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Review Article

NANOENCAPSULATION OF LUTEOLIN: ENHANCING BIOAVAILABILITY AND MEDICINAL BENEFITS

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ABSTRACT

Luteolin is a naturally occurring chemical widely found in plants ranging from Bryophyta to Magnoliophyta. It can be obtained from several dietary sources such as carrots, olive oil, celery, spinach, oregano, and, fossils of some organisms such as *Celtis* and *Ulmus* dating back 36 to 25 million years. It is synthesized by the Shikimate pathway. The major qualities and therapeutic benefits of luteolin include cytoprotective abilities, Antioxidant, Anti-inflammatory, Anticancer, Antidepressant, Antidiabetic, Antiallergic, Reactive Oxygen Species Scavenging and High radical scavenging. The antioxidant and Reactive Oxygen Species scavenging activity of luteolin aids in treating and curing inflammatory skin processes. It has been proven to act as a therapeutic drug with a wide spectrum of scope in the prevention and treatment of a vast range of malignant and benign cancers, extending from bladder cancer to breast cancer and from oral cancer to glioblastoma, which is achieved by its anticancer, antioxidant properties and cytoprotective abilities. Apart from its anticancer properties, it has a great scope in the restoration from neuropsychiatric disease and high-level fatigue due to Long COVID syndrome-associated brain fog and Chemo fog. The poor solubility and low bioavailability of luteolin limit its use in food and medicine. Synthetic and Natural polymer-based delivery systems have been developed to improve its stability and bioavailability. This review will highlight recent research on its nanoencapsulation and provide more information on luteolin to help readers have a better grasp of the compound's medicinal benefits.

Keywords: Luteolin, Antioxidant, Anticancer, Anti-inflammatory, Flavonoid, Nanoencapsulation, COVID, Antidepressant, Neuroprotector, Anti-diabetic

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INTRODUCTION

For this comprehensive review, we conducted a thorough search of specialized databases covering the years 1977-2023, including renowned sources such as Elsevier and Pubmed. We utilized a range of targeted keywords, such as "Luteolin," "Luteolin anti-cancer activity," "Luteolin antioxidant," "Luteolin nanoencapsulation," and "Luteolin updated review," to ensure a comprehensive and thorough analysis. In addition, we also included articles from top-tier journals like Springer, reputable internet sources, and online publications from well-known journals such as International Journal of Agriculture and Life Sciences, Planta Medica, International Journal of Current Pharmaceutical Research, The Asian Journal of Pharmaceutical and Clinical Research, The International Journal of Pharma and Biosciences, and International Journal of Applied Pharmaceutics.

The great majority of chemical substances utilized daily are found in plants. As we are aware of the medicinal advantages that plants offer, the bioactive substances in them are being widely investigated in the past few decades to treat and prevent a variety of human ailments [1]. Flavonoids are polyphenols that have a significant part in protecting plant cells from ultraviolet (UV) irradiation, insects, and microorganisms [2]. Cell culture, animal, and human population research gives an idea that flavonoids are advantageous to both animal and human health [3]. Luteolin, also known as 3′,4′,5,7 - tetrahydroxyflavone, is a naturally occurring chemical that belongs to flavonoids, which are extensively distributed in the plant kingdom [2]. Luteolin belongs to the flavone group of flavonoids and has a C6-C3-C6 structure that contains two benzene rings, a third ring that contains oxygen, and a double bond between two and three carbon atoms fig. 1. It also has hydroxyl groups at carbons 3', 4', 5 and 7 [4]. The vast majority of luteolin's bioactivity is caused by the presence of a hydroxyl moiety at carbon positions of 3', 4', 5, and 7. Being mostly derived from fruits, vegetables, and other edible plant parts, luteolin is a flavonoid chemical that is widely distributed.

The biological importance of Luteolin compounds has been studied in recent decades, and these researches have revealed their anti-cancer, antioxidant, anti-inflammatory, and neuroprotective properties [5, 6]. The luteolin's pharmacological effects may be connected on a functional level. For example, luteolin's ability to reduce inflammation may be related to its ability to fight cancer. Luteolin's anticancer function is connected with initiating apoptosis, which involves DNA damage, redox regulation, and protein kinases in limiting cancer cell proliferation, reducing angiogenesis and metastasis. Furthermore, luteolin makes cancer cells more susceptible to medically induced cell toxicity by decreasing cell survival pathways and energizing the apoptotic pathways. Notably, luteolin may pass through the blood-brain barrier, making it useful for treating illnesses of the central nervous system, such as brain tumors [7].

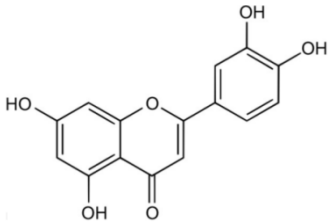

Fig. 1: Diagrammatic representation of luteolin compound

Sources of luteolin

Luteolin is a flavone that can be found in a variety of vegetables and medicinal plants [8]. Plants are the primary source of luteolin and its derivatives [9]. However, concentrations are often low when compared to other flavonols, such as quercetin or kaempferol [8]. It makes up a minimal proportion of our daily diet (less than 1 mg/d) when compared to other secondary plant substances [10]. Luteolin and its glycosides are found in many different plant families, including the Bryophyta, Pteridophyta, Pinophyta, and Magnoliophyta, and are widely distributed across the plant world

[9]. Some spices, such as thyme, sage, and parsley as well as wild carrots and, artichokes, contain significant amounts [8]. Carrots, peppers, celery, spinach, lettuce, olive oil, peppermint, thyme, rosemary, and oregano are all good sources of luteolin [8, 9]. Even while luteolin only makes up a small amount of the flavonoids found in food, it can be obtained in large quantities from peanut hulls and the plant *Reseda luteola L.*, which is being used as a dyeing agent because of its high luteolin concentration for thousands of years [11]. Even the fossils of the *Celtis* and *Ulmus* species, which date back 36 and 25 million years, respectively, attest to its existence [12].

SOURCES OF LUTEOLIN
Parsley
Thyme
Peppermint
Carrot
Artichoke
Rosemary
Pepper
Sage
Celery
Peanut hulls
Spinach
Olive oil
Wild carrots
Lettuce
Reseda luteola L
Oregano

Fig. 2: Sources of luteolin [8, 9, 11]

Biosynthesis of luteolin

Plants contain a diverse set of metabolic substances that let them perform basic processes and respond to different stimuli [13]. Phenyl propanoids are compounds derived from the phenylalanine amino acid that are involved in plant development, cellular metabolism, and biotic and abiotic stimuli [13]. The phenylpropanoid pathway follows the shikimate pathway, which has been investigated for decades [14]. Via the phenylpropanoid and flavonoid pathways, which branch off from the principal secondary metabolite pathway, the Luteolin molecule is synthesized.

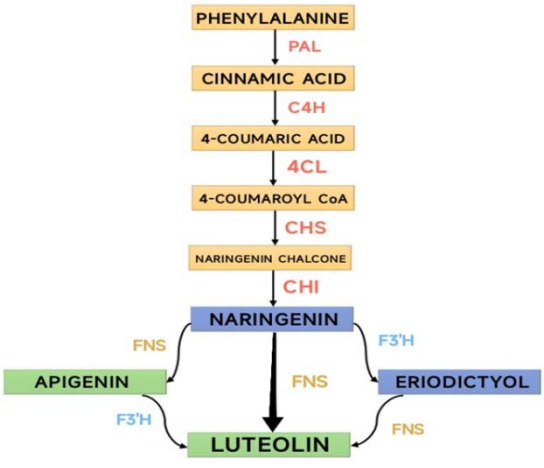

Fig. 3: Diagrammatic representation of biosynthesis of luteolin. PAL-phenylalanine ammonia lyase; C4H-trans-cinnamate 4-hydroxylase; 4CL-coumarate 4-ligase; CHS-chalcone synthase; CHI-chalcone isomerase; F3'H-flavonoid 3'-hydroxylase; FNS-flavone synthase [13, 15-20]

Luteolin biosynthesis starts with the conversion of amino acid phenylalanine to trans-cinnamic acid by the enzyme phenylalanine ammonia-lyase, followed by the formation of trans-coumaric acid from trans-cinnamic acid with the help of the enzyme trans-cinnamate 4-hydroxylase (C4H) [fig. 3]. Then, p-coumaroyl CoA is formed from trans-coumaric acid by the action of enzyme coumarate 4-ligase (4CL) [13, 15]. It is followed by the conversion of p-coumaroyl CoA into naringenin chalcone (NC) by chalcone synthase (CHS) [16]. The next step is the key to the biosynthesis of Luteolin and it happens through the action of the enzyme chalcone isomerase (CHI), which converts naringenin chalcone into naringenin [17]. The introduction of a hydroxyl group at the 3' position in the beta ring of naringenin occurs through the action of the enzyme flavonoid 3'-hydroxylase (F3'H), leading to the formation of eriodictyol [18]. Eventually, Luteolin is produced from the substrates naringenin and eriodictyol by the enzyme flavone synthase (FNS) [19, 20].

Qualities of luteolin

Plants produce luteolin molecule in two different forms: as an aglycone without sugar moiety and as a glycoside with sugar moiety attached. It has a molecular weight of 286.236 g/mol and with the molecular formula of $C_{15}H_{10}O_6$ [21]. It is predominantly found in plants as glycosides that are cleaved following nutritional absorption. The aglycones are subsequently conjugated and processed [22]. Luteolin, like other flavonoids, is a pleiotropic compound, which means that its pharmacological properties may not be explained by a single biochemical activity [22].

Luteolin as an antioxidant

The most important effect of luteolin includes its effective anti-oxidative activity, which includes high radical scavenging and cytoprotective abilities [23, 24]. It acts as a reactive oxygen species (ROS) scavenger by oxidizing itself [25]. As a result, the anti-inflammatory properties of luteolin may be linked in part with its anti-oxidative properties. This is especially essential, considering oxidative stress plays a significant role in many inflammatory skin processes [26, 27]. Other anti-oxidants include vitamins and cellular redox mechanisms as well as luteolin interact with one another. Luteolin can enhance its anti-oxidative strength in this way [28]. Because of its glycosidic group, it has anti-scavenging activity, which aids in the eradication of reactive nitrogen and oxygen species [29-33].

In Wister rats, luteolin (50 mg/kg orally) pre-treatment protects from renal failure via a detoxifying mechanism mediated by antioxidation activity, as well as anti-inflammatory and anti-apoptotic mechanisms [34]. It aids in minimizing the impact of intestinal mucositis-related mucosal damage brought on by cancer treatment [35]. Furthermore, Luteolin antioxidant activity has been shown to cause apoptosis through increasing antioxidant activity [36]. By enhancing the activity of several antioxidant enzymes, the rat model's hepatotoxicity caused by carbon tetrachloride (CCl_4) was minimized [37]. Due to its antioxidant properties, it also functions as a chemoprotective molecule while treating patients with doxorubicin, a medicine that damages the hepatorenal system and increases the effectiveness of treatment by removing the drug's adverse effects [38]. Thus, flavonoids, which function as primary antioxidants or free radical scavengers, aid in numerous health ailments [39].

Luteolin as an anti-cancer agent

Each year, over 18 million new cases of cancer are recorded worldwide. Cancer has a greater impact on vulnerable groups and strains health and the economy [40]. Epidemiological research shows that flavonoids provide a variety of health advantages. Dietary flavonoids' anticancer abilities have been demonstrated by several studies [41]. According to research by Sabzichi *et al.*, luteolin packed in phytosomes increases the passive targeting of breast cancer cells in MDA-MB 231 cells. On the other hand, the treatment of cells with doxorubicin and luteolin-containing nanoparticles resulted in the highest percentage of cells dying. To a larger extent than luteolin alone, nanoparticles loaded with luteolin reduced the expression of downstream Nrf2 gene genes at the messenger Ribonucleic acid (mRNA) level in cells. Likewise, these nanoparticles loaded with luteolin strongly decreased the

expression of Nrf2 downstream genes, including heme oxygenase 1 (Ho1) inhibition and multi-drug resistance gene (MDR1), and significantly increased cancer cell mortality [42].

Luteolin's efficient inhibition of cancer cell progression when examined *in vivo* at doses of 3 to 50 μM and *in vitro* at doses of 5 to 10 mg/kg demonstrated its effectiveness [43]. In another study, luteolin was administered to MCF-7 cells at a dose of 60 mol/l for 48 h, which inhibited the growth of cancer in a dose and time-dependent manner by lowering the expression of Bcl-2 protein, lowering the migration rate by 71.07% and lowering the expression of AEG-1 and MMP-2 by 82.34% and 85.70% respectively [44].

It has the benefit of treating skin cancer due to its capacity to penetrate the skin. Its action against stomach cancer was demonstrated in studies using human carcinoma cells at an IC50 value of 7.1 g/ml. Its effective action against lung cancer was seen at an IC50 value of 11.7 g/ml and it was effective against bladder cancer at IC50 value of 19.5 g/ml [45].

Leukaemia, a type of blood cancer that generates abnormal white blood cells and frequently results in fatalities, is another serious illness that affects people. This Luteolin substance inhibited the growth of the human leukemic cell lines CEM-C7 and CEM-C1 [46, 47].

Epidemiological research suggests that human lung, prostate, stomach, and breast cancer risk is inversely correlated with dietary intake of flavonoids [48-50]. In human breast cancer treatment, Luteolin and paclitaxel, when combined with MDA-MB-231 cells, reduced tumor size and weight, activated caspases-8 and-3, and improved Fas ligand expression. In an orthotropic tumor model, the rise in Fas expression was also ascribed to the inhibition of STAT3 [51].

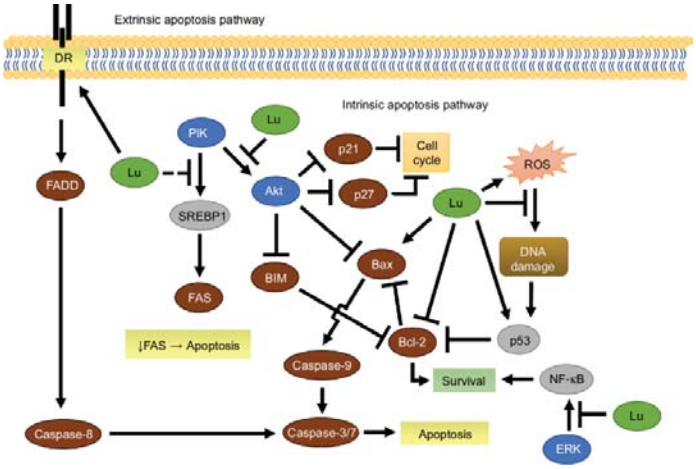

Fig. 4: Luteolin-mediated extrinsic and intrinsic apoptosis in breast cancer [52]

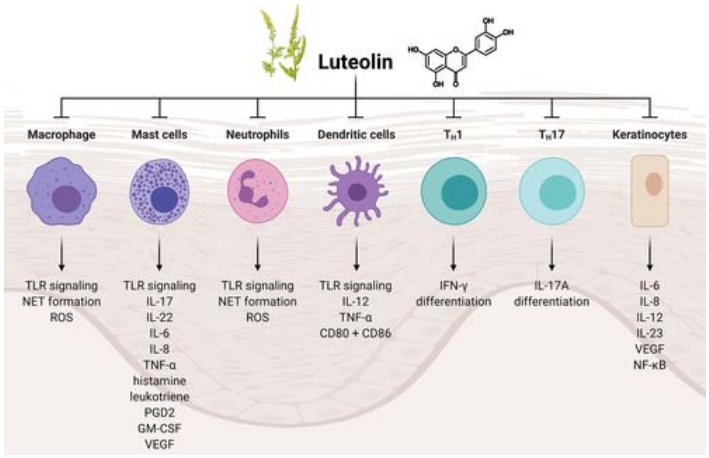

Fig. 5: Potential therapeutic targets for luteolin in psoriasis and dermatitis [53]

Table 1: Luteolin affections in different types of cancer [54]

Cancer type	Cell proliferation	Cell survival signaling	Apoptosis	Angiogenesis	Metastasis	Dose of luteolin	Reference
Breast cancer	Inhibit MAPKs, PI3K-Akt, CDK2	Inhibit PI3K-Akt, EGFR, NF-κB, MAPKs	Activate DR5, caspases-8 and-9, Fas, Bax	Inhibit VEGF, MMP-9, PI3K/Akt	Inhibit PI3K/Akt	10 mg/kg 60μmol/l for 48 h, suppressed the proliferation of cancer	[54]
Colon cancer	-	-	-	Inhibit MMP-9	-	1.2 mg/kg b. w	[54]
Pancreatic cancer	-	Inhibit EGFR, NF-κB	Activate Bax	Inhibit NF-κB	Inhibit NF-κB	-	[54]
Prostate cancer	-	-	Inhibit FASN	Inhibit VEGF, MMP-9	Inhibit IL-6	-	[54]
Glioblastoma	Inhibit	Inhibit	Activate P53,	Inhibit NF-κB,	Inhibit NF-κB,	-	[54]

Cancer type	Cell proliferation	Cell survival signaling	Apoptosis	Angiogenesis	Metastasis	Dose of luteolin	Reference
	P13K-Akt	P13K-Akt, PKC	Inhibit XIAP	PI3K/Akt	PI3K/Akt		
Oral cancer	-	-	Activate Fas, P53		Inhibit IL-6	-	[54]
Lung cancer	Inhibit MAPKs	Inhibit NF-κB, MAPKs	Activate caspases-3 and-9, Bax, JNK Inhibit Bcl-XL	Inhibit VEGF, MMP-9, NF-κB, HIF-1α	Inhibit IL-6, FAK, NF-κB	50μM	[54]
Kidney cancer	-	-	Activate DR5, Capsases, Bax, p53, JNK	-	-	-	[54]
Cervical and placental cancer	Inhibit P13K-Akt	Inhibit P13K-Akt	Activate DR5 Inhibit Bcl-XL	Inhibit P13K-Akt		-	[54]
Ovarian cancer	-	-	-	-	Inhibit FAK	-	[54]
Skin cancer	-	-	-	Inhibit MMP-9		-	[54]
Liver cancer	Inhibit PI3K-Akt	Inhibit PI3k-Akt, NF-κB	Activate Bax, P53 Inhibit Bcl-XL	Inhibit NF-κB	Inhibit NF-κB	-	[54]
Gastric cancer	-	-	Activate Bax, P53	Inhibit VEGF, MMP-9	-	40 mg/kg	[54]
Oesophageal and bladder cancer	-	-	Activate p53, JNK	-	-	-	[54]

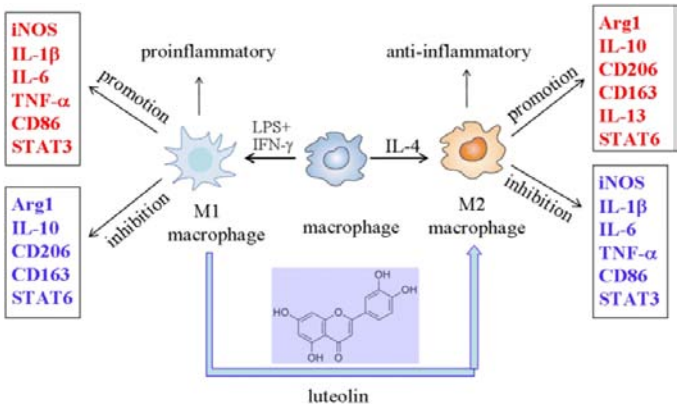

Fig. 6: Luteolin can alter macrophage polarization from M1 to M2 phenotype [55]

Anti-diabetic activity of luteolin

Diabetes is a serious health issue that exists worldwide. Every developed nation as well as a developing one is affected by its prevalence. According to the International Diabetic Federation (IDF) estimate of 2017, about 451 million people are affected by it, and by 2045, that number is expected to rise to 693 million. Additionally, it has negative socioeconomic effects. Type 2 diabetes among the growing younger population alarmed society. Diabetes is one of the most common illnesses that influence the health of the global population and can result in a number of life-threatening conditions [56]. As a result of oxidative stress, diabetes damages heart muscles and results in myocardial ischemia/reperfusion (I/R). The redirection of the oxidation reaction caused by activating the sestrin 2-Nrf2-based feedback loop during Luteolin therapy lowers oxidative stress and cardiac damage [57].

Long-term diabetes damages the neurons in the cerebral cortex; the treatment of luteolin greatly reduces diabetic symptoms such as peroxidation of lipids, which rises in diabetic rat brains. In addition, it lowers GS4, superoxide dismutase, and catalase activity which sharply declines in the hippocampus and cerebral cortex of rats after luteolin administration. It is believed that luteolin's antioxidant effect enhances CA1 neurons by minimizing neuronal apoptosis since ChE activity is a result of diabetes and leads to progressive cognitive decline and neurological dysfunction. Luteolin inhibits the ChE activity, which improves the situation in diabetic rats [58].

Anti-inflammatory and anti-allergic properties of luteolin

One of the body's defense mechanisms, inflammation, aids in the healing of wounds and protects against infection. However, persistent inflammation can lead to dangerous conditions like cancer, chronic obstructive pulmonary disease, and arthritis [59-61]. The inflammation action is necessary to lessen the influence of the stimuli, which would otherwise disrupt the normal cells, but it must be minimized because chronic inflammation interferes with proper functioning. Anti-inflammatory molecules are introduced to treat it in order to safeguard cells from negative effects [62]. During inflammation, macrophages are triggered by a variety of chemicals, including cytokines from the host and pathogen toxins. Lipopolysaccharide (LPS), a part of Gram-negative bacteria's outer membrane, is frequently used as an endotoxin and inflammatory trigger. Tumor necrosis factor (TNF), free radicals-ROS and reactive nitrogen species (RNS), and interleukins (ILs) are vigorously produced by the activated macrophages, which attract inflammatory cells like neutrophils and lymphocytes to the site of infection and clear the pathogens [61, 63, 64]. Luteolin, which is a flavonoid, is said to possess an anti-allergic effect [65]. Persistent synthesis of these chemicals during the time of chronic inflammation can lead to illnesses such as cancer. Luteolin exhibits an anti-inflammatory effect as it blocks the synthesis of such cytokines and their signal transduction pathways [66-68]. Luteolin reduces oxLDL-activated inflammation *in vitro* by blocking STAT3, a signal transducer as well as an activator of transcription. Its interaction with STAT3 was primarily demonstrated in one study by hydrogen bonding [69].

Luteolin as a neuroprotector

Important disorders with a high global occurrence are anxiety and depression [70]. The most ubiquitous neurodegenerative diseases are Parkinson's disease (PD) and Alzheimer's disease (AD). Although oxidative stress is thought to play a significant part in the development of both illnesses, other variables such as the buildup of misfolded proteins, also play a role [71]. Some of their symptoms can be alleviated by antidepressant medications, but they are accompanied by many negative effects. Luteolin was given to male 129 Sv/Ev mice along with palmitoylethanolamide in a trial to determine its possible antidepressant impact. The results

demonstrated a strong antidepressant effect at low doses, suggesting that this combination could be considered a new approach to treating depressive symptoms [70].

Luteolin as protection against alzheimer's disease

The most prevalent cause of memory loss in the world's population is Alzheimer's disease. The disease's primary symptom is the buildup of amyloid peptides within the brain's extracellular matrix [72]. There is currently no cure known for the illness. The search for an Alzheimer's disease cure is still ongoing worldwide. According to this theory, the secondary metabolite Luteolin may be able to decrease the impact of the disease. Due to the (direct) interaction between the gene expression of an antioxidant enzyme involved in free radical scavenging and ROS, Luteolin efficiently lowers the signs and symptoms of Alzheimer's disease as well as the formation of A42 aggregation in transgenic drosophila. This is shown by the concentration-mediated reduction of AchE activity, which delays the emergence of symptoms like those of Alzheimer's disease [73]. Luteolin prevents ER (Endoplasmic Reticulum) stress, which impairs learning and memory in mice, from causing neuro-inflammatory aggravation. As a result, it enhances 3XTg's brain histomorphology and minimizes protein plaques in mice with Alzheimer's illness [74].

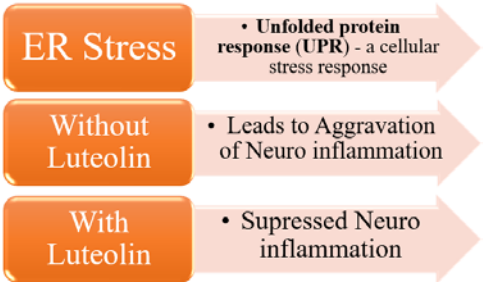

Fig. 7: Luteolin's action in ER stress. Unfolded proteins are created as a result of ER stress in the cells. The UPR leads to neuroinflammatory aggravation, which leads to memory and learning impairment in mice. Luteolin suppresses neuroinflammation [74]

Additionally, it boosts the expression of Bcl2 and significantly decreases the expression of Bax and caspase-3. High concentrations of Luteolin may be hazardous, blocking A25-35 and causing cell death. Additionally, it causes apoptosis by selectively acting on ER to protect Bcl2 cells from A-25-35 and stimulates the ER/ERK/MAPK transmission pathway [75]. Insulin resistance in the brain may be reduced by luteolin. The current research discovered that the Luteolin therapy enhanced hepatic insulin sensitivity and tightly controlled cell function, which boosted glucose metabolism and potentiated insulin signaling in the hippocampus [76].

Luteolin in Parkinson's disease treatment

Coherently, drugs that can trigger autophagy, the process by which intracellular trash is degraded, may aid in the removal of harmful chemicals from neurons, having a neuroprotective impact. According to this theory, injection of luteolin into male C57/BL6 mice with palmitoylethanolamide as an endogenous autophagic promoter improved tissue structure stimulated autophagy, and improved neurobehavioral functioning [71]. The luteolin generated during defense in the *in vitro* effect on oxidation is connected to the erratic amplification of endogenous free radical repression of the mitochondrial viability of membrane potential of mitochondria and a decrease in glutathione content. The catalyzing activity suggests that the multilayer modulatory route contributes to the neuroprotective effects of luteolin. The possible maintaining of the antioxidation or pro-oxidation ratio leads to protection.

Additionally, the neuroprotective pathway aids in reviving the ROS scavenging activity, a depleted endogenous enzymatic and non-enzymatic antioxidative defense system [77]. Luteolin improves mouse behavior in the traction and pole trait test, suggesting its potential in applied Parkinson's disease therapy by boosting the Bcl2/Bax ratio by lowering caspase-3 and also preventing the loss of TH+ve neurons in the substantia nigra (SN) and neural fibers in the striatum [78].

Luteolin in obesity treatment

Obesity acts as a major public health risk and contributes significantly to the burden of non-communicable diseases in the world, such as type 2 diabetes, hypertension, cardiovascular disease, and some malignancies. It is believed to cause premature mortality [79]. It is characterized by an abnormal buildup of body fat and associated with a significant risk of metabolic comorbidities, such as non-alcoholic fatty liver disease, type 2 diabetes, and cardiovascular disease. Adipose tissue is an essential immunological and endocrine organ as well as a key regulator of energy storage and metabolism in lean individuals. A persistent energy imbalance causes Adipose tissue remodeling, adipocyte hypotrophy and hyperplasia, chronic low-grade inflammation, and adipocyte malfunction in Adipose tissue. These changes eventually result in ectopic lipid accumulation and systemic insulin resistance [80].

Luteolin has been shown to help manage obesity when taken as a dietary supplement. By altering the Toll-like receptor signaling pathway, luteolin supplementation reduced macrophage infiltration and adipokine/cytokine dysregulation in rat models [81]. It has been shown to help combat obesity and related metabolic illnesses by increasing Adipose tissue thermogenesis and systemic energy expenditure. It has also been shown to reduce Adipose tissue lipogenesis, inflammation, and ectopic lipid deposition [80].

In a study, luteolin was found to be involved in the regulation of efflux genes of cholesterol, such as liver ATP-binding cassette transporter G1 (ABCG1), X receptor (LXR-), and scavenger receptor class B member 1 (SRB1). It demonstrated that luteolin lowers cholesterol by controlling the different genes associated with the cholesterol export process [82]. By lowering proinflammatory mediators in macrophages like tumor necrosis factor (TNF), monocyte chemoattractant protein (MCP-1), and NO while co-cultivating with 3T3-L1 adipocytes and RAW264 macrophages, luteolin reduces the obesity-related adipocyte inflammation that is observed after administration. The ability of luteolin to lessen inflammation in adipose tissue serves as proof of this [83].

Luteolin in cardiac health

Any condition, abnormality, or poor function linked to the heart, blood vessels, or circulation is referred to as cardiovascular disease (CVDs) [84]. The most effective approach for preventing the start of this illness is to improve dietary and lifestyle uses and make them affordable and accessible to the general public. Diet is a significant external factor in the development of CVDs [85, 86]. The luteolin molecule mitigates the likelihood of myocardial infarction as integrating it into food may help lower the risk of CVD. In a study using rats with myocardial ischemia/reperfusion (I/R) (MIRM) damage, treatment with luteolin decreased the damage to the heart valves by downregulating the Src homology 2 domain-containing protein tyrosine phosphatase 1 (SHP-1) regulation and upregulating the STAT3 pathway, which reduced the inflammatory response [87].

The anti-apoptosis property proves essential in avoiding harm to cardiac tissue. In one study, giving luteolin prevented apoptosis by enhancing AKT signaling in the simulated ischemia/reperfusion (sI/R) paradigm [88]. Luteolin serves to avoid cardiac abnormalities such as Ca^{+2} transport and contractile dysfunction, which worsen in failing cardiomyocytes and are stopped by controlling the SERCA2a gene. As a result, it improves cardiac health [89]. The SERCA proteins are important for maintaining heart health. By triggering the p38 MAPK pathway in the cardiomyocytes and simulated ischemia/reperfusion rat models, luteolin aids in upregulating its expression [90].

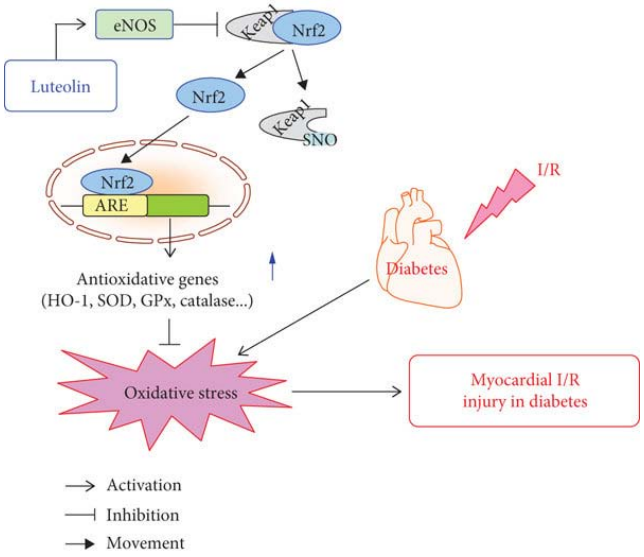

Fig. 8: Schematic diagram for the cardioprotection of luteolin against I/R injury in the diabetic heart [91]

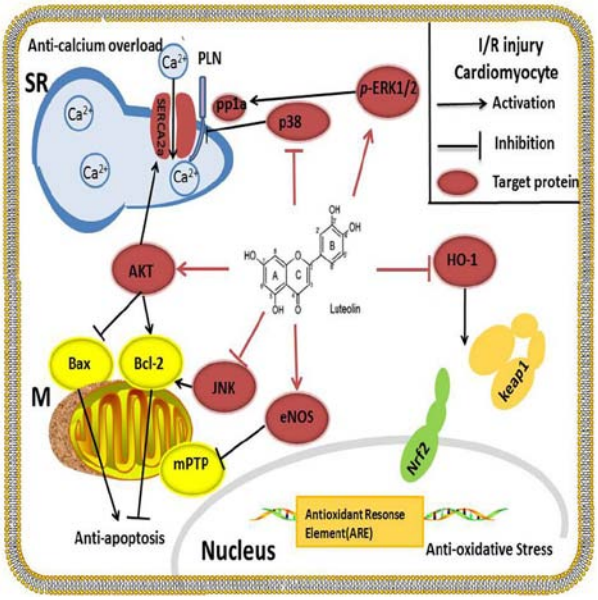

Fig. 9: By up-regulating AKT, up-regulating BCL-2, and down-regulating BAX, lut reduces I/R injury by suppressing apoptosis. The main protein involved in Ca^{2+} absorption from the cytosol into the SR is called SERCA2a. Following PI3K/AKT signaling pathway activation, SERCA2a activity is increased. At the same time, luteolin functions as a p38 mapk pathway inhibitor to prevent the phosphorylation of PLN, increasing SERCA2a activity and decreasing Ca^{2+} overload. Through HO-1, lut prevents oxidative damage and improves nrf2's ability to bind to the ARE. Lut inhibits JNK and raises p-ERK1/2 to promote cardiomyocyte contraction. to shield the heart from I/R injury, lut activates the myocardial eNOS pathway and suppresses the mitochondrial permeability transition pore [92]

Luteolin for Long-COVID syndrome-associated brain fog and chemo fog

SARS-CoV-2 infection causes COVID-19, whose severity is a result of the host's inflammatory response and the release of a cascade of pro-inflammatory cytokines [93]. As a result of COVID-19, auto-immune and inflammation-related diseases are in particular, becoming increasingly prevalent [94]. Additionally, multiple "mystery" illnesses have been attributed to cytokine storms [95]. One such illness called "brain fog", affects survivors of COVID-19 and is linked to extremely high levels of fatigue and neuropsychiatric symptoms [89]. The terms "chronic COVID syndrome," "post-COVID syndrome," and "long haulers COVID syndrome" are also used to describe this condition [96]. Patients with long-COVID syndrome report symptoms that are strikingly similar [97] to those of those with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [98, 99], mast cell activation syndrome (MCAS) [100, 101], or systemic mastocytosis (SM) [102], conditions in which stress, pathogens, and environmental stimuli activate the body's special tissue immune cells called mast cells.

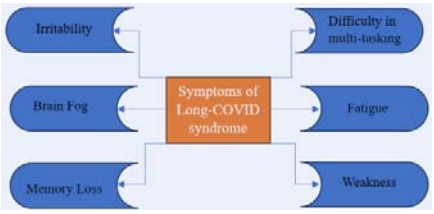

Fig. 10: Symptoms of long-COVID syndrome [93]

Patients receiving chemotherapy are more prone to getting COVID-19 infection [103]. Additionally, cognitive dysfunction, often considered a sign of long-COVID syndrome, is experienced by more than 50% of patients undergoing or finishing chemotherapy [93]. Cognitive dysfunction, also known as "chemofog" [104, 105] or "chemobrain," [106-110] has been linked to specific neuroimaging findings [89]. Several medications, including doxorubicin [111-113], methotrexate [114, 115], lenalidomide [116], rituximab [116], and trastuzumab [117], have been associated with "chemobrain". The hypothalamic-pituitary-adrenal (HPA) axis, normally stimulated by stress and has the ability to further impair the emotional stability of those affected by COVID-19 [118, 119], is also susceptible to being impacted by COVID-19 [120].

It seems that long-COVID syndrome does not have any clinically viable treatments [121, 122]. Furthermore, since T cells and antibody production seem to be protective but proinflammatory cytokines appear to be harmful, it is difficult to determine whether it would be preferable to stimulate or repress the immune system [123, 124]. Inhibition of mast cell-related neuroinflammation would be a reasonable strategy, particularly for brain fog linked with long-COVID syndrome, MCAS, ME/CFS, and chemotherapy-induced "chemobrain" [93]. The COVID-19 or long-COVID syndrome might be helped by mast cell inhibition; however, there are currently no known potent inhibitors of mast cells [125, 126]. Alternatively, the commonly accessible and generally well-regarded safe [127-131] natural flavonoids quercetin and luteolin [132-136], which have structurally similar properties, could suppress mast cells [132-136]. Both flavonoids have wide anti-viral characteristics, inhibiting virus entry into host cells, inhibiting neuroinflammation [137], and reducing cognitive loss [138]. In addition, luteolin has been shown to have improved brain penetration, inhibit microglia and mast cells, and lessen neuroinflammation as well as cognitive impairment, including Alzheimer's disease, in both people and animal models [93].

Nanoencapsulation of luteolin

Flavonoids have a variety of biological effects and may be utilized to treat or prevent disease. Because they showcase a remarkable range of biochemical and pharmacological actions, including anti-inflammatory, anti-oxidant, cytostatic, apoptotic, and estrogenic activities, flavonoids have attracted considerable interest for research and application in functional foods, nutraceutical products, and pharmaceuticals [139, 140]. Among the flavonoids, luteolin (3',4',5,7-tetrahydroxyflavone) is capable of improving insulin sensitivity and is present in a variety of plants, including celery, green peppers, perilla leaves, chamomile tea, broccoli, and carrots. Additionally, because luteolin can pass through the brain-blood barrier, it can be used to treat ailments of the central nervous system [141-144]. Due to luteolin's low oral bioavailability and the need for high bioavailability for it to demonstrate pharmacological activity *in vivo*, the development of innovative formulations may be useful in maximizing luteolin's pharmacological activity [145]. The stability, bioactivity, and bioavailability of these substances must, therefore, be preserved by product formulators in order to ensure that they are delivered to consumers in their active molecular form. The main objective of nanoparticle systems is to have these characteristics [146, 147]. By enhancing bioavailability, solubility, and retention duration, biodegradable nanoparticles are widely employed to enhance the beneficial value of diverse water-soluble/insoluble medical medicines and bioactive compounds. These drug-nanoparticle compositions improve the therapeutic index, specificity, tolerability, and efficacy of the related medications. They also lower costs for the patient toxicity risks and have a number of benefits, such as preventing premature degradation and interaction with biological systems and enhancing intracellular penetration [148].

The use of luteolin in food and medicine is severely constrained by its poor solubility and low bioavailability. Some delivery systems based on synthetic polymers, such as hyaluronic acid/poly (N-isopropyl acrylamide) polymer network hydrogels and monomethoxy poly (ethylene glycol)-poly (-caprolactone) (MPEG-PCL) micelles, have been advanced to increase the stability and bioavailability of the compound luteolin. However, there are few reports of the nano-delivery system made from plant-based polymers for encapsulating luteolin [149].

Due to their tiny size, high surface-to-volume ratio, and potent dispersibility, many nanoscale delivery methods, including emulsifiers and liposomes have been extensively exploited in recent years to increase the bioavailability and stability of bioactive chemicals. When designing delivery systems for nanoparticles with great encapsulating capacity, high penetration of biological barrier, and well-controlled release property, starch is frequently used because of its accessibility, availability at a lesser cost, renewability, and biodegradable quality. According to reports, molecular modification may be able to give starch the physiochemical characteristics it needs for use in encapsulating systems [149].

The usage of oxidized lotus root starch nanoparticles, which are utilized to encapsulate luteolin, has amylopectin (70%–80%) and amylose (20%–30%). Currently, traditional meals are frequently prepared using lotus root starch as a food additive. However, due to its limited solubility in water at ambient temperature (25 °C), the potential applications of this starch have undergone little research. According to earlier research, oxidation may increase starch's solubility and have an impact on its capacity to encapsulate substances. Sodium hypochlorite (NaClO)-mediated 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) can oxidize lotus root starch. Because of its low cost, easy operating conditions, and low possibility of sample contamination, the resulting oxidized lotus root starch (OLRS) was subsequently utilized to create luteolin-OLRS nanoparticles [149]. This nanoencapsulation of luteolin may enhance its various properties, including its free radical scavenging property [150].

CONCLUSION

This article covers almost every aspect of luteolin's biological, physical, and chemical properties, including its anti-oxidant, anti-cancer, anti-diabetic, anti-inflammatory, neuroprotective, cardioprotective, anti-depressant, and aid in long-covid syndrome effects. The nano-encapsulated luteolin in synthetic and bio-polymers, with increased bioavailability and activity, was also reviewed. However, there has to be further investigation done on how to integrate luteolin alongside additional therapeutic compounds and treatments.

ABBREVIATIONS

Reactive oxygen species (ROS), Ischemia/reperfusion (I/R), cardiovascular disease (CVDs)

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All the authors have contributed equally.

CONFLICT OF INTERESTS

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