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Oral Administration of *Cassia Alata L.* Leaves Ethanol Extracts Prevented the Increase of Cortisol Level and the Decrease of Estrogen Level in Female Wistar Rats (*Rattusnorvegicus*) Exposed to Cell Phone Radiation

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Abstract: ***Background:*** ***Cell phones are a source of electromagnetic radiation that can cause premature aging through increase cortisol levels and decrease estrogen levels. Cortisol is the main hormone that plays a role in the responese to stress and causes a decrease in estrogen levels, leading to aging-related complications. To prevent pathological conditions due with exposed to cell phone radiation, administration of compound with high amounts of flavonoids is expected to prevent aging. Cassia alata L. contains flavonoids and has antioxidant activity.The aim of study was to prove that the Cassia alata l. leaves ethanol extracts orally prevented the increase of cortisol and decrease of estrogen in female wistar rat (Rattusnorvegicus) exposed to cell phone radiation.*** ***Methods:*** ***This study used randomized pretest and posttest control group design, carried out using rats (Rattusnorvegicus), female, Wistar strain, healthy (active and willing to eat), aged 6 months, weighing 180-200 grams,that were exposed to cell phone radiation. The number of sample was 16 rats which were divided into two groups, namely: the control group (8 rats) that was given 2 ml aquabidest once a day and with exposure to cell phone radiation for 2 hours every day, and the treatment group (8 rats) that was given an ethanol extract of Cassia alata l. leaves of 20mg/kgBW dissolved in aquabidest 2 ml once a day with exposure to cell phone radiation for 2 hours every day. Before and after treatment for 21 day, of cortisol levels and estrogen levels were assessed using the ELISA methods.*** ***Results:*** ***The results showed that in the control group there was a significant increase in cortisol levels (from 68,8 ± 6,24 ng/mL to 88,9 ± 5,52 ng/mL; p <0.001) and also a significant decrease in estrogen levels (from 27,2 ± 1,29 ng/L to 17,4 ± 0,758 ng/L; p <0.001) On the other hand, in the treatment group, cortisol levels did not change (from 71.0±5.10 ng/mL to 70.9±4.02 ng/mL; p = 0.989) and also there was no change in estrogen levels (from 27.4±1.84 ng/L to 24.4±2.99 ng/L; p = 0.059). Before treatment, there were no differences in cortisol levels (p = 0.453) and estrogen levels (p = 0.819) between groups. After 21 days of treatment there were differences in cortisol levels (p <0.001) and estrogen levels (p <0.001) between groups.*** ***Conclusion:*** ***It can be concluded that administration of Cassia alata l. leaves ethanol extract prevented the increase of cortisol and the decrease of estrogen in female Wistar rat (Rattusnorvegicus) exposed to cell phone radiation.***

Keywords: Ethanol extract of *Cassia alata L.* leaves, cortisol, estrogen, cell phone radiation

1. Introduction

Physiological damage is a characteristic of the aging phenotype, including (1) damage resulting from intrinsic life processes; (2) damage due to extrinsic factors, such as diet, lifestyle, personal habits, and psychosocial factors; and (3) age-related diseases.[1]

One extrinsic factor that is rarely explored is the effect of electromagnetic radiation. It can regulate pathways that control the aging process such as inducing hormonal imbalances.[2] Physiological and biological effects that interfere with health due to exposure to cell phone radiation to electromagnetic fields (EMF) have been investigated for years. Exposure standards have been developed internationally, which provide adequate protection against all known adverse effects from EMF radiation exposure. Electromagnetic radiation has various effects, causing deterioration of large molecules in cells and imbalances in ionic balance leading to the formation of harmful byproducts, known as reactive oxygen species (ROS). [4]

These reactive oxygen species can damage cellular components such as proteins, lipids and DNA, thereby causing aging.[5] Some research also shows that EMS from cell phones can affect biological systems by increasing free radicals, which appear to primarily increase lipid peroxidation, and by altering the antioxidant defense systems of human tissue, leading to oxidative stress. [6,7]

The effect of exposure to EMS cellular phones on adrenal corticoid responses was first studied in the early 1960s. [2]

Other independent studies show that exposure to cellphone electromagnetic waves can act as a chronic stressor. [8]

Several reports indicate that long-term electromagnetic wave stimulation increases ACTH and plasma cortisol levels. [2,9]

In vivo studies in rat animals have shown that cell electromagnetic exposure under different conditions (amount of radiation, exposure distance, and duration of exposure) changes cortisol and ACTH levels and improves stress-related rat behavior. [10]

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In women, elevated cortisol levels are antagonistic to estrogen activity, thereby reducing estrogen levels in the entire menstrual cycle but not affecting progesterone levels. [11]

Cortisol suppresses the pituitary response to GnRH and decreases the amplitude of the LH pulse, thereby reducing estrogen production and ovarian secretion. Previous studies have shown that long-term exposure to electromagnetic radiation from cell phones and Wi-Fi devices reduces levels of prolactin, progesterone, and estrogen. [12]*Cassia alataL.* leaves can be found easily in Indonesia and contains tannins, alkaloids, saponins, flavonoids, and glycosides and has antioxidant activity. [13]

Because *Cassia alata L.* leaves also have high levels of antioxidants and flavonoids, it needs to be done however until now Currently, there are no studies that prove the effect of *Cassia alata L.* leaf extract. Moral prevents increased cortisol levels and decreased estrogen in female white rats (*Rattusnovergicus*) strain of Wistar strains by exposure to cellular cell phone radiation.

2. Research Methods

This study uses a randomized pretest-posttest control group design, carried out using experimental animals of albino rats (*Rattusnorvegicus*), females, Wistar strains exposed to cell phone radiation, healthy, 6 months, body weight 180-200 grams, who were exposed to cell phone radiation. The number of samples used was 16 white rats which were then divided into two groups randomly, namely: the control group (8 individuals) were given 2 ml of *aquabidest* 1 time / day and were given cellular phone radiation exposure every day for 2 hours, and the Treatment group (8 heads) by giving ethanol extract of *C. alata.L*leaves as much as 20mg / kgBB, which was dissolved with 2 ml of *aquabidest*given 1 time / day, then given exposure to cell phone radiation every day for 2 hours. Cell phone radiation is mounted sideways and above a wire cage, inside a cage containing 2 mice, and the size of the cage is 30 x 20 x 10 cm. 2,9,14,15 Before and after 21 days of treatment, cortisol and estrogen levels were examined using the ELISA method.

3. Results

The results showed that in the control group there was a significant increase in cortisol levels (from 68.8 ± 6.24 ng / mL to 88.9 ± 5.52 ng / mL; p <0.001) andalso a significant decrease in estrogen levels (from 27.2 ± 1.29 ng / L to 17.4 ± 0.758 ng / L; (p <0.001). In the treatment group cortisol levels did not change (from 71.0 ± 5.10 ng / mL to 70.9 ± 4.02 ng / mL; p = 0.989) and there was no change in estrogen levels (from 27.4 ± 1.84 ng / L to 24.4 ± 2.99 ng / L; p = 0.059). Before treatment there were no significant differences in cortisol levels (p = 0.453) and estrogen levels (p = 0.819) between groups.After treatment for 21 days there were significant differences in cortisol levels (p <0.001) and estrogen levels (p <0.001) between control groups and treatment group.

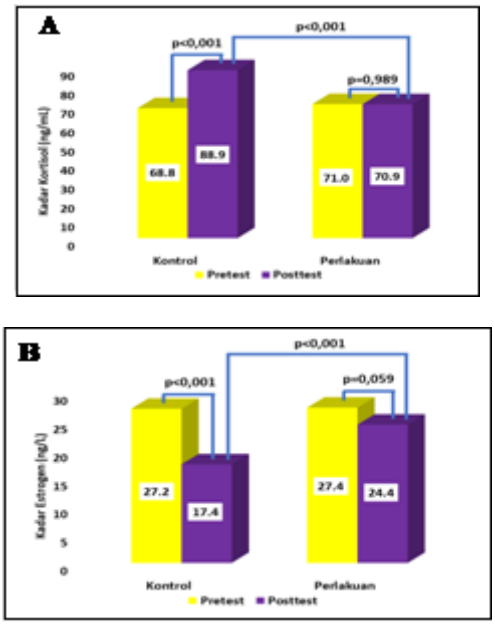

Figure 1: Comparison of (A) cortisol and (B) estrogen levels between the groups before (pre-test) and after 21 days (post-test) treatment.

4. Discussion

The Effect of Cassiaalata L. leaves ethanol extract on Cortisol

Advances in communication technology will be followed by a better level of life, which will lead to the level of conveniences in communication, with the creation of cellular phones (cellphones). Cellphones are two-way communication devices using radio waves, also known as radio frequency (RF), wherever you make a call, the sound will be written in a certain code into the radio waves and then forwarded through the cellphone antenna to the nearest base station where you make call. These radio waves cause radiation and a lot of controversy from various circles about the security of using cellphones. [16]

According to The National Radiological Protection Board (NPRB) UK, UK. Effects caused by electromagnetic wave radiation from cellular phones are divided into two namely:

1) Physiological effects are effects caused by electromagnetic wave radiation which causes interference with the organs of the human body in the form, brain and hearing cancer, tumors, changes in eye tissue, including the retina and lens of the eye, disorders of reproduction, memory loss, headache.
2) Psychological effects Is a psychological effect caused by radiation such as the emergence of stress and discomfort due to repeated radiation irradiation. [16]

Cell phones are a source of electromagnetic wave radiation that can cause crucial changes and damaging effects in biological systems. [4]

Research shows that cell phones continue to emit radiation when not in use. Cell phones emit electric fields, magnetic fields and radiofrequency (RF) radiation. Cell phones emit higher RF radiation levels when used to access networks for data such as checking GPS information. The highest

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emission from a cell phone is when activating WiFi or Bluetooth or in call mode

Research on other mice reports that electromagnetic radiation can cause changes in physiological indices, cause genetic effects, and impair immune function and affect health and immune function. [18]

Other experimental studies in vitro and in vivo have shown that electromagnetic radiation emitted from cell phones can change biological functions, such as the balance between oxidants, antioxidants, and gene / protein expression[7], which are risk factors for the emergence of degenerative diseases and cause aging. [6]

The effect of cell phone electromagnetic wave exposure on adrenal corticoid responses was first studied in the early 1960s. [2]

Other independent research shows that cell phone electromagnetic wave exposure can act as a chronic stressor.8 This is supported by the results of this study which showed that the control group given a placebo in the form of 2ml aquabidest 1 time per day then every day was given cellular phone radiation exposure for 2 hours, carried out consecutively for 21 days, proving a significant increase in cortisol levels from 68.8 ± 6.24 ng / mL to 88.9 ± 5.52 ng / mL. This shows that cell phone radiation exposure causes stress in this control group so cortisol levels increase.

The effects of cellphone electromagnetic waves on stress hormones, conditions such as depression, and anxiety-related behaviors, have been observed in many studies. [8,9,16] Some studies suggest that long-term electromagnetic wave stimulation increases plasma ACTH and cortisol levels. [2,9] Supported with other experiments in rat animals, it has been shown that cell phone electromagnetic exposure under different conditions (amount of radiation, exposure distance, and duration of exposure) changes cortisol, ACTH levels, and improves stress-related rat behavior. [10]

These elevated cortisol levels have various physiological effects that lead to the rapid aging process. The dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis, characterized by elevated basal cortisol levels, is often associated with accelerated aging. [20]

To prevent the negative effects of cellular phonephones radiation on aging, especially those caused by elevated cortisol levels, ethanol extract is given in this study *Cassia alata L.* Leaves.

In accordance with the research hypothesis, in the group given 2ml ethanol extract of *Cassia alata.L* leaves dose of 20mg / KgBB 1 times per day, then given exposure to cell phone radiation for 2 hours / day, carried out consecutively for 21 days, prove that cortisol levels did not experience significant changes. This shows that the ethanol extract of oral *Cassia alataL.* leaves can prevent an increase in cortisol in rats (*Rattusnovergicus*) female Wistar strain with exposure to cell phone radiation. This cannot be separated from the antioxidant content and bioactive compounds found in the ethanol extract of *Cassia alata L.* leavesPrevious studies have shown that it contains bioactive compounds including tannins, alkaloids, saponins, flavonoids, and glycosides. [13]

Flavonoids have been shown to actively inhibit the stress response so that it can be used to prevent negative effects caused by stress on health.

Flavonoids can increase the response of GR receptors, inhibit activity, and reduce levels of CRF and ACTH, thus preventing an increase in cortisol. [18]

In addition, flavonoids can prevent the activation of the HPA axis including inhibition of stress hormone levels and increase glucocorticoid receptors (GR) in the hippocampus, and prevent damage to the HPA PC12 nerve cells caused by high concentrations ofcorticosterone and flavonoids can bind to 5-HT1A. [19]

In addition, in another study it was reported that flavonoids significantly reduced plasma corticosterone levels and plasma adrenocorticotropic hormone levels, and the expression of mRNA Corticotropin realizing factor CRF) in rat hypotalamus. Flavonoids can regulate CRF mRNA expression because flavonoids are able to modulate the DNA binding activity of glucocorticoid receptors and cAMP, as well as regulate phosphorylation of extracellular 1/2 (ERK1 / 2) signals in the hypothalamus. [20]

The Effect of C. alata L. leaves ethanol extract on Estrogen

Estrogen is known as the main female hormone along with progesterone, because it has an important role in shaping a woman's body and preparing a woman's special functions such as pregnancy, breast and pelvic growth. In relation to aging, a decrease in estrogen levels is one of the biomarkers of aging and is also one of the causes of the emergence of degenerative diseases in elderly women. [1]

Stress can be triggered by the level of exposure to electromagnetic waves of various frequencies, increased exposure to light at night, changes in ambient temperature and other pressures from both external and internal. One exposure to electromagnetic waves is through cell phones. Cellphone users are increasingly high, making users have to pay more attention to the side effects of cell phone use on human health. The side effect that is feared by users is the body's exposure to cell phone electromagnetic radiation radiation which is used as a data transfer media. [24]

Stress can mean tension, inner stress, and meaningful conflicts such as frustration and psychological conditions caused by anxiety and fear perception. In stressful conditions, the hypothalamus secretes CRH which has a negative influence on the regulation of GnRH secretion, CRH imbalance has an influence on the suppression of human reproductive function during stress. [25]

In stressful situations, decreasing GnRH levels will also affect FSH and LH levels. Decreased LH levels will affect ovulation and inhibit the corpus luteum to produce progesterone. Whereas decreased FSH levels will inhibit the enlargement of ovarian follicles and together LH will inhibit

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estrogen and ovarian secretion. [26] At the ovarian level, cortisol which is affected by CRH directly inhibits the production of steroid hormones and induces apoptosis. Cortisol inhibition of estradiol will affect the function of granulosa cells and affect the maturation of the follicle and decrease the number of active oocytes. [27]

Exposure to electromagnetic radiation can cause aging through induction of decreased estrogen levels. This can also be preceded by increased cortisol levels which cause dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis. [20]

In women, elevated cortisol levels are antagonistic to estrogen activity, thereby reducing estrogen levels. [28]

Cortisol is increased due to telephone electromagnetic radiation. cellular can bind to its receptors in the hypothalamus and then inhibit GnRH secretion. [29]

GnRH is an important hormone to stimulate the pituitary gland to secrete FSH and LH which results in decreased estrogen production by the follicle de graff in the ovary. The direct effect of cortisol on gonadal levels is inhibiting estrogen production

Previous research has shown that long-term exposure to electromagnetic radiation from cell phones and Wi-Fi devices decreases levels of prolactin, progesterone, and estrogen. [12]
This is consistent with the results of this study which showed that the control group given placebo in the form of 2 ml aquabidest 1 time per day for 2 hours every day with exposure to cell phone radiation for 21 days, a significant decrease in estrogen levels of 27.2 ± 1.29 ng / L to 17.4 ± 0.758 ng / L.

This happens because cell phone exposure causes an increase in ovarian intracellular reactive oxygen species (ROS), which causes apoptosis in de graf follicles and decreases estrogen production and secretion. [30]

Other studies in rats have shown that there is a decrease in the number of de graf follicle follicles and an increase in ovarian follicles in the ovaries female mice exposed to cell phone radiation. This is mediated by a decrease in LH and FSH levels, indicating an indirect effect but through inactivation of the HPA axis. [31]

For this reason, in this study rats were given ethanol extract of *Cassia alata .L* leaves so that estrogen levels did not decrease. The results showed that the group given ethanol extract of *Cassia alata .L* leaves 1 time per day then for 2 hours every day were given consecutive cell phone radiation exposure, for 21 days, proving that estrogen levels did not experience significant changes (from 27.4 ± 1, 84 ng / L to 24.4 ± 2.99 ng / L; p = 0.059). This is most likely due to the flavonoid content in the ethanol extract of *Cassia alata .L*leaves. Other studies have shown that flavonoids have an effect as phosphodiesterase 5 (PDE5) inhibitors. [32]

PDE5 plays a key role in the cGMP pathway.[33] Barriers to PDE5 by flavonoids can increase estrogen biosynthesis by increasing aromatase expression. As previously reported that PDE5 inhibitors, such as tadalafil and sildenafil, can increase the expression of aromatase in human adipocytes. [34] With the same mechanism, flavonoids can increase estrogen production by inhibiting PDE5 activity as observed in tadalafil and sildenafil. [32]

Furthermore, the effect of PDE5 inhibitors, in this case flavonoids, on the development of the female reproductive system and sexual dysfunction is mainly associated with effectiveness at estrogen receptors.35 However, more recent research shows that flavonoids improve estrogen biosynthetic regulation through inhibition of PDE5. [32]

cAMP and cGMP are second messenger which is important in the regulation of estrogen production. In ovarian granulosa cells, cAMP-PKA-CREB is a classic pathway for the regulation of aromatase transcription. [36]

Another study also found that cGMP-cAMP crosstalk can also be involved in regulation of ovarian function and aromatase expression.37 Research shows that flavonoids increase aromatase expression by activating cAMP phosphorylation of element-binding protein (CREB) response. [32]

The cGMP pathway is regulated spatially and temporally through PDE5 compartmentalization. Therefore, different cGMP concentrations can show different roles in estrogen biosynthesis. cGMP can activate protein kinase G (PKG) to increase aromatase expression through CREB. However, it can also use classic cAMP signaling to regulate aromatase expression. PDE3 is a PDE inhibited by cGMP which hydrolyzes cAMP which can mediate cross-talk between cGMP and cAMP signaling pathways.[32] Therefore, an increase in cGMP levels resulting from PDE5 inhibition by flavonoids can suppress the cAMP hydrolysis activity of PDE3, which leads to an increase in the level of cGMP signaling. intracellular cAMP; this activates the classic PKA-CREB pathway and increases the expression of aromatase and estrogen biosynthesis. [32]

The Effect of C. alata L. leaves ethanol extract as Anti-Aging Medicine

Increased cortisol levels and a decrease in estrogen levels due to electromagnetic radiation from cell phone radiation has wide-ranging and accumulative effects that cause the aging process, one of which is early menopause. Therefore, any attempt to prevent an increase in cortisol levels and a decrease in estrogen levels is caused by cell phone radiation which is important and can be considered an Anti-Aging Medicine step.[1]One step that can be done is to consume bioactive compounds that have the effect of inhibiting the increase in cortisol and a decrease in estrogen levels. In this study, we proved that the ethanol extract of *Cassia alata L.* leaves prevented elevated cortisol levels and decreased estrogen levels in female Wistar rats exposed to radiation, so that was one of the efforts of Anti-Aging Medicine.[1]

5. Conclusion

It can be concluded that the administration of *C. alata*L. leaves ethanol extracts prevented the increased cortisol

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levels and decreased estrogen levels in female rats (*Rattusnovergicus*) Wistarstrain with exposed to cell phone radiation.

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