**Journal Of Nursing Practice**
https://thejnp.org/
ISSN: 2614-3488 (print); 2614-3496 (online) Vol.8 No.2. January 2025. Page.282-291

# Bengkuang as an Alternative for Hypoestrogen Problems in the Reproductive System

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## ABSTRACT

**Background:** Hypoestrogenism is a condition characterized by a deficiency of the hormone estrogen. This condition is commonly experienced by women who are menopausal or those using hormonal contraceptives like Depot Medroxyprogesterone Acetate. Exposure to this synthetic progesterone can suppress the production of estrogen, leading to a decrease in the expression of estrogen receptors. One alternative to overcome the problem of hypoestrogenism is the use of natural ingredients known as phytoestrogens, which are chemically and functionally similar to estrogen. Bengkuang is known as one of the sources of phytoestrogens.

**Purpose:** This study aims to assess the impact of bengkuang ethanol extract on estrogen levels and the expression of estrogen receptor beta in a hypoestrogenic rat model exposed to DMPA.

**Methods:** This experimental study involved 25 rats, which were divided into five groups. One group served as the negative control and did not receive DMPA or Bengkuang extract, while the four treatment groups were administered DMPA at a dose of 2,7 mg every three days, repeated four times. Three of the treatment groups received Bengkuang extract at varying doses. The data were analyzed using a one-way ANOVA test.

**Results:** The findings indicated significant differences ($p < 0,05$) in estrogen levels and the expression of estrogen receptor beta.

**Conclusion:** Administration of bengkuang extract can enhance the female reproductive system with low estrogen levels.

**Keywords:** bengkuang, female reproductive system, hypoestrogen

Received November 10, 2024; Revised December 12, 2024; Accepted January 3, 2025
**DOI:** https://doi.org/10.30994/jnp.v8i2.742

ISSN: 2614-3488 (print); 2614-3496 (online) Vol.8 No.2. January 2025. Page.282-291

## BACKGROUND

Family planning is a strategy aimed at regulating the timing and spacing of children in order to promote quality family life. A commonly used method of contraception is Depot Medroxyprogesterone Acetate (DMPA), which is a hormonal injectable contraceptive that contains the hormone progesterone. It is administered as an intramuscular injection in a dosage of 150 milligrams. In Indonesia, the percentage of new acceptors of DMPA injection as a contraceptive is the highest at 49.93%, while the percentage for old acceptors is 47.78%. (Kemenkes RI, 2022). DMPA primarily works by preventing the LH surge, which is essential for ovulation. It does not systematically suppress FSH (Follicle-Stimulating Hormone) like some other hormonal contraceptives. In addition to blocking LH, the progestin-dominant hormonal environment leads to the thickening of cervical mucus and changes in the endometrium (the lining of the uterus). Estrogen levels during DMPA use are similar to those observed in the early follicular phase of women who are not using contraception. As a result, symptoms typically associated with estrogen deficiency, such as hot flashes or vaginal dryness, are not experienced with this contraceptive method (Sathe, 2024).

Administering hormones from external sources, such as hormonal contraceptives containing estrogen and progesterone, results in elevated levels of these hormones in the bloodstream. This increase is detected by the anterior pituitary gland, which responds by decreasing the secretion of the hormones FSH (follicle-stimulating hormone) and LH (luteinizing hormone) due to negative feedback. Additionally, exposure to progesterone enhances the inhibitory effect of estrogen. Over time, the body may attempt to recover by increasing its secretion of estrogen to maintain normal levels. However, long-term use of these external hormones can lead to a reduced ability for recovery and a decrease in hormone secretion, particularly estrogen (Andryani, et al., 2021; Nurhayati, et al., 2023).

In addition, the progesterone found in Depot Medroxyprogesterone Acetate can reduce the expression of estrogen receptors. These receptors play a crucial role in mediating estrogen's effects during the menstrual cycle and the functioning of the related organs. Estradiol, a form of estrogen produced in the ovaries, is vital for female reproduction. When estradiol levels are low, it disrupts the process of folliculogenesis by inhibiting ovulation. As a result, the follicles cannot develop properly and undergo atresia due to apoptosis. Widespread apoptosis can lead to tissue damage, which is characterized by reduced ovarian function. Consequently, the ovaries may become atrophic, ovulation ceases, estradiol levels in circulation decline, and overall reproductive function diminishes (Bastianelli et al., 2020).

Estrogen has two receptors that play different roles. During the menstrual cycle, the administration of Depot Medroxyprogesterone Acetate leads to the production of estrogen (estradiol) in smaller amounts than normal. This decrease in estradiol due to DMPA results in the inactivation of estrogen receptors. Both estrogen receptors can bind to estradiol with the same affinity, but they can respond differently to various estrogen agonists and antagonists. Research with mice has shown that estrogen receptor beta can modulate the effects of estrogen receptor alpha on the endometrium in response to estradiol. As a result, the ratio of estrogen receptor alpha to estrogen receptor beta in the endometrium can influence how the tissue responds to estradiol and its analogs (Kennedy et al., 2020; Sereepapong et al., 2019).

To mitigate the effects of DMPA (Depot Medroxyprogesterone Acetate) use, consider incorporating natural ingredients containing phytoestrogens plant compounds with a chemical and functional structure similar to 17β-estradiol. One well-known source of phytoestrogens is soybeans. However, it's important to note that while many studies highlight the health benefits of soy, processed soybean products have the potential to contribute to conditions like arthritis (gout). This is due to soybeans having a moderate purine content, ranging from 100

ISSN: 2614-3488 (print); 2614-3496 (online) Vol.8 No.2. January 2025. Page.282-291

to 400 mg per 100 grams. Therefore, it's advisable to limit purine intake to maintain normal uric acid levels (Eun et al., 2021).

Another alternative source of phytoestrogens that does not risk triggering arthritis is Bengkuang. Research has identified four phytoestrogen compounds in yam tubers: daidzein, daidzein7-0-ß-glucopyranose, 5-hydroxy-daidzein7-O-ß-glucopyranose, and (8,9)-furanyl-pterocarpan-3-ol (Lukitaningsih & Holzgrabe, 2013; Jaiswal & Lee, 2021). These compounds are believed to play a significant role in influencing estrogen receptors (Dewiani, 2020).

*Pachyrhizus erosus*, commonly known as jicama, is a plant recognized in Indonesia as bengkuang or besusu. It contains phytoestrogens, with the highest levels of isoflavones, specifically daidzein and genistein. Analyses using High-Performance Liquid Chromatography (HPLC) have revealed that Bengkuang tubers contain daidzein at a concentration of 108.831 mg per 100 grams and genistein at 163.079 mg per 100 grams (Primiani, 2015; Sholihah, 2016). Identification of isoflavone compounds in bengkuang ethanol extract, conducted through Liquid Chromatography-Mass Spectrometry (HPLC-MS), indicated that daidzein has a molecular weight of 254 g/mol, while genistein has a molecular weight of 270 g/mol. Bengkuang contains phytoestrogen compounds that mimic estrogen and can bind to estrogen receptors. Regarding gout, the daidzein compound is known to reduce uric acid concentrations by inhibiting xanthine oxidase, an enzyme involved in uric acid production (Laddha & Kulkarni, 2023).

## OBJECTIVE

This study aimed to assess the impact of administering bengkuang ethanol extract to enhance estrogen levels and estrogen receptor beta expression in a hypoestrogenic model of rats (*Rattus norvegicus*) induced by DMPA.

## METHODS

This study is a true experimental research project featuring a post-test-only control group design. The interventions involved administering Depo-medroxyprogesterone acetate (DMPA) injections, followed by various doses of Bengkuang extract (*Pachyrhizus erosus*) to white rats (*Rattus norvegicus*). After the treatment, the results measured included estrogen levels and the expression of estrogen receptor beta. This research was conducted at the Faculty of Medicine, Brawijaya University, during July and August 2024. The Bengkuang extraction process was carried out at the Pharmacy Laboratory, Faculty of Health Sciences, Kadiri University using the maceration method using 96% concentration ethanol solvent.

Before the intervention, the mice were acclimatized for one week to facilitate adaptation. The initial vaginal smear examination was conducted to determine the estrus phase in the mice, serving as an indicator for the start of the intervention. The researchers established five groups: a negative control group that received neither DMPA nor ethanol extract of Bengkuang, a positive control group, and three treatment groups. Treatment group 1 (P1) received DMPA and extract at a dosage of 70 mg per 200 g of body weight per day, treatment group 2 (P2) received DMPA and extract at 140 mg per 200 g of body weight per day, and treatment group 3 (P3) received DMPA and extract at 280 mg per 200 g of body weight per day. DMPA was administered intramuscularly at a dosage of 2,7 mg into the quadriceps muscle every three days, repeated four times. A second vaginal smear examination was performed after the final DMPA injection. Bengkuang extract was given to treatment groups 1, 2, and 3 daily for 14 days. The mice were termination during the proestrus phase. During the proestrus phase, FSH hormone levels increase, and follicles that produce estrogen develop. Blood samples were collected to measure estrogen levels using an Enzyme-linked Immunosorbent Assay (ELISA) Kit for Estradiol (E2). Additionally,

endometrial tissue samples were collected to assess the expression of estrogen receptor beta using immunohistochemistry. Hypothesis testing using One-way ANOVA test.

This study was approved by the Research Ethics Commission of the Institute of Health Science Strada Indonesia number 001461/EC/KEPK/I/07/2024.

## RESULTS

### Results of vaginal smear examination

The purpose of DMPA injection is to create a hypoestrogenic animal model in rats. Hypoestrogenic conditions were confirmed by examining vaginal smears after the fourth dose injection. Furthermore, rats received ethanol extract of bengkuang according to the dose determined for each treatment group, excluding the positive control group and the negative control group. After the last dose of bengkuang extract, a vaginal smear examination was performed again to identify the proestrus phase for further termination (Figure 1).

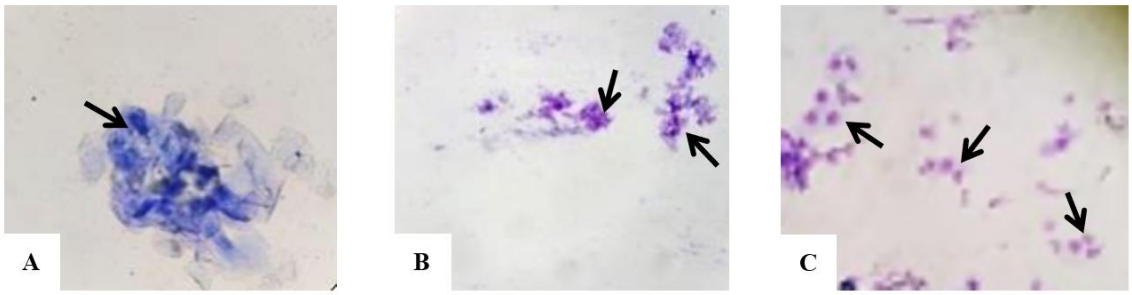


**Figure 1. Results of vaginal smear examination (400x zoom in)**

Figure 1A shows a vaginal smear of a mouse in the estrus phase before exposure to DMPA. The number of cornified cells present in the vaginal lumen can recognize this phase. The arrow indicates a group of squamous epithelial cells that have undergone cornification, characterized by the absence of visible cell nuclei, granular cytoplasm, and irregular shapes. Figure 1B illustrates a hypoestrogen condition following exposure to DMPA. The arrow points to leukocytes' presence and cornified cells' absence. Epithelial peeling and the arrangement of leukocytes occur when estrogen levels decrease. Once the influence of estrogen diminishes, the vaginal epithelium reverts to an inactive state. Figure 1C depicts the proestrus phase, which occurs after administration of ethanol extract of bengkuang. In this phase, there is a dominance of nucleated epithelial cells that appear either singly or in groups, as indicated by the arrow. This is due to the development of follicles under the influence of FSH, which stimulates the production of large amounts of estrogen.

### Comparison Test Results of Estrogen Levels Between Treatment Groups

A comparison of the average estrogen levels with One Way ANOVA in the five observation sample groups found a significant difference with a p-value = 0.000 < ∝.

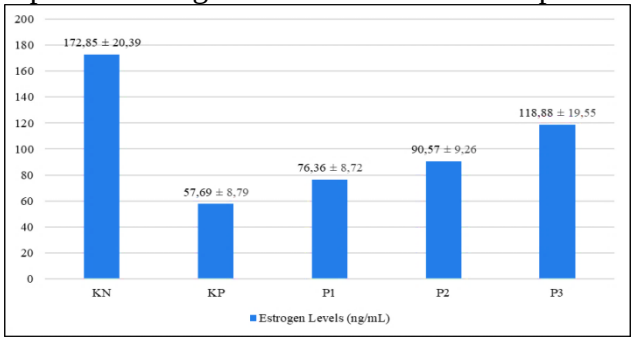


**Figure 2. Comparison of Estrogen Levels (ng/mL)**

ISSN: 2614-3488 (print); 2614-3496 (online) Vol.8 No.2. January 2025. Page.282-291

The test results (Figure 2) showed that there was a significant difference in the average estrogen levels between the negative control group (KP) (without DMPA administration) (172,85 ± 20,39 ng/mL) and the positive control group (exposed to DMPA) (57.69 ± 8.79 ng/mL). It appears that the average estrogen levels in the negative control group were much higher when compared to the average estrogen levels in the positive control group. That means that rats given DMPA will show lower estrogen levels than rats not exposed to DMPA. So, it can be said that DMPA administration can result in decreased estrogen levels.

The highest average estrogen levels were observed in the negative control group (KN), while the lowest average levels were found in the positive control group (KP). Administering DMPA to the rats led to a decrease in estrogen levels. However, in groups P1, P2, and P3, the average estrogen levels increased compared to the positive control group. This increase in estrogen levels is correlated with the increasing doses of bengkuang ethanol extract that is administered. Therefore, the use of three doses of bengkuang ethanol extract can elevate estrogen levels in rats that have been exposed to DMPA. Among the three doses of bengkuang ethanol extract tested, a dose of 280 mg per 200 g/BW/day (P3) resulted in the highest average estrogen level, measuring 118.46 ± 19.55 ng/mL.

**Eestrogen Receptor Beta Expression**

The examination of beta estrogen receptors was conducted using the immunohistochemistry method. The resulting images were observed under an Olympus XC10 microscope, magnified at 400x. A total of 10 fields of view were counted manually to assess the presence of the receptors. The arrows in the images indicate the cell nuclei that express beta estrogen receptors.

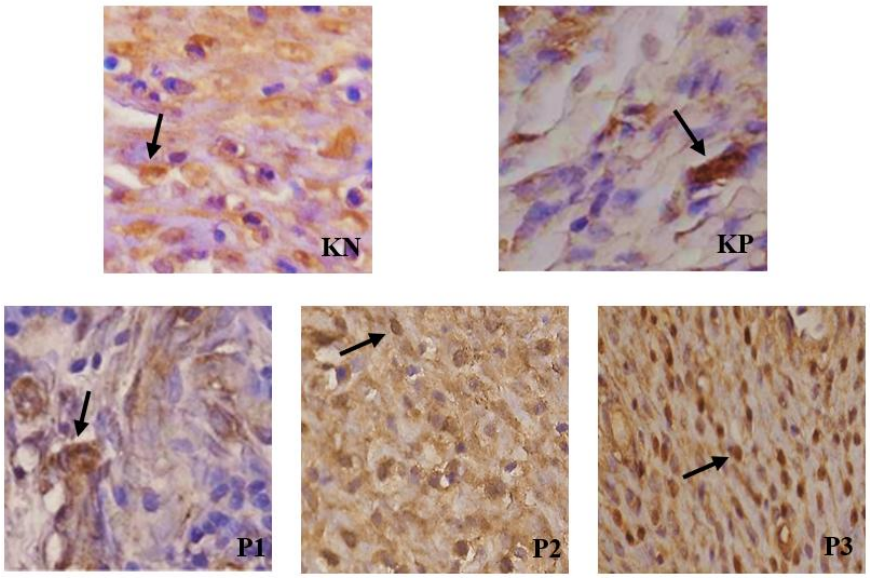


**Figure 3. Observation Results of Estrogen Receptor Beta Expression in the Endometrium of Female Rats**

Figure 3 shows the difference in estrogen receptor beta expression between groups KN, KP, P1, P2, and P3. Estrogen receptor beta expression expression in each group appears to vary by the brown color in group P3 while more dominant than the other groups. The cells expressed in each image look different, compared to brown colors, where the brown color is in group P3 while the least is in group KP.

A comparison of the mean ERβ expression in the five observation sample groups

using the One Way ANOVA test showed significant differences. That is indicated by the p-value = 0.000 < ∝.

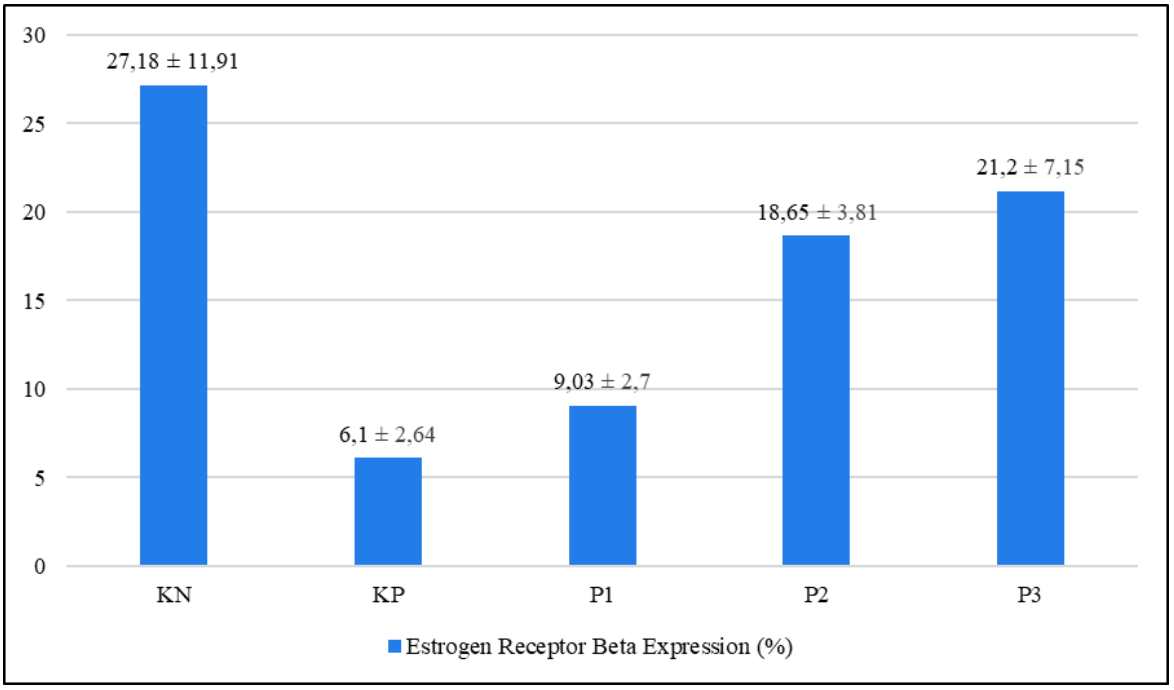


**Figure 4. Estrogen Receptor Beta Expression (%)**

Figure 4 illustrates that the highest average expression of beta estrogen receptors was observed in group P3, while the lowest average was found in the positive control group. This suggests that administering DMPA to female rats can enhance the expression of beta-estrogen receptors. Additionally, the average expression of these receptors increased in groups P1, P2, and P3 when compared to the positive control group. This increase in estrogen receptor beta expression correlates with the increasing doses of bengkuang extract administered. Therefore, all three doses of bengkuang extract were effective in enhancing the expression of beta estrogen receptors in rats treated with DMPA. The dose of bengkuang extract that produced the fastest increase in estrogen receptor beta expression was 280 mg per 200 g body weight per day, with an average of 21,2 ± 7,15.

## DISCUSSION

### The Effect of DMPA Exposure on Estrogen Levels and Estrogen Receptor Beta Expression

From the research results, it was found that the value of p = 0.000 < 0.05, which means that there is an effect of bengkuang (*Pachyrhizus erosus*) ethanol extract on estrogen levels and ERβ expression in *Rattus norvegicus* hypoestrogenic model with DMPA. This study showed that exposure to DMPA at a dose of 2,7 mg every three days and repeated four times caused a significant decrease in estrogen levels and lower estrogen receptor beta expression compared to the negative control group (KN). Hypoestrogenic conditions in rats from vaginal smear results are characterized by the presence of leukocytes and the absence of keratin cells. Epithelial peeling and leukocyte arrangement occur when estrogen levels decrease, and when the influence of estrogen disappears, the vaginal epithelium returns to an inactive state. This condition is induced by the large number of mitotic divisions that occur in the vaginal mucosa and the accumulation of new cells.

High progesterone levels will stimulate neurons in the central nervous system to release opioids, dopaminergic, and gabaergic, thereby inhibiting the release of GnRH. Low GnRH production will stimulate the release of FSH and LH from the anterior pituitary in smaller amounts, thus changing ovarian regulation. Low FSH inhibits follicle development, thereby preventing an increase in estrogen levels (Wahyuni, 2020). The results of a study conducted by Andryani (2021) showed that there was a significant relationship between estradiol hormone levels in Depo Medroxy Progesterone Acetate users (p = 0.000). The results of data analysis showed that the duration of use of Depo Medroxy Progesterone Acetate injections significantly reduced estradiol hormone levels in acceptors (Andryani, et al., 2021).

The dose and duration of exposure to DMPA were adjusted to give DMPA to women every three months for a year. The result of this study showed that the mean estrogen levels in the positive control group exposed to DMPA were lower when compared to the negative control group. Based on the discussion above, this research can prove that the effect of DMPA exposure can reduce estrogen levels.

In this study, that was found that with the administration of DMPA, the average number of ERβ in the positive control group was lower compared to the negative control group. The average estrogen receptor beta expression showed a significant difference (p < 0,05) between the positive and negative control groups. It indicates that the administration of DMPA will reduce ERβ expression. DMPA contains synthetic progesterone that can be metabolized rapidly in humans (Shoupe & Kjos, 2006). Progestin in DMPA circulates through the blood and inhibits the LH hormone, thereby inhibiting ovulation. Inhibition of ovulation results in lower estradiol levels compared to normal women (Melmed, 2016). The impact of DMPA use can reduce estrogen levels which play a role in helping uterine growth through estrogen receptors which have the highest concentration in the proliferation phase and decrease after ovulation in response to increased progesterone. Low estrogen levels result in decreased expression of estrogen receptors in the endometrium (Matthews & Gustafsson, 2003).

**Effect of Bengkuang (*Pachyrhizus erosus*) Ethanol Extract on Estrogen Levels and Estrogen Receptor Beta Expression**

Giving three doses of bengkuang ethanol extract (*Pachyrhizus erosus*) to the treatment group in this study showed an increase in estrogen levels compared to the positive control group (KP). The highest mean estrogen levels were found in treatment group 3 (P3) which was given ethanol extract of bengkuang at a dose of 280 mg/200 g BW/day. In addition, this study also showed an increase in estrogen receptor beta expression along with the increase in the dose of bengkuang extract given, where all three doses given were able to increase estrogen receptor beta expression in rats given DMPA.

The results of this study are supported by research conducted by Lukitaningsih (2009) if bengkuang contains isoflavone compounds with a chemical structure similar to estrogen. The chemical structure of isoflavones resembles 17β-estradiol and has properties like the hormone estrogen. The largest components of isoflavones are genistein and daidzein. Based on the results of the analysis using the High-Performance Liquid Chromatography (HPLC) method on bengkuang tubers, daidzein levels were 108.831 mg/100 g and genistein 163.079 mg/100. Isoflavones (daidzein and genistein) in bengkuang have a structure similar to 17 β-estradiol and estrogen-like activity. So it can be concluded that bengkuang is a source of natural estrogen (Primiani, 2013).

Research conducted by Jefferson (2010) proved that consuming foods containing isoflavones (genistein and daidzein) can affect ovarian function. This is because the function

of the ovaries is controlled by hormones circulating in the body. The main hormone responsible for a woman's reproductive cycle is estrogen. Estrogen stimulates the hypothalamus to produce GnRH which then signals the anterior pituitary to produce FSH and LH. These hormones enter the circulation and signal the ovaries to ovulate. Compounds with estrogenic activity have the potential to affect this signaling and cause a response. Consumption of foods containing estrogenic compounds (phytoestrogens) can bind to estrogen receptors alfa and beta (Jefferson, 2010).

Bengkuang is a plant that contains phytoestrogens with a chemical structure similar to estrogen. Phytoestrogens can bind to estrogen receptors, especially estrogen receptor beta expression. Harris (2005) in his in vitro research on MCF-7 cells evaluated the response to various doses of phytoestrogens based on the presence or absence of 17beta-estradiol with the results of the phytoestrogen content having differential and strong transactivation of estrogen receptor alfa expression and estrogen receptor beta expression induced transcription with estrogen receptor beta expression activation 100 times stronger. Estrogen receptor beta expression expression in the epithelium is related to the menstrual cycle, where when estrogen levels are high, estrogen receptor beta expression can increase. This is associated with the action of estrogen via estrogen receptor alfa expression and progesterone via the progesterone receptor which has been shown to increase estrogen receptor beta expression transcription (harris, et al., 2005). So, it can be said that the mechanism of estrogen receptor beta expression is to help maintain normal endometrium related to the proliferation of endometrial cells.

Based on the discussion above, this study can prove the research hypothesis that the administration of ethanol extract of bengkuang (*Pachyrhizus erosus*) can increase estrogen levels and estrogen receptor beta expression in rats (*Rattus norvegicus*) in a hypoestrogen model with DMPA.

## CONCLUSION

The conclusion of this study is that the administration of ethanol extract of bengkuang (*Pachyrhizus erosus*) can increase estrogen levels and increase receptor beta expression in female rats (*Rattus norvegicus*) in a hypoestrogen model with DMPA.

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