



Effectiveness Of Ciplukan Stem Water Extract (*Physalis Minima L.*) On Malondialdehyde Levels Of Mandibular Bones Of White Rats (*Rattus Norvegicus*) Wistar Strain Post Ovariectomy

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ABSTRACT

Estrogen functions as an antioxidant that plays an important role in suppressing free radicals; therefore, hypoestrogenic conditions can lead to increased oxidative stress. Periodontitis is a disease closely associated with oxidative stress, which is commonly indicated by elevated levels of malondialdehyde (MDA). Phytoestrogens are plant-derived compounds that exhibit estrogen-like biological activity. The ciplukan plant (*Physalis angulata L.*) is suspected to contain phytoestrogenic compounds, particularly physalin, which may exert effects similar to estrogen. This study aimed to evaluate the effectiveness of ciplukan stem aqueous extract in reducing malondialdehyde levels in the mandibular bone of ovariectomized Wistar rats. This experimental study involved 24 female Wistar rats that were randomly divided into six groups, consisting of three control groups and three treatment groups. The treatment groups received ciplukan stem aqueous extract at doses of 500 mg/kg body weight, 1,500 mg/kg body weight, and 2,500 mg/kg body weight for four weeks. Malondialdehyde levels in the mandibular bone were measured using the thiobarbituric acid (TBA) assay and analyzed with a spectrophotometer to generate an MDA standard curve. The results showed that administration of ciplukan stem aqueous extract at a dose of 500 mg/kg body weight was able to inhibit the increase in MDA levels, while doses of 1,500 mg/kg body weight and 2,500 mg/kg body weight further reduced MDA levels approaching normal values. A strong negative correlation was observed between the dose of ciplukan stem aqueous extract and mandibular bone MDA levels ($r = -0.507$). In conclusion, ciplukan stem aqueous extract effectively reduces malondialdehyde levels in the mandibular bone of ovariectomized Wistar rats, indicating its potential antioxidant and phytoestrogenic effects in hypoestrogenic conditions.

Keywords: Stem Spit, Estrogen, Ovariectomy, MDA Mandibular Bone



INTRODUCTION

Menopause is the cessation of menstruation for 12 consecutive months at the age of 45 - 55 years which marks the beginning of a woman's age, related to a decrease in fertility through a decrease in the number of ovarian follicles produced. During menopause, the ovaries will stop producing estrogen¹⁰. In the literature, there are several studies that correlate between menopause or estrogen and susceptibility to periodontal disease (AHMED et al., 2025). Periodontitis, which involves the response of a local microbial host, is an irreversible condition characterized by damage to the supporting tissues of the teeth, periodontal ligaments, alveolar bones, and cement (Kinane et al., 2017). Oxidative stress is a state in which there is an imbalance between prooxidants and antioxidants, where free radical production exceeds the ability of natural radical inhibitors or scavenging mechanisms (Chaudhary et al., 2023). Periodontitis is one of the diseases related to oxidative stress. Steroid hormones affect the health of periodontal tissue (AHMED et al., 2025). Steroid hormones can cause changes in inflammatory mediators, vascular permeability, as well as fibroblast growth and differentiation. There are estrogen receptors in osteoblasts and fibroblasts of periodontal tissue, which respond to different levels of hormones in different stages of reproduction and thus affect the health of the peridons (Reeves, 2025). Menopausal women are at greater risk of developing periodontal disease and in more severe forms (Martelli et al., 2017).

Estrogen is a sex steroid hormone produced by the ovaries, adrenal cortex, testicles, and placenta during pregnancy (Tal & Taylor, 2015). One of the functions of estrogen is as an antioxidant that can suppress free radical activity. Hypoestrogenic conditions in menopausal women will increase oxidative

stress in the body (Leanza et al., 2023). Malondialdehyde (MDA) is the end product of lipid peroxidation in the body that can be found in most biological samples including foodstuffs, serum, plasma, urine, and human and animal body tissues, including the mandible (Bey et al., 2024). MDA is commonly used as a biological biomarker of lipid peroxidation to assess oxidative stress (Tsikas, 2017). High concentrations of MDA are evidence of the body's low antioxidant status, so it cannot prevent the reactivity of free radical compounds (Jadoon & Malik, 2017).

Today, hormone therapy is widely used to alleviate oral cavity-related menopausal symptoms (Dongiovanni et al., 2023). Hormone replacement therapy has many side effects and is expensive, so it is looking for an alternative to TSH that has the same benefits (Jonklaas, 2022). Another such alternative is phytoestrogens (Rietjens et al., 2017). Phytoestrogens are components of plants that have biological activity similar to estrogen (17- β -estradiol), because they are derived from plants, so there are no significant side effects when compared to regular estrogens. Ciplukan is one of the natural or plant materials that is suspected to be phytoestrogen compounds. In endothelial cell cultures (HUVECs), the administration of ciplukan leaf extract can trigger Ca²⁺ transduction signals, the expression of endothelial nitric oxide (eNOS) and nitric oxide (NO). This suggests that ciplukan leaf extract may stimulate the transcription of genes that play a role in eNOS expression, so it can be suspected that ciplukan stem extract works similarly to estrogen (estrogen like substance), namely it can bind to estrogen receptors, especially beta16 receptors.

The results of theoretical studies show that the ciplukan stem contains a compound with a steroid element, namely physalin (Rakhmawati et al., 2024). Thus, it is suspected that physin has a similar effect to the action of estrogen (Permatasari et al., 2010). Ciplukan stem extract contains alkaloids and flavonoids that have antioxidant potential¹⁴. The dose of the extract used for the study was 500 mg/kg BB, 1,500 mg/kg BB, 2,500 mg/kg BB¹⁶. The extract that is suspected to have an effect on normalizing is at a dose of 2,500 mg/kg BB. In this study, ciplukan stem water extract (*Physalis minima L.*) to lower MDA levels of the mandibular bone in female white rats of the post-ovariectomy wistar strain (Nguyen, 2022).

Menopause is defined as the permanent cessation of menstruation for 12 consecutive months, typically occurring between the ages of 45 and 55 years, and is associated with a decline in ovarian estrogen production (Ambikairajah et al., 2022). Decreased estrogen levels during menopause increase susceptibility to periodontal disease, a chronic and irreversible condition characterized by the destruction of periodontal ligaments, alveolar bone, cementum, and supporting tooth structures (AHMED et al., 2025). Periodontitis is closely linked to oxidative stress, a condition marked by an imbalance between prooxidants and antioxidants, which can be assessed by measuring malondialdehyde (MDA) as a biomarker of lipid peroxidation (Mohideen et al., 2023). Hypoestrogenic conditions contribute to elevated oxidative stress, thereby exacerbating periodontal tissue damage (Lucisano et al., 2021). Although hormone replacement therapy is commonly used to manage menopausal symptoms, its high cost and potential side effects have encouraged the exploration of safer and more affordable alternatives, such as phytoestrogens (Comparetto & Borruto, 2023).

The purpose of this study was to evaluate the effectiveness of ciplukan stem water extract (*Physalis minima L.*), which contains phytoestrogenic and antioxidant compounds such as physalin, flavonoids, and alkaloids, in reducing MDA levels in the mandibular bone of ovariectomized Wistar rats as a model of menopausal conditions. The extract was administered at doses of 500 mg/kg body weight, 1,500 mg/kg body weight, and 2,500 mg/kg body weight (Yun et al., 2018).

The benefit of this study lies in providing scientific evidence supporting the antioxidant and estrogen-like potential of ciplukan stem extract as a natural therapeutic option to mitigate oxidative stress associated with estrogen deficiency, particularly in periodontal tissues.

The implications of this research suggest that ciplukan stem extract may serve as a promising, low-cost, and safer alternative to hormone replacement therapy for preventing or reducing oxidative stress-related periodontal damage in menopausal conditions. These findings contribute to the development of plant-based complementary therapies and support further preclinical and clinical studies to explore their application in menopausal oral health management.

METHOD

1. Research Design

This study uses true *experimental design* in the laboratory using *the Randomized Post Test Only Controlled Group Design method*

2. Large Sample

In this study, there were 6 treatment groups. The number of test animals for each treatment can be searched using the formula $p(n-1) \geq 15$, with n = the number of repetitions of each treatment, p = the number of treatments²⁴.

$$\begin{aligned} p(n-1) &\geq 15 \\ 6(n-1) &\geq 15 \\ 6n - 6 &\geq 15 \\ 6n &\geq 21 \\ n &\geq 3.5 \end{aligned}$$

So for 6 groups 24 rats are needed because the number of repetitions of profit for each group is 4.

3. Research Procedure

a. Preparation for Animal Breeding

The mice were adapted in the laboratory for 7 days.

b. Oophorectomy

1. Sterilized tools and materials are arranged on a workbench.
2. The weight of the rats was weighed, then the rats were fixed in the supination position.
3. Anesthesia was carried out using *ketamine* i.m with a dose of 40 mg/kg BB
4. The abdominal hair is shaved about 1 cm above the second line of the ovaries then sterilized using 70% alcohol and *betadine solution*. After that, it is covered with a sterile doppelgänger.
5. The incision is made trans abdominal approximately above the uterus along 1.5 – 2 cm layer by layer until it penetrates the peritoneal wall.
6. The incisional wound is pulled to the right and left laterals using the right.
7. The uterus is searched by carefully tracing the *corneal uterus-oviduct-ovaries*, the left ovary being seen as a translucent cluster of grapes.
8. *The oviduct* and ovaries are freed from the surrounding fatty tissue and connective tissue. Next, the distal oviduct and ovary are ligated, then the *oviduct* and ovary are removed. The cut wound was given *powdered baccisin (Nebacetin)*. The same procedure is performed for the right ovary.

9. The incision wound was closed or sutured layer by layer with a thread, then the wound was smeared with *betadine* and given *Nebacetin*, closed with sterile gauze, then *Gentamycin* i.m with a dose of 60-80 mg/kg BB 1 time per day for 3 days, and *Novalgine* i.m with a dose of 0.3 ml for 1 day.
10. Mice that have been ovariectomy are transferred into a recovery cage. Each cage contains 1 tail. The rats were observed continuously until they regained consciousness. During maintenance, the rats are fed and drinking enough, alternating light or dark light for 12 hours and at room temperature.
11. The assessment of the success of *ovariectomy* was carried out 2 weeks after *ovariectomy*, where *estradiol* levels decreased markedly. This has been proven by Davis (2006) and a reduction in *estradiol* levels with a sensitivity of 9 pg/ml was obtained by the ELFA (*Enzyme Linked Fluorescent Assay*) technique.

c. Making Ciplukan Stem Water Extract

a. Drying process

1. The stalk of the spruce to be dried is washed clean
2. Cut into small pieces
3. Dried in the heat of the sun

b. Extraction process

1. Once dry, blend with a blender until smooth
2. Dried powder of the ciplukan stem weighed as much as 100 grams
3. 100 grams of dried powder of ciplukan stems are put in a 50 ml cup cup
4. Put boiling water at 100°C. Stir until completely combined. Cover with aluminum foil. Let stand for 1 hour.

c. Screening Process

1. Prepare an Erlenmeyer glass, a glass funnel, and filter paper
2. The ciplukan stem extract solution that has been left for 1 hour is filtered using filter paper
3. After everything is filtered, a filter paper containing the pulp from the ciplukan stem powder is squeezed by hand to obtain the remaining solution
4. The extraction results are put into the bottle.

d. Provision of Ciplukan Stem Water Extract

The administration of ciplukan stem water extract using a syringe with the end of a probe so that it can enter the mouth of the rat up to the stomach.

e. Thiobarbituric Acid (TBA) Test

The mandibular bones that have been crushed into powder using *round diamond bur* and *fissure diamond bur* installed on *the contra angle handpiece* and micromotor, are weighed as much as 20 mg and then reacted with the addition of 1 cc phosphate buffer. Furthermore, 15% TCA is added as much as 200 microliters, HCl 1 N 200 microliters, 1% Natio Barbiturate as much as 200 microliters, then heated in water at a temperature of 100°C for 25 minutes. The centrifuge at a speed of 3000 rpm is then taken supernatant on top to be made into 2 cc with

the addition of aquabides or phosphate buffers. Furthermore, the results were measured using a 532 nm wavelength spectrophotometer. MDA concentrations are measured using MDA work curves.

4. Data Analysis

Each group was seen to distribute their data with the *Shapiro Wilk Test data normality*. The results of the normality test had a significance value of 0.224 which means that the data was normal. Then a variance homogeneity test was carried out and a significance value of 0.054 was obtained, which means that the data has the same variant. Next, the *One Way ANOVA* test was carried out. The test results obtained a significance value of 0.000 which means that there are significantly different groups. Then a *Post hoc test* was carried out. After that, a Pearson correlation test was carried out.

RESULTS AND DISCUSSION

The experimental animals were divided into 6 groups, namely 3 control groups and 3 treatment groups with each group consisting of 4 experimental animals. The control group included the negative control group, the 5-week oophorectomy group, and the 9-week oophorectomy group. The treatment groups included 3 groups who had a 5-week oophorectomy which was then given a semen stem extract at a dose of 500 mg/kg BB, 1500 mg/kg BB, and 2500 mg/kg BB for 4 weeks. MDA levels were measured using a spectrophotometer with a wavelength of 532 n.

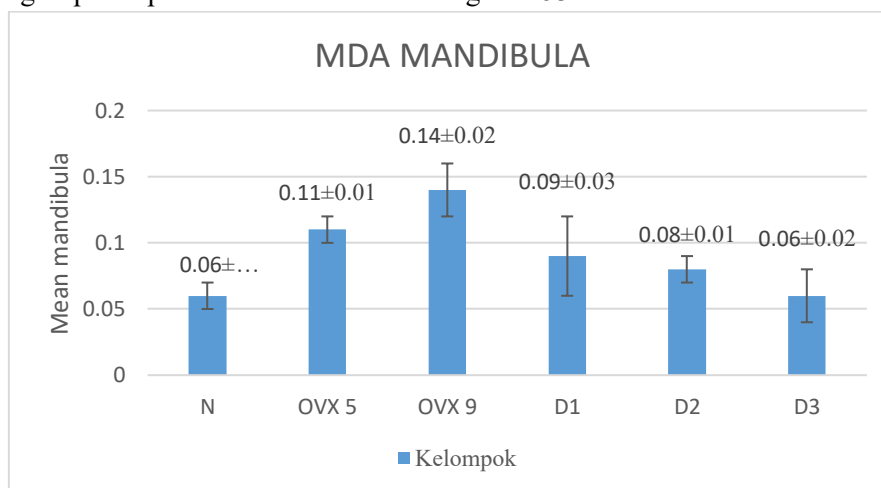


Figure 1. Chart of Average and Standard Deviation of MDA Levels of Mandibular Bone in Each Group

Description :

Group N: Negative control group, rats not given treatment

OVX Group 5: A group of mice treated with oophorectomy for 5 weeks

OVX Group 9: A group of mice treated with oophorectomy for 9 weeks

Group D1 : A group of rats that had been diovariectomy for 5 weeks and given ciplukan stem extract 500 mg/kg BB for 4 weeks

Group D2: A group of mice that had been divariectomy for 5 weeks and were given ciplukan stem extract of 1500 mg/kg BB for 4 weeks

Group D3 : A group of mice that had been divariectomy for 5 weeks and given ciplukan stem extract of 2500 mg/kg BB for 4 weeks

Post Hoc Test Multiple Comparisons

The *Post Hoc* test was carried out to find out the differences from each group because in the ANOVA test the conclusion of H0 was rejected. The method used in this test is the LSD (*Least Significant Difference*) test. A data can be said to be significantly different if the significance value is less than 0.05.

Table 1. Results of Multiple MDA Levels of Mandibular Bone MDA

Value p	N	OVX 5	OVX 9	D1	D2	D3
N	-	0.000	0.000	0.006	0.060	0.894
OVX 5	0.000	-	0.023	0.068	0.007	0.000
OVX 9	0.000	0.023	-	0.000	0.000	0.000
D1	0.006	0.068	0.000	-	0.238	0.008
D2	0.060	0.007	0.000	0.238	-	0.077
D3	0.894	0.000	0.000	0.008	0.077	-

Description7:

p < 0.05 = There is a significant difference between the two groups

p > 0.05 = There was no significant difference between the two groups

Based on the results of the LSD test, it was concluded that:

1. The 5-week and 9-week post-oophorectomy rat groups that were not given ciplukan stem water extract experienced significant increases in mandibular bone MDA levels compared to the MDA levels of the mandibular bone of the untreated negative control group.
2. The 9-week post-oophorectomy group of mice that were not given ciplukan stem water extract experienced a significant increase in mandibular bone MDA levels compared to the MDA levels of the 5-week post-oophorectomy group of mice that were not given ciplukan stem water extract
3. A group of 5-week post-oophorectomy mice who were given a 500 mg/kg BB dose of semen extract for 4 weeks experienced a significant increase in mandibular bone MDA levels compared to the MDA levels of the mandibular bone of the untreated negative control group.
4. The 5-week group of post-oophorectomy mice who were given semen extract at a dose of 1500 mg/kg BB for 4 weeks experienced a non-significant increase in mandibular bone MDA levels compared to the MDA levels of the mandibular bone of the untreated negative control group.
5. The 5-week group of post-oophorectomy mice who were given semen extract at a dose of 2500 mg/kg BB for 4 weeks experienced a non-significant increase in mandibular bone MDA levels compared to the MDA levels of the mandibular bone of the untreated negative control group.

6. The 5-week post-oophorectomy rat group given ciplukan stem water extract at a dose of 500 mg/kg BB for 4 weeks experienced a significant decrease in mandibular bone MDA levels compared to the mandible bone MDA levels of the 9-week post-oophorectomy group of rats who were not given ciplukan stem water extract, while the decrease was not significant compared to the MDA levels of mandibular bone in the 5-week post-oophorectomy group of mice that were not given ciplukan stem water extract.
7. The 5-week post-oophorectomy group of mice given a dose of 1500 mg/kg BB and 2500 mg/kg BB for 4 weeks experienced a significant decrease in mandibular bone MDA levels compared to the 5-week and 9-week post-oophorectomy group of mice that were not given ciplukan stem water extract.

Pearson Correlation Test

The Pearson correlation test functions to measure the strength of the linear relationship between two variables that can be seen from the correlation coefficient. The relationship between two variables can consist of two types of relationships, namely positive relationships and negative relationships. In this study, the Pearson correlation test was used to prove the correlation between the increased dose of ciplukan stem water extract and the MDA level of the mandible bone.

The results of the Pearson correlation test that have been carried out are that:

1. The correlation strength (r) is -0.507. There was a strong correlation between the dose of ciplukan stem water extract and the MDA levels of the mandibular bone
2. Negative correlation direction. The larger the dose of ciplukan stem water extract, the smaller the MDA level of the mandibular bone
3. The p value = 0.011, so it can be said that there is a significant correlation ($0.011 < 0.05$) between the dose of ciplukan stem water extract and the MDA level of the mandible bone.

DISCUSSION

This study was carried out with the aim of determining the effectiveness of ciplukan stem water extract (*Physalis minima L.*) on the level of malondialdehyde of the mandibular bone in white rats (*Rattus norvegicus*) strain of wistar post-ovariectomy. This study used a *true experimental design* in the laboratory using the *Randomized Post Test Only Controlled Group Design* method because the group selection was carried out randomly, and was divided into treated and untreated groups. The experimental animals were divided into 6 groups, namely 3 control groups and 3 treatment groups. The results of the negative control group's MDA value were 0.06 ± 0.01 . This is because under normal conditions, the body also produces free radicals. Under normal circumstances, cells produce free radicals as a consequence of biochemical reactions in cell metabolism². Free radicals can be produced endogenous or exogenous. Endogenously free radicals are produced through normal metabolic reactions in the body involving oxidation-reduction^{reactions21}. Aerobic organisms need oxygen to produce a compound that is a source of energy for living things through oxidative phosphorylation that occurs in mitochondria. The compound is called Adenosine Triphosphate or ATP². Free radical attack on lipid components causes a lipid peroxidation reaction that will produce the final product, MDA, which is highly toxic to cells⁸.

Based on the results of statistical analysis, it was found that there was a significant increase in the MDA levels of the mandible bone in the 5 week and 9 week post-oophorectomy groups of mice that were not given semen extract compared to the MDA levels of the mandible bone of the negative control group of mice that were not given treatment. There is an increase in MDA levels in hypoestrogenic conditions because during menopause there is an increase in oxidative stress²⁵. During the hypoestrogenic condition, there is also a decrease in SOD levels due to free radicals being formed⁸, as a result of which the body cannot neutralize ROS²⁶.

Antioxidants have a function as an antidote to free radicals²⁵. Giving 17 β -estradiol to estrogen can lower MDA levels¹¹. A free hydroxyl group at the carbon 3 position is said to have an important role in antioxidant effects. This hydroxyl group can bind to free radicals in the human body, making free radicals a stable compound that does not damage the body's cells and tissues¹⁷, through interaction with ER β , estrogen can also improve antioxidant status by regulating gene expression of antioxidants⁴. Based on these estrogen functions, it can be concluded that hypoestrogenic conditions cause MDA levels to increase. Under normal circumstances, there is a balance between prooxidants and antioxidants in the body's biochemical system, so that body tissues are prevented from damage due to ROS¹⁹.

Phytoestrogens are components of plants that have estrogen-like biological activity (17- β -estradiol). The chemical structure of phytoestrogens is mostly non-steroidal whereas estrogen is generally steroid. Phytoestrogens are a group of nonsteroidal polyphenols found in plants that have a biological response bound to the estrogen^{receptor}¹⁸. Ciplukan plants are suspected to be phytoestrogens. In a study conducted by Permatasari (2007), it was found that ciplukan leaf extract is a vasodilator and works through a non-competitive antagonist of the adrenergic alpha-1 receptor. In subsequent studies, the administration of ciplukan leaf extract can trigger Ca²⁺ transduction signals, *endothelial nitric oxide* (eNOS), and *nitric oxide* (NO) expression. Based on theoretical studies, it is proven that the leaves and stems of ciplukan contain compounds with steroid elements, namely *physalin*. In subsequent studies, *physaline* administration may also trigger the transduction signal of Ca²⁺, eNOS expression in endothelial cells. These results further prove the allegation that ciplukan and *physalin leaf and stem* extracts have effects similar to the work of estrogen (*estrogen-like* substances).

Based on test results *Post Hoc LSD*, The 5-week group of post-oophorectomy rats who were given ciplukan stem water extract at a dose of 500 mg/kg BB for 4 weeks experienced a not significant decrease in mandibular bone MDA levels compared to the MDA levels of 5-week post-oophorectomy mice that were not given ciplukan stem water extract. However, in the 5-week group of post-oophorectomy rats who were given ciplukan stem water extract at doses of 1500 mg/kg BB and 2500 mg/kg BB for 4 weeks, there was a significant decrease in mandibular bone MDA levels compared to the MDA levels of mandible bone of the 5-week and 9-week post-oophorectomy groups that were not given ciplukan stem water extract.

The hypothesis of this study is proven, namely the administration of ciplukan stem extract (*Physalis minima L.*) may lower MDA (Malondialdehyde) levels of the mandible bone in white rats of the post-wistar strain *Ovariectomy*. The 5-week post-oophorectomy group of mice given ciplukan stem water extract at a dose of 500 mg/kg BB for 4 weeks experienced significant improvement in mandibular bone MDA levels compared to the mandible bone MDA levels of mice in the untreated negative control group, while the results were not significant at doses of 1500 mg/kg BB and 2500 mg/kg BB when compared to the negative control group. This proves that at a dose of 500 mg/kg BB can only inhibit the increase in mandibular MDA levels, while at a dose of 1500 mg/kg BB and 2500 mg/kg BB can reduce the level of mandible MDA close to normal. This is in accordance with the target of the classic estrogen and phytoestrogen pathways, which can modulate eNOS and the expression of antioxidant genes through complex receptor interactions with *Estrogen Response Element* (ERE) and/or *Antioxidant Response Element* (ARE) in the region of the target gene promoter. Natural antioxidants in ciplukan plants can increase SOD production followed by a decrease

in ROS, which is characterized by a decrease in MDA levels. Decreased MDA levels occur because oxidative stress decreases so that the risk of periodontitis also decreases⁶.

The results of the Pearson correlation test found that the correlation strength (r) was -0.507 . It can be said that there is a strong correlation between the dose of ciplukan stem water extract and the MDA level of the mandibular bone. Negative correlation direction. So, the larger the dose of ciplukan stem water extract, the smaller the MDA level of the mandibular bone. The value of $p = 0.011$, so it can be said that there is a significant correlation ($p < 0.05$) between the dose of ciplukan stem water extract and the MDA level of the mandible bone. The results of the study prove the hypothesis that the administration of ciplukan stem water extract (*Physalis minima L.*) may lower MDA (Malondialdehyde) levels of the mandible bone in white rats of the post-wistar strain ovariectomy. The administration of ciplukan stem water extract at a dose of 500 mg/kg BB can inhibit the increase in MDA levels of the mandibular bone because the results of the reduction in MDA levels of the mandible bone mandibles are not significant compared to the MDA levels of the mandible bone of the 5-week group of mice who were not given ciplukan stem water extract. The administration of water extract at a dose of 1500 mg/kg BB 2500 mg/kg BB can improve MDA levels close to normal.

CONCLUSION

Based on the results of this study, it can be concluded that the administration of ciplukan stem water extract (*Physalis minima L.*) effectively reduces malondialdehyde (MDA) levels in the mandibular bone of ovariectomized Wistar rats, thereby confirming the research hypothesis. The findings also indicate that MDA levels in the mandibular bone increase with the duration of menopausal conditions following oophorectomy and exhibit a dose–response relationship, in which higher doses of ciplukan stem water extract are associated with a greater reduction in MDA levels in a negative direction. Furthermore, administration of the extract at a dose of 500 mg/kg body weight was sufficient to inhibit the increase in MDA levels, while higher doses of 1,500 mg/kg body weight and 2,500 mg/kg body weight were able to further reduce MDA levels to values approaching normal conditions. These results highlight the potential of ciplukan stem water extract as an effective antioxidant and phytoestrogenic agent in mitigating oxidative stress in menopausal models.

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