RESEARCH PAPER

Luteolin: A Comprehensive Review of Its Pharmacological Activities and Therapeutic Potential

Leena Joge[1*], Snehal Manekar[1], Manisha More[2], Sushma Rathod[3], Neha Giri[4], Suchita Bhoyar[5], Vikas Ghait[6], Ganesh Bhojane[7], Nitin Lodhe[8]

[1*]Department of Pharmacognosy, Dr. Rajendra Gode College of Pharmacy, Malkapur, Maharashtra, India.
Email: leenapjoge@gmail.com (Corresponding Author)

[1]Department of Pharmacognosy, Dr. Rajendra Gode Institute of Pharmacy, Amravati, Maharashtra, India

[2]Department of Pharmacognosy, Dr. Rajendra Gode Institute of Pharmacy, Amravati, Maharashtra, India

[3]Department of Pharmacognosy, SGSPS Institute of Pharmacy, Akola, Maharashtra, India

[4]Department of Pharmacognosy, Royal College of Pharmacy, Raipur, Chhattisgarh, India

[5]Department of Pharmacognosy, Anurag College of Pharmacy, Warthi, Bhandara, Maharashtra, India

[6]Department of Pharmacognosy, Dr. Rajendra Gode College of Pharmacy, Malkapur, Maharashtra, India

[7]Department of Pharmacognosy, N.K. College of Pharmacy, Khamgaon, Maharashtra, India

[8]Department of Pharmacognosy, R. N. Lahoti College of Pharmacy, Sultanpur, Maharashtra, India

ABSTRACT

Plants have been found to frequently contain luteolin (3′,4′,5,7-tetrahydroxyflavone). Ethnopharmacologically, luteolin-rich plants have been utilized to treat inflammation-related ailments. Utilizing diverse models, research has been conducted on isolated luteolin as well as extracts from plants high in luteolin, and both have demonstrated anti-inflammatory properties.

Keywords: Luteolin, Pharmacokinetics, Pharmacodynamics

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1. Introduction:

Yellow-crystalline in nature, luteolin is a flavone, a kind of flavonoid. Though luteolin can also be found in rinds, barks, clover blossoms, and ragweed pollen, leaves are the most common place to find it. The fragrant blooming plant Salvia tomentosa, which belongs to the Lamiaceae family of mints, has also been isolated from it.

A few examples of dietary supplies are carrots, olive oil, peppermint, rosemary, navel oranges, oregano, celery, broccoli, artichokes, green pepper, parsley, thyme, dandelion, and perilla. Furthermore, Aiphanes aculeata palm seeds contain it.

One flavonoid, or natural nutrient, that is present in plants—including cannabis—is luteolin. By lessening oxidative stress, an imbalance in the body that can precede many major diseases, including cancer, flavonoids like luteolin have been discovered to have positive impacts on human health. Although leaves are the main source of luteolin, it is also naturally occurring in bark and clover blooms. Oranges, broccoli, celery, mint, and artichokes are among the foods high in luteolin. Lutein is also present in common herbs like oregano, thyme, parsley, and rosemary.

The plant receives bursts of color and flavor from the flavonoids in cannabis. The yellow crystalline material luteolin affects how well you can see, taste, and smell any particular cannabis product. For instance, strains high in this flavonoid may become yellowish due to luteolin.

More significantly, the cannabis plant is endowed with medicinal effectiveness by the flavonoid luteolin. Flavonoids maximize any health advantages through a synergistic entourage effect with terpenes and cannabinoids. Together, these plant components bind to receptors in your body's endocannabinoid system and/or other receptor

systems, forming connections and exchanging healing signals.[1]

Background of Lutein

Fig. 1 : Luteolin Plant

One compound that is categorized as a citrus bioflavonoid is luteolin. As is typical of flavonoids, it is a pure yellow crystal. Because of its anti-inflammatory and antioxidant qualities, luteolin is a versatile health supplement. These characteristics enable luteolin to scavenge oxygen- and nitrogen-containing reactive chemicals that can harm cells. The dopamine transporter is one of luteolin's other biological actions.

Numerous plants, many of which are edible, produce luteolin. Oranges and other citrus fruits are important dietary sources of luteolin. Green pepper, celery, carrots, broccoli, and celery are more vegetables that contain luteolin. Herbs such as parsley, peppermint, rosemary, and oregano are rich in luteolin. One of the most significant commercial sources of luteolin is peanut hulls. Because these hulls are a by-product of processed peanuts, they are a cheap source.

Lutein may be commonly extracted from peanut hulls using ethanol reflux. To achieve a liquid/solid ratio of 20:1, this procedure basically entails combining the powdered hulls with 70% ethanol.

Then, for at least 1.5 hours, this combination is heated to 85 degrees Celsius. The mixture releases a high concentration of luteolin vapor, which can be further condensed to a very high degree of purity.[4]

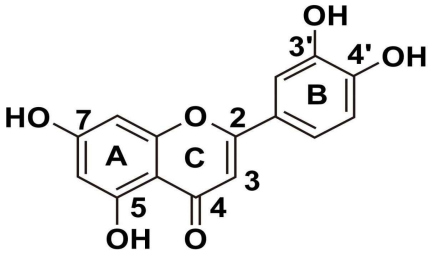

Fig 2 : Luteolin molecular structure.

1. Natural occurrences:

The most common source of luteolin is leaves, however it can also be found in rinds, barks, clover blossoms, and pollen from ragweed.[1] Additionally, it has been isolated from Salvia tomentosa, an aromatic flowering plant belonging to the Lamiaceae family of mints.[5]

2. Effects:

Plant elements such as flavonoids have been found to give healthful advantages. Luteolin (Lut), a form of flavonoid, contains anti-oxidative, anti-tumor, and anti-inflammatory activities. The heart-protective properties of lutein both in vitro and in vivo have been doumented in recent scientific literature.

3. Benefits :

Although most luteolin research has been conducted on animals, it is expanding as more is learned about the potential medical uses of dietary flavonoids. According to recent studies, luteolin may have the following pharmacological applications:

Allergies :

The extract known as luteolin, which is derived from peppermint leaves, may reduce histamines and alleviate allergy symptoms. Research published in the scientific journal Integrative Medicine suggests that luteolin-rich peppermint oil may help lessen the itching associated with contact dermatitis and allergies, including allergic asthma. Histamines are what cause skin to itch. Lutein may lessen the inflammation in allergy nasal passages, according to other research.

Inflammation

Reduced non-allergic inflammation, such as that seen in the brain in MS patients, may also be

possible with the flavonoid luteolin. Additional data suggests that luteolin may lessen MS-related inflammation, which was published in the journal Nutrition and Lifestyle in Neurological Autoimmune Diseases. This and other studies have shown that luteolin may contribute to the reduction of intestinal inflammation. Crohn's disease and GI tract malignancies are among the numerous grave illnesses that are associated with intestinal inflammation.

Cancer:

Lutein may be beneficial for a variety of cancer forms. The flavonoid may have the ability to control estrogen levels, which may have a beneficial effect on ovarian and breast malignancies, two forms of cancer that affect women. Moreover, luteolin may function to prevent the occurrence of colon cancer and exert an antioxidant action on human lung cancer cells.[3]

Side Effects of Luteolin:

In general, luteolin is safe to eat. Some people may experience side effects, particularly if they take high amounts of the flavonoid as a dietary supplement; however, they are uncommon and not well understood. Lutein exacerbated chemically induced colitis in a rat research; however, it is unclear if this holds true for humans.

Lutein and quercetin "display progesterone antagonist activity beneficial in a breast cancer model but deleterious in an endometrial cancer model," according to a cell line study. But since this is merely a cell line study, it only advises being cautious when taking luteolin supplements rather than getting it from a diet high in plants.[3]

Pharmacological Activity

1. Anti-breast Cancer Effects and Mechanisms

Flavonoids such as luteolin have antibacterial, anti-inflammatory, anti-oxidant, anti-proliferative, and antidiabetic effects. Research has indicated that luteolin, via triggering cell cycle arrest and death and by modifying cell signaling, may suppress angiogenesis, metastasis, and proliferation of many cancer forms, including breast cancer. The current research on luteolin's inhibitory effects and underlying mechanisms in breast cancer has been compiled into this overview. According to these research, luteolin shows promise as a medication for the treatment of breast cancer. [5]

The compound 3′, 4′, 5, 7-tetrahydroxyflavone is known by the name luteolin. It is a member of the class of widely distributed, physiologically active flavonoids found in plants.[6] There is an inverse relationship between dietary flavonoid intake and the risk of breast, stomach, prostate, and lung cancer in people.[7-9] The molecule of luteolin is made up of three rings: the C6-C3-C6 structure, which is made up of an oxygen-containing (C) ring and two benzene rings (A, B). The oxygen-containing (C) ring has a C2-3 double bond, and each benzene ring has two hydroxyl groups.[10] On C3.6, luteolin does not have a -OH substitution.[11] The biochemical and biological activities of luteolin, such as its antibacterial, anti-inflammatory, anti-inflammatory, and antiproliferative properties, depend on the C2–3 double bond as well as the C3– and C4–hydroxyl groups in the compound.[12-14] The anticancer properties of luteolin have been shown in recent decades for a variety of cancer types, including ovarian, colorectal, breast, gastric, hepatic, and melanoma malignancies. [15-27]

The most frequent and potentially fatal cancer to be detected in women worldwide is breast cancer.[28] Breast cancer is classified into five subtypes based on genomic expression profiles and immunohistochemical staining of specific molecular markers, including ER, PR, Her2, and Ki67. These subtypes are: luminal A (ER/PR+HER2−Ki-67low), luminal B (ER/PR+HER2−/+Ki-67high), Her-2-enriched (ER/PR−HER2+Ki-67high), triple negative/basal-like (ER/PR−HER2−Ki-67high), and "other" (which includes all cases that cannot be assigned to one of the four subtypes). This molecular classification guides the selection of therapeutic modality and forecasts the course of cancer.[29-34]

It was discovered that patients with high levels of HER-2 and Ki-67 expression had a dismal prognosis. Compared to other subtypes, the luminal A subtype responds well to endocrine therapy. Chemotherapy is an effective treatment for the luminal B subtype. Chemotherapy using anthracyclines and HER-2-targeted treatment are used to treat the Her-2-enriched subtype. Treatment options for the triple

negative/basal-like subtype include PARP inhibitors and chemotherapy based on platinum.[29-34]

Even though treatment approaches have been discovered, the heterogeneity and resistance to different pharmacological regimens in breast cancer still make the cure unsatisfying.[29-34],35 Innovative medications are required to regulate metastasis and proliferation during breast cancer treatment. The research on luteolin's anticancer properties on breast cancer has been compiled in this paper.[5]

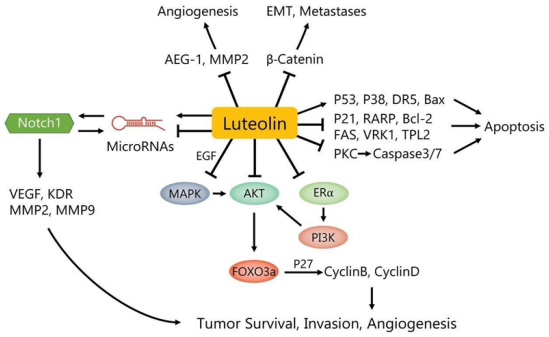

Fig 1.1 : Luteolin modulates the signaling pathways and inhibits the growth andmigration as well as promotes apoptosis of breast cancer cells.

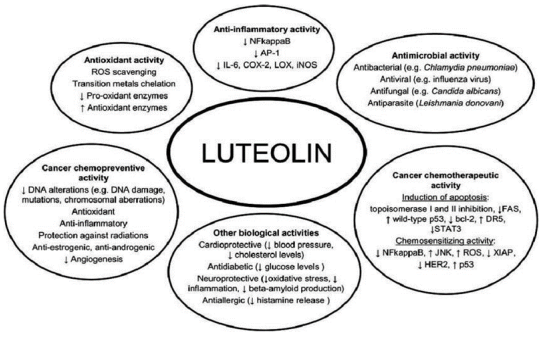

Fig. 1.2 : Biological activities and possible mechanisms of action of luteolin.

2. Immunopharmacological Activities of Luteolin in Chronic Disease

Numerous natural compounds contain flavonoids. A carbon–carbon bridge connects the aromatic A ring, heterocyclic C ring, and aromatic B ring that make up the basic structure of flavonoids. Based on their molecular backbone structure and hydroxyl group, flavonoids are classified into several subgroups: flavones (2-phenyl-chromen-4-one), flavanols (3-hydroxy-2-phenylchromen-4-one), flavanones 3 dihydro-2-phenylchromen-4-one), flavanols (2-phenyl-3,4-dihydro-2Hchromen(flavan)-3-ol,lavan-4-ol,flavan-3,4-diol), flavanonols (3-hydroxy-2,3-dihydro-2-phenylchromen-4-one), isoflavones (3-phenylchromen-4-one), and anthocyanidins (2-phenylchromeny-lium).

Flavonoids are abundant in fruits, vegetables, tea, and wine. Flavonoids have numerous uses in the pharmaceutical, nutraceutical, medical, and cosmetic fields due to their anticancer, anti-oxidative, anti-inflammatory, anti-mutagenic, anti-allergy, and cardioprotective properties.[10]

Lutein (3′, 4′, 5,7-tetrahydroxyflavone) is a naturally occurring flavone with a yellow crystalline form that is one of the most used ones. Luteolin's molecular formula is C15H10O6, and Figure 2 depicts its chemical structure. Carrots, broccoli, cabbages, parsley, thyme, peppermint, basil, celery, artichokes, and apples are just a few of the luteolin-rich fruits, vegetables, and medicinal herbs. It has been reported that luteolin's active metabolite and its derivatives, such as luteolin glucuronide and luteolin 7-glucoside, possess anti-oxidant, anti-tumor, anti-microbial, anti-inflammatory, anti-apoptotic, anti-allergy, anti-diabetic, chemoprotective, cardioprotective, and neuroprotective functions. The anti-inflammatory properties of luteolin have been the subject of the majority of research [11].

The complex biological reaction of body tissues and cells to infections and harmful chemical or physical stimuli includes inflammation. Inflammation aids in removing necrotic cells and tissue destroyed by the initial insult and the inflammatory process, as well as in starting the healing process for injured tissue. Heat, discomfort, redness, swelling, and loss of function are its five primary symptoms. An acute or persistent inflammation is possible. Acute inflammation is the body's initial reaction to damaging stimuli and causes an increase in the migration of leukocytes, particularly granulocytes, and plasma from the bloodstream to the damaged tissue.

The local vascular system, the immune system, and different cells inside the wounded tissue are all involved in the biochemical events that proliferate and mature the inflammatory response. On the other hand, chronic inflammation is a long-lasting, dysregulated, and maladaptive reaction that results in tissue damage, active inflammation, and attempts at tissue repair. Chronic inflammation has been

connected to a number of long-term human ailments, including autoimmune disorders, cancer, atherosclerosis, allergies, and arthritis.

The mechanisms behind the genesis and progression of acute inflammation are well established, whereas the molecular and cellular mechanisms and causes of chronic inflammation are not as well understood. The identification of biomarkers for inflammation, such as cytokines like tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6, IL-8, and monocyte chemotactic protein 1, as well as other proteins and enzymes like cyclooxygenase-2 (COX-2) and matrix metalloproteinases (MMP), is becoming more and more crucial in the study of different illnesses.[12]

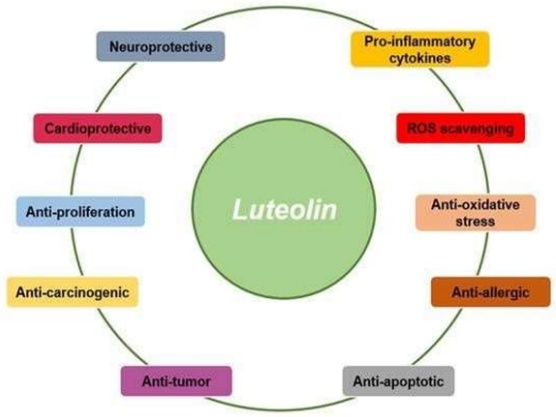

Fig. 2: Various biological activities of luteolin

3. Emphasis on In Vivo Pharmacological Effects and Bioavailability Traits:

Preclinical Pharmacological Activities of Luteolin:

3.1 In Vivo Evidence

Numerous in vitro and in vivo investigations have thoroughly examined and validated the pleiotropic nature of luteolin. This flavone's diverse range of actions is linked to its interactions with cell proteins and pathways, the modification of which is frequently essential for the onset of a particular ailment. Although luteolin is best known for its anti-inflammatory and antioxidant properties, over the past ten years, preclinical research has demonstrated that it also has antiproliferative and proapoptotic properties in addition to its ability to inhibit angiogenesis, metastasis, and carcinogenesis. These findings suggest that luteolin has potential therapeutic value as an anticancer flavonoid. Because luteolin has well-known anti-inflammatory, anticancer, and antioxidant properties, the many pharmacological actions of this compound are covered in the following sections.[13]

3.2 Anti-Inflammatory Activity

The anti-inflammatory property of luteolin is one of the most well-known and studied by scientists within its range of activities. Ziyan et al. investigated the anti-inflammatory effects of luteolin given orally in mouse models used for both acute and chronic conditions. Paw edema caused by carrageenan was reduced by luteolin at dosages of 10 and 50 mg/kg. Subsequent research showed that luteolin selectively reduces the inflammatory response by cyclooxygenase-2 (COX-2). Furthermore, because synthetic anti-inflammatory medications are expensive, difficult to obtain, and have unfavorable side effects, researchers from developing nations are still searching for more affordable and effective therapeutic plant-derived chemicals. In light of this, a team of scientists looked at how luteolin affected the levels of interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) in male Wistar rats' inflammation caused by lipopolysaccharide (LPS). They found that luteolin significantly reduced these two inflammatory mediators. [14]

3.3 Neuroprotective Effects

Studies have shown that a number of neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), stroke, and traumatic brain injury, are significantly influenced by neuroinflammation.

spinal cord damage, demyelinating conditions, and infections pertaining to the central nervous system (CNS). Among these, severe spinal cord injuries have the potential to result in long-term neurological impairments. Among its various pharmacological effects is the improvement of memory. Based on this, luteolin and palmitoyl-ethanol-amide were mixed, and the results showed that they had both neuroprotective and anti-inflammatory effects when tested on CD1 mice. Co-ultra-micronized palmitoyl-ethanol-amide/luteolin was shown in a different study conducted on the same animal model to alleviate the symptoms of traumatic disorders such

as spinal cord injury; therefore, this composite may be useful in the treatment of neuroinflammation associated with spinal cord injury. [15]

3.4 Protection from Metal Overload Toxicity

"Research has shown that luteolin can help counteract the negative health effects caused by exposure to toxic heavy metals. For example, when male Wistar albino rats were given luteolin supplements, it reduced lead buildup in their liver tissues by decreasing the release of inflammatory mediators and suppressing the apoptotic cascade. This suggests that luteolin could be used as a dietary supplement to protect against lead exposure in environmental and occupational settings without any side effects.

Lead exposure can occur through cosmetics, pipes, pigments, and paints, and it can have harmful effects on the central nervous system by displacing zinc and calcium ions, thereby increasing the risk of developing neurodegenerative diseases. Studies examining the effects of luteolin on lead-induced neurotoxicity have found that this flavone significantly improves cortical injury following lead intoxication and protects neuronal tissue [16]."

3.5 Protection from Metabolic Dysfunctions

Several experiments have shown that consuming luteolin could be a potential therapeutic approach for metabolic dysfunctions like obesity, diabetes, hepatic steatosis, and postmenopausal metabolic syndrome. Obesity is a growing health concern, particularly in high-income and developed countries. A comparison of C57BL/6 mice fed low-fat and high-fat diets, as well as high-fat diets supplemented with 0.002% and 0.01% luteolin for 12 weeks, revealed that luteolin improved diet-induced obesity and insulin resistance.

Diabetes mellitus is a common chronic metabolic disease. It is associated with various complications such as diabetic neuropathy and nephropathy. Luteolin, a versatile molecule, has been found to be effective in addressing this complex disorder. For example, in an insulin-resistant mouse model, oral administration of luteolin improved glucose intolerance and insulin sensitivity.

The complications of diabetes-related nerve disorders are known to be caused by apoptosis, which in turn is mediated by high levels of blood sugar. A study on male Sprague Dawley rats found that administering luteolin twice a day for 15 days inhibited apoptosis caused by high blood sugar and also improved learning and memory in diabetic neuropathy. Vascular disease induced by high blood sugar is a major cause of illness and death in diabetes. These disorders are known to begin with endothelial dysfunction, as the endothelium plays a vital role in regulating blood vessel tone and structure. Luteolin is able to effectively protect endothelium-dependent relaxation from damage caused by high glucose by reducing oxidative stress and increasing the activity of the NOS-NO pathway.[17]

3.6 Protection from Cardiovascular and Vascular Alterations

Cardiovascular diseases are the leading cause of death. The powerful antioxidant effect of luteolin could be helpful in treating these diseases. Heart failure is one of the main cardiovascular syndromes, and its frequency increases as the population ages. In an experiment examining the protective effects of luteolin on chronic heart failure, male Sprague Dawley rats were used. The study found that long-term administration of this flavonoid might improve cardiac function alteration induced by doxorubicin, as well as inhibiting the apoptotic process in myocardial cells.

Doxorubicin is an anthracycline antibiotic used in cancer treatment, but its clinical efficacy is limited due to its cardiotoxicity. Luteolin has been shown to have a protective effect against doxorubicin-induced cardiotoxicity. This effect is achieved by inhibiting NADPH-dependent lipid peroxidation in a concentration-dependent manner, suppressing phlpp1 activity, and activating the AKT/Bcl-2 signaling pathway. Additionally, as an anti-inflammatory molecule, luteolin can protect the heart against diet-induced myocardial inflammation by reducing the levels of major proinflammatory cytokines.

Luteolin, a compound found in TNF-α and IL-18, shows promise as a supplement for preventing coronary arterial spasm. It has been demonstrated to

counteract different substances that cause blood vessels to constrict in rat coronary arteries. Additionally, luteolin has been found to enhance voltage-gated potassium channels and inward rectifier potassium channels in the smooth muscle cells of rat coronary arteries.

Luteolin has been found to inhibit the development of thrombosis in a FeCl3-induced carotid arterial thrombus model. Additionally, glaucoma, which is the second most common reason for blindness, is considered a vascular disease. Glaucoma encompasses a diverse group of diseases related to various factors such as vascular dysregulation and intraocular pressure (IOP) elevation. Research on white New Zealand rabbits has shown that luteolin has an antiglaucoma effect by reducing intraocular pressure, providing neuroprotection, and acting as an antioxidant by preserving structural integrity and enhancing the outflow of aqueous humor. Therefore, administering luteolin could be a new approach to reducing the effects of glaucoma. [18]

3.7 Treatment of Psychiatric and Behavioral Disorders

Depression and anxiety are significant disorders with a high incidence worldwide. While antidepressant drugs can help relieve symptoms, they often come with various side effects. In a study that aimed to investigate its potential antidepressant effect, luteolin was administered to 129Sv/Ev male mice in combination with palmitoyl-ethanol-amide. The results showed a significant antidepressant activity at low doses. This combination may be considered a new approach to alleviate depression symptoms. [19]

3.8 Hepatoprotective Activity

The liver plays a crucial role in metabolism and excretion in the body and is therefore exposed to environmental toxins and chemotherapeutic agents. The accumulation of these substances can lead to liver diseases and chronic damage. Flavonoids such as luteolin have been found to interact with cell membranes in various organs, forming hydrogen bonds and protecting the membranes from deterioration. Similarly, natural antioxidants from plants such as zeaxanthin have also been shown to have a protective effect on cell membranes. In an in vivo model of galactosamine/lipopolysaccharide-induced hepatotoxicity, luteolin demonstrated anti-inflammatory and antioxidant activities, providing protection against acute liver injury by regulating inflammatory mediators and phase II enzymes.[20]

3.9 Protection from Musculoskeletal Diseases

Osteoporosis is a complex skeletal disease characterized by reduced bone mass, disruption in bone microarchitecture, and increased bone fragility. Some flavonoids can prevent bone loss in animals that have undergone ovary removal, and they can also inhibit osteoclast differentiation. In a study, it was found that oral administration of luteolin significantly increased bone mineral density and prevented the increase in bone turnover that occurs after ovary removal. Therefore, this flavonoid might be used as an alternative to current therapeutic agents for managing postmenopausal bone loss [21].

3.10 Organ Transplantation

The activity of luteolin in the cardiovascular context has led to its potential application in heart transplantation. Heart transplantation is performed for end-stage cardiac failure, but the hypothermic preservation of the heart is currently limited to 4-6 hours, leading to cell death due to calcium accumulation over time. Luteolin has been shown to reduce calcium overload and suppress the accumulation of regulatory proteins and specific enzymes responsible for calcium circulation in cardiomyocytes over a preservation period of 6 hours. Therefore, adding luteolin to the preservation process may extend the time for which the heart can be preserved. [22]Bioavailability of Luteolin

Luteolin has been shown to have numerous positive effects on health. However, understanding its bioavailability, absorption, and metabolism is essential for determining its health benefits and safety. Despite its therapeutic potential, there is limited research on the bioavailability of luteolin in humans and animals. Bioavailability refers to the proportion of a substance that can be absorbed and is available in the bloodstream, taking into account absorption in the

intestines and first-pass metabolism.

Absorption occurs when a molecule enters the biological membrane barrier, which, in the case of dietary compounds, is the gut epithelium. After absorption, the molecule must pass through the gut wall and undergo hepatic metabolism, known as the first-pass effect. This highlights the need for a deeper understanding of luteolin's absorption and metabolism to fully grasp its bioavailability. [23]

3.11 Absorption of Luteolin

The absorption of polyphenols across the gut epithelium is the primary biological barrier for oral administration. Understanding the intestinal uptake and efflux mechanisms is crucial for determining the efficacy of these beneficial compounds. Luteolin is commonly found in vegetables, fruits, and natural herbs either in a free-aglycone form or in glycoside structures represented by one or more conjugated sugars. As depicted in the figure, the typical forms of luteolin glycosides mainly occur through glycosylation of the aglycone. This can happen through free hydroxyl (OH) groups, referred to as O-glycosides, and/or through C-C bonds, termed as C-glycosides. These glycosylated forms of luteolin are commonly found in the leaves of celery, green pepper, parsley, thyme, peppermint, and perilla. [24]

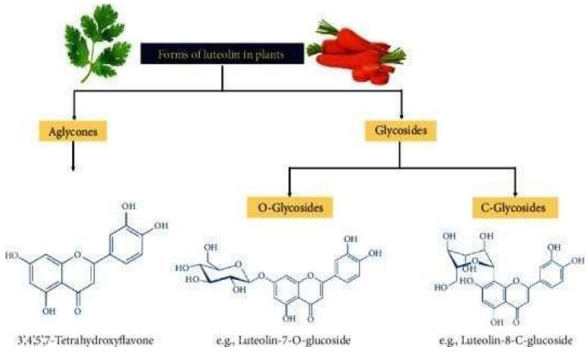

Fig. 4.1: General classification of the typical forms of luteolin.

3.12 Metabolism of Luteolin

After being absorbed, cytochrome monooxygenases in the liver extensively metabolize flavonoids through phase I metabolism. There are 18 families with many different isoforms of cytochrome genes involved in flavonoid metabolism. The products of phase I metabolism-derived oxidation are typically minor metabolites, as rapid glucuronidation, sulphation, or methylation of potential phase I substrates by phase II conjugating enzymes, such as urine-5′-diphosphate glucuronosyltransferases (UGTs), sulphotransferases, and catechol-O-methyltransferases (COMTs), are believed to be the major metabolism routes. Glucuronide conjugates are mostly present in abundance in the plasma and urine. Limited studies on the metabolism of luteolin result in continued uncertainty in the field. A simplified illustration of this flavonoid metabolism is depicted in Figure [25].

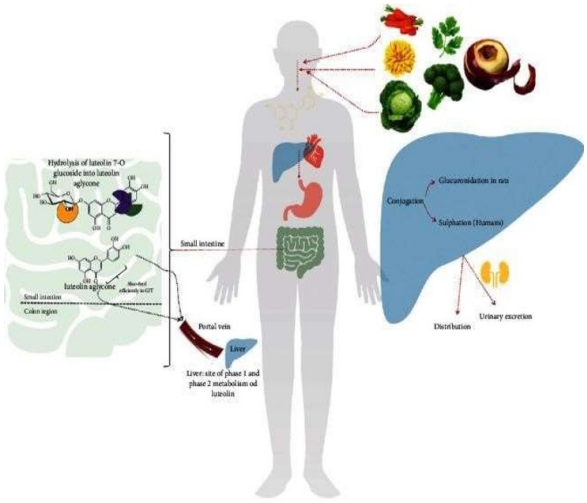

Fig. 4.2 overview of 2:
Simple flavonoid postabsorptive metabolism. Simple overviewof flavonoid postabsorptive metabolism.

3.13 Strategies to Enhance Luteolin Bioavailability

Methods for Improving the Bioavailability of Luteolin Because of its significant first-pass digestion by phase II enzymes, luteolin's low bioavailability is one of its main therapeutic usage constraints [146]. Various distribution techniques, such as lipid carriers and nano formulations, have been created and explored to address this problem. [26]

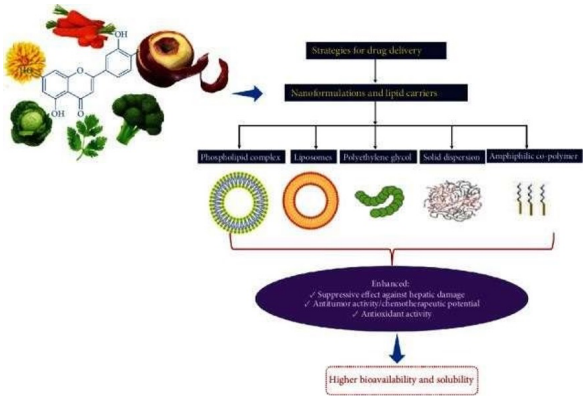

Fig. 4.3: Proposed strategies to increase luteolin's delivery

In a series of studies, a group of researchers investigated the bioavailability of two formulations of luteolin in rats: a nanostructured lipid carrier (solid) and a microemulsion (liquid). Both forms increased the oral bioavailability of luteolin, but the microemulsion showed better results. Additionally, the solubilized drug concentration was higher in the microemulsion, suggesting faster absorption and higher bioavailability. The researchers also found that the complexation of luteolin with phospholipid matrix (LPC) enhanced its solubility, bioavailability, and efficacy. Specifically, LPC treatment resulted in a greater reduction in ear and paw edema in rats compared to treatment with pure luteolin. Furthermore, the same research group demonstrated that oral treatment of rats with LPC was more effective at reducing hepatic damage compared to luteolin treatment by targeting inflammation sites in the liver. [27]

5. Biological Activity:

Luteolin, a flavonoid with potentials for cancer prevention and therapy:

The biological effects of luteolin may be functionally related. For example, its anti-inflammatory activity may be connected to its anticancer properties.

Luteolin's anticancer effects are associated with inducing apoptosis and inhibiting cell proliferation, metastasis, and angiogenesis.

Redox Modulation Activity:

The majority of flavonoids, including luteolin, are considered to be antioxidants. Reactive oxygen species (ROS) are a group of reactive, short-lived oxygen-containing compounds, such as superoxide ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), hydroxyl radical ($^{\bullet}OH$), singlet oxygen ($^1O_2$), and lipid peroxyl radical ($LOO^{\bullet}$). ROS act as second messengers for cellular signaling. However, excessive production of ROS leads to oxidative stress and damage to DNA, lipids, and proteins, which is associated with cancer, cardiovascular diseases, and neurodegenerative diseases. Luteolin has been found to inhibit ROS-induced damage to lipids, DNA, and proteins [28].

5.1 Pro-oxidant Activity :

"Although the ability of flavonoids to protect cells from oxidative stress has been well-documented, there is increasing evidence for their pro-oxidant property. The pro-oxidant activity of flavonoids may be related to their ability to undergo autoxidation, catalyzed by transition metals to produce superoxide anions. In other reports, however, it was observed that the phenol rings of flavonoids are metabolized by peroxidase to form pro-oxidant phenoxyl radicals, which are sufficiently reactive to co-oxidize glutathione (GSH) or nicotinamide-adenine hydrogen (NADH), accompanied by extensive oxygen uptake and ROS formation. The structure-activity relationship study on pro-oxidant cytotoxicity of flavonoids shows that flavonoids with a phenol ring are generally more bioactive than the catechol ring-containing ones. Cytotoxicity induced by flavonoids is correlated with their electrochemical oxidation susceptibility and lipophilicity."

5.2 Estrogenic And Anti-Estrogenic Activity:

Estrogens are hormones that play a role in the growth and specialization of specific cells. When estrogens are present, they activate the estrogen receptor (ER), which then prompts DNA synthesis and cell growth. Flavonoids act as natural phytoestrogens by binding to ERs and triggering their signaling processes.

Due to luteolin's strong estrogenic activity at low levels, it might be beneficial for hormone replacement therapy.

5.3 Anti-Inflammation:

Inflammation is a natural defense mechanism in the body that helps fight infection and heal injuries. However, prolonged or chronic inflammation can lead to harmful diseases like arthritis, chronic obstructive pulmonary disease, and cancer. During inflammation, macrophages are activated by different molecules, including cytokines from the host and toxins from the pathogens..

5.4 Anti-Cancer Activities:

Carcinogenesis is a complex and gradual process resulting from the clonal expansion of mutated cells. The process can be divided into three stages: initiation, promotion, and progression. In the initiation stage, a potential carcinogen (pro-mutagen) is converted to a mutagen by enzymes such as cytochrome P450. The mutagen then interacts with DNA, causing irreversible genetic changes such as mutations, transversions, transitions, and small deletions. The promotion stage involves alterations in genome expression that promote cell growth and proliferation. Finally, during the progression stage, tumorigenicity is established, characterized by karyotypic instability and uncontrolled malignant growth.

5.5 Luteolin As Anticancer or Chemoprevention Agent:

As previously discussed, luteolin has been found to trigger apoptotic cell death in various types of cancer, inhibit the proliferation of cancer cells, and hinder tumor angiogenesis. This suggests that luteolin could be a potential therapeutic agent for treating cancer. In line with findings from laboratory studies, experiments conducted in nude mice with xenografted tumors demonstrated that luteolin effectively suppressed the growth of tumors originating from human skin carcinoma, hepatoma, human ovarian cancer cells, or mouse Lewis lung carcinoma in a dose-dependent manner. Notably, in a Wistar rat model induced with 7,12-dimethylbenz(a)anthracene (DMBA) mammary carcinogenesis, luteolin reduced the incidence of tumors and significantly decreased tumor volume without affecting the total body weight of the animals. Long-term administration of luteolin to rats at a dosage of 30mg/kg per day for 20 days did not show any evident toxicity. Additionally, luteolin exhibited minimal cytotoxicity in normal cells, indicating its relative safety when utilized as an anticancer agent (29).

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