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Effect of Moringa Leaf Extract (*Moringa Oleifera*) on Increasing the Number of Osteoblas as a Marker of Bone Remodeling

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ABSTRACT

Introduction: The process of bone remodeling will continue to occur when a balance between cell activities such as osteoblasts and osteoclasts also occurs. This process is controlled by hormones such as estrogen. Estrogen is known to increase the process of osteoblast differentiation and bone formation so that estrogen therapy is currently considered an effective therapy in preventing bone damage. The activity of estrogen hormone is similar to phytoestrogen activity). One type of phytoestrogens is quercetin. One of the plants in nature which contains the most quercetin is *Moringa oleifera*.

Objective: To determine the effect of quercetin obtained from natural ingredients namely Moringa leaf extract to increase the number of osteoblasts as a marker for bone remodeling.

Literature Review: Leaf extract of *Moringa oleifera* plant contains many flavonoids. One of the most common types of flavonoids found in Moringa plants is quercetin. Quercetin is proven to increase bone formation by suppressing osteoclast formation and activity. Quercetin also has anti-oxidant and anti-inflammatory effects.

Conclusion: Leaf extract of *Moringa oleifera* plant can increase the number of osteoblasts as a marker of bone remodeling.

Keywords: *Moringa leaf extract, quercetin, osteoblasts, osteoclasts, bone remodeling*

Introduction

The process of bone remodeling is likened to a "circle" that will continue to occur when a balance between cell activity also occurs. These cells are osteoblasts and osteoclasts. Osteoblasts are cells that can produce bone organic matrices and stimulate the mineralization process. Whereas osteoclasts are one type of exocrine cell that prevents bone mineralization and can chemically damage the extracellular matrix. The process of bone resorption by osteoclasts is systemically controlled by four main hormones, calcitonin, PTH, vitamin D3 (1,25 vitamin D3), and estrogen. The main role of estrogen in the skeletal system is bone-sparing hormone which acts as a receptor produced by osteoblasts and osteoclasts. This hormone is very crucial in regulating the survival of osteoclasts and can cause osteoclast apoptosis.[1] The activity of estrogen hormone is similar to the activity of phytoestrogens (estrogen-like activity), but the effect is still under the hormone estrogen. However, phytoestrogens are known to be safer in long-term use because they come from plants.[2]

Quercetin is the largest polyphenol compound in nature, which belongs to the flavonoid group. Flavonoids have antioxidant effects and have bioactivity as a drug. These compounds can be found in stems, leaves, flowers, and fruit. Quercetin is also categorized as water-soluble pigments that cannot be produced by humans. Quercetin is also called phytoestrogen. Phytoestrogens are components of non-steroidal plants that can bind to estrogen receptors (ERs) and have estrogen-like action. As is known, estrogen is known to increase the process of osteoblast differentiation and bone formation so that estrogen therapy is currently considered an effective therapy in preventing bone damage.[3] One of the plants in nature which contains the most quercetin is *Moringa oleifera*.

Based on this description, this paper is a literature review about effect of quercetin (phytoestrogens) obtained from natural ingredients namely Moringa leaf extract on increasing the number of osteoblasts as markers of bone remodeling so that it can be used as literature for the development of research for bone remodeling therapy in humans and utilization of herbal ingredients, especially *Moringa oleifera*.

Bone Structure and Bone Remodeling Process: Bone is a dynamic network that has a complex cellular regeneration system. Bone consists of 4 types of cells namely osteogenic cells (osteoprogenitor), osteocytes, osteoblasts, and osteoclasts.[4]

a. **Osteogenic cells (osteoprogenitor):** Osteogenic cells are pluripotent stem cells that have not differentiated and originate from mesenchymal connective tissue. These cells are usually found on the surface of the bone in the inner layer of the periosteum, in the endosteum, and in the vascular ducts of the fracture bone. There are two types of osteoprogenitor cells: 1) preosteoblasts that have little endoplasmic reticulum and will produce osteoblasts; and 2) preosteoclasts which contain more free mitochondria and ribosomes, and produce osteoclasts.

b. **Osteocytes:** Osteocytes or bone cells are osteoblasts which are buried in the bone matrix. The amount ranges from 90-95% of the total number of cells. It is the most cell and has the longest life span in bone (up to 25 years). Electron microscopy shows that the osteocytes and branches do not attach directly to the surrounding matrix, but are separated from the walls of the lacuna and canaliculi by thin amorphous regions. This area seems to function as a metabolite exchange medium.

c. **Osteoblast:** Osteoblasts are cuboidal cells along the bone surface. The amount is about 4-6% of the total number of cells in the bone and the cell that has the most role in bone formation. Osteoblasts are derived from mesenchymal stem cells (MSC), but can also be derived from osteogenic cells. Osteoblasts make, secrete, and precipitate organic elements of the new bone matrix called osteoid. Osteoblast contains an alkaline phosphatase enzyme which indicates that these cells are not only related to matrix making, but also to their mineralization. Osteoid is a bone matrix that has not calcified, is newly formed, and does not contain minerals, but shortly after deposition, the osteoid is immediately mineralized and becomes bone.

d. **Osteoclasts:** Osteoclasts are large multinuclear cells located along the bone surface where resorption, remodeling, and bone repair occur. Osteoclasts are often found in a shallow curve in bone that is absorbed or enzymatically eroded called lakuna Howship. Osteoclasts which were originally inside the bone came from monocyte-like precursors. These cells secrete collagenase and other proteolytic enzymes which cause the bone matrix to release part of the calcifying base substance. After the resorption process is complete, the osteoclasts disappear, degenerate or change again into their original cells.

The remodeling process is two stages of cellular activity that occur cyclic, namely the resorption of old bones by osteoclasts and new bone formation by osteoblasts. First of all, osteoclasts will resorb through a proteolytic acidification and digestion process. As soon as osteoclasts leave the resorption area, the osteoblasts invade the area and begin the formation process by secreting osteoid (matrix of collagen and other proteins) which then undergo mineralization. Normally, the speed of resorption and bone formation takes place at the same speed so that bone mass remains constant.

Resorption activity and bone formation are regulated by various complex systemic factors. The balance between osteoclastic and osteblastic activity is maintained by a constant supply of steroid hormones in bone cells. Disruption in the regulation is evident in aging and estrogen hormone deficiency. In addition to age and menopause, risk factors also known to affect bone mass and density include initial bone density (brought at birth) and calcium availability. Another factor that plays a role in regulation of bone remodeling is vitamin D, where vitamin D supplementation has been shown to increase bone density, even in menopausal women. Parathyroid hormones can increase bone resorption by releasing calcium from the bone matrix into the blood circulation to keep blood calcium levels normal. Other regulators are parathyroid hormones and various cytokines and enzymes which act as coregulers and coreceptors in the differentiation and activity of bone cells.[1,4]

***Moringa oleifera* and Quercetin leaves extract:** *Moringa oleifera* is one of the herbal plants, belonging to the family Moringaceae and is native to South Asia.5 All parts of this plant such as leaves, roots, stems, fruits and flowers are beneficial for health. Leaves from Moringa plants are the most frequently processed parts for consumption as well as herbal medicines.[5]

The largest chemical content in Moringa leaf extract is flavonoids. Flavonoids have the benefit of overcoming microbial infections due to the presence of benzo-yr-pyrone bonds in flavonoids. Flavonoids have been shown to have a positive effect on chronic diseases associated with oxidative stress. Most flavonoids are found in the leaves of Moringa plants. One of the most common types of flavonoids found in Moringa plants is quercetin, with a concentration of 1362.6 mg/kg).[7] Quercetin is a strong anti-oxidant. This is because quercetin consists of three clusters that help maintain stability and act as antioxidants when reacting with free radica The three groups are: O-dihydroxyl group on ring B, 4-oxo group in conjugation with 2,3 alkene, and 3- and 5- hydroxyl groups. The functional group can donate electrons to the ring which will increase the number of resonances of the benzene structure of quercetin compounds. Another benefit possessed by quercetin is that it can reduce oxidative stress reactions (ROS) in the brain meuron, effective as an antiviral agent (such as HSV-1, parainfluenza type 3, pseudorabies, and cardio viruses), as anti-cancer, as well as anti-inflammatory.[8]

Correlation of Quercetin and Bone Remodeling: Based on the results, leaves of Moringa plants are very rich in flavonoids. Flavonoids are chemicals in plants which are very important in health. The most common type of flavonoids found in Moringa leaves is quercetin.[9,10]

Quercetin is the main phytoestrogen found in plants. Phytoestrogens are components in non-steroidal plants that can bind estrogen receptors (E and have estrogen-like activities.[11] Estrogens have an important role in bone tissue hemostasis in the form of estrogen levels decreasing during menopause is the main cause of bone damage and osteoporosis. The mechanism of action of estrogen in bone tissue is completely unknown, but several studies have reported that estrogen preserves bone hemostasis by inhibiting osteoblast and osteoclast apoptosis and preventing excessive bone resorption. Estrogen suppresses the formation and activity of osteoclasts as estrogen inhibits osteoclast apoptosis. Estrogen inhibits osteoclast formation by inhibiting the synthesis of osteoclastogenic cytokine RANKL by osteoblasts and osteocytes. In addition, estrogen inhibits osteoclast formation through reducing levels of other osteoclasogenic cytokines such as IL-1, IL-6, IL-11, TNF-α, TNF-β, and M-CSF.[12,13]

The estrogen activity described above is the same as phytoestrogen activity, the difference lies in the source. Estrogen cannot be produced by plants, while phytoestrogens can only be produced by plants, except algae. Therefore, phytoestrogens began to be developed in skeletal therapy. Interesting phytoestrogens are studied because they have the potential to prevent and treat diseases such as osteoporosis, menopausal symptoms, and so on. Kanno et al. reported that there were effects of phytoestrogens and estrogen on the differentiation of osteoblasts using MC3T3-E1 cells, an osteoblast in mice. Phytoestrogens increase alkaline phosphate activity and stimulate bone mineralization in these mouse cells. This shows that there is a possibility that quercetin can improve the process of bone formation locally. The effect of quercetin on the differentiation and proliferation of human adipose tissue-derived stromal cells (hADSC) also began to be investigated.[14]

Quercetin also has anti-oxidant and anti-inflammatory effects. In a study conducted by Napimoga et.al., quercetin can inhibit bone damage in mice that experience periodontitis. The mechanism of action of quercetin is to reduce the production of inflammatory molecules, inhibit intracellular entry pathways such as mitogen-activated protein kinase (MAPK) and NFKB so that inflammation and oxidative stress decrease, and inhibit cytokine production (IL-1β, TNF-α).[15] As it is known, increasing the amount of TNF-α will lead to increased osteoclast activity. In another study it was stated that TNF-α was actually produced by osteoblasts and superimposed by binding to RANK receptors (receptor activator for nuclear factor kB) macrophages which would later lead to differentiation of macrophages into osteoclasts and increase bone resorption. TNF-α production by either macrophages or osteoblasts alone caused by infection can cause an increase in the number of osteoclasts which in turn causes an increase in bone resorption activity and decreases bone density. If the production of TNF-α can be inhibited, then of course osteoclast production can also be inhibited.[16]

Quercetin is found to increase osteogenic differentiation at certain doses (the dose of flavonoids in the body is around 23 mg, of which 60-75% is quercetin).[13] Quercetin in excessive amounts can also cause toxic effects. A case report states that a 69-year-old man was diagnosed with carcinoma of the heart after consuming quercetin (400 mg/day) and bromelain (100 mg/day). [17,18,19] Normally, the supply of quercetin from fruits and vegetables in the body is 15-40 mg/day. However, for therapeutic purposes such as allergic, anti-inflammatory, and other diseases, quercetin can be prescribed. The therapeutic dose of quercetin ranges from 250-500 mg three times a day. Quercetin is available in capsules (250 mg, 300 mg and 500 mg) and tablets (50 mg, 250 mg and 500 mg). Recommended quercetin doses for adults vary depending on the patient's health condition during treatment.[8]

Conclusion

Based on the literature review that has been done it can be concluded that the leaves of *Moringa oleifera* are rich in flavonoids. The most common type of flavonoids is quercetin. Quercetin is proven to increase bone formation by suppressing osteoclast formation and activity. Quercetin also has anti-oxidant and anti-inflammatory effects. Quercetin can reduce the production of inflammatory molecules, inhibit intracellular entry pathways such as mitogen-activated protein kinase (MAPK) and NFKB so that inflammation and oxidative stress decrease, and inhibit cytokine production (IL-1β, TNF-α).[14] As is known, increase the amount of TNF-α will increase osteoclast activity.

Conflict of Interest: There is no conflict of interest in this study.

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Ethical Clearance: This study obtained a label of ethics escaped by the number: 0038/PL09/KEPKFKG - RSGMUNHAS/2018 and register number UH 17120029 on Oktober 8, 2018.

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