Gastrodin for Osteoporosis Treatment

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Gastrodin, a traditional Chinese medicine ingredient, is widely used to treat vascular and neurological diseases. However, recently, an increasing number of studies have shown that gastrodin has anti-osteoporosis effects, and its mechanisms of action include its antioxidant effect, anti-inflammatory effect, and anti-apoptotic effect. In addition, gastrodin has many unique advantages in promoting bone healing in tissue engineering, such as inducing high hydrophilicity in the material surface, its anti-inflammatory effect, and pro-vascular regeneration. Gastrodin promotes the viability and osteogenic differentiation of osteoprogenitor cells, preosteoblasts, and periodontal stem cells, and inhibits osteoclast differentiation, thereby improving bone formation and reducing bone loss.

gastrodin osteoporosis bone regeneration osseointegration

1. Protection of Osteogenesis

1.1. Antioxidant Effect

Mitochondria are the powerhouses in the cellular microenvironment and provide an impetus for cell survival and function. Bone formation and bone remodeling require significant energy consumption, and the energy produced by the mitochondria is essential for maintaining the growth, differentiation, and biological functions of the osteocytes [1]. Any interference with the oxidative phosphorylation pathway in the mitochondria impairs osteogenic gene expression and extracellular matrix (ECM) synthesis in C3H10T1/2 mesenchymal progenitor cells [2]. However, oxidative stress can also lead to cellular dysfunction. When several ROS are generated in the cell, they attack the mitochondrial membrane and mitochondrial DNA, which enhances the autophagy of mitochondria and changes the permeability of the outer mitochondrial membrane. These behaviors disrupt the mitochondrial structure and function, resulting in reduced cellular adenosine triphosphate production and increased ROS production, eventually triggering mitochondrial and cellular dysfunction [3].

The mitochondrial ROS balance is achieved by mitochondrial antioxidants, including Nrf2 [4]. Gastrodin effectively scavenges oxygen radicals to exert antioxidant activity, downregulates lipid peroxidation levels, inhibits uncoupled oxidative phosphorylation, and increases the expression of genes encoding antioxidant proteins such as Nrf2 and HO-1 [5] [6]. By upregulating the expression of the Nrf2/KEAPl antioxidant pathway (NRF2, HO-1, and NADPH quinone oxidoreductase-1), gastrodin reduces the dexamethasone-induced oxidative stress levels in MC3T3-E1 cells and mitochondria, increases osteoblast viability, promotes the expression of osteogenesis-related markers such as Runx2, osterix, bone morphogenetic protein (BMP) 2, and osteocalcin (OCN), and improves the alkaline

phosphatase (ALP) activity and osteogenic mineralization capacity. On the other hand, the antioxidant protective effect of gastrodin is diminished by knocking out Nrf2 [7] [8].

Both bone marrow-derived mesenchymal stem cells (BMSCs) and osteoblasts are involved in bone formation, with the former mainly differentiating into osteoblasts or adipocytes [9]. In vitro studies suggest that oxidative damage may partly contribute to OP by inhibiting the osteogenic differentiation of BMSCs [10]. In elderly patients with OP, the decrease in BMD is accompanied by a decrease in osteoblasts and increase in adipocytes, suggesting that the balance between osteogenic differentiation and lipogenic differentiation of BMSCs is one of the important factors affecting bone quality [11] [12]. Gastrodin inhibits H_2O_2-mediated overproduction of ROS in human bone marrow stromal stem cells (hBMMSCs), significantly promotes the proliferation of hBMMSCs, upregulates the expression of the osteogenic genes ALP, BGLAP, and COL1A1, protects cellular ALP activity and calcification mineralization, and reduces the expression of the lipogenic genes CFD and LPL. Eventually, gastrodin promotes osteogenic differentiation and inhibits lipogenic differentiation of hBMMSCs under oxidative stress [13].

Sirtuin 3 (SIRT3) is a protein deacetylase member of the sirtuin family that is located mainly in the mitochondria. SIRT3 is involved in energy metabolic processes, including the respiratory chain, tricarboxylic acid cycle, fatty acid β-oxidation, and ketogenesis. Thus, SIRT3 controls the flow of the mitochondrial oxidative pathway and the rate of ROS production [14]. It can also affect malondialdehyde (MDA) levels [15], which is an important marker of oxidative stress. It has been reported that SIRT3-deficient mice present OP [16]. Human periodontal ligament stem cells (hPDLSCs) can differentiate into alveolar bone and periodontal ligament-like tissues and in multiple directions [17]. In a lipopolysaccharide (LPS)-induced oxidative damage model of hPDLSCs, gastrodin inhibited oxidative stress in hPDLSCs by upregulating SIRT3 gene expression and decreasing the levels of MDA and lactate dehydrogenase, which are markers of oxidative stress. Gastrodin significantly promoted hPDLSC's proliferative viability and ALP activity, mineralized nodules, and increased the expression of the osteogenic differentiation-related proteins ALP, Runx2, OCN, and osteopontin [15].

In vivo, gastrodin reduced oxidative stress, promoted osteogenic differentiation and mineralization processes, and enhanced bone microstructure and biomechanical strength in glucocorticoid-treated osteoporotic rats [8]. In OVX mice and T2DM rat OP models, gastrodin significantly reduced serum MDA activity, increased glutathione and SOD activity, enhanced antioxidant status, and alleviated bone loss [13] [18]. Gastrodin reduced serum MDA levels, increased SOD activity, reduced ROS accumulation, and alleviated femoral and alveolar bone damage in rats with fluorosis [5].

1.2. Anti-Apoptotic Effect

Apoptosis induction is closely associated with the release of apoptotic factors such as Bax, cytochrome C, pro-caspases, and apoptosis-inducing factor (AIF) [19]. When the mitochondria are subjected to stress disorders, Bax aggregates and oligomerizes at different sites in the mitochondria and regulates cytochrome C translocation release [20]. Cytochrome C release initiates caspase-protease-dependent apoptosis. Additionally, AIF can induce chromosomal DNA-independent cell division and enhance apoptosis. However, gastrodin can block this cascade

response, reduce the protein expression of Bax, cytochrome C, caspase-3 and AIF, and increase the production of the anti-apoptotic factor Bcl-2 to inhibit apoptosis in osteoblasts [7] [8]. In a chondrocyte-mimicking in vitro osteoarthritis model, gastrodin attenuated interleukin (IL)-1β-induced chondrocyte apoptosis by inhibiting the nuclear factor kappa B (NF-kB) signaling [20]. LPS stimulation significantly decreased the expression of Bcl-2 and increased the expression of Bax, caspase-3, and caspase-9. However, gastrodin pretreatment inhibited the LPS-induced apoptosis of the hPDLSCs [12].

In vivo, gastrodin reduced Bax, caspase-3, and caspase-9 protein expression levels and increased Bcl-2 expression in rats with fluorosis [5]. Gastrodin reduced the incidence of osteonecrosis by exerting an anti-apoptotic effect in rats with osteonecrosis [21]. It also improved the peri-implant cancellous bone quality through an anti-apoptotic effect in T2DM rats [18]. Furthermore, gastrodin improved the balance of expression between apoptotic and anti-apoptotic factors in osteoarthritic rats, increased the deposition of proteoglycans in the ECM, and reduced damage to the subchondral bone plate [22].

1.3. Anti-Inflammatory Effect

NF-kB signaling, one of the most important intracellular signaling pathways, is involved in the regulation of inflammatory and pro-inflammatory stress-related responses [23]. When stimulated by inflammatory factors, NF-kB is activated to undergo nuclear translocation and trigger the transcription of inflammation-related genes. Gastrodin-attenuated NF-kB nuclear translocation in chondrocytes reduces the ratio of p-IkB-α/IkB-α, decreases the expression of the inflammatory factors such as tumor necrosis factor (TNF)-α and IL-6, reduces the degradation of the ECM and matrix metalloproteinase 3, and maintains intracellular homeostasis in the chondrocytes. Gastrodin improved cartilage degeneration in an osteoarthritis rat model in vivo [22]. In LPS-induced injury of hPDLSCs, gastrodin significantly reduced the expression of TNF-α and IL-6 and alleviated inflammatory injury [19]. Moreover, gastrodin inhibited the expression of TNF-α and IL-6 in hBMMSCs under oxidative stress [13], and factors such as receptor activator of NF-kB ligand (RANKL), TNF-α, and IL-6 are highly involved in estrogen-deficient OP cases [24].

2. Inhibition of Bone Resorption

2.1. Gastrodin Inhibits Osteoclast Differentiation under Oxidative Stress through Antiox-Idant Effect

Osteoclasts are derived from a monocyte/macrophage cell line (RAW264.7 cells). They are mainly involved in bone resorption and can secrete hydrochloric acid and lysozyme extracellularly to destroy and dissolve the surrounding bone tissue. The normal function of osteoblasts and osteoclasts is to maintain the homeostasis of bone metabolism [25]. Substantial evidence suggests that ROS can increase bone resorption by directly promoting osteoclast differentiation and activity [26]. However, gastrodin reduces the level of ROS in RAW264.7 cells under oxidative stress, inhibits increased osteoclast-specific gene expression (NFATc1, TRAP, CTR, and CTSK) induced by H_2O_2

, and reduces the number of osteoclasts. Thus, gastrodin may exert potential anti-osteoporotic effects by inhibiting osteoclast differentiation [13].

2.2. Gastrodin Inhibits Osteoclast Differentiation in Normal Environment through Antioxidant Effect

Nuclear factor of activated T cells cl (NFATc1) plays a key role in osteoclast differentiation. RANKL activates NFATc1 expression through a series of cascade signals (recruitment of TNF receptor-associated factor 6, mitogen-activated protein kinase, AKT, and NF-kB pathway), which leads to the differentiation and maturation of osteoblasts [27]. Exogenous NFATc1 can still induce osteoclast differentiation in the absence of RANKL, whereas NFATc1-deficient embryonic stem cells cannot differentiate into osteoclasts in the presence of RANKL [28]. However, gastrodin effectively delays the differentiation of the bone marrow-derived macrophages (BMMs) into osteoclasts by downregulating the transcriptional and translational expression of NFATc1. The expression of osteoclast-specific genes, such as TRAP, Cts K, and DC-STAMP, is significantly reduced by gastrodin [29].

Osteoclast differentiation is a multistep process that involves cell proliferation, commitment, fusion, and activation, and the migration of pro-osteoclasts is necessary during the fusion process. In wound-healing experiments, gastrodin significantly inhibited the migration of pro-osteoclasts. Moreover, the bone resorption by osteoclasts in bone fragments was inhibited by gastrodin intervention [29].

In a healthy organism, ROS at normal levels participate in the regulation of normal operation of various biological functions. The differentiation of osteoclasts requires the activation of RANKL, and this process needs the involvement of moderate ROS [26]. Compared with other bone cells, osteoclasts need more ROS [30]. Therefore, in normal environments, such as this study, gastrodin still inhibits osteoclast differentiation by reducing ROS levels. This low level of ROS is insufficient to maintain the activation of RANKL, which is required for osteoclast differentiation.

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