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A Review of The Potential *Marsilea crenata* Presl. Leaves to Prevent Osteoporosis in Menopausal Women

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ABSTRACT

Women going through menopause often experience osteoporosis. One preventive measure comes from herbal plants, especially those containing isoflavones like *Marsilea crenata* Presl. leaves. This plant was chosen because it has been proven as antioxidant, anti-inflammatory, and estrogenic effects that similar to natural hormones. The aim of this study is to investigate the potential of *Marsilea crenata* Presl. leaves as herbal therapy for preventing osteoporosis. The study employs a literature review approach collected from various scientific databases such as Science Direct, PubMed, and Google Scholar. Articles were selected by exclusion and inclusion criteria. The results indicate that isoflavones from *Marsilea crenata* Presl. leaves interact with estrogen receptors, helping to maintain balance between osteoblast and osteoclast activity and reducing bone resorption. Based on in vitro and in vivo studies, the isoflavones in *Marsilea crenata* Presl. leaves include daidzein, genistein, biochanin A, and formononetin. In addition, the antioxidant and anti-inflammatory properties of *Marsilea crenata* Perl. leaves extract can enhance its therapeutic potential. A comprehensive study explains the oral consumption of *Marsilea crenata* Presl. leaves extract in postmenopausal women can increase bone density and alleviate vasomotor symptoms.

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1. INTRODUCTION

Menopause is a natural phase experienced by women, usually marked by the cessation of menstrual cycles due to a decline in ovarian function. Women around 50's years old enter this phase. Before that, perimenopause, the transition phase to menopause, already experience of menopausal symptoms. These symptoms due to significant drop in estrogen levels triggers various short-term symptoms such as sleep disturbances, mood swings, hot flashes, headache, irritability, excessive sweating, joint and bone pain, attention deficit disorder. It also increase in long-term chronic diseases such as osteoporosis, cardiovascular disease, and cognitive decline [1][2].

One of the serious complications that often occurs in menopausal women is osteoporosis, a condition characterized by bone degeneration, low bone mass, and fragility in bone structure. Bone fractures bring about lowering patient's quality of life, increasing complication, and mortality. Epidemiological studies have indicated that the global prevalence of osteoporosis reaches 18.3%. This number can be various among countries with different continent. Most postmenopausal women having a higher risk of developing osteoporosis, particularly in the hip and spine [3]. In Indonesia, The Ministry of Health reported that approximately 23% of women aged 50–

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80 years and 53% of women aged 80 years and older are at risk of developing osteoporosis, which can be prevented by increasing physical activity and ensuring adequate calcium intake [4].

Various pharmacological approaches have been developed to treat osteoporosis, such as hormone replacement therapy (HRT), medication through bisphosphonates, vitamin D and calcium supplements. However, these interventions often cause side effects due to long term consumption. The side effects are allergy, nausea, osteonecrosis of the mandible and atypical femoral fractures, osteosclerosis, osteosarcoma, chest pain, thrombosis, ovarian cancer, breast cancer, and endometrial cancer [3]. Therefore, preventive efforts derived from herbal plants should be done. Based on previous research, phytoestrogens do not escalate the risk of clotting in postmenopausal women. This causes phytoestrogens to be a safe alternative to hormone replacement therapy and prevention of osteoporosis [5][6][7].

Phytoestrogens, found in plant, are compounds that can mimic the function of estrogen hormones in the body. The structure of phytoestrogens similar to 17β-estradiol that can interact with alpha and beta estrogen receptors. Phytoestrogens can decrease menopausal symptoms because of lowly endogeneous estrogen level. Phytoestrogens have many biological effects through molecular mechanism like induction of DNA methylation, RNA expression, histon modification and others. Therefore, phytoestrogens can acts as antioxidant, antiproliferative, antimutagenic to support health and longevity. The main compounds of phytoestrogens are isoflavonoid, flavonoid, stilbene and lignan that belongs to phenolic group [6][7].

One of the herbal plants containing isoflavonoid is *M. crenata* Presl. leaves. This plant has antiosteoporotic activity of n-hexane fraction based on the previous research [5][8]. Osteoporosis as major health problem should be prevented since early stage before menopause comes over. Research about *M. crenata* Presl. leaves as a preventive measure against osteoporosis are still limited. Therefore, the purpose of this study was to explore the potential of *M. crenata* Presl. leaves as an alternative way in preventing osteoporosis in menopausal women.

2. METHOD

This study applies literature review approach to collect scientific evidence and analyze the potential of *M. crenata* Presl. leaves as an herbal therapy in preventing osteoporosis on menopausal women. Literature was collected from various scientific databases such as Science Direct, PubMed, and Google Scholar. Literature searches used keywords such as "*Marsilea crenata* Presl." and "osteoporosis". All articles were selected by exclusion and inclusion criteria. The inclusion criteria were open access articles, published articles between 2020-2025, and all article both review or original research. The exclusion criteria were closed access articles, article language other than English and Indonesian language, other function of *M. crenata* Presl. leaves. Articles were chosen by reading the abstract first and then made a summary for each article. Article's selection process were explained in the following flowchart (Figure 1).

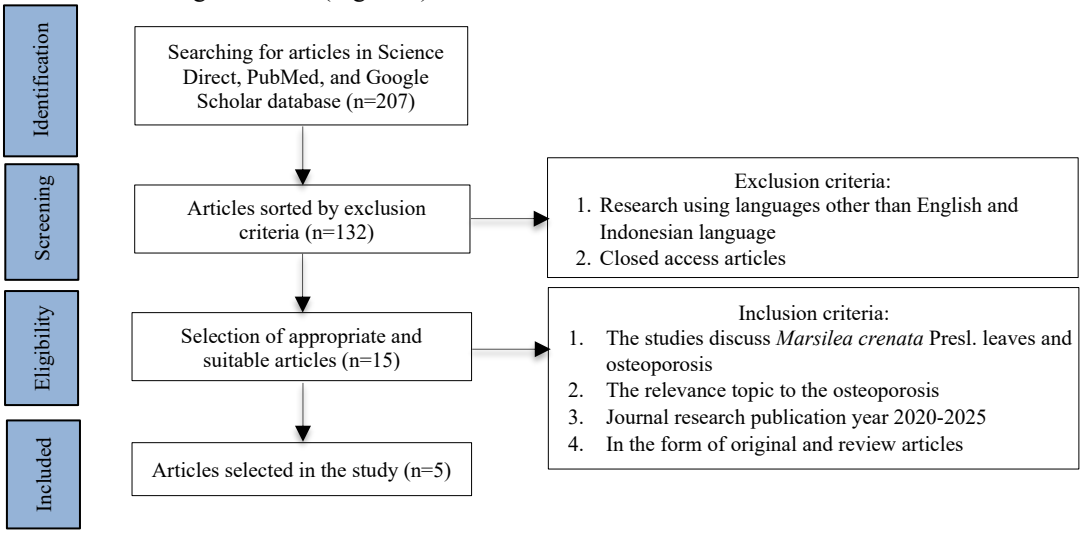

Figure 1. Flowchart of article selection

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3. RESULT AND DISCUSSION

Articles of this study followed PRISMA guideline to select the appropriate article based on potential of *M. crenata* Presl. leaves in preventing osteoporosis (Figure 1). There were 207 articles from various database like Science Direct, PubMed and Google Scholar. Based on exclusion criteria, there were 132 articles and 15 articles sorted by inclusion criteria. After identifying titles, abstracts and relevancies to this study, there were 5 articles met to the topic of this study. Article's summary based on author, title, year and main findings were presented in Table 1.

Tabel 1. Summary of main findings based on study

Author	Year	Title	Main findings
Aditama, A.P.R., Ma'arif, B., Mirza, D. M., Laswati, H., Agil, M. [8]	2020	In Vitro and In Silico Analysis on the Bone Formation Activity of *N*-Hexane Fraction of Semanggi (*Marsilea crenata* Presl.)	This study investigated the bone-forming (osteogenic) activity of the n-hexane fraction of *Marsilea crenata* Presl. leaves. Using human fetal osteoblast (hFOB 1.19) cells, the fraction significantly increased the expression of osteocalcin, a key marker for bone formation, with an optimal dose of 62.5 ppm. Metabolite profiling identified 40 compounds in the fraction. In silico molecular docking studies predicted that 10 of these compounds act as agonists for the estrogen receptor-beta (ER-β), which is known to promote bone formation. The study concludes that the n-hexane fraction of *M. crenata* has high potential as a bone formation agent, likely due to its phytoestrogen content, making it a promising natural alternative for preventing or treating postmenopausal osteoporosis.
Aditama, A.P.R., Ma'arif, B., Laswati, H., Agil, M. [9]	2022	The Effect of Ethyl Acetate Fraction of *Marsilea crenata* Presl. Leaves in Increasing Osterix Expression in hFOB 1.19 Cells	The ethyl acetate fraction highly increased the expression of Osterix (a key transcription factor for bone formation) in human osteoblast (hFOB 1.19) cells. The optimal concentration was 250 ppm, which was comparable to the positive control (Genistein). This indicates the fraction enhances bone-forming activity.
Aditama, A.P., Ma'arif, B., Laswati, H., Agil, M. [10]	2021	In vitro and in silico analysis of phytochemical compounds of 96% ethanol extract of semanggi (*Marsilea crenata* Presl.) leaves as a bone formation agent	The 96% ethanol extract improve the expression of osteocalcin (a bone formation marker) in hFOB 1.19 cells, with an optimal dose of 125 ppm. In silico analysis identified six compounds in the extract that act as phytoestrogens and ER-β agonists, suggesting a mechanism for its bone formation activity.
Ma'arif, B., Aditama, A.P.R., Muslikh, F.A., et al. [11]	2021	Inhibitory Effect of Free-ERβ Expression by n-Butanol Fraction of Semanggi (*Marsilea crenata* Presl.) Leaves on hFOB 1.19 Cells	The n-butanol fraction decreased the expression of free ERβ in hFOB 1.19 cells. The optimal concentration was 62.5 ppm. Activating the ERβ receptor promotes osteoblast proliferation and differentiation, demonstrating the fraction's potential as an

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Author	Year	Title	Main findings
			anti-osteoporosis agent.
Ma'arif, B., Suryanto, Muslikh, F.A., Suryadinata, A., Fauziyah, B. [12]	2022	Systematic Review: Anti-Osteoporosis Potential Activities Of Phytoestrogen Compounds In *Chrysophyllum cainito* L., *Elaeis guineensis* Jacq., *Lannea acida* Rich., *Marsilea crenata* Presl., and *Medicago sativa* L.	The review confirms that *M. crenata* contains phytoestrogens and cites in vivo studies showing that its n-hexane extract increased trabecular bone density in female rats, demonstrating its anti-osteoporotic potential.

Based on Table 1, we found 5 articles related to the topic of this study. Literature studies show that menopause is a physiological phase characterized by decreasing estrogen levels. Estrogen plays an important role in maintaining bone health. Estrogen deficiency is one of the primary pathogenic factors of osteoporois. Decreasing estrogen levels significantly upgrade the risk of osteoporosis [13]. The use of herbal plant can be a good solution to overcome this problem due to low side effect.

Marsilea crenata Presl. leaves show the antiosteoporotic activity based on previous study. The ethyl acetate fraction of this plant escalate osterix--the transcription factor in osteoblast differentiation and maturation process--in human fetal osteoblast (hFOB 1.19) cells. The 96% ethanol extract of *M. crenata* Presl. leaves also have an important effect in bone forming activity by increasing the expression of osteocalcin--a bone formation marker--in hFOB 1.19 cell. This result were also shown by n-hexane extract of *M. crenata* Presl. leaves. Osteocalcin is used as serum marker in osteoblastic bone formation [8] [9] [10]. Other study on n-hexane *M. crenata* Presl. leaves extract showed increasing trabecular bone density in female rat (in vivo study) [12]. All results leading to anti-osteoporotic potential of *M. crenata* Presl. leaves.

In vitro and in silico studies reveals that the compounds in *M. crenata* Presl. leaves have estrogenic activity. This plant contains isoflavone compounds such as daidzein, genistein, and biochanin A, which are phytoestrogens, natural compounds that mimic estrogen hormones. These compounds play a role in balancing osteoblast and osteoclast activity and inhibiting bone resorption. Isoflavone compounds can bind to estrogen receptor beta (ERβ) in the body. When phytoestrogens bind to these receptors, the process of bone cell formation (osteoblasts) increases, while the process of bone resorption decreases [11].

The activation of estrogen receptors also stimulates the production of TGF-β, a substance that helps bone formation and suppresses inflammatory substances such as IL-1, IL-6, and TNF-α, which can accelerate bone damage. This helps balance the activity of osteoblasts (bone-forming cells) and osteoclasts (bone-destroying cells) [11]. Daidzein, in addition to mimicking the function of estrogen hormones in the body, binds to estrogen receptor beta (ERβ) in bone tissue. This compound can activate molecular signaling pathways, such as supporting the osteogenesis process, having anti-inflammatory effects, antioxidant effects, and preventing bone damage caused by oxidative stress [3].

Genistein is similar to estrogen that can bind estrogen receptor (ER). Genistein can probably replace estrogen because it milder agonist compared to estrogen [14]. This compound activates the Wnt/β-catenin signaling pathway, which is important for forming and maintaining bone-forming cells (osteoblasts and osteocytes). This effect occurs through the interaction of genistein with estrogen receptors, thereby normalizing the disrupted bone formation process [15]. Biochanin A compounds can inhibit the activity of osteoclasts, which are cells involved in the breakdown of bone tissue. Levels of reactive oxygen species (ROS) in the body tend to increase and can stimulate a signaling pathway known as mitogen-activated protein kinase (MAPK). This pathway promotes excessive osteoclast formation, thereby accelerating bone damage [16].

Biochanin A works by reducing ROS production and inhibiting the MAPK pathway, thereby suppressing osteoclast formation. In addition, biochanin A also helps increase osteoblast activity, which are cells that form bone, and prevents stem cells from developing into fat cells, which typically increase in conditions of brittle bones. Through this mechanism, biochanin A has the potential to prevent bone damage while supporting the formation of new bone [15]. Through this mechanism, *M. crenata* Presl. leaves have the potential to prevent osteoporosis in postmenopausal women. The antioxidant and anti-inflammatory properties of *M. crenata* Presl. leaves extract can enhance its therapeutic potential in maintaining bone health [17].

A comprehensive study explains that oral consumption of *M. crenata* Presl. leaves extract in menopausal women can increase bone density and relieve vasomotor symptoms [16]. However, this study has several limitations, such as the fact that most of the studies analyzed are still preclinical and conducted on a laboratory scale, so their effectiveness and safety in humans have not been fully confirmed. Additionally, there is a lack of long-term data on potential side effects. Therefore, further clinical research is recommended to evaluate the efficacy and safety of using *M. crenata* Presl. leaves in postmenopausal women over the long term. Developing appropriate herbal formulations, testing the bioavailability of active compounds, and assessing interactions with conventional therapies are also important aspects that require further investigation to enable the potential of *M. crenata* Presl. leaves as a preventive therapy to be implemented in clinical practice.

4. CONCLUSION

M. crenata Presl. leaves can be a choice for preventing osteoporosis because this plant contains phytoestrogen compound. Main compound of *M. crenata* Presl. leaves is isoflavones consisted of daidzein, genistein, and biochanin A. These compounds act by binding to estrogen receptors in bone tissue, thereby helping to balance the activity of osteoblasts (bone-forming cells) and osteoclasts (bone-resorbing cells). Additionally, *M. crenata* Presl. leaves reveal antioxidant and anti-inflammatory properties that can protect bone cells from damage.

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