cells and they conclude that it can be suggested as a potential candidate for breast cancer therapy.

In another study, authors performed a cell-based screening for the identification of Anoctamin 1 inhibitors as potential anticancer therapeutic agents for prostate cancer. At the end, the results showed that luteolin is a novel potent inhibitor of Anoctamin 1, potently inhibited ANO1 chloride channel activity with an IC50 value of 9.8 μM and did not alter intracellular calcium signaling in PC-3 prostate cancer cells. Furthermore, it strongly decreased protein expression levels of Anoctamin 1. (84) Additionally, Luteolin was found to upregulate miR-384 and downregulate PTN expressions both in colorectal cancer cells and tissues. They demonstrated that luteolin exerts anticancer effects against CRC cells by modulating PTN via miR-384 expression suggesting that PTN may serve as a promising candidate for therapeutic applications in CRC treatment. (85) Investigating the role of endoplasmic reticulum stress in anti-carcinogenic effects using p53-wild type and p53-null HCC cells treated with luteolin, the results suggest that luteolin-induced ER stress may exert anticancer effects in a p53-independent manner. (86) Other data indicated that luteolin inhibited the proliferation, migration and invasion of A375 cells, induced the apoptosis of A375 cells, reduced the expressions of MMP-2 and MMP-9 and increased the expression of TIMP-1 and TIMP-2. Furthermore, it inhibited the tumor growth of A375 cells in a xenograft mouse model. It acts as reducing agent of expressions of MMP-2 and MMP-9 through the PI3K/AKT pathway, and can be considered as a promising anti-cancer agent for the treatment of human melanoma. (87)

Several experimental results provide insight into the action and mechanism of luteolin that underlie the anticancer effects of luteolin on colon cancer by involving the upregulation of Nrf2 and its interaction with the tumor suppressor, (88) the inhibition of HCC growth in vitro and vivo, (89) and the safe therapeutic effect in diminishing breast cancer. (90) Accumulating studies confirmed that luteolin inhibited cell cycle progress, colony formation, proliferation, migration, invasion and promoted apoptosis *in vitro* and *in vivo*. (91) It may represent another natural product-derived therapeutic agent that acts against bladder cancer by upregulating p21 and inhibiting mTOR signaling, (92) and plays an important role in the treatment of human choriocarcinoma cells by inhibiting the PI3K/AKT/mTOR/SREBP cascade and expression of lipogenic genes. (93) It may be a valuable, non-toxic, naturally-occurring anticancer compound which may potentially be used to combat progestin-accelerated mammary tumors. The suppressive effects of luteolin on tumor incidence and volume, together with its ability to reduce VEGF and blood vessels, persisted even after treatment was terminated. (94) Luteolin also induced apoptosis in human liver cancer SMMC-7721 cells, partially via autophagy. Luteolin increased the number of intracellular autophagosomes, promoted LC3B-I conversion to LC3B-II, and increased Beclin 1 expression. Thus, luteolin could be used as a regulator of autophagy in Hepatocellular carcinoma treatment. (95)

Luteolin is beneficial for the treatment of cancer cells with highly expressed PTTG1 oncoprotein. PTTG1-knockdown cells with luteolin exposure presented a reduction of the apoptotic proteins and maintained higher levels of the anti-apoptotic proteins such as Mcl-1, Bcl-2 and p21, which exhibited greater resistance to apoptosis. Twenty genes associated with cell proliferation, such as *CXCL10*, *VEGFA*, *TNF*, *TP63* and *FGFR1*, were dramatically down-regulated in PTTG1-knockdown cells. The findings of the authors demonstrate that luteolin-triggered leukemic cell apoptosis is modulated by the differential expression of the PTTG1. (96) Accumulation of reactive oxygen species induced by luteolin plays a pivotal role in suppression of NF-kappaB and potentiation of JNK to sensitize lung cancer cells to undergo TNF-induced apoptosis. (97) However, heat processed significantly reduced the ability of luteolin to inhibit cell migration, cell invasion, and endothelial cell angiogenesis. (98) In addition, the flavonoid reduced the migration of glioblastoma cells by altering p-IGF-1R/PI3K/AKT/mTOR activation, and may have potential applications for chemoprevention in a clinical setting. (99) The results of another study indicated that luteolin may inhibit breast cancer cell growth by targeting human telomerase reverse transcriptase (hTERT). Nevertheless, the authors suggest that the mechanism of hTERT regulation by luteolin may justify further study regarding its potential as a therapeutic target for breast cancer treatment. (100)

The research of Ma L et al, 2015, (101) demonstrated that luteolin exerted an anticancer effect against NCI-H460 cells through Sirt1-mediated apoptosis and the inhibition of cell migration.

Antioxidant effects

Studies have showed that luteolin reduces high glucose -induced inflammatory phenotype and oxidative stress in H9C2 cardiomyocytes. Its mechanisms involved inhibition of nuclear factor-kappa B (NF-κB) pathway and the activation of antioxidant nuclear factor-erythroid 2 related factor 2 (Nrf2) signaling pathway. **Therefore** luteolin protects heart tissues in STZ-induced diabetic mice through modulating Nrf2-mediated oxidative stress and NF-κB-mediated inflammatory responses. (102) However luteolin protects the diabetic heart against ischemia/reperfusion injury by enhancing eNOS-

mediated *S*-nitrosylation of Keap1, with subsequent upregulation of Nrf2 and the Nrf2-related antioxidative signaling pathway. (103) Its antioxidant activity was extensively evaluated as affected by the 1,4-pyrone moiety and 3-OH group. (104) Acute and prolonged supplementation with mangiferin combined with luteolin enhances performance, muscle O_2 extraction, and brain oxygenation during sprint exercise, at high and low doses. (105) Human umbilical vein endothelial cells have been pre-treated with luteolin followed by hydrogen peroxide induction (H_2O_2) and the results showed that luteolin protected against H2O2-induced oxidative stress and ameliorated ROS and superoxide generation. Its treatment inhibited the H2O2-induced membrane assembly of NADPH oxidase subunits, which was further confirmed by specifically inhibiting NADPH oxidase. (106) A study was designed to assess the antioxidant potential of luteolin against benzo(a)pyrene-induced lung carcinogenesis in Swiss albino mice. The authors reported that oral administration of benzo(a)pyrene (50mg/kg body weight) to mice resulted in raised lipid peroxides, lung specific tumor markers such as carcinoembryonic antigen and neuron specific enolase with concomitant decrease in the levels of both enzymatic antioxidants such as superoxide dismutase, catalase, glutathione reductase, glutathione peroxidase and glutathione-s-transferase, and non-enzymatic antioxidants such as reduced glutathione, vitamin E and vitamin C. (107) Luteolin also protects against myocardial ischaemia/reperfusion injury through promoting signalling through the endogenous antioxidant enzyme, peroxiredoxin II, indicating the important beneficial role of this antioxidant system in the heart. (108)

Antiviral effects

Japanese encephalitis virus is one of the most important causative agents of viral encephalitis in humans. The disease leads to high fatality rates. Authors in the research of effective antiviral agents the disease found that luteolin has potent antiviral activity against Japanese encephalitis virus replication in A549 cells. It showed extracellular virucidal activity on the virus. (109) Dengue, a highly endemic infectious disease of the tropical countries, is rapidly becoming a global burden. It is caused by any of the 4 serotypes of dengue virus and is transmitted within humans through female Aedes mosquitoes. The disease varies from mild fever to severe conditions of dengue hemorrhagic fever and shock syndrome. (110) The authors found that luteolin inhibits the replication of four serotypes of dengue virus. It was found to reduce infectious virus particle formation. Biochemical interrogation of human furin showed that luteolin inhibited the enzyme activity and exhibited in vivo antiviral activity in mice infected with dengue virus. (111) A group of researchers infected several cell lines with two subtypes of influenza A virus and demonstrated that luteolin suppressed the replication of influenza A virus. Their assay indicated that this compound interfered with viral replication at the early stage of infection and suppressed coat protein I complex expression, which was related to influenza virus entry and endocytic pathway. (112)

Heart protective effects

Zhang X et al. (2017), (113) reported that Luteolin exhibited strong favorable cardioprotective effect on myocardial ischemia/reperfusion injury and this action might be related to the down-regulation of the TLR4-meidated NF-κB/NLRP3 inflammasome in vivo and in vitro. Additionally Yan Q et al. 2019, (114) proved that Luteolin improves heart preservation through inhibiting hypoxia-dependent L-type calcium channels in cardiomyocytes. In review, it has been demonstrated that the flavonoid has multiple cardio-protective effects. (115) In investigating the protective effect of luteolin on isolated rat heart in hypothermic preservation, research concluded that luteolin as a supplementation in cardiac preservation solution can significantly improve the hypothermic preservation effects on rat heart and have myocardial protection effect. (116)

Heart transplantation has been applied in the clinic as an optimal solution for patients with end stage cardiac failure. However, hypothermic preservation of the heart remains limited to 4-6 h and calcium accumulation over time is an important factor resulting in cell death. To provide longer and safer storage for donor hearts, it was demonstrated in previous study that luteolin used to treat cardiovascular diseases, inhibits cell death and L-type calcium currents during hypothermic preservation. The protective role of luteolin in modulating cardiomyocyte calcium cycling was investigated and the results demonstrated luteolin supplementation attenuated calcium overload over a 6 h preservation period. It also suppressed the accumulation of important regulatory proteins and enzymes for cardiomyocyte calcium circulation, mitochondria Ca^{2+} uniporter and calmodulin. (117)

Myocardial infarction, which is characterized by chamber dilation and left ventricular dysfunction, is associated with substantially higher mortality. Investigation on the effects of luteolin on post-infarction cardiac dysfunction and assay demonstrated that Luteolin up-regulated autophagy in the cardiomyocytes subjected to simulated myocardial infarction injury. Furthermore, it increased mitochondrial membrane potential, adenosine triphosphate content, citrate synthase activity and complexes I/II/III/IV/V activities in the cardiomyocytes subjected to simulated myocardial infarction injury. Its protective effects are associated with up-regulation of autophagy and improvement of mitochondrial biogenesis through Mst1 inhibition. (118)

Inorganic mercury is a toxic metal of worldwide concern, and causes serious cardiac injury. Against the injury, Luteolin significantly ameliorated cardiac histopathological damage, oxidative stress, and apoptosis induced by $HgCl_2$ in the rat heart. Furthermore, Luteolin evidently increased levels of phosphatidylinositol 3-kinase (PI3K), protein kinase B (AKT), and nuclear factor-erythroid-2-related factor 2 (Nrf2) and its downstream proteins, and inhibited NF-κB activation in the heart of rats treated by $HgCl_2$. (119)

Neurological impairments protection

Processes of synaptic plasticity, such as long-term potentiation, has been considered a cellular correlate of learning and memory and many neurological disorders accompanied by cognitive deficits exhibit abnormal synaptic function. The flavonoid luteolin has been found to enhance basal synaptic transmission and facilitate the induction of long-term potentiation by high frequency stimulation in the dental gyrus of rat hippocampus. Finally, the authors demonstrate that luteolin modulates long-term potentiation formation, and protects synapses from the detrimental effects of chronic cerebral hypoperfusion on long-term potentiation formation. (120)

Another experiment examined the neuroprotective potential of a Co-ultramicronized Palmitoylethanolamide /Luteolin in the Treatment of Cerebral Ischemia. At baseline and after 30 days of treatment, neurological status, impairment of cognitive abilities, the degree of spasticity, pain, and independence in daily living activities showed significant gains at study end. (121) However Luteolin has also been proven to exert neuroprotection in a variety of neurological diseases by lowering the intracellular reactive oxygen species level and increasing the neuron survival. (122)

5. Conclusion

The data summarized in this review suggest that Luteolin (LTL) exerts a variety of beneficial properties, including those as an anti-inflammatory, anticancer agent. This statement may still open new venues for therapeutic interventions. Nevertheless, further in vitro and in vivo investigations are required to explore fundamental issues in theory, research and practice about Luteolin (LTL) within the health sciences.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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