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Application of Luteolin in the Prevention and Treatment of Osteoporosis

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Abstract: ***With the acceleration of global population aging, osteoporosis has emerged as a significant public health issue threatening elderly health. Its high prevalence rate (13% in China) and associated fracture risks impose a heavy burden on socioeconomic development and medical resources. Conventional therapeutic agents face limitations in both efficacy and safety, necessitating the exploration of novel preventive and therapeutic strategies. Luteolin (LUT), a natural flavonoid compound abundant in plants, demonstrates unique advantages in osteoporosis prevention and treatment through its o-dihydroxyphenyl structure endowing potent antioxidant activity and multi-target synergistic effects. Research indicates that LUT establishes a dynamic equilibrium in bone metabolism via multiple mechanisms, including antioxidant stress response, regulation of inflammatory cytokine networks (such as suppression of pro-inflammatory cytokines and tumor necrosis factor expression), promotion of osteogenic differentiation in bone marrow mesenchymal stem cells, activation of the Wnt/β-catenin signaling pathway, and improvement of bone matrix composition. Furthermore, LUT derivatives modulate reactive oxygen species scavenging enzyme activities while inducing apoptosis and autophagy, thereby reinforcing its osteoprotective effects. Despite clinical application challenges posed by LUT's poor water solubility, its multi-pathway action modes offer innovative approaches for personalized treatment. This review synthesizes current understanding of LUT's mechanisms and research progress in osteoporosis management, emphasizing its promising potential as a therapeutic agent. Future efforts should focus on structural optimization and delivery system improvements to facilitate LUT's clinical translation, addressing the pressing challenges in osteoporosis prevention and treatment.***

Keywords: Luteolin, Osteoporosis, Clinical Progress.

1. Epidemiology and Treatment Challenges of Osteoporosis

With the accelerating global aging population, osteoporosis has evolved from a "silent epidemic" into a "silent killer" threatening the health of the elderly. Epidemiological surveys estimate that the current prevalence of osteoporosis in China has reached 13%, and the incidence continues to rise [1]. It is projected that fractures caused by osteoporosis will increase at an annual rate of 135% [2]. Characterized by reduced bone density and deterioration of bone microarchitecture, osteoporosis significantly elevates fracture risk, placing a heavy burden on socioeconomic and healthcare resources [3, 4].

However, public awareness and treatment of osteoporosis still face multiple challenges [5, 6]. Moreover, anti-resorptive and bone-forming drugs used in osteoporosis treatment have their limitations [7-9]. Against this backdrop, developing personalized treatment strategies that balance efficacy and safety has become a central issue in addressing the prevention and management of osteoporosis.

Luteolin (LUT; 3′, 4′, 5, 7-tetrahydroxyflavone) is a natural flavonoid compound widely found in fruits, flowers, herbs, and other plants. The catechol structure in its chemical composition confers significant antioxidant activity [10, 11]. LUT has a molecular weight of 286.24 g/mol and a log P value of 2.26. It is soluble in organic solvents but poorly soluble in water (1.93×10^{-5} mol/kg at 20°C) [12]. This poor water solubility limits its clinical application [13]. Nevertheless, LUT exhibits excellent antioxidant, anti-inflammatory, and bone-regenerative properties, giving it unique advantages in addressing osteoporosis.

In recent years, in-depth studies have revealed that LUT and its derivatives can exert antioxidant or pro-oxidant properties, modulate the activity of ROS-scavenging enzymes, regulate the expression and activation of pro-inflammatory cytokines and tumor necrosis factors, induce apoptosis and autophagy, and target key signaling pathways [14]. Concurrently, research has found that LUT, as a chimeric antioxidant, can promote bone mineralization and regeneration [15]. Through multi-target synergistic effects—including mitigating oxidative stress, regulating inflammatory cytokine networks, promoting osteogenic differentiation of bone marrow mesenchymal stem cells, activating the Wnt/β-catenin pathway, and improving bone matrix composition—LUT establishes a dynamic regulatory network for bone metabolism. This article reviews the mechanisms and research progress of LUT in the prevention and treatment of osteoporosis, with the aim of facilitating its future application in combating osteoporosis.

2. Research Progress on LUT in the Prevention and Treatment of Osteoporosis

2.1 Antioxidant Effects

The antioxidant effect of LUT is crucial in the treatment of osteoporosis. During the progression of osteoporosis, oxidative stress exacerbates the condition by damaging bone microstructure [16]. LUT modulates relevant signaling pathways through its unique mechanism of action, thereby alleviating the development of osteoporosis. Research by de Aguiar ASN found that intermolecular interactions between LUT and hydroxyl groups of water molecules finely regulate the dissociation energy of O-H bonds in oxidation reactions. This microscopic mechanism is closely related to its antioxidant efficacy, enabling LUT to enhance the body's

defense system against oxidative damage and providing an important molecular basis for preventing chronic metabolic diseases and delaying aging processes [17]. Scholars such as Kabir A discovered that when using zein-based nanocomposites incorporating LUT as a material, it can effectively promote calcium and phosphorus deposition, thereby enhancing osteogenesis [15]. Simultaneously, Calabrese EJ et al. found that LUT, at different doses, could induce hormonal responses and promote enhanced osteogenesis in osteoporosis models [10]. Furthermore, Jing Z et al. pointed out that LUT promotes proliferation by attenuating oxidative stress and facilitates osteoblast differentiation by modulating the ERK/Lrp-5/GSK-3β pathway [18]. This suggests that LUT not only scavenges reactive oxygen species to maintain osteoblast function in bone homeostasis regulation but can also directly activate osteogenesis-related signaling pathways and improve the physicochemical properties of the bone microenvironment. However, the interaction mechanism between LUT's antioxidant effects and osteogenic signaling pathways, the impact of different administration concentrations on bioavailability, and the long-term safety still require systematic investigation.

2.2 Inhibition of Osteoclastic Bone Resorption

The imbalance between osteoclastic bone resorption and osteoblastic bone formation is a key factor in the occurrence of osteoporosis [19]. LUT can improve the progression of osteoporosis by inhibiting osteoclastic bone resorption and promoting osteoblastic bone formation. Kim TH et al. found that luteolin could inhibit RANKL-induced osteoclast differentiation and downregulate the expression of osteoclast-related genes [20]. Other studies confirmed that luteolin blocks RANKL-induced formation of mature TRAP-positive osteoclasts by inhibiting the downstream transcription factors p38 MAPK and NFATc1, specifically ATF2, thereby suppressing bone resorption [21]. These studies indicate that LUT inhibits RANKL-activated p38 MAPK phosphorylation, blocks the ATF2/NFATc1 signaling axis, subsequently suppresses the expression of key osteoclast genes, and ultimately reduces the formation and bone resorptive function of mature osteoclasts.

2.3 Promotion of Osteoblastic Bone Formation

LUT may promote the osteogenic differentiation of periodontal ligament cells by activating the Wnt/β-catenin pathway [22]. This suggests that LUT plays a significant role in both inhibiting osteoclastic bone resorption and promoting osteoblastic bone formation. Concurrently, studies have indicated that the Wnt/β-catenin signaling pathway can effectively act on osteoporosis and promote osteogenesis [23]. This pathway not only directly promotes the proliferation and differentiation of osteoblasts but may also simultaneously promote osteoblastic bone formation and inhibit osteoclastic bone resorption, thereby restoring the balance of bone metabolism. This dual mechanism of action gives LUT a unique advantage in the treatment of osteoporosis.

2.4 Anti-inflammatory Effects

LUT also exhibits significant anti-inflammatory properties. In vitro studies have shown that LUT alleviates spike protein-S1-induced cytokine-driven inflammation by inhibiting the activation of the NLRP3 inflammasome and the JAK1/STAT3 signaling pathway [24]. Parallel SARS-CoV-2 studies conducted in spike protein-S1 stimulated THP-1 cells further confirmed that LUT effectively reduces cell damage during infection by inhibiting the MAPK signaling pathway [25]. These findings reveal, at the molecular mechanism level, LUT's dual mode of anti-inflammatory action through multi-target regulation: LUT blocks the upstream signal transduction leading to the cascade release of pro-inflammatory cytokines such as IL-1β and IL-6 induced by spike protein-S1 by inhibiting NLRP3 inflammasome assembly and the JAK1/STAT3 phosphorylation cascade; in immune cells, by inhibiting endoplasmic reticulum stress-induced unfolded protein response and abnormal activation of the MAPK pathway, it both reduces the production of inflammatory mediators and maintains the integrity of cell survival signaling pathways. This suggests that LUT can serve as a natural anti-inflammatory agent with multi-pathway regulatory capacity, holding translational application value in the treatment of systemic inflammatory syndromes. In osteoporosis, microdamage in bone tissue, increased osteoclast activity, and decreased tissue repair capacity are key factors triggering inflammation. Luteolin, through its multi-target anti-inflammatory mechanisms including inhibition of the MAPK pathway, demonstrates unique advantages in osteoporosis treatment. Its synergistic anti-inflammatory and bone-protective effects provide a new strategy for developing natural, low-toxicity anti-osteoporosis drugs. Future research needs to further clarify the pharmacokinetic profile and long-term safety of luteolin in humans and explore its potential for combination with other anti-osteoporosis drugs.

2.5 Mechanism of Regulating Pyroptosis

It has been reported that pyroptosis is a novel hypothesis in the occurrence of osteoporosis [26]. Research by Chai S et al. found that LUT alleviates osteoblast pyroptosis by activating PI3K-AKT signaling, thereby rescuing OVX-induced postmenopausal osteoporosis [27]. The core of this mechanism lies in LUT significantly activating the PI3K/AKT axis, improving mitochondrial dysfunction, and reducing GSDME-mediated pyroptosis. These findings indicate that LUT can promote osteoblast-mediated bone formation by inhibiting GSDME (the executor of pyroptosis protein)-mediated cellular pyroptosis. This suggests that GSDME-mediated pyroptosis may occur in osteoblasts during postmenopausal osteoporosis, and the reduction of osteoblast pyroptosis through LUT treatment depends on PI3K/AKT activation. This mechanism not only deepens the understanding of cell death patterns in osteoporosis but also provides a theoretical basis for developing osteoporosis treatment strategies targeting pyroptosis.

2.6 Regulation of Bone Microenvironment Homeostasis

The formation of bone defects during osteoporosis poses a significant challenge in clinical practice. Improving bone microenvironment homeostasis using bone fillers can be a novel approach to treat bone defects caused by osteoporosis [28]. Kabir A et al. formulated zein-based nanocomposite

materials containing luteolin and applied them to a zebrafish osteoporosis model. They found that this new material has the potential to promote bone regeneration and fracture healing, while also promoting increased calcium/phosphorus deposition and upregulating osteogenic genes [15]. This indicates that novel materials containing LUT can not only fill bone defects but also further improve the osteoporotic microenvironment.

3. Preclinical Research Progress on LUT

Wang Jingjing et al. found that chitosan hydrogels loaded with LUT nanoparticles exhibit good biocompatibility in clinical settings and can effectively leverage the anti-inflammatory properties of LUT. This suggests that flavonoid-containing hydrogels possess unique efficacy in promoting wound healing [29]. Meanwhile, studies have indicated that formulating LUT into solid lipid nanoparticles can effectively enhance its bioavailability [30, 31]. This demonstrates that LUT not only has significant anti-inflammatory characteristics but can also effectively act on the organism to further exert its effects. Additionally, LUT can also be applied in the treatment of diseases such as diabetes [32] and colon cancer [33].

4. Challenges in Clinical Translation

It has been reported that LUT has poor water solubility but is readily soluble in lipids [34]. This necessitates that future research focus on overcoming its bioavailability limitations: by developing novel nano-delivery systems (such as liposomes or polymeric micelles) or structural modification techniques (like glycosylated derivatives) to enhance its gastrointestinal absorption efficiency and bone tissue targeting capability, thereby promoting clinical application translation.

5. Conclusion

Luteolin, through its multi-target and multi-pathway synergistic effects, emerges as a potential drug for preventing and treating osteoporosis. Future efforts should strengthen clinical translation research, address bioavailability and safety issues, and advance its progression from the laboratory to clinical application.

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